original reports

# Randomized Phase II Trial of Bevacizumab or Temsirolimus in Combination With Chemotherapy for First Relapse Rhabdomyosarcoma: A Report From the Children's Oncology Group

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abstract

**PURPOSE** The primary aim of this clinical trial was to prioritize bevacizumab or temsirolimus for additional investigation in rhabdomyosarcoma (RMS) when administered in combination with cytotoxic chemotherapy to patients with RMS in first relapse with unfavorable prognosis.

**PATIENTS AND METHODS** Patients were randomly assigned to receive bevacizumab on day 1 or temsirolimus on days 1, 8, and 15 of each 21-day treatment cycle, together with vinorelbine on days 1 and 8, and cyclophosphamide on day 1 for a maximum of 12 cycles. Local tumor control with surgery and/or radiation therapy was permitted after 6 weeks of treatment. The primary end point was event-free survival (EFS). Radiographic response was assessed at 6 weeks. The study had a phase II selection that was design to detect a 15% difference between the two regimens ($\alpha$ = .2; 1-$\beta$ = 0.8; two sided test).

**RESULTS** Eighty-seven of 100 planned patients were enrolled when the trial was closed after the second interim analysis after 46 events occurred in 68 patients with sufficient follow-up. The O'Brien Fleming boundary at this analysis corresponded to a two-sided *P* value of .058 with an observed two-sided *P* value of .003 favoring temsirolimus. The 6-month EFS for the bevacizumab arm was 54.6% (95% CI, 39.8% to 69.3%) and 69.1% (95% CI, 55.1% to 83%) for the temsirolimus arm. Objective response rates were 28% (95% CI, 13.7% to 41.3%) and 47% (95% CI, 31.5% to 63.2%) for the bevacizumab and temsirolimus arms, respectively (*P* = .12) and, 28% of patients on bevacizumab and 11% on temsirolimus had progressive disease at 6 weeks.

**CONCLUSION** Patients who received temsirolimus had a superior EFS compared with bevacizumab. Temsirolimus has been selected for additional investigation in newly diagnosed patients with intermediate-risk RMS.

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## INTRODUCTION

Rhabdomyosarcoma (RMS) is the most common soft-tissue sarcoma observed in the first two decades of life and rarely occurs beyond the third decade.[1] Standard treatment includes chemotherapy, surgery, and/or radiation therapy and results in approximately two thirds of patients being cured.[2,3] Patients with distant metastases at initial presentation have a less favorable prognosis,[4,5] whereas those with relapsed disease have a poor prognosis, particularly those with unfavorable features.[6-8] Unfavorable prognostic features identified at the time of first relapse include patients with a history of distant metastases at initial presentation, alveolar histology, primary tumor greater than 5 cm, lymph node metastases, and those treated with radiation therapy and/or at least three chemotherapy agents, including cyclophosphamide or ifosfamide. The Children's Oncology Group (COG) Soft Tissue Sarcoma (STS) committee conducted the only previous prospective clinical trial for first relapse of RMS, but this effort with risk-adapted multiagent therapy failed to improve survival compared with historic results in patients with a history of unfavorable prognostic features as defined.[7,9] To identify agents to prioritize for future front-line phase III studies and to improve outcomes for patients with recurrent RMS, the COG STS committee adopted a strategy to test molecularly targeted agents with a preclinical rationale in combination with cytotoxic chemotherapy in this population of patients with first relapse RMS with unfavorable features.

Bevacizumab and temsirolimus were the two molecularly targeted agents that were selected for study in combination with cytotoxic chemotherapy. Bevacizumab is a humanized monoclonal neutralizing antibody that binds all five isoforms of vascular endothelial growth factor (VEGF) and has an antiangiogenic effect.[10] Inhibition of angiogenesis reduces tumor

ASSOCIATED CONTENT

Data Supplement
Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

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growth in many ex vivo models of adult and pediatric malignancies, including RMS.[11-16] Bevacizumab has been approved for use as a single agent or in combination with chemotherapy for several malignancies in adults, including colorectal cancer, nonsquamous non–small-cell lung cancer, glioblastoma, renal-cell carcinoma, cervical cancer, and epithelial ovarian cancer.[17-22] Several pediatric clinical trials with single-agent bevacizumab or bevacizumab in combination with chemotherapy have also been completed.[23-27] Major toxicities of bevacizumab include GI perforation and non-GI fistula formation, delayed wound healing, arterial thromboembolic events, hypertension, reversible posterior leukoencephalopathy syndrome, proteinuria, and infusion reactions.[28,29] Temsirolimus is a soluble ester of rapamycin, a natural product that has antifungal, immunosuppressive, and anticancer activity.[30] Temsirolimus forms a complex with FK506 binding protein and prevents the activation of mammalian target of rapamycin. Its anticancer activity has been demonstrated in a variety of preclinical models.[31-33] Increased mammalian target of rapamycin pathway activation has been reported in childhood RMS and is associated with decreased survival.[34,35] In addition, temsirolimus has also been shown to inhibit growth in RMS xenografts, in part, through inhibition of angiogenesis.[36-38] Furthermore, the Pediatric Preclinical Testing Program (PPTP) reported activity of rapamycin, both alone and in combination with vincristine or cyclophosphamide in RMS xenografts.[39,40] Temsirolimus as a single agent is approved for the treatment of advanced renal-cell carcinoma and has also been studied in combination with chemotherapy in several malignancies.[41-46] The main adverse effects of temsirolimus include hypersensitivity, hyperglycemia, hyperlipidemia, mucositis, anemia, thrombocytopenia, infections, interstitial pneumonitis, abnormal wound healing, and renal failure.[47] A pediatric phase I clinical trial of single-agent temsirolimus did not identify a maximum tolerated dose.[48]

Vinorelbine and cyclophosphamide were selected for the cytotoxic chemotherapy backbone. Vinorelbine is active in patients with relapsed RMS as a single agent.[49,50] Cyclophosphamide is among the most active chemotherapy agents in RMS and has been administered intravenously at various doses in the primary treatment of patients and at the time of relapse.[9,51-53] The combination of vinorelbine and oral cyclophosphamide is active in patients with relapsed RMS[54] and has also been investigated in the treatment of metastatic RMS.[55] Preclinical data from the PPTP demonstrated synergy of rapamycin with parenterally administered vincristine and intermittent bolus infusion of cyclophosphamide.[39] Vinorelbine has not been previously combined with intravenous cyclophosphamide for the treatment of RMS; however, vinorelbine has been safely combined with ifosfamide in children.[56] Intravenous vincristine and cyclophosphamide are used in the standard treatment of most patients with newly diagnosed RMS; therefore, if a targeted agent was selected for additional study in treatment-naïve patients, the combination of an intravenous vinca alkaloid and oxazophorine was desirable. These data formed the basis for the design of this clinical trial (ARST0921).

The primary aims of ARST0921 were to determine the feasibility of administering bevacizumab or temsirolimus in combination with intravenous vinorelbine and cyclophosphamide chemotherapy in first relapse of RMS, and to estimate the event-free survival (EFS) of patients treated with bevacizumab compared with those treated with temsirolimus.

## PATIENTS AND METHODS

### Patient Eligibility

Patients who were eligible for ARST0921 included those with biopsy-proven RMS—embryonal, alveolar, or not otherwise specified—at first relapse or disease progression and younger than age 30 years at the time of enrollment with an Eastern Cooperative Oncology Group performance status of 0, 1 or 2 and a life expectancy of at least 8 weeks. Patients with primary refractory disease, defined as first progression after at least one cycle of cyclophosphamide or ifosfamide-containing chemotherapy without a prior response to chemotherapy were also eligible. Other protocol-specific patient eligibility criteria are included in the Data Supplement. Written informed consent was required from all participants and/or their parents/legal guardians after all institutional, US Food and Drug Administration, and National Cancer Institute (NCI) requirements for human studies were met.

### Clinical Trial Design

The overall experimental design for ARST0921 is shown in Figure 1. Patients were randomly assigned to either Regimen A (bevacizumab) or Regimen B (temsirolimus). The schedule and route of administration of drugs is depicted in Table 1. Treatment was administered in 21-day cycles and a maximum of 12 cycles was allowed in the absence of disease progression. Myeloid growth factor was administered starting on day 9 of each cycle. Surgery and radiation were not allowed during the first 6 weeks of treatment and patients were taken off protocol therapy if they underwent surgery or received radiation therapy in the first 6 weeks of treatment. Patients with measurable disease as defined by NCI Response Evaluation Criteria in Solid Tumors (RECIST) were evaluable for response.[58] Disease response was assessed after 6 weeks of treatment at the end of cycle 2 and subsequently after cycles 4, 6, 9, and 12. Patients who achieved complete response (CR), partial response (PR), or stable disease could continue with the assigned treatment until disease progression or completion of 12 cycles of treatment. Bevacizumab was withheld 4 weeks before and 4 weeks after a surgical procedure. Temsirolimus was not withheld before surgery and was resumed at the same time as chemotherapy after surgery. Both bevacizumab and temsirolimus were withheld during radiation therapy.

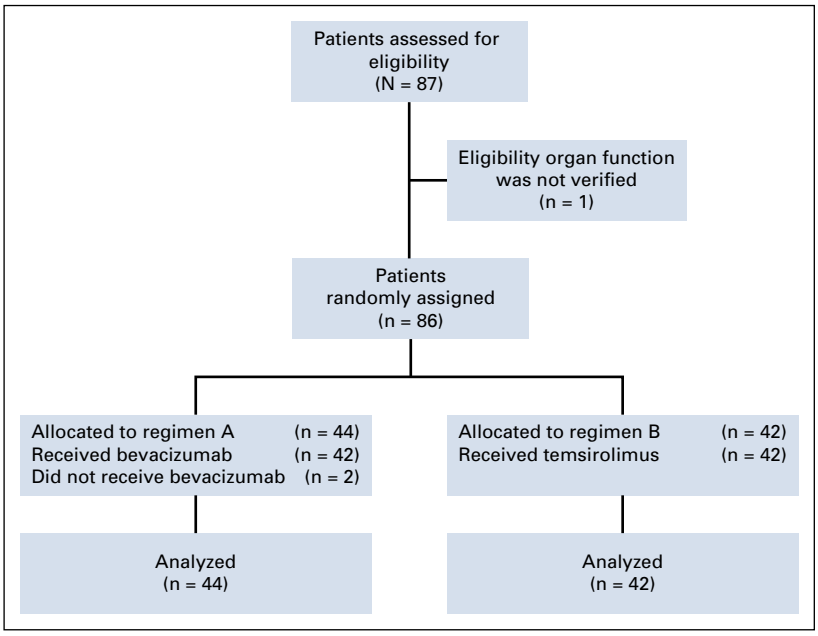


**FIG 1.** CONSORT diagram for ARST0921.

Patients were taken off protocol therapy if bevacizumab or temsirolimus was interrupted for more than 9 weeks.

### Statistical Analysis

The current study was designed as a randomized phase II selection trial[59] to determine whether bevacizumab or temsirolimus should be chosen for additional evaluation in RMS. This analysis describes the toxicities and compares EFS, overall survival (OS), and response rate of patients who were treated with bevacizumab and temsirolimus. Anticipating a median EFS of 20% at 2 years, a sample size of 100 patients with 79 expected failures was required to detect a difference in the relative risk of failure between the two treatment groups of 0.62:1.00, corresponding to EFSs of 50% and 65% at 6 months ($\alpha = .2$; $1\text{-}\beta = 0.8$; two sided log-rank test). EFS was defined as the time from study enrollment to disease progression, disease recurrence, second malignant neoplasm, or death from any cause, whichever occurred first. OS was defined as the time from study enrollment to death from any cause. EFS and OS were censored at the patient's last contact date. EFS and OS were estimated using the Kaplan-Meier method[60] and curves were compared using the log-rank test. CIs for EFS and OS were estimated using the Peto-Peto method.[61] Interim monitoring of EFS was performed using an alpha-spending approach with an O'Brien-Fleming boundary with monitoring beginning after 30% of the expected events with additional analysis performed at approximately 50% and 75% of the expected events. As histology has been shown to be prognostic in first relapse RMS[6] and not stratified for at the time of random assignment, a Cox proportional hazards regression model was used to calculate the hazard ratio for treatment failure after adjusting for histology. The assumption of proportional hazards was checked graphically by plotting log[-log(EFS)] by log(time).

The feasibility of administering bevacizumab or temsirolimus in combination with vinorelbine and cyclophosphamide was assessed in the first 10 randomly assigned patients in each arm during the first two cycles of therapy. Toxicities were reported using NCI Common Toxicity Criteria, version 4. Adverse events of interest that defined dose-limiting toxicities (DLTs) in both treatment arms are detailed in the Data Supplement. A DLT rate of 40% or greater during the first two cycles in the first 10 randomly assigned patients in each arm was considered unacceptable and would require a protocol amendment to reduce the dose of bevacizumab or temsirolimus. A 25% increase in the toxicity rate over baseline expected 50% grade 3 or greater nonhematologic toxicities and toxic deaths in any

**TABLE 1.** Treatment Regimen (21-day cycle) for Randomly Assigned Patients

| Regimen A* | Regimen B* |
|---|---|
| Bevacizumab 15 mg/kg per dose (IV) on day 1 | Temsirolimus† 15 mg/m$^2$ per dose (IV) on days 1, 8, and 15 |
| Vinorelbine 25 mg/m$^2$ per dose (IV) on days 1 and 8 | Vinorelbine 25 mg/m$^2$ per dose (IV) on days 1 and 8 |
| Cyclophosphamide 1,200 mg/m$^2$ per dose (IV) on day 1 | Cyclophosphamide 1,200 mg/m$^2$ per dose (IV) on day 1 |

Abbreviation: IV, intravenous.
*Maximum 12 cycles.
†Maximum dose 30 mg.

group would also be sufficient to suspend the study and require a protocol amendment to reduce the dose of the investigational agents.

## RESULTS

### Patient Population

ARST0921 enrolled 87 randomly assigned patients between October 2010 and July 2013, when the trial was closed to accrual on the recommendation of the Data Safety Monitoring Committee, which was based on the second scheduled interim analysis. Patient follow-up is current through September 30, 2017, for this report. One patient who was randomly assigned to the temsirolimus arm was ineligible as a result of not meeting an inclusion criterion for organ function requirements. Two patients who were randomly assigned to the bevacizumab arm did not receive study treatment because of a rapid decline in performance status after enrollment and before initiating chemotherapy. Clinical characteristics of eligible patients are shown in

**TABLE 2.** Patient Characteristics

| Characteristic | Regimen A (bevacizumab; n = 44) | Regimen B (temsirolimus; n = 42) |
|---|---|---|
| Age, years | | |
| < 10 | 19 (43) | 13 (31) |
| 10-19 | 20 (46) | 24 (57) |
| > 19 | 5 (11) | 5 (12) |
| Sex | | |
| Male | 22 (50) | 23 (55) |
| Female | 22 (50) | 19 (45) |
| Histology | | |
| Embryonal | 15 (34) | 17 (40) |
| Alveolar | 27 (61) | 25 (60) |
| Other | 2 (5) | 0 |
| Primary site at original diagnosis | | |
| Head/neck/orbit | 3 (7) | 3 (7) |
| Parameningeal | 13 (29) | 9 (21) |
| GU non-bladder/prostate | 1 (2) | 2 (5) |
| Bladder/prostate | 2 (5) | 5 (12) |
| Extremity | 12 (27) | 12 (29) |
| Retroperitoneum/perineum | 8 (18) | 6 (14) |
| Intrathoracic/trunk | 3 (7) | 3 (7) |
| Other | 2 (5) | 2 (5) |
| Primary tumor size at original diagnosis, cm | | |
| ≤ 5 | 17 (39) | 12 (29) |
| > 5 | 27 (61) | 30 (71) |
| Distant metastases at original diagnosis | | |
| Yes | 26 (59) | 24 (57) |
| No | 18 (41) | 18 (43) |
| Site of recurrence | | |
| Local only | 8 (18) | 14 (33) |
| Regional only | 5 (12) | 2 (5) |
| Metastatic only | 23 (52) | 20 (48) |
| Local and regional | 2 (5) | 3 (7) |
| Local and metastatic | 1 (2) | 3 (7) |
| Regional and metastatic | 4 (9) | 0 |
| Local, regional and metastatic | 1 (2) | 0 |

NOTE. Data are provided as No. (%).
Abbreviation: GU, genitourinary

Table 2. Patient populations were balanced in the two arms, including such factors as tumor histology, disease extent at original diagnosis, and pattern of recurrence.

### Survival Outcomes

At the second interim analysis, 46 events had occurred—58% of expected—in 68 patients with sufficient follow-up. The O'Brien-Fleming boundary at this analysis corresponded to an adjusted two-sided *P* value of .058 with an observed two-sided *P* value of .003 favoring the EFS of the temsirolimus arm. The 6-month EFS in the bevacizumab arm was 50% (95% CI, 32% to 66%) and 65% (95% CI, 44% to 79%) in the temsirolimus arm. There were no deaths as a first event in either regimen. Two patients developed second malignant neoplasm—both acute myelogenous leukemia/treatment-related myelodysplastic syndrome—one each in the bevacizumab and temsirolimus arms. The 6-, 12-, and 24-month EFS and OS are shown in Table 3. After a median follow up of 4 years for surviving patients, those who were treated with vinorelbine, cyclophosphamide, and temsirolimus had significantly better EFS compared with patients who were treated in the bevacizumab arm ($P = .018$, two sided; Fig 2). There was no difference in OS between the two regimens ($P = .23$; Fig 3). The assumption of proportional hazards was upheld and the estimated hazard ratio for treatment failure (bevacizumab:temsirolimus) was 1.71 (95% CI, 1.08 to 2.69; $P = .02$).

### Tumor Response

Seventy-eight of 86 eligible patients were evaluable for response after 6 weeks of treatment in the bevacizumab arm (n = 40) and temsirolimus arm (n = 38). There were four CRs and seven PRs in the bevacizumab arm versus five CRs and 13 PRs in the temsirolimus arm. There was no significant difference between the objective response rate (CR + PR) in the bevacizumab arm (28%; 95% CI, 13.7% to 41.3%) compared with the temsirolimus arm (47%; 95% CI, 31.5% to 63.2%; $P = .12$). Eleven patients (28%) in the bevacizumab arm and four patients (11%) in the temsirolimus arms experienced progressive disease after 6 weeks of therapy.

### Toxicity

There were no toxic deaths and no unexpected toxicities. Patients who were treated with temsirolimus had a higher incidence of grade 3 and 4 toxicities compared with those who received bevacizumab; however, the difference was not statistically significant (data not shown). There were three DLTs in the bevacizumab arm, including one grade 3 hypertension, one grade 3 bleeding, and one grade 3 oral mucositis. There were eight DLTs in the temsirolimus arm, including four grade 3 oral mucositis, two grade 3 hypertriglyceridemia, one grade 3 pneumonitis, and one grade 3 elevation of ALT that did not resolve to less than grade 1 in 14 days. Table 4 displays the grade three or greater toxicities that occurred in at least 10% of patients in either the bevacizumab arm or temsirolimus arm in each of the four reporting periods, together with the corresponding incidence in both treatment arms. Febrile neutropenia was the most common toxicity reported. Oral mucositis and hypokalemia were observed almost exclusively in the temsirolimus arm in the first two cycles of treatment. In the bevacizumab arm, bleeding or thrombotic events, hypertension, cardiac toxicity, fistula or leak (GI or other organ), proteinuria, intra-abdominal infection/abscess, wound complications, reversible posterior encephalopathy, microangiopathy, hemolytic uremic syndrome, and thrombotic thrombocytopenic purpura were toxicities of particular interest. Of these, the highest incidence of grade 3 or greater nonhematologic toxicities noted across any reporting period were hypertension (2.4%), bleeding (4.5%), and wound infection (4.5%). Targeted toxicities in the temsirolimus arm were infusion reactions, hyperglycemia, hypertriglyceridemia, hypercholesterolemia, mucositis, cardiac toxicity, pneumonitis, liver enzyme elevation, wound complications, and GI perforation, fistula or obstruction. Of these, the highest incidence of grade 3 or greater nonhematologic toxicities noted across any reporting period were hypertriglyceridemia (9.5%), mucositis (11.9%), pneumonitis (2.4%), and liver enzyme elevation (4.8%). In addition, one patient in the temsirolimus arm suffered acute kidney injury that was attributed to temsirolimus.

## DISCUSSION

This randomized clinical trial is only the second reported in patients with first relapse RMS. The first trial (ARST0121), also conducted by COG, demonstrated a median EFS of 50% at 6 months in first relapsed patients with unfavorable prognostic features as defined who were treated with

**TABLE 3.** Outcome by Treatment Arm

| | EFS (95% CI) | | OS (95% CI) | |
|---|---|---|---|---|
| Time (Months) | Regimen A (bevacizumab) | Regimen B (temsirolimus) | Regimen A (bevacizumab) | Regimen B (temsirolimus) |
| 6 | 54.6 (39.8 to 69.3) | 69.1 (55.1 to 83) | 84.1 (73.3 to 94.9) | 90.5 (81.6 to 99.4) |
| 12 | 18.2 (6.8 to 29.6) | 40.5 (25.6 to 55.3) | 59.1 (44.6 to 73.6) | 78.4 (65.8 to 91.1) |
| 24 | 6.8 (0 to 14.3) | 19.1 (7.2 to 30.9) | 29.6 (16.1 to 43) | 39.2 (24.2 to 54.2) |

NOTE. Data are given as percentages.

Abbreviations: EFS, event-free survival; OS, overall survival.

  

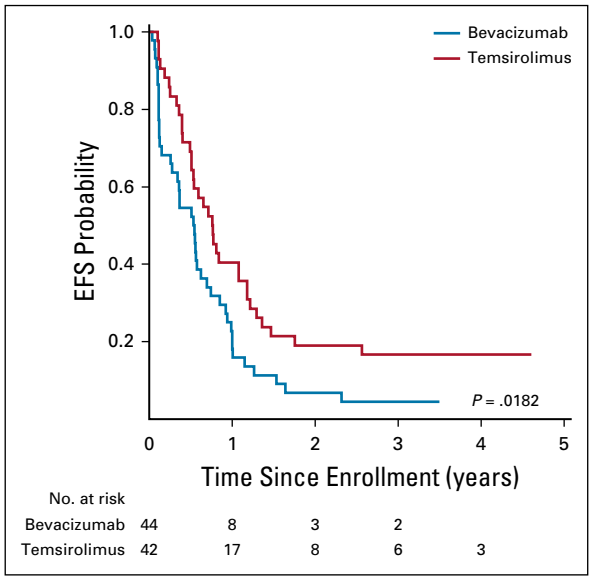


**FIG 2.** Event-free survival (EFS) by treatment regimen.

multiagent cytotoxic chemotherapy.[7,9] ARST0921 is also the first randomized clinical trial in patients with RMS to incorporate molecularly targeted therapy, together with cytotoxic chemotherapy, with the goal to prioritize a molecularly targeted agent to test in newly diagnosed patients with RMS. To that end, ARST0921 succeeded in selecting temsirolimus as a biologically active agent in RMS worthy of additional investigation.

Combination bevacizumab and chemotherapy has shown activity in some pediatric tumors, including low-grade gliomas and Wilms tumor.[26,62] However, addition of bevacizumab to cytotoxic chemotherapy resulted in a 6-month EFS of 54.6% in patients with first relapse RMS with unfavorable features and was similar to the median EFS in ARST0121, which used only multiagent chemotherapy.[9] Furthermore, bevacizumab has also been tested in children and adolescents with newly diagnosed metastatic soft-tissue sarcoma, where it was administered together with cytotoxic chemotherapy and did not affect survival.[55] These data suggest that bevacizumab did not add to or detract from the efficacy of the vinorelbine–cyclophosphamide chemotherapy back bone. Similarly, bevacizumab did not improve outcomes when combined with chemotherapy in patients with high-grade gliomas, osteosarcoma, and neuroblastoma.[63-65] These data led to questions about the role of VEGF-targeted agents in contributing to a therapeutic pathway to cure childhood cancer[66]; however, more recently, oral small-molecule tyrosine kinase inhibitors that target VEGF have demonstrated activity in soft-tissue sarcomas other than RMS and in osteosarcoma.[67-70] Of interest, temsirolimus as a single agent had limited clinical activity in phase I and II single-agent trials, including only a 6% objective response rate in patients with recurrent RMS.[48,71] Strong preclinical data generated by PPTP in RMS xenografts that supported the combination of rapamycin with chemotherapy[39,40] was the main reason that led us to investigate temsirolimus in combination with vinorelbine and cyclophosphamide. This highlights the importance of considering combination trials that include molecularly targeted agents when there is a relevant biologic rationale and strong preclinical data, despite a low level of single-agent activity with the agent in early-phase clinical trials.

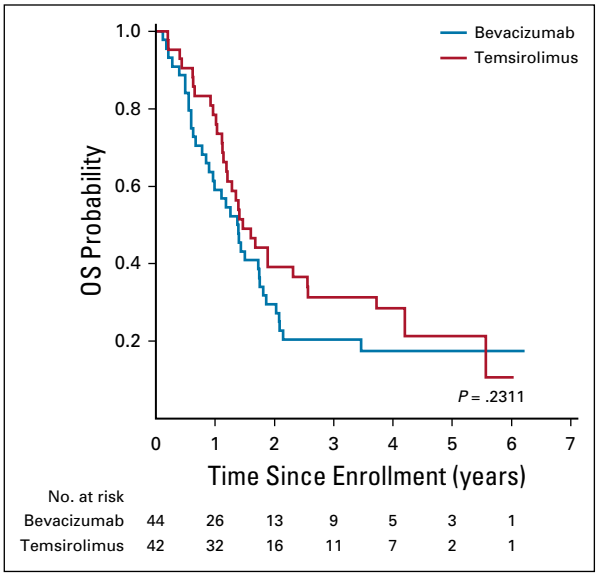


**FIG 3.** Overall survival (OS) by treatment regimen.

Therapy in ARST0921 was tolerated reasonably well. None of the toxicities noted secondary to bevacizumab or temsirolimus was unexpected. The most common serious adverse event was febrile neutropenia, observed in approximately 20% of patients. This compares favorably with the 50% nonhematologic serious adverse event rate noted in ARST0121.[7] Furthermore, all therapy in ARST0921 could be administered in an ambulatory setting. Considering the similar median EFS and more favorable toxicity profile compared with ARST0121, which included therapy with vincristine/irinotecan (weeks 1 to 6, 20 to 25, and 47 to 52), interval compression with vincristine/doxorubicin/cyclophosphamide alternating with etoposide/ifosfamide (weeks 7 to 19 and 26 to 34), and vincristine/dactinomycin/cyclophosphamide (weeks 38 to 46), vinorelbine, cyclophosphamide, and temsirolimus is a reasonable alternative treatment for patients with unfavorable features at the time of first relapse RMS. In addition, this well-tolerated chemotherapy backbone of vinorelbine and cyclophosphamide can be used to investigate other promising new agents in combination; however, as vinorelbine and intravenous cyclophosphamide were not studied independently of bevacizumab or temsirolimus in this trial, these data cannot necessarily be extrapolated to the combination of vinorelbine and oral cyclophosphamide that has been more extensively studied by the European Pediatric Soft tissue sarcoma Study Group.

Local control of disease sites at the time of relapse and time to relapse after initial diagnosis of nonmetastatic RMS are

**TABLE 4.** Incidence of Grade 3 and 4 Toxicities That Occurred in at Least 10% of Patients in Either Regimen A or B in One of the Four Reporting Periods

| | RP-1 (cycle 1-2) | | RP-2 (cycle 3-5) | | RP-3 (cycle 6-8) | | RP-4 (cycle 9-12) | |
|---|---|---|---|---|---|---|---|---|
| Toxicity | Reg A (bev*; n = 42) | Reg B (tem; n = 42) | Reg A (bev; n = 27) | Reg B (tem; n = 34) | Reg A (bev; n = 22) | Reg B (tem; n = 22) | Reg A (bev; n = 14) | Reg B (tem; n = 13) |
| Febrile neutropenia | **11.9** | **26.2** | **18.5** | **17.6** | **13.6** | **18.2** | **14.3** | **23.1** |
| Oral mucositis | 2.4 | **11.9** | 0 | 0 | 4.5 | 0 | 0 | 7.7 |
| Hypokalemia | 2.4 | **11.9** | 3.7 | 5.9 | 4.5 | 0 | 0 | 0 |

NOTE. Data are given as percentages.

Abbreviations: bev, bevacizumab; Reg, regimen; RP, reporting period; tem, temsirolimus.

*Two patients randomly assigned to regimen A did not receive bevacizumab and are excluded.

prognostic factors for relapsed RMS.[8,72] ARST0921 enrolled patients at first relapse with a history of both nonmetastatic disease or metastatic disease. As ARST0921 was designed solely to select a molecularly targeted agent for additional investigation, local treatment and time to relapse data were not collected in ARST0921 and their impact on outcome could not be analyzed.

The only other published positive randomized clinical trial in RMS dates backs to 1974[73] and confirms the benefit of adjuvant vincristine and dactinomycin chemotherapy in children with completely resected RMS. Subsequently, multiple randomized clinical trials conducted in RMS have failed to improve outcomes compared with the control arm.[51-53,55,74-77] On the basis of the results of ARST0921, the COG STS committee is now conducting a randomized phase III clinical trial (ARST1431; ClinicalTrials.gov identifier: NCT02567435) investigating the addition of temsirolimus to vincristine, dactinomycin, and cyclophosphamide, alternating with the vincristine and irinotecan chemotherapy backbone in newly diagnosed patients with intermediate-risk RMS.


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## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

**Randomized Phase II Trial of Bevacizumab or Temsirolimus in Combination With Chemotherapy for First Relapse Rhabdomyosarcoma: A Report From the Children's Oncology Group**

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