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ORIGINAL REPORT

Randomized Phase II Study of Gemcitabine and Docetaxel Compared With Gemcitabine Alone in Patients With Metastatic Soft Tissue Sarcomas: Results of Sarcoma Alliance for Research Through Collaboration Study 002

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ABSTRACT

Purpose
Gemcitabine as a single agent and the combination of gemcitabine and docetaxel have activity in patients with metastatic soft tissue sarcoma. To determine if the addition of docetaxel to gemcitabine improved clinical outcome of patients with metastatic soft tissue sarcomas, we compared a fixed dose rate infusion of gemcitabine versus a lower dose of gemcitabine with docetaxel.

Patients and Methods
In this open-label phase II clinical trial, the primary end point was tumor response, defined as complete or partial response or stable disease lasting at least 24 weeks. A Bayesian adaptive randomization procedure was used to produce an imbalance in the randomization in favor of the superior treatment, accounting for treatment-subgroup interactions.

Results
One hundred nineteen of 122 randomly assigned patients had assessable outcomes. The adaptive randomization assigned 73 patients (60%) to gemcitabine-docetaxel and 49 patients (40%) to gemcitabine alone, indicating gemcitabine-docetaxel was superior. The objective Response Evaluation Criteria in Solid Tumors response rates were 16% (gemcitabine-docetaxel) and 8% (gemcitabine). Given the data, the posterior probabilities that gemcitabine-docetaxel was superior for progression-free and overall survival were 0.98 and 0.97, respectively. Median progression-free survival was 6.2 months for gemcitabine-docetaxel and 3.0 months for gemcitabine alone; median overall survival was 17.9 months for gemcitabine-docetaxel and 11.5 months for gemcitabine. The posterior probability that patients receiving gemcitabine-docetaxel had a shorter time to discontinuation for toxicity compared with gemcitabine alone was .999.

Conclusion
Gemcitabine-docetaxel yielded superior progression-free and overall survival to gemcitabine alone, but with increased toxicity. Adaptive randomization is an effective method to reduce the number of patients receiving inferior therapy.

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INTRODUCTION

Soft tissue sarcomas are rare, accounting for less than 1% of all cancers that occur in the United States each year.[1] The standard of care for most primary soft tissue sarcomas is surgery, with radiation also used for larger primary extremity tumors.[2] Despite good local control, 40% to 50% of patients will develop distant recurrence, which is nearly always fatal.

The most active chemotherapy agents for metastatic soft tissue sarcoma are doxorubicin and ifosfamide.[2] Gemcitabine and docetaxel each have modest activity in sarcomas alone.[3-9] Gemcitabine may have greater activity when given as a fixed dose rate infusion (10 mg/m^2/min) compared with the recommended schedule (a 30-minute infusion).[4,10] The combination of fixed dose rate infusion gemcitabine and docetaxel has been shown to be effective against metastatic leiomyosarcoma (LMS)[11] and other soft tissue sarcomas.[12,13] However, it is unclear if the activity of the combination is due to the prolonged infusion of gemcitabine or synergy between the two drugs.

We therefore conducted a multicenter, open-label, phase II study of gemcitabine given via fixed dose rate infusion versus a lower dose of fixed dose

rate infusion gemcitabine with docetaxel in patients with metastatic soft tissue sarcomas. The goal was to select the better of two treatment regimens, within each of the four prognostic subtypes, defined by LMS histology versus other, and prior pelvic irradiation versus none.

PATIENTS AND METHODS

Study Design

In the gemcitabine-only arm, gemcitabine was administered as a fixed dose rate of 10 mg/m^2/min[10] during a 120-minute intravenous infusion, at 1,200 mg/m^2 days 1 and 8, every 21 days. In the gemcitabine-docetaxel arm, the gemcitabine dose was a fixed dose rate 900 mg/m^2 intravenous infusion during 90 minutes days 1 and 8, with docetaxel 100 mg/m^2 intravenously during 60 minutes day 8, every 21 days. Gemcitabine and docetaxel were provided by the manufacturers and distributed by a third-party central pharmacy to participating sites. Filgrastim 5 μg/kg subcutaneously daily for 7 to 10 days, or pegfilgrastim 6 mg subcutaneously once, was administered to all patients starting on day 9 to 10 of each cycle. Up to two 25% dose reductions of each agent were permitted in subsequent cycles of therapy for patients experiencing febrile neutropenia (temperature $>$ 38°C with neutrophil count $<$ 1,000/μL), grade $\geq$ 2 neuropathy, grade $\geq$ 3 liver function test abnormalities, or other grade 3 to 4 nonhematologic toxicity. Patients with prior pelvic irradiation started therapy with 25% dose reductions. The clinicaltrials.gov identifier for this study was NCT00142571.

The study was performed at eight Sarcoma Alliance for Research through Collaboration sites in the United States. An institutional review board or ethics committee approved the study protocol and the informed consent form at each site. Each participant provided written informed consent. Patients were stratified at the time of enrollment according to histology (LMS versus other) and prior pelvic radiation. Given that we used an outcome adaptive randomization (AR) procedure based on the interim data, data were collected and analyzed continuously during the trial. Specifically, once a result was entered by a treating institution, those data were immediately incorporated into the randomization model. Data were collected from each participating institution via a secure Web site in the Biostatistics and Applied Mathematics department of M.D. Anderson Cancer Center (Houston, TX) and analyzed automatically each time a patient was randomly assigned. Response Evaluation Criteria in Solid Tumors (RECIST)[14] response determinations were made by radiologists familiar with sarcomas at the treating institutions; these images were not reviewed centrally.

Eligibility Criteria

Patients were eligible if they met the following criteria: diagnosis of soft tissue sarcoma (excluding GI stromal tumor and Kaposi sarcoma); age older than 10 years; recurrent or progressive disease by examination or imaging studies; lack of clinical evidence that a second cancer, if present, was the disease requiring therapeutic intervention; zero to three prior chemotherapy regimens; disease measurable per RECIST; Eastern Cooperative Oncology Group (ECOG) performance status (PS) $\leq$ 2; peripheral neuropathy grade $\leq$ 1 by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 3.0; at least 3 weeks since prior radiation or cytotoxic chemotherapy; neutrophil count $\geq$ 1,000/μL, hemoglobin $\geq$ 8.0 g/dL; platelet count $\geq$ 100,000/μL; total bilirubin $\leq$ institutional upper limit of normal; ALT and AST $\leq$ 5$\times$ the institutional upper limit of normal; alkaline phosphatase $\leq$ 2.5$\times$ the institutional upper limit of normal; serum creatinine $\leq$ 2.0 mg/dL, negative serum pregnancy test in women of child-bearing potential; use of effective contraception while on study; and ability to provide written informed consent. Patients were excluded if active or uncontrolled infection was present, if prior therapy with gemcitabine or docetaxel had been administered, if a known hypersensitivity to polysorbate 80 was present, if the patient was pregnant or lactating, or if uncontrolled CNS metastases were present.

Clinical examinations and laboratory testing were performed at a screening visit, at the time of the first dose of therapy, and at the start of each subsequent cycle of therapy for as many as eight cycles of therapy. At that point, patients could either continue therapy or stop at the investigator's discretion. A physical examination, ECOG PS, complete blood count, and biochemical profile were performed on day 1 of each cycle of therapy, and complete blood counts were continued weekly for at least the first six cycles of therapy. Tumors were measured or imaged again after every two cycles of therapy.

Statistical Methods

The primary end point of the study was tumor response, defined as complete or partial response within 24 weeks, or stable disease lasting at least 24 weeks. Bayesian AR was used to assign patients to the two treatment arms, based on the estimated probabilities of treatment success (S), defined as RECIST complete or partial response at the end of two, four, six, or eight 3-week cycles of therapy, or stable disease through all eight cycles, and treatment failure (F), defined as RECIST disease progression or death during any of the eight cycles.[15] Patients' data for application of the AR procedure were recorded based on the first finding of RECIST response or failure. A RECIST confirmed response was not used by the AR procedure. Denoting the S and F probabilities of these events by P_S and P_F, respectively, the AR procedure was based on the weighted average $P = .435(P_S) + 0.565(1 - P_F)$; the weights reflect the utilities elicited from the investigators that nonfailure was 30% more important than treatment success.

The AR method allowed for possible treatment-subgroup interactions for the four subgroups: LMS, prior pelvic radiation (PPR); non-LMS, PPR; LMS, no PPR; or non-LMS, no PPR. Thus, the value of P was permitted to vary among the four subgroups depending on treatment-subgroup interactions.[15] Toxicity was evaluated using NCI CTCAE version 3.0. Patients were assessed on an intention-to-treat basis with respect to overall survival. For progression-free survival (PFS), patients were observed from the first day of treatment until progression, toxicity, or completion of at least eight cycles (24 weeks) of therapy. Patients stopping treatment due to toxicity before the first radiologic evaluation on therapy were removed from study and deemed inassessable for response (n = 1, gemcitabine; n = 3, gemcitabine-docetaxel); these four patients were observed for overall survival (OS). Patients developing toxicity after at least one radiologic assessment were censored at the time of their toxicity, and their evaluations were used by the randomization model. Thus, stable disease at a re-evaluation was a positive development, in that treatment did not overtly fail.

Bayesian regression analyses of the ability of the covariates LMS, PPR, ECOG PS, and treatment to predict PFS and OS were conducted assuming a log-normal distribution for PFS or OS time.[16] The log-normal distribution was chosen based on preliminary goodness-of-fit analyses considering several possible models, including the Weibull, exponential, and log logistic. Model selection was based on posterior model probabilities[17] and the Bayes information criterion. Two log-normal regression models were fit, defined in terms of their linear predictors. The first model included only main effects, treatment + LMS + PPR + PS; the second model included these main effects plus treatment-covariate interactions. For each model, noninformative prior distributions were assumed on all parameters. All Bayesian computations were carried out in Winbugs V1.4[18] and using the custom program that was the basis for implementing the AR. All other computations were carried out in S-Plus (version 3.3; Statistical Sciences, Seattle, WA).[19]

RESULTS

During the recruitment period from January 2003 to December 2005, 122 patients at eight sites were randomly assigned using the AR procedure to receive gemcitabine with or without docetaxel. Accrual was terminated on January 1, 2006. The research database was locked on April 1, 2006. The disposition and baseline characteristics of the two treatment groups are listed in Table 1 and the CONSORT diagram (Fig 1). The median number of patients per site was 15 (range, two to 30).

Table 1. Patient Demographics and Clinical Characteristics

Characteristic	Gemcitabine		Gemcitabine-Docetaxel	
	No. of Patients	%*	No. of Patients	%*
Patients designated to receive treatment by adaptive randomization	49		73	
Age, years				
Median	55		55	
Range	21-79		23-80	
Female sex	26	53	33	45
Primary site (number of patients)				
Extremity/trunk	24	49	28	38
Retroperitoneal/abdominal	23	47	41	56
Other	2	4	4	5
Prior pelvic radiation	11	22	18	25
Histology				
Leiomyosarcoma	9	18	29	40
Nonleiomyosarcoma	40	82	44	60
Liposarcoma	12		8	
Malignant fibrous histiocytoma/high-grade undifferentiated pleomorphic sarcoma	8		11	
Other	20		25	
Prior lines of therapy				
Median	1		1	
Mean	1.1		1.1	
Median initial ECOG performance status	0		0	
Median cycles of therapy administered	4		4	
Subsequent anthracycline-based therapy	5	10	10	14

Abbreviation: ECOG, Eastern Cooperative Oncology Group.
*Numbers may not add up to 100% because of rounding.

Outcome of the AR Procedure

The median number of prior therapies received by patients in both study arms was one (mean, 1.1; Table 1). After equal random assignment of the first 30 patients to the two treatment regimens, subsequent patients were assigned treatment using the AR procedure.[15] After the study completed enrollment, the principal investigator found that 12 of the first 17 patients were miscategorized as having LMS when they actually had another sarcoma subtype. Given that these data were entered incorrectly at the time of patient randomization, the sizes of the imbalances within subgroups were altered when histologic assignments were corrected. Specifically, the odds of being randomly assigned to the gemcitabine-docetaxel arm were decreased on the LMS arm, and increased on the non-LMS arm as a result of the data entry errors. Fortunately, given that no treatment-subgroup interactions occurred, the imbalance remained in favor of the superior treatment arm in all four subgroups. The corrected pathology data were used to calculate the final patient randomization criteria listed in Table 2.

Table 2 lists the posterior probability that the AR criterion for gemcitabine-docetaxel (P_{G+D}) is larger than for gemcitabine alone (P_G) within each prognostic subgroup, determined by LMS histology and prior pelvic radiation. Larger probabilities correspond to greater superiority of gemcitabine-docetaxel over gemcitabine, in terms of the 24-week outcome.

Seventy-three patients (60%) were randomly assigned to gemcitabine-docetaxel and 49 patients (40%) were randomly assigned to gemcitabine alone by the AR procedure, indicating that gemcitabine-docetaxel had superior outcomes as defined, compared with gemcitabine alone. Given the final data, the posterior probability that the two-drug combination was superior to gemcitabine alone was .98 for PFS for all subgroups, and .97 for OS (Table 3).

Clinical Outcomes

The primary end point (complete or partial response, or stable disease after more than 24 weeks) was reached by 13 patients (27%) receiving gemcitabine and 23 patients (32%) receiving gemcitabine-docetaxel. Eighteen patients (37%) receiving gemcitabine experienced disease progression at first re-evaluation, whereas 18 patients (25%) receiving gemcitabine-docetaxel experienced disease progression at the first reassessment.

The RECIST partial response rate for patients receiving gemcitabine-docetaxel (16%; 12 of 73) was greater than the partial response rate for gemcitabine alone (8%; four of 49; Table 3), and includes two unconfirmed RECIST partial responses (gemcitabine, malignant fibrous histiocytoma/high-grade undifferentiated pleomorphic sarcoma [MFH/HGUPS]; gemcitabine-docetaxel, uterine LMS). One of nine LMS patients receiving gemcitabine had a partial response (11%), compared with five of 29 (17%) who received gemcitabine-docetaxel. Six of 19 patients (32%) with MFH/HGUPS experienced partial responses (two of eight receiving gemcitabine, and four of 11 receiving gemcitabine-docetaxel, including one complete response). Best responses by treatment arm and histology are listed in Table 4.

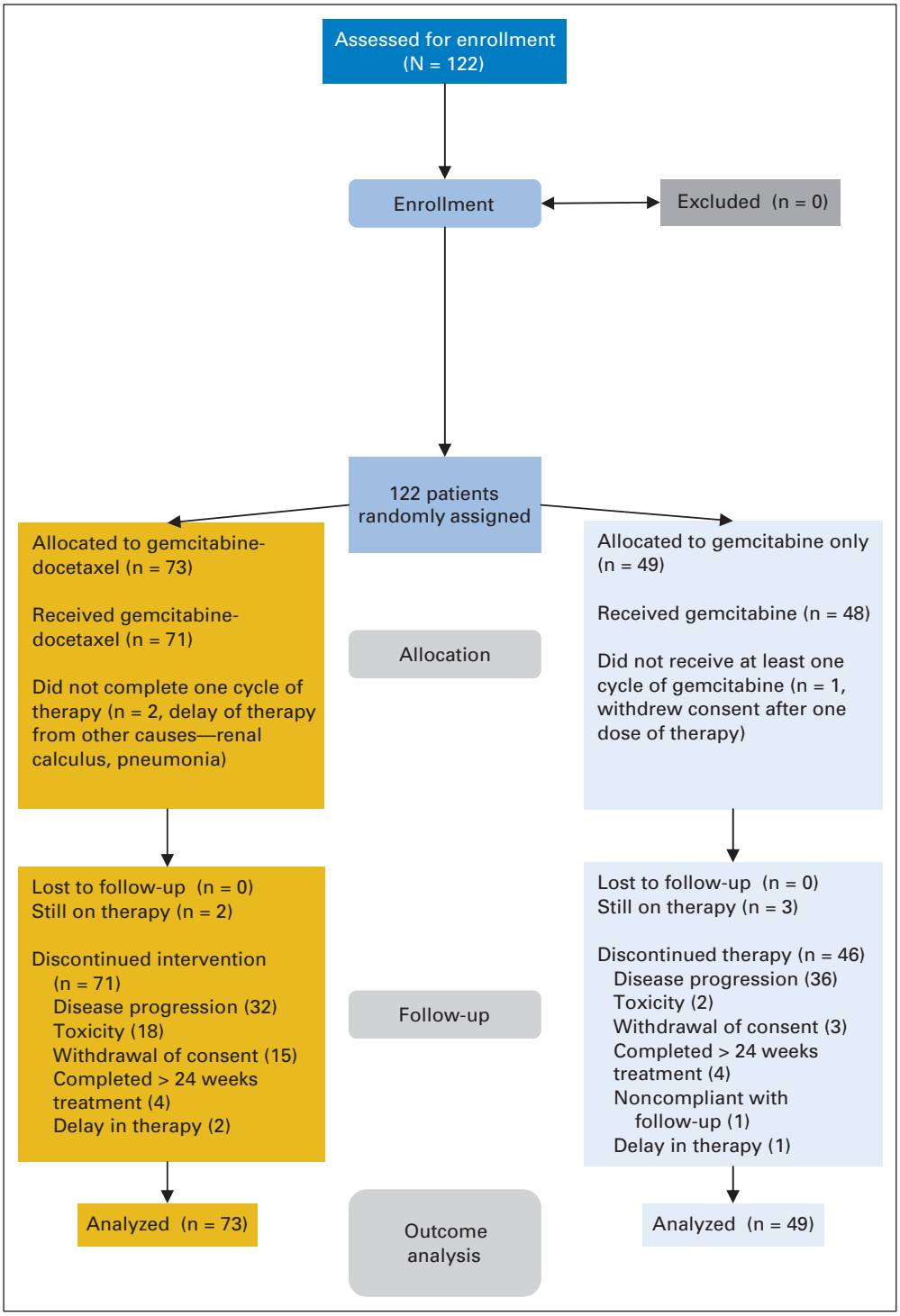

Fig 1. CONSORT diagram.

Appendix Tables A1 and A2 (online only), and Fig A1 (online only) summarize the fitted Bayesian log-normal model for PFS. The survival models with treatment-covariate interactions had inferior fit when compared with the model without interactions; thus, we only present the results for the main effects model. Statistical details for the main effects model have been described[15] and are outlined in the Appendix. To interpret the results in Table A1, Pr is the posterior probability that the *j*th covariate is significant, given the data, beta is the coefficient for a given covariate, and the coefficient for the *j*th predictor is denoted by β_j. Values of $\Pr(\beta_j > 0 \mid \text{data})$ closer to either 0 or 1 correspond to a stronger effect of the predictor, and values close to .5 correspond to no effect. The fitted model indicates that gemcitabine-docetaxel therapy (represented by GD in the following equations) is associated with a longer PFS time than gemcitabine alone in all groups, $\Pr(\beta_{GD} > 0 \mid \text{data}) = .98$. The superiority of gemcitabine-docetaxel over gemcitabine in terms of PFS is consistent with the results of the

Table 2. Summary of Adaptive Randomization

Subgroup	Gemcitabine			Gemcitabine-Docetaxel			Adaptive Randomization Criterion $Pr(P_{G+D} > P_G \mid data)$†
	No. of Patients	No. Experiencing Treatment Failure	% on Specific Study Arm*	No. of Patients	No. Experiencing Treatment Failure	% on Specific Study Arm*	
LMS, no PPR	6	6	12	19	9	26	.52
LMS, PPR	3	2	6	10	5	14	.91
Non-LMS, no PPR	32	23	65	36	19	49	.79
Non-LMS, PPR	8	8	16	8	6	11	.97
Total	49	39		73	39		

Abbreviations: LMS, leiomyosarcoma; PPR, prior pelvic radiation.
*Percentages may not add up to 100% because of rounding.
†Probability that treatment with gemcitabine-docetaxel is better than gemcitabine given the data, using the success criterion noted in Statistical Methods. The criterion was recalculated after identifying clerical errors regarding patient pathology diagnosis, which affected the randomization model.

24-week outcome summarized in Table 2. Median PFS was 6.2 months for gemcitabine-docetaxel versus 3.0 months for gemcitabine alone (Table 3). Patients were also analyzed by stratifying for ECOG PS (PS = 0 *v* PS > 0; Table A3, online only). ECOG PS was also a prognostic factor, $Pr(\beta_{PS>0} > 0 \mid data) = .01$ (ie, PS > 0 was prognostic of a shorter PFS; Appendix Table A1, online only). Figures 2A and 2B and Appendix Tables A2 and A4 (online only) provide PFS and OS data for subgroups stratified by ECOG PS.

OS was also longer for patients receiving gemcitabine-docetaxel than single-agent gemcitabine. The Kaplan-Meier curves for OS by ECOG PS are shown in Figures 2C and 2D, and for each of the subgroups (based on histology and prior pelvic irradiation) in Appendix Figure A2 and Tables A4 and A5 (online only). Median OS was 17.9 months with gemcitabine-docetaxel versus 11.5 months with gemcitabine. The posterior probability that median OS with gemcitabine-docetaxel was greater than with gemcitabine is $Pr(\beta_{GD} > 0 \mid data) = .97$, and is the same for all subgroups because there was no treatment-covariate interaction (Appendix Fig A3, online only).

Safety and Tolerability

The safety analysis is based on the 120 patients who received at least one dose of chemotherapy. Twenty-six percent of patients receiving gemcitabine and 46% patients receiving gemcitabine-docetaxel required at least one dose reduction. The mean dose intensities per cycle were 94% (gemcitabine) and 90% (gemcitabine-docetaxel). Toxicity by patient is listed in Table 5. The most common NCI CTCAE grade 3 to 4 toxicity was thrombocytopenia (46 of 120 assessable patients; 38%). Febrile neutropenia was observed in seven of 120 patients (6%). Grade 3 fatigue and/or grade 3 myalgias or muscle weakness were observed in 25% of patients receiving gemcitabine-docetaxel versus 10% of patients receiving gemcitabine only. Despite planned dose reductions, patients were removed from study more frequently on the combination arm (Fig 2E). When a Bayesian analysis with uninformative priors is to calculate the median time to removal for toxicity on each treatment arm, there is a .999 probability that the median time to removal for toxicity is shorter with gemcitabine-docetaxel than with gemcitabine alone.

DISCUSSION

OS and PFS were superior with gemcitabine-docetaxel versus gemcitabine alone (17.9 *v* 11.5 and 6.2 *v* 3.0 months, respectively). This

Table 3. Clinical Outcomes

Outcome	Gemcitabine (n = 49)		Gemcitabine-Docetaxel (n = 73)		Probability That Gemcitabine-Docetaxel Is Superior
	No. of Patients	%*	No. of Patients	%*	
Best overall response					
Patients meeting primary end point (CR + PR + SD > 24 weeks)	13	27	23	32	
CR	0		2	3	
PR	4	8	10	14	
SD ≥ 24 weeks	9	18	11	15	
SD < 24 weeks	17	35	28	38	
Disease progression	18	37	18	25	
Not assessable	1	2	3	4	
Median progression-free survival (months)	3.0		6.2		.98
Median overall survival (months)	11.5		17.9		.97

Abbreviations: CR, complete response; PR, partial response; SD, stable disease.
*For patients on the specific arm of the study.

Table 4. Best Response by Treatment Arm and Histology*

Histology	Gemcitabine						Gemcitabine-Docetaxel					
	CR	PR	Stable Disease ≥ 24 Weeks	Stable Disease < 24 Weeks	Progressive Disease	Not Assessable	CR	PR	Stable Disease ≥ 24 Weeks	Stable Disease < 24 Weeks	Progressive Disease	Not Assessable
Leiomyosarcoma		1	2	5	1			5	3	13	8	
MFH/HGUPS		2	2	1	3		1	3	3	2	1	1
Liposarcoma												
Well differentiated/dedifferentiated			2	3	3					4		1
Myxoid-round cell				2	1	1						
Pleomorphic								2		1		
Synovial sarcoma			1	1	2				1	1	2	1
Malignant peripheral nerve sheath tumor				1	1				1		3	
Unclassified sarcoma			1	2	1					1		
Fibrosarcoma			1		2				1	2		
Rhabdomyosarcoma							1				1	
Other sarcoma histology	1			2	4				2	4	4	

Abbreviations: CR, complete response; PR, partial response; MFH/HGUPS, malignant fibrous histiocytoma/high-grade undifferentiated pleomorphic sarcoma.
*Includes one Response Evaluation Criteria in Solid Tumors Group unconfirmed PR on each arm: gemcitabine (MFH/HGUPS); gemcitabine-docetaxel (uterine leiomyosarcoma).

finding compares favorably to randomized data from previous phase III studies of active chemotherapy agents in sarcoma (eg, 13.3 *v* 11.9 and 6.1 *v* 3.9 months, respectively, in the study of doxorubicin-dacarbazine with and without ifosfamide[20]). It is possible that a combination of factors that we did not incorporate into our model accounts for the differences in outcomes. For example, we did not examine the presence of age as a covariate in our model,[21] and 14% of patients (10 of 73) on the gemcitabine-docetaxel arm later received anthracycline-based therapy, compared with 10% of patients (five of 49) receiving gemcitabine alone. Nonetheless, this study shows the greatest difference in OS of any randomized study performed for metastatic soft tissue sarcoma, including studies that examined less heavily treated patients.[20,22-24] This study also confirmed prior experience that LMS and MFH/HGUPS[25] are relatively responsive to gemcitabine-docetaxel.[11-13]

The reason LMS and MFH/HGUPS respond better to this combination is unknown. Both LMS and MFH/HGUPS are tumors with aneuploid karyotypes, unlike the approximately 25% to 30% of translocation-associated sarcomas. LMS and MFH/HGUPS are different qualitatively from well-differentiated and dedifferentiated liposarcomas, which are also aneuploid, but have ring and giant chromosomes bearing amplification of chromosome 12q and genes *CDK4* and *HDM2*.[25] Interestingly, patients with pleomorphic liposarcoma also responded to this combination; pleomorphic liposarcomas appear more like MFH/HGUPS than other sarcomas by gene expression array analysis.[26] These data support the idea that as high-grade sarcoma genotypes evolve, they lose features consistent with their primary lineage, reaching a more undifferentiated state. This also accounts for data that many MFH/HGUPS have features of other more differentiated sarcoma subtypes.[27]

Although hematologic toxicity was similar in both treatment arms, more than 40% of patients receiving gemcitabine-docetaxel discontinued treatment for a variety of nonhematologic toxicities within 6 months of therapy, despite dose reductions. Constitutional symptoms such as myalgias and fatigue were the most significant cumulative adverse effects of gemcitabine-docetaxel, suggesting that the dose and schedule used in this study are too high for long-term use. Nonetheless, the relative ease of administration and toxicity profile of gemcitabine-docetaxel compare favorably with that of doxorubicin-ifosfamide, another commonly used combination in metastatic soft tissue sarcomas.

Bayesian AR was first proposed in 1933.[28] AR was first used in a study of extracorporeal membrane oxygenation for respiratory failure.[29] Bayesian study designs have been used in clinical trials involving anesthesia,[30] stroke,[31,32] and medical devices.[33] The US Food and Drug Administration recently issued draft guidance for use of Bayesian statistical designs in medical device clinical trials, reflecting increased acceptance of these designs in the medical and regulatory communities.[34] Notably, although Bayesian study designs have been used in numerous phase I and standard phase II trials by oncologists,[35-39] AR has been used infrequently. Although standard so-called frequentist phase III study designs examine long-term trends of repeated random events, Bayesian designs use an approach of assigning a prior belief of an event, and observing how that prior belief is modified by the data, yielding a posterior probability. Thus, rather than using traditional *P* values for comparing treatment arms, Bayesian methods use posterior probabilities and credible intervals to quantify the treatment effect magnitude, which provide an intuitive way to think about outcomes of a clinical study such as this one.

We enrolled 73 patients on the superior treatment and 49 on the inferior treatment. Thus, 24 more patients (20%) enrolled on study received superior therapy or avoided inferior therapy than would have been the case with conventional 1:1 randomization. This trial highlights AR as clinically and ethically attractive for comparative trials of new systemic agents for metastatic cancer, given that data can be fed quickly back into a randomization model in real time to treat potentially fewer patients with inferior therapy in comparison to standard frequentist clinical trial designs. In any case, due to the likelihood principle,[16] which states that all of the information for making statistical inferences is contained in the data actually observed, use of AR to conduct the trial does not invalidate its results in comparison to traditional randomized study designs.

The use of Bayesian analysis of a standard clinical trial design was highlighted recently in an editorial commenting on a phase III

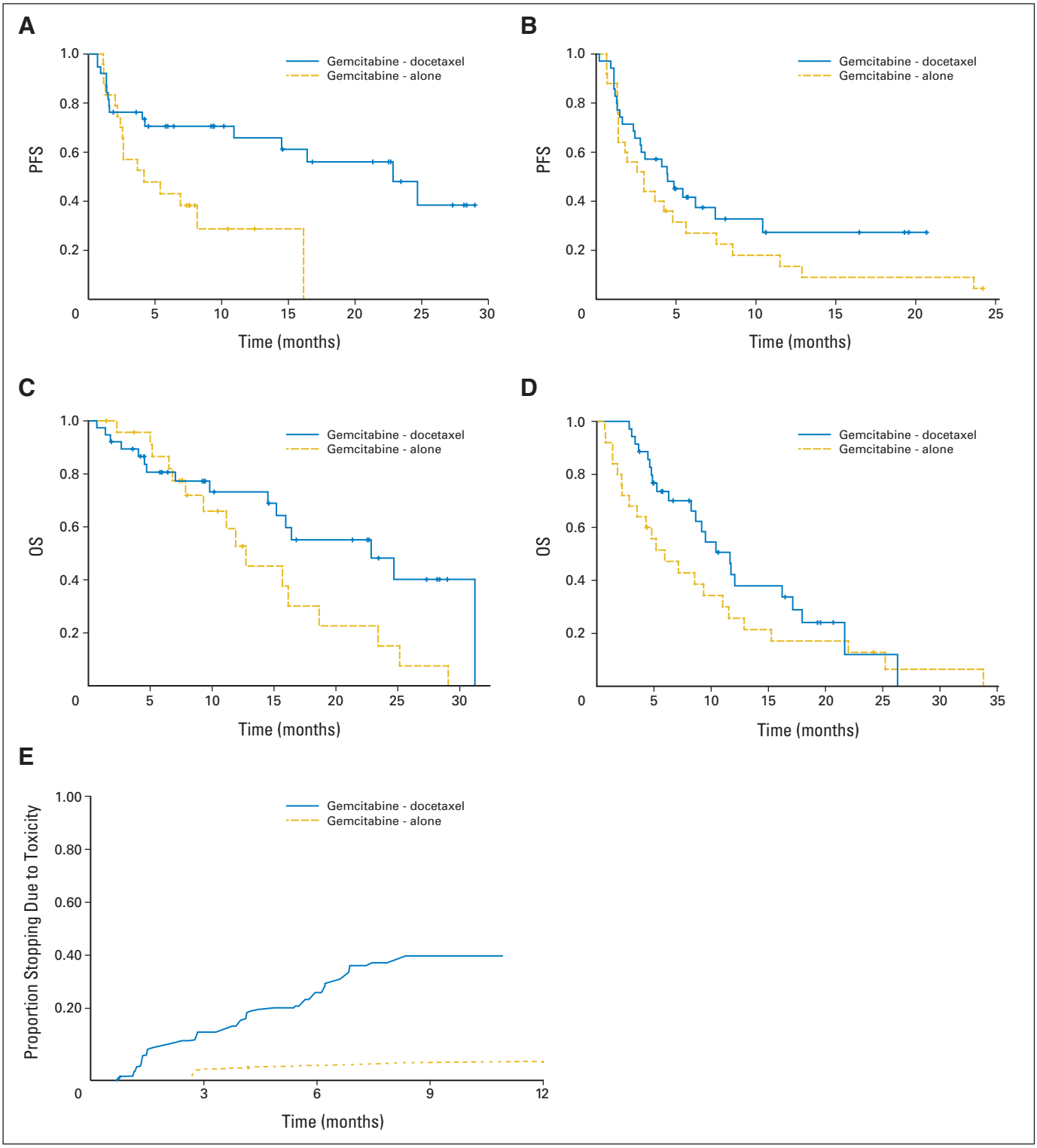

Fig 2. Kaplan-Meier curves for (A, B) progression-free survival (PFS) and (C, D) overall survival (OS) for patients with Eastern Cooperative Oncology Group (ECOG) performance status (A, C) 0 and (B, D) more than 0 in the gemcitabine and gemcitabine-docetaxel arms. (E) Cumulative probability of stopping therapy for toxicity as a function of time for each treatment arm.

randomized study of salmeterol and fluticasone in 6,112 patients with chronic obstructive pulmonary disease.[40] Despite the study size, the hazard ratio for death for patients receiving both agents versus placebo was only of borderline significance ($P = .052$). The editorial concluded, "Believe it or not, we still need more data, from even larger trials."[41] However, a Bayesian interpretation of the clinical trial was clear: "On further weighing these results, however, I think the treatment with long-acting beta agonists was a winner and that with

Table 5. Toxicity by Treatment Arm (by percentage of patients affected on the specific study arm)

Event	Gemcitabine (n = 49)	Gemcitabine-Docetaxel (n = 73)
Neutrophils, grade* 3-4	28%	16%
Hemoglobin, grade 3	13%	7%
Blood transfusion	20%	16%
Platelets, grade 3-4	35%	40%
Platelet transfusion	11%	15%
Febrile neutropenia	7%	5%
Pulmonary, grade 3-4	6%	7%
Fatigue, grade 3-4	8%	16%
Myalgias or muscle weakness, grade 3	2%	8%
All other,† grade 3	2%	23%

*By National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0.
†Includes (one each unless noted): deep venous thrombosis/pulmonary embolus (n = 5), nausea/vomiting or anorexia (n = 4), lymphopenia (n = 4), edema (n = 3), GI bleeding (n = 2), high serum glucose, abdominal pain, diarrhea, mucositis, cough, pleural effusion, hiccups, bone pain, back spasm/pain, rash, nail changes, hypokalemia.

inhaled corticosteroids was a clear loser."[41] However, Bayesian trial designs are not a panacea. Our study raises a note of caution to investigators interested in AR models. Despite involving centers familiar with sarcoma clinical trial conduct, clerical errors caused randomization misassignments when the randomization model was most sensitive to such errors.

We conclude that the combination of gemcitabine-docetaxel is superior to a higher dose of gemcitabine, given the data from this study, and conclude that the synergy of gemcitabine-docetaxel accounts for the bulk of the combination arm's activity, rather than the fixed dose rate infusion of gemcitabine. Given that RECIST response rates on both treatments were low, but a number of patients had prolonged stable disease, our data also lend support to the idea of stable disease as an important clinical end point for patients with metastatic soft tissue sarcomas.[42]

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following authors or their immediate family members indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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Appendix

The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).