Published in final edited form as:

Gynecol Oncol. 2017 September ; 146(3): 531–537. doi:10.1016/j.ygyno.2017.06.018.

Efficacy and Safety of Trabectedin or Dacarbazine in Patients with Advanced Uterine Leiomyosarcoma after Failure of Anthracycline-based Chemotherapy: Subgroup Analysis of a Phase 3, Randomized Clinical Trial

Martee L. Hensley^a, Shreyaskumar R. Patel^b, Margaret von Mehren^c, Kristen Ganjoo^d, Robin L. Jones^{e,1}, Arthur Staddon^{f,2}, Daniel Rushing^g, Mohammed Milhem^h, Bradley Monkⁱ, George Wang^j, Sharon McCarthy^j, Roland E. Knoblauch^j, Trilok V. Parekh^j, Robert G. Maki^{k,3}, and George D. Demetri^l

^aMemorial Sloan Kettering Cancer Center, New York, NY, USA

^bThe University of Texas M.D. Anderson Cancer Center, Houston, TX, USA

^cFox Chase Cancer Center, Philadelphia, PA, USA

^dStanford Hospital and Clinics, Stanford, CA, USA

^eSeattle Cancer Care Alliance/University of Washington/Fred Hutchinson Cancer Research Center, Seattle, WA, USA

^fArthur James Cancer Center, Columbus, OH, USA

Corresponding author: Martee L. Hensley, MD, 300 E. 66th Street, Memorial Sloan Kettering Cancer Center, New York, NY 10065, USA, gynbreast@mskcc.org, Tel: +1 646-888-4222.

¹Present address: Royal Marsden Hospital/Institute of Cancer Research, London, UK

²Present address: Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA, USA

³Present address: Monter Cancer Center and Cold Spring Harbor Laboratory, Lake Success, NY, USA

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

CONFLICT OF INTEREST STATEMENTS

Martee L. Hensley: grants from Janssen during the conduct of the study; personal fees from Janssen, Lilly, EMD Serono, Tesaro, OncLive, and UpToDate outside the submitted work; spouse is an employee of Sanofi.

Shreyaskumar R. Patel: grants and personal fees from Janssen, Eisai, and Morphotek; personal fees from EMD-Serono, CytRx, Bayer, Eli Lilly, Epizyme, and Novartis outside the submitted work.

Margaret von Mehren: personal fees from Janssen and Eisai outside the submitted work.

Kristen Ganjoo: Janssen advisory board outside the submitted work.

Robin L. Jones: has worked as a consultant for PharmaMar.

Daniel Rushing: personal fees from Eisai Pharmaceutical, Bayer Pharmaceutical, and Lilly Pharmaceutical outside the submitted work.

Arthur Staddon and Mohammed Milhem: nothing to disclose.

Bradley Monk: St Joseph's Hospital institution has received research grants from Novartis, Amgen, Lilly, Genentech, Janssen/Johnson & Johnson, Array, TESARO, and Morphotek; he has received honoraria for speaker bureaus from Roche/Genentech, AstraZeneca, Janssen/Johnson & Johnson, Myriad, TESARO, and Clovis; he has been a consultant for Roche/Genentech, Merck, TESARO, AstraZeneca, Gradalis, Advaxis, Cerulean, Amgen, Vemillion, ImmunoGen, Pfizer, Bayer, NuCana, Insys, GlaxoSmithKline, Verastem, Mateon, PPD, Clovis, Precision Oncology, Biodesix, Perthera, ImmunoGen, and Cue.

George Wang, Sharon McCarthy, Roland E. Knoblauch, and Trilok V. Parekh: each is an employee with stock options at Janssen Research & Development, LLC.

Robert G. Maki: personal fees (consulting) and previously received support to conduct clinical trials at his institution from Janssen/PharmaMar.

George D. Demetri: personal fees and non-financial support from Janssen Oncology.

^gIndiana University, Simon Cancer Center, Indianapolis, IN, USA

^hUniversity of Iowa Hospitals and Clinics, Iowa City, IA, USA

ⁱSt. Joseph's Hospital & Medical Center, Phoenix, AZ, USA

^jJanssen Research & Development LLC, Raritan, NJ, USA

^kMount Sinai School of Medicine New York, NY, USA

^lDana-Farber Cancer Institute, Harvard Medical School, and Ludwig Center at Harvard, Boston, MA, USA

Abstract

Objective—Trabectedin demonstrated significantly improved disease control in leiomyosarcoma and liposarcoma patients in a global phase 3 trial (NCT01343277). A post hoc analysis was conducted to assess the efficacy and safety of trabectedin or dacarbazine in women with uterine leiomyosarcoma (uLMS), the largest subgroup of enrolled patients (40%).

Methods—Of 577 patients randomized 2:1 to receive trabectedin 1.5 mg/m² by 24-hour IV infusion or dacarbazine 1 g/m² by 20–120-minute IV infusion once every three weeks, 232 had uLMS (trabectedin: 144; dacarbazine: 88). The primary endpoint was overall survival (OS); secondary endpoints were progression-free survival (PFS), objective response rate (ORR), clinical benefit rate (CBR: complete responses + partial responses + stable disease [SD] for at least 18 weeks), duration of response (DOR), and safety.

Results—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*=.0012). OS was similar (trabectedin 13.4 months vs. dacarbazine 12.9 months, HR=0.89; 95% CI 0.65–1.24; *P*=.51) between groups. ORR was 11% with trabectedin vs. 9% with dacarbazine (*P*=.82). CBR for trabectedin was 31% vs. 18% with dacarbazine (*P*=.05); median DOR was 6.5 months for trabectedin vs. 4.1 months for dacarbazine (*P*=.32). Grade 3/4 treatment-emergent adverse events observed in 10% of patients in the trabectedin group included transient aminotransferase (aspartate/alanine) elevations, anemia, leukopenia, and thrombocytopenia.

Conclusions—In this post hoc subset analysis of patients with uLMS who had received prior anthracycline therapy, trabectedin treatment resulted in significantly longer PFS versus dacarbazine, with an acceptable safety profile. There was no difference in OS.

Keywords

trabectedin; dacarbazine; uterine leiomyosarcoma; phase 3

INTRODUCTION

Leiomyosarcoma (LMS) is a common histologic subtype of soft tissue sarcomas (STS), most of which arise in the uterus. Although uterine leiomyosarcomas (uLMS) account for fewer than 5% of all uterine malignancies, they represent approximately half of all uterine sarcomas.[1–3] The treatment of metastatic uLMS remains a considerable challenge. First- and second-line chemotherapy options include fixed dose rate gemcitabine plus docetaxel,

which achieves an objective response in approximately 30% of patients [4, 5], single-agent gemcitabine, which achieves an objective response in approximately 20% of patients, and doxorubicin-based treatment, with similar objective responses [6]. Systemic treatment options are limited for patients with uLMS after anthracycline failure.[7, 8]

Trabectedin, a drug derived from a marine organism, has a set of unique and complex mechanisms of action, affecting key biological processes in tumor cells and the tumor microenvironment through its tumor cell-autonomous effects and its effects on macrophages and tissue resident histiocytes [9–11]. Trabectedin interacts with the minor groove of the deoxyribonucleic acid (DNA) double helix, thereby affecting gene transcription and DNA repair pathways, resulting in cell cycle arrest and, ultimately, p53-independent apoptosis [12, 13].

In several prospective clinical trials and retrospective analyses, trabectedin has demonstrated prolonged disease control in patients with LMS or liposarcoma (LPS) [14]. Although trabectedin has achieved modest objective response rates in patients with advanced uLMS, ranging from 6% to 17%, disease control rates (ie, patients with complete and partial responses or stable disease for some period of time) have exceeded 50% in some studies [15]. Furthermore, a retrospective case series analysis performed at two reference centers demonstrated that trabectedin was active in a subset of patients who were heavily pretreated for metastatic uLMS [16]. In a prospective phase 2 trial of trabectedin as first-line treatment for advanced, persistent, or recurrent uLMS (N=20), trabectedin achieved an objective response rate of 10% and a median progression-free survival (PFS) of 5.8 months [17].

Based on these findings, a large (N=577) phase 3, randomized, open-label, international, multicenter trial was conducted of trabectedin versus dacarbazine in patients with locally advanced or metastatic LMS or LPS who had received prior anthracycline treatment. Trabectedin demonstrated superior disease control compared with dacarbazine, with a median PFS of 4.2 months vs. 1.5 months, respectively (hazard ratio [HR] 0.55, $P<.001$) [18]. Results of this study led to the approval of trabectedin in the United States for the treatment of patients with advanced LMS or LPS who previously received anthracycline-containing chemotherapy [19]. The majority of patients in this trial (73%) had LMS (40% uLMS and 33% non-uterine LMS). This post hoc analysis was designed to compare treatment outcomes in the subset of patients with advanced uLMS who were enrolled in this phase 3 trial. The aim of this analysis was to evaluate PFS with trabectedin compared with dacarbazine among patients with this common subtype of STS.

METHODS

Study Design and Patients

This was a post hoc analysis in the subset of women with uLMS who participated in this randomized, phase 3, open-label, active-controlled, parallel-group, multicenter trial, which was conducted at 90 sites in 4 countries (US, Australia, Brazil, New Zealand). Full details of the study design, patient population, statistical analyses, and primary results of this pivotal phase 3 trial (registered as NCT01343277, and also known as ET743-SAR-3007) have been published [18].

Briefly, eligible patients were ≥ 15 years old with histologically proven unresectable locally advanced and/or metastatic LMS or LPS and measurable disease in accordance with Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 [20]. All patients had previously received anthracycline-based chemotherapy for advanced disease. Patients were permitted to have also received any number of prior lines of treatment. Other eligibility criteria included an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, recovery from any prior treatment-related toxicity (grade ≤ 1) according to National Cancer Institute Common Toxicity Criteria of Adverse Events (NCI-CTCAE, version 4.03), and adequate renal, hepatic, and bone marrow function according to standard laboratory parameters.

The study was approved by the institutional review boards or ethics committees at all participating institutions, and was conducted according to the Declaration of Helsinki, International Conference on Harmonisation, and the Guidelines for Good Clinical Practice. All patients provided written informed consent before participation in the study.

Treatments and Administration

Patients were randomized in a 2:1 ratio to receive either trabectedin (1.5 mg/m^2 , 24-hour intravenous [IV] infusion via central access catheter) (Yondelis[®], Janssen Products, LP, Horsham, PA) or dacarbazine (1 g/m^2 , 20–120 minute IV infusion) on day 1 of each 21-day treatment cycle. Patients were stratified by the number of prior lines of chemotherapy (1 vs. 2), ECOG performance status (0 vs. 1), and sarcoma subtype (LPS vs. LMS). Trabectedin was administered via central venous access starting 30 minutes after dexamethasone 20 mg IV premedication. Study treatment was continued until disease progression or unacceptable toxicity. Antiemetic use was permitted according to participating institutional guidelines. Dose reductions and dose delays for treatment-related toxicities were permitted as per protocol-defined criteria.

Assessments

The primary endpoint of the original phase 3 trial was overall survival (OS); secondary endpoints included investigator-assessed PFS, objective response rate (ORR), duration of response (DOR), clinical benefit rate [21] (CBR; defined as the sum of complete responses + partial responses + stable disease for at least 18 weeks), duration of stable disease, and safety outcomes. In addition, an independent radiology review of PFS (rPFS) was carried out in a subset of approximately 60% of the overall study population to confirm the investigator assessments. Assessments and procedures were described in the primary publication [18], and included baseline and end-of-treatment cardiac ejection fraction monitoring, quality-of-life (QOL) assessments prior to each dose on day 1 of each cycle, as well as the clinical setting (inpatient or outpatient) of the first dose administered for each patient.

The clinical cut-off (05 January 2015) for the final OS analysis was determined prospectively after 381 death events (66% of all randomized patients) had occurred in the total population, at which time there were 161 deaths in the uLMS subset. The clinical cut-off for the final analysis of the secondary endpoints was at the time of the interim analysis of

OS (16 September 2013), at which time 212 patients with uLMS had been randomized and were included in the PFS assessment.

Statistical Analyses

In this exploratory post hoc analysis, the efficacy population comprised all patients with uLMS who were enrolled and randomized, and the safety population comprised all patients who received at least one dose of study treatment. Efficacy analyses of OS, PFS, and DOR were performed using an unstratified log-rank test. A Cox proportional hazard model was used to estimate hazard ratios for OS and PFS. The ORR and CBR were evaluated using Fisher's exact test. Because OS findings in this phase 3 trial may have been influenced by subsequent treatments after patients discontinued study treatments, subsequent anticancer therapies were recorded. Safety data were summarized descriptively by frequency and severity of treatment-emergent adverse events (TEAEs), and by investigator-assessed relationship to treatment.

RESULTS

Patient Characteristics

A total of 577 patients, stratified by LMS or LPS, were randomized and included in the final analysis of OS. The trial was initiated on May 27, 2011 and completed on January 5, 2015. The subset analysis included 232 women with uLMS who were randomized to the trabectedin (n=144) or dacarbazine (n=88) groups (Figure 1), representing the largest histologic subset of the trial (40%). Baseline demographic and disease characteristics were well balanced between groups, except for small differences in prior radiation therapy (trabectedin vs. dacarbazine: 49% vs. 36%, respectively) and median time (range) from last disease progression (trabectedin vs. dacarbazine: 0.76 [0, 13.7] vs. 0.99 [0.1, 8.7] months, respectively); both differences favored the dacarbazine group (Table 1). More than 90% of patients in both groups had previously undergone surgery. The number of prior lines of therapy was also similar between groups. Approximately 78% of trabectedin-treated patients and 75% of dacarbazine-treated patients had received 2 or 3 lines of prior chemotherapy, and approximately 20% of patients in each group had received at least 4 prior lines of chemotherapy. All patients had received prior anthracycline, primarily doxorubicin, and more than 90% had also received gemcitabine-docetaxel.

Study Treatment

Treatment exposure and dose intensities are shown in Appendix Table S1. At the time of the final OS analysis, the median number of treatment cycles administered was 4 (range 1 to 44) for patients assigned to trabectedin and 2 (range 1 to 30) for patients assigned to dacarbazine. Of patients receiving trabectedin, 75% were treated as outpatients compared with 99% of patients receiving dacarbazine. Prolonged treatment courses were observed for patients in both treatment arms; the maximum number of cycles administered was 44 in the trabectedin group and 30 in the dacarbazine group. In total, 39% of patients in the trabectedin group and 19% patients in the dacarbazine group received 6 cycles of treatment, and 16% and 5%, respectively, received at least 12 cycles.

Cycle delays and dose reductions, as required by protocol-specified criteria to limit toxicity, were more commonly observed in patients receiving trabectedin than dacarbazine (trabectedin: 60% and 39%; dacarbazine: 38% and 6%, respectively). A total of 27% of patients assigned to trabectedin required one dose reduction compared with 6% of patients assigned to dacarbazine, and 12% of patients in the trabectedin group required 2 dose reductions. As for the total population, the most frequent reason for dose reductions with trabectedin was increased transaminases ($n=25$), and the most frequent reason for dose delays was neutropenia ($n=47$).

Efficacy

The final OS analysis for the uLMS subset, performed after 161 deaths, demonstrated that median OS was similar in the trabectedin and dacarbazine groups (trabectedin 13.4 months vs. dacarbazine 12.9 months, $HR=0.89$, $P=.51$) (Figure 2A).

The PFS analysis for patients with uLMS was performed after 141 disease progression events, corresponding to the interim analysis of OS. Median PFS was significantly longer in the trabectedin group (4 months [range 2.43 to 4.60]) compared with the dacarbazine group (1.5 months [range 1.48 to 2.83]; $HR=0.57$, $P=.0012$) (Figure 2B).

Regarding ORR, there were no complete responses in either treatment group, and partial responses in 11% and 9% of patients in the trabectedin and dacarbazine groups, respectively ($P=.82$) (Table 2). The median DOR was 6.5 months in the trabectedin group and 4.1 months in the dacarbazine group ($P=.32$). The CBR was 31% in the trabectedin group and 18% in the dacarbazine group ($P=.05$).

For this subset of patients with uLMS, the proportion of patients treated with subsequent anticancer chemotherapy was comparable between treatment groups (trabectedin: 76%; dacarbazine: 75%) (Table 3). Pazopanib was the most commonly received subsequent treatment in both groups, but was more frequently utilized in the dacarbazine group (trabectedin group: 35% vs dacarbazine group: 46%). Other common post-trabectedin treatments included dacarbazine (23%), gemcitabine (16%), and radiation 15%. Other common post-dacarbazine treatments included gemcitabine (22%), radiation (19%), and docetaxel (14%). For the trabectedin and dacarbazine groups, respectively, 6 (4%) and 9 (10%) patients received gemcitabine and docetaxel as a combination therapy.

Safety

Treatment-emergent AEs observed in the trabectedin and dacarbazine groups were consistent with established safety and toxicity profiles of both drugs. All patients in both groups experienced a TEAE, of which 97% and 91% were deemed to be related to trabectedin or dacarbazine, respectively (Appendix Table S2). Treatment-related grade 3–4 TEAEs occurred in 69% and 42% of patients in the trabectedin and dacarbazine groups, respectively, and treatment-related TEAEs leading to treatment discontinuation occurred in 13% and 9% of patients, respectively (Appendix Table S2).

Table 4 shows all TEAEs of any cause reported in 20% of patients in either group. The most commonly reported TEAEs of any grade were nausea (74% vs. 44%) and fatigue (66%

vs. 51%) in the trabectedin and dacarbazine groups, respectively. Toxicities of grade 3–4 severity were observed more frequently in the trabectedin group, and were predominantly laboratory-related toxicities reflecting myelosuppression (neutropenia, thrombocytopenia) and transient elevation of hepatic transaminases. The most frequently reported grade 3–4 TEAEs in the trabectedin group (10% of patients) were transaminitis (aspartate aminotransferase/alanine aminotransferase [AST/ALT] elevation), neutropenia, thrombocytopenia, leukopenia, and anemia (Table 4). In addition, creatinine phosphokinase (CPK) elevation of grade 3–4 severity was observed in 6 patients (4%), and CPK elevation of any grade was observed in 15 patients (11%). Grade 3–4 CPK elevations required trabectedin dose reduction.

In the dacarbazine group, grade 3–4 TEAEs occurring in 10% of patients were neutropenia and anemia. Febrile neutropenia occurred more frequently with trabectedin than with dacarbazine (5% vs. 2%, respectively). Two patients in the trabectedin group died as a result of a treatment-related TEAE, one from acute renal failure and one from respiratory distress.

DISCUSSION

We previously reported the results of a large phase 3, international, randomized trial of trabectedin versus dacarbazine in patients with advanced LMS or LPS who had received prior anthracycline therapy [18]. Here we report a post hoc subset analysis that was conducted in the 232 women in this trial who had uLMS, most of whom had received multiple lines of prior chemotherapy therapy, in addition to prior surgery and radiation. In patients with uLMS, trabectedin significantly improved disease control, as measured by PFS, compared with dacarbazine, with median PFS of 4.0 vs. 1.5 months, respectively (HR=0.57; $P=.0012$). This finding was similar to the results obtained in the total study population after 329 PFS events (median PFS for trabectedin vs. dacarbazine: 4.2 vs. 1.5 months; HR=0.55; $P=.0001$), which were validated through a central and blinded radiographic audit of 60% of the total population [18]. Furthermore, the median PFS results observed in the trabectedin group of the uLMS subset are similar to median PFS values reported in other studies of trabectedin in patients with uLMS (5.8 to 6 months) [14, 17]. The additional secondary endpoints reflect the disease stabilization that is characteristic of trabectedin treatment: the ORR was low for both trabectedin and dacarbazine (11% vs. 9%, respectively), while the CBR (reflecting both objective response and durable stable disease) was 31% in the trabectedin group compared with 18% in the dacarbazine group ($P=.051$). Correspondingly, 39% of patients in the trabectedin group and 19% of patients in the dacarbazine group received 6 or more cycles of treatment at the time of the final OS analysis.

In an earlier report of trabectedin in 11 patients with uLMS, objective responses were observed in 5 (45%) patients, with response or stable disease in 7 (64%) patients [22]. However, in a prospective phase 2 trial of trabectedin as first-line treatment in 20 patients with advanced uLMS, ORR was observed in 2 patients (10%), with a median PFS of 5.8 months [17]. Given that patients in this phase 3 uLMS subset had received multiple prior therapies, stabilization of disease for an extended period of time represents successful disease control. In the total ET43-SAR-3007 study population, disease stabilization in both

treatment groups was associated with maintenance of a low level of baseline symptomology, without clinically significant differences across treatment arms, as assessed by MD Anderson Symptom Inventory (MDASI) scores [23]. These findings confirm that prolonged disease control can be achieved with maintenance of quality of life in this patient population.

Despite the improved PFS observed with trabectedin, the final median overall survival demonstrated a statistically non-significant 11% reduction in the risk of death, with similar median overall survival observed in both groups (trabectedin 13.4 months vs. dacarbazine 12.9 months, HR=0.89, $P=.51$). These results were consistent with the observed median OS in the overall study population (trabectedin 13.7 months vs. dacarbazine 13.1 months; HR=0.92, $P=.49$). The absence of a survival benefit may have reflected differences in subsequent therapies utilized across the treatment groups, which included increased rates of pazopanib and combination gemcitabine-docetaxel in the dacarbazine treatment group.

The TEAEs reported for trabectedin and dacarbazine in this subset analysis were consistent with the known safety profiles of these agents. The incidence of grade 3/4 treatment-related TEAEs was higher in the trabectedin group, and predominantly reflected laboratory-related toxicities, including transient elevations of ALT and AST, and cytopenias. In a separate analysis of the overall population in the current phase 3 trial (ET743-SAR-3007), the occurrence of grade 3/4 transaminase elevations did not result in reduced efficacy (PFS and OS) relative to patients with lesser transaminase elevations, demonstrating the importance of complying with trabectedin dosing guidelines to provide patients with the best opportunity to experience clinical benefit [24].

In the current study, no routine antiemetics were required, apart from the single dose of IV dexamethasone premedication. There was a high incidence of nausea (74%) in the trabectedin group, suggesting that routine use of prophylactic antiemetic medication may be prudent. The clinically equivalent reporting of nausea severity across treatment arms in a QOL analysis of the 495 patients with LMS or LPS in this phase 3 trial supports this antiemetic approach [23]. Nearly half of the patients in the trabectedin group had received prior radiation therapy. It is possible that this radiation therapy history contributed to the moderately high frequency of grade 3/4 myelosuppression observed. Such patients may benefit from prophylactic myeloid growth factor use with trabectedin treatment.

The lack of cumulative toxicity with either agent in the present analysis permitted prolonged treatment courses, with maximum exposures of 44 and 30 cycles in the trabectedin and dacarbazine groups, respectively. Dose reductions and delays occurred more frequently in the trabectedin group than in the dacarbazine group, but were protocol-specified with the intent of minimizing trabectedin-related toxicity. These dosage adjustments were similar to those reported in other trabectedin studies, and were primarily due to transaminase elevations, neutropenia, or anemia [17, 22, 25]. The improved disease control, with equivalent reported QOL reported in the total ET43-SAR-3007 study population, suggests the importance of proper dose adjustment in patients receiving trabectedin, the majority of whom were treated as outpatients in the current study.

Despite not being observed in other studies with trabectedin, an increased rate of cardiac-related AEs was reported in the trabectedin group of the overall population in this phase 3 study. Objective declines in left ventricular ejection fraction were observed in both treatment groups (14% of assessed trabectedin patients vs. 11% of assessed dacarbazine patients), although these assessments were confounded by incomplete compliance in both groups, and increased exposure (and therefore observation time) in the trabectedin group [26]. Therefore, monitoring of cardiac function is noted as “required” in the US prescribing information in patients being treated with trabectedin, and is especially important in patients with higher cumulative doxorubicin exposure, an agent well known to be associated with cardiomyopathy [19].

In summary, in this post hoc subset analysis of data from a large randomized phase 3 trial, women with uLMS who had received prior anthracycline treatment achieved a significant improvement in PFS with trabectedin compared with dacarbazine. The observed efficacy and toxicity profile of trabectedin was similar to that reported in the overall LMS and LPS population [18]. This subset analysis confirms the ability of trabectedin to achieve clinically meaningful disease control rates for prolonged treatment periods, thereby supporting its use for women with advanced uLMS.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank the patients who volunteered to participate in this study and their families; the investigators and coordinators at each of the clinical sites; the sponsor staff involved in data collection and analyses. This work was funded by Janssen Research & Development, LLC, Raritan, NJ, USA. Dr. Hensley is supported in part by the MSK Cancer Center Support Grant P30 CA008748. Dr. Demetri is supported for this work in part by a grant from the Dr. Miriam and Sheldon G. Adelson Medical Research Foundation. Yvonne E. Yarker, PhD, ISMPP CMPP™ of the InSeption Group (Lansdale, PA, USA) provided medical writing services in the development of the manuscript, funded by Janssen Research and Development, LLC, Raritan, NJ, USA. The authors had complete access to all data and maintained control over the manuscript, including final wording and conclusions.

Study support: Funded by Janssen Research & Development, LLC. Dr. Hensley is supported in part by the MSK Cancer Center Support Grant P30 CA008748. Dr. Demetri is supported for this work in part by a grant from the Dr. Miriam and Sheldon G. Adelson Medical Research Foundation.

References

1. Hosh M, Antar S, Nazzal A, Warda M, Gibreel A, Refky B. Uterine Sarcoma: Analysis of 13,089 Cases Based on Surveillance, Epidemiology, and End Results Database. *Int J Gynecol Cancer*. 2016; 26:1098–104. [PubMed: 27177280]
2. Lange SS, Novetsky AP, Powell MA. Recent advances in the treatment of sarcomas in gynecology. *Discovery medicine*. 2014; 18:133–40. [PubMed: 25227754]
3. Ducie JA, Leitao MM Jr. The role of adjuvant therapy in uterine leiomyosarcoma. Expert review of anticancer therapy. 2016; 16:45–55. [PubMed: 26558647]
4. Hensley ML, Blessing JA, Degeest K, Abulafia O, Rose PG, Homesley HD. Fixed-dose rate gemcitabine plus docetaxel as second-line therapy for metastatic uterine leiomyosarcoma: a Gynecologic Oncology Group phase II study. *Gynecologic oncology*. 2008; 109:323–8. [PubMed: 18394689]

5. Hensley ML, Blessing JA, Mannel R, Rose PG. Fixed-dose rate gemcitabine plus docetaxel as first-line therapy for metastatic uterine leiomyosarcoma: a Gynecologic Oncology Group phase II trial. *Gynecologic oncology*. 2008; 109:329–34. [PubMed: 18534250]
6. Look KY, Sandler A, Blessing JA, Lucci JA 3rd, Rose PG, Gynecologic Oncology Group S. Phase II trial of gemcitabine as second-line chemotherapy of uterine leiomyosarcoma: a Gynecologic Oncology Group (GOG) Study. *Gynecologic oncology*. 2004; 92:644–7. [PubMed: 14766260]
7. Schoffski P, Cornillie J, Wozniak A, Li H, Hompes D. Soft tissue sarcoma: an update on systemic treatment options for patients with advanced disease. *Oncology research and treatment*. 2014; 37:355–62. [PubMed: 24903768]
8. van der Graaf WT, Blay JY, Chawla SP, Kim DW, Bui-Nguyen B, Casali PG, et al. Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet (London, England)*. 2012; 379:1879–86.
9. Allavena P, Signorelli M, Chieppa M, Erba E, Bianchi G, Marchesi F, et al. Anti-inflammatory properties of the novel antitumor agent yondelis (trabectedin): inhibition of macrophage differentiation and cytokine production. *Cancer research*. 2005; 65:2964–71. [PubMed: 15805300]
10. Germano G, Frapolli R, Belgiovine C, Anselmo A, Pesce S, Liguori M, et al. Role of macrophage targeting in the antitumor activity of trabectedin. *Cancer cell*. 2013; 23:249–62. [PubMed: 23410977]
11. Germano G, Frapolli R, Simone M, Tavecchio M, Erba E, Pesce S, et al. Antitumor and anti-inflammatory effects of trabectedin on human myxoid liposarcoma cells. *Cancer research*. 2010; 70:2235–44. [PubMed: 20215499]
12. Zewail-Foote M, Hurley LH. Ecteinascidin 743: a minor groove alkylator that bends DNA toward the major groove. *J Med Chem*. 1999; 42:2493–7. [PubMed: 10411470]
13. D’Incalci M, Jimeno J. Preclinical and clinical results with the natural marine product ET-743. *Expert opinion on investigational drugs*. 2003; 12:1843–53. [PubMed: 14585059]
14. Amant F, Lorusso D, Mustea A, Duffaud F, Pautier P. Management strategies in advanced uterine leiomyosarcoma: focus on trabectedin. *Sarcoma*. 2015; 2015:704124. [PubMed: 26089739]
15. Hyman DM, Grisham RN, Hensley ML. Management of advanced uterine leiomyosarcoma. *Current Opinion in Oncology*. 2014; 26:422–7. [PubMed: 24840518]
16. Sanfilippo R, Grosso F, Jones RL, Banerjee S, Pilotti S, D’Incalci M, et al. Trabectedin in advanced uterine leiomyosarcomas: a retrospective case series analysis from two reference centers. *Gynecologic oncology*. 2011; 123:553–6. [PubMed: 21917307]
17. Monk BJ, Blessing JA, Street DG, Muller CY, Burke JJ, Hensley ML. A phase II evaluation of trabectedin in the treatment of advanced, persistent, or recurrent uterine leiomyosarcoma: a gynecologic oncology group study. *Gynecologic oncology*. 2012; 124:48–52. [PubMed: 21996263]
18. Demetri GD, von Mehren M, Jones RL, Hensley ML, Schuetze SM, Staddon A, et al. 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. *Journal of Clinical Oncology*. 2016; 34:786–93. [PubMed: 26371143]
19. YONDELIS® (trabectedin) injection for intravenous use. Horsham, PA, USA: Janssen Products, LP; Jul. 2016
20. Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *Journal of the National Cancer Institute*. 2000; 92:205–16. [PubMed: 10655437]
21. Chmielowski B, Federman N, Tap WD. Clinical trial end points for assessing efficacy of novel therapies for soft-tissue sarcomas. *Expert Reviews in Anticancer Therapy*. 2012; 12:1217–28.
22. Amant F, Coosemans A, Debiec-Rychter M, Timmerman D, Vergote I. Clinical management of uterine sarcomas. *Lancet Oncology*. 2009; 10:1188–98. [PubMed: 19959075]
23. Demetri GD, von Mehren M, Jones RL, Hensley ML, Schuetze S, Elias AD, et al. Patient-reported outcomes from randomized, phase-3 study of trabectedin (T) vs. dacarbazine (D) in advanced leiomyosarcoma (LMS) or liposarcoma (LPS). *Journal of Clinical Oncology*. 2016; 34(suppl)

24. Calvo, E., Rodon, J., Dirix, L., Huizing, M., Senecal, F., Lorusso, P., et al. Trabectedin (T)-related liver toxicity: Results of a pharmacokinetic study with T in patients with hepatic dysfunction (OVC1004) and experience from a phase 3 clinical trial (SAR3007). Poster 190 presented at the American Society of Clinical Oncology Annual Meeting; Chicago, IL, USA. June 3–7, 2016;
25. Gounaris I, Hatcher HM, Davidson D, Sherbourne K, Alam S, Zaki KA, et al. Trabectedin for advanced soft tissue sarcomas: a single institution experience. *Future oncology*. 2014; 10:1843–51. [PubMed: 24450573]
26. Schuetze S, Patel S, von Mehren M, Ryan CW, Milhem MM, Van Tine BA, et al. Cardiac safety analysis of trabectedin (T) vs. dacarbazine (D) in patients (Pts) with advanced leiomyosarcoma (LMS) or liposarcoma (LPS) after prior anthracycline chemotherapy. *Journal of Clinical Oncology*. 2016; 34(suppl) abstr 11060.

RESEARCH HIGHLIGHTS

- Patients with advanced uterine leiomyosarcoma received trabectedin or dacarbazine
- Trabectedin significantly improved progression-free survival vs dacarbazine
- Lack of cumulative toxicity with trabectedin allows for prolonged treatment

No. Patients at Risk													
Dacarbazine	88	89	55	47	42	29	24	17	11	3	2	0	
Trabectedin	144	127	107	85	75	59	41	21	12	7	3	2	1

a

No. Patients at Risk

Dacarbazine	78	18	4	1	0	0
Trabectedin	134	49	21	8	1	0

b

FIGURE 2.
 Kaplan-Meier estimates for (A) OS and (B) PFS in the trabectedin and dacarbazine groups:
 uLMS subset.

TABLE 1

Patient Baseline demographics, disease characteristics, and prior treatment: uLMS subset.

	Trabectedin (N=144)	Dacarbazine (N=88)
Age, years, median (range)	54 (27.0; 81.0)	55 (31.0; 79.0)
Age category, years, n (%)		
18–<65	122 (85)	75 (85)
65–<75	18 (13)	11 (13)
75	4 (3)	2 (2)
Baseline BMI, kg/m ² , median (range)	28.40 (16.7; 78.1)	27.08 (17.5; 66.7)
Baseline ECOG performance status, n (%)		
0	69 (48)	41 (47)
1	75 (52)	47 (53)
Time from initial diagnosis to randomization, months, median (range)	31.64 (5.3; 130.4)	25.35 (1.9; 267.1)
Time from last disease progression to randomization, months, median (range)	0.76 (0.0; 13.7)	0.99 (0.1; 8.7)
Lines of prior chemotherapy, n (%)		
1	4 (3)	3 (3)
2	66 (46)	34 (39)
3	46 (32)	32 (36)
4	18 (13)	10 (11)
≥4	10 (7)	9 (10)
Best response to last line of previous chemotherapy therapy, n (%)		
Complete response	1 (1)	1 (1)
Partial response	16 (11)	6 (7)
No change (stable disease)	44 (31)	26 (30)
Progression of disease	82 (57)	55 (63)
Unknown/missing	1 (1)	0
Common prior chemotherapies, n (%)		
Anthracycline	143 (99)*	88 (100)
Doxorubicin	127 (88)	79 (90)
Gemcitabine–Docetaxel	132 (92)	84 (96)
Previous surgery, n (%)	140 (97)	85 (97)
Previous radiation, n (%)	70 (49)	32 (36)

BMI, body mass index; ECOG, Eastern Cooperative Oncology Group; uLMS, uterine leiomyosarcoma.

* Prior anthracycline treatment could not be confirmed in 1 patient who, despite the protocol deviation, was randomized and treated. This patient was included in efficacy and safety analyses in accordance with the statistical plan.

TABLE 2

Other secondary endpoints: uLMS subset.

Endpoints	Trabectedin (N=134)	Dacarbazine (N=78)	OR (95% CI)	P value
Overall response rate (complete response + partial response), * n (%)	15 (11.2)	7 (9.0)	1.279 (0.463–3.888)	.82
Clinical benefit rate, † n (%)	41 (31)	14 (18)	2.015 (0.976–4.332)	.05
	Trabectedin (N=134)	Dacarbazine (N=78)	HR (95% CI)	P value
Time to response, months, median (range)‡	3.22 (1.2; 10.4)	2.79 (1.3; 8.3)	–	–
Duration of response, months, median (95% CI)‡	6.47 (1.12–7.62)	4.07 (2.14–4.17)	0.463 (0.099–2.156)	.32

HR, hazard ratio; OR, odds ratio; uLMS, uterine leiomyosarcoma.

* All partial responses.

† Clinical benefit rate defined as complete response, partial response, or stable disease for ≥ 18 weeks (6 cycles).

‡ n=15 for trabectedin; n=7 for dacarbazine.

TABLE 3

Subsequent anticancer therapies: uLMS subset.

Therapy	Trabectedin (N=144), n (%)	Dacarbazine (N=88), n (%)
Patients with selected subsequent anticancer chemotherapy	109 (76)	66 (75)
Pazopanib	50 (35)	40 (46)
Dacarbazine	33 (23)	7 (8)
Gemcitabine	23 (16)	19 (22)
Radiation	21 (15)	17 (19)
Temozolomide	15 (10)	8 (9)
Surgery	12 (8)	9 (10)
Docetaxel	11 (8)	12 (14)
Ifosfamide	8 (6)	10 (11)
Vinorelbine	8 (6)	9 (10)
Doxorubicin	8 (6)	2 (2)
Eribulin	6 (4)	2 (2)
Trabectedin	0	2 (2)

uLMS, uterine leiomyosarcoma.

Note: Only subsequent anticancer therapies received by ≥ 5% of patients in either treatment group are reported, except for doxorubicin, eribulin, and trabectedin, which were reported regardless of their frequencies.

TABLE 4

Summary of adverse events of all grades (in 20% of patients in either group) and grades 3 or 4: uLMS subset.

	Trabectedin (N=140) n (%) [*]			Dacarbazine (N=81) n (%) [*]		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Nausea	104 (74)	12 (9)	0	36 (44)	20 (3)	0
Fatigue	92 (66)	12 (9)	0	41 (51)	0	1 (1)
ALT increased	69 (49)	46 (33)	1 (1)	6 (7)	1 (1)	0
Vomiting	68 (49)	10 (7)	0	18 (22)	1 (1)	0
Anemia	66 (47)	27 (19)	1 (1)	26 (32)	11 (14)	0
Neutropenia	65 (46)	29 (21)	22 (16)	24 (30)	13 (16)	5 (6)
Constipation	49 (35)	0	0	32 (40)	0	0
Decreased appetite	47 (34)	2 (1)	0	16 (20)	0	1 (1)
Diarrhea	46 (33)	2 (1)	0	24 (30)	0	0
Leukopenia	45 (32)	29 (21)	7 (5)	13 (16)	8 (10)	3 (4)
AST increased	44 (31)	20 (14)	1 (1)	6 (7)	0	0
Thrombocytopenia	37 (26)	7 (5)	14 (10)	22 (27)	8 (10)	5 (6)
Headache	37 (26)	1 (1)	0	15 (19)	0	0
Peripheral edema	36 (26)	1 (1)	0	8 (10)	1 (1)	0
Abdominal pain	34 (24)	12 (9)	0	18 (22)	6 (7)	0
Dyspnea	34 (24)	6 (4)	0	14 (17)	1 (1)	0
Cough	32 (23)	0	0	17 (21)	0	0
Pyrexia	29 (21)	1 (1)	0	12 (15)	0	0

ALT, Alanine aminotransferase; AST, aspartate aminotransferase; uLMS, uterine leiomyosarcoma.

^{*} Values represent the number and % of patients experiencing adverse events.