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Research article

Current treatment patterns in advanced soft tissue sarcoma: real-world evidence of over 5,000 European patients

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Abstract

Introduction: The aim of this analysis is to understand the treatment of advanced Soft Tissue Sarcomas (aSTS) in the real-life setting, with a special focus on the use of trabectedin (Yondelis®) according to treatment line and histological subtype.

Materials and Methods: The data source for this study was the Oncology Advantage™ (OA), which is a trademark of IQVIA Information S.A. We utilized anonymized patient-level data on aSTS from OA of cancer-treating physicians in France, Germany, Spain, and Italy from January 2015 to December 2018.

Results: A total of 5,298 patients with aSTS were enrolled, 36% of patients were diagnosed with leiomyosarcoma, and 21% with liposarcoma. The vast majority of patients with all studied histologies received anthracycline-based regimen as 1st line treatment, while trabectedin was the most common 2nd line therapy (around 30% of patients) and pazopanib was the regimen most frequently used in the 3rd line setting. Among the 2,257 patients who were treated with trabectedin at any line, almost 70% received this agent right after a doxorubicin-based therapy, with a median of 6.9 cycles of trabectedin in 2nd line per patient in the studied period.

Conclusions: The studied database illustrates how the management of aSTS at daily clinical practice is well aligned with recommendations of International and National Guidelines: anthracycline-based therapy is the most common regimen in the 1st line setting while trabectedin is the agent most frequently used as 2nd line therapy.

Key words: Soft Tissue Sarcoma. Trabectedin. L-sarcoma. Leiomyosarcoma. Liposarcoma.
20% of all STS, are the most frequent subtypes of STS. The four histological subtypes of LPS are well-differentiated or de-differentiated (over 50%), followed by myxoid, including hypercellular transformed variant (30%) and only 5% are pleomorphic, while 40% uterine and 60% non-uterine are the most frequent subtypes of LMS.

Nearly half of all STS patients with high-grade tumors develop metastatic disease requiring systemic treatment; the 5-year overall survival (OS) is approximately 55% with median survival increasing, in the last decade, from 12 months to approximately 20-22 months from diagnosis of metastases.

Although treatment outcomes for patients with STS have improved greatly over the past few decades due to the adoption of a multidisciplinary approach and the availability of new agents, patients with advanced disease still have a poor prognosis, with < 10% of patients alive at 5 years. Improving OS is the main objective for the development of new drugs. Conventional chemotherapy remains a mainstay in the treatment of sarcomas and treatment of advanced diseases usually involves a combination of various strategies, often implemented sequentially in patients with a prolonged disease course. Performance status, young age, and long metastasis-free interval have been described as predictor factors of a good response to chemotherapy and improved survival. The sensitivity of sarcomas to the different treatments varies among histological subtypes, being synovial sarcoma, leiomyosarcoma and myxoid LPS, the subtypes that generally show the highest rates of response to chemotherapy. On the other hand, the identification of molecular aberrations as the underlying cause of specific sarcoma subtypes has led to the development of targeted therapies with substantial improvement in treatment outcome. As the understanding of this complex disease increases, it becomes more feasible to tailor treatment to each sarcoma subtype.

Doxorubicin monotherapy or in combination with an optimal dose of ifosfamide or DTIC, continues to be the standard first-line therapy for locally advanced or metastatic STS of most subtypes. The combination has not been shown to improve survival in comparison with doxorubicin monotherapy, although it provides a higher response rate and improved progression-free survival (PFS) at the cost of increased toxicity. Therefore, the treatment of choice may be multi-agent chemotherapy with adequate-dose anthracyclines plus ifosfamide, especially in subtypes sensitive to ifosfamide, when a tumor response is felt to be potentially advantageous and patient performance status is good. The combination of doxorubicin with olaratumab (anti-PDGFRA agent) represents the latest attempt to overthrow doxorubicin as a first-line treatment of advanced STS. After having shown a promising survival improvement over doxorubicin alone in a randomized phase II-II trial, it has recently been reported that the confirmatory phase III trial was negative since there was no improvement of the median OS with the combination. Therefore, European Medicines Agency (EMA) has recommended the withdrawal of the marketing authorization for Europe.

At present, available evidence-based on retrospective studies casts doubt on the activity of ifosfamide in LMS. The combination of doxorubicin plus dacarbazine represents a valuable first-line alternative therapy for these patients.

The main options for second- or later-line therapy include trabectedin, pazopanib, eribulin, and gemcitabine-based regimens. The sensitivity of sarcomas to each of these drugs may vary by histologic subtype and their safety profiles differ; hence, when determining optimal treatment, histologic subtype, and patient characteristics must be considered as key factors.

Trabectedin is a marine-derived antineoplastic drug approved by the EMA and in many other countries for the treatment of adult patients with advanced STS, after failure of anthracyclines and ifosfamide, or who are unsuited to receive these agents. In a randomized phase III trial evaluating the effectiveness of trabectedin against dacarbazine in patients with advanced LPS or LMS (L-STS), it was reported a median PFS (mPFS) of 4.2 versus 1.5 months in favor of trabectedin (hazard ratio, 0.55; p < .001). Other several additional studies have demonstrated that trabectedin confers also clinically meaningful long-term benefits to patients with multiple STS histotypes. It exhibits a convenient safety profile, with less hematological toxicity than doxorubicin or ifosfamide and without cumulative toxicities, allowing long-term treatment. Importantly, trabectedin administration until disease progression is associated with a statistically significant improvement of PFS and OS compared to earlier treatment interruption in responding patients.

Divergent findings were reported in two randomized phase II trials that compared the efficacy of gemcitabine plus docetaxel versus gemcitabine monotherapy in patients with advanced STS. In the US study by Maki et al., the combination improved PFS and OS compared with gemcitabine monotherapy (mPFS: 6.2 vs. 3.0 months and median OS: 17.9 vs. 11.5 months), but benefits came at the cost of increased toxicity (more than 40% of patients receiving gemcitabine-docetaxel discontinued treatment for a variety of nonhematologic toxicities.
within 6 months of therapy, despite dose reductions). A similar study in leiomyosarcoma patients by Pautier et al. showed no advantage for the combination of gemcitabine plus docetaxel over gemcitabine monotherapy (mPFS 3.4 vs. 6.3 months).

Pazopanib is indicated in the USA, Europe, and Japan for use in adults with selected subtypes of advanced STS who have received prior chemotherapy for metastatic disease or have progressed within 12 months of neoadjuvant therapy. The PALETTE randomized phase III trial showed a benefit in PFS averaging 3 months for pazopanib compared to placebo in advanced, previously treated STS patients (excluding LPSs). This benefit did not translate into a significant difference in OS (12.5 vs. 10.7 months; HR = 0.86; p = 0.25). Pazopanib is an option in non-adipogenic STS.

Finally, in the eribulin randomized phase III trial vs. DTIC, LPS or LMS patients who had received at least two previous systemic regimens (including an anthracycline) were enrolled. Significant improvement in OS was reported with eribulin in the entire population, despite comparable numbers of patients who responded to the drugs and no significant difference between treatment groups for PFS. A planned subgroup analysis suggested that the survival benefit with eribulin was mostly observed in patients with LPS, leading to the limitation of eribulin regulatory approval to LPSs.

There is little data available to analyze whether the recommendations published in the Clinical Practice Guidelines are similar to the actual management of patients with advanced/metastatic STS in routine clinical practice. For that reason, the aim of this analysis is to understand the actual trends about the treatment of advanced STS in the real-life setting, with a special focus on the use of trabectedin according to treatment line and histological subtype.

Materials and methods

The data source for this analysis was the Oncology Advantage (OA), which is a trademark of IQVIA Information S.A. OA-STS is a cross-sectional survey that collects anonymized patient-level data on STS from a panel of cancer-treating physicians in France, Germany, Spain, and Italy. Patient case information is generated through a pre-defined web-based questionnaire complying with the relevant rules for protecting patient privacy. It captures full current and retrospective patient treatment patterns in cancer treated population and it also collects data on the patient’s profile, surgical procedures, and oncological treatment. Data are collected on a quarterly basis. Physicians are invited to participate in the web-based survey over a 3-months period and data are published at the end of the 3-months collection. This analysis contains information of data from January 2015 to December 2018.

Physicians were included in the survey only if they personally treat STS patients during the study period (13-14 physicians per country). They were asked to report the most recent consecutive cases they had treated during the last 2-week period (up to a maximum of number of 5-7 patients). A maximum of 3 doctors was recruited from the same hospital to avoid potential duplication of patient cases.

Patients were included in the study if they have had a diagnosis of metastatic (Stage IV) STS and they were receiving 2nd line therapy (45-55% of patients) or 3rd line + treatment (to make up the rest of the patients collected). Patients included have specific histological subtypes of STS (LMS, LPS, synovial sarcoma, fibrosarcoma, angiosarcoma, undifferentiated pleomorphic sarcoma, rhabdomyosarcoma, malignant peripheral nerve sheath tumors [MPNST], unclassified sarcoma, and others). Patients must be treated with a cancer drug (L01 class) at the time of the survey.

Variables collected through the survey were: histology, stage of the disease, details of all drug regimens that patients have received since diagnosis by line, dosages given, and duration of therapy.

Data collection, coding, and creation of the final dataset were conducted with quality control to assess the data quality as an integral part of the OA. Quality was ensured by consistent procedures that include: controlled code lists and choice lists to minimize manual data entry, filters to show questions only relevant to specific cancer types, or some responses were compared with previous answers to detect incongruities.

OA is a market research study that complies with the EphMRA Code of Conduct 2017. Moreover, as per EMA Guideline on Good Pharmacovigilance Practices Module VI, “Management and reporting of adverse reactions to medicinal products,” the offering does not require search or reporting of individual adverse events or any other special reporting situation.

Results from this study are presented descriptively using absolute and relative frequencies by year of analysis. No additional statistical analyses were performed. Submission to an independent ethics committee was not required for OA, as data are collected on the basis of a questionnaire where physicians provide anonymized data.
Results

A total of 5,298 cases of patients with advanced STS were reported during the 4-year period of this study. The ranking of most common histological subtypes included in the database was: 36% of LMS (50% LMS uterine and 50% non-uterine); 21% of LPS (including 29% pleomorphic LPS, 26% dedifferentiated, and 26% myxoid); 8% angiosarcoma; 8% fibrosarcoma, and 7% synovial sarcoma (Fig. 1). Figure 2 represents the distribution of the different treatment regimens used in each line of therapy. Anthracycline-based regimen leads 1st line treatment in STS for all studied histologies, increasing during the studied period and exceeding 80% during 2018. Gemcitabine-based therapy stays as the second option along with other therapies (ifosfamide, trabectedin, or pazopanib), with a 1st line use of < 10% (Fig. 2A).

Trabectedin was the most common regimen administered as second-line therapy in the 4-year study period. Around 30% of all STS patients received trabectedin in the 2nd line setting. A decrease in the use of gemcitabine-based therapy is shown, being administered as 2nd line to 25% of patients in 2015 and to 19% in 2018. The use of anthracycline-based therapy was also reduced along the same period (from 12% to 7%). However, an increasing use of trabectedin, pazopanib, and eribulin treatments can be observed (Fig. 2B).

Among regimens administered as 3rd line therapy (Fig. 2C), the most common treatment was pazopanib (from 28% in 2015 up to 34% in 2018), followed by trabectedin (from 26% in 2015 to 21% in 2018). The use of eribulin as 3rd line treatment increased from 0% in 2015 to 6% during 2018.
Figure 2. Treatment evolution by year in soft tissue sarcomas patients. (A) Treatment evolution by year in 1st line, (B) evolution by year in 2nd line, (C) evolution by year in 3rd line.
When analyzing the position of trabectedin in the STS treatment algorithm, it should be noted that almost 70% of patients treated with trabectedin receive this agent right after doxorubicin-based therapy (Fig. 3). Only 4% of patients treated with trabectedin have received prior treatment with pazopanib.

In the 4-year study period, the distribution of patients by STS subtype treated with trabectedin at any line was: 35% of LMS, 32% of LPS, 7% of synovial sarcoma, and 7% of fibrosarcoma, followed by other less common subtypes (Fig. 4).

The use of trabectedin in the most common STS subtypes, LMS and LPS, is described in more detail in figures 5 and 6, respectively. The analyzed database includes a total of 1,912 LMS patients: 50% non-uterine and 50% uterine. When analyzing the percentage of LMS patients treated with trabectedin at any line, 433 patients (55%) had non-uterine LMS and 361 (45%) had uterine LMS. Furthermore, a total of 1,090 patients included in the database had LPS: 29% pleomorphic LPS, 26% myxoid, 26% dedifferentiated LPS, and 18% LPS not otherwise specified (NOS). A total of 721 LPS patients received trabectedin at any line: 215 patients (30%) with pleomorphic LPS, 220 patients (31%) with myxoid LPS, 164 (23%) with dedifferentiated LPS and 122 patients (17%) with NOS LPS. There were no relevant differences in the distribution of LMS or LPS patients between the total population and those treated with trabectedin.

Regarding the duration of trabectedin treatment when used as 2nd line therapy in all studied histologies, there is an increasing trend in the average number of administered cycles: from 6.2 cycles in 2015 to 7.7 cycles during 2018 (Fig. 7).

Second-line treatment with trabectedin was administered for six or more cycles in 54% of patients in 2015, increasing up to 74% within 2018 (Fig. 8). Data are very similar when analyzed by histological subtype. From 2015 to 2018, LMS patients who received more than six cycles of trabectedin increase from 65% to 75%; LPS patients from 66% to 72%; and other histotypes from 33% to 74% (Table 1).

**Discussion**

In the field of advanced STS, the decision making is complex, depending on diverse presentations and histologies, and a multidisciplinary approach is needed\textsuperscript{15}. The management of STS is complex. The results of our study illustrate the real-life experience of stage IV STS patients treated in four participating European countries. The analyzed database, with more than 5,000 patients included, allowed the study of key aspects for the management of STS, such as the distribution of the different subtypes or the different treatments used in each line of therapy.
Despite optimal local treatment, about 50% of patients with localized high-grade adult-type STS will develop distant metastases and die of metastatic disease. Treatment of a metastatic or unresectable disease with systemic therapy is often given for palliative rather than curative purposes, with the exception of highly selected cases. As European and American Guidelines describe, in advanced-metastatic STS, the choice of 1st line chemotherapy will be between single-agent doxorubicin or the combination of doxorubicin and ifosfamide (or dacarbazine in LMS) (according to European Guidelines). There is no formal demonstration of survival benefit with multi-agent chemotherapy compared to single agent doxorubicin. However, a higher response rate can be expected, particularly in ifosfamide-sensitive subtypes. Therefore, multi-agent chemotherapy with anthracyclines plus ifosfamide may be the treatment of choice for ifosfamide-sensitive subtypes when the main goal of treatment is tumor shrinkage. In our database, anthracycline-based therapy (in monotherapy or in combination) is
the most common 1st line treatment, administered in up to 80% of patients in the last year of this analysis.

In the 2nd line setting, trabectedin is the treatment most frequently used for the total STS population and in the most frequent histological subtypes. It should be noted that the use of trabectedin is maintained during our study period: around 30% of patients receiving trabectedin as 2nd line therapy.

Moving to the 3rd line, pazopanib was the most used treatment followed by trabectedin. In 2018, 3% and 6% of patients were treated with eribulin in 2nd and 3rd line, respectively, having in mind that eribulin is only indicated in advanced LPS.

Trabectedin is approved for the treatment of advanced STS, after failure of anthracyclines and ifosfamide, or when patients are unsuited to receive these agents. In our study, 2,257 STS patients were treated with trabectedin at any line. Among them, the vast majority (68%) received trabectedin subsequently after doxorubicin-based therapy. There was an increase in the average number of trabectedin cycles given in 2nd line: from 6.2 cycles in 2015 to 7.7 cycles in 2018. The increasing duration of trabectedin treatment can be associated with a better knowledge of the efficacy (i.e., increase of use in L-STS overtime during this period), safety profile, and correct management of this agent. The prolonged use of trabectedin, generally administered until disease progression or patient refusal, is also endorsed by results in clinical trials\(^1\)\(^9\)\(^,\)\(^2\)\(^9\). Data from the randomized phase II study that led to trabectedin European registration showed that 52.3% of patients were able to obtain a long-term benefit (under treatment for ≥ 6 cycles) when the agent was used in 2nd line\(^3\)\(^0\). In our analysis, these data are even more positive, following an

![Figure 8. Number of trabectedin cycles given in 2nd line in all soft tissue sarcomas patients. N = 734 (patients who had relapsed to subsequent lines).](image)
increasing pattern: the percentage of patients receiving more than six cycles of trabectedin in the 2nd line was 54% in 2015 and 74% in 2018. Importantly, trabectedin has been administered for prolonged periods (up to 59 cycles) without apparent cumulative toxicities21.

Since a differential response to systemic therapy according to histological subtype has been noted, the management of STS is increasingly subtype-dependent, especially after failure to standard 1st line treatment. The rate of L-STS observed in the population of our database, is similar to those reported in large retrospective studies21 and controlled recent randomized trials31. LMSs are divided into non-uterine and uterine subgroups, with a roughly equal proportion of cases per subgroup32, as reported in our analysis. In contrast, our results show a different distribution in LPS subtypes when comparing to published data: a higher percentage of patients with pleomorphic LPS (29%) was registered in our database, compared with the observed in the bibliography (pleomorphic LPS is the less frequent subtype of LPS, comprising approximately 5% of LPS cases33). These discrepancies highlight the more dismal prognosis of such unfavorable LPS subtypes more frequently seen in advanced settings than in the localized presentation.

In our database, there were no relevant differences in the histological classification of LMS or LPS patients between the total population and those treated with trabectedin, meaning that this treatment is generally used in LMS and LPS patients independently of more specific sub-classifications. The observed use of trabectedin in these subtypes is largely scientifically supported by data generated in clinical trials and real-life studies:

- In the subgroup of 378 LMS patients enrolled in the randomized phase III trial comparing trabectedin versus dacarbazine, the mPFS was superior in the trabectedin arm (mPFS 4.3 vs. 1.6 months)19. In this study, trabectedin demonstrated superiority over dacarbazine in both, patients with uterine and non-uterine LMS, showing similar PFS medians in both subtypes (4 and 4.9 months, respectively)19,34. Efficacy results from large “real life” studies of LMS patients treated with trabectedin are well aligned with the above-mentioned clinical data: mPFS of 5.5 months with a PFS rate at 3 months of 69%, reported in 321 patients35. In the same way, a mPFS of 5.4 months was recently reported in 36 metastatic uterine LMS patients treated with trabectedin in different Spanish centers36.

- In the subset of 154 LPS patients included in the randomized phase III study, treatment with trabectedin led to a 45% reduction in the risk of disease progression or death when compared to dacarbazine37. Likewise, a mPFS of 6 months and a PFS rate at 3 months of 64% have been reported with trabectedin in 161 LPS patients treated at daily clinical practice35.

Finally, it is important to explain that our study was subject to several limitations. First, database only captures retrospective patient treatment profiles. Patient case history information is collected by means of forms completed by clinicians themselves. Data on socioeconomic status and lifestyle-related factors, which might have a significant impact on treatment patterns, were not part of the database and could, therefore, not be included in our analysis. Since the study is based on a quarterly physician panel survey that provides an overall perspective on cancer patient care from diagnosis onward, only patients treated by the reporting physician could be observed.

Conclusions

Results of this real-life series on more than 5,000 patients with advanced STS are well aligned with recommendations from International and National Guidelines:

- Anthracyclines-based therapy is the most common regimen in the 1st line setting (around 80%)
- Trabectedin is the agent most frequently used as 2nd line therapy (around 30%).
- Trabectedin was frequently used in multiple STS subtypes. In the most common ones, LMS and LPS, patients received trabectedin independently of more specific sub-classifications. The majority of patients treated with trabectedin receive this agent right after doxorubicin-based therapy. In accordance with published evidence, patients were treated with trabectedin for prolonged periods.

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Conflicts of interest

Piero Picci has received travel support from PharmaMar, Takeda, and Amgen.

Peter Reichardt has served on advisory boards for MSD, Roche, Clinigen and has received honoraria from PharmaMar, and Lilly.

Prof. Jean-Yves Blay has received research support and honoraria from PharmaMar, Novartis, Bayer, BMS, Astra-Zeneca, GSK, MSD, and Roche.

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Ethical approval
Non-applicable. Submission to an independent ethics committee was not required for OATM, as data are collected on the basis of a questionnaire where physicians provide anonymized data.

Informed consent
Non-applicable as data are collected on the basis of a questionnaire where physicians provide anonymized data.

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