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Clinical Trial Results

A Randomized, Double-Blind, Placebo-Controlled, Phase II Study of Regorafenib Versus Placebo in Advanced/Metastatic, Treatment-Refractory Liposarcoma: Results from the SARC024 Study

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Trial Information

- **ClinicalTrials.gov Identifier**: NCT02048371
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- **Principal Investigator**: Richard F. Riedel
- **IRB Approved**: Yes

Lessons Learned

- The results from the liposarcoma cohort of SARC024 confirm previously published data and do not support the routine use of regorafenib in this patient population.
- Continued exploration of novel therapies, including combination approaches, is warranted for a patient population in whom limited treatment options exist.

Abstract

Background. Regorafenib is a multitargeted kinase inhibitor with a kinase profile overlapping, but distinct from, pazopanib, an agent approved for recurrent and metastatic non-gastrointestinal stromal tumor (GIST), non-adipocytic soft tissue sarcoma. We conducted a randomized, phase II study of regorafenib versus placebo in refractory liposarcoma patients.

Methods. Patients with advanced or metastatic, treatment-refractory liposarcoma were randomized 1:1 to receive regorafenib 160 mg or placebo once daily (3 weeks on, 1 week off). Patients with well-differentiated liposarcoma only were excluded. Crossover for placebo was allowed upon progression. The primary endpoint was progression-free survival (PFS), according to RECIST version 1.1.

Results. Forty-eight subjects with liposarcoma (34 dedifferentiated, 12 myxoid/round cell, 2 pleomorphic) were enrolled. Median PFS was 1.87 (95% confidence interval [CI], 0.92–3.67) months for regorafenib versus 2.07 (95% CI,

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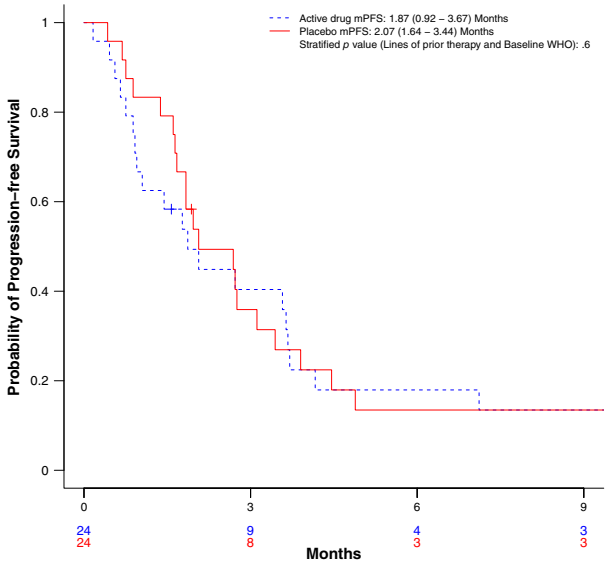

Figure 1. Kaplan-Meier curves for progression-free survival with *p* value from stratified log rank test. The stratification factors are prior lines of therapy (1 vs. 2 or more) and WHO performance status (0–1 vs. 2).
Abbreviations: mPFS, median progression-free survival; WHO, World Health Organization.

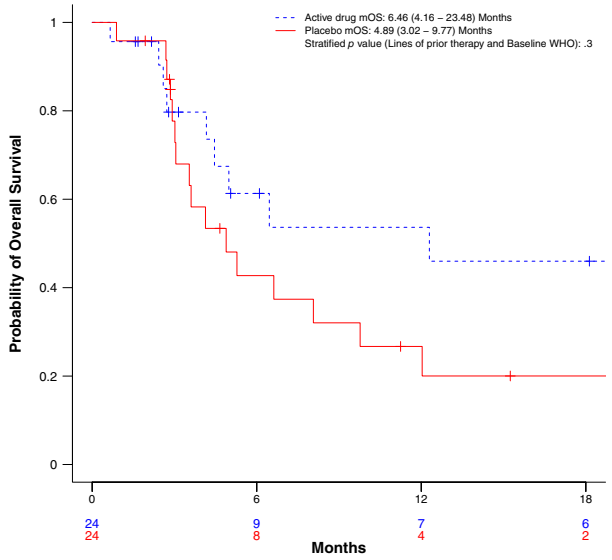

Figure 2. Kaplan-Meier curves for overall survival with *p* value from stratified log rank test. The stratification factors are prior lines of therapy (1 vs. 2 or more) and WHO performance status (0–1 vs. 2).
Abbreviations: mOS, median overall survival; WHO, World Health Organization.

1.64–3.44) months for placebo; stratified hazard ratio [HR], 0.85 (95% CI, 0.46, 1.58), $p = .62$. No responses were seen on regorafenib. One PR was observed on placebo. Median overall survival was 6.46 (95% CI, 4.16–23.48) months for regorafenib and 4.89 (95% CI, 3.02–9.77) months for placebo, stratified HR, 0.66 (95% CI, 0.31–1.40), $p = .28$). Treatment-related adverse events were similar to the known safety profile of regorafenib.

Conclusion. Regorafenib did not appear to improve PFS in treatment-refractory liposarcoma. No new significant safety signals were observed. ***The Oncologist*** 2020;25:e1655–e1662

Discussion

Sarcomas represent a family of mesenchymal neoplasms with varied clinical behavior and outcomes. Liposarcomas represent one of the more common soft tissue sarcomas, with five distinct subtypes being recognized. Despite the recent approval of eribulin and trabectedin for the treatment of advanced disease, effective treatment options remain an area of unmet medical need.

Regorafenib is a multitargeted receptor tyrosine kinase inhibitor (TKI) with activity against a number of important targets, including but not limited to KIT, PDGFR, FGFR-1, RET, BRAF, and VEGFR1–3 [1]. The Sarcoma Alliance for Research through Collaboration (SARC) performed the SARC024 trial, a multicohort phase II study, in select histologies of soft tissue and bone sarcoma, including liposarcoma ($n = 48$), osteosarcoma ($n = 48$), Ewing sarcoma ($n = 30$), and rhabdomyosarcoma and mesenchymal chondrosarcoma ($n = 24$ between the two cohorts). The Ewing cohort met its primary endpoint of 8-week progression-free survival, and the osteosarcoma cohort showed an improved PFS compared with placebo [2, 3].

This study did not meet its primary endpoint of an improvement in PFS. No responses were seen in subjects who received regorafenib. At the time of the analyses, 46 (96%) patients in each arm experienced a progression event: 23 on regorafenib and 23 on placebo. The PFS between the two arms did not differ (Fig. 1). Subjects randomized to regorafenib had a median PFS of 1.9 (95% CI, 0.9–3.7) months compared with 2.1 (95% CI, 1.6–3.4) months for placebo. The unstratified hazard ratio was 0.93 (95% CI, 0.51–1.69), $p = .81$. The stratified hazard ratio was 0.85 (95% CI, 0.46–1.58), $p = .62$. The median OS between the treatment arms did not differ (Fig. 2). Adverse events were consistent with the known side effect profile of regorafenib.

These results are consistent with two prior studies exploring a multitargeted TKI in advanced soft tissue sarcomas, both of which included liposarcoma cohorts: REGOSARC, a randomized, double-blind, placebo-controlled, phase II trial exploring safety and efficacy of regorafenib in four advanced soft tissue sarcoma cohorts [4], and EORTC 62043, a phase II trial of the multitargeted TKI pazopanib in advanced soft tissue sarcomas [5]. Exploration of novel therapies, including combination approaches, is warranted for this patient population with limited treatment options.

Trial Information	
Disease	Sarcomas – adult
Stage of Disease/Treatment	Metastatic/advanced
Prior Therapy	1 prior regimen
Type of study	Phase II, randomized
PFS	p = .616, HR: 0.85
Primary Endpoint	Progression-free survival
Secondary Endpoints	Overall survival, overall response rate, toxicity

Additional Details of Endpoints or Study Design

The primary endpoint of the study was PFS, which was defined as the time from randomization to radiographic tumor progression (assessed by RECIST 1.1) or death from any cause, whichever occurs first. Progression is defined, according to RECIST 1.1 criteria, as a 20% increase from nadir and a minimum of 5 mm increase over the lowest sum, the appearance of one or more new target or nontarget lesions, or unequivocal progression of existing nontarget lesions determined by radiographic assessment. For patients alive without progression, patients were censored at the time of their last tumor assessment. The study was powered to detect a difference of at least a 3-month improvement in median PFS. The anticipated median PFS for the placebo arm was 2 months, with a minimum detectable median PFS in the treatment arm of 5 months, for a minimum detectable HR of 0.40 (treatment/control group). A total of 42 PFS events were needed to detect a targeted difference with 90% power and 5% one-sided significance level. A sample size of 48 eligible patients was expected to be randomized to achieve the 42 required PFS events.

Secondary endpoints included overall survival (OS), overall response rate (ORR), and adverse events (AEs). OS was defined as the time from randomization until death from any cause, and patients who have not died were censored at the date of last contact. Overall response rate (ORR as assessed by RECIST 1.1) was defined as the portion of patients evaluable for response who achieved partial response or better. AEs were assessed according to National Cancer Institute's Common Terminology Criteria for Adverse Events version 4.03.

Analyses were performed on an intent to treat basis. Time-to-event outcomes were compared between treatment groups using a one-sided stratified log rank test with stratification for World Health Organization (WHO) performance status (0–1 vs. 2) and number of prior therapies (1 vs. >2). Proportions were compared using Fisher's exact test. Logistic regression and Cox proportional hazard models, with stratification variables included, were used to generate estimates of odds ratios and hazard ratios, respectively. Kaplan-Meier curves were generated for time-to-event data. Point estimates and corresponding 95% CIs are provided as estimates of effects. The data were last updated on March 15, 2019, and were analyzed using R (version 3.5.2) and SAS 9.4 (SAS Institute, Cary, NC).

Investigator's Analysis	Inactive because results did not meet primary endpoint

Drug Information: Placebo	
Generic/Working Name	Placebo
Schedule of Administration	Four tablets ("matching placebo") p.o. daily for adult subjects on days 1–21, followed by a 7-day rest period. Cycles were repeated every 28 days

Drug Information: Regorafenib	
Generic/Working Name	Regorafenib
Trade Name	Stivarga
Company Name	Bayer
Drug Type	Small molecule
Drug Class	VEGFR
Dose	160 mg per flat dose
Route	p.o.
Schedule of Administration	160 mg (4 x 40 mg tablets) p.o. daily for adult subjects on days 1–21, followed by a 7-day rest period. Cycles were repeated every 28 days

Patient Characteristics: Placebo	
Number of Patients, Male	18 (75%)
Number of Patients, Female	6 (25%)
Stage	92% (*n* = 22) with metastatic disease
Age	Median (range): 64.17 years (37.94–78.73)
Number of prior systemic therapies	Median (range): 2 (1–4)
Performance Status: WHO	0 — 10 1 — 13 2 — 1 3 — 0
Ethnicity	Hispanic or Latino: 1 (4%) Not Hispanic or Latino: 22 (92%) Unknown: 1 (4%)
Race	American Indian or Alaskan Native: 0 (0%) Asian: 3 (13%) Black or African Heritage: 1 (4%) White: 20 (83%) Unknown: 0 (0%)
Tumor Location	Abdominopelvic/retroperitoneal: 17 (71%) Extremity/limb girdle: 6 (25%) Upper torso/thorax: 1 (4%)
Cancer Types or Histologic Subtypes	Dedifferentiated liposarcoma 16 (67%) Myxoid and/or round cell liposarcoma 7 (29%) Pleomorphic liposarcoma 1 (4%)

Patient Characteristics: Regorafenib	
Number of Patients, Male	10 (42%)
Number of Patients, Female	14 (58%)
Stage	83% (n = 20) with metastatic disease
Age	Median (range): 61.22 years (27.03–79.65)
Number of Prior Systemic Therapies	Median (range): 1 (1–4)
Performance Status: WHO	0 — 8 1 — 14 2 — 2 3 — 0
Ethnicity	Hispanic or Latino: 0 (0%) Not Hispanic or Latino: 23 (96%) Unknown: 1 (4%)
Race	American Indian or Alaskan Native: 1 (4%) Asian: 0 (0%) Black or African Heritage: 5 (21%) White: 16 (67%) Unknown: 2 (8%)
Tumor Location	Abdominopelvic/retroperitoneal: 18 (75%) Extremity/limb girdle: 4 (17%) Upper torso/thorax: 2 (8%)
Cancer Types or Histologic Subtypes	Dedifferentiated liposarcoma, 18 (75%) Myxoid and/or round cell liposarcoma, 5 (21%) Pleomorphic liposarcoma, 1 (4%)

Primary Assessment Method (Placebo)	
Title	Progression-free survival (PFS)
Number of Patients Evaluated for Efficacy	24
Evaluation Method	Kaplan-Meier method
(Median) Duration Assessments PFS	2.07 months, CI: 1.64–3.44

Secondary Assessment Method (Placebo)	
Title	Objective response (ORR)
Number of Patients Evaluated for Efficacy	22
Evaluation Method	RECIST 1.1
Response Assessment PR	*n* = 1 (4.5%)
Title	Overall survival (OS)
Number of Patients Evaluated for Efficacy	24
Evaluation Method	Kaplan-Meier method
(Median) Duration Assessments OS	4.89 months, CI: 3.02–9.77

Primary Assessment Method (Regorafenib)	
Title	Progression-free survival (PFS)
Number of Patients Evaluated for Efficacy	24
Evaluation Method	Kaplan-Meier method
(Median) Duration Assessments PFS	1.87 months, CI: 0.92–3.67
Outcome Notes	PFS (regorafenib vs. placebo; unstratified) HR, 0.93 (CI 0.51, 1.69); *p* = .81 PFS (regorafenib vs. placebo; stratified) HR, 0.85 (95% CI 0.46, 1.58); *p* = .616

Secondary Assessment Method (Regorafenib)	
Title	Overall response rate (ORR)
Number of Patients Evaluated for Efficacy	20
Evaluation Method	RECIST 1.1
Response Assessment CR	*n* = 0 (0%)
Response Assessment PR	*n* = 0 (0%)
Title	Overall survival (OS)
Number of Patients Evaluated for Efficacy	24
Evaluation Method	Kaplan-Meier method
(Median) Duration Assessments OS	6.46 months, CI: 4.16–23.77
Outcome Notes	OS (regorafenib vs. placebo; unstratified) HR, 0.60 (95% CI 0.29, 1.25); *p* = .171 OS (regorafenib vs. placebo; stratified) HR, 0.66 (95% CI 0.31, 1.40); *p* = .275

Adverse Events (Placebo)							
All Cycles							
Name	**NC/NA**	**1**	**2**	**3**	**4**	**5**	**All grades**
Abdominal pain	92%	0%	0%	8%	0%	0%	8%
Anemia	83%	0%	0%	17%	0%	0%	17%

Anorexia	92%	8%	0%	0%	0%	0%	8%
Blood bilirubin increased	92%	0%	0%	8%	0%	0%	8%
Diarrhea	92%	8%	0%	0%	0%	0%	8%
Fatigue	83%	0%	0%	17%	0%	0%	17%
Generalized muscle weakness	100%	0%	0%	0%	0%	0%	0%
Hypertension	84%	0%	8%	8%	0%	0%	16%
Hypoalbuminemia	84%	0%	8%	8%	0%	0%	16%
Hypocalcemia	92%	0%	8%	0%	0%	0%	8%
Hypomagnesemia	100%	0%	0%	0%	0%	0%	0%
Hyponatremia	96%	0%	0%	0%	4%	0%	4%
Hypophosphatemia	92%	0%	0%	8%	0%	0%	8%
Lipase increased	100%	0%	0%	0%	0%	0%	0%
Nausea	79%	13%	0%	8%	0%	0%	21%
Pain	92%	0%	0%	8%	0%	0%	8%
Palmar-plantar erythrodysesthesia syndrome	100%	0%	8%	0%	0%	0%	0%
Rash maculo-papular	100%	0%	0%	0%	0%	0%	0%
Skin and subcutaneous tissue disorders	100%	0%	0%	0%	0%	0%	0%

Adverse events occurring in >5% of subjects at any time during study treatment according to initial randomization. There were three nondrug-related grade 5 events in the cohort initially randomized to placebo.
Abbreviation: NC/NA, no change from baseline/no adverse event; CI: confidence intervals.

Adverse Events (Regorafenib)

All Cycles

Name	NC/NA	1	2	3	4	5	All Grades
Abdominal pain	87%	0%	0%	13%	0%	0%	13%
Anemia	92%	0%	0%	8%	0%	0%	8%
Anorexia	92%	0%	0%	8%	0%	0%	8%
Blood bilirubin increased	100%	0%	0%	0%	0%	0%	0%
Diarrhea	100%	0%	0%	0%	0%	0%	0%
Fatigue	92%	0%	0%	8%	0%	0%	8%
Generalized muscle weakness	92%	0%	0%	8%	0%	0%	8%
Hypertension	70%	0%	17%	13%	0%	0%	30%
Hypoalbuminemia	100%	0%	0%	0%	0%	0%	0%
Hypocalcemia	100%	0%	0%	0%	0%	0%	0%
Hypomagnesemia	92%	8%	0%	0%	0%	0%	8%
Hyponatremia	100%	0%	0%	0%	0%	0%	0%
Hypophosphatemia	100%	0%	0%	0%	0%	0%	0%
Lipase increased	92%	0%	0%	8%	0%	0%	8%
Nausea	100%	0%	0%	0%	0%	0%	0%
Pain	100%	0%	0%	0%	0%	0%	0%
Palmar-plantar erythrodysesthesia syndrome	71%	0%	21%	8%	0%	0%	29%
Rash maculo-papular	87%	0%	0%	13%	0%	0%	13%
Skin and subcutaneous tissue disorders	92%	0%	8%	0%	0%	0%	8%

Adverse events occurring in >5% of subjects at any time during study treatment according to initial randomization. There was one nondrug-related grade 5 event in the cohort initially randomized to regorafenib.
Abbreviation: NC/NA, no change from baseline/no adverse event.

Assessment, Analysis, and Discussion

Completion	Study completed
Investigator's Assessment	Inactive because results did not meet primary endpoint

Liposarcomas represent one of the more common soft tissue sarcoma subtypes, with the World Health Organization recognizing atypical lipomatous tumor/well-differentiated liposarcoma, dedifferentiated liposarcoma, pleomorphic liposarcoma, myxoid liposarcoma, and liposarcoma as distinct entities [6]. Despite the recent approval of eribulin and trabectedin for the treatment of advanced disease, liposarcoma treatment remains an area of unmet medical need. [7–10]. Tyrosine kinase inhibitors have been explored and approved in a variety of metastatic soft tissue sarcomas, including imatinib, sunitinib, and regorafenib in gastrointestinal tumors (GISTs) and pazopanib in non-GIST and nonadipocytic sarcomas [11–14]. In a multicohort phase II study, pazopanib's efficacy in liposarcomas was limited [5]. As a result, liposarcomas were excluded from the phase III PALETTE study that led to regulatory approval [14]. However, a recent, single-arm, prospective phase II study revealed potential activity of pazopanib in liposarcoma based on an encouraging progression-free survival rate at 12 weeks [15]. As a result, there has been continued interest in exploring tyrosine kinase inhibitor (TKI)-based therapy in various histologic subtypes of sarcoma.

The Sarcoma Alliance for Research through Collaboration (SARC) performed the SARC024 trial (NCT02048371), a multicohort phase II study, in select histologies of soft tissue and bone sarcoma, including liposarcoma, osteosarcoma, and Ewing sarcoma. This phase II study of regorafenib versus placebo in liposarcoma did not meet its primary endpoint of an improvement in PFS. In addition, no responses were seen in subjects who received regorafenib, and no statistically significant differences were noted in PFS or OS. These results confirm the results of the previously published randomized phase II REGOSARC study of multitargeted TKI regorafenib and the phase II EORTC 62043 study of the multitargeted TKI pazopanib in advanced soft tissue sarcomas [4, 5]. Reasons for the limited activity of multitargeted TKIs in liposarcoma from randomized prospective data published to date remain unknown. Despite the available data, there has been continued interest in exploring multitargeted TKI therapies in liposarcoma. Anlotinib, a multitargeted antiangiogenic inhibitor, has recently been explored in a phase II study in patients with metastatic soft tissue sarcoma [16]. Multiple cohorts of soft tissue sarcoma were enrolled, including liposarcomas. Among the liposarcoma cohort, a progression free rate at 12 weeks of 63% was observed, with a median PFS of 5.6 months and OS of 12 months. These results are encouraging but limited by the small number of patients with liposarcoma enrolled and the generalizability of the patient population (Chinese only). Although these appear to be the most promising results for a TKI to date in liposarcoma, the ongoing, phase III APROMISS study is exploring anlotinib in limited histologic subtypes, specifically leiomyosarcoma, synovial sarcoma, and alveolar soft part sarcoma (NCT03016819).

There are several ongoing studies actively enrolling and exploring a number of novel therapies in liposarcoma, including, but not limited to, cabozantinib (NCT01913652) and sitravatinib (NCT02978859). The phase II/III SEAL trial, exploring a selective inhibitor of nuclear export (selinexor) versus placebo, in dedifferentiated liposarcomas, is continuing actively enrolling (NCT02606461). Given the known amplification of *CDK4* in the majority of dedifferentiated liposarcomas, there has been continued interest in exploring CDK4 inhibition, with trials completed using palbociclib and abemaciclib [17, 18]. Pembrolizumab has been explored in a cohort of patients with liposarcoma, and although initial data suggested modest activity, a recent update failed to confirm the results [19–20].

Continued exploration is warranted in this patient population with limited treatment options. Inclusion of embedded correlatives to identify potential biomarkers of response with a goal of providing individualized therapies most likely to provide benefit and improve patient outcomes should be emphasized.

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