ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ESMO ANNALS OF ONCOLOGY DRIVING INNOVATION IN ONCOLOGY

ORIGINAL ARTICLE

# Efficacy and safety of ramucirumab plus carboplatin and paclitaxel in untreated metastatic thymic carcinoma: RELEVENT phase II trial (NCT03921671)

C. Proto[1*†], M. Ganzinelli[1†], S. Manglaviti[1], M. Imbimbo[1,2], G. Galli[1], M. Marabese[3], F. Zollo[4], M. F. Alvisi[4], M. Perrino[5], N. Cordua[5], F. Borea[6], F. de Vincenzo[5], A. Chella[7], S. Cappelli[7], E. Pardini[7], Z. Ballatore[8], A. Lucarelli[8], E. Ambrosini[9], M. Giuliano[10,11], E. Pietroluongo[10], C. Mulargiu[12], A. Fabbri[13], A. Prelaj[1], M. Occhipinti[1], M. Brambilla[1], L. Mazzeo[1], T. Beninato[1], R. Vigorito[14], M. Ruggirello[14], F. G. Greco[14], G. Calareso[14], D. Miliziano[1], E. Rulli[4], I. De Simone[4], V. Torri[4], F. G. M. de Braud[1,15], G. Pasello[12,16], P. De Placido[10], R. Berardi[9], I. Petrini[17], P. Zucali[5,6], M. C. Garassino[1,18] & G. Lo Russo[1]

[1]Medical Oncology Department, Fondazione IRCCS Istituto Nazionale Dei Tumori, Milan, Italy; [2]Oncology Institute of Southern Switzerland, EOC, Bellinzona, Switzerland; [3]Laboratory of Molecular Pharmacology, Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Milan; [4]Methodology for Clinical Research Laboratory, Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Milan; [5]Department of Oncology, IRCCS Humanitas Research Hospital, Rozzano, Milan; [6]Department of Biomedical Sciences, Humanitas University, Pieve Emanuele, Milan; [7]Pneumology Unit, Azienda Ospedaliero Universitaria Pisana, Pisa; [8]Department of Medical Oncology, Azienda Ospedaliera Universitaria delle Marche, Ancona; [9]Department of Clinical and Molecular Sciences, Università Politecnica delle Marche, Ancona; [10]Department of Clinical Medicine and Surgery, University Federico II, Naples; [11]Rare Tumors Coordinating Center of Campania Region (CRCTR), Naples; [12]Medical Oncology 2, Istituto Oncologico Veneto—IRCCS, Padua; [13]Department of Pathology, Fondazione IRCCS Istituto Nazionale Dei Tumori, Milan; [14]Department of Interventional Radiology, Fondazione IRCCS Istituto Nazionale Dei Tumori, Milan; [15]Department of Oncology and Hemato-Oncology, University of Milan, Milan; [16]Department of Surgery, Oncology and Gastroenterology, University of Padua, Padova; [17]Medical Oncology, Department of Translational Research and New Technologies in Medicine and Surgery, University of Pisa, Pisa, Italy; [18]Thoracic Oncology Program, Department of Medicine, Section of Hematology/Oncology, The University of Chicago, Chicago, USA

Available online 8 June 2024

**Background:** Thymic carcinoma (TC) is a rare tumor with aggressive behavior. Chemotherapy with carboplatin plus paclitaxel represents the treatment of choice for advanced disease. Antiangiogenic drugs, including ramucirumab, have shown activity in previously treated patients. The RELEVENT trial was designed to evaluate the activity and safety of ramucirumab plus chemotherapy as first-line treatment in advanced TC.

**Patients and methods:** This phase II trial was conducted within the Italian TYME network. Eligible patients had treatment-naïve advanced TC. They received ramucirumab, carboplatin and paclitaxel for six cycles, followed by ramucirumab maintenance until disease progression or intolerable toxicity. Primary endpoint was objective response rate (ORR) according to RECIST v1.1 as assessed by the investigator. Secondary endpoints were progression-free survival (PFS), overall survival (OS) and safety. Centralized radiologic review was carried out.

**Results:** From November 2018 to June 2023, 52 patients were screened and 35 were enrolled. Median age was 60.8 years, 71.4% of patients were male and 85.7% had Masaoka—Koga stage IVB. The Eastern Cooperative Oncology Group performance status was 0 in 68.5% and 1 in 31.4% of patients. At the present analysis carried out some months after the interim analysis (earlier than expected) on 35 patients, ORR was 80.0% [95% confidence interval (CI) 63.1% to 91.6%]. At the centralized radiological review of 33/35 assessable patients, ORR was 57.6% (95% CI 39.2% to 74.5%). After a median follow-up of 31.6 months, median PFS was 18.1 months (95% CI 10.8-52.3 months) and median OS was 43.8 months (95% CI 31.9 months-not reached). Thirty-two out of 35 patients (91.4%) experienced at least one treatment-related adverse event (AE), of which 48.6% were AE $\geq$ grade 3.

**Conclusions:** In previously untreated advanced TC, the addition of ramucirumab to carboplatin and paclitaxel showed the highest activity compared to historical controls, with a manageable safety profile. Despite the small number of patients, given the rarity of the disease, the trial results support the consideration of this combination as first-line treatment in TC.

**Key words:** thymic carcinoma, ramucirumab, antiangiogenics, first line, chemotherapy

*Correspondence to: Dr Claudia Proto, Department of Medical Oncology, Fondazione IRCCS Istituto Nazionale dei Tumori, Via Giacomo Venezian 1, 20133 Milan, Italy. Tel: +39-0223903829

E-mail: claudia.proto@istitutotumori.mi.it (C. Proto).

†These authors contributed equally.



## INTRODUCTION

Thymic epithelial tumors (TETs) are rare and very heterogeneous thoracic cancers, with an overall incidence of 0.15 cases per 100 000 person-years. TETs include thymomas (T)—further classified into type A, AB, B1, B2 and B3 based

on epithelial cell morphology and lymphoid cell abundance—and thymic carcinomas (TCs) and exhibit different behavior.[1,2] The biology of TET is still largely unknown and there are currently no approved drugs for specific targets. This is particularly relevant for patients affected by the most aggressive histotypes (TC and B3 T) for whom few therapeutic options exist.[3] Most of these patients are diagnosed in advanced stage and are therefore not candidates for locoregional therapies (surgery and/or radiotherapy). In advanced/metastatic TETs, chemotherapy has shown to be active with a response rate ranging from 55% to 90% and a 5-year survival rate of 30%-55%. However, the majority of studies included only a small proportion of TC and B3 T which are generally less chemoresponsive.[4-6] In this population, the combination of carboplatin and paclitaxel represents the standard first-line option with the highest reported response rates.[7,8]

Ramucirumab is a recombinant human immunoglobulin (Ig)G1 monoclonal antibody with high affinity for the extracellular domain of vascular endothelial growth factor receptor 2 (VEGFR2). Its binding to the receptor results in the inhibition of downstream proangiogenic pathways. Although limited, there is some evidence that angiogenesis plays an important role in TETs.[9] Vascular endothelial growth factor (VEGF) is overexpressed in these neoplasms and the density of newly formed vessels is generally associated with invasiveness and more advanced stages. Higher serum levels of VEGF and basic fibroblast growth factor have been reported in patients with TETs. Antiangiogenic drugs have recently been reported to regulate immune responses in solid tumors. Immune dysfunction at multiple levels has been demonstrated in patients with TETs and abnormal immune surveillance may play a role in the tumorigenesis and progression of these tumors.[10] Several molecules with antiangiogenic activity (e.g. sunitinib, sorafenib)[11-13] have been shown to be active in the treatment of TETs specifically in TC and B3 T.[14-16] In addition, several studies have shown that ramucirumab could act synergistically with taxanes.[17]

Based on this rationale, we designed the RELEVENT trial, an investigator-initiated phase II study to evaluate the activity and safety of ramucirumab plus carboplatin and paclitaxel as first-line treatment in patients with advanced, relapsed and/or metastatic TC or B3 T with carcinoma areas.

## PATIENTS AND METHODS

### *Study design and patients*

The RELEVENT study was a prospective open-label, single-arm phase II trial conducted in six centers of the Italian Collaborative Group for the ThYmic MalignanciEs, TYME network, (Fondazione IRCCS Istituto Nazionale dei Tumori, Milan; Humanitas Research Hospital, Rozzano; Azienda Ospedaliero-Universitaria e Policlinico Federico II, Naples; A.O.U. Ospedali Riuniti, Ancona; A.O.U. Pisana, Pisa; IRCCS Istituto Oncologico Veneto, Padova). Patients were eligible if they were aged $\geq$18 years, had a centrally confirmed diagnosis of advanced, recurrent or metastatic TC or B3 T with carcinoma areas, not previously treated for metastatic disease, had measurable disease according to the Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) and an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0-1. Patients with untreated brain metastases or major standard contraindications to anti-angiogenics were excluded from the study. The study was originally planned to enroll 55 patients.

The protocol and all amendments were approved by the local ethical committees and the Italian Competent Authority. 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 for study participation and data processing before enrollment and were centrally registered using a secure, web-based software platform, REDCap electronic data capture tools hosted at the Istituto di Ricerche Farmacologiche Mario Negri IRCCS.[18,19]

The data collected were pseudoanonymized to guarantee the protection of privacy as for D. Lgs. 196/2003 and Del n. 52, 24 July 2008 and for the GDPR 679/16—'European regulation on the protection of personal data'. Data collection was carried out electronically through a remote data entry and complied with Good Clinical Practice procedures, which guarantees the integrity and transparency of the data and the memory of the changes made.

The study was registered in ClinicalTrials.gov, NCT0392 1671.

### *Treatment and procedures*

After the centralized histological review and the confirmation of the study eligibility criteria, enrolled patients received ramucirumab 10 mg/kg infused intravenously (i.v.) followed by paclitaxel 200 mg/m$^2$ i.v. and carboplatin at an area under the curve of 5 i.v. on day 1 of each 21-day cycle, for a maximum of six cycles or until disease progression (PD) or intolerable toxicity. A 1-h observation period was required after the administration of the first and second doses of ramucirumab. In the absence of any withdrawal criteria, patients who completed combination therapy with disease control at radiological assessment continued to receive ramucirumab monotherapy every 3 weeks as maintenance therapy, until PD or death or unacceptable toxicity. Baseline tissue and blood samples were collected at specific study time points for translational analyses (data not shown).

Clinical and radiological tumor evaluations were carried out every 6 weeks during combination therapy and every 9 weeks during the maintenance phase. Evaluation of disease according to RECIST v1.1 criteria was carried out locally by the investigator. Per protocol, a blinded central radiological review was carried out retrospectively, according to both RECIST v1.1 criteria and International Thymic Malignancy Interest Group (ITMIG)-modified RECIST criteria for TET (mRECIST). All adverse events (AEs) were recorded and graded according to the National Cancer Institute's

Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.0.

### *Endpoints and statistical analysis*

The study followed a two-stage Green—Dahlberg statistical design. The primary endpoint was objective response rate (ORR) assessed by investigators, defined as the proportion of patients who achieved during treatment a complete response (CR) or partial response (PR) as best response according to RECIST v1.1. The null hypothesis that the true ORR is 20% was tested against a one-sided alternative. In the first stage, 30 patients had to be accrued. If there were four or fewer responses in these 30 patients, the study would have been stopped. Otherwise, an additional 25 patients had to be accrued for a total of 55. The null hypothesis was rejected if 18 or more responses were observed in 55 patients.

ORR was reported as the absolute and relative frequency of patients with response; the 95% confidence intervals (95% CIs) were computed by means of exact binomial methods. Logistic regression models were used to explore the relationship between response and histological type, biological markers status and histopathological characteristics. Results were presented as odds ratios and their 95% CIs.

Secondary endpoints were progression-free survival (PFS), overall survival (OS) and safety. PFS was defined as the time from the first experimental treatment administration to PD or death by 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 treatment administration to death by any cause. Subjects alive at the time of the final analysis were censored at the time last known to be alive. Survival curves were estimated using the Kaplan—Meier (KM) method and their CIs were computed with the log—log method. Median PFS, OS and follow-up were calculated according to the KM method. Disease control rate (DCR), defined as the proportion of patients who achieved CR, PR or stable disease (SD), was evaluated as additional information.

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 drug. For AE type, the absolute and relative frequencies of events and the maximum grade experienced by each subject were reported.

Continuous variables were expressed as mean, standard deviation, 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 using SAS software, version 9.4 (SAS Institute, Cary, NC).

Exploratory endpoints were the genomic and micro-RNA (miRNA) landscape evaluations and patient-reported outcomes in patients newly diagnosed with TETs (data not shown).

## RESULTS

From November 2018 to June 2023, 52 patients entered the screening phase of the study and 41 were included in the trial (Figure 1). Eleven patients were excluded due to unconfirmed histology at central pathological review (three patients had a diagnosis other than TET, while the other eight patients were diagnosed with a different TET histology). Out of 41 patients, 35 (85%) received study treatment and were considered for efficacy and survival analyses, and six were considered screening failures for violation of eligibility criteria and did not receive experimental treatment. Patients' baseline characteristics are summarized in Table 1.

Median age was 60.8 years (Q1-Q3 44.5-69.9 years); 25 (71.4%) patients were male and the majority were Caucasian (31 patients, 91.2%). ECOG PS was 0 in 24 (68.6%) and 1 in 11 (31.4%) patients, respectively. Five patients (14.3%) had baseline stage IVA, while 30 patients (85.7%) had stage IVB, according to the Masaoka—Koga staging system. All patients were diagnosed as TC.

At data cut-off (13 October 2023), 10 (28.6%) patients were still on treatment, 4 in the combination and 6 in the maintenance phase. Of the 25 patients who were off treatment, 4 patients discontinued combination treatment (2 for toxicity and 2 for subsequent surgical indication); three patients completed six cycles of combination treatment and never started maintenance (two for PD, one for toxicity). Eighteen patients discontinued the maintenance phase: 13 due to PD, 3 due to toxicity and 2 for subsequent surgical indication (Figure 1). The median number of administered cycles was 6 (from a minimum of 2 to a maximum of 6) for the combination therapy and 10.5 (Q1-Q3 4.5-24.0) for the maintenance phase. Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2024.06.002, shows patients' compliance with the combination therapy.

In March 2023 the interim analysis of the first stage was carried out. Out of 33 patients included, 30 were assessable for response. The ORR—as assessed by local radiological review—was 80.0% (95% CI 61.4% to 92.3%), with 24 patients (80.0%) achieving PR. The remaining six patients (20.0%) showed SD as best response. Since the minimum number of responders to proceed with the second step was reached, the accrual was continued. However, due to accrual constraints caused by the coronavirus disease 2019 (COVID-19) pandemic and the rarity of the disease, considering the positive trial result with an ORR higher than expected and sufficient to achieve the primary endpoint, in June 2023 the sponsor decided to stop the accrual before reaching the planned sample size.

At the final analysis for the primary endpoint, 35 patients were assessable for response and survival analyses. Based on local assessment, 28 (80.0%) patients experienced a PR and 7 (20.0%) an SD as best response. Since, according to the study design, at least 18 responder patients were needed to consider the study positive (in order to exclude an ORR $<$ 20%), and the observed number of responders

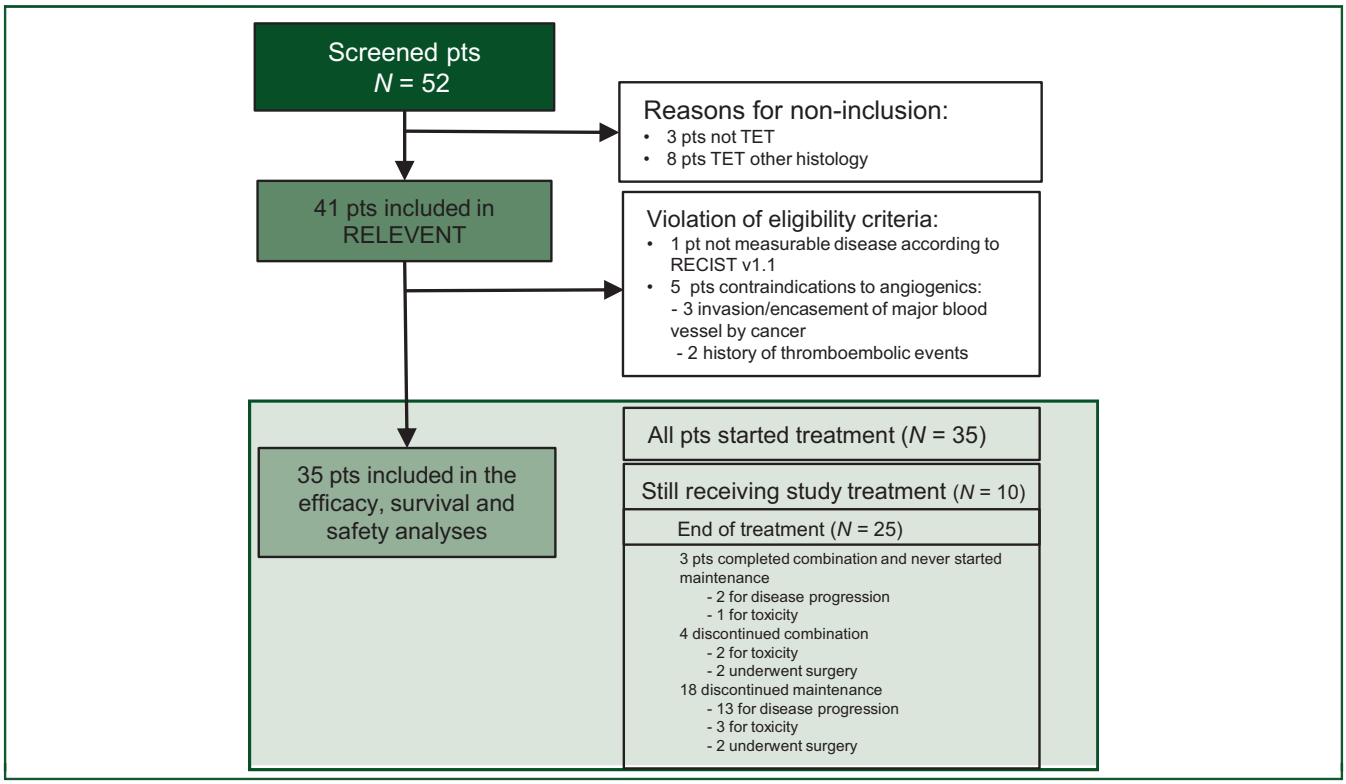


**Figure 1. Patients' disposition.**
pts, patients; TET, thymic epithelial tumors.

were 28, the study reached its primary endpoint: ORR was 80.0% (95% CI 63.1% to 91.6%, binomial test $P < 0.0001$). The results of the univariable logistic regression model for ORR are shown in Supplementary Table S2, available at https://doi.org/10.1016/j.annonc.2024.06.002. Age, sex and Masaoka–Koga staging at enrollment did not show a statistically significant impact on ORR. The median duration of response (DOR) was 15.7 months (95% CI 12.5-50.8 months). Figure 2 depicts the percentage of the best change achieved in target lesions. KM curves for DOR are reported in Figure 3A. After a median follow-up of 31.6 months (95% CI 24.0-40.9 months), 19 (54.3%) patients had died or experienced disease progression and 11 patients (31.4%) had died. The median PFS was 18.1 months (95% CI 10.8-52.3 months) and median OS was 43.8 months (95% CI 31.9 months-not reached) (Figure 3B and C).

**Table 1. Demographic, baseline and tumor characteristics**

| Characteristics | Overall $N = 35$ (%) |
|---|---|
| Sex | |
| Male/female | 25 (71.4)/10 (28.6) |
| Age, median years (Q1-Q3) | 60.8 (44.5-69.9) |
| Race | |
| Caucasian/other | 31 (91.2)/4 (8.8) |
| ECOG performance status | |
| 0/1 | 24 (68.6)/11 (31.4) |
| Masaoka–Koga stage | |
| IVA/IVB | 5 (14.3)/30 (85.7) |
| Histological subtype | |
| Thymic carcinoma | 35 (100) |
| - Squamous cell carcinoma | 30 (85.7) |
| - Sarcomatoid carcinoma | 1 (2.9) |
| - Lymphoepithelioma-like carcinoma | 1 (2.9) |
| - Poorly differentiated carcinoma | 3 (8.5) |
| B3 Thymoma with carcinoma areas | 0 (0) |

ECOG, Eastern Cooperative Oncology Group.

As planned by study protocol, a centralized blinded review by an expert radiologist according to both RECIST v1.1 and mRECIST criteria was carried out. Two patients were excluded due to the absence of target lesions at baseline computed tomography (CT) scan. The ORR by central review according to RECIST v1.1 was 57.6% (95% CI 39.2% to 74.5%, $P < 0.0001$), with 19 patients reaching a PR and 14 an SD. DCR was 100% (95% CI 89.4% to 100.0%). According to mRECIST, the ORR was 60.6% (95% CI 42.1% to 77.1%, $P < 0.0001$), with 20 patients experiencing PR and 13 SD as best response. The DCR was 100% (95% CI 89.4% to 100.0%).

Overall, 518 AEs were reported, of which 267 AEs were related to at least one drug (ARs), of which 168 (62.9%) were grade 1 (G1), 68 (25.5%) G2, 22 (8.2%) G3 and 9 (3.4%) G4; 138 ARs were assessed as related to ramucirumab, of which 88 (63.8%) were G1, 35 (25.4%) G2, 9 (6.5%) G3 and 6 (4.4%) G4. Out of 35 patients, 32 (91.4%) experienced at least one any-grade AR and 17 (48.6%) a grade $\geq 3$ AR. The most common ARs of any grade were peripheral sensory neuropathy (45.7%), decreased platelet count (42.9%), fatigue (40.0%), anemia (31.4%) and neutrophil count decreased (31.4%). The most common ARs of grade $\geq 3$ were decreased neutrophil count (20.0%), hypertension (8.6%), peripheral sensory neuropathy (5.7%) and febrile neutropenia (5.7%). Figure 4 reports the ARs with a 10% prevalence cut-off. Supplementary Table S3, available at

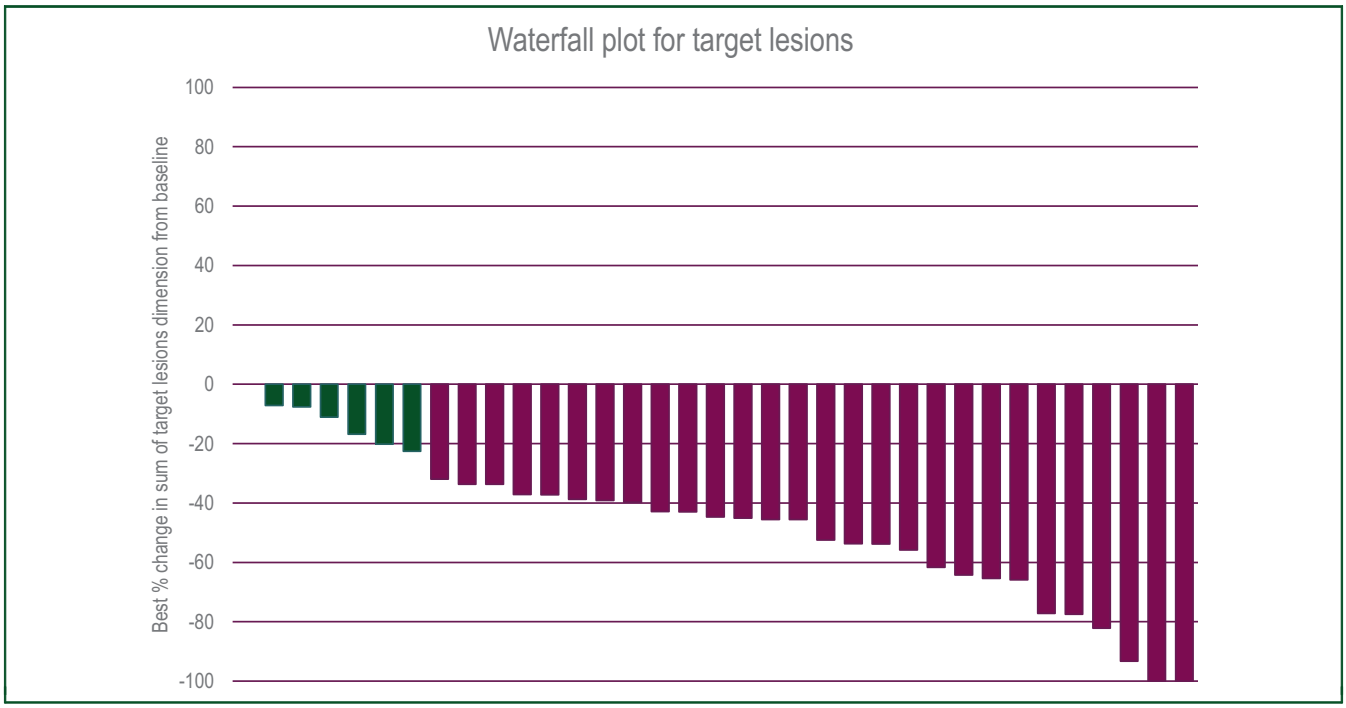


**Figure 2. Waterfall plot for change in target lesions.** Best percentage of change in target lesions are reported. Considering the best response, patients evaluated by RECIST 1.1 with stable disease are colored in green, patients with partial response in burgundy.

https://doi.org/10.1016/j.annonc.2024.06.002, reports all ARs. Eight (22.8%) serious adverse events (SAEs) occurred in five patients. Of these, all five were considered related to the study treatment and four (11.4%), in particular, were judged as related to ramucirumab (two cases of acute myocardial infarction G3, one of pulmonary embolism G4, one of arterial hemorrhage G3 and one of neutropenia G4) (Supplementary Table S4, available at https://doi.org/10.1016/j.annonc.2024.06.002). All SAEs underwent complete resolution.

## DISCUSSION

The prospective investigator-initiated phase II RELEVENT trial was the first to show important activity of ramucirumab added to carboplatin and paclitaxel in previously untreated advanced TC. The study met its primary endpoint with an ORR of 80% (95% CI 63.1% to 91.6%), and a DCR of 100% (95% CI 90% to 100%). After a median follow-up of 31.6 months, median DOR was 15.5 months (95% CI 12.5-50.8 months) and median PFS and OS were 18.1 months (95% CI 10.8-52.3 months) and 43.1 months (95% CI 31.9 months-not estimated), respectively. The study reached the primary endpoint also at central radiological review although with lower ORR compared to that assessed by the investigators (57.6% and 60.6% according to RECIST v1.1 and ITMIG mRECIST, respectively).

TC is a rare tumor and all available data on activity and safety of different drugs and regimens in TETs derive from retrospective studies or small non-randomized phase II trials. To date, carboplatin plus paclitaxel is the best treatment choice for these patients. In the phase II study by Lemma et al.,[7] this regimen demonstrated an ORR of 21.7%, a median PFS of 5.0 months and a median OS of 20.0 months in the subgroup of 23 treatment-naïve TC. These results were confirmed in a larger phase II trial on 39 TC patients, conducted by Hirai et al.,[8] with ORR of 36%, median PFS of 7.5 months and 1-year OS of 85%. Of note, in this study, 7.7% of patients had stage III and four patients (10.2%) were not confirmed to have TC at histological review. Our study shows a doubling of both ORR and PFS in 35 centrally confirmed TC patients.

According to the statistical design, 55 patients with TC or B3 T with carcinoma areas were planned to be enrolled in the study. Due to the rarity of the disease and the difficulties of the intercurrent COVID-19 pandemic, accrual was slower than expected. The null hypothesis was rejected if 18 or more responses were observed in 55 patients. So, at least 18 responses were required to define the study positive. Considering the exceeding and sufficient number of disease responses at interim analysis (24 PRs instead of the 18 PRs required), some months later the sponsor decided to prematurely stop enrollment at 35 patients, before reaching the predefined target number. Of course, the lower number of the enrolled patients causes a low precision of the estimate (CI width) of the primary endpoint, but the achievement of such high ORR granted the positivity of the study as defined by the statistical plan.

Different antiangiogenic agents have been evaluated after failure of first-line platinum-based chemotherapy and the multi-target tyrosine kinase inhibitor, sunitinib, has become one of the therapeutic options in pretreated TC.[11-16] Ramucirumab is a monoclonal antibody directed against the extracellular domain of VEGFR2. It has been

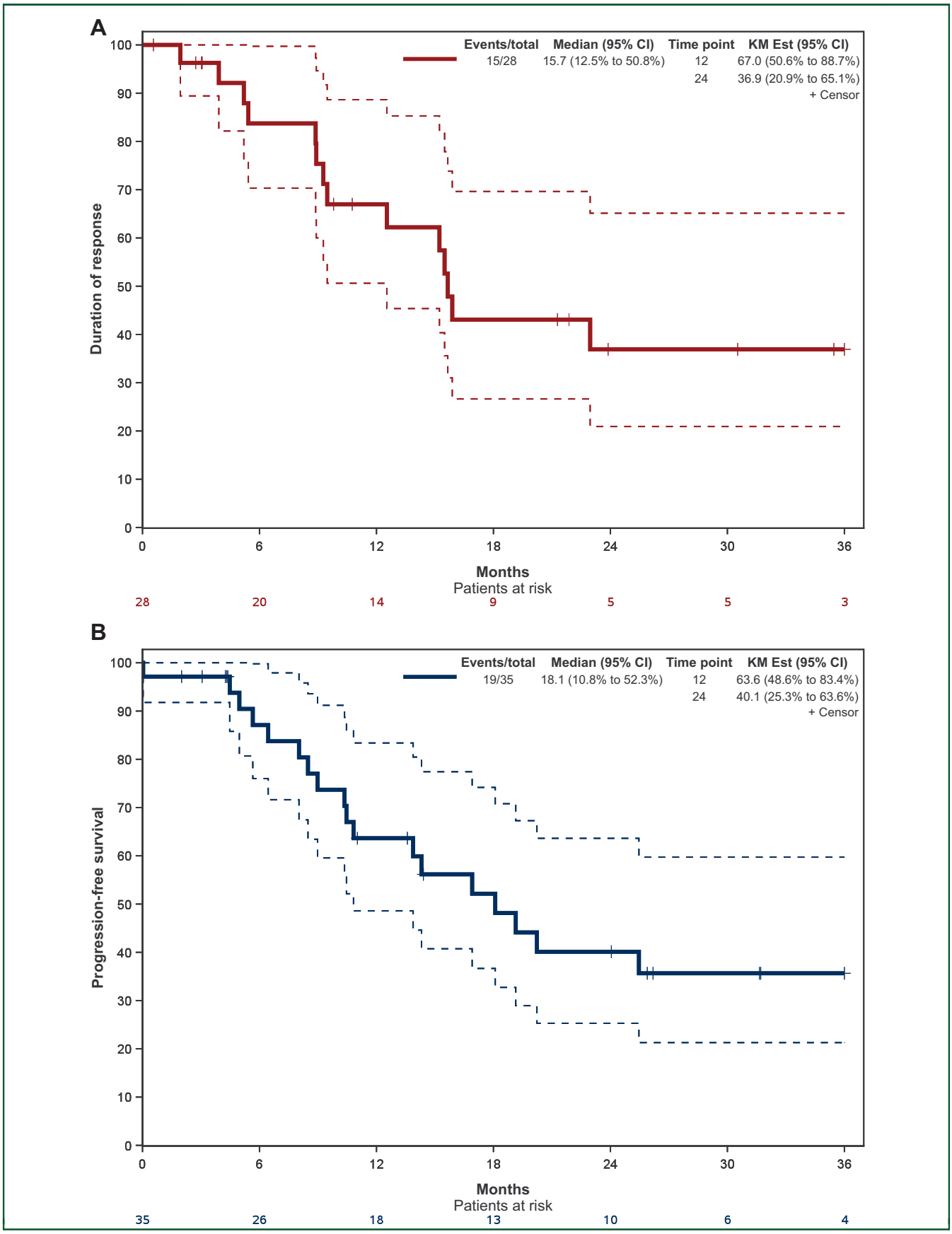


**Figure 3. Kaplan-Meier curves of duration of response (A), progression-free survival (B) and overall survival (C).**
CI, confidence interval; KM est, Kaplan–Meier estimation.

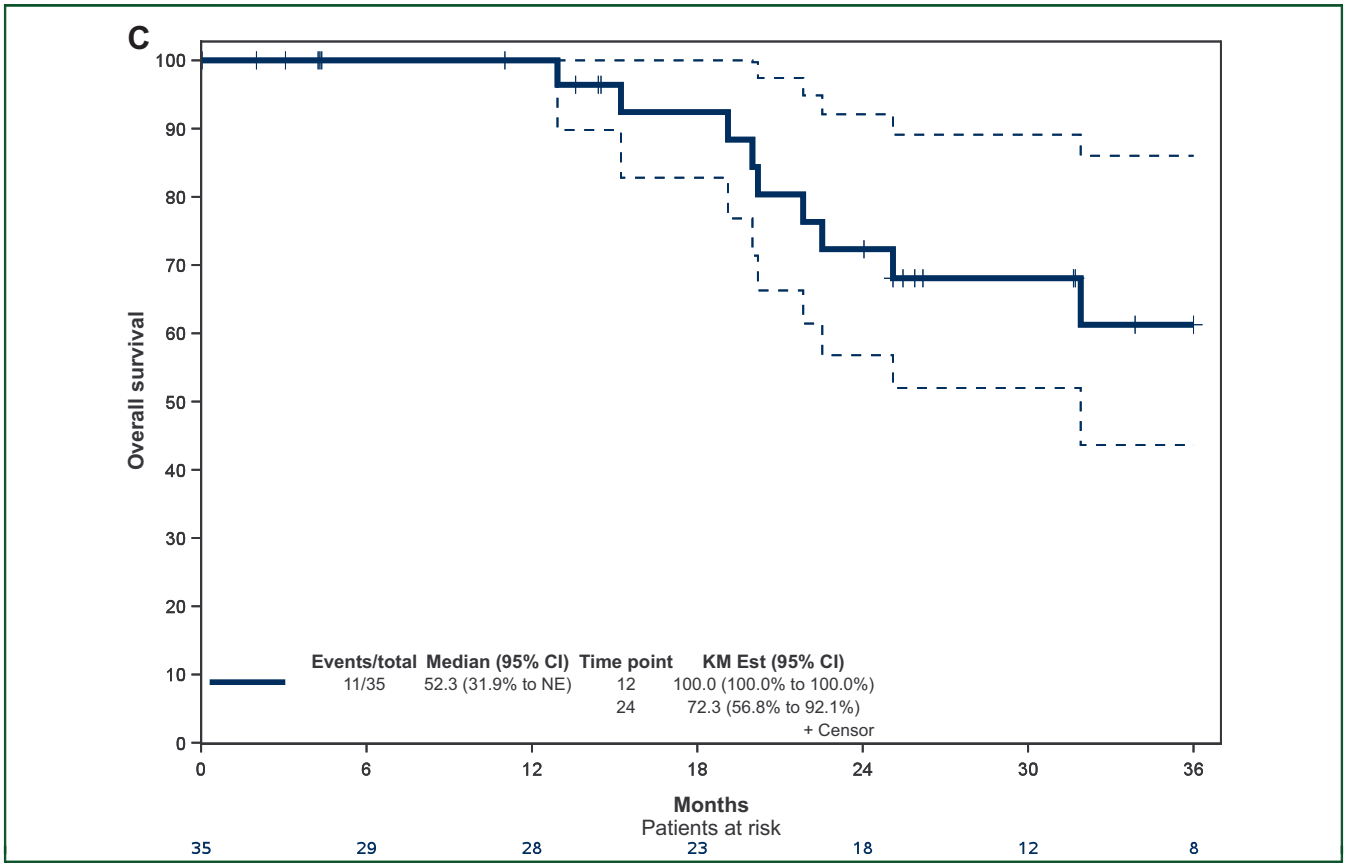


**Figure 3. Continued.**

already evaluated for other malignancies also in combination with carboplatin and paclitaxel, showing efficacy and manageable toxicity profile.[20,21] The reported anti-angiogenic activity of paclitaxel both on the microenvironment and tumor may suggest a synergistic effect of the agent when combined with an antiangiogenic drug.[22] To the best of our knowledge, these are the first data on the combination of an antiangiogenic drug, ramucirumab, with chemotherapy as the first-line option in this very rare cancer population.

Since antiangiogenic drugs show significant cardiovascular toxicity, patients with major treatment contraindications, such as invasion or encasement of major blood vessels by cancer, thromboembolic history or uncontrolled hypertension, are generally considered not eligible for treatment with antiangiogenic drugs and were excluded from RELEVENT. With regard to safety results, they were consistent with available data on both ramucirumab and chemotherapy and no new emergent toxicities were reported. In general, the combination was quite manageable, with grade G1-2 AEs; however, four cardiovascular events (two cases of acute myocardial infarction G3, one of pulmonary embolism G4, one of arterial hemorrhage G3) were reported as SAEs and we cannot exclude the correlation with ramucirumab. We have to consider that, due to the site in which it develops, TC has often important connections with the heart and the great vessels. This aspect may give rise to cardiovascular events regardless of the used drug for treatment. We cannot even rule out that the reported cardiovascular events were due exclusively to the disease rather than to the experimental drug, ramucirumab. In any case, in this rare tumor, often affecting young patients, few therapeutic options currently exist and the need for new combinations still remains an issue. For these reasons, according to the important results in terms of ORR, DoR, PFS and OS, the combination of ramucirumab, carboplatin and paclitaxel represents a valid option in these rare pathologies. Of course, an adequate patient selection at baseline to exclude from the treatment patients with major contraindications to antiangiogenics and an active and close cardiovascular monitoring during treatment have to be carried out to prevent cardiovascular event.

The RELEVENT trial highlighted the need for an accurate and correct histological diagnosis in this setting. Per protocol, all histological diagnoses had to be centrally confirmed at Istituto Nazionale dei Tumori of Milan by an expert pathologist before the enrollment. Eleven out of 52 (21%) central pathological reviews did not confirm TC histology, and, particularly, in almost 6% of cases, the diagnosis was other than TET.

Also the radiological disease evaluation revealed some criticisms. After central radiological review, two patients were not eligible for the study because of the lack of target lesions at basal CT scan. Moreover, the ORR was 57.6% and 60.6% according to RECIST v1.1 and ITMIG mRECIST, respectively, at centralized radiological review, instead of the reported 80% by local investigator assessment. However, based on both the rarity of the disease and its specific localization, such

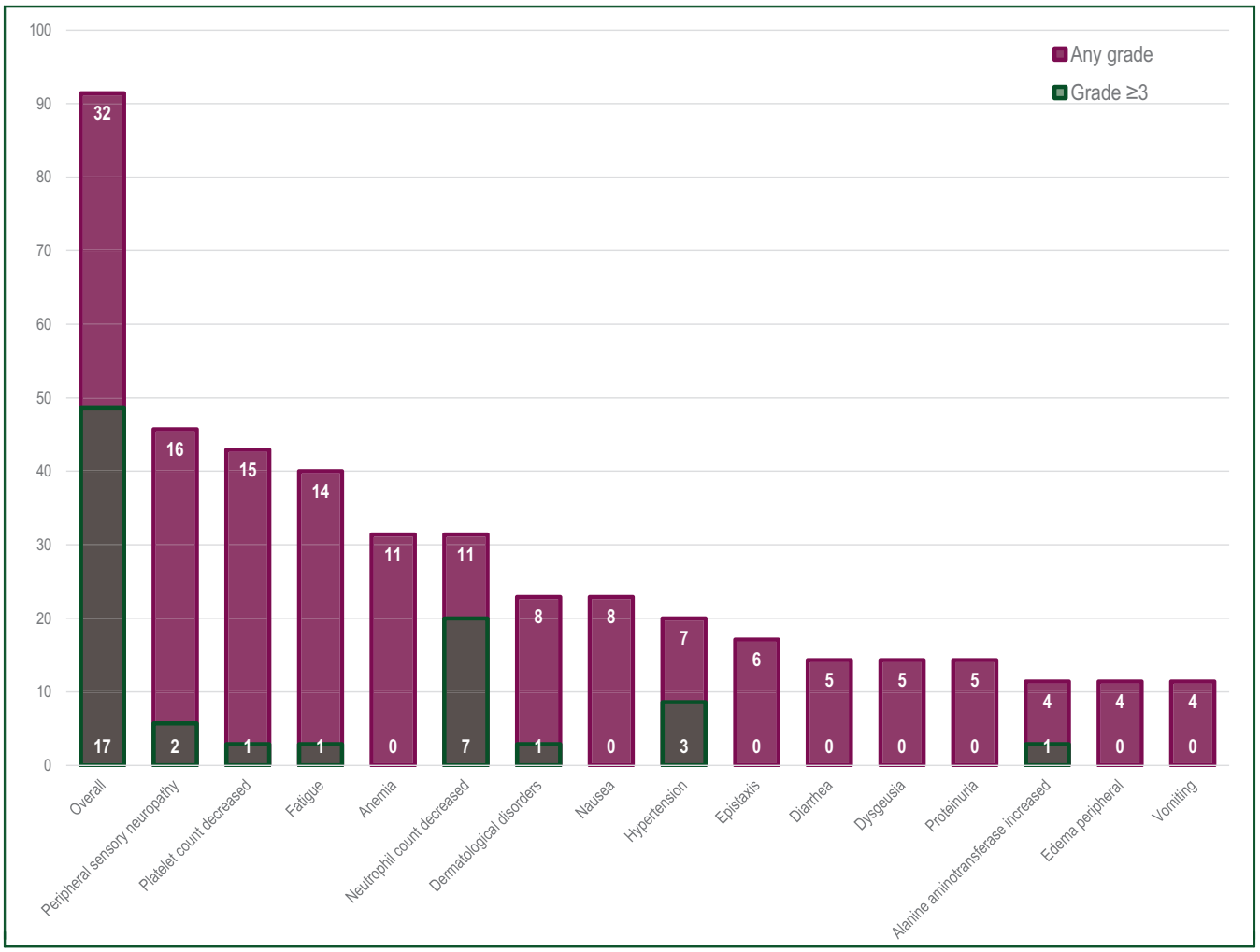


**Figure 4.** **Adverse events related to study treatment (>10% prevalence).**

discrepancy was predictable. Disease evaluation is often difficult and interobserver variability exists. These aspects, certainly dependent on the rarity of pathology, suggest the need for referral centers and expert pathologists and radiologists during the diagnostic phase. The ORR by RECIST v1.1 and mRECIST were quite similar, confirming the already reported lack of significant differences between the two systems in TC radiological evaluation.[23]

Compared to previous studies, the RELEVENT trial has some strengths. Firstly, the required central pathological review before enrollment ensured the exclusive enrollment of TC patients. Moreover, to our knowledge, it is the first trial on TC with a blinded central radiological review carried out by an expert radiologist. Taken together, these aspects support the quality of study results. Regarding the enrolled population, all the patients had stage IV TC with 88.6% of patients showing distant metastases. These characteristics define a homogenous population with a high burden aggressive disease, further supporting the efficacy of the combination.

On the other hand, the trial has some limitations. The single-arm design with the lack of a control group prevented from carrying out a direct comparison with historical regimens. Nevertheless, carrying out a randomized trial in such a rare disease is very hard, especially in an academic setting. Another limitation derives from the small sample size of the study population, although it was comparable or larger than the sample size of previous studies, including Hirai et al.[8] Unfortunately, it was not possible to enroll the preplanned 55 patients in the established study timeline. The lower number of enrolled patients caused a lower precision of the estimate; however, given the higher-than-expected ORR, the study results have to be considered conclusive according to the study hypothesis. Moreover, the stop of the accrual in advance had ensured an earlier availability of the trial results.

RELEVENT results are very impressive compared to the available literature data. In particular, the importance of the activity of the combination of carboplatin, paclitaxel and ramucirumab has to be emphasized in light of the prognostically unfavorable population under study: all patients with advanced TC, with 88.6% of cases in stage IVB with distant metastasis. Of course, this is only a small not randomized phase II study and results may not be confirmed in larger trials as often it happens. However, in such a rare disease, where the absence of therapeutic options is an issue and where carrying out large randomized studies is almost impossible, the availability of this combination could represent a valid therapeutic chance for patients.

To further confirm the role of this regimen, the randomized phase II SWOG trial is actually evaluating the activity of carboplatin and paclitaxel with or without ramucirumab on patients with untreated advanced TC using PFS as the primary endpoint. It will be interesting to see the results of the comparison with standard chemotherapy.

Finally, as regards the exploratory endpoints of the study, translational analyses on tissue and blood samples are now ongoing to evaluate genomic landscape and circulating miRNA profile to better select patients for the combination. They will be presented in a future work.

### *Conclusions*

In this prospective trial, the addition of ramucirumab to carboplatin and paclitaxel showed important activity in untreated advanced/metastatic TC, with a manageable toxicity profile. Therefore, the RELEVENT trial may support the use of this combination as first-line treatment in patients with advanced TC. Potential biomarkers (mutations and circulating miRNAs) and their correlation with response and clinical outcomes are under investigation with the objective of a better patient selection.

## ACKNOWLEDGEMENTS

We would like to thank the Italian Collaborative Group for the ThYmic MalignanciEs, TYME network, and the patient's association Tumori Toracici Rari Onlus (TUTOR).

## FUNDING

The study was sponsored by Fondazione IRCCS Istituto Nazionale dei Tumori that played the role of not-for-profit sponsor and was funded by the Agenzia Italiana del Farmaco [grant number AIFA-2016-02364595]. It was also supported by Eli Lilly Italia S.p.A., which supplied the participating centers with ramucirumab, without any costs or expenses. Eli Lilly Italia S.p.A had no role in study design, data collection, data analysis, data interpretation or writing of the study report. The corresponding author had full access to all the data in the study and had the final responsibility to submit it for publication.

## DISCLOSURE

CP declares having personal financial interest with AstraZeneca, Roche, MSD, Bristol Myers Squibb, Janssen, Sanofi; Pfizer, Lilly, Spectrum Pharmaceuticals, outside of the submitted work. MG reports receiving travel accommodation by Sanofi and research funding from AIRC, MOH, and 5X1000 MOH. SM reports serving on the advisory board for Italpharma and receiving travel accommodation by Merck Sharp & Dohme and Sanofi, outside of the submitted work. GG reports serving on the advisory board for Italpharma; receiving travel accommodation by Roche; and receiving honoraria from AstraZeneca, Bristol-Myers Squibb, and Merck Sharp & Dohme, outside of the submitted work. MI reports having institutional safety board committee membership from Immatics and serving as a principal investigator of AstraZeneca, Bristol-Myers Squibb, Takeda, and T3 Pharmaceuticals, outside of the submitted work. MG declares to be consulting/advisor for Roche, AstraZeneca, Lilly, Daichii Sankyo, Novartis, Pfizer, Seagen, MSD, Eisai; to receive honoraria from Novartis, Pfizer, Lilly, AstraZeneca, Daichii Sankyo; and travel, accommodation, expenses by Lilly, Pfizer, AstraZeneca. AP reports receiving personal fees from AstraZeneca, Italfarmaco, F. Hoffmann-La Roche and Bristol-Myers Squibb, outside of the submitted work. MO reports receiving personal fees from Merck Sharp & Dohme, Bristol-Myers Squibb, AstraZeneca and Eli Lilly outside of the submitted work. MB reports receiving personal fees from AstraZeneca; travel accommodation by Merck Sharp & Dohme, LEO Pharma and Eli Lilly outside of the submitted work. GC reports receiving personal fees from Bristol-Myers Squibb, AstraZeneca and Merck Sharp & Dohme; serving on the advisory board for Italpharma; and receiving travel accommodation by Roche, outside of the submitted work. FGMDB reports having provided consultation, attended advisory boards and/or provided lectures for the following organizations, from whom received honoraria or education grants: Amgen, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, F. Hoffmann-La Roche, Ignyta, Merck Sharp & Dohme, Merck Serono, Novartis and Pfizer, outside of the submitted work. IP reports receiving personal fees from Roche, Bristol-Myers Squibb, Amgen, Sanofi, Takeda and Boehringer Ingelheim, outside of the submitted work. RB reports receiving personal financial interests with the following organizations: AstraZeneca, Boehringer Ingelheim Italia S.p.A., Merck Sharp & Dohme, Eli Lilly, Roche, Amgen, GlaxoSmithKline, Eisai and Bristol-Myers Squibb, outside of the submitted work. PZ reports receiving speaker engagements and travel and accommodation expenses from Merck Sharp & Dohme (Merck Sharp & Dohme), Astellas, Janssen, Sanofi, Ipsen, Pfizer, Novartis, Bristol-Myers Squibb, Amgen, AstraZeneca, Roche and Bayer, outside of the submitted work. MCG declares having personal financial interests with AstraZeneca, Merck Sharp & Dohme International GmbH, Bristol-Myers Squibb, Boehringer Ingelheim Italia S.p.A., Celgene, Eli Lilly, Ignyta, Incyte, Inivata, MedImmune, Novartis, Pfizer, Roche and Takeda; having institutional financial interests with Eli Lilly, Merck Sharp & Dohme, Pfizer (MISP), AstraZeneca, Merck Sharp & Dohme International GmbH, Bristol-Myers Squibb, Boehringer Ingelheim Italia S.p.A., Celgene, Ignyta, Incyte, Inivata, MedImmune, Novartis, Pfizer, Roche, Takeda, Tiziana and Foundation Medicine; and receiving research funding from AIRC, AIFA, Italian Moh and TRANSCAN. GLR declares receiving personal fees from Eli Lilly, Bristol-Myers Squibb, Italfarmaco, Novartis, AstraZeneca, Merck Sharp & Dohme, Takeda, Amgen, F. Hoffmann-La Roche, Sanofi, Pfizer and Glaxo SmithKline, outside of the submitted work. All other authors have declared no conflicts of interest.

## REFERENCES

1. Travis WD, Brambilla E, Nicholson AG, et al. The 2015 World Health Organization Classification of lung tumors. *J Thorac Oncol*. 2015;10(9):1243-1260.

2. Imbimbo M, Ottaviano M, Vitali M, et al. Best practices for the management of thymic epithelial tumors: a position paper by the Italian collaborative group for ThYmic MalignanciEs (TYME). *Cancer Treat Rev*. 2018;71:76-87.
3. Girard N, Ruffini E, Marx A, Faivre-Finn C, Peters S. Thymic epithelial tumours: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2015;26:v40-v55.
4. Serpico D, Trama A, Haspinger ER, et al. Available evidence and new biological perspectives on medical treatment of advanced thymic epithelial tumors. *Ann Oncol*. 2015;26(5):838-847.
5. Okuma Y, Saito M, Hosomi Y, Sakuyama T, Okamura T. Key components of chemotherapy for thymic malignancies: a systematic review and pooled analysis for anthracycline-, carboplatin- or cisplatin-based chemotherapy. *J Cancer Res Clin Oncol*. 2015;141(2):323-331.
6. Berruti A, Borasio P, Gerbino A, et al. Primary chemotherapy with adriamycin, cisplatin, vincristine and cyclophosphamide in locally advanced thymomas: a single institution experience. *Br J Cancer*. 1999;81(5):841-845.
7. Lemma GL, Lee JW, Aisner SC, et al. Phase II study of carboplatin and paclitaxel in advanced thymoma and thymic carcinoma. *J Clin Oncol*. 2011;29(15):2060-2065.
8. Hirai F, Yamanaka T, Taguchi K, et al. A multicenter phase II study of carboplatin and paclitaxel for advanced thymic carcinoma: WJOG4207L. *Ann Oncol*. 2015;26(2):363-368.
9. Cimpean AM, Raica M, Encica S, Cornea R, Bocan V. Immunohistochemical expression of vascular endothelial growth factor A (VEGF), and its receptors (VEGFR1, 2) in normal and pathologic conditions of the human thymus. *Ann Anat*. 2008;190(3):238-245.
10. Tomita M, Matsuzaki Y, Edagawa M, et al. Correlation between tumor angiogenesis and invasiveness in thymic epithelial tumors. *J Thorac Cardiovasc Surg*. 2002;124(3):493-498.
11. Thomas A, Rajan A, Berman A, et al. Sunitinib in patients with chemotherapy-refractory thymoma and thymic carcinoma: an open-label phase 2 trial. *Lancet Oncol*. 2015;16(2):177-186.
12. Remon J, Girard N, Mazieres J, et al. Sunitinib in patients with advanced thymic malignancies: cohort from the French RYTHMIC network. *Lung Cancer*. 2016;97:99-104.
13. Pagano M, Sierra NMA, Panebianco M, et al. Sorafenib efficacy in thymic carcinomas seems not to require c-KIT or PDGFR-alpha mutations. *Anticancer Res*. 2014;34(9):5105-5110.
14. Sato J, Satouchi M, Itoh S, et al. Lenvatinib in patients with advanced or metastatic thymic carcinoma (REMORA): a multicentre, phase 2 trial. *Lancet Oncol*. 2020;21(6):843-850.
15. Perrino M, De Pas T, Bozzarelli S, et al. Resound trial: a phase 2 study of regorafenib in patients with thymoma (type B2-B3) and thymic carcinoma previously treated with chemotherapy. *Cancer*. 2022;128(4):719-726.
16. Proto C, Manglaviti S, Lo Russo G, et al. STYLE (NCT03449173): a phase 2 trial of sunitinib in patients with type b3 thymoma or thymic carcinoma in second and further lines. *J Thorac Oncol*. 2023;18(8):1070-1081.
17. Garon EB, Ciuleanu TE, Arrieta O, et al. Ramucirumab plus docetaxel versus placebo plus docetaxel for second-line treatment of stage IV non-small-cell lung cancer after disease progression on platinum-based therapy (REVEL): a multicentre, double-blind, randomised phase 3 trial. *Lancet*. 2014;384(9944):665-673.
18. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform*. 2009;42(2):377-381.
19. Harris PA, Taylor R, Minor BL, et al. The REDCap consortium: building an international community of software platform partners. *J Biomed Inform*. 2019;95:103208.
20. Reck M, Garassino MC, Imbimbo M, et al. Antiangiogenic therapy for patients with aggressive or refractory advanced non-small cell lung cancer in the second-line setting. *Lung Cancer*. 2018;120:62-69.
21. Camidge DR, Berge EM, Doebele RC, et al. A phase II, open-label study of ramucirumab in combination with paclitaxel and carboplatin as first-line therapy in patients with stage IIIB/IV non–small-cell lung cancer. *J Thorac Oncol*. 2014;9(10):1532-1539.
22. Bocci G, Di Paolo A, Danesi R. The pharmacological bases of the antiangiogenic activity of paclitaxel. *Angiogenesis*. 2013;16(3):481-492.
23. Kim HS, Lee JY, Lim SH, et al. Assessment of objective responses in thymic epithelial tumors using ITMIG modified criteria. *Lung Cancer*. 2016;96:48-51.