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# Real-world comparison of doxorubicin–ifosfamide versus gemcitabine–docetaxel regimens in metastatic uterine leiomyosarcoma: a multicenter retrospective study

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## Abstract

**Background** Uterine leiomyosarcoma is a rare and aggressive malignancy with limited responsiveness to standard therapies. We conducted a real-world, multicenter study to compare the clinical efficacy and safety of two commonly used first-line chemotherapy regimens—doxorubicin–ifosfamide and gemcitabine–docetaxel—in patients with metastatic uterine leiomyosarcoma.

**Methods** This retrospective cohort included 271 patients with advanced or metastatic uterine leiomyosarcoma treated between 2010 and 2023 across 30 centers in Turkey. Patients received either doxorubicin–ifosfamide (n = 142) or gemcitabine–docetaxel (n = 129) as first-line therapy. The primary endpoint was overall survival; secondary endpoints included progression-free survival, objective response rate, disease control rate, and safety. Adverse events were graded according to the Common Terminology Criteria for Adverse Events version 5.0, while survival outcomes were estimated using the Kaplan–Meier method and further analyzed with Cox proportional hazards models.

**Results** Median overall survival was 19.7 months with doxorubicin–ifosfamide and 20.2 months with gemcitabine–docetaxel (P = .26). Median progression-free survival was 5.5 months with doxorubicin–ifosfamide and 7.0 months with gemcitabine–docetaxel (P = .62). The objective response rate was numerically higher with gemcitabine–docetaxel (35% vs. 26%), although not statistically significant (P = .11).



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Grade 3–4 neutropenia (16% vs. 12%) and febrile neutropenia (7% vs. 6%) were more frequent with doxorubicin–ifosfamide.

**Conclusions** In this largest-to-date real-world cohort of metastatic uterine leiomyosarcoma, doxorubicin–ifosfamide and gemcitabine–docetaxel demonstrated comparable survival outcomes. Gemcitabine–docetaxel, however, was associated with a more favorable hematologic safety profile. These findings support the clinical utility of both regimens while underscoring the need for prospective, biomarker-driven studies to refine treatment selection and improve personalization in this rare malignancy.

**Keywords** Uterine leiomyosarcoma, First-line chemotherapy, Doxorubicin–ifosfamide, Gemcitabine–docetaxel, Real-world study, Metastatic soft tissue sarcoma

## 1 Introduction

Soft tissue sarcomas (STS) are rare, diverse malignancies of mesenchymal origin, comprising less than 1% of all solid tumors [1]. Leiomyosarcoma (LMS) represents approximately 11% of adult sarcomas and commonly arises in the retroperitoneum, extremities, or uterus, with a higher prevalence among females. Uterine leiomyosarcoma (ULMS), a distinct subtype, is characterized by aggressive clinical behavior, high recurrence and progression rates, and a strong tendency for early lymphovascular spread [2–5]. ULMS accounts for 60% of uterine sarcomas and 1–2% of uterine malignancies, with an annual incidence of 0.8 per 100,000 women [6].

Although 60% of patients are diagnosed at an early stage, LMS remains a highly aggressive disease with poor outcomes. Reported 5-year survival rates range from 25 to 76%, dropping to 10–15% in patients with metastatic disease at presentation [7]. Recurrence occurs in 45–75% of cases, most commonly in the lungs (40%), with a median time to recurrence of 12–24 months [8, 9].

The standard treatment for early-stage ULMS is total abdominal hysterectomy. Lymphadenectomy is not routinely performed, as nodal involvement is uncommon and does not improve survival. Postoperative radiotherapy (RT) does not provide survival benefit over observation, and studies have shown no clear advantage of adjuvant chemotherapy in early-stage disease. In contrast, systemic chemotherapy remains the mainstay of treatment in advanced or metastatic LMS [10].

In metastatic LMS, doxorubicin-based regimens have been associated with objective response rates (ORRs) of 15–17%, median progression-free survival (mPFS) around 5 months, and median overall survival (mOS) between 12 and 30 months in recent studies. Trabectedin has shown greater activity in LMS compared to other STS subtypes, with a 6-month PFS rate of 26–30% in pretreated patients. As first-line therapy, trabectedin yielded ORRs of 10% and OS exceeding 26 months in ULMS. Importantly, in combination with doxorubicin, trabectedin demonstrated a significant OS benefit compared with doxorubicin alone in patients with advanced STSs, particularly LMS, as shown in the LMS-04 trial [11]. Gemcitabine–docetaxel (GD) was first studied in LMS in 2002, with response rates exceeding 50% in early-phase trials [12], and subsequent studies have supported its efficacy in both LMS and unselected sarcoma populations [13–19].

Current guidelines recommend multiple first-line chemotherapy options for patients with advanced or metastatic LMS [20]. These include single-agent doxorubicin, anthracycline-based combinations such as doxorubicin–ifosfamide (AI) or

doxorubicin–trabectedin, and the GD regimen. Treatment choice is guided by patient factors, toxicity profiles, and prior therapies.

Existing studies comparing anthracycline-based regimens and GD often include heterogeneous sarcoma populations, with limited data specific to ULMS. To date, no study has directly compared AI and GD as first-line therapy in advanced, unresectable, or metastatic ULMS. Although doxorubicin–trabectedin has demonstrated a survival benefit in randomized trials, trabectedin is not reimbursed for first-line treatment in our country, and its administration requires prior exposure to an anthracycline. Furthermore, considering the toxicity profile of this combination, first-line treatment in our clinical practice still primarily consists of either GD or anthracycline-based chemotherapy. This multicenter retrospective study aims to directly compare the efficacy and safety of AI versus GD in this setting.

## 2 Materials and methods

### 2.1 Patients and data collection

This retrospective, multicenter study included patients with histologically confirmed, unresectable, metastatic LMS who were treated at 30 centers in Turkey between 2010 and 2023. Data were extracted from electronic and paper-based medical records at each participating center. Eligible patients were  $\geq 18$  years old, had no prior chemotherapy for sarcoma, an Eastern Cooperative Oncology Group (ECOG) performance status  $\leq 2$ , and adequate organ function, including: absolute neutrophil count  $\geq 1.0 \times 10^9/L$ , platelets  $\geq 100 \times 10^9/L$ , total bilirubin  $\leq 1.5 \times$  upper limit of normal (ULN), aspartate aminotransferase/alanine aminotransferase  $\leq 3.0 \times$  ULN, creatinine clearance  $\geq 30$  mL/min, and a normal cardiac ejection fraction. Patients with localized disease, prior systemic therapy, incomplete records, recent myocardial infarction ( $< 6$  months), or congestive heart failure were excluded.

The AI regimen included doxorubicin  $25 \text{ mg/m}^2$  and ifosfamide  $2 \text{ g/m}^2$  administered on days 1 through 3 of each 21-day cycle, along with mesna for uroprotection, adequate intravenous hydration, and prophylactic granulocyte colony-stimulating factor (G-CSF) support. The GD regimen was administered every 21 days. For patients without prior pelvic RT, gemcitabine  $900 \text{ mg/m}^2$  was given on days 1 and 8, and docetaxel  $100 \text{ mg/m}^2$  on day 8. For those with prior RT, gemcitabine  $675 \text{ mg/m}^2$  and docetaxel  $75 \text{ mg/m}^2$  were used. G-CSF was administered in all patients.

Treatment response and progression status were determined by the study team using radiological and clinical information documented in the medical records. Radiologic assessments were performed after every three cycles, and responses were categorized according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Toxicity information was systematically abstracted from physician notes, nursing documentation, and laboratory findings in the medical records. Because this study included patients treated over a long time span (2010–2023), adverse events were not always documented with a standardized grading system at the time of treatment. To ensure consistency, all available descriptions of hematologic and non-hematologic toxicities were carefully reviewed and retrospectively reclassified according to the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0, using the information available in the medical records. This approach allowed the application of a uniform toxicity grading

system across the entire cohort, even though many patients had been treated before the release of CTCAE v5.0.

## 2.2 Outcomes

The primary outcome of this study was OS, defined as the time from the initiation of first-line chemotherapy (AI or GD) to death from any cause. Secondary outcomes included PFS, defined as the time from treatment initiation to disease progression or death from any cause; ORR, defined as the proportion of patients achieving a complete response (CR) or partial response (PR) according to RECIST 1.1 criteria; disease control rate (DCR), defined as the proportion of patients with CR, PR, or stable disease (SD); and safety, including grade 3–4 hematologic and non-hematologic toxicities assessed according to CTCAE version 5.0.

## 2.3 Statistical analysis

Categorical variables were summarized as counts and percentages; continuous variables as medians with ranges. Survival curves were estimated via the Kaplan–Meier method and compared using the log-rank test. Univariable and multivariable Cox proportional hazards models were used to identify predictors of OS. Variables with  $p < 0.1$  in univariable analysis or considered clinically relevant were included in multivariable models. Final models adjusted for treatment group, ECOG performance status, age, number and site of metastases, disease status at diagnosis, and prior adjuvant RT. Hazard ratios (HRs) and 95% confidence intervals (CIs) were reported. Chi-square tests were used for categorical comparisons, and t-tests or Mann–Whitney U tests for continuous variables as appropriate. A two-sided  $p$ -value  $< 0.05$  was considered statistically significant. Analyses were performed using IBM SPSS Statistics version 26 (IBM Corp., Armonk, NY, USA).

## 3 Results

### 3.1 Patient characteristics

Our study included 271 patients who were followed in 30 centers across Turkey between 2010 and 2023. Among them, 142 patients received AI, while 129 patients received GD. The median age of the entire population was 54 years (range: 18–84) and was comparable between the groups, with a median of 52 years in the AI group and 55 years in the GD group ( $P = 0.16$ ). Most patients had an ECOG performance status of 0–1 (93.7% in the AI group and 91.5% in the GD group;  $p = 0.491$ ), whereas 20 patients had a performance status of 2. At initial diagnosis, 98 patients had localized disease but subsequently developed metastases and were included at the time of metastatic progression, whereas 173 patients presented with de novo metastatic disease. Primary surgery was performed on 106 patients, and additionally, 43 patients received adjuvant RT. The lungs were the most common site of metastasis in both groups, followed by the liver, bone, and peritoneum-retroperitoneum. A comparison of the baseline characteristics revealed no statistically significant differences, indicating that the groups were well-balanced. Patient characteristics are summarized in Table 1.

**Table 1** Patients characteristics

|                                              | Doxorubicin and Ifos-<br>famide (n, %) | Gemcitabine and Docetaxel<br>(n; %) | p<br>value |
|----------------------------------------------|----------------------------------------|-------------------------------------|------------|
| Age                                          | 52 (18–80)                             | 55 (31–84)                          | 0.16       |
| ECOG PS                                      |                                        |                                     |            |
| PS 0–1                                       | 133 (93)                               | 118 (91)                            | 0.49       |
| PS 2                                         | 9 (6)                                  | 11 (8)                              |            |
| Patients by tumor stage at initial diagnosis |                                        |                                     |            |
| Localized                                    | 48 (33)                                | 50 (38)                             | 0.44       |
| De novo metastatic                           | 94 (66)                                | 79 (61)                             |            |
| Primary surgery                              |                                        |                                     |            |
| Yes                                          | 48 (33)                                | 58 (45)                             | 0.06       |
| No                                           | 94 (66)                                | 71 (55)                             |            |
| Received adjuvant radiotherapy               |                                        |                                     |            |
| Yes                                          | 18 (12)                                | 25 (19)                             | 0.13       |
| No                                           | 124 (87)                               | 104 (80)                            |            |
| Metastatic site                              |                                        |                                     |            |
| Lung                                         | 90 (63)                                | 78 (60)                             | 0.62       |
| Bone                                         | 19 (13)                                | 16 (12)                             | 0.81       |
| Liver                                        | 36 (25)                                | 29 (22)                             | 0.58       |
| Peritoneum, retroperitoneum                  | 17 (12)                                | 15 (11)                             | 0.93       |
| Others                                       | 7* (4)                                 | 5 <sup>†</sup> (3)                  | 0.67       |
| Second-line treatment                        |                                        |                                     |            |
| Yes                                          | 126 (88)                               | 117 (90)                            | 0.59       |
| No                                           | 16 (11)                                | 12 (9)                              |            |

All data are presented as the median (range) or absolute number (%). Abbreviations: ECOG PS—Eastern Cooperative Oncology Group Performance Status. \* Adrenal: n=2, Mediastinal lymphadenopathy: n=2, Heart: n=1, Kidney: n=1, Pancreas: n=1. <sup>†</sup>Adrenal: n=2, Ureter: n=2, Pancreas: n=1

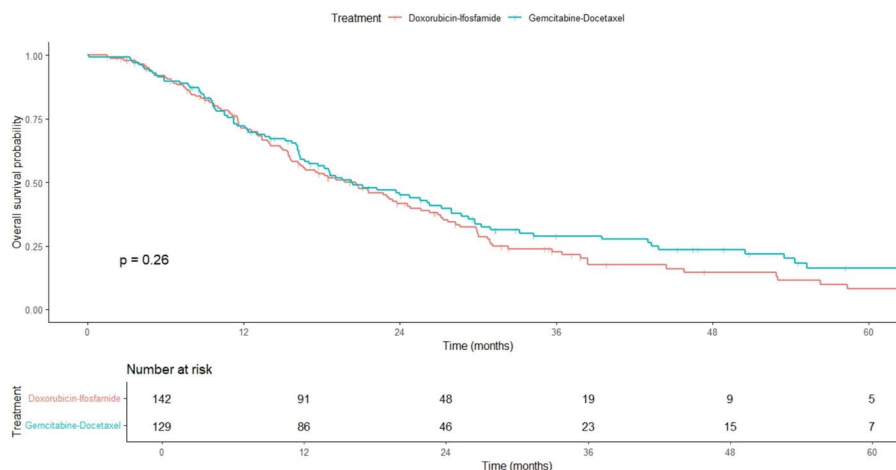


**Fig. 1** Kaplan–Meier curve for overall survival (OS) according to first-line treatment regimen. Overall survival was similar between the AI and GD groups (median OS: 19.7 vs. 20.2 months;  $P = .26$ , log-rank test). Censoring is indicated by tick marks. AI, doxorubicin–ifosfamide; GD, gemcitabine–docetaxel

### 3.2 Survival outcomes

At the data cutoff, 271 patients were included in the analysis, of whom 196 had died and 75 were alive. The mOS for the entire population was 20.29 months (95% CI: 17.52–24.00). A comparison of the two treatment arms revealed no statistically significant difference in OS, with a median of 19.74 months (95% CI: 16.19–24.77) in the AI arm and 20.29 months (95% CI: 16.88–27.97) in the GD arm ( $P = 0.26$ ) (Fig. 1). While the

Kaplan–Meier analysis with the log-rank test showed no significant difference in OS between the two treatment arms, a multivariable Cox regression analysis was performed to adjust for potential confounders, including age, ECOG performance status, number and site of metastases, adjuvant RT, and disease status at diagnosis. After adjusting for these covariates, no significant difference in OS between the treatment arms remained, with a HR of 0.91 (95% CI: 0.68–1.22;  $P=0.52$ ) (Table 2). These findings suggest that both regimens have comparable OS efficacy.

In the univariate analysis, age  $\geq 50$  years, ECOG performance status  $\geq 2$ , and the number of metastatic sites were associated with worse OS. However, after adjusting for potential confounders in the multivariable analysis, only age and ECOG performance status remained as independent prognostic factors, with age  $\geq 50$  years associated with poorer OS (HR 1.41, 95% CI: 1.02–1.94;  $P=0.03$ ) and ECOG performance status  $\geq 2$  showing significantly worse OS compared to ECOG 0–1 (HR 2.40, 95% CI: 1.45–3.98;  $P=0.001$ ). While the number of metastatic sites ( $\geq 2$ ) did not remain statistically significant in the multivariable analysis ( $P=0.68$ ), the presence of liver and lung metastases indicated a trend toward worse OS without reaching statistical significance ( $P=0.06$  and  $P=0.07$ , respectively).

The mPFS for the entire population was 6.42 months (95% CI: 5.23–7.58). In the AI arm, the mPFS was 5.5 months (95% CI: 4.84–7.84), while in the GD arm, it was 7.0 months (95% CI: 5.48–8.52). No statistically significant difference was observed between the two arms ( $P=0.62$ ) (Fig. 2).

### 3.3 Response to treatment regimen

Among the 271 patients enrolled in the study, 249 were evaluable for response (Table 3). Among these, 142 patients received AI, while 129 patients were treated with GD. The

**Table 2** Univariate and multivariate analysis of baseline characteristics for overall survival

| Variable                    | All (n, %) | HR, univariable (95%CI) | Univariable p-value | HR, multivariable (95%CI) | Multi-variable p-value |
|-----------------------------|------------|-------------------------|---------------------|---------------------------|------------------------|
| First-line treatment        |            |                         |                     |                           |                        |
| GD vs AI                    | 129 (47)   | 0.85 (0.64–1.13)        | 0.26                | 0.91 (0.68–1.22)          | 0.52                   |
| Age group                   |            |                         |                     |                           |                        |
| $\geq 50$ vs $< 50$         | 171 (63)   | 1.62 (1.19–2.19)        | $< 0.01$            | 1.41 (1.02–1.94)          | 0.03                   |
| Adjuvant radiotherapy       |            |                         |                     |                           |                        |
| Yes vs No                   | 43 (15)    | 0.82 (0.56–1.22)        | 0.03                | 1.08 (0.68–1.71)          | 0.73                   |
| Number of metastatic sites  |            |                         |                     |                           |                        |
| $\geq 2$ vs $< 2$           | 99 (36)    | 1.37 (1.03–1.82)        | 0.03                | 1.08 (0.74–1.59)          | 0.68                   |
| ECOG                        |            |                         |                     |                           |                        |
| $\geq 2$ vs 0–1             | 20 (7)     | 2.89 (1.78–4.68)        | $< 0.01$            | 2.40 (1.45–3.98)          | $< 0.01$               |
| Disease status at diagnosis |            |                         |                     |                           |                        |
| De novo vs localized        | 164 (60)   | 1.56 (1.16–2.11)        | $< 0.01$            | 1.34 (0.92–1.95)          | 0.12                   |
| Metastasis site             |            |                         |                     |                           |                        |
| Present vs absent           |            |                         |                     |                           |                        |
| Liver                       | 65 (24)    | 1.14 (0.82–1.57)        | 0.44                | 1.52 (0.97–2.37)          | 0.06                   |
| Lung                        | 168 (62)   | 1.34 (0.99–1.81)        | 0.05                | 1.45 (0.97–2.18)          | 0.07                   |
| Cutaneous                   | 32 (11)    | 1.08 (0.71–1.64)        | 0.72                | 1.36 (0.84–2.22)          | 0.21                   |
| Bone                        | 35 (12)    | 1.08 (0.72–1.63)        | 0.70                | 1.11 (0.69–1.81)          | 0.66                   |

This table presents the results of the univariate and multivariate Cox regression analyses evaluating the association between baseline characteristics and overall survival. HR and 95% CI are shown for each variable.: ECOG PS—Eastern Cooperative Oncology Group Performance Status; HR—Hazard ratios; CI—confidence intervals; AI—doxorubicin-ifosfamide; GD—gemcitabine-docetaxel

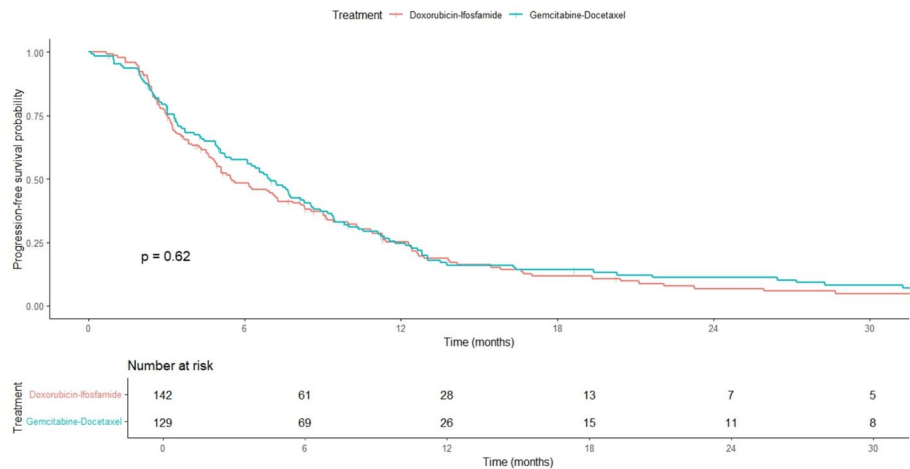


**Fig. 2** Kaplan–Meier curve for progression-free survival (PFS) according to first-line treatment regimen. Progression-free survival was similar between the AI and GD groups (median PFS: 5.5 vs. 7.0 months;  $P = .62$ , log-rank test). Censoring is indicated by tick marks. AI, doxorubicin–ifosfamide; GD, gemcitabine–docetaxel

**Table 3** Tumor response by RECIST v1.1

|                                      | Doxorubicin and Ifosfamide (n, %) | Gemcitabine and Docetaxel (n, %) | p value |
|--------------------------------------|-----------------------------------|----------------------------------|---------|
| Complete response                    | 3 (2)                             | 2 (1)                            |         |
| Partial response                     | 32 (22)                           | 40 (31)                          |         |
| Stable disease                       | 57 (40)                           | 36 (27)                          |         |
| Progressive disease                  | 40 (28)                           | 39 (30)                          |         |
| Not evaluable*                       | 10 (7)                            | 12 (9)                           |         |
| Objective Response Rate, % (95%, CI) | 26.5 (19–34%)                     | 35.9 (27–44%)                    | 0.11    |
| Disease Control Rate, % (95%, CI)    | 69.7 (61–76%)                     | 66.7 (57–74%)                    | 0.60    |

\* Radiological evaluation could not be performed in 10 patients in the doxorubicin and ifosfamide group, consisting of 9 early deaths and 1 Grade 4 acute ejection fraction decline leading to treatment discontinuation. In the gemcitabine and docetaxel group, radiological evaluation was not possible in 12 patients, consisting of 8 early deaths and 4 cases of Grade 4 adverse effects: 1 anaphylaxis, 1 elevated liver enzymes (ALT increase), 1 thrombocytopenia, and 1 pulmonary embolism. Treatment-related responses were assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1

GD arm demonstrated a numerically higher ORR compared to the AI arm (35.9% [95% CI: 27.3–44.9%] vs. 26.5% [95% CI: 19.7–34.6%],  $P = 0.11$ ), although this difference was not statistically significant. A CR was observed in 2.1% of patients in the AI arm and 1.6% in the GD arm, while a PR was reported in 22.5% of AI patients and 31% of GD patients. The DCR was comparable between the two treatment arms (69.7% [95% CI: 61.4–76.9%] vs. 66.7% [95% CI: 57.7–74.6%],  $P = 0.60$ ), with no statistically significant difference observed. All responses were assessed using the RECIST 1.1 criteria. Additionally, 126 patients in the AI arm and 117 patients in the GD arm received second-line treatment. Following systemic therapy, 10 patients (3.7%) underwent secondary surgery with curative intent (AI: 7, GD: 3), and 28 patients (10.3%) received consolidative radiotherapy (AI: 16, GD: 12).

**3.4 Safety**

Toxicity information was obtained from medical records. Adverse events were evaluated according to the CTCAE version 5.0. Hematologic toxicities were reported in 91.5% of AI patients and 89.1% of GD patients (Table 4). Grade 3–4 hematologic toxicities occurred in 29.5% of AI patients and 23.2% of GD patients, with anemia observed in 7%

**Table 4** Chemotherapy-related adverse events according to the Common Terminology Criteria for Adverse Events v 5.0

|                                    | Doxorubicin and Ifosfamide<br>(n, %) | Gem-<br>citabine and<br>Docetaxel<br>(n, %) |
|------------------------------------|--------------------------------------|---------------------------------------------|
| Any hematologic toxicity           | 130 (91)                             | 115 (89)                                    |
| Grade 3–4 Hematologic toxicity     | 42 (29)                              | 30 (23)                                     |
| Anemia                             | 10 (7)                               | 12 (9)                                      |
| Thrombocytopenia                   | 18 (12)                              | 9 (7)                                       |
| Neutropenia                        | 24 (16)                              | 16 (12)                                     |
| Febrile neutropenia                | 10 (7)                               | 8 (6)                                       |
| Grade 3–4 Non-hematologic toxicity |                                      |                                             |
| Fatigue                            | 4 (2)                                | 8 (6)                                       |
| Nausea                             | 22 (15)                              | 4 (3)                                       |
| Vomiting                           | 12 (8)                               | 2 (1)                                       |
| Diarrhoea                          | 1 (1)                                | 5 (3)                                       |
| Oral mucositis                     | 2 (1)                                | 1 (1)                                       |
| Alanine aminotransferase increased | 1 (1)                                | 1 (1)                                       |
| Hypoalbuminaemia                   | 1 (1)                                | 0 (0)                                       |
| Hyponatremia                       | 1 (1)                                | 3 (2)                                       |
| Fluid retention                    | 0 (0)                                | 1 (1)                                       |
| Allergic reaction                  | 0 (0)                                | 1 (1)                                       |
| Anaphylaxis                        | 0 (0)                                | 1 (1)                                       |
| Thromboembolic event               | 1 (1)                                | 1 (1)                                       |
| Heart failure                      | 1 (1)                                | 0 (0)                                       |
| Peripheral sensory neuropathy      | 0 (0)                                | 0 (0)                                       |

Data are n (%)

of AI patients and 9.3% of GD patients. Neutropenia occurred in 16.9% of AI patients and 12.4% of GD patients, while febrile neutropenia was reported in 7% and 6.2%, respectively. Thrombocytopenia was present in 12.6% of AI patients compared to 7% of GD patients.

The most common low-grade non-hematologic adverse event was alopecia, affecting 87.3% of AI patients and 69.7% of GD patients. Grade 3–4 non-hematologic toxicities were less frequent, with fatigue observed in 2.8% of AI patients and 6.2% of GD patients. Nausea was more common in the AI arm (15.4%) compared to the GD arm (3.1%), while vomiting was reported in 8.4% and 1.6%, respectively. No grade 3–4 peripheral sensory neuropathy was identified. Grade 1–2 neuropathy was inconsistently documented in the medical records and therefore could not be systematically assessed in this retrospective analysis.

In the AI arm, four patients discontinued treatment due to adverse events: one case of acute ejection fraction decline, one case of pulmonary embolism, and two cases of recurrent or life-threatening febrile neutropenia requiring hospitalization. In the GD arm, six patients discontinued treatment due to adverse events, including one case each of anaphylaxis, elevated liver enzymes (ALT increase), pulmonary embolism, thrombocytopenia, prolonged neutropenia, and diarrhea. Dose delays and reductions were common in both arms, with 36.6% of AI patients experiencing dose delays and 25.3% requiring dose reductions, while in the GD arm, 31% experienced dose delays and 19.3% requiring dose reductions. Notably, no treatment-related deaths were observed in either treatment arm.

#### 4 Discussions

To our knowledge, this is the largest real-world study to date directly comparing the efficacy and safety of the AI regimen with GD in the first-line treatment of metastatic ULMS. Current guidelines recommend anthracycline-based regimens or GD as standard systemic options for advanced LMS [20]. However, direct comparative data in a ULMS-specific population have been lacking, and evidence to guide regimen selection remains limited. Our study therefore provides real-world insights that complement and extend findings from prior clinical trials.

The activity of anthracycline-based regimens in ULMS has been demonstrated in multiple clinical trials. In a Gynecologic Oncology Group (GOG) trial, doxorubicin monotherapy achieved an ORR of 25%, which increased to 30% with the addition of dacarbazine, though without improvement in OS [21]. A subsequent phase II study of AI in chemotherapy-naïve patients reported an ORR of 30%, but treatment was complicated by severe toxicities, including febrile neutropenia and treatment-related deaths [22]. Similarly, a large phase III trial of intensified AI in STSs significantly improved PFS and ORR compared with doxorubicin alone, but conferred no OS benefit and was associated with markedly higher toxicity [23]. More recently, trabectedin has been explored in combination with doxorubicin. In the LMS-02 phase II trial, the ULMS subgroup achieved an ORR of 60%, with mPFS of 8.2 months and OS of 20.2 months [24]. The phase III LMS-04 trial confirmed that the addition of trabectedin significantly prolonged both PFS (10.0 vs. 4.1 months,  $P < 0.001$ ) and OS (33 vs. 24 months,  $P = 0.02$ ), albeit with increased toxicity [11]. Collectively, these findings highlight that anthracycline-based combinations, while active in ULMS, are consistently limited by tolerability concerns.

Gemcitabine–docetaxel has been widely investigated as an alternative first-line regimen. In a randomized phase II trial, GD demonstrated superior outcomes compared with gemcitabine alone in STSs, with improvements in ORR, PFS, and OS; these benefits were also observed within the LMS subgroup [19]. The GOG subsequently evaluated fixed-dose-rate GD specifically in ULMS, reporting an ORR of 36% and a median OS of 16.1 months [13]. These findings supported GD as an active regimen, although hematologic toxicity, particularly myelosuppression, was frequent. In the phase III GEDDIS trial, which compared GD with doxorubicin in advanced sarcomas, including 71 patients with ULMS, no significant differences in efficacy outcomes were observed. Myelosuppression was common with both regimens but occurred more frequently with doxorubicin [25]. Collectively, these studies, summarized in Table 5, indicate that both AI and GD are active regimens in ULMS.

In our study, efficacy outcomes were broadly comparable between AI and GD, with no statistically significant differences in OS or PFS. These findings are consistent with the GEDDIS trial and other prospective studies, reinforcing that both regimens demonstrate similar effectiveness in ULMS. Regarding safety, grade 3–4 hematologic toxicities were more frequent with AI, including neutropenia, thrombocytopenia, and febrile neutropenia, whereas GD was associated with fewer severe hematologic events but a higher incidence of fatigue. Nausea and vomiting were more common in the AI arm. This toxicity profile aligns with the GEDDIS trial and is consistent with prior reports, underscoring the distinct but predictable adverse event patterns of each regimen. Importantly, no grade 3–4 cases of peripheral sensory neuropathy were documented in our cohort.

**Table 5** Summary of key clinical trials and the present real-world study in uterine leiomyosarcoma

| Study / reference          | Population                                | Regimen                                              | ORR (%)  | mPFS (months) | mOS (months)  | Key adverse events                                                                                                                                  |
|----------------------------|-------------------------------------------|------------------------------------------------------|----------|---------------|---------------|-----------------------------------------------------------------------------------------------------------------------------------------------------|
| GOG (Ref [21])             | Advanced uterine sarcoma (n = 146)        | Doxorubicin vs. Doxorubicin + DTIC                   | 25 vs 30 | NA            | No OS benefit | Combination increased toxicity, including myelosuppression                                                                                          |
| Phase II (Ref [22])        | Uterine Leiomyosarcoma (n = 34)           | Doxorubicin + Ifosfamide                             | 30       | NA            | NA            | Myelosuppression                                                                                                                                    |
| Phase III (Ref [23])       | Soft tissue sarcomas (n = 455)            | Doxorubicin vs. intensified Doxorubicin + Ifosfamide | 14 vs 26 | 4.6 vs. 7.4   | No OS benefit | Combination increased toxicity, including myelosuppression                                                                                          |
| LMS-02 (Ref [24])          | Advanced Leiomyosarcoma (n = 108)         | Doxorubicin + Trabectedin                            | 60       | 8.2           | 20.2          | Myelosuppression, fatigue                                                                                                                           |
| LMS-04 (Ref [11])          | Advanced Leiomyosarcoma (n = 150)         | Doxorubicin vs Doxorubicin + Trabectedin             | 14 vs 26 | 4.1 vs. 10.0  | 24 vs. 33*    | Combination increased toxicity, including myelosuppression and liver toxicity                                                                       |
| Phase II (Ref [19])        | Soft tissue sarcomas (n = 122)            | Gemcitabine vs. Gemcitabine + docetaxel              | 8 vs 16  | 3.0 vs. 6.2   | 11.5 vs. 17.9 | Combination increased toxicity, including fatigue and myalgias                                                                                      |
| GOG (Ref [13])             | Uterine Leiomyosarcoma (n = 42)           | Gemcitabine + docetaxel                              | 36       | 4.4           | 16.1          | Myelosuppression, peripheral sensory neuropathy                                                                                                     |
| GEDDIS (Ref [25])          | Soft tissue sarcomas (n = 257)            | Doxorubicin vs. Gemcitabine + docetaxel              | 19 vs 20 | 5.4 vs. 5.3   | 17.4 vs. 15.5 | Doxorubicin → more myelotoxicity, nausea, vomiting; Gemcitabine + docetaxel → more fatigue, more peripheral sensory neuropathy                      |
| Current study (Real-world) | Advanced Uterine Leiomyosarcoma (n = 271) | Doxorubicin + Ifosfamide vs. Gemcitabine + docetaxel | 26 vs 35 | 5.5 vs. 7.0   | 19.7 vs. 20.2 | Doxorubicin + Ifosfamide → more myelotoxicity, nausea, vomiting; Gemcitabine + docetaxel → more fatigue; No grade 3–4 Peripheral sensory neuropathy |

ORR—objective response rate; mPFS—median progression-free survival; mOS—median overall survival; GOG—Gynecologic Oncology Group; NA—not available; DTIC, dacarbazine

\*Statistically significant overall survival benefit observed in LMS-04 (Ref 11)

This study has several limitations. Its retrospective, non-randomized design introduces the potential for selection bias, as treatment choice was made at the discretion of individual physicians. Prognostic factors such as tumor grade, molecular subtype, and comorbidities were not consistently available across institutions. Radiologic assessments were not centrally reviewed, and adverse events were abstracted from medical records, which could have contributed to underreporting. Documentation of low-grade

peripheral sensory neuropathy was inconsistent across medical records, preventing systematic assessment of this clinically relevant, potentially dose-limiting toxicity. Nonetheless, the large sample size, multicenter participation, and exclusive focus on metastatic ULMS constitute major strengths and provide robust insights into outcomes in real-world practice.

## 5 Conclusion

Our findings demonstrate that AI and GD regimens yield comparable clinical efficacy in the first-line treatment of metastatic ULMS. However, GD appears to offer a more favorable hematologic safety profile, making it a compelling option for patients who may not tolerate intensive anthracycline-based therapy. Importantly, no grade 3–4 peripheral sensory neuropathy was observed in our cohort. As the largest real-world, head-to-head comparison of these regimens in this setting, our study provides clinically meaningful evidence to support treatment decision-making. Further investigation through prospective trials is warranted to refine treatment strategies and explore personalized approaches in this rare disease.

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### Author contributions

Conceptualization: S.T., I.A., H.A., M.I., C.K., P.G., E.G., G.S., U.A.S., H.C.Y., C.A.; Methodology: S.T., H.B., A.C., A.S.; Software: M.S., M.S.D., M.K., C.A.; Validation: F.K., I.K.K., Z.A., A.A., Ö.D., B.D., S.T.; Formal Analysis: H.Y., S.B., T.K., E.B., A.U., A.O., A.S., D.O., M.B., A.U., P.G.; Investigation: A.K., C.K.; Resources: M.Y., G.C.U., O.S., E.K.; Data Curation: T.D., E.Z.; Writing – Original Draft: S.T., T.S.; Writing – Review & Editing: E.S., I.T., H.C.Y.; Visualization: G.E., A.Y.; Supervision: C.M., I.U.; Project Administration: I.H., S.T., H.C.Y.

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### Data availability

The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

## Declarations

### Ethics approval and consent to participate

Ethical approval for this study was obtained from the Institutional Review Board of Ege University Hospital (Izmir, Turkey) on March 6, 2025 (Approval No: 25-3 T/50), in accordance with the Declaration of Helsinki and local ethical regulations. Patient consent was waived due to the retrospective nature of the study.

### Consent for publication

All authors have read and approved the final version of the manuscript and consent to its publication.

### Competing interests

The authors declare no competing interests.

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