Original Article

A Randomized, Open-Label, Phase 2, Multicenter Trial of Gemcitabine With Pazopanib or Gemcitabine With Docetaxel in Patients With Advanced Soft-Tissue Sarcoma

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BACKGROUND: Therapeutic options for patients with advanced soft-tissue sarcoma (STS) are limited. The goal of the current phase 2 study was to examine the clinical activity and safety of the combination of gemcitabine plus pazopanib, a multityrosine kinase inhibitor with activity in STS. **METHODS:** The current randomized, phase 2 trial enrolled patients with advanced nonadipocytic STS who had received prior anthracycline-based therapy. Patients were assigned 1:1 to receive gemcitabine at a dose of 1000 mg/m^2 on days 1 and 8 with pazopanib at a dose of 800 mg daily (G+P) or gemcitabine at a dose of 900 mg/m^2 on days 1 and 8 and docetaxel at a dose of 100 mg/m^2 on day 8 (G+T) every 3 weeks. Crossover was allowed at the time of disease progression. The study used a noncomparative statistical design based on the precision of 95% confidence intervals for reporting the primary endpoints of median progression-free survival (PFS) and rate of grade ≥3 adverse events (AEs) for these 2 regimens based on the intent-to-treat patient population (AEs were graded using version 4.0 of the National Cancer Institute Common Terminology Criteria for Adverse Events). **RESULTS:** A total of 90 patients were enrolled: 45 patients on each treatment arm. The median PFS was 4.1 months for each arm (P = .3, log-rank test). The best overall response of stable disease or better (complete response + partial response + stable disease) was the same for both treatment arms (64% for both the G+T and G+P arms). The rate of related grade ≥3 AEs was 82% for the G+T arm and 78% for the G+P arm. Related grade ≥3 AEs occurring in ≥10% of patients in the G+T and G+P arms were anemia (36% and 20%, respectively), fatigue (29% and 13%, respectively), thrombocytopenia (53% and 49%, respectively), neutropenia (20% and 49%, respectively), lymphopenia (13% and 11%, respectively), and hypertension (2% and 20%, respectively). **CONCLUSIONS:** The data from the current study have demonstrated the safety and efficacy of G+P as an alternative to G+T for patients with nonadipocytic STS. ***Cancer* 2021;127:894-904**. © *2020 American Cancer Society*.

KEYWORDS: adverse events, best overall response, gemcitabine and pazopanib, soft-tissue sarcoma.

INTRODUCTION

Chemotherapy is widely used in the treatment of patients with nonresectable or metastatic soft-tissue sarcoma (STS).[1,2] Initial standard chemotherapy for these tumors consists of an anthracycline given as a single agent or in combination with ifosfamide,[3,4] although the cardiotoxicity of cumulative anthracycline use often is dose limiting.[5-7] The combination of gemcitabine and docetaxel (G+T) is another regimen frequently used to treat patients with metastatic STS based on a phase 2 study reported by Maki et al that demonstrated a survival benefit for this combination versus single-agent gemcitabine.[8,9] The median progression-free survival (mPFS) of gemcitabine therapy alone was 3 months; when combined with docetaxel, the mPFS increased to 6.2 months, with the leiomyosarcoma (LMS) and undifferentiated pleomorphic sarcoma subtypes deriving the most benefit. However, the combination of G+T was a relatively poorly tolerated regimen, with 46% of patients requiring at least 1 dose reduction, and many patients discontinuing therapy within 6 months because of toxicity.[8,9] The TAXOGEM study,[10] which was performed by the French Sarcoma Group and focused only on patients with recurrent LMS, found a PFS of 5.5 months and 6.3 months, respectively, in patients with uterine and nonuterine LMS when using gemcitabine and 4.7 months and 3.8 months, respectively, for the G+T combination. The GeDDiS

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trial[11] compared G+T at a lower starting dose than previous studies examining doxorubicin as front-line treatment for patients with advanced sarcoma, demonstrating a similar mPFS of approximately 5.5 months. In these studies, unlike those performed for pancreatic cancer, gemcitabine is given as a fixed dose regimen at 10 mg/m^2/minute.

An alternative to G+T might involve the use of pazopanib, which is an oral targeted tyrosine kinase inhibitor that blocks multiple growth factor receptors including vascular endothelial, platelet-derived, and fibroblast growth factor receptors, among many others.[12] Pazopanib was approved for the treatment of sarcoma based on a double-blind, placebo-controlled, randomized phase 3 trial (PALETTE) that demonstrated significant prolongation of PFS in patients with pretreated nonadipocytic sarcoma.[13] However, despite the overall increase in PFS observed,[13] there was no overall survival (OS) benefit noted. Multivariant analysis of long-term survivors demonstrated that both performance status and tumor grade had significance for PFS and OS with pazopanib.[14] This study excluded patients with adipocytic sarcomas because this subtype cohort was halted early in the preceding phase 2 trial because it did not meet the prespecified efficacy cutoff value. Although subsequent studies in patients with liposarcomas[15] demonstrated results similar to those of the PALETTE trial with a mPFS and OS of 4.4 months and 12.6 months, respectively, these results were presented after the current study was enrolling patients, and to our knowledge have not led a change in the label indication for pazopanib.

To build on the activity of pazopanib and to develop a new combined therapy for sarcoma, pazopanib was combined with a MEK inhibitor, trametinib, in 25 patients.[16] In this trial, the mPFS was 2.27 months and the 4-month PFS rate was 21.1%, suggesting that the combination did not improve efficacy. Antiangiogenic therapies such as pazopanib work by inducing vascular normalization, thereby alleviating hypoxia and increasing the delivery of cytotoxic chemotherapies to cancer cells.[17] Increased penetration of drugs throughout the tumor could enhance the antitumor benefit of chemotherapy; therefore, we explored the combination of pazopanib with chemotherapy. To examine further whether a potential combination of pazopanib and gemcitabine (G+P) might be developed as a sarcoma therapy, our team randomized 90 patients with nonadipocytic sarcomas to receive either G+P or the currently used regimen of G+T. This trial excluded patients with adipocytic sarcomas based on the initial results of the PALETTE trial. Crossover was allowed after disease progression (PD); patients on each treatment arm were evaluated for PFS and toxicity, and secondarily for OS and quality of life (QOL).

MATERIALS AND METHODS

Patient Eligibility

Eligible patients had to have metastatic or locally advanced and/or recurrent, histologically or cytologically confirmed nonadipocytic sarcoma of soft tissue and be aged ≥18 years. All patients provided written informed consent prior to any study interventions. Human investigations were performed after approval by the local human investigations committee and/or institutional review board at each study institution and in accordance with an assurance filed with and approved by the Department of Health and Human Services. Patients should have received a prior anthracycline-based regimen unless otherwise contraindicated. Additional criteria included an Eastern Cooperative Oncology Group performance status of 0 to 2, disease that was not amenable to curative surgical resection, ≤3 prior chemotherapy regimens for recurrent and/or metastatic disease, measurable disease by Response Evaluation Criteria in Solid Tumors (RECIST) or cutaneous disease that was amenable to serial measurements if present, ability to swallow and retain oral medication, and adequate organ system function including alanine aminotransferase (ALT) and aspartate aminotransferase levels ≤2.5 the upper limit of normal and a serum creatinine <1.5 mg/dL.

Patients were excluded if they had a history of untreated central nervous system metastases, active peptic ulcer disease, intraluminal metastatic lesions with a risk of bleeding, a corrected QT interval (QTc) >480 milliseconds, poorly controlled hypertension, a history of a pulmonary embolism or transient ischemic attack, or major surgery within 28 days of registration.

Study Design and Treatments

Patients were randomized 1:1 to either the G+P or G+T treatment arm. Randomization was stratified by both LMS histology (yes or no) and by receipt of prior pelvic radiotherapy (RT) (yes or no) using blocks of size 4.

The trial was designed to enroll 90 patients who were randomized 1:1 to receive gemcitabine at a dose of 1000 mg/m^2 intravenously (iv) over 100 minutes on days 1 and 8 of a 21-day cycle along with pazopanib at a dose of 800 mg orally once daily on days 1 through 21 (G+P) or gemcitabine at a dose of 900 mg/m^2 iv over 90 minutes on days 1 and 8 along with docetaxel at a dose of 100 mg/m^2 iv over 60 minutes on day 8 every 21 days (G+T). The starting dose of G+P was the recommended phase 2 dosing established by the sponsor based on the phase 1 study,[18] and the starting dose for G+T was the established maximum dosing used in prior phase 2 studies.[9,10]

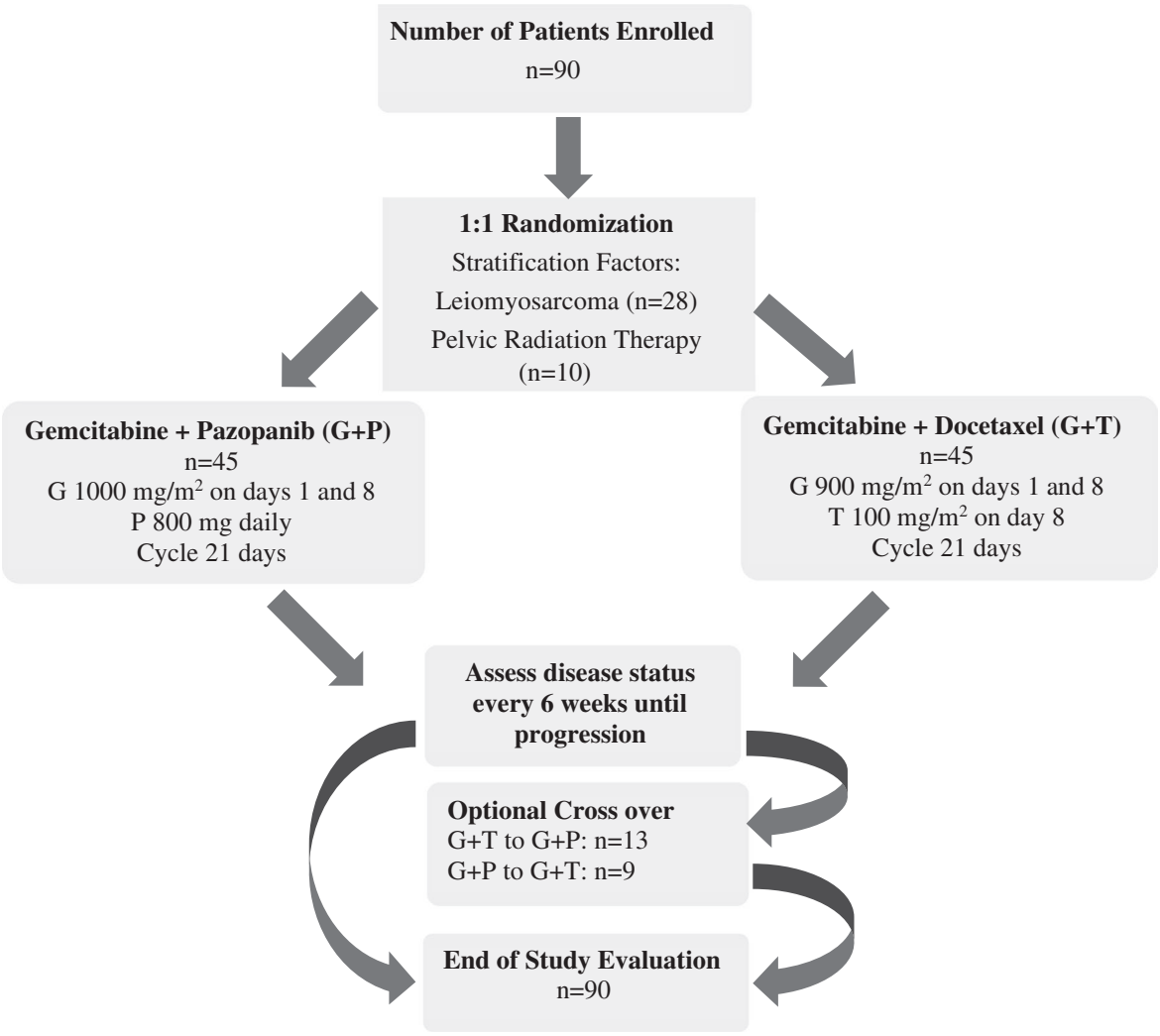

Figure 1. Consolidated Standards Of Reporting Trials (CONSORT) diagram.

Gemcitabine was given at a fixed dose rate of 10 mg/m^2/hour based on higher efficacy compared with a 30-minute infusion in patients with sarcoma.[19-22] Pegfilgrastim or filgrastim could be used on either treatment arm at the discretion of the investigator. Patients discontinued treatment for PD, intolerable toxicity, or if treatment was interrupted for >21 days. Because G+T may be more active in patients with LMS compared with other STS subtypes, patients were stratified by sarcoma subtype (LMS vs other) prior to randomization. Randomization also was stratified based on prior pelvic RT because of the potential for differential response by prior pelvic RT. Each patient was followed for a minimum of 18 months for the events of PD and death.

PD was assessed every 2 cycles (6 weeks) for the first 24 weeks and then every 3 cycles thereafter. Optional blood draws for biomarkers and pharmacokinetics (G+P arm) and specimen banking (both treatment arms) was performed at baseline, at 6 weeks, and at the time of PD. Predefined early stopping rules allowed for early stopping in each treatment arm for excessive toxicity. At the time of PD, patients were allowed to cross over to the other treatment arm (Fig. 1), allowing for the evaluation of PFS with G+P after exposure to G+T and vice versa. To cross over, patients must have maintained an Eastern Cooperative Oncology Group performance status of 0 to 2, have measurable disease by RECIST (version 1.1), have toxicities resolved to grade ≤1, and have adequate organ function. If the patient had their dose reduced during therapy, then this dose reduction would carry over to the crossover.

Dose delays and modifications for nonhematologic toxicities of grade ≥3 with gemcitabine, pazopanib, and

docetaxel were permanent. Dose re-escalation to 1 level higher if the counts permitted was allowed if reductions occurred for treatment-related hematologic toxicities. For pazopanib-specific side effects, an isolated dose reduction of pazopanib was allowed. If a second reduction was required, re-escalation was not permitted. The dose levels (DL) were as follows: G+P: DL-1 of gemcitabine of 800 mg/m^2 and pazopanib of 600 mg and a DL-2 of gemcitabine of 675 mg/m^2 and pazopanib of 400 mg; G+T: DL-1 of gemcitabine of 700 mg/m^2 and docetaxel of 75 mg/m^2 and a DL-2 of gemcitabine of 600 mg/m^2 and docetaxel of 60 mg/m^2.

Study Objectives and Assessments

The primary objective of the current study was to estimate the mPFS and the rate of grade ≥3 toxicities for the G+P and G+T treatment arms. Key secondary objectives included estimating the hazard ratio (HR) for PFS, and the best overall response rates, QOL, and median OS in each arm.

The European Organization for Research and Treatment of Cancer (EORTC) core QOL QLQ-C30 questionnaire was administered to patients at 4 time points (registration, cycle 2, cycle 6, and the end of treatment). Tumor response (complete response [CR], partial response [PR], stable disease [SD], and PD) was assessed by the treating or site investigator and was based on version 1.1 of RECIST. The best overall response was defined as the best recorded response from the initiation of study treatment until PD or the end of treatment. For a best overall response of SD, the criteria for SD were met at least once for ≥6 weeks from the pretreatment assessment. Adverse events (AEs) were graded according to version 4.0 of the National Cancer Institute Common Terminology Criteria for Adverse Events, and their attribution was determined by the local principal investigator.

Statistical Analysis

The coprimary endpoints were PFS and toxicity of grade ≥3, with estimation of the mPFS and rate of grade ≥3 toxicity as coprimary objectives. The sample size was derived based on the precision of the 95% confidence intervals (95% CIs) for reporting toxicity rates and the mPFS in each treatment arm. With 45 patients per arm and assuming an observed toxicity rate of <30%, the maximum half-width of the 95% CI was <14%. For PFS, the precision of the 95% CI depended heavily on the observed mPFS. With an observed mPFS of 3 months, 6 months, or 8 months, the estimated half-widths of the 95% CIs would be expected to be 1.4 months, 2.9 months, or 3.9 months, respectively, based on results from Kaplan-Meier curves and using the Greenwood formula for variance. Hypothesis testing was not implemented because of the uncertainty in choosing a historical control PFS rate. With 45 patients per arm and assuming an observed toxicity rate of <30%, the maximum half-width of the 95% CI would be <14%. For PFS, the precision of the 95% CI depended heavily on the observed mPFS. With an observed mPFS of 3 months, 6 months, or 8 months, the estimated half-widths of the 95% CIs would be expected to be 1.4 months, 2.9 months, or 3.9 months, respectively, based on results from Kaplan-Meier curves and using Greenwood formula for variance. These estimates would be considered sufficiently precise for determining whether the efficacy and safety profile warrant further exploration of G+P as combined therapy. HRs were estimated between the 2 groups using Cox proportional hazards regression models adjusting for stratification variables. Data were compared between arms using the Fisher exact test and chi-square test for binary and categorical data, as appropriate, and via 2-sample Student *t* tests and Wilcoxon rank sum tests for continuous data, as appropriate. All randomized patients (intention-to-treat population) were assessed for response to treatment. PFS and OS were described using Kaplan-Meier curves, and curves were compared using stratified log-rank tests. For the crossover portion of the study, comparison of a best overall response of SD or better (CR+PR+SD) was performed using exact logistic regression adjusting for stratification variables, and corresponding exact binomial 95% CIs were constructed. The percentages of patients in each arm with grade ≥3 at least possibly related toxicities were reported with their 95% CIs. Toxicity profiles were described by estimating the rate of serious AEs per treatment arm and tabulating toxicities per arm by type and grade. QOL measurements were evaluated via general linear mixed models to examine the relationship with time, treatment arm, and the interaction between the 2. Nonsignificant interaction terms were removed from the model to evaluate the main effects of treatment arm and time.

This trial was registered at ClinicalTrials.org (ClinicalTrials.gov identifier NCT01593748).

RESULTS

A total of 90 patients with nonadipocytic sarcoma were accrued to the current study across 10 sites (range, 1-21 patients per site) with 45 patients randomized to each treatment arm over the years 2011 through 2018 (Table 1). The mean age of the patients was 56 years (range, 21.7-82.2 years), with approximately 50% of

TABLE 1. Patient Characteristics

Characteristics	Overall No. (%)	Gemcitabine + Docetaxel No. (%)	Gemcitabine + Pazopanib No. (%)
No. of patients	90	45	45
Mean age (SD) y	56.27±13.95	54.60±14.10	57.93±13.76
Sex			
Female	46 (51)	22 (49)	24 (53)
Male	44 (49)	23 (51)	21 (47)
Leiomyosarcoma	28 (31)	13 (29)	15 (33)
Prior therapies received			
Pelvic RT	10 (11)	5 (11)	5 (11)
Surgery	81 (90)	42 (93)	39 (87)
RT	51 (57)	23 (51)	28 (62)
Chemotherapy	74 (82)	37 (82)	37 (82)
Other prior therapy	6 (7)	4 (9)	2 (4)
Received prior doxorubicin-based therapy	70 (78)	35 (78)	35 (78)
No. of lines of prior chemotherapy[a]			
Median (IQR)	1 (1-2)	1 (1-2)	1 (1-2)
0	16 (18)	8 (18)	8 (18)
1	45 (50)	21 (47)	24 (53)
2	21 (23)	12 (27)	9 (20)
3	8 (9)	4 (9)	4 (9)

Abbreviations: IQR, interquartile range; RT, radiotherapy.
[a]Maximum of 3 prior therapies were allowed.

patients being male and evenly distributed between the 2 arms. Eighty-one of the patients (90%) had undergone prior surgery and these patients were equally balanced between both treatment arms as well. The majority of the patients (82%) received at least 1 line of prior therapy before being enrolled on this protocol. Overall, 10 patients (11%) had received prior pelvic RT. Among the 28 patients with LMS, 3 had received prior pelvic RT. There were no statistically significant differences in these characteristics observed between treatment arms.

Treatment Administered

Patients in the G+T arm received a median number of 4 cycles (range, 2-8 cycles) whereas those treated on the G+P arm received a median number of 3 cycles (range, 2-10 cycles). The median time to best response for both the G+P and G+T arms was similar with 42 days (interquartile range [IQR], 38-49 days) reported for G+T and 43 days (IQR, 37-49 days) reported for G+P. The median duration of therapy for the 2 arms was not statistically significantly different ($P = .90$) at 62 days (range, 28-203 days) for G+P and 70 days (range, 28-161 days) for G+T (Table 2). The most common reason for study discontinuation on both treatment arms was PD (Table 3). A total of 13 patients (29%) in the G+T arm crossed over to G+P, whereas a total of 9 patients (20%) in the G+P arm were treated with G+T after PD (Table 2).

Efficacy End Points

The mPFS was 4.1 months (95% CI, 2.7-11.4 months) in the G+T arm and 4.1 months (95% CI, 2.4-8.6 months) in the G+P arm ($P = .29$) (Fig. 2A). The median OS was 15.9 months (95% CI, 9.2-24.2 months) in the G+T arm and 12.4 months (95% CI, 8.8-21.8 months) in the G+P arm (Fig. 2B). The distribution of responses by RECIST (version 1.1) in the G+P arm was 11% for PR (5 of 45 patients), 53% for SD (24 of 45 patients), and 31% for PD (14 of 45 patients). Two patients in the G+P arm were withdrawn prior to the first radiographic assessment and were not evaluable for response: one because of toxicity and one because of investigator decision. The best overall response rate of SD or better (CR+PR+SD) in the G+P arm was 64%. In comparison, for patients in the G+T arm, the PR rate was 18% (8 of 45 patients), the SD rate was 47% (21 of 45 patients), and the PD rate was 36% (16 of 45 patients), for a best overall response rate of SD or better of 64% (Table 4). The HR for PFS when comparing the patients treated with G+P with those treated with G+T was 1.23 (95% CI, 0.77-1.94; $P = .38$); the HR for OS also was 1.23 (95% CI, 0.74-2.04; $P = .42$) when comparing the 2 treatment arms.

TABLE 2. Chemotherapy Cycles, Duration of Therapy Received, and Dose Withheld and/or Skipped

	Gemcitabine + Docetaxel	Gemcitabine + Pazopanib
Median no. of cycles (IQR)	4 (2-8)	3 (2-10)
Median duration of therapy, d (IQR)	70 (28-161)	62 (28-203)
Dose reduction, no. (%)	26 (58)	36 (80)
Dose withheld and/or skipped, no. (%)	26 (58)	42 (93)
No. of patients crossed over, no. (%)	13 (29)	9 (20)

Abbreviation: IQR, interquartile range.

TABLE 3. Reason for Patient Being Taken Off Study (Main Study Only)

Reason for Treatment Termination	Overall No. (%)	Gemcitabine + Docetaxel No. (%)	Gemcitabine + Pazopanib No. (%)
No. of patients	90	45	45
Progression as per RECIST version 1.1	44 (49)	21 (47)	23 (51)
Clinical disease progression	11 (12)	4 (9)	7 (16)
Toxicity; treatment termination medically required	20 (22)	11 (24)	9 (20)
Investigator decision for reasons other than toxicity	5 (6)	2 (4)	3 (7)
Patient refusal due to toxicity	2 (2)	1 (2)	1 (2)
Patient refusal for reasons other than toxicity	1 (1)	0 (0)	1 (2)
Death	2 (2)	1 (2)	1 (2)
Other	5 (6)	5 (11)	0 (0)

Abbreviation: RECIST, Response Evaluation Criteria in Solid Tumors.

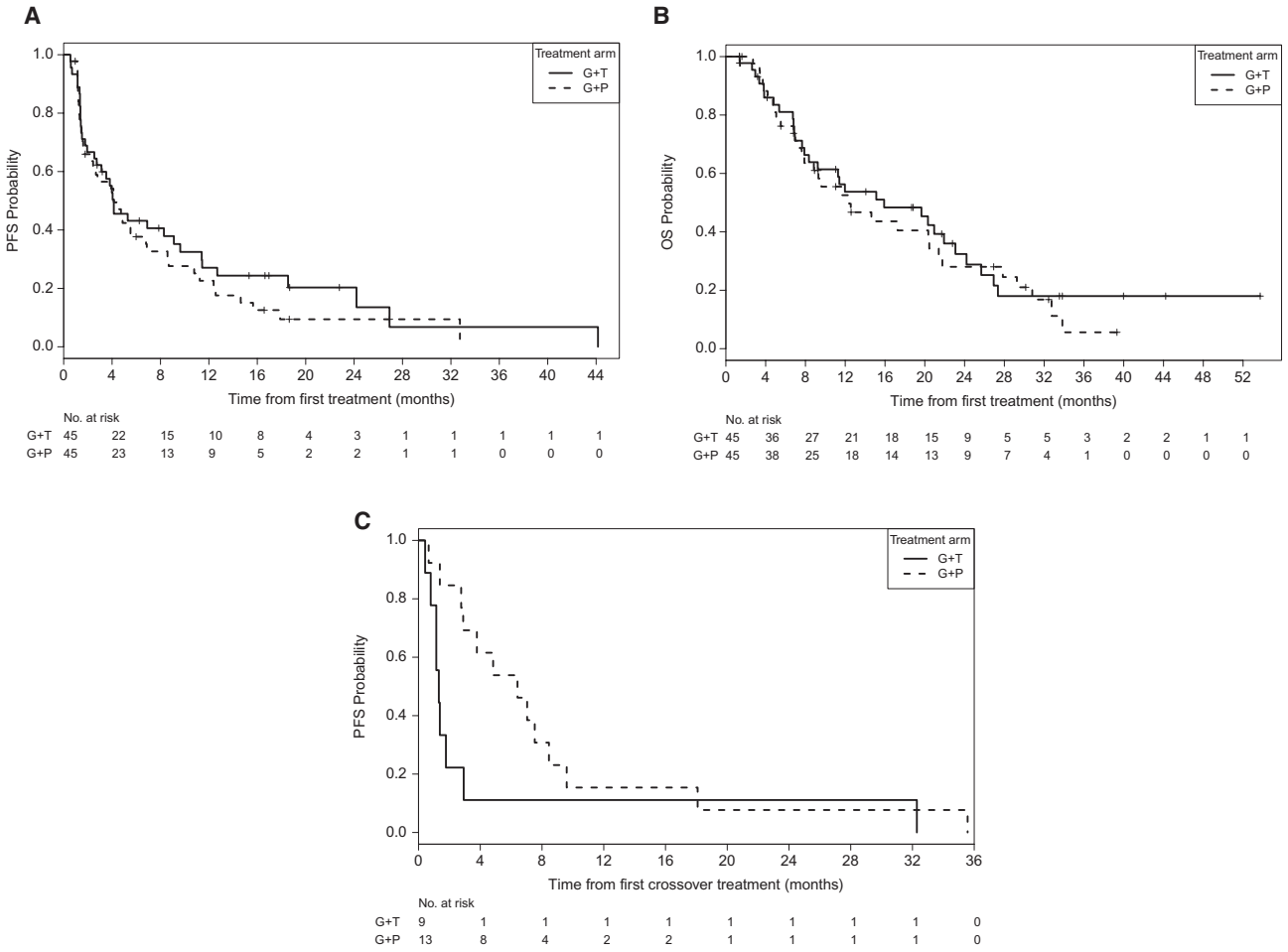

Figure 2. (A) Kaplan-Meier curves demonstrating the median progression-free survival (PFS) for both treatment arms in the study as well as the number of patients at risk over time. (B) Kaplan-Meier curves showing the median overall survival (OS). (C) Kaplan-Meier curve demonstrating the PFS of patients who crossed over after the initial treatment. The number of patients at risk after crossover treatment is shown. G+P indicates gemcitabine and pazopanib; G+T, gemcitabine and docetaxel.

Crossover Patients

Twenty-three patients agreed to participate in the crossover study after PD while receiving the initial treatment. However, 1 patient was taken off study prior to treatment because of declining performance status. Twenty-two patients were included in the crossover study: 13 patients crossed over from G+T to G+P and 9 patients crossed over from G+P to G+T. For those crossing over to G+P, the PR rate was 15% (2 of 13 patients) with 62% demonstrating SD (8 of 13 patients)

TABLE 4. Efficacy Endpoints

Endpoint	Gemcitabine + Docetaxel No. (%)	Gemcitabine + Pazopanib No. (%)
No. of patients	45	45
Median PFS (95% CI), mo	4.1 (2.7-11.4)	4.1 (2.4-8.6)
Median OS (95% CI), mo	15.9 (9.2-24.2)	12.4 (8.8-21.8)
Best response, no. (%)		
CR	0 (0)	0 (0)
PR	8 (18)	5 (11)
SD	21 (47)	24 (53)
PD	16 (36)	14 (31)
Nonevaluable[a]	0	2 (4)
Best overall response (CR+PR+SD)[b]	29 (64)	29 (64)
Crossover Portion	From G+P to G+T	From G+T to G+P
No. of patients	9	13
Median PFS (95% CI), mo	1.3 (1.2 to NA)	6.4 (2.9 to NA)
Best response, no. (%)		
CR	0 (0)	0 (0)
PR	0 (0)	2 (15)
SD	1 (11)	8 (62)
PD	8 (89)	3 (23)
Best overall response (CR+PR+SD)[b]	1 (11)	10 (78)

Abbreviations: 95% CI, 95% confidence interval; CR, complete response; G+P, gemcitabine and pazopanib; G+T, gemcitabine and docetaxel; NA, not available; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.
[a]Two patients in the G+P treatment arm were not evaluable for response and were removed prior to the first postbaseline scan. One patient was removed due to toxicity and the second was removed due to investigator decision.
[b]Included CR, PR, and SD at 6 weeks.

and 23% having PD (3 of 13 patients). For patients who crossed over to G+T, none demonstrated a response, 1 patient demonstrated SD (11%), and the remaining 89% of patients had PD (8 of 9 patients). Although the numbers were small, the best overall response rate of SD or better in the crossover portion of the study favored G+P (rate, 0.77; 95% CI, 0.46-0.95) over G+T (rate, 0.11; 95% CI, 0.003-0.48) ($P = .0093$). The mPFS for patients who crossed over from G+P to G+T was 1.3 months (95% CI, 1.2 months to not estimable). The mPFS for patients who crossed over from G+T to G+P was 6.4 months (95% CI, 2.9 months to not estimable). The Kaplan-Meier curve detailing these results is shown in Figure 2C. The HR for the PFS of the G+P regimen compared with the G+T regimen for the crossover was 0.43 (95% CI, 0.17-1.10; $P = .077$).

QOL Measurements

The QLQ-C30 symptom scale was measured at baseline at the time of study registration, after cycle 2, after cycle 6, and at the end of treatment. In comparing these 2 treatment groups, there was no difference noted with regard to fatigue, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, or financial stress. With regard to nausea and vomiting after adjusting for baseline values, the G+T group was found to remain largely stable over time, whereas patients in the G+P group had lower scores over time, demonstrating an improvement in this symptom ($P = .0001$).

Safety and Tolerability

Grade ≥3 AEs suspected to be related to study treatment occurred in approximately 78% of patients in the G+P arm and in 82% of patients in the G+T arm (Table 5). Table 2 summarizes modifications that occurred during the cycles. In the G+P arm, 42 patients (93%) had doses withheld or skipped compared with 26 patients (58%) in the G+T arm ($P = .0001$), potentially because pazopanib was dosed daily and could be independently withheld for side effects, which counted toward doses skipped. In the G+P arm, 36 patients (80%) had dose reductions compared with 26 patients (58%) in the G+T arm who had dose reductions and 26 patients (58%) who had doses withheld. Conversely, patients treated on the G+T arm were more likely to delay dosing, which did not count toward withheld and/or skipped doses. The number of dose reductions for each treatment arm also was significantly different (G+P: 36 patients [80%] vs G+T: 26 patients [58%]; $P = .04$) (Table 2).

Table 6 examines the day 1 doses and demonstrates changes in dosing over all cycles. In the G+T arm, this included both the day 1 and the day 8 docetaxel dose. The pattern shown in Table 2 also was evident, with patients in the G+P arm having a greater number of overall dose reductions (Table 5).

In the G+P arm, the most common related grade ≥3 toxicities were neutropenia (49%), thrombocytopenia (49%), anemia (20%), hypertension (20%), fatigue (13%), lymphopenia (11%), ALT increase (9%), and thromboembolic events (4%). In the G+T arm, the most common grade ≥3 related toxicities included thrombocytopenia (53.3%), anemia (35.6%), fatigue (28.9%), neutropenia (20%), lymphopenia (13.3%), and edema (8.9%) (Table 5). The total number of at least possibly related grade 3 and 4 AEs was similar in the 2 treatment arms; there were 160 events in the G+P arm and 156 events in the G+T arm. In the patients treated with pazopanib either with or without an anthracycline, there were no cardiac events reported.

DISCUSSION

The current randomized, phase 2 study in patients with nonadipocytic sarcoma demonstrated the efficacy and toxicity of G+P in patients with advanced STS and its similarity to the standard G+T regimen. In this study, 45

TABLE 5. Summary of AEs at Least Possibly Related to Study Treatment[a]

AE[b]	Gemcitabine + Docetaxel N = 45					Gemcitabine + Pazopanib N = 45				
Grade	1	2	3	4	% Patients With Grade ≥3 (95% CI)[c]	1	2	3	40	% Patients With Grade ≥3 (95% CI)[b]
Neutropenia	0	2	3	6	20 (10-35)	1	6	16	6	49 (34-64)
Thrombocytopenia	7	7	13	11	53 (38-68)	10	9	11	11	49 (34-64)
Anemia	2	18	16	0	36 (22-51)	3	22	9	0	20 (10-35)
Hypertension	0	0	1	0	2 (0-12)	2	7	9	0	20 (10-35)
Fatigue	8	7	13	0	29 (16-44)	21	10	6	0	13 (5-27)
Lymphopenia	3	1	5	1	13 (5-27)	1	5	2	3	11 (4-24)
ALT increase	10	1	1	0	2 (0-12)	12	7	3	1	9 (3-21)
Edema	4	7	4	0	9 (3-21)	6	1	0	0	0 (0-0)
Thromboembolic event	0	0	0	0	0 (0-0)	0	3	2	0	4 (1-15)

Abbreviations: 95% CI, 95% confidence interval; AE, adverse event; ALT, alanine aminotransferase.
[a]Adverse events were graded using version 4.0 of the National Cancer Institute Common Terminology Criteria for Adverse Events.
[b]Only those AEs that affected ≥10% of patients are reported here.
[c]Binomial 95% CI.

TABLE 6. Dose Summary

Gemcitabine + Docetaxel No. (%)		Gemcitabine + Pazopanib No. (%)	
Gemcitabine		*Gemcitabine*	
No. of cycles (day 1 dose)	234 (100)	No. of cycles (day 1 dose)	294 (100)
900 mg/m^2	155 (66)	1000 mg/m^2	86 (29)
700 mg/m^2	54 (23)	800 mg/m^2	107 (36)
600 mg/m^2	23 (10)	675 mg/m^2	101 (34)
525 mg/m^2	2 (1)		
Any dose reduction	18 (40)	Any dose reduction	30 (67)
Lowest dose administered		Lowest dose administered	
900 mg/m^2	27 (60)	1000 mg/m^2	15 (33)
700 mg/m^2	12 (27)	800 mg/m^2	15 (33)
600 mg/m^2	5 (11)	675 mg/m^2	15 (33)
525 mg/m^2	1 (2)		
Docetaxel		*Pazopanib*	
No. of cycles (day 8 dose)	220 (100)	No. of cycles (day 1 dose)	289 (100)
100 mg/m^2	92 (42)	800 mg	75 (26)
75 mg/m^2	80 (36)	600 mg	78 (27)
60 mg/m^2	44 (20)	400 mg	136 (47)
56.25 mg/m^2	4 (2)		
Any dose reduction	25 (56)	Any dose reduction	35 (78)
Lowest dose administered		Lowest dose administered	
100 mg/m^2	16 (36)	800 mg	10 (22)
75 mg/m^2	17 (38)	600 mg	13 (29)
60 mg/m^2	10 (22)	400 mg	22 (49)
56.25 mg/m^2	2 (4)		

patients were randomized to each treatment arm and patient characteristics were found to be well balanced. The estimated median time to best response and the rate of best overall response of SD or better for each arm were the same. The mPFS and the grade 3 and 4 toxicity rates for each regimen were very similar. The QOL estimates indicated that these regimens were comparable except for a lower cumulative rate of nausea in the G+P arm. It is interesting to note that the current study allowed the crossover of patients from the initial therapy. In those who did cross over, the best overall response of SD or better favored moving to the G+P arm ($P = .0093$), which contained PRs to second-line therapy. In the absence of a larger comparative study, these data demonstrated that G+P could be considered in select patients with sarcoma who would benefit from combination therapy in the second line and who are not candidates for G+T.

It is interesting to note that the current study noted a mPFS of 4.1 months for each treatment arm, including G+T, which was lower than the mPFS of 6.2 months noted in the initially reported studies of this regimen.[9] One contributing factor could have been the prior study's inclusion of patients with liposarcoma, who were excluded in the current trial, and variability in the distribution of other subtypes. The majority of the liposarcomas included were well-differentiated or dedifferentiated liposarcomas (5 cases), which tend to have a longer PFS, and were reported in the study by Maki et al[9] as having SD as the best response on the G+T arm. The remaining patients were those with pleomorphic liposarcomas, 2 of whom had PRs and 1 who had SD as a best response. However, the percentage of total patients with LMS was nearly identical (approximately 30%) between the current study and the prior one. There also could have been a difference in dose intensity. In the G+T arm in the current study, approximately 56% of patients required a dose reduction of docetaxel and 34% required a decrease in the gemcitabine dose. The study by Maki et al reported a dose intensity of 90% for G+T. Strict dose reduction guidelines in this study may have contributed toward a higher number of dose reductions. A French Sarcoma Group study (LMSO3)[23] examined the combination of G+P (gemcitabine at a dose of 1000 mg/m^2 on days 1 and 8 with 800

mg daily of pazopanib for a maximum of 8 cycles followed by maintenance pazopanib) for the treatment of LMS after the failure of first-line doxorubicin chemotherapy. The 9-month PFS rate was 32% in this single-arm study, which was lower than the prespecified target PFS rate of 44%, making it a negative study. Patients treated with the same starting doses of G+P as in this study demonstrated a PFS of 6.5 months (95% CI, 5.6-8.2 months), which was similar to that obtained for G+T in the TAXOGEM study[10] for patients with LMS, again suggesting the similarity of these regimens. The higher sensitivity of patients with LMS to these chemotherapy agents might account for the higher PFS observed in the LMS03 and TAXOGEM studies compared with the current study, which included subtypes other than LMS.

Although cross trial comparisons are not statistically valid, the PFS result of 4.1 months for the G+P combination compares well with other gemcitabine combination regimens. A study of gemcitabine plus dacarbazine from the Spanish Sarcoma Group reported a PFS of 4.2 months[24] whereas the same group also examined the use of gemcitabine plus sirolimus, resulting in a PFS of 1.8 months.[25] A single-institution study of gemcitabine and vinorelbine[26] produced a PFS of 3.4 months. These studies all focused on patients with STS, albeit with different eligibility criteria. Nonetheless, the activity of G+P appears to compare favorably with that noted among these other phase 2 studies.

Our crossover data were limited by the small number of patients. The reasons for the low rate of crossover were multifactorial; toxicity was not an allowable reason to cross over and RECIST PD was required, and these regimens, especially G+T, were available off study and could be administered at local centers. In our small data set, patients who switched from G+T to G+P (13 patients) appeared to benefit more (PR rate of 15%; mPFS, 6.4 months) than patients switching from G+P to G+T (9 patients; PR rate of 0%; mPFS, 1.3 months). However, after G+T, it is difficult to ascertain whether combining gemcitabine with pazopanib adds to the use of pazopanib alone. Results from the PALETTE study of pazopanib versus placebo demonstrated a response rate of 6% for pazopanib alone, with a mPFS of 4.6 months.[13] For patients who progress while receiving the G+T regimen, the current standard recommendation would be for single-agent pazopanib.

The side effects of the G+P therapy were consistent with the expected side effects of pazopanib and gemcitabine. The major toxicities of grade ≥3 included neutropenia (49%), thrombocytopenia (49%), anemia (20%), hypertension (20%), fatigue (13%), lymphopenia (11%), ALT increase (9%), and thromboembolic events (4%), all of which have been detailed previously. Although the side effects with the use of G+T were different, with a higher incidence of leg edema noted, the overall number of grade 3 and 4 toxicities was not significantly different between the 2 regimens. These toxicities associated with docetaxel occasionally make it challenging to continue using G+T as a long-term regimen.

When G+P was administered at a starting dose of 1000 mg/m^2 of gemcitabine on days 1 and 8 and 800 mg daily of pazopanib (Table 6), the results of the current study suggested that approximately 70% of patients may require 1 or multiple dose reductions for gemcitabine and a similar percentage for pazopanib. The lack of or infrequent use of granulocyte colony-stimulating factor in this treatment arm likely contributed to the higher rates of neutropenia observed. A similar rate of grade ≥3 toxicity (87%) was reported on the recent LMS03 study, which used similar starting doses for G+P, with 53% of patients requiring dose reductions and 27% discontinuing therapy because of toxicity.[23] On the basis of these findings, patients most likely should initiate therapy at lower starting doses, with doses being escalated or de-escalated based on patient tolerance. The majority of patients were able to maintain dosing of gemcitabine of ≥800 mg/m^2, whereas approximately 50% of patients ultimately experienced a dose reduction of pazopanib to 400 mg daily in the G+P arm. This suggests that the combination of G+P would be better tolerated with gemcitabine administered at a dose of 900 mg/m^2 on days 1 and 8 with pazopanib at a dose of 400 mg of daily, allowing, if well tolerated, for dose escalation by 200 mg each cycle to a maximum dose of 800 mg daily. For G+T, we would recommend the starting dose of gemcitabine to be 900 mg/m^2 on days 1 and 8, with docetaxel administered at a dose of 75 mg/m^2 on day 8, as is often used in standard practice.

The results of the current study have suggested the similarity of the G+P regimen compared with G+T with regard to efficacy and tolerability. In patients who are not suitable for treatment with G+T (because of a contraindication or intolerance to docetaxel), G+P would be a reasonable alternate regimen for the second-line treatment of those with metastatic nonadipocytic sarcomas.

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CONFLICT OF INTEREST DISCLOSURES

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