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Trabectedin use in soft-tissue sarcoma patients in a real-world setting: Data from an Italian national drug-access registry

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Abstract

Trabectedin is a marine-derived anticancer drug approved for the treatment of patients with advanced soft-tissue sarcomas (STS). Here, we aimed to analyze its use in a large cohort of STS patients treated in Italy in a real-world setting. Data on STS patients treated with trabectedin in Italy were prospectively collected from January 2013 to December 2019 by the national drug regulator, the Italian Medicines Agency (AIFA). Time-to-off-treatment (TToT) was defined as the time between the initial prescription of trabectedin and the date of treatment discontinuation for any cause. The impact of the different baseline covariates, including the initial prescribed dose of trabectedin, on TToT was evaluated using an accelerated failure time (AFT) models with log-logistic distribution. In total, we analyzed data from 2633 sarcoma patients and 14 950 individual cycles of trabectedin. The median number of cycles of trabectedin received per patient was 3 (interquartile range 2-7). The labeled 1.5 mg/sqm dose was used in 27.3% of all first prescriptions. Overall, the median TToT was 93 days. In the final AFT model, the variables significantly associated to longer TToT were female gender (+13% increase in TToT); ECOG performance status 0 (+50%); histological diagnosis of leiomyosarcoma (+22%), well-differentiated/dedifferentiated liposarcoma (+72%) or myxoid liposarcoma (+61%); receiving treatment in a high-volume center (+23%). In this large real-world cohort of STS patients treated with trabectedin, our findings support the use of trabectedin in STS patients, in particular in leiomyosarcoma and liposarcoma patients, and highlight the role of treatment center volume in their management.

KEYWORDS
AIFA, Italy, registry, sarcoma, trabectedin

Abbreviations: AFT, accelerated failure time; AIFA, Italian Medicines Agency (Agenzia Italiana Farmaco); ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range; LMS, leiomyosarcoma; LS, liposarcoma; MyxLS, myxoid liposarcoma; PS, performance status; STS, soft tissue sarcomas; TToT, time-to-off-treatment; WD/DDLS, well-differentiated/de-differentiated liposarcoma.

Pierluigi Russo and Paolo G. Casali are co-last authors.

What's new?

The anticancer drug trabectedin, originally isolated from a marine species, is used for the treatment of advanced pretreated soft-tissue sarcoma (STS). Here, to support evidence from randomized clinical trials, the authors evaluated real-world use of trabectedin in STS patients treated between 2013 and 2019 in Italy. Analyses show that patients treated at high-volume centers underwent trabectedin therapy for a significantly longer time compared to patients treated at low-volume centers. The drug was notably effective in patients with leiomyosarcoma or liposarcoma. The findings highlight the utility of trabectedin for STS and the influence of treatment center volume on STS patient management.

1 | INTRODUCTION

Trabectedin (Yondelis) is an anticancer drug originally isolated from the Caribbean tunicate *Ecteinascidia turbinate* approved as a single agent for advanced pretreated soft-tissue sarcomas (STS) patients.[1] In STS patients, trabectedin given as a 24-hours continuous infusion after failure of an anthracycline-based chemotherapy has shown significant activity in prospective trials,[2-4] especially in liposarcoma (LS) and leiomyosarcoma (LMS).[5,6] Preclinical and clinical evidence also suggests that myxoid LS (MyxLS), a specific histological subtype of LS, might also be exquisitely sensitive to trabectedin.[7,8]

In Italy, the use of trabectedin for STS patients has been monitored since 2013 through a registry run by the Italian Medicines Agency (AIFA). We can postulate that this monitoring system intercepted roughly 100% of patients treated Italy, considering that trabectedin prescription required the inclusion in the registry of prespecified data for each patient to confirm their eligibility for the treatment.

To support and complement the results obtained in randomized clinical trials, real-world evidence is becoming increasingly important,[9,10] particularly at local or national level, as a tool to inform the process of healthcare decision-making.[11] Here, we present an analysis of real-world data derived from this registry on a very large cohort of STS patients treated with trabectedin, with a particular focus on the role of treatment center volume on the duration of treatment.

2 | PATIENTS AND METHODS

Data on STS patients treated with trabectedin in Italy were prospectively collected from January 2013 to December 2019. The data lock was on December 31, 2019. Baseline variables recorded for each patient included: gender; age; Italian region of residence; Eastern Cooperative Oncology Group (ECOG) performance status (PS); stage of disease; indication, that is, previous failure of or contraindication to anthracycline treatment; histological subtype, that is, LMS, well-differentiated/de-differentiated (WD/DD) LS, MyxLS, synovial sarcoma, other. Treating centers (n = 302) were divided between "high-volume" (n = 76) and "low-volume" (n = 226), based on the yearly average number of treatments, respectively as those with a yearly average above or below the third quartile of the overall distribution.

At each cycle, data on the dose of trabectedin administered were collected. At the end of treatment, the reasons for treatment discontinuation were also recorded. To investigate the extent, directions, and impact of interregional mobility, we also collected data on the Italian region(s) of treatment for each patient. All data were recorded on the national AIFA web platform of the monitoring registry.[12] According to Italian laws, monitoring for public health reasons does not require a patient informed consent or a formal approval from ethical committees. However, all included patients did receive information about the purposes of this monitoring.

Patient characteristics were described using measures of frequency for binary and categorical variables and with median (interquartile range, IQR) for numerical variables. All the patients included in the analysis did not have missing information in any baseline variable, as compilation of the registry form in all its parts was mandatory to prescribe the drug. Time-to-off-treatment (TToT) was defined as the time occurring between the initial prescription and the date of treatment discontinuation for any cause, including death and loss to follow-up. A patient was defined "lost to follow-up" in the absence of any prescription or reevaluation for at least 180 days after the last observed drug's coverage day, in absence of an end-of-treatment form. TToT were investigated using Kaplan-Meier's estimator, which is presented as median value (95% confidence intervals, CI). Proportions of patients still on treatment at the 12- and 24-months milestones were also assessed. The impact of the different covariates on TToT was evaluated using an accelerated failure time (AFT) model with log-logistic distribution. This model was chosen because the Cox model's proportional hazards assumption was not met by all covariates. Variables included in the AFT model were gender; age; stage of disease; ECOG PS; histology; indication for treatment; trabectedin dose in mg/sqm at cycle 1; treatment center volume. To further characterize the effects of treatment center volume on the TToT in the histological subtypes where trabectedin is mostly effective, we developed separate AFT models with log-logistic distribution for LMS, WD/DDLS and MyxLS and generated adjusted Kaplan-Meier's curves based on centers' volume. *P*-values were considered significant when <.05. All the analyses were conducted using the R software, version 3.6.3.[13]

3 | RESULTS

3.1 | Patients and treatment characteristics

In total, we analyzed data from 2633 patients. Baseline characteristics are reported in Table 1. Briefly, about 60% of the patients were males; the median age at the beginning of treatment was 60 years (IQR 50-68, range 17-90); in about 90% of cases the disease was metastatic and trabectedin was administered after progression to an anthracycline-based regimen; in about 43% of the cases the histological subtype was LMS; finally, about 56% of the patients had a baseline ECOG PS of 0.

Overall, data on 14 950 cycles of trabectedin were recorded. The median number of cycles received per patient was 3 (IQR 2-7), with a positively skewed distribution (Figure 1).

Table 2 summarizes the distribution of the different doses of trabectedin used at the first cycle of treatment or considering all the cycles administered. The labeled 1.5 mg/sqm dose was used in 27.3% of first prescriptions, 61.5% of patients received a range of doses between 1.1 and 1.4 mg/sqm and 10.8% received 1 mg/sqm or less. Considering all cycles, the most common administered dose was 1.2 mg/sqm (3608/14 950, 24.1%). Moreover, 32.8% of patients experienced dose reduction after the first dose.

At the time of data lock, the median follow-up was 91 days (IQR 50-206 days) and 3.6% of the patients were still receiving treatment. About 10.6% of the patients were lost to follow-up. In 72.2% of the cases, the cause for treatment interruption was disease progression (Figure S1).

Of the 2633 patients included, 1824 (69.3%) were treated in a high-volume center. Baseline characteristics between patients treated

TABLE 1 Baseline patient characteristics

Gender (N, % of the total)		
Male	1051	60.08%
Female	1582	39.92%
Age in years (median, first quartile-third quartile)	60	50–68
Stage (N, % of the total)		
Locally advanced	253	9.61%
Metastatic	2380	90.39%
ECOG PS (N, % of the total)		
0	1484	56.36%
1	1043	39.61%
>1	106	4.03%
Histology (N, % of the total)		
LMS	1136	43.14%
WD/DDLS	263	9.99%
MyxLS	276	10.48%
Synovial sarcoma	146	5.55%
Other	812	30.84%
Indication (N, % of the total)		
Progressive disease after anthracycline	2372	90.09%
Contraindication to anthracycline	261	9.91%

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; LMS, leiomyosarcoma; MyxLS, myxoid liposarcoma; WD/DDLS, well differentiated/dedifferentiated liposarcoma.

TABLE 2 Trabectedin dose administered

Trabectedin dose (mg/sqm)	Frequency (first cycle) N (% of the total)	Frequency (any cycle) N (% of the total)
<1.0	99 (3.8%)	1000 (6.7%)
1.0	185 (7.0%)	1673 (11.2%)
1.1	293 (11.1%)	2095 (14.0%)
1.2	578 (22.0%)	3608 (24.1%)
1.3	491 (18.6%)	2571 (17.2%)
1.4	257 (9.8%)	1048 (7.0%)
1.5	719 (27.3%)	2902 (19.4%)
>1.5	11 (0.4%)	53 (0.4%)
Total	2633 (100%)	14 950 (100%)

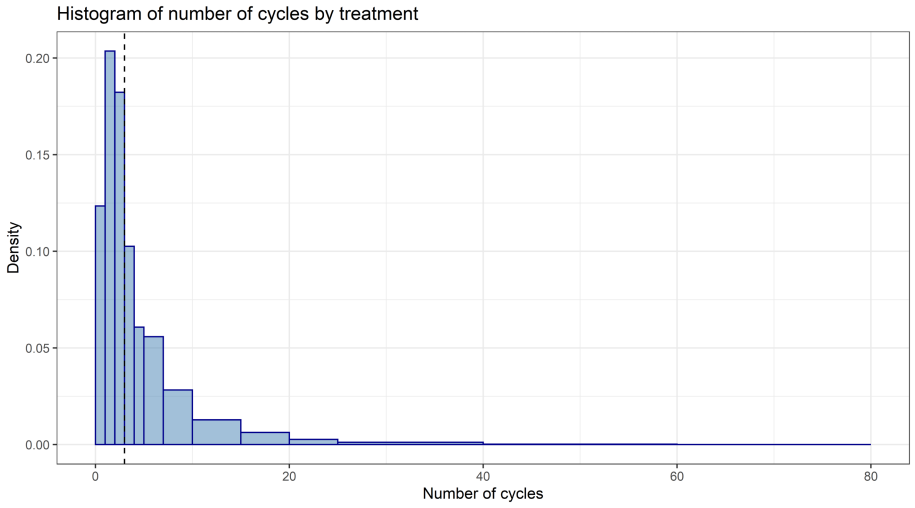

FIGURE 1 Histogram of number of cycles of trabectedin administered [Color figure can be viewed at wileyonlinelibrary.com]

in high- and low-volume centers varied, with low-volume centers treating relatively more female patients, more patients with PS ECOG >0, more patients with a histological diagnosis of LMS and fewer patients with synovial sarcomas and other rare sarcomas. Low-volume centers also used more frequently an initial dose of trabectedin <1.1 mg/sqm or >1.3 mg/sqm (Table S1).

Comparing the region of treating institutions and the place of residence of patients, it was possible to assess the interregional mobility associated to trabectedin treatment. Lombardia, Emilia-Romagna, and Friuli-Venezia Giulia showed the largest attraction for nonresident patients, whereas Veneto, Campania and Puglia had the highest number of resident patients starting treatment in other regions (Figure S2).

3.2 | Survival outcomes

Overall, the median TToT was 93 days (95% CI 89-100) (Figure 2A). Considering individual TToT estimates in each of the main histological

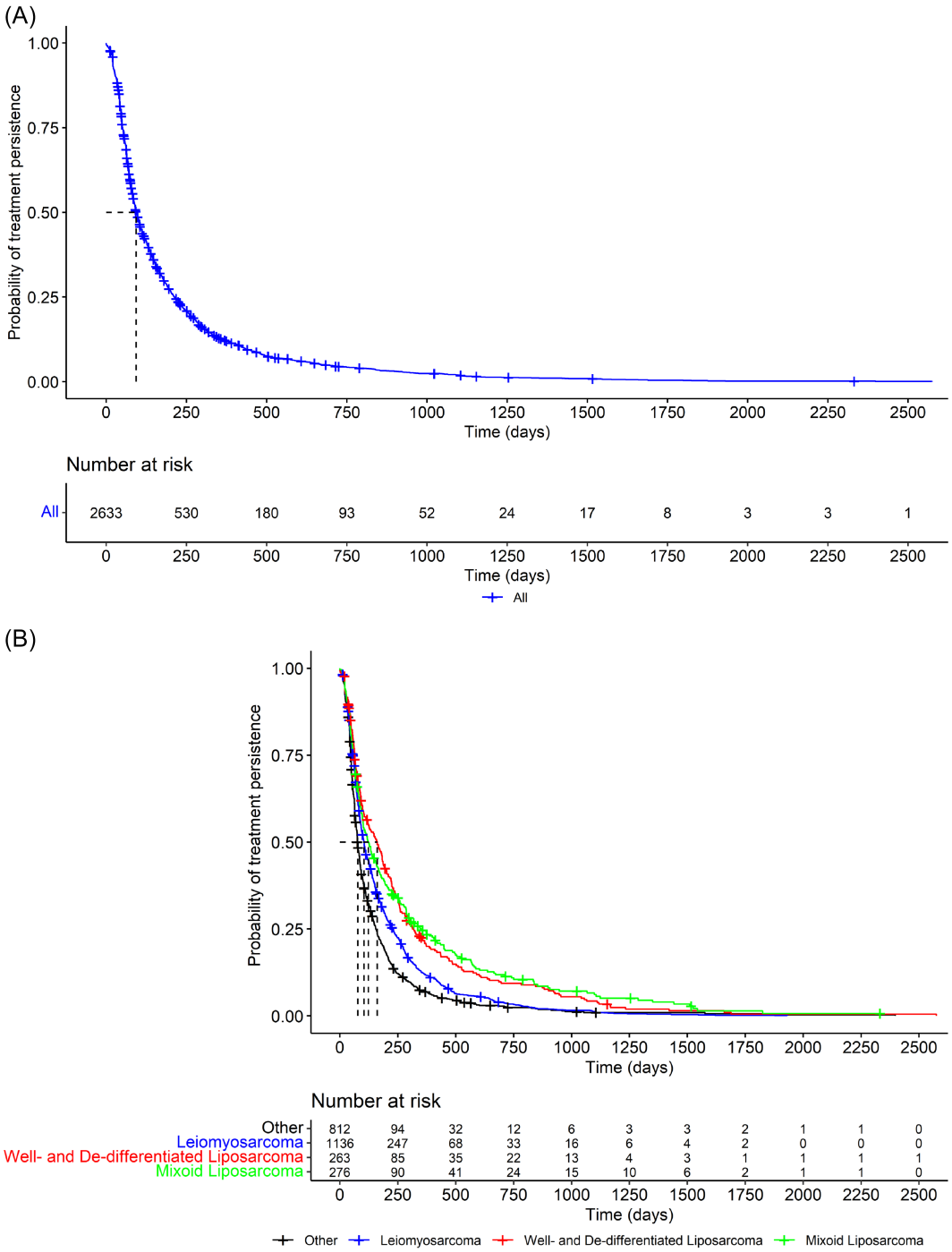

FIGURE 2 (A) TToT in the whole population. (B) TToT in the main histological subtypes [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 3 Multivariable AFT model for TToT

Variable	Coef (SE)	Exp(Coef)	*P* value
Intercept	4.00 (0.151)	54.75	<.01
Gender (male vs female)	−0.141 (0.043)	0.868	<.01
Age	0.003 (0.002)	1.003	n.s.
Stage (metastatic vs locally advanced)	−0.021 (0.070)	0.979	n.s.
ECOG PS (0 vs >0)	0.405 (0.041)	1.499	<.01
Histology (vs other)			
LMS	0.199 (0.046)	1.220	<.01
WD/DDLS	0.545 (0.075)	1.725	<.01
MyxLS	0.476 (0.073)	1.610	<.01
Indication (progressive disease vs contraindication)	0.006 (0.067)	1.006	n.s.
Trabectedin dose in mg/sqm at cycle 1 (vs 1.5)			
1.0	−0.100 (0.054)	0.905	n.s.
1.2	−0.011 (0.053)	0.988	n.s.
1.3	0.023 (0.058)	1.023	n.s.
Treatment center volume (high- vs low-volume)	0.209 (0.043)	1.231	<.01

Abbreviations: ECOG PS: Eastern Cooperative Oncology Group performance status; LMS: leiomyosarcoma; MyxLS: myxoid liposarcoma; WD/DDLS: well differentiated/dedifferentiated liposarcoma.

categories, the median duration was 104 days (95% CI 96-112) for LMS, 123 days (95% CI 100-158) for MyxLS and 161 days (95% CI 120-188) for WD/DDLS. Although the median TToT for MyxLS was intermediate compared to the two other major histologies, its survival curve largely overlapped with the one for WD/DDLS from the 250-day mark onward (Figure 2B).

When analyzing the proportion of patients still on treatment at two critical milestones defining long-responders (12 and 24 months), WD/DDLS and MyxLS showed higher percentages compared to LMS and other histological subtypes (Table S2). Eleven patients (4 LMS, 3 WD/DDLS, 4 MyxLS) received more than 40 cycles of trabectedin. They were all metastatic patients who had progressed on a previous anthracycline and all treated in high-volume centers.

To evaluate the impact of the different covariates on TToT, we used an AFT model. In the final model, four variables were significantly associated to TToT: gender, ECOG PS, histological diagnosis and treating center (Table 3). In particular, TToT was increased in patients of female gender (+13%); with ECOG performance status 0 (+50%); with histological diagnosis of leiomyosarcoma (+22%), well-differentiated/dedifferentiated liposarcoma (+72%) or myxoid liposarcoma (+61%); when receiving treatment in a high-volume center (+23%).

Then, we derived specific AFT models for LMS, WD/DDLS and MyxLS and generated TToT curves based on treatment center volume. In LMS, median TToT was 110 days (95% CI 100-127) in high-volume centers vs 96 days (95% CI 89-106) in low-volume centers ($P < .01$) (Figure 3A); in WD/DDLS median TToT was 184 days (95% CI 148-238) in high-volume centers vs 95 days (95% CI 82-169) in low-volume centers ($P = .02$) (Figure 3B); finally, in MyxLS median TToT was 161 days (95% CI 119-224) in high-volume centers vs 93 days (95% CI 79-120) in low-volume centers ($P < .01$) (Figure 3C).

4 | DISCUSSION

This was a real-world analysis of more than 2600 sarcoma patients treated with trabectedin in Italy over 9 years, including a total of nearly 15 000 cycles of therapy. These virtually represents all the patients treated with trabectedin in Italy during the study period. Its population-based design with unselected patients and the possibility to prospectively collect data represents another strength of this real-world approach.

In this registry, a dose different from the labeled one was used in most cases. About 40% of the patients were started at a dose between 1.2 and 1.3 mg/sqm, and this was more often the case in high-volume centers. A lower initial dose of trabectedin is frequently offered in reference centers in Italy, to improve tolerability and compliance to the treatment without loss of activity. In fact, the initial dose of trabectedin administered was not associated to a shorter treatment duration in our multivariable analysis. Dose reductions were also frequently reported, in approximately one third of all patients. Although the specific reasons leading to these reductions were not recorded in the registry, they indirectly confirm the narrow therapeutic window of trabectedin.

A clear limitation of our study is indeed the lack of exhaustive data on toxicities, as well as the absence of long-term survival outcomes, which might limit the interpretation of some of the results. Especially when TToT is short, it may be assumed to be a proxy for progression-free survival. When longer, TToT may underestimate the true treatment benefit, since therapy could be interrupted after a number of cycles and response may last for longer. With these premises, our median TToT of 93 days (3.1 months) was consistent with published clinical studies on trabectedin in soft tissue sarcomas, as well as with available evidence from real-world studies (Table S3),

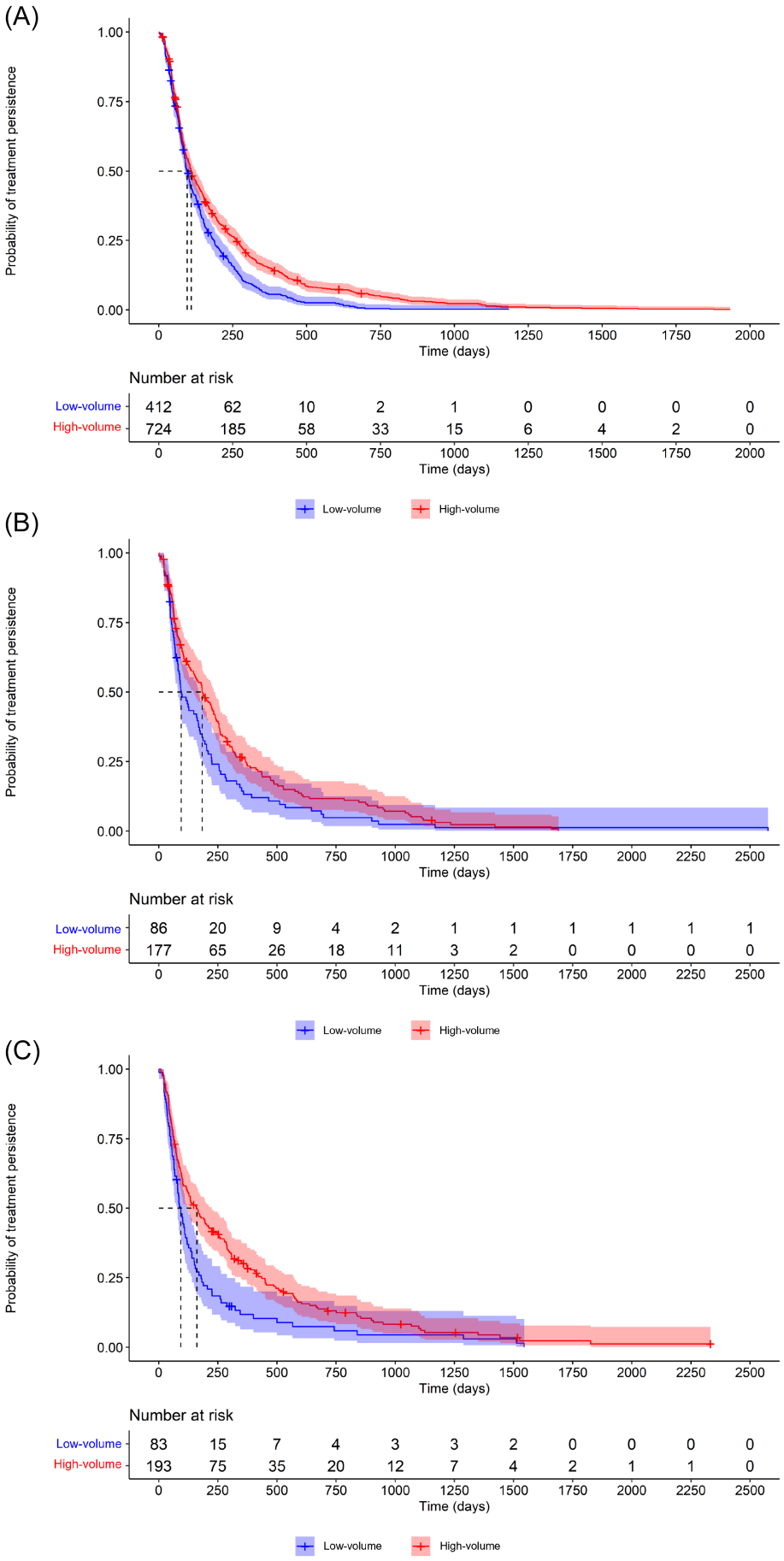

FIGURE 3 (A) TToT in leiomyosarcoma patients by treatment center volume. (B) TToT in well-differentiated/de-differentiated liposarcoma patients by treatment center volume. (C) TToT in myxoid liposarcoma patients by treatment center volume [Color figure can be viewed at wileyonlinelibrary.com]

which point to a median progression-free survival ranging between 3.0 and 5.9 months.[2-4,14] In our multivariable analysis we observed that LMS, WD/DDLS and MyxLS have a longer TToT compared to other subtypes. This is consistent with published studies, which point to a specific effect of trabectedin in these histologies. The effect of the drug in MyxLS is reported to be more marked. In our cohort, MyxLS did not show a significantly longer median TToT compared to WD/DDLS. However, its survival curve largely overlapped with the one for WD/DDLS from the 250-day mark onward. Overall, a subgroup of approximately 12% of patients received their treatment for at least 12 months. This proportion was 20% to 25% in patients with WD/DDLS or MyxLS. Regarding the other histologic subtypes, we lacked information on the histological subtypes of the patients recorded in the "other" group (just below one third of the total). This derived from the limited information required by the registry to allow patients to received trabectedin. Thus, additional information could not be gained on rarer histologic subtypes, though this would nevertheless have been limited by the absence of a central pathological review. This is a major limitation of all epidemiological or real-world evidence about soft tissue sarcomas, with a published high degree of inappropriateness of pathologic diagnoses outside reference centers.[15]

Interestingly, TToT varied significantly between high-volume and low-volume centers across histologies, markedly for MyxLS. This may reflect a selection bias in favor of high-volume centers, which may miss poor-prognosis patients. For example, low-volume centers treated relatively more patients with ECOG PS >0 and a slightly older population. Nevertheless, an impact of therapeutic skills among centers with different specific expertise in the treatment of rare cancers as sarcomas cannot be ruled out, as insufficient exposure to rare cancers like sarcomas and specifically to the use of trabectedin may lead to a potential inappropriateness of management in low-volume centers. For example, the optimal management of treatment-related toxicities varies with the center experience: early liver tests alterations, frequently associated with the lack of premedication with steroids, may represent a deterrent leading doctors in low-volume centers to untimely discontinue trabectedin.[16] Furthermore, another factor potentially influencing the TToT is the experience of the center in evaluating treatment-related radiological modifications. In the registry, responses to trabectedin were evaluated locally and the criteria used to determine responses might have differed between centers. Response Evaluation Criteria in Solid Tumors (RECIST) are the most utilized tool, and they are only based on tumor size. However, RECIST may be limited if tumor response is nondimensional (ie, associated to changes in CT attenuation and/or functional imaging), especially in an early phase of treatment. It is possible that in centers with less skilled radiologists or without a multidisciplinary tumor board to discuss radiological images, patients could be prematurely discontinued because (mistakenly) considered with progressive disease. Independent radiological review of the evaluation scans of the patients present in the registry was not possible, and it is therefore difficult to confirm this possibility.

In published literature, an impact on survival of patients receiving their treatment at reference centers has been often shown in STS.[17,18] Thus, our observation of a different TToT in STS patients treated with trabectedin between high- and low-volume centers is supporting the case for the identification of national reference centers and for health care networking between hubs and spokes. This is exceedingly relevant due to the high interregional mobility of STS patients in Italy and thus crucial from a public health perspective. Given the rarity of STS, strengthening reference centers and healthcare collaborative networks would be highly important, as widely underlined by many.[19] In conclusion, our data confirm published efficacy data of trabectedin in STS patients, while once more highlighting the importance of centers' treatment volume as well as the issue of health migration of rare cancer patients in Italy.

AUTHOR CONTRIBUTIONS

Bruno Vincenzi: study conceptualization, study supervision, writing—reviewing and editing. **Andrea Napolitano**: writing—original draft, writing—reviewing and editing. **Alessandro Comandone**: writing—reviewing and editing. **Roberta Sanfilippo**: writing—reviewing and editing. **Simone Celant**: data curation, formal analysis, writing—reviewing and editing. **Pier P. Olimpieri**: data curation, formal analysis, writing—reviewing and editing. **Susanna Di Segni**: data curation, formal analysis, writing—reviewing and editing. **Pierluigi Russo**: study supervision, writing—reviewing and editing. **Paolo G. Casali**: study supervision, writing—reviewing and editing. The work reported in the paper has been performed by the authors, unless clearly specified in the text.

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CONFLICT OF INTEREST

Paolo G. Casali, Roberta Sanfilippo and Bruno Vincenzi received honoraria and institutional grants from PharmaMar. Andrea Napolitano received honoraria from PharmaMar. The other authors declare no conflict of interests.

DATA AVAILABILITY STATEMENT

The data that support the findings of our study are available on request from the corresponding author.

ETHICS STATEMENT

According to Italian laws, monitoring for public health reasons does not require a patient informed consent or a formal approval from ethical committees. However, all included patients did receive information about the purposes of this monitoring.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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