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REVIEW

Trabectedin for Soft Tissue Sarcoma: Current Status and Future Perspectives

Erlinda M. Gordon · K. Kumar Sankhala · Neal Chawla · Sant P. Chawla

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ABSTRACT

Trabectedin (ET743, Yondelis®, manufactured by Baxter Oncology GmbH, Halle/Westfalen, Germany, for Janssen Products, LP, Horsham, PA), derived from the marine ascidian, *Ecteinascidia turbinata*, is a natural alkaloid with multiple complex mechanisms of action. On 23 October 2015, 15 years after the results of the first Phase 1 clinical trial using trabectedin for chemotherapy-resistant solid malignancies was reported, and 8 years after its approval in Europe, the United States Food and Drug Administration (USFDA) finally approved trabectedin for the treatment of unresectable or metastatic liposarcoma or leiomyosarcoma that has failed a prior anthracycline-containing regimen. Approval was based on the results of a pivotal Phase 3 trial involving a 2:1 randomization of 518 patients (who were further stratified by soft tissue sarcoma subtype), in which a significant improvement in progression-free survival was reported in the trabectedin-treated group vs. the dacarbazine-treated group ($p < 0.001$). In this trial, the most common adverse reactions were nausea, fatigue, vomiting, constipation, anorexia, diarrhea, peripheral edema, dyspnea, and headache, while the most serious were neutropenic sepsis, rhabdomyolysis, cardiomyopathy, hepatotoxicity, and extravasation leading to tissue necrosis. The most common grade 3–4 adverse events were laboratory abnormalities of myelosuppression in both arms and transient transaminitis in the trabectedin arm. In a recent Phase 2 trial, trabectedin had a similar outcome as doxorubicin when given as a single agent in the first-line setting. Studies are also being conducted to expand the use of trabectedin not only as a first-line cancer drug, but also for a number of other clinical indications, for example, in the case of mesenchymal chondrosarcoma, for which trabectedin has been reported to be exceptionally active. The possibility of combining trabectedin with targeted therapies, immune checkpoint inhibitors or virotherapy would also be an interesting concept. In short, trabectedin is an

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E. M. Gordon (✉) · K. K. Sankhala · N. Chawla · S. P. Chawla
Sarcoma Oncology Center/Cancer Center of Southern California, Santa Monica, CA 90403, USA
e-mail: egordon@sarcomaoncology.com

old new drug with proven potential to impact the lives of patients with soft tissue sarcoma and other solid malignancies.

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OVERVIEW

Soft tissue sarcoma is a rare tumor of the mesenchymal tissue, with many histological subtypes. It comprises about 1% of all adult cancers. The American Cancer Society estimated that in the USA in 2015, about 11,930 new cases would be diagnosed and 4870 Americans would die of soft tissue sarcomas [1]. The most common types of sarcoma in adults are undifferentiated pleomorphic sarcoma (formerly known as malignant fibrous histiocytoma), liposarcoma, and leiomyosarcoma. There is a tendency for certain types of sarcoma to originate from specific anatomic sites, such as the abdomen for leiomyosarcoma or the extremities for liposarcoma and undifferentiated pleomorphic sarcoma [2]. Surgical resection is the treatment of choice for localized disease, with radiation given as first-line therapy for unresectable cases. Nonetheless, 50% of high-grade tumors tend to recur [3]. For decades, treatment options for soft tissue sarcoma have been limited to doxorubicin and/or ifosfamide, and the outcome for metastatic disease is poor, with an estimated median survival of 8–13 months, as reported from results of randomized studies conducted over the last 20 years [4–7]. Targeted therapies have recently come of age for soft tissue sarcoma, with the USFDA approval of pazopanib for locally advanced unresectable or metastatic soft tissue sarcoma with the exception of liposarcoma in 2012. Approval was based on the results of a randomized placebo-controlled Phase 3 (PALETTE) trial showing a significant, but modest, benefit in progression-free survival (PFS) for patients treated with pazopanib [8]. The approval of trabectedin in the USA in late 2015 shows promise for further improving the quality of life and progression-free survival of patients with soft tissue sarcoma.

Trabectedin is a natural alkaloid derived from the Caribbean tunicate, *Ecteinascidia turbinata*. It has multiple complex mechanisms of action [2, 9–13] and consequently the potential for extensive clinical applications. Further, several features of trabectedin's clinical performance differentiate it from other oncologic agents. These include prolonged tumor growth stabilization, favorable outcomes in sarcomas with genetic mutations, durability of response—even upon treatment reinstitution after interruption of therapy, and absence of cumulative toxicity [14]. This article reports on the critical stages of drug development of trabectedin in the US and worldwide and provides perspectives on its future as a uniquely effective oncologic agent for soft tissue sarcomas and other solid malignancies.

This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

CRITICAL STAGES OF TRABECTEDIN DRUG DEVELOPMENT

Preclinical Studies

Trabectedin, derived from the marine tunicate, *Ecteinascidia turbinata,* has multiple complex mechanisms of action. In preclinical studies,

trabectedin has been shown to bind to the N2 amino group of guanine residues in the minor groove of the DNA double helix and cause double-strand breaks [2, 9, 10]. Second, trabectedin interrupts the cell cycle, causes apoptosis of cancer cells and downregulates abnormal transcription factor expression such as FUS-CHOP or EWS-CHOP [10]. Third, trabectedin inhibits cytokine release by monocytes and macrophages in the tumor microenvironment via its direct cytotoxic effects on tumor-associated macrophages [11, 12]. This drug effect on the tumor microenvironment is deemed critically important in cancer therapy because of the resultant inhibition of neoangiogenesis and the metastatic potential of cancer cells [13].

Clinical Studies

Efficacy Studies

Table 1 lists selected Phase 1 clinical trials using trabectedin for advanced solid tumors and the Phase 2 and 3 studies for soft tissue sarcoma, including retrospective analytical reports and data from the expanded access program. There are more studies of trabectedin conducted for other clinical indications that are not listed in the tables.

Phase 1 Studies

The goal of the Phase 1 clinical trials, which involved patients with advanced solid malignancies, was to determine the dose-limiting toxicity and maximum tolerated dose of trabectedin as well as to evaluate its pharmacokinetics, pharmacodynamics, and potential for adverse drug reactions. There were at least seven reported Phase 1 studies using trabectedin as a single agent for advanced solid tumors [15–21] and five Phase 1 studies using trabectedin in combination with either doxorubicin, doxil, gemcitabine, or cisplatin (Table 1) [22–26].

In 2001, Delaloge et al. [16] first reported on the clinical activity of trabectedin in 29 patients with soft tissue sarcoma who had failed treatment with doxorubicin and one other chemotherapeutic agent (12 from a phase 1 trial and 17 from a compassionate use program cohort). In this study, there were 4/29 partial responses (PR), 2/29 minor responses with tumor reduction of at least 30% in both cases, and 10/29 stable disease (SD) lasting more than 2 months and median time to progression of 2.8 months. In the same year, Taama et al. [17] determined the optimal regimen of trabectedin to be 1.5 mg/m^2 as a 24-h continuous intravenous infusion once every 3 weeks from a Phase 1 study involving 52 patients. Trabectedin was characterized by a moderate plasma clearance (31.5 and 37.5 l/h in the absence and presence of coadministered dexamethasone, respectively) and a large volume of distribution at steady state (in excess of 5000 l) [27]. The biologic half-life of trabectedin ranged from 27 to 89 h in pharmacokinetic studies [15, 18, 19], depending on the mode of administration and infusion schedule. The terminal half-life calculated using data from 14 Phase 1 and Phase 2 studies using non-linear mixed effects models was longer, in the range of 175 h [27].

Of the five Phase 1 studies using trabectedin and one other chemotherapeutic agent, the most promising combination regimen in advanced soft tissue sarcomas (STS) and breast cancer was trabectedin with doxorubicin, with an overall response rate (ORR) of 18%, SD of 56%, and disease control rate (DCR) of 74% [26].

Table 1 Phase 1–3 clinical trials using trabectedin for soft tissue sarcoma

Publication, year	No. of patients	Study features	Results and conclusions
Phase 1 single agent			
Van Kesteren, 2000	52	First report on pharmacokinetics of trabectedin in all solid tumors	Biologic half-life = 89 h Recommended Phase 2 dose = 1500 μg/m^2 as 24 h CIV infusion
Delalogue, 2001	29	First report of activity of trabectedin in soft tissue sarcoma	PR = 4/29, SD = 10/29, DCR = 48%, median time to progression = 2.8 months
Taama, 2001	52	Established optimal regimen of trabectedin 1.5 mg/m^2 as a 24-h CIV infusion once every 3 weeks	PR = 3/52 (5.7%), SD = 4/52 (7.7%), DCR = 7/52 (13%) lasting ≥3 months
Ryan, 2001	21	Report on pharmacokinetics of trabectedin given as 72 h CIV infusion every 3 weeks	Biologic half-life = 69 h No objective responses; anti-tumor activity noted by PET scan in epithelioid mesothelioma Recommended Phase 2 dose: 1050 μg/m^2
Villalona-Calero, 2002	42	Report on pharmacokinetics of trabectedin in escalating doses, daily, given as 1-h IV infusion for 5 days every 3 weeks	Biologic half-life = 27 h Antitumor activity was noted in 3 patients with leiomyosarcoma and primary peritoneal and ovarian carcinomas Recommended Phase 2 dose: 325 μg/m^2/day daily × 5 every 3 weeks
Twelves, 2003	72	Report on pharmacokinetics of trabectedin given as 1 or 3 h IV infusion	Pharmacokinetics linear, not cumulative Recommended dose for Phase 2 clinical trial is 1.65 mg/m^2
Forouzesh, 2009	63	Report on the maximum tolerated dose of trabectedin at different dosing and infusion schedules	Trabectedin, 0.61 mg/m^2 and 0.58 mg/m^2, are the respective maximum tolerated doses (MTD) for trabectedin administered as a 1- and 3-h infusion in weekly regimens

Table 1 continued

Publication, year	No. of patients	Study features	Results and conclusions
Phase 1 combination regimen			
Blay, 2008	41	Phase 1 study of trabectedin and doxorubicin in soft tissue sarcoma	ORR = 12%, median PFS = 9.2 months
Messersmith, 2008	15	Phase 1 study of trabectedin and gemcitabine in advanced solid tumors	Lack of pharmacokinetic interaction and potential efficacy of trabectedin and gemcitabine combination therapy
Von Mehren, 2008	36	Phase 1 study of trabectedin and pegylated liposomal doxorubicin in advanced malignancies	ORR = 6/36 (16.7%), SD = 14/36 (38.9%), DCR = 20/36 (55.6%)
Sessa, 2009	39	Phase 1 study of trabectedin and cisplatin in solid tumors	The administration of trabectedin and cisplatin on days 1 and 8 resulted in prolonged neutropaenia requiring treatment delay
Sessa, 2009	29	Phase 1 study of trabectedin and doxorubicin in advanced STS and breast cancer	The most promising results in STS with ORR = 18%, SD = 56%, DCR = 74%
Phase 2 single agent			
Ryan, 2002	20	Phase 2 study of trabectedin in GIST Phase 2 study of trabectedin, 1500 μg/m^2, administered as a 24-h CIV infusion every 3 weeks	SD = 2/20 (10%), median PFS = 1.25 months, median OS = 8.6 months (w/o imatinib)
Yovine, 2004	54	Phase 2 study of trabectedin, 1500 μg/m^2, administered as a 24-h CIV infusion every 3 weeks	PR = 3.7%, SD = 17%, median PFS = 1.9 months
Garcia-Carbonero, 2004	36	Phase 2 study of trabectedin, 1500 μg/m^2, administered as a 24-h CIV infusion every 3 weeks	CR = 1/36 (2.8%), PR = 2/36 (5.6%), ORR = 8%, median PFS = 1.7 months, median OS = 12.1 months

Table 1 continued

Publication, year	No. of patients	Study features	Results and conclusions
EORTC Blay, 2004	28	Phase 2 study of trabectedin in GIST Trabectedin, 1500 μg/m^2, administered as a 24-h CIV infusion every 3 weeks	SD = 9/28 (32%), median PFS = 1.7 months, median OS = 19.3 months (may be due to imatinib use)
EORTC Le Cesne, 2005	104	Phase 2 study of trabectedin, 1500 μg/m^2, administered as a 24-h CIV infusion every 3 weeks	PR = 8/104 (7.7%), SD = 45/104 (43.3%), DCR = 51%, median PFS = 3.4 months, median OS = 9.2 months
Morgan, 2007	270	A randomized Phase 2 study comparing trabectedin given at 580 μg/m^2 on a weekly schedule to the "standard" 1500 μg/m^2 24-h continuous infusion every 3 weeks schedule	Median PFS = 2.3 months, in 580 μg/m^2 arm every week; median PFS = 3.3 months in 1500 μg/m^2 arm every 3 weeks ($p = 0.0418$)
ET 743-STS-201 Demetri, 2009	270	A randomized Phase 2 study comparing different dosing schedules of trabectedin	Median TTP = 3.7 months for the every 3 week 24-h CIV group, compared with 2.3 months for the every week 3-h group ($p = 0.0302$). Median OS = not significant
Monk, 2012	20	Phase 2 study of trabectedin in uterine leiomyosarcoma only	PR = 2/20 (10%), SD = 10/20 (50%), median PFS = 5.8 months. Median OS $\geq$ 23.1 months
Gronchi, 2012	23	Phase 2 study using trabectedin in the neoadjuvant setting in advanced localized myxoid liposarcoma	CR = 3/23 (13%), PR = 7/23 (30.4%), ORR = (43.4%), SD = 13/23 (56.5%), DCR (100%), no PD

Table 1 continued

Publication, year	No. of patients	Study features	Results and conclusions
Phase 2 combination regimen			
Pautier, 2015	109	Phase 2 study using trabectedin with doxorubicin as first-line therapy for uterine leiomyosarcoma and soft tissue leiomyosarcoma	Uterine leiomyosarcoma ($n = 47$): PR = 28/47 (59.6%); SD = 13/47 (27.6%); DCR = 41/47 (87.2%); soft tissue leiomyosarcoma ($n = 61$): CR = 2/61 (3.3%), PR = 22/61 (36.1%), ORR = 39.4%), SD = 32/61 (52.5%), DCR = 56/61 (91.9%)
Retrospective study			
Huygh, 2006	89	Retrospective study of 15 patients in Phase 2 study, and compassionate use of 74 patients Trabectedin 1500 μg/m^2 administered as a 24-h CIV infusion every 3 weeks	ORR = 6/89 (7%; 1 CR, 5 PR), SD = 32/89 (36%), DCR = 43%, median PFS = 2 months, median OS = 8.2 months
Schöffski, 2006	92	Retrospective analysis of the NER and HRR status, using RT-PCR, in tumors of trabectedin-treated patients ERCC1 is part of the NER machinery and BRCA1 is part of the HRR system	Patients whose tumors expressed higher ERCC1 had improved 6-month PFS rate and median OS compared with patients whose tumors expressed lower levels of ERCC1 (32% vs. 15%, $p = 0.07$, and 12 vs. 7 months respectively) Patients whose tumors expressed lower levels of BRCA1 had improved 6-month PFS rate and median OS compared with patients whose tumor expressed high levels of BRCA1 (33% vs. 11%, $p = 0.02$ and 15 vs. 5 months, $p = 0.0003$, for PFS and OS respectively). ERCC1 and BRCA1 are independent predictors of PFS. Only BRCA1 predicted OS

Table 1 continued

Publication, year	No. of patients	Study features	Results and conclusions
Grosso, 2007	51	Retrospective analysis of patients with myxoid liposarcoma treated with trabectedin in 5 European and American insitutions	ORR = 26/51 (51%) (CR = 4%, PR = 47%), SD = 20 (39%), DCR = median PFS = 14 months
San Filippo, 2011	66	Retrospective study of trabectedin in uterine leiomyosarcoma only	PR = 11/66 (16%), SD = 23/66 (35%), DCR = 51%, median PFS = 3.3 months
Le Cesne, 2015 French Sarcoma Group	885	Retrospective analysis from 25 French centers using trabectedin at 1.5 mg/m^2 as CIV infusion for 24 h q 3 weeks	ORR = 150/885 (17%), DCR = 592/885 (67%), median PFS = 4.4 months; median OS = 12.2 months; 227 patients who continued trabectedin up to disease progression, had a median PFS of 11.7 months, median OS = 24.9 months Conclusion: Longer trabectedin treatment until disease progression is associated with a significantly improved PFS and OS
Blay, 2015	129	Retrospective analysis of patients treated with trabectedin in a second-line setting vs. third- or fourth-line setting	Conclusion: all efficacy outcomes were better in patients who received trabectedin as second-line treatment compared with patients with more extensive prior therapy
Syed, 2015	18	Retrospective analysis of patients treated with trabectedin in chemotherapy-resistant advanced chondrosarcoma	Mesenchymal type: median PFS = 36 months. Other subtypes: median PFS = 4 months
Phase 2b			
Bui-Nguyen, 2015	133	Phase 2b randomized trial using trabectedin vs. doxorubicin as first-line treatment for advanced metastatic soft tissue sarcoma	Study terminated because of lack of significance in outcome; doxorubicin remains standard first-line treatment

Table 1 continued

Publication, year	No. of patients	Study features	Results and conclusions
Expanded access			
Samuels, 2013	1895	Expanded access program for advanced soft tissue sarcomas following failure of prior chemotherapy	Patients with leiomyosarcoma and liposarcoma had significantly longer OS compared to all other histological subtypes (16.2 vs. 8.4 months, respectively), as well as a higher objective response rate (6.9% vs. 4%, respectively)
Phase 3 soft tissue sarcoma			
Blay, 2013	121	Phase 3 randomized study comparing doxorubicin and trabectedin as first-line therapy in translocation-related sarcomas	No significant difference in PFS or OS between the two arms of the trial. The response rate by RECIST was significantly higher in the doxorubicin (27%) arm compared to the trabectedin (5.9%) arm of the trial
Demetri, 2015	518	Pivotal Phase 3, 2:1 randomized study using trabectedin vs. dacarbazine in locally advanced, unresectable or metastatic leiomyosarcoma and liposarcoma; trabectidin 1.5 mg/m^2 as a 24-h CIV every 3 weeks ($n = 345$) vs. dacarbazine 1000 mg/m^2 IV over 20–120 min every 3 weeks ($n = 173$)	Statistically significant improvement in progression-free survival, gained US FDA approval on 23 October 2015

BRCA1 breast cancer 1, *CIV* continuous intravenous infusion, *DCR* disease control rate, *ERCC1* excision repair cross-complementing 1, *GIST* gastrointestinal stromal tumor, *HRR* homologous recombination repair, *IV* intravenous, *NER* nucleotide excision repair, *ORR* overall response rate, *OS* overall survival, *PD* progressive disease, *PET* positron emission tomography, *PFS* progression-free survival, *PR* partial response/s, *SD* stable disease, *RECIST* response criteria in solid tumors, *RT-PCR* reverse transcription polymerase chain reaction, *STS* soft tissue sarcoma/s, *TTP* time to progression

Phase 2 Studies

The goal of the Phase 2 clinical trials was to evaluate the safety and efficacy of trabectedin at the recommended dosage and mode of administration derived from the results obtained from Phase 1 trials in a larger number of patients with STS who have failed standard chemotherapy. Some investigators reported on the use of trabectedin in the first-line and the neoadjuvant settings. At least nine Phase 2 clinical studies have been conducted worldwide (Table 1) [28–36]. The efficacy and safety of trabectedin in soft tissue sarcoma are based on a randomized trial, STS-201, in patients with locally advanced or metastatic lipo- or leiomyosarcoma, whose disease had progressed or relapsed after treatment with at least anthracyclines and ifosfamide. Additionally, in 2005, Le Cesne and the EORTC [32] reported the results of a Phase 2 study using trabectedin at 1.5 mg/m^2 CIV in 104 patients. In that study, there were 8 (7.7%) PRs and 45 (43.3%) SDs. After a median follow-up of 34 months, the median PFS was 3.4 months, and the median overall survival was 9.2 months. The results of these Phase 2 trials led to the accelerated approval of trabectedin by the European Union for advanced soft tissue sarcoma in 2007. The best Phase 2 results were reported by Monk et al. [34] in 2012, with a PFS of 5.8 months in patients with uterine leiomyosarcoma.

Retrospective Studies

At least five retrospective studies were conducted between 2006 and 2015 [37–41]. One study involved the analysis of 885 patients from 25 French centers using trabectedin at 1.5 mg/m^2 as CIV infusion for 24 h every 3 weeks [41]. In this study, the reported ORR was 17%, with a DCR of 67%, PFS of 4.4 months, and median overall survival (OS) of 12.2 months. In a report by Grosso et al. (2007) [39], retrospective analysis of patients with myxoid liposarcoma in five European and American institutions showed an ORR of 51%, DCR of 90%, and median PFS of 14 months. In 2011, San Filippo et al. [40] reported a PR of 16%, SD of 35%, and PFS of 3.3 months in patients with uterine leiomyosarcoma.

Phase 3 Studies

Two Phase 3 randomized clinical trials were conducted. One study compared the efficacy of trabectedin vs. doxorubicin in translocation-related sarcomas [42]. The other compared the PFS using trabectedin vs. dacarbazine [43].

The Phase 3 randomized study comparing doxorubicin and trabectedin as first-line therapy for translocation-related sarcomas enrolled 121 patients and reported no significant difference in PFS or OS between the two arms of the trial, with the response rate by response criteria in solid tumors (RECIST) significantly higher in the doxorubicin arm (27%) compared to the trabectedin arm (5.9%). Consequently, doxorubicin remains the first-line treatment for translocation-related sarcoma. It is important to note, however, that the study was underpowered because of the high censoring rate and high rate of ineligible patients.

In the pivotal Phase 3 study using trabectedin vs. dacarbazine in locally advanced, unresectable, or metastatic leiomyosarcoma and liposarcoma, patients were randomized at a 2:1 trabectedin:dacarbazine ratio. The study enrolled a total of 518 patients, with 345 randomized to the trabectedin arm and 173 to the dacarbazine arm [43]. Trabectedin was given at a dose of 1.5 mg/m^2 as a 24-h CIV every 3 weeks and dacarbazine at 1000 mg/m^2 IV over 20 to 120 min every 3 weeks. The median patient age

was 56 years (range 17–81), and 30% were male, 77% white, 12% black, and 4% Asian. The study was further stratified based on subtype (leiomyosarcoma vs. liposarcoma), Eastern Cooperative Oncology Group (ECOG) score (0 or 1), and number of previous chemotherapies (1 vs. 2 or more). Previous chemotherapy included doxorubicin and ifosfamide, or doxorubicin or ifosfamide and one other drug. Doxorubicin was used in 90% of cases, gemcitabine in 81%, docetaxel in 74%, ifosfamide in 59%, and pazopanib in 10%. Seventy-three percent of patients had leiomyosarcoma, and 27% had liposarcoma. Forty-nine percent had an ECOG score of 0, and 89% had two prior chemotherapy regimens. Median PFS for trabectedin vs. dacarbazine was 4.2 and 1.5 months, respectively (hazard ratio, 0.55; $p < 0.001$). Based on a significant improvement in PFS for the trabectedin arm, the USFDA gave full marketing approval of trabectedin for leiomyosarcoma and liposarcoma on 23 October 2015.

Expanded Access Program

The expanded access program for advanced soft tissue sarcomas following failure of prior chemotherapy enrolled 1895 patients worldwide (Table 1) [44]. Analysis of the data revealed that patients with leiomyosarcoma and liposarcoma had a higher ORR (6.9% vs. 4%, respectively) and significantly longer OS (16.2 vs. 8.4 months, respectively) than all other histological subtypes. Patient enrollment has continued beyond this publication.

Toxicity Studies

The adverse events reported in the Phase 3 trial of trabectedin vs. dacarbazine in leiomyosarcoma and liposarcoma patients who had failed at least one anthracycline-based regimen and one of another chemotherapeutic agent are listed in the USFDA Product Information document [45]. The most common adverse reactions occurring in greater than 10% of patients, and at a higher incidence than the control arm receiving dacarbazine, include nausea in 75%, fatigue in 69%, vomiting in 46%, constipation and decreased appetite in 37%, and diarrhea in 35%. Less common adverse reactions were dyspnea and headache in 25%, arthalgia and insomnia in 15%, and myalgia in 12%. Grade 3–4 adverse reactions were uncommon (<10%). The most common laboratory abnormalities include anemia in 96%, increased alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase levels in 90, 84, and 70%, respectively, neutropenia in 66%, hypoalbuminemia in 63%, thrombocytopenia in 59%, increased creatine phosphokinase in 33%, and hyperbilirubinemia in 13%. Among the common grade 3–4 adverse events (>10%) were neutropenia in 43%, thrombocytopenia in 21%, anemia in 19%, and increased ALT and AST levels in 31% and 17%, respectively.

An important factor in reducing toxicity is the use of dexamethasone as pre-medication before starting trabectedin infusion. In a previous study by Grosso et al., the incidence of grade 3–4 liver enzyme elevation, neutropenia, and thrombocytopenia fell to 3, 10, and 0%, respectively, in patients who received routine antiemetic prophylaxis with steroids on day 0 and possibly on day +1, compared with 70, 39, and 35%, respectively, in the group who received dexamethasone prophylaxis 4 mg PO BID the day before trabectedin infusion ($p = 0.0001$) [46, 47].

TRABECTEDIN APPLICATIONS IN THE CLINIC

In the European Union, trabectedin (Yondelis® manufactured by Baxter Oncology GmbH, Halle/Westfalen, Germany, for Janssen Products, LP, Horsham, PA) gained marketing approval for ovarian cancer and soft tissue sarcoma under "exceptional circumstances" from the European Commission in September 2007 based on favorable results of Phase 2 studies [48]. The following is a summary of the European Public Assessment Report (EPAR) for trabectedin, which explained the process used by the Committee for Medicinal Products for Human Use (CHMP) in granting marketing approval and provided recommendations for optimum drug administration. For soft-tissue sarcoma, patients who received trabectedin at 1.5 mg/m^2 every 3 weeks had an average of 3.8 months PFS compared with 2.1 months in patients who received a lower dose—three times per month. For ovarian cancer, patients who received the combination of trabectedin and pegylated liposomal doxorubicin (PLD) had a longer average PFS (7.3 months) compared to those patients who received PLD alone (5.8 months). In these Phase 2 studies, 10% of patients treated with trabectedin as a single agent and 25% treated with trabectedin in combination therapy had serious side effects. The most common side effects of any severity were neutropenia, nausea, vomiting, increase in liver enzymes, anemia, fatigue, thrombocytopenia, anorexia, and diarrhea. Trabectedin gained full marketing approval for ovarian cancer and soft tissue sarcoma from the European Commission in May 2015.

In the US, trabectedin (Yondelis,) gained FDA approval on 23 October 2015 for unresectable or metastatic liposarcoma or leiomyosarcoma patients who received a prior anthracycline-containing regimen [45]. The recommended dose is 1.5 mg/m^2 administered as a continuous intravenous infusion over 24 h through a central venous line every 21 days in patients with normal bilirubin and AST or ALT $\leq$2.5 times the upper limit of normal. Since there was no evidence of cumulative toxicity in the Phase 3 clinical trials, trabectedin may be given until disease progression or unacceptable toxicity occurs. There is no recommended dose of trabectedin in patients with serum bilirubin levels above the institutional upper limit of normal. The product information recommends premedication with 20 mg dexamethasone intravenous over 30 min prior to each trabectedin dose to reduce documented liver toxicity [45, 46].

Based on the toxicity profile of trabectedin, the USFDA product information [45] recommends dose modifications for neutropenia, thrombocytopenia, elevated bilirubin, serum transaminases, and creatine phosphokinase, decreased left ventricular ejection fraction or clinical evidence of cardiomyopathy, or any grade 3 or 4 non-hematologic adverse reactions. The first recommended dose reduction is to 1.2 mg/m^2 every 3 weeks, the second to 1.0 mg/m^2 every 3 weeks. Once reduced, the dose of trabectedin should not be increased in subsequent treatment cycles. Recommended dose modifications include permanently discontinuing trabectedin for persistent adverse reactions requiring a delay in dosing of more than 3 weeks, for adverse reactions requiring dose reduction following trabectedin administered at 1.0 mg/m^2, and for severe liver dysfunction in the prior treatment cycle.

Drug interactions can also occur between trabectedin and cytochrome CYP3A inhibitors or inducers. Therefore, the use of strong CYP3A

inhibitors (e.g., oral ketoconazole, itraconazole, posaconazole, voriconazole, clarithromycin, telithromycin, indinavir, lopinavir, ritonavir, boceprevir, nelfinavir, saquinavir, telaprevir, nefazodone, and conivaptan) should be avoided in patients taking trabectedin. Grapefruit or grapefruit juice should also be avoided during trabectedin treatment, as well as the use of strong cytochrome CYP3A inducers such as rifampin, phenobarbital, and St. John's wort [45].

THE FUTURE OF TRABECTEDIN

In the European Union, trabectedin has been approved for ovarian cancer and soft tissue sarcoma. Given that USFDA approval of trabectedin is limited to only two subtypes of soft tissue sarcoma, i.e., unresectable or metastatic liposarcoma or leiomyosarcoma patients who received a prior anthracycline-containing regimen, trials for other types of sarcoma that respond well to trabectedin, such as mesenchymal chondrosarcoma, will provide additional data to support its use in the absence of an FDA-approved clinical indication.

Evidence to support the use of trabectedin in mesenchymal chondrosarcoma involves the reported positive results of a single-center retrospective analysis of patients treated in various IRB-approved trials [49]. The objective was to examine the clinical benefit of trabectedin to various chondrosarcoma subtypes in a cohort of patients with advanced unresectable disease. Patients included in this retrospective analysis received trabectedin administered at doses of 1.2–1.5 mg/m^2 by 24-h infusion every 3 weeks. Tumor response was evaluated from serial scans (computed tomography/magnetic resonance imaging/positron emission tomography) by RECIST 1.1 criteria every 8 weeks. Treatment adverse effects were assessed by clinical evaluation and laboratory investigations.

Briefly, there were a total of 18 patients studied: 5 with conventional chondrosarcoma, 5 with mesenchymal chondrosarcoma, 5 with myxoid chondrosarcoma, and 3 with de-differentiated chondrosarcoma. Mean age was 53 years with a male-to-female ratio of 11:7. Adverse events were as follows: 33% of patients had CTCAE grade 3–4 thrombocytopenia at least once; 11% had grade 3–4 neutropenia not associated with febrile episodes; one patient had grade 3–4 anemia; one patient had grade 3–4 elevated liver enzymes; none developed cardiotoxicity or nephrotoxicity during treatment; one patient discontinued treatment because of port infiltration after one cycle. Treatment dosage was reduced in 10 of 18 (56%) patients in response to adverse events and side effects.

Analyses of the safety and efficacy of trabectedin use in mesenchymal chondrosarcoma are as follows: (1) patients with mesenchymal chondrosarcoma had a higher median PFS and percentage PFS at 3 and 6 months than patients with other chondrosarcoma subtypes, (2) trabectedin has manageable hematological side effects and did not result in any cardiotoxicity or nephrotoxicity in our cohort, and (3) there was no evidence of cumulative toxicity even with prolonged duration of treatment.

Other promising studies include a recent report of trabectedin activity in patients with translocation-related sarcomas. In this Phase 2 open-label randomized study, trabectedin was compared with best supportive care as second or later line treatment. A total of 76 patients were enrolled with 73 evaluable patients. Median PFS was 5.6 months for trabectedin-treated patients

vs. 0.9 months for patients who received best supportive care ($p < 0.0001$). These data suggest a significant increase in PFS in trabectedin-treated patients compared to those who received best supportive care [50]. A number of clinical trials are ongoing using combination regimens of trabectedin with olaparib [a poly (ADP-ribose) polymerase (PARP) inhibitor] or with radiotherapy [51]. Retrospective analysis of patients treated with trabectedin in second- and third-line settings shows a trend toward earlier treatment with trabectedin [52]. Prospective investigations could include combination regimens with trabectedin and promising chemotherapeutic agents, such as eribulin and aldoxorubicin. Cancer immunotherapy is also coming of age, and combination regimens of trabectedin—to expose tumor neoantigens in the TME—with immune checkpoint inhibitors and/or oncolytic viruses expressing granulocyte macrophage colony stimulating factor (GM-CSF) to recognize the neoantigens, may evoke a favorable immunologic response in certain patients with soft tissue sarcomas.

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