J Med Drug Rev 2015;5:33 – 42

Efficacy of trabectedin in patients with some rare advanced soft tissue sarcoma subtypes other than liposarcoma and leiomyosarcoma

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ABSTRACT

Trabectedin is indicated for the treatment of adult patients with advanced soft tissue sarcoma (STS) after failure of anthracyclines and ifosfamide, or who are unsuited to receive these agents. Efficacy data, however, were based mainly on liposarcoma and leiomyosarcoma patients. In addition to these sarcoma subtypes, commonly abbreviated as L-sarcomas, clinical data and research on trabectedin has increasingly focused on other histological subtypes. Evidence is emerging that distinct histopathological differences between subtypes may have a significant impact on the optimal management and outcomes in patients with specific soft tissue sarcomas. The low incidence of the more than 50 histological sarcoma subtypes makes the collection of data very difficult. The results from numerous studies, case reports and analyses of "real-life" patient series treated in compassionate use and expanded access programs have provided encouraging results, demonstrating that patients with non-L-sarcoma histologies may also benefit from treatment with trabectedin.

This review focuses on the available evidence regarding the use of trabectedin for the treatment of a broad range of non-L-sarcomas, supporting its valuable role in these rare sarcoma subtypes.

Keywords : trabectedin · Yondelis · soft tissue sarcomas · retreatment · maintenance treatment

1. Introduction

Soft tissue sarcomas (STS) are a heterogeneous group of rare tumors of mesenchymal origin, some of which are characterized by specific chromosomal and molecular abnormalities (Table 1). To date, at least fifty histological STS subtypes have been identified, and their number continues to increase. STS account for approximately 1 % of all adult and 15 % of all childhood malignancies. Apart from undifferentiated pleomorphic sarcomas (15 – 25 %), the most common STS subtypes developing in adulthood are the so-called L-sarcomas, i.e., leiomyosarcomas (15 – 25 %) and liposarcomas (10 – 15 %). The remaining subtypes are occasionally summarized as non-L-sarcomas. In children and adolescents, rhabdomyosarcomas, Ewing's sarcomas and synovial sarcomas are among the most common subtypes. Depending on their histology and cytogenetic abnormalities which can often be used to verify diagnosis, many STS subtypes also exhibit specific clinical features. In view of the increasing complexity of diagnostic evaluation, staging and treatment of STS, primary treatment of these tumors should be carried out in a specialized sarcoma center.

A series comparison that included more than 1,000 patients from the French Sarcoma Group database has demonstrated that the median overall survival (OS) of patients with metastatic STS has markedly improved by approximately 50 % over the past 20 years.[1] This remarkable progress seems to be essentially related to the improved knowledge regarding the clinical and biologic characteristics of STS histologic subtypes, which forms the basis for new, effective therapeutic strategies. For example, imatinib has shown promising efficacy in advanced

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dermatofibrosarcoma protuberans, paclitaxel in angiosarcoma, dacarbazine or gemcitabine alone or combined with docetaxel in leiomyosarcoma, mammalian target of rapamycin (mTOR) inhibitors in perivascular epitheloid cell tumors, and trabectedin in leiomyosarcomas and liposarcomas. These new agents have opened the possibility of offering patients further lines of treatment after failure of an established anthracycline-based first-line regimen. In addition, those findings have also resulted in an increasing number of patients being enrolled in clinical trials.

Trabectedin (Yondelis®) is an alkylating agent originally isolated from the Caribbean sea squirt *Ecteinascidia turbinata* and is currently manufactured by chemical synthesis.[2] In 2007 trabectedin obtained marketing authorization from the European Commission and afterwards in many other countries worldwide for the treatment of adult patients with advanced STS following failure of anthracyclines and ifosfamide, or as front-line therapy for those patients who are unsuited to receive these agents. Since 2009 the European Commission also granted a marketing authorization for the non-platinum combination of trabectedin with pegylated liposomal doxorubicin (PLD) for the treatment of patients with relapsed platinum-sensitive ovarian cancer.

Approval of trabectedin in STS was based on the results of a pivotal, open-label, randomized, phase II registration study (ClinicalTrials.gov Identifier: NCT00060944; EudraCT Number: 2004-002106-29) that evaluated two trabectedin regimens in 270 adult patients with unresectable advanced or metastatic leiomyosarcoma (66 %) or liposarcoma (34 %).[3] The data from that study show that trabectedin 1.5 mg/m² given as a 24-hour intravenous infusion every three weeks (q3w) provided a superior disease control compared with weekly trabectedin 0.58 mg/m² in terms of longer time to progression (median TTP: 3.7 vs. 2.3 months; p = 0.0302), progression-free survival (median PFS: 3.3 vs. 2.3 months; p = 0.0418) and OS (13.9 vs. 11.8 months; p = 0.1920).[3] Noteworthy, the benefits from trabectedin given as a 24-hour infusion q3w were highlighted by PFS rates at 3 months (51.5 %) and 6 months (35.5 %), which largely surpassed the threshold criteria established by the European Organization for Research and Treatment of Cancer (EORTC) to define drug activity in pretreated STS (i.e., 39 % at 3 months and 14 % at 6 months).[4] It is worth mentioning that trabectedin has also shown activity in unselected patients with recurrent STS treated in three single-arm, phase II trials[5-7], in chemotherapy-naive patients with unresectable advanced disease[8] as well as in compassionate use programs[9-11], and that its authorization in Europe is not restricted specifically to lipo- and leio-

Table 1. Most common histological subtypes of soft tissue sarcomas in adults, with associated genetic abnormalities of major diagnostic significance

Histological subtype	Relative frequency	Genetic abnormalities	Gene(s)
Leiomyosarcomas	15 – 25%	Complex abnormalities of karyotype + genomic instability	–
Liposarcomas (LS)	10 – 15%	Myxoid/round cell LS: t(12;16)(q13;p11)	FUS-CHOP/ DDIT3
Pleomorphic sarcomas (PS)/ Undifferentiated sarcomas, NOS (formerly MFH)	15 – 25%	Complex abnormalities of karyotype + genomic instability	–
Synovial sarcomas	6 – 10%	t(X;18)(p11;q11)	SS18-SSX1, -SSX2, -SSX4
Gastrointestinal stromal tumors (GIST)	3 – 5%	Multiple	KIT mutations
Malignant peripheral nerve sheath tumors (MPNST)	3 – 5%	Complex abnormalities of karyotype	–
Fibrosarcomas (FS)	2 – 3%	E.g., congenital/infantile FS: t(12;15)(p13;q25)	ETV6-NTRK3
Angiosarcomas	2 – 3%	–	–
Rhabdomyosarcomas (RMS)	~ 2%	E.g., alveolar RMS: t(2;13)(q35;q14) t(1;13)(p36;q14) t(X;2)(q13;q35)	PAX3-FKHR PAX7-FKHR PAX3-AFX
Endometrial stromal sarcomas	1 – 2%	t(7;17)(p15;q11) t(6;7)(p12;p15) t(6;10)(p21;p11) t(10;17)(q23;p13)	JAZF1-JJAZ (SUZ12) JAZF1-PHF1 EPC-PHF1 YWHAE-FAM22
Epitheloid cell sarcomas	~ 1%	abnormal 22q11	INI1 mutation/ deletion
Clear cell sarcomas	~ 1%	t(12;22)(q13;q12) t(2;22)(q33;q12)	EWSR1-ATF1 EWSR1-CREB1
Alveolar soft part sarcomas	~ 1%	der(17)t(X;17)(p11;q25)	ASPSCR1-TFE3
Solitary fibrous tumors (SFT)	~ 1%	12q13 (intrachromosomal inversion)	NAB2-STAT6
Desmoid/ Aggressive fibromatosis (AF)	< 1%	–	–
Dermatofibrosarcoma protuberans	< 1%	t(17;22)(q22;q13)	COLIA1-PDGFB

Abbreviations: MFT, malignant fibrous histiocytoma; NOS, not otherwise specified.

myosarcomas. It is also important to note that trabectedin was well tolerated in the long-term treatment of STS; it could be administered for 6 or more cycles in 29.5 % of patients and for up to 38 cycles in patients treated at the recommended dose (1.5 mg/m^2 body surface, administered as an intravenous infusion over 24 hours q3w).

In the following review we present the results of clinical trials and experiences with trabectedin obtained in routine practice, with particular focus on non-L-sarcomas. As has also been suggested in a recent paper by Reichardt[12], these data confirm that trabectedin may represent a useful additional therapeutic option for these rare histological subtypes.

2. Cytotoxic and targeted mechanisms of action

Trabectedin is a "multi-target agent" that exerts its antineoplastic activity through pleiotropic mechanisms of action including anti-proliferative and cytotoxic effects. It binds to the DNA minor groove causing double helix bending towards the major groove[13], it modulates inflammatory responses in the tumor microenvironment[14-16] and promotes tumor cell differentiation[17-19].

Trabectedin's interaction with the minor groove of the DNA double helix triggers a cascade of events that interfere with several transcription factors, DNA binding proteins and DNA repair pathways, resulting in G2-M cell cycle arrest and ultimately apoptosis.[13,20] The drug's mechanism of action was investigated in more detail in myxoid liposarcoma (MLS), a subtype responding particularly well to trabectedin. MLS is associated with the chromosomal translocation t(12;16)(q13;p11) which results in the fusion of the FUS and CHOP genes. Trabectedin was shown to abrogate the transforming effect of the oncogenic FUS-CHOP fusion protein by displacing the molecule from its binding site on promoters in tumor cells; this was reported to induce differentiation of tumor cells to normal adipocytes *in vitro*.[17]

Emerging evidence also indicates that in addition to inducing direct growth inhibition, cell death and differentiation of malignant cells, trabectedin at therapeutic concentrations has selective immunomodulatory properties, resulting from the inhibition of factors that promote tumor growth, progression, and tumor-promoted angiogenesis.[13] Trabectedin selectively inhibits the tumor growth-promoting activity of tumor-associated macrophages (TAM) by blocking differentiation of monocytes to macrophages and suppressing the production of particular cytokines.[13,14,16,21] Trabectedin was also reported to exhibit direct cytotoxic effects on mononuclear phagocytes, with rapid induction of apoptosis, rarefaction of tumor vasculature and down-regulation of the production of inflammatory mediators, leading to changes in the tumor microenvironment which further contributes to its antitumor activity.[16] The markedly reduced production of proinflammatory mediators, such as CCL2, interleukin-6 (IL – 6) and the pro-angiogenic VEGF, may emphasize the strong association between chronic inflammation and cancer progression.[14,16,21,22] The anti-inflammatory and antiangiogenic effects of trabectedin observed *in vitro* have also been demonstrated in a tumor specimen obtained from an STS patient after neoadjuvant treatment with trabectedin, thus supporting the clinical relevance of this mode of action.[21] Taken together, trabectedin is more than a cytotoxic drug, given that it also has immunomodulatory and anti-angiogenic properties. This may contribute to the frequently observed delay in response to trabectedin, but also prolonged tumor stabilization.[23]

3. Clinical studies and case reports

3.1 Phase II trials

An analysis of pooled data from adult patients with recurrent STS treated with trabectedin 1.5 mg/m^2 in three initial non-randomized phase II studies[5-7] showed that 83 out of 183 treated patients (45 %) had recurrent non-L-type sarcomas[24]. The most common STS subtype was synovial sarcoma (n = 25). Among the patients with non-L-type sarcomas, two patients achieved partial responses (2.4 %) and 35 disease stabilization (42.2 %), for an overall disease control rate (DCR) of 44.6 %. Although the results of time-to-event analysis always favored L-type sarcoma patients, the 95 % confidence intervals (CI) overlapped, indicating no statistically significant difference in median PFS (1.8 months, 95 % CI: 1.5 – 2.9 vs. 2.7 months, 95 % CI: 1.7-3.7), TTP (1.9 months, 95 % CI: 1.6 – 3.0 vs. 3.4 months, 95 % CI: 1.7 – 3.9) and OS (8.7 months, 95 % CI: 5.7 – 13.9 vs. 11.2 months, 95 % CI: 9.1 – 17.2) between patients with non-L-type sarcomas vs. those with L-type sarcomas.

3.2 Synovial sarcomas

A retrospective analysis was carried out in patients with advanced pretreated synovial sarcoma treated with trabectedin at four European reference sarcoma centers and within the Italian Rare Cancer Network between 2000 and 2013.[25] This retrospective analysis included 61 patients with a median age of 37 years (range: 18 – 68 years) and a median number of 2 previous chemotherapy regimens (range: 1 – 6). The patients were treated with a median number of 3 cycles of trabectedin per patient (range: 1 – 22). All but one of the patients were evaluable for response. Nine patients achieved a RECIST partial response (15 %), 21 patients had SD (35 %), with two of them showing minor tumor shrinkage, for a DCR of 50 %. The median PFS of the entire patient group was 3 months (7 months in responding patients), and 23 % of the patients were progression-free at 6 months.

In a retrospective pooled analysis including data from patients with translocation-related sarcomas (TRS) treated with

trabectedin in eight phase II trials, 45 patients had synovial sarcoma.[24] Among those patients median PFS was 3.0 months (95 % CI: 1.6 – 4.1 months), with a 6-month PFS rate of 22 % (95 % CI: 9 – 34 %), notably exceeding the cutoff value of 14 % proposed by the EORTC to consider a therapy as active in pretreated STS. Median OS was 13.9 months (95 % CI: 7.2 – 19.4 months), with 2-year survival rate of 28 % (95 % CI: 13 – 43 %). This value of median OS is comparable to that observed in patients with L-sarcomas in the STS-201 trial.

Even complete responses were described in case reports of patients with metastatic synovial sarcoma treated with trabectedin. Postiglione et al. [27] reported two such cases, a woman aged 59 and a man aged 32. The first patient experienced a relapse with lung metastases 11 months after primary chemotherapy with three cycles of epirubicin/ifosfamide followed by tumor resection. The pulmonary nodules completely disappeared after four cycles of trabectedin 1.5 mg/m^2 as a 24-hour infusion q3w, and the patient was still disease-free after treatment with 15 cycles of trabectedin. The second patient received trabectedin after failure of three prior chemotherapies and multiple tumor resections. He achieved a partial response of his pulmonary metastases after two cycles. The response was maintained after 8 cycles, and lung disease eventually relapsed only after 5 months of complete CT response.

Chevalier et al.[28] reported the case of a 42-year-old patient who underwent resection of a 15-cm (French Federation of Cancer Centers stage III) high-grade monophasic synovial sarcoma of the inguinal-scrotal region, followed by chemotherapy with doxorubicin/ifosfamide. However, a CT scan after 3 cycles of chemotherapy revealed four pulmonary lesions so that second-line treatment with the standard schedule of trabectedin was initiated. After four cycles, two of the four pulmonary lesions had completely disappeared; the two remaining lesions decreased in size, and histology of the resection specimens revealed inflammatory scar tissue without evidence of tumor cells. Seven months later and after three additional cycles of trabectedin as consolidation the patient was still disease-free.

3.3 Desmoplastic small round cell tumors

Desmoplastic small round cell tumors (DSRCT) are extremely rare and very aggressive neoplasms preferably affecting young men. The tumor develops in the serous membranes, predominantly the peritoneum, leading to obstructive symptoms in the abdomen and pelvis and, eventually, peritoneal dissemination and metastasis to the liver, lungs and lymph nodes. Its prognosis is dismal with current treatment options, including the combination of aggressive surgery, multi-agent chemotherapy, radiation therapy, autologous stem cell transplantation and hyperthermic intraperitoneal chemotherapy (HIPEC), as about 75 % of the patients die within three years. Several patients with DSRCT who were treated with trabectedin outside of clinical trials were described in case reports.

Brunetti et al.[29] presented the case of a 20-year-old man whose intra-abdominal DSRCT had already reached a size of 12 cm at diagnosis. In addition, he had ascites and several peritoneal lesions. After failure of first-line chemotherapy with cisplatin, epirubicin and vinorelbine as well as second-line high-dose ifosfamide, the patient underwent two surgical debulking procedures including intraoperative HIPEC. However, only two months later new lesions were detected so that treatment with trabectedin at the recommended dose was initiated. After four cycles, CT and 18-fluoro-deoxyglucose positron emission tomography (FDG-PET) scans confirmed a partial response that remained stable until cycle 8. The patient became asymptomatic and only after six months of disease stabilization FDG-PET imaging indicated disease progression.

Frezza et al.[30] presented two other cases of metastatic peritoneal DSRCT responding to trabectedin. The first patient, a 23-year-old man, was treated with trabectedin as fourth-line therapy and experienced an improvement in pain control and dyspnea, which was associated prolonged radiologic stabilization of disease (until cycle 6). The second patient aged 19 years presenting with extensive peritoneal, liver and lung disease received trabectedin as third-line treatment. After three cycles of trabectedin, the newly developed lesions had markedly decreased in size, with nearly complete resolution of the ascites.

Another case report described an 18-year-old patient with DSRCT who had a complete resection of his intra-abdominal tumor, but a local relapse occurred two months after termination of adjuvant chemotherapy.[31] Once again, a complete resection was performed, but this was no longer possible when the next recurrence occurred 12 months later. Response to chemotherapy with cisplatin/irinotecan was only short-lived. Therefore, third-line therapy with trabectedin was administered, resulting in a reduction in size in one lesion and disease stabilization in the others. An exploratory laparotomy was performed showing a significant reduction in miliary dissemination, and eight months after surgical removal of the macroscopic lesions the patient was still without evidence of progression.

3.4 Advanced alveolar soft part sarcomas

Alveolar soft part sarcomas (ASPS) typically affect young adults. This subtype is associated with a peculiar metastatic pattern with common brain metastases. The prognosis is poor if primary radical resection is not possible, and chemotherapy seems to be even less effective than in other sarcoma subtypes. To assess the efficacy of trabectedin in patients with metastatic ASPS, seven patients registered in the databases of the Sarcoma Center Berlin-Brandenburg and the Greifswald University Hospital, Germany, were retrospectively evaluated.[32] Five

of these patients were pretreated with up to four chemotherapy regimens prior to trabectedin. A median number of 10 cycles of trabectedin (range: 4 – 23) were administered as a 24-hour infusion q3w. Six patients with documented disease progression achieved disease stabilization according to RECIST lasting more than three months, while only one patient experienced disease progression. Four patients were still progression-free at 6 months from initiation of treatment. Median PFS was 7 months (range: 3 – 20) and median OS was 21 months (range: 4 – 40), calculated from the start of trabectedin treatment. In all six responding patients, time to progression while receiving trabectedin was longer by a factor of 1.33 or more compared with the previous chemotherapy. Three of the seven patients are still alive at 15+, 16+ and 45+ months. Trabectedin was well tolerated, and no severe adverse events were reported.

3.5 Solitary fibrous tumors and hemangiopericytomas

Current understandings comprehend solitary fibrous tumors (SFT) and hemangiopericytomas (HPC) as different manifestations of a single disease entity with known histologic and immunohistochemical overlap.[33] Whenever possible, complete surgical resection is the mainstay of treatment for localized disease (and the most important prognostic factor), while radiotherapy is a treatment option for locally advanced disease and chemotherapy for metastatic disease.

The efficacy of the current treatment options was examined in a retrospective non-interventional multicenter study that included a total of 68 patients with SFT.[34] In that study chemotherapy for recurrence among 12 relapsed pretreated patients had a modest benefit, with response and disease control rate as low as 9 % and 39 %, respectively. Still, the highest DCR was achieved with trabectedin (7/9 patients, 78 %; partial responses: n = 3) with a median TTP of 3.4 months.

Other case reports have provided some evidence that trabectedin may be a promising treatment option for patients with SFT. Burcoveanu et al.[35] described a 37-year-old female patient in whom a synovial sarcoma was diagnosed 14 years ago, with the affected leg amputated following neoadjuvant chemotherapy. The newly developed disease presenting with two large intra-abdominal masses and bilateral pulmonary metastases was identified as SFT by histopathologic analysis, and the initial diagnosis was corrected accordingly when the former tissue sections were re-examined. After 6 cycles of trabectedin and seven months of SD the residual tumor could be completely resected. Three months later the patient was still disease-free.

A patient reported by Chaigneau et al.[36] developed lung and liver metastases five months after primary resection of a pleural SFT. Chemotherapy with 6 cycles of mesna, doxorubicin, ifosfamide and dacarbazine (MAID) led to disease stabilization for several months. When disease progression occurred, the patient received second-line treatment with four cycles of trabectedin. This resulted in a significant regression of metastatic lesions that persisted for five months following completion of therapy.

Martinez-Trufero et al.[37] reported a patient with meningeal HPC in whom pulmonary metastases were detected four years after complete resection of the primary tumor and postoperative irradiation. Chemotherapies with ifosfamide/doxorubicin and gemcitabine/dacarbazine each resulted in SD for only a few months. The tumor further progressed under treatment with interferon-α so that fourth-line therapy with trabectedin was administered. Shrinking of the mediastinal tumor approximately equivalent to a partial response was seen after three cycles of treatment; liver and peritoneal metastases remained stable. Ten months after treatment with trabectedin was commenced and a total of eight cycles the disease was still stable. This was the longest response of all treatments the patient had received.

3.6 Undifferentiated and pleomorphic sarcomas

High-grade pleomorphic sarcomas and undifferentiated sarcomas – historically subsumed under the diagnosis of malignant fibrous histiocytoma (MFH) – are among the most common STS in adults. At an early stage surgical resection is attempted, while advanced disease is usually treated with doxorubicin and/or ifosfamide. Activity of trabectedin has first been reported in heavily pre-treated patients. One partial response and four SD lasting more than six months were seen in a single-arm phase II trial in six patients with this sarcoma subtype.[5]

Another case of malignant fibrous histiocytoma reported in the literature was a 25-year-old woman presenting with a rare skeletal origin of the tumor that involved the vertebral body T5.[38] After several surgical treatments and three chemotherapies failed to control local recurrences and metastatic lesions, the patient eventually received trabectedin. After only two cycles there was a progressive resolution of the pericardial and pleural effusion. After four cycles the patient's condition had substantially improved, and CT imaging confirmed the very good response. So far, the patient had tolerated eight cycles of trabectedin with granulocyte-colony stimulating factor (G-CSF) support without any significant toxicity.

Particularly noteworthy is the case of a 39-year-old woman because it is the first report of a second response to trabectedin experienced after re-exposure to the drug.[39] The patient presented with a high-grade undifferentiated sarcoma originating from the fascia of the rectus abdominis muscle. Staging examinations did not reveal distant metastases and the patient underwent surgical treatment. She remained free of disease for nearly three years when CT scans showed an abdominal mass around the transverse mesocolon. Adjuvant chemotherapy with

epirubicin/ifosfamide was only given after initial surgery. Half a year after the second surgery multiple pelvic metastases were detected, but all of these lesions completely disappeared after eight cycles of trabectedin at the recommended schedule. New metastatic lesions only became apparent after nearly two years. Again trabectedin was administered, and once again – after only two cycles – a complete response, as documented by CT and PET-CT scanning, was achieved. Treatment was continued thereafter with no relevant adverse events.

3.7 Other sarcomas

In a single-arm phase II study, 36 patients with advanced STS were treated with trabectedin. One of the observed six responses was in a fibrosarcoma patient. This patient received eight cycles of trabectedin, achieving a PFS of 7 months and an OS of 19 months.[8]

De Sanctis et al.[40] reviewed all patients treated with trabectedin for advanced STS in a single Italian cancer center to evaluate the efficacy of the drug in specific histological subtypes. From 2008 to 2012, a total of 35 patients treated with trabectedin at the recommended dose for a median of 2 cycles (range: 1 – 6), almost exclusively after previous anthracycline-based therapy, were identified. Two (7 %) of 28 evaluable patients achieved a partial response and 10 (36 %) SD. DCR was attained not only in four patients with retroperitoneal liposarcoma and two patients with leiomyosarcoma, but also in four patients with synovial sarcoma and one patient each with Ewing sarcoma/primitive neuroectodermal tumor (PNET) and undifferentiated STS not otherwise specified. The median duration of response across all subtypes was 2.8 months, median PFS was 2.5 months (95 % CI: 2 – 5.4) and median OS 15.5 months (95 % CI: 12 – 17.6).

Another histological subtype with promising sensitivity to trabectedin is uterine adenosarcoma. It is an exceedingly rare malignancy with relatively low malignant potential. Localized disease is treated with radical hysterectomy but relapses occur in about 25 % of these cases. Three patients with this subtype who were treated with trabectedin for metastatic disease were retrospectively identified from a prospectively maintained sarcoma database.[41] Two of these patients derived prolonged clinical benefit from treatment, with disease stabilization for 11 and 17 cycles, respectively. Both patients tolerated trabectedin very well. Palmieri et al.[42] described a patient in whom an endometrial adenocarcinoma was associated with sarcomatous components, constituting an extremely malignant mixed Mullerian tumor (carcinosarcoma). Following the failure of treatment with carboplatin/paclitaxel the patient received second-line trabectedin with pegylated liposomal doxorubicin. Nine months later her disease was still stable.

The heterogeneous histological appearance of low-grade fibromyxoid sarcoma (LGFMS) makes the diagnosis particularly challenging. Making a correct diagnosis is of utmost importance given the relatively high risk of metastases and the atypical metastatic pattern of this subtype. In a Danish sarcoma registry, only 14 patients with LGFMS were captured since 1979, corresponding to a raw incidence of 0.18 cases per million, representing 0.6 % of all STS.[43] Three of these patients developed metastatic disease, and two of them were treated with trabectedin. One patient received numerous different chemotherapy regimens over a period of 12 years from the first detection of metastatic spread until death, and of these treatments, trabectedin was the most effective. This patient received the agent twice for eight and six cycles, respectively, and both treatments resulted in stabilization of progressive disease. In the second patient, trabectedin was administered after several new metastatic lesions developed following treatment with doxorubicin. No further progression occurred over the course of 12 cycles.

4. Experience with trabectedin in clinical routine practice

An analysis evaluated treatment results obtained with trabectedin within a worldwide expanded access program.[10] This program was designed to provide trabectedin access for patients with incurable STS following progression of disease with standard therapy. A total of 1895 patients were enrolled in the program during five years, of whom 1803 received at least one dose of trabectedin. The median number of cycles was 3, with 30 % of the patients having 6 or more cycles, and 7 % being treated for one year or longer. A total of 807 patients were evaluable for objective response. Of these, four patients (< 1 %) achieved a complete response, 44 (5 %) a partial response and 343 (43 %) SD for a DCR of 48 % (54 % in patients with L-sarcomas and 38 % among those with non-L-sarcomas). Median OS among 903 evaluable patients was 11.9 months. Patients with L-sarcomas exhibited longer OS compared with other histologies (median OS, 16.2 vs. 8.4 months) and also had a slightly higher objective response rate (6.9 % vs. 4.0 %). The safety profile of trabectedin was in accordance with that observed during the entire clinical development of the drug.

Between 2003 and 2008, patients with advanced STS who had previously failed doxorubicin-based chemotherapy could be treated with the recommended schedule of trabectedin within a French compassionate use program.[9] A total of 181 patients from 11 institutions with a minimum of five treated patients were retrospectively identified and the files updated; these patients represented 55 % of the total population of patients participating in this program. The eligibility criteria were those of the EORTC phase II study of trabectedin[5], but with no restriction on the previous number of lines. The vast majority of patients had leiomyosarcoma (30 %), liposarcoma (27 %) or synovial sarcoma (9 %). Prior to trabectedin, patients

had received a median of 3 chemotherapy lines (range: 1–4), and a median of 3 cycles of trabectedin (range: 1–19) were administered per patient, with 31% of the patients receiving six or more cycles. Eighteen patients (10%) achieved a partial response and 69 (39%) had disease stabilization. PFS and OS by histological subtype and line of treatment with trabectedin are shown in Table 2. These treatment results are at least comparable to those achieved with trabectedin in clinical trials. Notably, among patients with non-progressive disease after six cycles of trabectedin, outcome was significantly better for those who continued trabectedin as maintenance therapy (n=40) compared with those who discontinued treatment at that point (n=16), with a median PFS of 10.5 vs. 5.3 months (p=0.001) and a median OS of 33.4 vs. 13.9 months (p=0.009). Only 17% of the patients required hospitalization for toxicity.

A third retrospective analysis evaluated 885 patients with advanced STS who were registered at the French Retrospect-Yon database from early 2008 to late 2011 and received trabectedin at the recommended dose of 1.5 mg/m^2, administered as a 24-hour infusion q3w, for the treatment of recurrent disease or because doxorubicin or ifosfamide were contraindicated.[44] The majority of patients had leiomyosarcoma (36%), liposarcoma (18%) or synovial sarcoma (11%). Patients with a partial response or disease stabilization after the initial six cycles could continue trabectedin as maintenance therapy. A median of 4 cycles (range: 1–28) were given as second (41%), third (39%) or fourth line of treatment (20%). The objective response rate was 17% (6 complete responses and 127 partial responses) and the SD rate was 50% for a DCR of 67%. At a median follow-up of 22.0 months, median PFS with second, third and fourth-line therapy was 4.8, 4.5 und 3.8 months, respectively, and median OS was 12.9, 12.2 and 9.5 months. Multivariate independent favorable predictors of PFS included the histological subtypes of leiomyosarcoma and liposarcoma and an early line of trabectedin. Median PFS and OS were 5.5 and 15.1 months for leiomyosarcoma (n=321), 6.1 and 15.0 months for liposarcoma (n=161), and 3.9 and 9.9 months, respectively, for synovial sarcoma (n=101). Remarkably, 3-month PFS rates for 13 specific STS subtypes exceeded the 39% threshold as determined by the EORTC to suggest activity of a drug as second-line treatment in phase II trials[4] (Table 3). Of 304 patients with non-progressive disease after six cycles, 227 continued trabectedin as maintenance therapy. The latter patients had a significantly longer median PFS (11.7 vs. 7.6 months; $p < 0.003$) and OS (24.9 vs. 16.9 months; $p < 0.001$) than those who stopped trabectedin after the six initial cycles. Toxicity-related deaths and unscheduled hospitalizations occurred in only 0.5% and 9.4% of patients, respectively.

The results from those two large retrospective studies in France[9,44], which suggested that continued long-term therapy with trabectedin until progression or intolerance may improve PFS and OS, provided the rationale for performing the T-DIS study (ClinicalTrials.gov Identifier: NCT01303094; EudraCT N°: 2010-022613-26) by the French Sarcoma Group as a prospective, randomized phase II study to assess interruption (I arm) vs. continuation (C arm) of trabectedin after the initial six cycles of trabectedin in pretreated patients with advanced STS.[45] The results of this prospective trial support that trabectedin should be given until intolerance or progression, as early discontinuation of trabectedin may result in a rapid disease progression (median PFS: C arm 7.2 months vs. I arm 4.0 months; p=0.03 and PFS at 6 months: C arm 51.9%

Table 2. Progression-free survival and overall survival from initiation of treatment with trabectedin according to selected baseline characteristics, as reported from a compassionate use program[9]

Characteristic	n (%)	Median PFS (months)	Median OS (months)
Subtype			
Leiomyosarcoma	55 (30)	3.4	17.4
Myxoid liposarcoma	28 (16)	10.5	33.4
Other liposarcomas	21 (11)	3.2	20.0
Undifferentiated/NOS	22 (12)	2.2	14.0
Synovial sarcoma	16 (9)	4.0	9.2
Others	39 (22)	2.1	6.7
Treatment line of trabectedin			
1*	10 (6)	4.5	33.4
2	67 (37)	5.3	18.2
3	60 (33)	3.2	14.3
4	42 (23)	2.8	10.2

* Prior doxorubicin and ifosfamide in the adjuvant setting.
Abbreviations: NOS, not otherwise specified.

Tabelle 3. Progression-free survival and overall survival by sarcoma histology: Results of the RetrospectYon database (modified according to[44]); numbers are rounded to the first decimal place

Histologie	n	PFS (months)			OS (months)	
		Median	95%-CI	PFS at 3 months (%)	Median	95%-CI
Solitary fibrous tumor	13	7.6	1.6 – 13.7	69	14.3	0.8 – 27.8
Chondrosarcoma	13	6.3	0.0 – 15.9	57	21.4	9.6 – 33.2
Liposarcoma	161	6.1	4.5 – 7.6	64	15.0	11.0 – 19.0
Leiomyosarcoma	321	5.5	4.5 – 6.5	69	15.1	13.4 – 16.9
Fibrosarcoma	10	5.4	2.5 – 8.3	70	13.7	7.2 – 20.2
Epithelioid sarcoma	10	4.6	2.5 – 6.8	70	12.0	8.3 – 15.7
Synovial sarcoma	101	3.9	2.1 – 5.8	53	9.9	6.7 – 13.0
DSRCT	5	3.4	0.0 – 9.1	60	14.0	0.0 – 34.8
Myxofibrosarcoma	20	2.8	1.5 – 4.2	47	8.1	4.8 – 11.4
Stromal sarcomas	14	2.8	1.7 – 3.9	43	12.8	8.2 – 17.3
Rhabdomyosarcoma	15	2.6	0.8 – 4.4	47	5.4	4.6 – 6.3
Sarcoma NOS	82	2.4	2.0 – 2.8	42	6.4	4.6 – 8.1
MPNST	19	2.4	1.0 – 3.7	42	7.8	3.3 – 12.2
Miscellaneous	89	2.3	1.0 – 3.6	46	8.0	6.7 – 9.3
Osteosarcoma	3	2.0	0.0 – 5.1	33	6.4	0.0 – 13.2
Angiosarcoma	9	0.9	0.8 – 1.0	22	6.6	0.5 – 12.6

Abbreviations: CI, confidence interval; DSRCT, desmoplastic small round cell tumor; MPNST, malignant peripheral nerve sheath tumors; NOS, not otherwise specified; OS, overall survival; PFS, progression-free survival

vs. I arm 23.1 %; p = 0.02) in responding patients regardless of the pattern of response they achieved during their initial treatment.

5. Concluding remarks

Trabectedin treatment is feasible in non-lipo/leiomyosarcomas and has demonstrated efficacy in patients with a variety of histologically different non-L-sarcoma subtypes. Regarding various histological subtypes of STS, data from numerous studies and case reports have indicated that even heavily pretreated patients can achieve long-lasting responses to treatment with trabectedin. Notably, treatment with trabectedin in compassionate use and expanded access programs, has provided results very similar to those obtained in clinical trials. Patients who respond to trabectedin and remain free of progression for an extended period of time may be effectively retreated with the agent. Finally, continued long-term therapy with trabectedin in responding patients is usually well-tolerated and should be considered due to the fact that no cumulative toxicities have been observed in patients treated with multiple cycles to date. Thus, according to accumulated clinical data and peer-reviewed articles trabectedin is active both in lipo- and leiomyosarcomas and shows proven activity in patients with a variety of histologically different pretreated non-lipo/leiomyosarcoma subtypes.

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