Efficacy and safety of trabectedin in metastatic uterine leiomyosarcoma: A retrospective multicenter study of the Spanish ovarian cancer research group (GEICO)

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ABSTRACT

Objective: We assessed trabectedin in patients with advanced uterine leiomyosarcoma (uLMS) in real-life clinical practice given according to the marketing authorization.

Methods: Thirty-six women from 11 tertiary hospitals across Spain who received trabectedin after anthracycline-containing regimen/s were retrospectively analyzed. The primary endpoint was progression-free survival (PFS).

Results: Median PFS and overall survival (OS) since starting trabectedin treatment were 5.4 (95% CI: 3.5–7.3) and 18.5 months (95% CI: 11.5–25.6), respectively. Median OS was significantly higher (P = 0.028) in patients receiving trabectedin in ≤ 2nd line (25.3 months) than in ≥ 3rd (15.1 months) and with ECOG performance status ≤ 1 at trabectedin start (19.8 months) than ECOG 2–3 (6.0 months, P = 0.013). When calculating OS since diagnosis, patients had longer OS with localized disease at diagnosis (87.4 months) vs. locally advanced (30.0 months) or metastatic (44.0 months, P = 0.041); and patients who received adjuvant therapy (87.4 months) compared with those who did not (30.0 months, P = 0.003), especially when receiving radiochemotherapy (106.7 months, P = 0.027). One patient (2.8%) had a complete response (CR) and nine patients (25.0%) achieved a partial response (PR) for an objective response rate of 27.8% with median response duration of 11 months (range: 4–93). Eighteen patients (50.0%) had disease stabilization for a disease control rate (DCR) of 77.8%. More patients receiving trabectedin in 1st-line of advanced disease achieved CR (16.7%) and PR (50.0%) than those in ≥ 2nd line/s (0.0% and 20.0%), whereas the DCR was similar across treatment lines. Reversible neutropenia was the most common grade 3/4 laboratory abnormality (19.4%).

Conclusions: Trabectedin confers clinical benefit in patients with recurrent/metastatic uLMS, given after failure to an anthracycline-based regimen being comparable to those reported in clinical trials and with a manageable safety profile.

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1. Introduction

Uterine leiomyosarcoma (uLMS) is an uncommon condition that accounts for approximately 1% of all uterine malignancies, and whose annual incidence is 0.6 per 100,000 women (D’Angelo and Prat, 2010). The uLMS is a very aggressive tumor, with a 5-year survival ranging between 16% and 57% depending on the disease stage at diagnosis (Kapp et al., 2008). In fact, the median overall survival in advanced or recurrent disease is less than 12 months (Zivanovic et al., 2009). Surgical resection is probably the only potential option for cure so far (Korets and Curtin, 2012). Despite adequate surgical resection, 40–70% of patients subsequently develop a recurrence (Arend et al., 2018). Drugs for the treatment of uLMS include doxorubicin (objective response rate [ORR]: 13–25%), ifosfamide (ORR: 17%), and gemcitabine (ORR: 21%) (Look et al., 2004; Amant et al., 2015). Studies evaluating the combination of gemcitabine and docetaxel have reported response rates ranging between 27% and 53%, depending on the number of previous chemotherapy lines (Hensley et al., 2002; Hensley et al., 2008; Hensley et al., 2008). Other cytotoxic agents, such as temozolomide and paclitaxel, have demonstrated more modest results (Gallup et al., 2003; Anderson and Aghajanian, 2005).

Trabectedin (Yondelis®; PharmaMar, S.A., Madrid, Spain) is a natural drug derived from the marine tunicate *Ecteinascidia turbinata* and currently produced synthetically (Monk et al., 2012). Trabectedin is indicated for the treatment of adult patients with advanced soft tissue sarcoma (STS) after failure of previous treatment with anthracycline and ifosfamide or are not a candidate to receive them (European Medicines Agency, 2019). The efficacy and manageable safety profile of trabectedin for the treatment of advanced uLMS have been demonstrated in diverse clinical trials (Monk et al., 2012; Hensley et al., 2017; Gadducci et al., 2018; Pautier et al., 2015), retrospective studies (Judson et al., 2010; Sanfilippo et al., 2011), and case series (Tewari et al., 2006; Amant et al., 2009; Corrado et al., 2011; Payne et al., 2014; Bongiovanni et al., 2015; Tavella et al., 2017; Niell et al., 2018; Henry et al., 2019). Gadducci et al. (2018) have recently reported the results from a phase II study on the activity of the single-agent trabectedin 1.3 mg/m² in 126 pretreated patients with metastatic or locally relapsed uLMS. The study met the condition for trabectedin activity as progression-free survival (PFS) rate after 6 months from the study entry, i.e., the primary end-point of this study, was 35.2% (95% confidence interval, CI 95%CI, 26.2–45%) of patients with no difference in PFS according with the number of previous chemotherapy lines. Noteworthly, Hensley et al. (2017) conducted a post hoc subgroup analysis of patients with uLMS pretreated with anthracycline-based therapy in the pivotal phase III SAR-3007 study (Demetri et al., 2016), which evaluated the efficacy and safety of trabectedin vs. dacarbazine in patients with unresectable, locally advanced or metastatic liposarcoma or leiomyosarcoma. Overall, 232 of 577 patients had uLMS and were treated with trabectedin 1.5 mg/m² by 24-hour intravenous infusion (n = 144) or dacarbazine 1 g/m² by 20–120-minute IV infusion (n = 88) once every three weeks. PFS for trabectedin was 4.0 months compared with 1.5 months for dacarbazine (hazard ratio [HR] = 0.57; 95% CI: 0.41–0.81; p = 0.012). Toxicity profile of trabectedin was similar to that reported in the overall leiomyosarcoma and liposarcoma population and were consistent with the known safety profile of trabectedin. Additionally, a retrospective analysis of 66 previously-treated unresected patients with metastatic uLMS treated with trabectedin 1.0 mg/m² to 1.5 mg/m² observed a partial response (PR) in eleven (16%) patients, whereas 23 (35%) patients achieved stable disease (SD) (Sanfilippo et al., 2011). Recorded responses as well as median PFS and OS of 3.3 months and 14.4 months, respectively, were consistent with those seen in more selective populations enrolled in clinical trials.

The aim of this retrospective analysis was to review the data of patients with advanced uLMS treated with anthracycline-containing regimens in tertiary hospitals across Spain to assess the efficacy of trabectedin in real-life routine clinical practice according to SmPC.

### Table 1

**Demographic and clinical information of patients, and treatments.**

| AT DIAGNOSIS                          | Patients (n = 36) |
|---------------------------------------|------------------|
| Age, median years (range)             | 54 (29–68)       |
| Disease, n (%)                        |                  |
| Localized                             | 19 (52.8)        |
| Locally advanced                      | 4 (11.1)         |
| Metastatic                            | 13 (36.1)        |
| Tumor size, n (%)                     |                  |
| < 50 mm                                | 5 (17.9)         |
| ≥ 50 mm                                | 23 (62.1)        |
| Histologic grade, n (%)               |                  |
| Low                                    | 7 (28.0)         |
| High                                   | 18 (72.0)        |
| Mitotic index, n (%)                  |                  |
| 0–15/10 HPF                           | 11 (50.0)        |
| > 15/10 HPF                           | 11 (50.0)        |

**PREVIOUS TREATMENTS**

| Adjuvant therapy, n (%)               | 21 (58.4)        |
| Radiotherapy                          | 10 (27.8)        |
| Chemotherapy                          | 5 (13.9)         |
| Both                                   | 6 (16.7)         |
| Chemotherapy prior to trabectedin (any line for relapsed disease), n (%) | 30 (83.3) |
| Number of lines, median (range)       | 2 (0–3)          |
| Anthracycline therapy immediately before trabectedin, n (%) | 5 (16.7) |

**TRABECTEDIN TREATMENT**

| Age at onset of trabectedin treatment, median years (range) | 57 (36–70) |
| ECOG performance status at starting treatment, n (%) | |
| 0–1                                                   | 28 (87.5) |
| 2–3                                                   | 4 (12.5)  |
| Number of trabectedin cycles, median (range)           | 6 (3–25)  |
| Reasons for trabectedin discontinuation, n (%)         | 30 (83.3) |
| Tumor progression                                     | 3 (8.3)   |
| Intolerance                                           | 3 (8.3)   |
| Complete tumor response                                | 1 (2.8)   |
| Patient’s decision                                     | 1 (2.8)   |
| Physician’s decision                                   | 1 (2.8)   |

**ECOG, Eastern Cooperative Oncology Group; HPF, high-power fields**

* Data not available for some patients.

2. Methods

2.1. Study design

This retrospective, observational, multicenter study involved patients who received trabectedin after an anthracycline-containing regimen/s for uLMS. Eligible patients were patients ≥ 18 years old with unresectable advanced or metastatic uLMS who had experienced either relapse or disease progression at the time of starting trabectedin treatment. All patients were treated between September 17th, 2007 and April 30th, 2016 with at least three cycles of trabectedin, administered according to the marketing authorization at a recommended dose of 1.5 mg/m² through a central venous line as a 24-h continuous infusion every 3 weeks. In accordance with the Summary of Product Characteristics (SmPC) (European Medicines Agency, 2019), other eligibility criteria included adequate baseline renal, hepatic and bone marrow function according to laboratory standard parameters before the first treatment cycle and complete recovery from any toxicity derived from prior treatment/s. The only exclusion criterion was not having available information from the medical record. As per SmPC patients treated in 1st-line of advanced disease with trabectedin were not candidates to receive more anthracyclines after having been treated with these drugs in the adjuvant setting. In the present manuscript, first
line of treatment in advanced disease represents the first systemic therapy in this setting, regardless adjuvant chemotherapy. All women signed the written consent to participate in the study, except for those who died before the analysis or who were not possible to contact. Procedures were in accordance with the Declaration of Helsinki and approved by Ethics Committees according to national legislation.

2.2. Endpoints and variables

The primary endpoint included the efficacy of trabectedin in relapsed/metastatic disease, as defined by PFS. The PFS was defined as the elapsed time between the date of starting trabectedin treatment (first dose) and disease progression or death, by any cause. Secondary endpoints included the OS, the determination of the best tumor response to trabectedin (with the special attention to the number of treatment line in advanced disease), and the safety profile of

Fig. 1. Progression-free survival and overall survival since starting trabectedin treatment, in all patients and considering the line of treatment in advanced disease.

Table 2

Survival analysis considering characteristics of patients or treatments.

| Since trabectedin treatment | Since diagnosis |
|----------------------------|----------------|
| Progression-free survival  | Overall survival |
| P                         | P           |
| Median line of trabectedin treatment of advanced disease |  |
| 1st-2nd (n = 15) | 5.4 (0.0–11.1) | 0.470 | 25.3 (0.0–66.7) | 0.028 | 87.4 (22.6–152.1) | 0.310 |
| 3rd or successive (n = 21) | 5.7 (3.8–7.7) | 15.1 (10.9–19.2) | 44.7 (42.4–47.0) |
| ECOG at trabectedin start * |  |
| 0–1 (n = 28) | 5.4 (3.7–7.0) | 0.260 | 19.8 (12.9–26.7) | 0.013 | 46.0 (32.7–59.9) | 0.930 |
| 2–3 (n = 4) | 3.1 (1.7–4.5) | 6.0 (2.4–9.6) | 30.0 (28.1–31.9) |
| Disease at diagnosis |  |
| Localized (n = 19) | 3.1 (0.0–6.9) | 0.410 | 21.1 (11.1–31.2) | 0.130 | 87.4 (28.2–146.5) | 0.041 |
| Locally advanced (n = 4) | 3.0 (1.4–4.6) | 4.1 (0.4–7.9) | 30.0 (0.0–68.8) |
| Metastatic (n = 13) | 6.8 (3.9–9.8) | 18.5 (8.0–29.1) | 44.0 (19.4–68.6) |
| Adjuvant therapy |  |
| Yes (n = 21) | 4.6 (0.6–8.6) | 0.830 | 19.8 (11.9–27.8) | 0.170 | 87.4 (25.8–148.9) | 0.003 |
| No (n = 15) | 5.9 (3.3–8.6) | 15.1 (0.0–30.9) | 30.0 (3.9–56.2) |
| Type of adjuvant therapy |  |
| Radiotherapy (n = 10) | 5.7 (0.0–15.0) | 0.088 | 21.8 (7.8–35.8) | 0.370 | 87.4 (21.9–152.8) | 0.027 |
| Chemotherapy (n = 5) | 13.6 (0.0–33.0) | 18.5 (10.4–26.7) | 63.7 (25.7–101.8) |
| Both (n = 6) | 2.9 (2.2–3.6) | 8.5 (3.6–13.4) | 106.7 (0.0–235.6) |

* Data not available for 4 patients.

Values are expressed as median (range). ECOG, Eastern Cooperative Oncology Group.
Table 3

Best tumor response to trabectedin.

| Tumor response, n (%) | CR     | PR    | SD   | PD    | ORR   | DCR   | P     |
|-----------------------|--------|-------|------|-------|-------|-------|-------|
| Overall (n = 36)      | 1 (2.8)| 9 (25.0)| 18 (50.0) | 8 (22.2) | 10 (27.8) | 28 (78.8) |       |
| Trabectedin line of advanced disease |        |       |      |       |       |       |       |
| 1st line (n = 6)      | 1 (16.7)| 3 (50.0) | 1 (16.7) | 1 (16.7) | 4 (66.7) | 5 (83.4) | 0.041 |
| 2nd or successive lines (n = 30) | 0 (0.0) | 6 (20.0) | 17 (56.7) | 7 (23.3) | 6 (20.0) | 23 (76.7) |       |

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, overall response rate; DCR, disease control rate.

Table 4

Adverse events associated with trabectedin treatment.

| Adverse event, n (%) | Hematological toxicity | Overall | Grade 1/2 | Grade 3/4 |
|----------------------|------------------------|---------|-----------|-----------|
| Neutropenia           | 11 (30.5)              | 4 (11.1) | 7 (19.4)  |
| Anemia                | 9 (25.0)               | 7 (19.4) | 2 (5.6)   |
| Febrile neutropenia   | 2 (5.6)                | 0 (0.0)  | 2 (5.6)   |
| Thrombocytopenia      | 1 (2.7)                | 0 (0.0)  | 1 (2.7)   |

Non-hematological toxicity

| Adverse event, n (%) | Fatigue | Nausea | Vomiting | Diarrhea | Decreased appetite | Elevation in ALT | Elevation in AST | Constipation | Myalgia | Hypotension | Hypocalcemia | Mucocele | Infection |
|----------------------|---------|--------|----------|----------|-------------------|-----------------|-----------------|--------------|---------|-------------|-------------|---------|-----------|
| Overall              | 9 (25.0)| 5 (13.9)| 4 (11.1)| 2 (5.6)  | 2 (5.6)           | 2 (5.6)         | 1 (2.7)         | 1 (2.7)      | 1 (2.7) | 1 (2.7)     | 1 (2.7)     | 1 (2.7) | 1 (2.7)   |
| Grade 1/2            | 8 (22.2)| 5 (13.9)| 4 (11.1)| 2 (5.6)  | 2 (5.6)           | 2 (5.6)         | 1 (2.7)         | 0 (0.0)      | 1 (2.7) | 1 (2.7)     | 1 (2.7)     | 1 (2.7) | 1 (2.7)   |
| Grade 3/4            | 1 (2.7) | 0 (0.0) | 0 (0.0) | 0 (0.0)  | 0 (0.0)           | 0 (0.0)         | 0 (0.0)         | 0 (0.0)      | 0 (0.0) | 0 (0.0)     | 0 (0.0)     | 0 (0.0) | 0 (0.0)   |

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Trabectedin. The OS was calculated as the elapsed time between the date of starting trabectedin treatment (first dose) and death, by any cause. Tumor response was assessed following the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (Eisenhauer et al., 2009). The ORR was calculated as the sum of complete response (CR) and PR, whereas DCR as the sum of CR, PR, and SD. The adverse events (AEs) were evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

ALT and AST were evaluated using the Aspartate Aminotransferase (AST) and Alanine Aminotransferase (ALT) of liver function test.

3. Results

3.1. Characteristics of patients and treatments

Thirty-six patients with metastatic uLMS from 11 Spanish tertiary hospitals were included in the study (Table 1). At diagnosis, patients had a median age of 54 years (range: 29–68), mostly with an Eastern Cooperative Oncology Group (ECOG) performance status 0–1 (92.2%), tumor size ≥ 50 mm (82.1%), and high-grade disease (72.0%). Twenty-one patients (58.4%) received adjuvant chemotherapy, mainly radiotherapy (27.8%), chemotherapy (13.9%), or both (16.7%). A total of 34 patients (out of 36) underwent a hysterectomy for the primary tumor. In the remaining 2 patients, hysterectomy was contraindicated by the metastatic disease. Thirty patients (83.3%) treated with trabectedin had received prior chemotherapy for relapsed disease (median number of lines 2; range 0–3). Six patients had not received any chemotherapy line before trabectedin since they were not candidates to receive more anthracyclines after having been treated with these drugs in the adjuvant setting. The median number of trabectedin cycles was 6 (range: 3–25). Reasons for trabectedin discontinuation included: tumor progression (n = 30), patient’s decision (n = 1), physician’s decision (n = 1), CR (n = 1), and unacceptable toxicity (hematological toxicity in two patients, and hepatic one in one patient).

3.2. Efficacy

After a median follow-up of 33 months (range: 7–93), median PFS and OS since starting trabectedin treatment were 5.4 months (95%CI: 3.5–7.3; Fig. 1A) and 18.5 months (95%CI: 11.5–25.6; Fig. 1C), respectively. No differences in PFS were found between trabectedin administered in 1st–2nd lines of advanced disease, and 3rd and successive endpoints (PFS and OS) and their fixed-time estimations were estimated according to the Kaplan–Meier method and comparisons of survival curves considering characteristics of patients and treatments were done using the log-rank test. Multivariate survival analysis was performed by using Cox regression. The statistical significance was established when P = 0.05. All statistical procedures were carried out by using SPSS version 20 and all data were obtained from medical records.

4. Conclusion

In conclusion, trabectedin has been associated with a significant ORR in patients with metastatic uLMS. Our analysis shows that trabectedin monotherapy is a feasible and safe option with good response rates in patients with no prior chemotherapy for relapsed disease or the primary tumour. Further studies are needed to evaluate the role of trabectedin in the adjuvant setting.
lines (Fig. 1B). In contrast, median OS for patients receiving trabectedin in 1st or 2nd line in advanced disease (25.3 months, 95%CI: 0.0–66.7) was significantly higher than in ≥ 3rd line/s (15.1 months, 95%CI: 10.9–19.2; P = 0.028; Fig. 1D). Furthermore, the median OS was significantly longer in patients with ECOG performance status 0–1 at trabectedin start (19.8 months, 95%CI: 12.9–26.7) than ECOG 2–3 (6.0 months, 95%CI: 2.4–9.6; P = 0.013). When calculating OS since diagnosis patients with localized disease at diagnosis had longer OS (87.4 months, 95%CI: 28.2–146.5) compared with locally advanced (30.0 months, 95%CI: 0.0–68.8) and metastatic disease (44.0 months, 95%CI: 19.4–68.6; P = 0.041). Additionally, patients who received adjuvant therapy had a longer OS (87.4 months, 95%CI: 25.8–148.9) compared with those who did not (30.0 months, 95%CI: 3.9–56.2; P = 0.003), especially when receiving radiotherapy and chemotherapy (106.7 months, 95%CI: 0.0–235.6; P = 0.027) (Table 2). One patient (2.8%) had a CR and nine patients (25.0%) achieved a PR for an ORR of 27.8% with a median response duration of 11 months (4–93; Table 3).

Eighteen patients (50.0%) had SD for a DCR of 77.8%. Tumor responses to trabectedin were significantly different (P = 0.041) regarding the line in advanced disease. More patients receiving trabectedin in 1st line of advanced disease achieved CR (16.7%) and PR (50.0%) than those in ≥ 2nd line/s (0.0% and 20.0%, respectively). Similarly, fewer patients in 1st line of advanced disease line had SD (16.7%) and PD (16.7%) than in ≥ 2nd line/s (56.7% and 23.3%). The DCR was similar across treatment lines (83.4% in 1st line of advanced disease vs. 76.7% in ≥ 2nd line/s).

3.3. Safety

Treatment-emergent AEs observed were consistent with established safety and toxicity profiles of trabectedin. Most frequent hematological AES were reversible neutropenia (11 patients, 30.5%), mainly grade 3/≥ in 95%CI: 19.4 vs treatment lines (83.4% in 1st line of advanced disease than in ≥ 3rd line/s (0.0% and 20.0%, respectively). Similarly, fewer pa-

patients were in concordance with extensive prior experience and re-

ports reflecting the well-characterized transient and non-cumulative
toxicities of bone marrow suppression and hepatotoxicity (Le Cesne et al., 2015; Samuels et al., 2013). In our study, the patients received a median of 6 trabectedin cycles, suggestive of an acceptable safety profile that allowed prolonged treatment up to 25 cycles. No new or unexpected adverse reactions or qualitative differences in the adverse reactions were observed.

Regarding major limitation of this analysis, the retrospective nature and the low number of participating women were the main weaknesses of the study. Therefore, our results should be interpreted with caution as they may be subject to bias.

In conclusion, trabectedin confers clinical benefit in patients with recurrent/metastatic uLMS, after failure to an anthracycline-containing regimen, especially when administered in earlier lines, with the manageable safety profile of trabectedin. Real-life results from the present study are largely comparable to previously shown in clinical studies.

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CRediT authorship contribution statement

María Jesús Rubio: Methodology, Investigation, Formal analysis, Writing - original draft, Writing - review & editing, Supervision. María José Lecumberri: Investigation, Writing - review & editing. Silvia Varela: Investigation, Writing - review & editing. Jesús Alarcón: Investigation, Writing - review & editing. María Eugenia Ortega: Investigation, Writing - review & editing. Lydia Gaba: Investigation, Writing - review & editing. Jaume Espinós: Investigation, Writing - review & editing. Julia Calzás: Investigation, Writing - review & editing. Pilar Barretina: Investigation, Writing - review & editing. Ana Santaballa: Methodology, Investigation, Formal analysis, Writing - original draft, Writing - review & editing.

Declaration of Competing Interest

All of the authors declare that have disclosed conflict of interests within the Conflict of Interest Forms.

References

D’Angelo, E., Prat, J., 2010. Uterine sarcomas: a review. Gynecol. Oncol. 116, 131–139.

Kapp, D.S., Shin, J.Y., Chan, J.K., 2008. Prognostic factors and survival in 1996 patients with uterine leiomyosarcomas: emphasis on impact of lymphadenectomy and oophorectomy. Cancer 112, 820–830.

Zivanovic, O., Leitao, M.M., Iasonos, A., Jacks, L.M., Zhou, Q., Abu-Rustum, N.R., et al., 2009. Stage-specific outcomes of patients with uterine leiomyosarcoma: a comparison of the International Federation of Gynecology and Obstetrics and American Joint Committee on Cancer Staging Systems. J. Clin. Oncol. 27, 2066–2072.

Korets, S.B., Curtin, J.P., 2012. Surgical options for recurrent uterine sarcomas. Am. Soc. Clin. Oncol. Educ. Book 362–366.

Arend, R.C., Tchobani, M.D., Montgomery, A.M., Burger, R.A., Ollaweye, A.B., Monk, B.J., et al., 2018. Systemic treatment of metastatic/recurrent uterine leiomyosarcoma: A changing paradigm. Oncologist 23, 1533–1545.

Look, K.Y., Sandler, A., Blessing, J.A., Lucci 3rd, J.A., Rose, P.G., 2004. Phase II trial of gemcitabine as second-line chemotherapy of uterine leiomyosarcoma: A Gynecologic...
Oncology Group (GOG) Study. Gynecol. Oncol. 92, 644–647.
Aman, F., Lorusso, D., Mustea, A., Duffaud, F., Pautier, P., 2015. Management strategies in advanced uterine leiomyosarcoma: Focus on trabectedin. Sarcoma 2015, 704124.
Hensley, M.L., Maki, R., Venkatraman, E., Geller, G., Lovegren, M., Aghajanian, C., et al., 2002. Gemicitabine and docetaxel in patients with unresectable leiomyosarcoma: results of a phase II trial. J. Clin. Oncol. 20, 2824–2831.
Hensley, M.L., Blessing, J.A., Degeest, K., Abulafia, O., Rose, P.G., Homesley, H.D., 2008. Fixed-dose rate gemcitabine plus docetaxel as second-line therapy for metastatic uterine leiomyosarcoma: a Gynecologic Oncology Group phase II study. Gynecol. Oncol. 109, 323–328.
Hensley, M.L., Blessing, J.A., Mannel, R., Rose, P.G., 2008. Fixed-dose rate gemcitabine plus docetaxel as first-line therapy for metastatic uterine leiomyosarcoma: a Gynecologic Oncology Group phase II trial. Gynecol. Oncol. 109, 329–334.
Gallup, D.G., Blessing, J.A., Andersen, W., Morgan, M.A., 2003. Evaluation of paclitaxel in previously treated leiomyosarcoma of the uterus: a Gynecologic Oncology Group study. Gynecol. Oncol. 89, 48–51.
Anderson, S., Aghajanian, C., 2005. Temozolomide in uterine leiomyosarcomas. Gynecol. Oncol. 98, 99–103.
Monk, B.J., Dalton, H., Benjamini, I., Tanovic, A., 2012. Trabectedin as a new chemotherapy option in the treatment of relapsed platinum sensitive ovarian cancer. Curr. Pharm. Des. 18, 3754–3769.
European Medicines Agency. Yondelis (trabectedin). European public assessment report. https://www.ema.europa.eu/en/medicines/human/EPAR/yondelis. Accessed date: 24 March 2019.
B.J. Monk, J.A. Blessing, D.G. Street, C.Y. Muller, J.J. Burke, M.L., A phase II evaluation of trabectedin in the treatment of advanced, persistent, or recurrent uterine leiomyosarcoma: a Gynecologic Oncology Group study. Gynecol. Oncol. 124 (2012) 48–52.
Hensley, M.L., Patel, S.R., von Mehren, M., Ganjoo, K., Jones, R.L., Staddon, A., et al., 2017. Efficacy and safety of trabectedin or dacarbazine for the treatment of patients with uterine leiomyosarcoma after prior chemotherapy: A subgroup analysis of the randomized phase 3 SAR-3007 study. Gynecol. Oncol. 146, 531–537.
Gadducci, A., Grosso, F., Scambia, G., Raspagliesi, F., Colombo, N., Grignani, G., et al., 2018. A phase II randomised (calibrated design) study on the activity of the single-agent trabectedin in metastatic or locally relapsed uterine leiomyosarcoma. Br. J. Cancer. 119, 566–571.
Pautier, P., Floquet, A., Chevreaux, C., Penel, N., Guillemet, C., Delcambre, C., et al., 2015. Trabectedin in combination with doxorubicin for first-line treatment of advanced uterine or soft-tissue leiomyosarcoma (LMS-02): a non-randomised, multicentre, phase 2 trial. Lancet Oncol. 16, 457–464.
Judson, I.R., Blay, J., Chawla, S.P., Radford, J.A., Le Cesne, A., Verweij, J., et al., 2010. Trabectedin (Tr) in the treatment of advanced uterine leiomyosarcomas (U-LMS): results of a pooled analysis of five single-agent phase II studies using the recommended dose. Clin. Oncol. 28, 10628.
Sanfilippo, R., Grosso, F., Jones, R.L., Banerjee, S., Pilotto, S., D’Incalci, M., et al., 2011. Trabectedin in advanced uterine leiomyosarcomas: a retrospective case series analysis from two reference centers. Gynecol. Oncol. 123, 553–556.
D. Tewari, B. Saffari, C. Cowan, A.C. Wallick, M.Z. Koontz, B.J., Activity of trabectedin (ET-743, Yondelis) in metastatic uterine leiomyosarcoma. Gynecol. Oncol. 102 (2006) 421–424.
Aman, F., Coosemans, A., Renard, V., Everaert, E., Vergote, I., 2009. Clinical outcome of ET-743 (Trabectedin; Yondelis) in high-grade uterine sarcomas: report on five patients and a review of the literature. Int. J. Gynecol. Cancer. 19, 245–248.
Carrado, G., Salutari, V., Fusco, G., Lucidi, A., Ferrandina, G., 2011. Prolonged clinical response to trabectedin in a heavily pretreated patient with advanced uterine leiomyosarcoma: a case report and literature review. Gynecol. Oncol. 121, 416–417.
Payne, M.J., MacPherson, R.E., Bradley, K.M., Hassan, A.B., 2014. Trabectedin in advanced high-grade uterine leiomyosarcoma: A case report illustrating the value of (18)FDG-PET-CT in assessing treatment response. Case Rep. Oncol. 7, 132–138.
Bongiovanni, A., Riva, N., Ricci, M., Mercatali, L., Liverani, C., La Manna, F., 2015. Long-lasting activity of trabectedin in refractory uterine leiomyosarcoma: a case report. BMC Cancer. 15, 998.
Tavella, K., Villanacci, A., Vannini, I., Lavacchi, D., Montelatici, S., Amunni, G., 2017. Stable disease in a patient with metastatic leiomyosarcoma treated with trabectedin. Anticancer Drugs. 28, 465–468.
Nteli, V.A., Knauf, W., Janton-Klein, A., El-Safi, S., 2018. Long-lasting response to trabectedin in a patient with metastatic uterine leiomyosarcoma: A case report. Case Rep. Oncol. 11, 81–89.
Henry, T., Fabre, E., Baccar, L.S., Lamuraglia, M., 2019. Longer survival in patients with metastatic uterine leiomyosarcoma treated with trabectedin: A case report. Mol. Clin. Oncol. 10, 387–390.
Demetri, G.D., von Mehren, M., Jones, R.L., Hensley, M.L., Schuetze, S.M., Staddon, A., et al., 2016. Efficacy and safety of trabectedin or dacarbazine for metastatic liposarcoma or leiomyosarcoma after failure of conventional chemotherapy: Results of a phase III randomized multicenter clinical trial. J. Clin. Oncol. 34, 786–793.
Eisenhauer, E.A., Therasse, P., Bogaerts, J., Schwartz, L.H., Sargent, D., Ford, R., et al., 2009. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur. J. Cancer. 45, 228–247.
Hindi, N., Martin-BROTO, J., 2017. Current and future systemic treatment options for advanced soft-tissue sarcoma beyond anthracyclines and ifosfamide. Cancer Transl. Med. 3, 20–28.
Le Cesne, A., Blay, J.Y., Judson, I., Van Oosterom, A., Verweij, J., Radford, J., et al., 2005. Phase II study of ET-743 in advanced soft tissue sarcomas: a European Organisation for the Research and Treatment of Cancer (EORTC) soft tissue and bone sarcoma group trial. J Clin Oncol. 23, 576–584.
Grosso, F., Jones, R.L., Demetri, G.D., Judson, I.R., Blay, J.Y., Le Cesne, A., et al., 2007. Efficacy of trabectedin (etecnacinacid-743) in advanced pretreated myxoid liposarcoma: a retrospective study. Lancet Oncol. 8, 595–602.
Le Cesne, A., Ray-Coquard, I., Duffaud, F., Chevreau, C., Penel, N., Bui Nguyen, B., et al., 2015. Trabectedin in patients with advanced soft tissue sarcoma: a retrospective national analysis of the French Sarcoma Group. Eur. J. Cancer. 51, 742–750.
Ende, M., Takahashi, S., Anaki, N., Soujari, H., Ueda, T., Yosemoto, T., et al., 2020. Time lapse analysis of tumor response in patients with soft tissue sarcoma treated with trabectedin: A pooled analysis of two phase II clinical trials. Cancer Med. Mar 27.
Samuels, B.L., Chawla, S., Patel, S., von Mehren, M., Hamm, J., Kaiser, P.E., et al., 2013. Clinical outcomes and safety with trabectedin therapy in patients with advanced soft tissue sarcomas following failure of prior chemotherapy: results of a worldwide expanded access program study. Ann. Oncol. 24, 1703–1709.