

# Efficacy and Safety of TRC105 Plus Pazopanib vs Pazopanib Alone for Treatment of Patients With Advanced Angiosarcoma

## A Randomized Clinical Trial

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**IMPORTANCE** Angiosarcoma is a rare sarcoma subtype with a poor outcome. Carotuximab plus pazopanib produced a median progression-free survival (PFS) of 7.8 months in pazopanib-naïve patients with chemotherapy-refractory angiosarcoma in a phase 1/2 trial.

**OBJECTIVE** To determine whether carotuximab plus pazopanib improves PFS compared with pazopanib alone in patients with advanced angiosarcoma.

**DESIGN, SETTING, AND PARTICIPANTS** The TAPPAS Trial: An Adaptive Enrichment Phase 3 Trial of TRC105 and Pazopanib vs Pazopanib Alone in Patients With Advanced Angiosarcoma was a multinational, multicenter, open-label, parallel-group, phase 3 randomized clinical trial of 123 patients 18 years or older with advanced angiosarcoma that was conducted between February 16, 2017, and April 12, 2019, at 31 sites in the US and the European Union. Patients were randomized 1:1 to receive pazopanib alone or carotuximab plus pazopanib. The trial incorporated an adaptive enrichment design. Inclusion criteria were no more than 2 prior lines of systemic therapy and an Eastern Cooperative Oncology Group performance status of 0 or 1. The efficacy analysis used the intent-to-treat population; the safety analysis included all patients who received a dose of either study drug.

**EXPOSURES** Oral pazopanib, 800 mg/d, or intravenous carotuximab, 10 mg/kg, administered weekly, plus oral pazopanib, 800 mg/d, with dose modification allowed per patient tolerance or until disease progression.

**MAIN OUTCOMES AND MEASURES** The primary end point was PFS, assessed by blinded independent radiographic and cutaneous photographic review per Response Evaluation Criteria in Solid Tumors (RECIST) guidelines, version 1.1. Secondary end points included the objective response rate and overall survival. An interim analysis to determine the final sample size was conducted after enrollment of 123 patients. PFS in the group receiving pazopanib alone was compared with PFS in the group receiving carotuximab plus pazopanib using the log rank test.

**RESULTS** Of 114 patients with evaluable data (53 in the pazopanib arm and 61 in the carotuximab plus pazopanib arm), 69 (61%) were female and the median age was 68 years (range, 24-82 years); 57 (50%) had cutaneous disease and 32 (28%) had had no prior treatment. The primary end point (PFS) was not reached (hazard ratio [HR], 0.98; 95% CI, 0.52-1.84;  $P = .95$ ), with a median of 4.3 months (95% CI, 2.9 months to not reached) for pazopanib and 4.2 months (95% CI, 2.8-8.3 months) for the combination arm. The most common all-grade adverse events in the single-agent pazopanib arm vs the combination arm were fatigue (29 patients [55%] vs 37 [61%]), headache (12 patients [23%] vs 39 [64%]), diarrhea (27 patients [51%] vs 35 [57%]), nausea (26 patients [49%] vs 29 [48%]), vomiting (12 patients [23%] vs 23 [38%]), anemia (5 patients [9%] vs 27 [44%]), epistaxis (2 patients [4%] vs 34 [56%]), and hypertension (29 patients [55%] vs 22 [36%]).

**CONCLUSIONS AND RELEVANCE** In this phase 3 randomized clinical trial, carotuximab plus pazopanib did not improve PFS compared with pazopanib alone in patients with advanced angiosarcoma.

**TRIAL REGISTRATION** ClinicalTrials.gov Identifier: [NCT02979899](https://clinicaltrials.gov/ct2/show/study/NCT02979899)

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Angiosarcomas are rare, aggressive, and heterogenous tumors of endothelial cell origin and account for approximately 3% of soft-tissue sarcomas.<sup>1</sup> Angiosarcomas can occur in any soft-tissue structure or viscera; about half present with a primary cutaneous lesion.<sup>1</sup> The pathogenesis includes prior radiation exposure and inflammatory damage in chronically sun-exposed skin.<sup>1</sup> Noncutaneous angiosarcoma can be associated with prior radiation exposure or be idiopathic.<sup>1</sup> Angiosarcomas have also been associated with prolonged lymphedema.<sup>1</sup>

Complete surgical resection with or without perioperative radiotherapy is the optimal treatment for localized disease, but approximately 50% of patients die of metastases.<sup>1-3</sup> Treatment options are limited for advanced disease and are of modest benefit, with a median overall survival (OS) of less than 12 months.<sup>1,3-5</sup> Standard regimens include taxanes, anthracyclines, gemcitabine, and pazopanib, but tumor control is short-lived, with median progression-free survival (PFS) ranging from 3.9 to 6.6 months.<sup>3-9</sup>

Pazopanib, a vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitor, was approved based on improved PFS compared with placebo in patients with chemotherapy-refractory sarcomas (4.6 months vs 1.6 months).<sup>10</sup> However, activity in angiosarcoma is limited; no complete responses and a median PFS of 3.02 months were observed in a series of 30 patients with angiosarcoma.<sup>8</sup> Other VEGFR inhibitor trials confirmed a low response rate and PFS of 4 months or less.<sup>11-13</sup>

Endoglin (CD105) is a homodimeric cell membrane glycoprotein that is densely expressed on proliferating endothelial cells.<sup>14,15</sup> It is a transforming growth factor  $\beta$  coreceptor that is essential for angiogenesis<sup>16,17</sup> and is strongly expressed on the proliferating vascular endothelium of tumors.<sup>15,18</sup> Endoglin expression is upregulated in tumor endothelial cells after VEGF pathway inhibition.<sup>19,20</sup> Preclinical data suggest that targeting the endoglin and VEGF pathways concurrently may lead to more effective angiogenesis inhibition than targeting either pathway individually.<sup>21-23</sup>

Carotuximab is an IgG1 antibody that binds endoglin with high avidity to inhibit signal transduction through the endoglin ligand bone morphogenetic protein. It is also able to mediate antibody-dependent, cell-mediated cytotoxicity. Carotuximab plus pazopanib was studied in a single-arm, phase 1/2 trial of multiple soft-tissue sarcoma subtypes and showed durable complete responses in cutaneous angiosarcoma.<sup>24</sup> The median PFS was 7.8 months in patients with angiosarcoma without prior VEGF inhibitor therapy. The TAPPAS Trial: An Adaptive Enrichment Phase 3 Trial of TRC105 and Pazopanib Versus Pazopanib Alone in Patients With Advanced Angiosarcoma assessed the clinical benefit of carotuximab plus pazopanib in patients with angiosarcoma, using an adaptive design to allow for sample-size modification or selective enrollment of patients with cutaneous angiosarcoma based on the conditional power for showing improved PFS at the planned interim analysis.

## Methods

### Design and Participants

The TAPPAS trial was a multinational, multicenter, open-label, parallel-group, phase 3 randomized clinical trial con-

### Key Points

**Question** Does the combination of pazopanib plus carotuximab improve progression-free survival compared with pazopanib alone in patients with advanced angiosarcoma?

**Findings** This phase 3 randomized clinical trial of 123 patients found no significant difference in median progression-free survival between patients receiving pazopanib plus carotuximab compared with pazopanib alone.

**Meaning** The study's findings indicate that the combination of pazopanib plus carotuximab is not superior to pazopanib alone in treating patients with advanced angiosarcoma.

ducted between February 16, 2017, and April 12, 2019, at 31 sites in the US and the European Union. The trial protocol is available in [Supplement 1](#). Adult patients without prior VEGF inhibitor or carotuximab treatment were randomized 1:1 to receive standard-dose pazopanib (arm A) or carotuximab plus standard-dose pazopanib (arm B). Randomization was done using the TRACON Pharmaceuticals proprietary RStart Randomization System by means of randomly alternating 2- and 4-patient blocks. Patients were stratified by angiosarcoma type (cutaneous vs noncutaneous) and number of lines of prior systemic therapy (0 vs 1-2). For this trial, cutaneous angiosarcoma included primary skin and/or scalp angiosarcoma; all other angiosarcomas, including primary subcutaneous angiosarcoma, were categorized as noncutaneous. The trial was conducted in accordance with Good Clinical Practice as defined by the International Conference on Harmonisation. Local institutional review board or ethical committee approval was obtained at each site before commencing the study (eTable 3 in [Supplement 2](#)). All patients provided written informed consent before entering the trial. This study followed the Consolidated Standards of Reporting Trials ([CONSORT](#)) reporting guideline.

Patients randomized to arm A received oral pazopanib, 800 mg/d. Those randomized to arm B received intravenous carotuximab, 10 mg/kg (with appropriate premedication) weekly and oral pazopanib, 800 mg/d. Dose modifications of carotuximab and pazopanib were allowed per patient tolerance.

The primary end point was PFS, assessed by blinded independent review of radiographic lesions and 2-dimensional photographs of cutaneous lesions using the modified Response Evaluation Criteria in Solid Tumors (RECIST) guidelines, version 1.1,<sup>25</sup> whereby measurable lesions could have included up to 10 lesions in total, including up to 5 cutaneous lesions and up to 5 noncutaneous lesions representative of all involved organs (with a maximum of 2 lesions per organ other than skin). Imaging and photography were performed every 42 days from the date of randomization. Secondary end points included the objective response rate and OS, per RECIST guidelines, version 1.1.

### Participant Eligibility

The trial enrolled patients 18 years or older with histologically confirmed advanced angiosarcoma not amenable to cu-

rative surgical resection. Patients had disease measurable by RECIST guidelines, version 1.1, and were either treatment naive or had documented progression on or after the most recent systemic therapy within 4 months before screening. Other inclusion criteria included adequate hematologic, kidney, and liver function; Eastern Cooperative Oncology Group performance status of 0 or 1; and resolution of all adverse events of grade 1 or less from prior cancer therapy or pretrial baseline (except alopecia or neuropathy), as assessed per the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03. Women of child-bearing potential had a negative pregnancy test at enrollment and agreed to use 2 or more acceptable methods of contraception during the trial and for at least 180 days after the last dose of carotuximab or pazopanib. Similarly, men agreed to use contraception during the trial and for at least 180 days after the last dose of carotuximab or pazopanib. Exclusion criteria included receipt of wide field radiotherapy within 28 days or limited-field radiotherapy within 14 days of randomization, uncontrolled hypertension, ascites, pleural or pericardial effusions, active bleeding, hemoptysis, active viral hepatitis, and untreated brain metastases.

#### Endoglin Expression on Circulating Tumor Cells

Circulating tumor cells (CTCs) were enriched by separation using a dielectrophoretic device (ApoStream [Precision for Medicine]) that exploits differences in dielectrophoretic properties between cancer cells and normal cells. Endoglin-expressing cells stained with 4',6-diamidino-2-phenylindole (DAPI) were analyzed by 2-color immunofluorescence using an endoglin antibody recognizing an endoglin epitope distinct from that recognized by carotuximab. Results were reported as the number of endoglin-expressing cells per milliliter. Endoglin-expressing, DAPI-positive CTCs were quantified before dosing and 6 weeks after the initiation of dosing.

#### Statistical Analysis

The study population for efficacy (ie, the intent-to-treat population) included all randomized patients. The analysis of the primary end point of PFS compared arm A with arm B using a 1-sided log-rank test stratified by angiosarcoma location (cutaneous vs noncutaneous) and by prior lines of systemic therapy (0 vs 1-2), with significance set at  $\alpha = .05$  using a 2-tailed test. The trial population for safety included all patients who received a dose of either study drug.

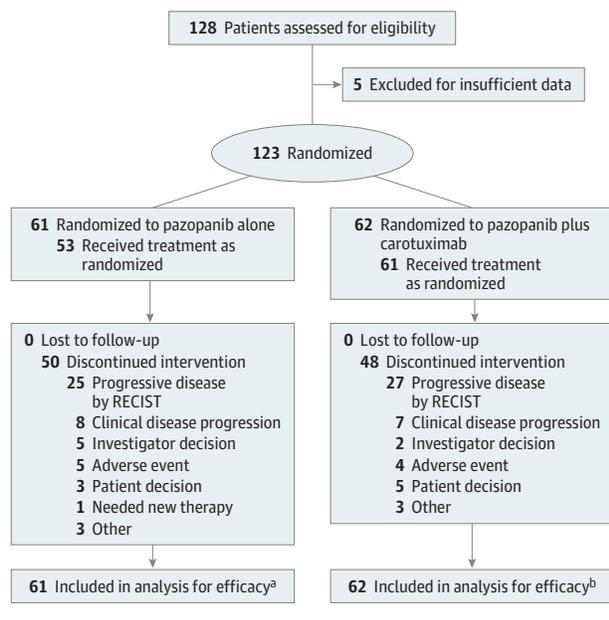
An increase in PFS of 3 months or longer was considered to be clinically relevant. The expected PFS of patients with angiosarcoma treated with pazopanib was estimated at 4 months. A hazard ratio (HR) of 0.55 corresponded to an improvement of median PFS from 4.00 months to 7.27 months. Given these assumptions, 95 events provided 83% power to detect an HR of 0.55. Owing to the uncertainty of the treatment effect and heterogeneity among the cutaneous and noncutaneous subgroups, an adaptive enrichment design was used. The initial study design called for enrolling 2 cohorts, with 120 patients in cohort 1 and 70 patients in cohort 2, and the initially planned final analysis was to be conducted when at least 60 events from

cohort 1 and at least 35 events from cohort 2 had been observed.

Owing to possible differences in the treatment effect in the cutaneous and noncutaneous angiosarcoma subgroups, an adaptive enrichment design was used.<sup>26</sup> An interim analysis was planned after 40 events had occurred or 30 days after the enrollment of 120 patients from cohort 1 and was to result in one of the following decisions by the independent data monitoring committee based on the conditional power (CP) to achieve the primary end point: (1) no change to the study design and sample size if the CP was greater than 0.95 (favorable zone), (2) no change to the study design but an increase in the sample size to a total of 340 patients if the CP was between 0.3 and 0.95 (promising zone), (3) termination of enrollment of an unresponsive noncutaneous angiosarcoma subtype and adjustment of the sample size of the cutaneous subtype to a total of 220 patients with cutaneous disease if the CP was less than 0.30 but the CP of only the cutaneous subgroup was 0.50 or greater (enrichment zone), or (4) no change to the study design and sample size if the CP was less than 0.30 and the CP of only the cutaneous subgroup was less than 0.50 (unfavorable zone). Conditional power was defined as the probability that, conditional on the current value of the test statistic, the trial would achieve statistical significance at the final analysis. The Kaplan-Meier method was used to estimate survival outcomes. Statistical comparisons of PFS and OS were made using a stratified log-rank test with the randomization strata to test for statistical significance of PFS and OS. Progression-free survival was defined as the time from randomization to either the first disease progression or death from any cause. For patients alive without progressive disease (PD) at the time of analysis, the following rules were applied: (1) the patient was censored on the date of the last tumor assessment documenting the absence of PD; (2) if the patient was given antitumor treatment other than the study drug, the patient would be censored at the date of the last tumor assessment before initiating that antitumor therapy; and (3) if the patient was removed from the trial owing to toxic effects or another reason, the patient would be censored at the date of the last tumor assessment during the trial. In the event of 1 missed tumor assessment followed by a subsequent assessment of PD, the subsequent PD assessment qualified as objective tumor progression. In the event of more than 1 consecutive missing tumor assessment followed by a subsequent assessment of PD, the patient would be censored at the last adequate tumor assessment. If individual scans were performed on different dates but contributed to the same overall assessment, the date of the earliest scan would be used. Univariate comparisons were done by the Cochran-Mantel-Haenszel method. Statistical analyses were conducted with SAS, version 9.1 (SAS Institute Inc).

Restricted mean survival time and the Fleming-Harrington (FH) test were used to assign different weights to early and late relapse using the R library FHtest package for R. For the FH test function, the following parameter was used:  $\rho = 0$  and  $\lambda = 1$ . The Rényi family of statistical tests was used to detect differences in survival curves that crossed, and these

Figure 1. CONSORT Diagram



Reasons for not beginning treatment or withdrawal from the trial were not captured in the case report form, but most cases were owing to patient decision. The primary end point (progression-free survival) was analyzed in the intent-to-treat population, which represented all randomized patients as of the data cutoff for the interim analysis.

<sup>a</sup> A total of 53 patients were included in the safety analysis.

<sup>b</sup> A total of 61 patients were included in the safety analysis.

tests were applied to ensure that there was no overfitting of the data.

## Results

A total of 128 patients were enrolled in the trial; 123 patients had sufficient data for inclusion in the interim analysis (Figure 1). Of 114 patients with evaluable data, 69 (60%) were female and the median age was 68 years (range, 24-82 years); 57 (50%) had cutaneous disease and 32 (28%) had had no prior treatment. Sixty-one patients, of whom 8 did not receive pazopanib after randomization, were randomized to receive only pazopanib (arm A). Sixty-two patients were randomized to receive carotuximab and pazopanib (arm B), of whom 1 did not receive either drug, 2 did not receive pazopanib, and 1 did not receive carotuximab. At the time of data cutoff, 50 of 61 patients in arm A and 48 of 62 in arm B had withdrawn from the trial. No patients were lost to follow-up. The 2 treatment groups were balanced with regard to age, performance status, and the proportion of patients with cutaneous angiosarcoma (Table 1). Half of the patients in each arm had cutaneous disease (53 [46%] in arm A and 61 [54%] in arm B). Fifteen patients (28%) in arm A received treatment as the first-line systemic therapy compared with 17 (28%) in arm B.

In arm A, the median number of pazopanib doses was 47 (range, 11-209); 32 patients (60%) required dose reduction. In arm B, the median number of pazopanib doses was 67 (range,

Table 1. Patient Demographic and Clinical Characteristics

Characteristic	Patients, No. (%) (N = 114) <sup>a</sup>	
	Arm A (pazopanib) (n = 53)	Arm B (carotuximab + pazopanib) (n = 61)
Mean (SD) age, y	62.6 (14.7)	63.9 (13.3)
Sex		
Female	35 (66)	34 (56)
Male	18 (34)	27 (44)
Race		
Asian	4 (8)	1 (2)
Black	1 (2)	1 (2)
Other	4 (8)	2 (3)
White	44 (83)	57 (93)
ECOG performance status		
0	24 (45)	28 (46)
1	29 (55)	33 (54)
Cutaneous disease	26 (49)	31 (51)
Prior lines of therapy		
0	15 (28)	17 (28)
1	22 (41)	21 (34)
2	14 (26)	23 (38)

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

<sup>a</sup> Data are presented as number (percentage) of patients unless otherwise indicated.

8-463); 35 patients (59%) required pazopanib dose reduction. Of the 58 participants receiving carotuximab in arm B, the dose was reduced to 8 mg/kg weekly in 12 patients; in 4 patients, the dose was subsequently reduced to 6 mg/kg weekly.

The date of the database cutoff for the primary analysis was March 14, 2019. The median follow-up time for overall survival was 4.6 years (range, >1 month to 23 months), calculated by a reverse Kaplan-Meier estimate. The primary end point (PFS) analysis based on blinded independent review was conducted on the basis of 45 events of progressive disease assessed by blinded independent review or of death while participating in the trial. As of the cutoff date, 50 of 61 patients randomized to receive pazopanib in arm A had withdrawn from the study and 19 completed follow-up. Of those randomized to receive carotuximab and pazopanib in arm B, 48 of 62 had withdrawn from the study and 18 completed follow-up.

### Efficacy

The median PFS, according to RECIST guidelines, version 1.1 and assessed by blinded independent review, was 4.3 months (95% CI, 2.9 months to not reached) in arm A vs 4.2 months (95% CI, 2.8-8.3 months) in arm B (HR, 0.98; 95% CI, 0.52-1.84;  $P = .95$ ) (eTable 1 and eFigure 1 in Supplement 2).

For the secondary (exploratory) end point, the median PFS by investigator review was 2.9 months (95% CI, 2.8-4.2 months) in arm A vs 3.5 months (95% CI, 2.7-7.0 months) in arm B (univariable HR, 0.72; 95% CI, 0.44-1.18;  $P = .19$ ). The Kaplan-Meier curves for PFS are shown in Figure 2. The post hoc analysis showed no difference in PFS between the arms at 2.9 months

Figure 2. Kaplan-Meier Plot of Progression-Free Survival by Blinded Independent Radiographic Review

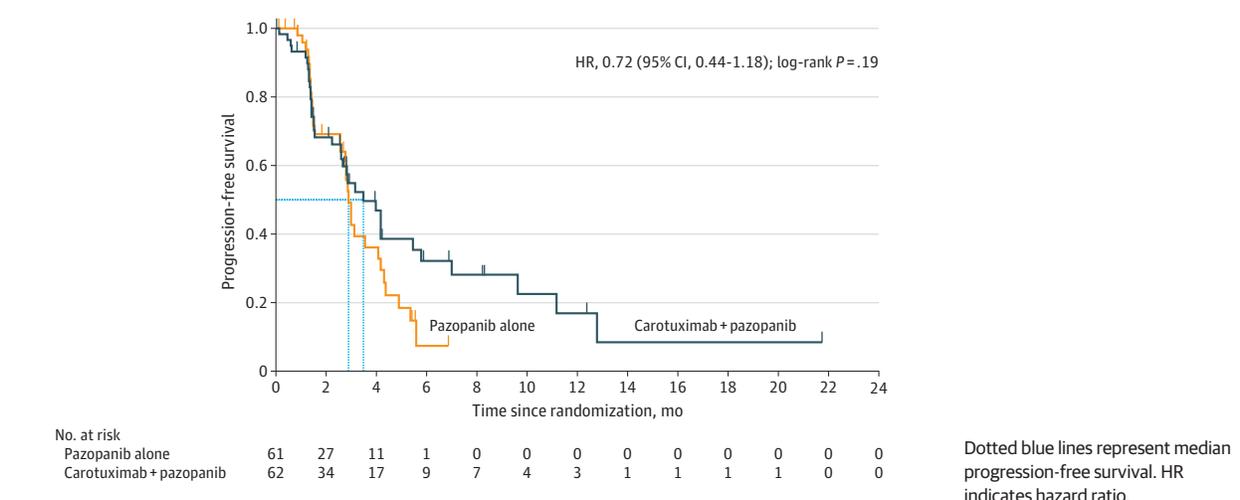
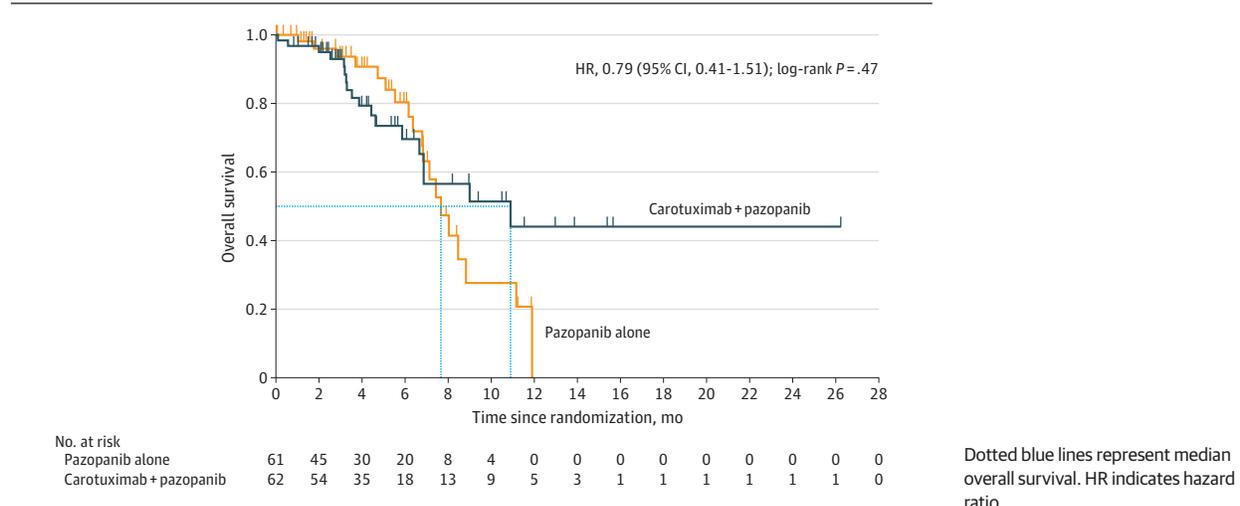


Figure 3. Kaplan-Meier Plot of Overall Survival



but a significant difference in favor of the combination arm after 3.5 months (FH test,  $\lambda = 1$ ;  $P = .02$ ).

The median OS was 7.7 months (95% CI, 6.8 months to not reached) in arm A and 10.9 months (95% CI, 6.8 months to not reached) in arm B (HR, 0.79; 95% CI, 0.41-1.51;  $P = .47$ ). The Kaplan-Meier curves for OS are shown in Figure 3. The objective response rate by blinded independent review in arm A was 13% (95% CI, 6%-24%) compared with 5% (95% CI, 1%-14%) in arm B ( $P = .09$ ).

In the 64 patients with cutaneous angiosarcoma, the median PFS in patients with cutaneous disease, according to RECIST guidelines, version 1.1, and assessed by blinded independent review, was 5.6 months (95% CI, 2.6-5.6 months) in arm A vs 4.2 months (95% CI, 2.8-8.3 months) in arm B ( $n = 64$ ; HR, 1.07; 95% CI, 0.43-2.67;  $P = .89$ ). The median OS was 8 months (95% CI, 6.7 months to not reached) in arm A and was not reached in arm B (95% CI, 6.8 months to not reached) ( $n = 63$ ; HR, 0.68; 95% CI, 0.25-1.84;  $P = .45$ ). The Kaplan-Meier curve for OS in the cutaneous angiosarcoma subgroup is shown in eFigure 2 in Supplement 2.

### Toxic Effects

Anemia and fatigue were more commonly observed after combination treatment compared with single-agent pazopanib. The most common adverse events of grade 3 or greater (occurring in 2 or more patients) are shown in Table 2, with hypertension being the most common in both arms (arm A, 15 patients [27%]; arm B, 12 patients [19%]). Other notable adverse events of grade 3 or greater were laboratory values outside the reference range, including increased enzyme levels and decreased electrolyte levels. Three patients (5%) in the pazopanib arm had nausea of grade 3 or greater compared with 7 (11%) in the combination arm. Three patients (5%) in the pazopanib arm had sepsis of grade 3 or greater, compared with no patients in the combination arm. The most common all-grade adverse events in the single-agent pazopanib arm vs the combination arm were fatigue (29 patients [55%] vs 37 [61%]), headache (12 patients [23%] vs 39 [64%]), diarrhea (27 patients [51%] vs 35 [57%]), nausea (26 patients [49%] vs 29 [48%]), vomiting (12 patients [23%] vs 23 [38%]), anemia (5 patients [9.4%] vs 27 [44%]), epistaxis (2 patients [4%] vs 34

[56%]), and hypertension (29 patients [55%] vs 22 [36%]). The most common adverse events (all grades) that occurred in at least 15% of patients are shown in eTable 2 in Supplement 2. Three patients (6%) in the pazopanib arm died within 30 days of the end of trial treatment (1 [2%] of multiple organ failure, 1 [2%] of liver failure, and 1 [2%] of sepsis), compared with 5 (8%) in the combination arm (3 [5%] of disease progression and 2 [3%] of respiratory failure).

### Circulating Tumor Cells

Endoglin-expressing DAPI-positive CTCs were evaluable in 76 patients. In arm A, 12 of 34 matched samples (35%) showed an increase in CTCs of more than 1 cell/mL and 15 (44%) showed a decrease of more than 1 cell/mL. In arm B, 12 of 42 matched samples (29%) showed an increase in CTCs of more than 1 cell/mL and 18 (43%) showed a decrease of more than 1 cell/mL. These differences were not statistically significant.

## Discussion

In this phase 3 randomized clinical trial, the combination of carotuximab and pazopanib did not show superior efficacy (improved PFS and OS) compared with single-agent pazopanib in patients with advanced angiosarcoma. This trial provides a rigorous, prospective benchmark for the activity of pazopanib as a first- or second-line therapy in patients with advanced angiosarcoma. More toxic effects were found in patients receiving the combination of carotuximab and pazopanib than in those receiving pazopanib alone. The optimal treatment strategy for advanced angiosarcoma remains to be defined, with multiple agents showing nondurable activity.<sup>3-9,27</sup> A prior retrospective study of pazopanib in patients with advanced angiosarcomas reported a median PFS of 3 months and a median OS of 9.9 months.<sup>10</sup> The results of the prospective TAPPAS trial are consistent with these data and highlight the continuing unmet need for effective systemic therapy in advanced angiosarcoma.

The TAPPAS trial was, to our knowledge, the first randomized phase 3 trial conducted among patients with advanced angiosarcoma. It showed that subtype-specific trials can be completed quickly and successfully, even in the setting of an uncommon tumor. Angiosarcomas have a complex karyotype and heterogeneous clinical behavior and are likely to comprise numerous biologically distinct subgroups. Data about the benefit of checkpoint inhibitors in cutaneous angiosarcomas, as compared with other types of angiosarcomas, show this biological heterogeneity.<sup>27</sup> Furthermore, despite the feasibility of performing subtype-specific trials, the profound biological heterogeneity within individual sarcoma types remains a major challenge. Other trials have shown that a proportion of patients with angiosarcoma can derive benefit from specific systemic therapies. A phase 2 trial of the angiopoietin 1 and 2 inhibitor trebananib in 16 patients with advanced angiosarcomas documented no partial responses, but 4 patients had prolonged PFS benefit.<sup>28</sup> A phase 2 trial of bevacizumab in patients with advanced angiosarcoma reported partial responses in 2 of 23 patients (9%).<sup>29</sup>

Designing phase 3 trials based on the results of small phase 1/2 trials is a continuing challenge in rare cancers. The incor-

**Table 2. Most Common Adverse Events of Grade 3 or Greater<sup>a</sup> Observed in More Than 2 Patients**

Adverse event	Patients, No. (%) (n = 114)	
	Arm A (pazopanib) (n = 53)	Arm B (carotuximab plus pazopanib) (n = 61)
Increased ALT level	7 (13)	3 (5)
Anemia	2 (4)	17 (27)
Increased AST level	5 (9)	2 (3)
Back pain	0	4 (6)
Diarrhea	2 (4)	3 (5)
Dyspnea	1 (2)	3 (5)
Fatigue	1 (2)	9 (14)
Headache	0	3 (5)
Hypertension	15 (27)	12 (19)
Hypoalbuminemia	1 (2)	3 (5)
Hypokalemia	0	3 (5)
Hyponatremia	3 (5)	3 (5)
Increased lipase level	1 (2)	5 (8)
Decreased lymphocytes	1 (2)	4 (6)
Nausea	3 (5)	7 (11)
Sepsis	3 (5)	0
Stomatitis	0	3 (5)
Vomiting	0	3 (5)

Abbreviations: ALT, alanine transaminase; AST, aspartate aminotransferase.

<sup>a</sup> Assessed per the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.

poration of putative molecular or imaging markers of efficacy could improve this process. The findings of the TAPPAS trial are consistent with evidence from previous prospective trials, including a randomized phase 2 trial of paclitaxel with or without bevacizumab in 52 patients.<sup>7</sup> Collectively, these trials show that it is possible to perform large randomized trials in rare sarcoma subtypes. The TAPPAS trial was designed as a phase 3 trial and had an interim analysis that dictated the final sample size based on conditional power. The adaptive design worked well and should be considered for future trials.<sup>26</sup>

Another challenge in interpreting the results of clinical trials involving sarcomas is the limitation of conventional response criteria. Angiosarcomas have a wide anatomic distribution. In particular, the application of dimensional response criteria in cutaneous angiosarcomas is extremely challenging because clinical benefit can manifest as change in color and appearance rather than a change in dimension.<sup>2</sup> Furthermore, in the context of a randomized trial with PFS as the primary end point, disease progression can be nondimensional (ie, tumor thickening and bleeding can be indicators of disease progression).<sup>2</sup>

### Limitations

The heterogeneity of angiosarcomas is a limitation of this trial. Despite the trial's randomized design, it was impossible for the randomization process to account fully for the biological and clinical diversity of angiosarcomas. The evaluation of response and PFS can be particularly challenging in patients with cutaneous angiosarcomas.

## Conclusions

The TAPPAS trial was, to our knowledge, the first randomized phase 3 trial conducted among patients with angiosar-

mas and represents the largest prospective angiosarcoma trial to date. The primary end point for PFS was not met. In view of the biological heterogeneity of angiosarcomas, future work should focus on developing biomarkers for specific systemic therapies.

### ARTICLE INFORMATION

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**Author Contributions:** Dr Jones had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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**Acquisition, analysis, or interpretation of data:** All authors.

**Drafting of the manuscript:** Jones, Ravi, Ganjoor, Italiano, Attia, Thornton, Liu, Robertson, Theuer, Maki.

**Critical revision of the manuscript for important intellectual content:** Jones, Ravi, Brohl, Chawla, Ganjoor, Italiano, Attia, Burgess, Cranmer, Cheang, Adams, Theuer, Maki.

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