

ORIGINAL RESEARCH

Pemetrexed plus cisplatin in patients with previously treated advanced sarcoma: a multicenter, single-arm, phase II trial

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Background: Patients with advanced sarcomas have a poor prognosis and few treatment options that improve overall survival. We assessed the efficacy and tolerability of pemetrexed and cisplatin combination therapy in patients with refractory bone and soft tissue sarcoma (STS).

Patients and Methods: Patients were included in this multicenter, phase II study ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT03809637) identifier NCT03809637) if they progressed after receiving one or more chemotherapy regimens containing an anthracycline and/or ifosfamide. Pemetrexed was first administered intravenously, followed by cisplatin, over a cycle of 21 days, for a maximum of six cycles. The primary endpoint was a progression-free rate (PFR) at 3 months (3-month PFR).

Results: From January 2017 to September 2019, we enrolled 37 patients; of these, 73% had previously undergone three or more rounds of chemotherapy. Five patients (13.5%) exhibited objective responses, including two patients (2/6, 33.3%) with malignant peripheral nerve sheath tumors, one patient (1/4, 25%) with synovial sarcoma, one patient (1/4, 25%) with undifferentiated pleomorphic sarcoma, and one patient (1/4, 25%) with angiosarcoma. The median progression-free survival was 2.6 months, and the 3-month PFR was 45.9% ($n = 17$). None of the four patients with osteosarcoma exhibited objective responses or were progression free at 3 months. The most frequent treatment-related grade 3-4 toxicities included neutropenia (16.2%), anemia (13.5%), thrombocytopenia (13.5%), and fatigue (8.1%). Among 26 patients (70.3%) available for immunohistochemical assessments, patients in the low-excision repair cross-complementation group 1 (ERCC1) and low-thymidylate synthase expression groups showed a tendency for longer overall survival.

Conclusions: Combination therapy with pemetrexed and cisplatin was associated with clinically meaningful and sustained responses among patients with advanced and refractory STS. The combination therapy met its predefined primary study endpoint.

Key words: soft tissue sarcoma, bone sarcoma, pemetrexed, cisplatin, thymidylate synthase, excision repair cross-complementation group 1

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INTRODUCTION

Sarcomas are rare solid tumors that account for 1% of all adult malignancies.¹ These lesions are categorized as soft tissue sarcomas (STSs) or bone sarcomas that represent a heterogeneous group of mesenchymal malignancies with >50 histologic subtypes.² Eighty percent of sarcoma subtypes originate from soft tissue, while 20% originate from bone tissue. However, therapeutic studies of STS are currently limited because of disease rarity and heterogeneity. Despite advances made in the last few decades, the survival of patients with advanced, unresectable, or metastatic disease remains poor.^{3,4}

For patients at advanced disease stages, palliative chemotherapy is usually combined with doxorubicin- or ifosfamide-based regimens.⁵ Beyond first-line treatment, pazopanib, trabectedin, dacarbazine, and eribulin have been approved for treating some subtypes of sarcoma.⁶⁻⁸ However, these options are generally unsatisfactory because of their modest efficacy and high treatment-limiting toxicity. Although combination therapies have shown high response rates, the benefits are often outweighed by high rates of severe toxicity, including thrombocytopenia (~40%) and neutropenia (~16%).^{9,10} Moreover, because some treatment regimens are only effective in patients with a specific histology, the treatment options are further limited. Therefore, more effective and tolerable treatments are needed for pretreated patients with advanced or metastatic sarcoma.

Pemetrexed is a newly developed antifolate drug that targets multiple enzymes, such as thymidylate synthase (TS), dihydrofolate reductase, and glycinamide ribonucleotide formyl transferase, which are involved in DNA synthesis and folate metabolism. Pemetrexed has a wider activity range than the other antifolate predecessor, methotrexate,¹¹ and affects multiple inhibition pathways for several key folate-requiring enzymes. Based on this mechanism of action, several clinical trials have demonstrated the efficacy and safety of pemetrexed monotherapy in STS,¹² osteosarcoma,¹³ and various solid tumours.¹⁴⁻¹⁶ These studies reported that pemetrexed monotherapy showed modest response rates of only 3%-5% and 1-year overall survival (OS) rates of ~27%-31% in patients with advanced STS and osteosarcoma.^{12,13} Furthermore, several studies have demonstrated that in head and neck cancer, malignant pleural mesothelioma, and non-small-cell lung cancer, the combination of pemetrexed and cisplatin may show improved efficacy compared with pemetrexed or cisplatin alone.¹⁷⁻¹⁹ In addition, this combined regimen may have promising efficacy and may be well tolerated in patients with refractory osteosarcoma.²⁰ Therefore given the favorable toxicity profile and synergistic effects of pemetrexed and cisplatin, combination treatment using pemetrexed and cisplatin should be investigated further in advanced STS and osteosarcoma.

The aim of this phase II study was to evaluate the activity and tolerability of pemetrexed and cisplatin combination therapy in patients with refractory sarcoma. We prospectively analyzed the role of putative biomarkers in determining treatment responses using immunohistochemical staining of tumor tissue samples.

PATIENTS AND METHODS

Study design and participants

Patients were recruited to this multicenter, phase II trial from three centers in Korea ([ClinicalTrials.gov](https://clinicaltrials.gov) identifier NCT03809637).²¹ Patients were eligible to participate in the study if they were at least 19 years old with locally advanced or metastatic STS or bone sarcoma that was histologically confirmed by a central specialized pathologist (S.H.K). Patients were required to have documented

progressive disease after failure of first-line adriamycin and/or ifosfamide and advanced/metastatic disease. Eligible patients had an Eastern Cooperative Oncology Group performance status of 0-2, measurable disease per RECIST version 1.1, and adequate hematological, biochemical, renal, and liver function. Key exclusion criteria included gastrointestinal stromal tumor or Kaposi's sarcoma, surgery or radiotherapy to a major organ within 2 weeks immediately prior to enrollment, or symptoms or active treatment of central nervous system metastasis.

This trial was conducted in accordance with the guidelines of the International Conference on Harmonization of Good Clinical Practice and the ethical principles of the Declaration of Helsinki. All patients provided written informed consent. The protocol and any protocol modifications were approved by the Institutional Review Board of the Yonsei Cancer Center (IRB 4-2016-0389).

Procedures

Chemotherapy was repeated every 3 weeks for a maximum of six cycles, unless earlier evidence of disease progression or intolerance was observed in the study. On day 1 of each 21-day cycle, pemetrexed was administered intravenously at 500 mg/m² over 10 min, followed 30 min later by intravenous administration of cisplatin at a dose of 75 mg/m² over 2 h. Patients who did not progress after the completion of six cycles received maintenance therapy with pemetrexed monotherapy. Treatment was continued until disease progression, unacceptable toxicity, death, or discontinuation from study treatment due to any other reason. For patients unable to tolerate pemetrexed or cisplatin due to adverse events, a maximum reduction of two doses was allowed (dose level-1: 75% initial dose; level-2: 50% initial dose).

Vitamin B₁₂ (1000 mcg) was administered intramuscularly within 14 days prior to the first dose of pemetrexed, every 9 weeks (starting on the same day as the study treatment) thereafter, and 21 days after the last dose of pemetrexed.

Tumor response was assessed locally via computed tomography or magnetic resonance imaging per RECIST version 1.1. Images were collected at baseline, every 6 weeks for the first 12 weeks, and every 9 weeks thereafter (or sooner if clinically indicated), until disease progression, death, withdrawal of consent, loss to follow-up, or investigator decision. Toxicity was graded according to the Common Terminology Criteria for Adverse Events (version 4.03). Briefly, the drug dose was decreased by 25% if grade 3 nonhematologic toxicity or grade 4 hematologic toxicity occurred. Any patient requiring a three-dose reduction was discontinued from participation in the study.

Immunohistochemical staining for thymidylate synthase and excision repair cross-complementation group 1

Immunohistochemical staining was carried out using the D6G6 anti-excision repair cross-complementation group 1 (ERCC1) monoclonal antibody (Cell Signaling Technology, Danvers, MA), the TS106 anti-TS monoclonal antibody

(Dako, Glostrup, Denmark), and a DAKO Link 48 system (Dako). Following deparaffinization, heat-induced antigen retrieval was carried out using EnVision FLEX Target Retrieval Solution, High pH (Dako).

The nuclear and cytoplasmic staining of TS and ERCC1 was evaluated by a pathologist (SHK) blinded to the clinical information. Staining was scored using an intensity scale of 0-3. Then, the percentages of cells in each category were calculated to yield semiquantitative histologic scores (H-scores). Finally, each staining score was multiplied by the percentage of cells, and H-scores were used to divide the samples into subgroups with low (<median) or high expression (\geq median).

Statistical analysis and sample size calculation

The primary endpoint was the progression-free rate (PFR) at 3 months (3-month PFR), which was defined as the absence of progression at 12 weeks after enrollment, according to RECIST version 1.1. The secondary endpoints were OS, overall response rate (ORR), and safety profile. The exploratory endpoints were the analyses of prognostic biomarkers for therapeutic response based on TS and ERCC1 expression.

Simon's two-stage testing procedure was applied with the following hypothesis: success in $\leq 20\%$ of the patients was considered insufficient and did not warrant further investigation (i.e. $P_0 = 20\%$), whereas success in $\geq 40\%$ of the patients was considered sufficient and warranted further investigation (i.e. $P_1 = 40\%$), with $\alpha = 0.1$ and $\beta = 0.1$ for errors. If four or more patients among the first 17 patients were progression free at 3 months, accrual was

continued until a total number of 37 patients was achieved. If 11 or more of these 37 patients became progression free at 3 months, further investigation was warranted on such a combination.

The Kaplan–Meier method was used to estimate the survival rate, and differences were analyzed using the log-rank test. Progression-free survival (PFS) was measured from the first day of chemotherapy until disease progression or death. OS was measured from the date of diagnosis until the date of death from any cause. ORR was defined as best overall response of complete response plus partial response based on local investigator assessment. All tests were two-sided, and P values < 0.05 were considered to reflect statistically significant differences. All statistical analyses were carried out using Statistical Package for the Social Sciences (SPSS) software, version 18.0 (SPSS Inc., Chicago, IL).

RESULTS

Patient characteristics

Forty patients were recruited from January 2017 to September 2019 (Figure 1). Of these patients, 37 received one or more dose of study drug and three were excluded due to screening failure ($n = 2$) or consent withdrawal ($n = 1$). Table 1 summarizes the pretreatment characteristics. The commonly observed histologic subtypes included leiomyosarcoma ($n = 10$, 27%), malignant peripheral nerve sheath tumors (MPNSTs; $n = 6$, 16.2%), undifferentiated pleomorphic sarcoma ($n = 4$, 10.8%), and synovial sarcoma ($n = 4$, 10.8%). The median interval since the initial diagnosis was

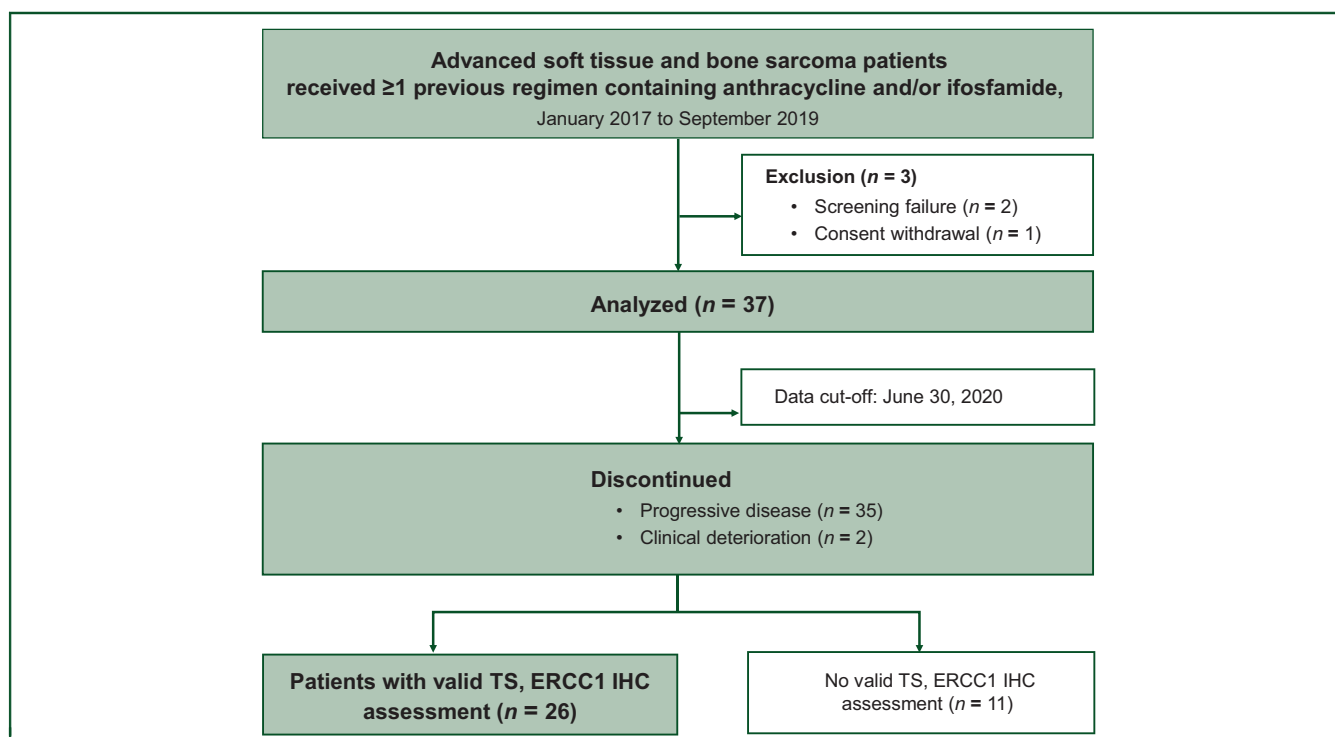


Figure 1. Consolidated Standards of Reporting Trials diagram.

ERCC1, excision repair cross-complementation group 1; IHC, immunohistochemistry; TS, thymidylate synthase.

Table 1. Baseline characteristics of the patients (N = 37)	
Characteristics	Values
Age, years, median (range)	48 (21-82)
Sex, n (%)	
Male	13 (35.1)
Female	24 (64.9)
ECOG, n (%)	
0	8 (21.6)
1	25 (67.6)
2	4 (10.8)
FNCLCC grade, n (%)	
1	2 (5.4)
2	10 (27.0)
3	16 (43.2)
Unknown	9 (24.3)
Number of previous chemotherapies, n (%)	
1	1 (2.7)
2	9 (24.3)
3	10 (27.0)
4	12 (32.4)
≥5	5 (13.5)
Type of previous chemotherapy received, n (%)	
Doxorubicin combination	31 (26.1)
Ifosfamide combination	10 (8.4)
Gemcitabine/docetaxel	28 (23.5)
Pazopanib	28 (23.5)
Doxorubicin monotherapy	6 (5.0)
Ifosfamide monotherapy	3 (2.5)
Taxane-based regimen	6 (5.0)
Cisplatin combination	6 (5.0)
Eribulin	1 (0.8)
Pathology, n (%)	
Leiomyosarcoma	10 (27.0)
Malignant peripheral nerve sheath tumor	6 (16.2)
Undifferentiated pleomorphic sarcoma	4 (10.8)
Synovial sarcoma	4 (10.8)
Osteosarcoma	4 (10.8)
Others ^a	9 (24.3)
Location, n (%)	
Extremities	11 (29.7)
Trunk	11 (29.7)
Abdomen/retroperitoneum	15 (40.5)

ECOG, Eastern Cooperative Oncology Group; FNCLCC, Fédération Nationale des Centres de Lutte Contre le Cancer.

^a Others: angiosarcoma (n = 4) liposarcoma (n = 1), alveolar soft part sarcoma (n = 1), myxofibrosarcoma (n = 1), hemangiopericytoma (n = 1), and rhabdomyosarcoma (n = 1).

2.5 years (range 0.4-11.1 years). The population was heavily pretreated, and the median number of previous lines of chemotherapy was 3 (range: 1-8).

Treatment, dose intensity, and tolerance

The median duration of exposure to pemetrexed and cisplatin was 63 days (range 15-420 days), and the median number of treatment cycles was 3 (range 1-19). Thirty-five of 37 patients (94.6%) stopped the study treatment due to disease progression, while two stopped treatment due to clinical deterioration.

The dose was reduced in 27% (n = 10) of patients and in 39.9% of treatment cycles. The cycle was delayed at least once in 18.9% (n = 7) of patients and in 5.9% of cycles. The median dose of pemetrexed was 463.4 mg/m², and the median relative dose intensity was 89.7%. The median dose of cisplatin was 66.1 mg/m², and the median relative dose intensity was 88.6%.

Supplementary Table S1, available at <https://doi.org/10.1016/j.esmooop.2021.100249>, summarizes all treatment-related toxicities. The most frequent hematologic toxicities were neutropenia (n = 9, 24.3%), thrombocytopenia (n = 9, 24.3%), and anemia (n = 7, 18.9%), with 16.2% and 13.5% of the patients experiencing grade 3-4 neutropenia and thrombocytopenia, respectively. Notably, one case of febrile neutropenia (2.7%) was observed. The most common treatment-related nonhematologic toxicities were fatigue (n = 8, 21.6%), nausea (n = 4, 10.8%), dyspepsia (n = 3, 8.1%), and peripheral neuropathy (n = 3, 8.1%). Treatment-related grade 3-4 nonhematologic events were limited to fatigue (n = 3, 8.1%) and creatinine level elevation (n = 1, 2.7%).

Tumor responses and survival outcomes

Data were collected until 30 June 2020. Among patients available for assessment at the primary endpoint, the 3-month PFR was 45.9% (n = 17; Table 2). Of the 37 evaluated patients, five achieved a partial response, 17 had stable disease, and 15 had progressive disease, resulting in an ORR of 13.5% (Figure 2A). The median time to response was 3.0 months (range 1.3-3.2 months), and the median duration of response was 2.0 months (range 1.1-8.3 months; Figure 2B). In total, 35 patients (94.5%) had progressive disease, with a median PFS of 2.6 months [95% confidence interval (CI) 0.9-4.2 months; Figure 2C]. After a median follow-up of 21 months (95% CI 9.8-41.3 months), 25 patients (67.6%) had died, with a median OS of 52 months (95% CI 30.5-73.5 months; Figure 2D).

Notably, the median PFS differed significantly according to the histological group (P = 0.024; Supplementary Figure S1A, available at <https://doi.org/10.1016/j.esmooop.2021.100249>): 5.2 months in patients with MPNSTs, 2.8 months in patients with synovial sarcoma, 2.6 months in patients with other STS subtypes, 1.6 months in patients with leiomyosarcoma, and 1.2 months in patients with osteosarcoma.

The different responses reported for each histologic subtype are shown in Supplementary Figure S1B, available at <https://doi.org/10.1016/j.esmooop.2021.100249> and Table 2. Five patients had partial responses: two patients (2/6, 33.3%) with MPNSTs, one patient (1/4, 25%) with synovial sarcoma, one patient (1/4, 25%) with undifferentiated sarcoma, and one patient (1/4, 25%) with angiosarcoma. However, none of the four osteosarcoma patients (three with osteoblastic type and one with chondroblastic type) exhibited an objective response.

Survival outcomes and correlations between ERCC1 and TS expression

Tissue sections from 26 of 37 patients (70.3%) were available for immunohistochemical assessments. Both TS and ERCC1 proteins mainly showed nuclear expression. Figure 3A and B show representative sections with different H-scores.

The median H-scores for TS and ERCC1 expression were 25 (range 0-240) and 60 (range 0-230), respectively. Using

Table 2. Response and status at 3 months after start of therapy and overall responses

Response/status	Leiomyosarcoma (n = 10)	Malignant peripheral nerve sheath tumor (n = 6)	Synovial sarcoma (n = 4)	Undifferentiated pleomorphic sarcoma (n = 4)	Osteosarcoma (n = 4)	Others ^a (n = 9)	Total (n = 37)
Best overall response							
Partial response	0	2	1	1	0	1	5
Stable disease	6	2	2	1	0	6	17
Progressive disease	4	2	1	2	2	1	12
Early death (progressive disease)	0	0	0	0	2	1	3
Response at 3 months							
Partial response	0	2	1	1	0	0	4
Stable disease	3	2	2	1	0	5	13
Progressive disease	6	2	1	1	1	3	14
Early death (progressive disease)	1	0	0	1	3	1	6
Number of patients progression free at 3 months	3	4	3	2	0	5	17
Proportion of patients progression free at 3 months, %	30.0	66.7	75.0	50.0	0	55.5	45.9

^a Others: angiosarcoma (n = 4), liposarcoma (n = 1), alveolar soft part sarcoma (n = 1), myxofibrosarcoma (n = 1), hemangiopericytoma (n = 1), and rhabdomyosarcoma (n = 1).

an optimal H-score cut-off point of 25, low TS expression (n = 13, 50%) was found to be associated with longer OS than high TS expression (n = 13, 50%), although this association was not significant (74.0 months; 95% CI 19.51-128.49 months versus 39.0 months; 95% CI 0.00-78.63 months; *P* = 0.096; Figure 3C). Using an optimal H-score cut-off point of 60, patients with low ERCC1 expression (n = 12, 46.1%) were found to show a tendency for longer OS than patients with high ERCC1 expression (n = 14, 53.9%), although this association was not significant (74.0 months; 95% CI 2.07-127.93 months versus 40.0 months 95% CI 15.56-64.45 months; *P* = 0.243; Figure 3D). The median PFS and ORR were not significantly different between patients with high and low TS and ERCC1 expression levels (Supplementary Figure S2, available at <https://doi.org/10.1016/j.esmooop.2021.100249>). In addition, there were no significant differences between TS and ERCC1 expression levels depending on the histologic subtype (Supplementary Figure S3, available at <https://doi.org/10.1016/j.esmooop.2021.100249>). There was no statistical significance, but 100% of undifferentiated pleomorphic sarcoma showed low TS and ERCC1 expression, whereas 100% of synovial sarcoma and MPNST showed high TS and ERCC1 expression.

DISCUSSION

The results of this study showed that combination treatment with pemetrexed and cisplatin was associated with clinically meaningful and sustained responses for patients with advanced and refractory STS. Although 73% of the patients enrolled in this study had previously been treated with three or more chemotherapy regimens, their 3-month PFR was found to be promising at 45.9%. These findings are considered clinically meaningful in the context of practically available salvage therapy options.

Single-agent anthracycline is the most widely accepted treatment option for advanced STS, with an ~20%

response rate.⁵ Combination chemotherapy with anthracycline and ifosfamide as first-line therapy has been reported to produce higher response rates of ~25%-30%.^{22,23} Given the limited improvements achieved with first-line treatments, several salvage treatments have received increasing attention during the last few decades, with objective responses of ~10%.^{7,8,10,24} Recently, several novel antineoplastic agents, such as trabectedin and eribulin monotherapy, were found to significantly improve the PFS or OS when compared with dacarbazine monotherapy.^{6,7} However, the relative benefits were modest, and histology-specific responses were reported. Therefore additional salvage treatments need to be investigated for more histologic subtypes of refractory STS and bone sarcoma.

Given the relatively low response in advanced sarcoma, the absence of progression at a fixed time point was explored as a new endpoint for conducting phase II trials. The European Organization for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group stated that a 3-month PFR of ≥40% correlates with survival and is suggested as a measure of drug activity for second-line therapy.²⁵ In this study, we found a 3-month PFR of 45.9%, with 27% of the patients being progression free at 6 months. Hence, our study met the predefined primary endpoint for demonstrating the efficacy of pemetrexed and cisplatin combination therapy, which supports its potential to serve as an alternative front-line therapy. Overall, 73% of patients in this study received three or more previous chemotherapy regimens including anthracycline and/or ifosfamide for advanced disease. These findings suggest that combined treatment with pemetrexed and cisplatin is effective and safe in a heterogeneous group with refractory STS.

Notably, the safety profile of the drugs used in this study was consistent with that observed for other approved indications.^{18,26} Up to 25% of patients experienced

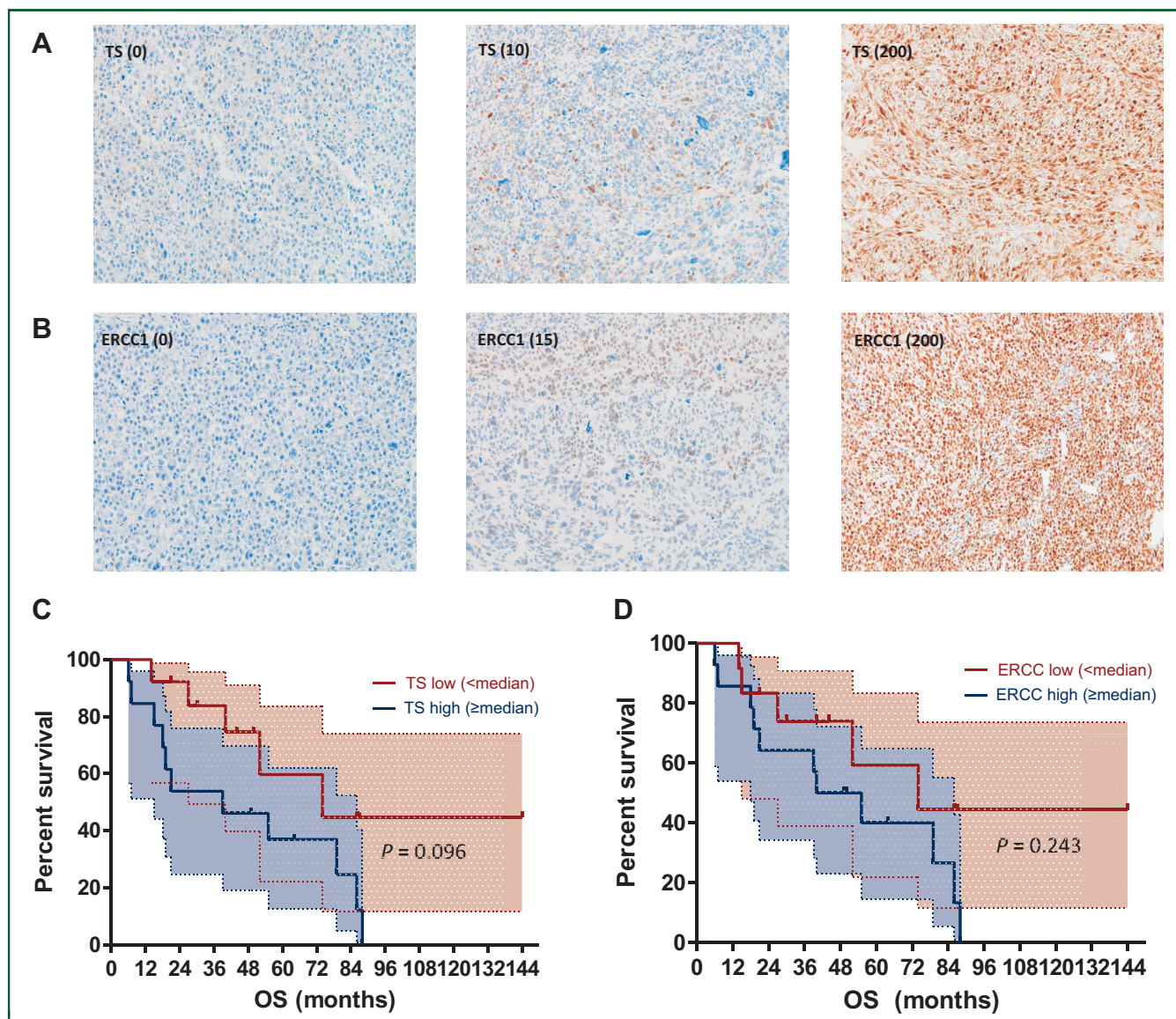


Figure 3. Survival outcomes according to excision repair cross-complementation group 1 (ERCC1) and thymidylate synthase (TS) expression. (A) Immunohistochemistry for TS expression in soft tissue sarcoma (STS). Representative images of both TS-negative (H-score: 0, ×200) and TS-positive (H-score: 10 and 200, ×200) sections. (B) Immunohistochemistry for ERCC1 expression in sections from patients with STS. Representative images of ERCC1-negative (H-score: 0, ×200) and ERCC1-positive sections (H-score: 15 and 200, ×200). (C) Kaplan–Meier analysis of overall survival (OS) according to TS expression, determined using a cut-off point of median H-score 25. (D) Kaplan–Meier analysis of OS according to ERCC1 expression, determined using a cut-off point of median H-score 60.

hematologic toxicities, and only 16% experienced grade 3-4 neutropenia. Nonhematologic grade 3-4 toxicities were infrequent and included fatigue, sensory neuropathy, and gastrointestinal toxic effects such as nausea and anorexia. In previous trials with gemcitabine and docetaxel, the percentages of patients with grade 3-4 neutropenia and thrombocytopenia were 10%-16% and 18%-40%, respectively. Although prophylactic hematopoietic growth factors were routinely used, a 5% incidence of febrile neutropenia was reported.^{10,27} For eribulin and trabectedin monotherapy, high rates of grade 3-4 neutropenia (35%-67%) and

thrombocytopenia (~17%) were reported with severe outcomes (12% febrile neutropenia).^{7,24} In our study, the combined pemetrexed and cisplatin therapy showed a manageable tolerability profile in patients with refractory sarcoma.

Four heavily pretreated patients with osteosarcoma were enrolled in this study. All of them had previously received adjuvant cisplatin-based regimens. The median time interval since previous cisplatin therapy was 20.5 months. However, none of the four osteosarcoma patients exhibited objective responses, and median PFS was only 1.2 months (95% CI

(A) Waterfall plot representing the percentage maximum tumor reduction after treatment, as assessed according to RECIST, version 1.1. The lower dotted line represents a tumor reduction of 30% according to the RECIST guidelines, which defines a partial response. Two patients with initial stable responses are indicated in blue [disease progression due to newly developed lesions (indicated with +)]. (B) Swimmer plot. Each lane represents data for a single patient. The x-axis represents the treatment duration for each patient. Closed triangles indicate the time of response per RECIST, version 1.1. Asterisks indicate that treatment was discontinued due to clinical deterioration. (C) Progression-free survival (PFS) for all patients. (D) Overall survival for all patients.

LMS, leiomyosarcoma; MPNST, malignant peripheral nerve sheath tumor; OS, osteosarcoma; SS, synovial sarcoma; UPS, undifferentiated pleomorphic sarcoma.

0.08-0.79 months). Metastatic osteosarcomas have a poor prognosis, and optimal management has not yet been defined by randomized clinical trials.^{28,29} Therefore, new therapeutic strategies and biomarkers of osteosarcomas are needed in clinical settings.

The results of this study showed that combined treatment with pemetrexed and cisplatin was associated with clinically meaningful objective responses in 13.5% of patients with STS. Despite this favorable efficacy, the mechanisms underlying such responses remain unclear, and certain types of sarcoma (i.e. osteosarcoma) may not benefit from this regimen. Recently, several translational studies have been conducted on the expression of molecular markers (such as TS, ERCC1, and regulatory ribonucleotide reductase catalytic subunit M1) in patients with lung and breast cancers who were treated with pemetrexed and cisplatin.³⁰⁻³³ Despite the controversial study results, it was observed that lower TS and ERCC1 levels were associated with better responses or survival. A significant survival benefit was observed among low ERCC1-expressing patients with non-small-cell lung cancer who received platinum-based chemotherapies.³³ In addition, ERCC1 overexpression indicated worse survival in osteosarcoma.^{34,35} A meta-analysis of the association between ERCC polymorphisms and osteosarcoma indicated that *ERCC1* rs11614 is associated with improved osteosarcoma prognosis.³⁶ This study also showed that patients with osteosarcoma had higher ERCC1 expression than those with other histologic subtypes, consistent with the poor prognosis findings from previous studies. However, in this study, single-nucleotide polymorphisms of ERCC in patients with osteosarcoma were not analyzed as predictive biomarkers of prognosis for pemetrexed and cisplatin. By contrast, several studies have investigated the prognostic or predictive value of the *ERCC1*, excision repair cross-complementation group 5/xeroderma pigmentosum group G (*ERCC5/XPG*), and breast cancer 1 (*BRCA1*) genes, which represent a potential DNA repair signature. Controversial results have been reported in patients with advanced STS who received other chemotherapies such as trabectedin.³⁷⁻³⁹ High expression levels of the common allele of *ERCC5* and *ERCC1* and *BRCA1* haplotypes were significantly associated with improved clinical response to trabectedin,³⁸ and the composite signature including low *BRCA1*, high *ERCC1*, and/or *ERCC5/XPG* mRNA expression was identified to indicate response to trabectedin treatment in advanced sarcoma.³⁹ Despite the lack of statistical significance due to the limitation of a small sample size, we observed that low TS and low ERCC1 expression levels tended to be correlated with better OS in patients with advanced sarcoma who were treated with pemetrexed and cisplatin, although there were no associations with PFS, response, or histologic subtypes (Supplementary Figures S2 and S3, available at <https://doi.org/10.1016/j.esmoop.2021.100249>). Although it did not reach statistical significance due to the small sample size, 100% of undifferentiated pleomorphic sarcoma showed low TS and ERCC1 expression, and 100% of synovial sarcoma and MPNST showed high TS and ERCC1 expression.

Alterations in folate pathway-related gene expression levels may result in different levels of pemetrexed efficacy, and such a correlation should be investigated in larger cohorts of patients with sarcoma.

Our study had several limitations. The main limitation was the nonrandomized, single-arm study design that was conducted without a central radiology review. Second, our sample size was too small to appropriately represent the large number of histologic sarcoma subtypes. Moreover, this study included patients with osteosarcoma who had received adjuvant cisplatin treatment. Despite the short median PFS and duration of response, our study met the primary endpoint of a 3-month PFR of at least 40%, which represents a clinically meaningful benefit in heavily pretreated patients with STS, particularly in patients with MPNSTs, who showed an ORR of 33.3% and a 3-month PFR of 66.7%, and in patients with synovial sarcoma, who showed a 3-month PFR of 75.0%. Because conventional agents have shown differing efficacies depending on the various histologic subtypes of STS, a confirmatory study to determine the clinical utility of a given regimen by subtype is also needed for pemetrexed and cisplatin combination therapy. Therefore, we intend to proceed with a phase II clinical trial (ALBATROSS; ClinicalTrials.gov identifier NCT04605770) to evaluate the efficacy and safety of pemetrexed and cisplatin combination therapy using histologic subtype-specific cohorts (synovial sarcoma, MPNST, leiomyosarcoma, and others) in patients with advanced, metastatic STS who have received up to two lines of prior palliative anticancer treatments. This would provide a basis for a subsequent phase III study wherein the efficacy of the study regimen would be evaluated in specific histologic subtypes selected based on the findings of the phase II clinical trial.

Conclusions

Overall, our results showed that combined treatment with pemetrexed and cisplatin showed acceptable toxicity and promising preliminary activity in heavily treated patients with advanced STS. The role of potential biomarkers in individual sarcoma subtypes should be validated in independent cohorts with larger sample sizes.

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DISCLOSURE

The authors have declared no conflicts of interest.

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