Trabectedin for Patients with Advanced Soft Tissue Sarcoma: A Non-Interventional, Prospective, Multicenter, Phase IV Trial

Viktor Grünwald 1,*, Daniel Pink 2,3,*, Gerlinde Egerer 4, Enrico Schalk 5,*, Marinela Augustin 6, Christoph K. W. Deinzer 7, Viola Kob 8, Dietmar Reichert 9, Maxim Kebenko 10, Stephan Brandl 11, Dennis Hahn 12, Lars H. Lindner 13, Mathias Hoizyk 14, Uta Ringsdorf 15, Lars C. Hanker 16, Dirk Hempel 17, Beatriz De Rivas 18, Tobias Wismann 19 and Philipp Ivanyi 20

Citation: Grünwald, V.; Pink, D.; Egerer, G.; Schalk, E.; Augustin, M.; Deinzer, C.K.W.; Kob, V.; Reichert, D.; Kebenko, M.; Brandl, S.; et al. Trabectedin for Patients with Advanced Soft Tissue Sarcoma: A Non-Interventional, Prospective, Multicenter, Phase IV Trial. Cancers 2022, 14, 5234. https://doi.org/10.3390/cancers14215234

Simple Summary: Active therapeutic options in advanced soft tissue sarcoma (STS), able to induce durable objective responses, are limited beyond first-line chemotherapy. Although results obtained in clinical trials suggest there is a high probability for patients with STS to benefit from treatment with trabectedin (Yondelis®), there is still a paucity of robust real-life data in more diverse patient populations. The prospective, non-interventional phase IV YON-SAR trial (NCT02367924) was designed to evaluate treatment effects of trabectedin in patients with advanced STS in real-life clinical practice across Germany. The efficacy results of this trial, conducted in 128 patients from 19 sites across Germany, further support trabectedin as a standard of care for a second- or further-line treatment of patients with advanced STS in routine clinical practice (median progression-free survival: 5.2 months; median overall survival: 15.2 months). The safety profile of trabectedin was manageable and in line with those observed in previous studies.
58.5 years (range: 23–84) and leiomyosarcoma was the most frequent histotype ($n = 45; 35.2\%$). Trabectedin was mostly used as second/third-line treatment ($n = 91; 71.1\%$). Median PFS was 5.2 months (95\% CI: 3.3–6.7), with 60.7\% and 44.5\% of patients free from progression at 3 and 6 months, respectively. Median overall survival was 15.2 months (95\% CI: 9.6–21.4). One patient achieved a complete and 14 patients a partial response, conferring an objective response rate of 11.7\%. Decreases in white blood cells (27.0\% of patients), platelets (16.2\%) and neutrophils (13.1\%) and increased alanine aminotransferase (10.8\%) were the most common trabectedin-related grade 3/4 adverse drug reactions. Two deaths due to pneumonia and sepsis were considered trabectedin-related. Trabectedin confers clinically meaningful activity in patients with multiple STS histotypes, comparable to that previously observed in clinical trials and other non-interventional studies, and with a manageable safety profile.

Keywords: trabectedin; STS; sarcoma; non-interventional; prospective

1. Introduction

Soft tissue sarcomas (STS) are a heterogeneous group of rare malignancies with mesenchymal origin that comprise approximately 1% of adult and 7% of pediatric malignancies [1–3]. Once metastatic or unresectable, prognosis for advanced STS is poor, and patients are not considered curable. For patients with advanced STS, systemic chemotherapy has been a cornerstone of treatment, although local therapies such as surgery and radiation therapy may achieve prolonged survival in selected patients [4].

Trabectedin (Yondelis®) is an alkylating agent with a multifaceted mechanism of action, which, apart from being a DNA-binding agent, also has selective anti-inflammatory, immunomodulatory and anti-angiogenic properties [5–7]. In 2007, trabectedin was the first marine-derived antineoplastic drug approved in the European Union for treatment of patients with advanced STS after failure of anthracyclines and ifosfamide, or who are unsuited to receive these agents [8]. Since 2015, following the analysis of a pivotal, active-controlled, randomized phase III trial in patients with advanced liposarcoma or leiomyosarcoma (commonly abbreviated as L-sarcomas) after failure of prior anthracycline-containing chemotherapy, trabectedin was also approved by the U.S. Food and Drug Administration [9]. Trabectedin was reported to be active in non-L-sarcomas as well since it has demonstrated efficacy in patients with a variety of sarcoma histotypes [10–13]. In a clinical trial setting, the efficacy of trabectedin compared to best supportive care is also supported by the results of trials conducted in patients with histologically different sarcoma subtypes [14,15]. In addition, trabectedin has a manageable safety profile and is without cumulative toxicities, including those in patients treated for prolonged periods [16].

Although results obtained in clinical trials suggest there is a high probability for patients with STS to benefit from treatment with trabectedin, at the time this study was launched, there was a paucity of robust real-life data on a more diverse patient population than that recruited in clinical trials. Indeed, such observational studies can provide useful insights into the real-life efficacy, safety and management of patients who may be underrepresented in clinical trials due to more restrictive eligibility criteria. Recently, one European and two national observational studies on the real-life use of trabectedin in patients with advanced STS reported clinically meaningful long-term benefits in patients with multiple STS histotypes, largely comparable to those previously reported in selected populations from clinical trials, and with a manageable safety profile [17–19].

Currently, data on the real-life use of trabectedin for STS in Germany are limited [20]. The constant change in patient selection and novel therapies applied in advanced STS mandate re-evaluation of real-life management in this evolving treatment landscape. Therefore, the prospective, non-interventional YON-SAR trial (http://www.ClinicalTrials.gov Identifier: NCT02367924) was designed with the aim of evaluating treatment effects of
trabectedin in patients with advanced STS across a contemporary treatment landscape in Germany.

2. Materials and Methods

This non-interventional, prospective, multicenter phase IV study evaluated trabectedin in routine clinical practice in patients with advanced STS in Germany [21]. Treatment decisions, dosing, monitoring as well as diagnostic or therapeutic procedures were at the discretion of the investigator, were performed according to routine care and were not mandated by the observational plan.

Eligible participants included adults (≥18 years old) with histologically diagnosed advanced STS and who signed an informed consent document. All eligible patients had either progressive disease following therapy with anthracyclines and ifosfamide or were unsuited to receive these agents, and were suitable to undergo treatment with trabectedin according to the Summary of Product Characteristics (SmPC). Patients with contraindications for treatment with trabectedin according to SmPC were excluded.

Trabectedin was administered in agreement with the marketing authorization, standard local clinical practice, and the treating clinician’s discretion. The recommended dose of trabectedin for the treatment of STS is 1.5 mg/m² body surface area, given intravenously over 24 h every 3 weeks. There were no predefined limits of administered trabectedin cycles, and treatment could continue until disease progression, intolerance or consent withdrawal.

The observational period for each patient enrolled in this study consisted of the treatment period and the follow-up period. The treatment period began from the date of the first administration of trabectedin until progressive disease, death or treatment termination (whichever occurred first). After the end of treatment, patients were followed up for at least 12 months. After trabectedin treatment discontinuation, patients could have been treated with subsequent anticancer therapies or supportive care as per the treating clinician’s clinical judgment.

All study procedures were conducted in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments, guidelines for Good Clinical Practice and local regulations on clinical trials, and were approved by the independent ethics committee.

The primary endpoint of this study was to assess the number of patients free from progression at 3 and 6 months after treatment (i.e., progression-free survival [PFS] rate at 3 and 6 months) as measured by institutional routine clinical standards. Secondary efficacy endpoints included unconfirmed disease control rate (DCR), defined as the percentage of patients with a complete response (CR) or partial response (PR) and/or stable disease (SD), PFS, overall survival (OS) and OS rates at 3 and 6 months after treatment. Secondary endpoints also included an assessment of the treatment with trabectedin and employed doses, treatment duration, causes for treatment discontinuation, and safety profile. The PFS was defined as the time interval from the first administration of trabectedin to the date of disease progression or death, regardless of cause (whichever occurred first), whereas OS was defined as the time between the start of trabectedin and patient death from any cause. Patients not experiencing an event or death or considered lost to follow-up were censored with the date of last contact or with the beginning of the following therapy (whichever occurred first). Response evaluations (i.e., CR, PR and SD) were measured according to local institutional standards, being preferred according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 [22] or Choi criteria [23]. Adverse events (AE) were reported according to CTCAE 4.03 and their relationship to trabectedin. Treatment-related AEs were followed until resolution or start of new therapy. Documentation of AEs and serious AEs (SAE) occurred until 30 days after the last dose.

All collected parameters were analyzed in a descriptive manner. Categorical variables were expressed as absolute and relative frequencies, and continuous variables were described by number of observations, median, and range (minimum to maximum). Frequency tables were prepared for categorical variables and checked for dependencies by Fisher’s
exact test. The exact binomial estimator and its 95% confidence interval (CI) were used in the analysis of categorical outcome parameters (e.g., tumor control rate). Time-to-event endpoints (i.e., PFS and OS) and their fixed-time estimations were estimated according to the Kaplan–Meier method and were compared using the log-rank test, while Cox regression models were performed for covariate analyses. All $p$-values were descriptive in nature and the significance level selected was 0.05. All statistical analyses were performed by means of SAS version 9.4 software (SAS Institute Inc., Cary, NC, USA). The efficacy analyses were based on the modified intention-to-treat (mITT) population, defined as all patients who received at least one dose of trabectedin, signed informed consent, and did not violate any inclusion or exclusion criterion. The analysis of safety was performed on the Safety Analysis Set (SAS) that included all enrolled patients who received at least one dose of trabectedin and provided consent to participate in the study.

3. Results

3.1. Patient Disposition and Characteristics

Between 16 July 2015 and 22 January 2019, a total of 130 patients from 19 medical centers in Germany were enrolled and received at least one dose of trabectedin (SAS). Two patients were excluded due to lack of STS diagnosis, and therefore, 128 patients were included in the mITT (Figure 1).

Figure 1. Description of included patients.

The mITT included 65 females (50.8%) and 63 males (49.2%) with a median age of 58.5 years (range: 23–84) (Table 1). An Eastern Cooperative Oncology Group (ECOG) performance status score of 0–1 was recorded in 100 (78.2%) patients. The most prevalent histological type of sarcoma was leiomyosarcoma ($n = 45, 35.2$%), followed by liposarcoma ($n = 23, 18.0$%) and pleomorphic undifferentiated sarcoma ($n = 20, 15.6$%), mostly being localized in lower extremity ($n = 23, 18.0$%), abdomen (retroperitoneal) ($n = 20, 15.6$%), upper extremity ($n = 17, 13.3$%) or uterus ($n = 15, 11.7$%). The most common tumor grade was grade 3 both in patients assessed according to FNCLCC ($n = 34, 45.3$%) and UICC ($n = 23, 42.6$%) system grading, and most had stage IV sarcoma as per AJCC staging system (Table 1). The majority of patients had metastatic disease ($n = 79, 61.7$%), mostly being localized in the lung ($n = 59, 74.7$%), liver ($n = 25, 31.7$%), or bones ($n = 22, 27.9$%).

Previous therapies included surgery in 111 (86.7$%) patients, while 64 (50$%) patients were treated with radiotherapy. The majority of patients received systemic therapy ($n = 101, 78.9$%), mostly with doxorubicin ($n = 87, 86.1$%) and/or ifosfamide ($n = 63, 62.4$%). Twenty-seven (21.1$%) patients were chemotherapy-naïve (Table 2). Most patients received one or two lines of prior systemic therapy ($n = 91, 71.1$%). Overall, 113 patients (88.3$%) reported
relevant concomitant disease, mainly being arterial hypertension \((n = 54, 47.8\%)\), other cardiac diseases \((n = 29, 25.7\%)\) or thyropathy \((n = 25, 22.1\%)\).

### Table 1. Patient and disease characteristics at baseline.

| Patients | Modified Intent-to-Treat Set (mITT) \(^1\) \(n = 128\) |
|----------|--------------------------------------------------|
| **Age at study entry (years)** |  |
| Median (range) | 58.5 (23–84) |
| \(\leq 60\) years | 70 (54.7\%) |
| \(>60\) years | 58 (45.3\%) |
| \(\leq 70\) years | 99 (77.3\%) |
| \(>70\) years | 29 (22.7\%) |
| **Gender** |  |
| Female | 65 (50.8\%) |
| Male | 63 (49.2\%) |
| **Histology** |  |
| Leiomyosarcoma | 45 (35.2\%) |
| Liposarcoma | 23 (18.0\%) |
| Pleomorphic undifferentiated sarcoma | 20 (15.6\%) |
| Synovial sarcoma | 8 (6.3\%) |
| Fibrosarcoma | 8 (6.3\%) |
| Angiosarcoma | 1 (0.8\%) |
| Other | 23 (18.0\%) |
| **Site of primary tumor** |  |
| Lower extremity | 23 (18.0\%) |
| Abdomen (retroperitoneal) | 20 (15.6\%) |
| Upper extremity | 17 (13.3\%) |
| Uterus | 15 (11.7\%) |
| Abdomen (intraperitoneal) | 11 (8.6\%) |
| Other | 42 (32.8\%) |
| **Eastern Cooperative Oncology Group (ECOG) performance status** |  |
| 0 | 34 (26.6\%) |
| 1 | 66 (51.6\%) |
| 2 | 10 (7.8\%) |
| 3 | 1 (0.8\%) |
| 4 | 1 (0.8\%) |
| Missing | 16 (12.5\%) |
| **Tumor grade according to the French Federation of Cancer Centers Sarcoma Group grading systems (FNCLCC) \(^2\)** |  |
| Grade 1 | 13 (17.3\%) |
| Grade 2 | 21 (28.0\%) |
| Grade 3 | 34 (45.3\%) |
| Grade X \(^3\) | 6 (8.0\%) |
| Missing | 1 (1.3\%) |
| **According to the Union for International Cancer Control (UICC) \(^2\)** |  |
| Grade 1 | 5 (9.3\%) |
| Grade 2 | 9 (16.7\%) |
| Grade 3 | 23 (42.6\%) |
| Grade 4 | 3 (5.6\%) |
| Grade X \(^3\) | 13 (24.1\%) |
| Missing | 1 (1.9\%) |
Table 1. Cont.

| Patients | Modified Intent-to-Treat Set (mITT) ¹  |
|----------|---------------------------------------|
|          | \( n = 128 \)                         |
| Tumor stage according to the American Joint Committee on Cancer (AJCC) | |
| Ia       | 3 (2.3)                               |
| Ib       | 7 (5.5)                               |
| IIa      | 4 (3.1)                               |
| IIb      | 5 (3.9)                               |
| III      | 15 (11.7)                             |
| IV       | 26 (20.3)                             |
| Unknown  | 68 (53.1)                             |
| Time from first diagnosis to first treatment (months); \( n = 125 \) | Median (range) 0.4 (0.0–149.7) |
| Time from diagnosis to last treatment before trabectedin (months); \( n = 125 \) | Median (range) 15.9 (0.0–250.2) |
| Time from last progression to trabectedin treatment (months); \( n = 95 \) | Median (range) 0.9 (0.0–2.5) |

¹ Modified intent-to-treat set (mITT) included all patients who received at least one dose of trabectedin, signed informed consent and did not violate any inclusion or exclusion criterion. ² One patient had no documented grading according to both FNCLCC and UICC and was counted in both grading categories as missing. ³ Tumor grade could not be assessed.

Table 2. Prior treatments.

| Patients | Modified Intent-to-Treat Set (mITT); \( n = 128 \) |
|----------|--------------------------------------------------|
| Prior treatments | Prior surgery 111 (86.7%) |
|              | Prior radiotherapy 64 (50.0%) |
|              | Prior chemotherapy/targeted treatments 101 (78.9%) |
| No. of lines of prior chemotherapy/targeted treatments, \( n = 128 \) | 0 lines 27 (21.1%) |
|              | 1 line 66 (51.6%) |
|              | 2 lines 25 (19.5%) |
|              | ≥3 lines (3 to 6 lines) 10 (7.8%) |
| Types of prior chemotherapy/targeted treatments, \( n = 101 \) (≥4% of patients) | Doxorubicin 87 (86.1%) |
|              | Ifosfamide 63 (62.4%) |
|              | Dacarbazine (DTIC) 18 (17.8%) |
|              | Trophosphamide 16 (15.8%) |
|              | Gemcitabine 13 (12.9%) |
|              | Docetaxel 12 (11.9%) |
|              | Epirubicin 12 (11.9%) |
|              | Olaratumab 10 (9.9%) |
|              | Pazopanib 8 (7.9%) |
| Best response to last prior chemotherapy/targeted treatments, \( n = 101 \) | Complete response (CR) 2 (2.0%) |
|              | Partial response (PR) 22 (21.8%) |
|              | Stable disease (SD) 39 (38.6%) |
|              | Progressive disease (PD) 22 (21.8%) |
|              | Non evaluated (NE) 16 (15.8%) |
Subsequent antineoplastic therapies were given to 78 (60.8%) patients, which consisted of gemcitabine \((n = 34, 43.6\%)\), pazopanib \((n = 31, 39.7\%)\), dacarbazine \((n = 24, 30.8\%)\) or other treatments \((n = 33, 42.3\%)\).

### 3.2. Extent of Exposure

Although all patients were suitable to undergo treatment with trabectedin according to SmPC, therapy deviated from the approved label in 67 patients (52.3%), commonly due to a reduced starting dose lower than 1.5 mg/m\(^2\) \((n = 53, 41.4\%)\), use of aprepitant as premedication at first cycle \((n = 14, 10.9\%)\), and lack of baseline biochemistry or hematology in 10 (7.8%) and 5 patients (3.9%), respectively.

Patients received a median of four trabectedin cycles, with 52 (40.6%) patients receiving \(\geq 6\) cycles and up to a maximum of 44 cycles (Table 3). Of note, four patients received \(>24\) cycles of treatment (approximately 18 months), one of whom reached 44 cycles of treatment with trabectedin (Table S1). Patients received a median cumulative total dose of 10.7 mg/m\(^2\) (range: 1.8–110.9) over a median infusion duration of 24 h (range: 3.0–24.2). Premedication consisted of corticosteroids in 96.7% and antiemetics in 75.0% or more patients in each trabectedin cycle. The use of aprepitant was registered in 4.4% to 20.0% of patients during the study.

**Table 3. Trabectedin exposure.**

| Treatment Delivery | Modified Intent-to-Treat Set (mITT); \(n = 128\) |
|--------------------|---------------------------------------------|
| Number of cycles received per patient | Median (range) |
| | 4 (1–44) |
| | <6 cycles | 76 (59.4%) |
| | \(\geq 6\) cycles | 52 (40.6%) |
| Dose reductions (per patient) | 0 cycle | 62 (48.4%) |
| | 1 cycle | 17 (13.3%) |
| | 2 cycles | 21 (16.4%) |
| | \(>2\) cycles | 18 (14.1%) |
| | Unknown | 10 (7.8%) |
| Cycle delays (per patient) | 0 cycle | 49 (38.3%) |
| | 1 cycle | 22 (17.2%) |
| | 2 cycles | 8 (6.3%) |
| | \(>2\) cycles | 44 (34.4%) |
| | Unknown | 5 (3.9%) |

Data shown are numbers and percentages of patients or median and range values with available data. 1 Patients who started the treatment with trabectedin before the signed informed consents and with unknown starting dose.

Dose reductions occurred in 61 patients (47.7%), and dose delays in 76 patients (59.4%). Among 125 (97.7%) patients who discontinued trabectedin, the most frequent reason for treatment discontinuation was progression \((n = 77, 60.2\%)\), followed by death or other reason \((n = 12, 9.4\%)\) each, patient’s wish \((n = 10, 7.8\%)\) and trabectedin-related adverse drug reactions (ADR) \((n = 9, 7.0\%)\).

### 3.3. Primary Efficacy Endpoint

The analysis of the primary endpoint revealed that 60.7% (95% CI: 51.5–68.8) and 44.5% (95% CI: 35.5–53.1) of patients were free from progression at 3 and 6 months after treatment, respectively (Figure 2).
In the mITT after a median follow-up of 28.7 months (range 0.07–53.5), a total of 113 progression or death events (88.3% of patients) were recorded, whereas 15 (11.7%) patients who were alive or not assessed for disease progression at the time of this analysis were censored. Median PFS was 5.2 months (95% CI: 3.3–6.7) (Figure 2).

Median PFS was similar between patients with reduced dosing during the study (i.e., patients who received at least one trabectedin dose <1.5 mg/m² throughout the study) and in those with reduced starting dose (7.1 months, 95% CI: 4.8–9.8 vs. 5.4 months, 95% CI: 3.7–9.8), as well as in patients fully treated according to the SmPC and those who had treatment deviations from the SmPC recommendations (4.6 months, 95% CI: 2.7–7.1 vs. 5.2 months, 95% CI: 3.3–7.3). Similarly, there were no statistically significant differences in median PFS ($p = 0.41$) among patients who received trabectedin as first- (6.4 months, 95% CI: 2.7–10.8), second (5.3 months, 95% CI: 2.8–7.7), third (4.0 months, 95% CI: 2.0–6.2) and ≥fourth- (3.4 months, 95% CI: 0.7–9.8) line of treatment. After 87 death events (68.5% of patients), treatment with trabectedin resulted in a median OS of 15.2 months (95% CI: 9.6–21.4), with 89.3%, 74.5%, and 52.4% of patients alive 3, 6 and 12 months after treatment (Figure 2), respectively. No statistical difference was detected for OS in patients with reduced dosing during the study (18.9 months, 95% CI: 8.9–not reached; second-line: 15.2 months, 95% CI: 6.9–21.8; third-line: 11.0 months, 95% CI: 6.1–19.4; and ≥fourth-line: 17.5 months, 95% CI: 3.5–not reached; $p = 0.1558$).

---

**Figure 2.** Kaplan–Meier plot of progression-free survival and overall survival.

### 3.4. Secondary Efficacy Endpoint

In the mITT after a median follow-up of 28.7 months (range 0.07–53.5), a total of 113 progression or death events (88.3% of patients) were recorded, whereas 15 (11.7%) patients who were alive or not assessed for disease progression at the time of this analysis were censored. Median PFS was 5.2 months (95% CI: 3.3–6.7) (Figure 2).

Median PFS was similar between patients with reduced dosing during the study (i.e., patients who received at least one trabectedin dose <1.5 mg/m² throughout the study) and in those with reduced starting dose (7.1 months, 95% CI: 4.8–9.8 vs. 5.4 months, 95% CI: 3.7–9.8), as well as in patients fully treated according to the SmPC and those who had treatment deviations from the SmPC recommendations (4.6 months, 95% CI: 2.7–7.1 vs. 5.2 months, 95% CI: 3.3–7.3). Similarly, there were no statistically significant differences in median PFS ($p = 0.41$) among patients who received trabectedin as first- (6.4 months, 95% CI: 2.7–10.8), second (5.3 months, 95% CI: 2.8–7.7), third (4.0 months, 95% CI: 2.0–6.2) and ≥fourth- (3.4 months, 95% CI: 0.7–9.8) line of treatment. After 87 death events (68.5% of patients), treatment with trabectedin resulted in a median OS of 15.2 months (95% CI: 9.6–21.4), with 89.3%, 74.5%, and 52.4% of patients alive 3, 6 and 12 months after treatment (Figure 2), respectively. No statistical difference was detected for OS in patients with reduced dosing during the study (18.9 months, 95% CI: 8.9–not reached; second-line: 15.2 months, 95% CI: 6.9–21.8; third-line: 11.0 months, 95% CI: 6.1–19.4; and ≥fourth-line: 17.5 months, 95% CI: 3.5–not reached; $p = 0.1558$).

---

**Table 1.** Baseline characteristics of patients included in the per-protocol (PP) analysis.

| Parameter | mITT, $n = 128$ |
|-----------|----------------|
| Censored | 15 (11.7%) |
| Patients with events | 113 (88.3%) |
| Progressive disease (PD) | 92 (81.4%) |
| Death, any cause | 21 (18.6%) |
| Median PFS (months), (95% CI) | 5.2 (3.3–6.7) |
| PFS at 3 months: (95% CI) | 60.7% (51.5–68.8) |
| PFS at 6 months: (95% CI) | 44.5% (35.5–53.1) |
| PFS at 12 months: (95% CI) | 22.1% (15.1–30.0) |

* Patients who had not died and did not have an assessment of progressive disease were censored.

CI, confidence interval; mITT, modified intention-to-treat population; OS, overall survival; PFS, progression-free survival.
Regarding the overall trabectedin activity, one patient (0.8%) had a CR, and 14 (10.9%) patients achieved a PR, reaching the ORR of 11.7%. Additionally, 43 (33.6%) patients had SD as a best result for a DCR of 45.3% (Table 4). Conversely, comparable DCR was observed between patients treated with trabectedin in different treatment lines, and a logistic regression analysis also revealed that presence or absence of tumor metastases at baseline was not statistically associated with DCR outcomes (odds ratio: 0.53, 95% CI: 0.23–1.24, \( p = 0.1421 \)). The ORR and DCR were similar among patients <70 and \( \geq 70 \) years old (ORR: 12.1% in <70 years and 10.3% in \( \geq 70 \) years; DCR: 45.4% in <70 years and 41.4% in \( \geq 70 \) years; post-hoc analysis). Regarding histology, CR was observed in one patient with liposarcoma, and PR was recorded in six patients with liposarcoma, in four patients with other histologies, and in two patients with leiomyosarcoma and synovial sarcoma, while stable disease was observed in patients with several histologies (Table S2).

### Table 4. Best response rate according to investigator assessment by number of treatment cycles.

| Best Response to Trabectedin per Patient (Unconfirmed) | Modified Intent-to-Treat Set (mITT); \( n = 128 \) |
|-------------------------------------------------------|--------------------------------------------------|
|                                                       | <6 Cycles  | \( n = 76 \) | \( \geq 6 \) Cycles  | \( n = 52 \) | Total  \( n = 128 \) |
| Complete response (CR)                               |           | 1 (1.9%)     | 1 (0.8%)               |
| Partial response (PR)                                | 1 (1.3%)  | 13 (25.0%)   | 14 (10.9%)             |
| Stable disease (SD)                                  | 10 (13.2%)| 33 (63.5%)   | 43 (33.6%)             |
| Progressive disease (PD)                             | 35 (46.1%)| 3 (5.8%)     | 38 (29.7%)             |
| Not evaluable                                        | 4 (5.3%)  | 2 (3.9%)     | 6 (4.7%)               |
| Not done                                             | 26 (34.2%)| -            | 26 (20.3%)             |
| Objective response rate (ORR; CR + PR)               | 1 (1.3%)  | 14 (26.9%)   | 15 (11.7%)             |
| Disease control rate (DCR; ORR + SD)                 | 11 (14.5%)| 47 (89.4%)   | 58 (45.3%)             |
| Fisher’s exact test (p-value) \(^1\)                 | <0.0001   | -            | -                      |

\(^{1}\) Unevaluated patients and those with missing best responses were excluded from the comparison.

Additionally, throughout the study, ECOG performance status improved by 1 in 10 (7.8%) patients, deteriorated by 1 in 38 (29.7%), and remained unchanged in 64 (50.0%) patients.

### 3.5. Safety

A total of 86 (66.2%) patients had at least one grade \( \geq 3 \) AE. Most common (\( \geq 10\% \) of patients) grade-3/4 AEs were decreased white blood cell count (\( n = 35, 26.9\% \) of patients), decreased platelet count (\( n = 22, 16.9\% \)), decreased neutrophil count (\( n = 17, 13.1\% \)), increased alanine aminotransferase and anemia (\( n = 14, 10.8\% \) each), and increased gamma-glutamyl transferase (\( n = 13, 10\% \)). Nine (6.9%) patients experienced 10 grade-5 AEs, namely sepsis (\( n = 4, 3.1\% \)), pneumonia, a combination of pneumonia and other infections and infestations, acute coronary syndrome, death not otherwise specified, and benign, malignant and unspecified neoplasm in one patient each (\( n = 1, 0.8\% \) each). Forty-two (32.3%) patients had at least one SAE.

A total of 105 (80.8%) patients had at least one trabectedin-related ADR of any grade, 71 (54.6%) of whom experienced grade \( \geq 3 \) ADRs (Table 5). Forty-four patients (33.8%) have grade \( \geq 3 \) ADRs leading to dose modifications. Treatment-emergent serious ADRs (SADR) were uncommon, as a total of 19 (14.6%) patients presented with at least one SADR. No new or unexpected safety concerns were identified for trabectedin.
Table 5. Treatment-related adverse drug reactions (ADRs) in at least ≥3% of patients and all grade-5 ADRs as reported by the investigators (all treated patients).

| Treatment-Related ADR as per NCI-CTC, Worst Grade per Patient (≥3% of Patients) | Safety Analysis Set | n = 130 |
| --- | --- | --- |
|  | Grade 1 | Grade 2 | Grade 3 | Grade 4 | Grade 5 |
| n | % | n | % | n | % | n | % | n | % |
| ALT increased | 9 | 6.9 | 11 | 8.5 | 14 | 10.8 | - | - | - | - | 34 | 26.2 |
| AP increased | 5 | 3.9 | 3 | 2.3 | 1 | 0.8 | - | - | - | - | 9 | 6.9 |
| Anemia | 10 | 7.7 | 16 | 12.3 | 12 | 9.2 | - | - | - | - | 38 | 29.2 |
| Anorexia | 15 | 11.5 | 5 | 3.9 | 3 | 2.3 | - | - | - | - | 23 | 17.7 |
| Arthralgia | 2 | 1.5 | 2 | 1.5 | - | - | - | - | - | - | 4 | 3.1 |
| AST increased | 9 | 6.9 | 9 | 6.9 | 5 | 3.9 | - | - | - | - | 23 | 17.7 |
| Leukopenia | 2 | 1.5 | 3 | 2.3 | 1 | 0.8 | - | - | - | - | 6 | 4.6 |
| Constipation | 16 | 12.3 | 2 | 1.5 | - | - | - | - | - | - | 18 | 13.9 |
| Diarrhea | 4 | 3.1 | 4 | 3.1 | 2 | 1.5 | - | - | - | - | 10 | 7.6 |
| Dry skin | 4 | 3.1 | - | - | - | - | - | - | - | - | 4 | 3.1 |
| Dysgeusia | 5 | 3.85 | 2 | 1.5 | - | - | - | - | - | - | 7 | 5.4 |
| Dyspnea | 3 | 2.3 | 2 | 1.5 | - | - | 1 | 0.8 | - | - | 6 | 4.6 |
| Edema limbs | 3 | 2.3 | - | - | 1 | 0.8 | - | - | - | - | 4 | 3.1 |
| Fatigue | 24 | 18.5 | 19 | 14.6 | 3 | 2.3 | - | - | - | - | 46 | 35.4 |
| Febrile neutropenia | - | - | - | - | 4 | 3.1 | 1 | 0.8 | - | - | 5 | 3.9 |
| Fever | 7 | 5.4 | 1 | 0.8 | - | - | - | - | - | - | 8 | 6.2 |
| Night sweating | 4 | 3.1 | - | - | - | - | c | - | - | - | - | 4 | 3.1 |
| GGT increased | 7 | 5.4 | 3 | 2.3 | 11 | 8.5 | 1 | 0.8 | - | - | 22 | 16.9 |
| Headache | 5 | 3.9 | 1 | 0.8 | - | - | - | - | - | - | 6 | 4.6 |
| Hypoalbuminemia | 3 | 2.3 | 1 | 0.8 | - | - | - | - | - | - | 4 | 3.1 |
| Pneumonia | - | - | - | - | 2 | 1.5 | 1 | 0.8 | - | - | 3 | 2.3 |
| Mucositis oral | 2 | 1.5 | 1 | 0.8 | 3 | 2.3 | - | - | - | - | 6 | 4.6 |
| Myalgia | 3 | 2.3 | 1 | 0.8 | 1 | 0.8 | - | - | - | - | 5 | 3.9 |
| Nausea | 33 | 25.4 | 16 | 12.3 | 5 | 3.9 | - | - | - | - | 54 | 41.5 |
| Neutrophil count decreased | 2 | 1.5 | 5 | 3.9 | 10 | 7.7 | 7 | 5.4 | - | - | 24 | 18.5 |
| Peripheral sensory neuropathy | 3 | 2.3 | 1 | 0.8 | 1 | 0.8 | - | - | - | - | 5 | 3.9 |
| Platelet count decreased | 14 | 10.8 | 5 | 3.9 | 13 | 10.0 | 8 | 6.2 | - | - | 40 | 30.8 |
| Sepsis | - | - | - | - | 2 | 1.5 | 1 | 0.8 | - | - | 3 | 2.3 |
| Vomiting | 16 | 12.3 | 7 | 5.4 | 3 | 2.3 | - | - | - | - | 26 | 20.0 |
| White blood cell decreased | 7 | 5.4 | 12 | 9.2 | 27 | 20.8 | 8 | 6.2 | - | - | 54 | 41.4 |

1 Safety Analysis Set included all patients who signed informed consent and received at least one dose of trabectedin. 2 The percentages relate to the number of patients in the Safety Analysis Set. 3 Grade-5 adverse drug reactions. ADR, adverse drug reactions; ALT, alanine aminotransferase; AP, alkaline phosphatase; AST, aspartate aminotransferase; GGT, Gamma-glutamyltransferase; NCI-CTC, National Cancer Institute Common Toxicity Criteria.

4. Discussion

YON-SAR was the first prospective, multicenter, non-interventional, phase IV study that evaluated trabectedin’s outcomes in routine clinical practice in patients with advanced
STS in Germany. While randomized controlled clinical trials are the cornerstone standard of medical evidence, their generalizability to daily clinical practice in a diverse and unselected patient populations always should be verified in non-interventional studies [24]. Of note, considering that in our study we included data from 130 patients from 19 sites across Germany, our data can surely provide a good representation of German real-life clinical practice.

The results of this study corroborate that trabectedin is an active treatment that offers clinical benefits to patients with multiple STS histotypes. In our study, trabectedin administration resulted in a median PFS of 5.2 months with 3- and 6-month PFS rates (primary endpoint) of 60.7% and 44.5%, respectively, which largely exceeded the 3- and 6-month PFS rate thresholds (i.e., 39% and 14%, respectively) established by the EORTC for active agents for the treatment of unselected STS [25] and are either close to or even exceed the new benchmarks proposed only for advanced/metastatic liposarcoma (63% and 44%) and synovial sarcoma (60% and 41%) [26]. However, the nature of our study may limit the interpretation of these observations. Recognizing that direct comparisons cannot be established, the efficacy outcomes of the present study are comparable with the reported median PFS previously reported in phase II (range: 3.3–7.2 months) [8,14,27] and phase III (range: 3.1–4.2 months) trials [9,15]. Furthermore, the results are in line with other observational studies investigating trabectedin in STS (Table 6). In TrObs and RetrospectYon studies, a tendency toward better PFS in patients treated in an early treatment line was demonstrated [18,19]. Although YON-SAR did not observe significant differences in median PFS with respect to treatment lines, PFS estimates indicate that higher PFS may be achieved in earlier lines. Unfortunately, the small sample size of these subgroups is a major limitation and precludes drawing definite conclusions. Conversely, retrospective data from 101 German patients with advanced STS revealed a similar finding [20]. A median PFS of 2.1 months was reported in that study. However, the majority of patients received trabectedin as third or later line (73%). In the fraction of patients who received trabectedin as first or second line, the median PFS was 5.7 months.

Table 6. Relevance of the YON-SAR results within the context of trabectedin treatment for recurrent advanced STS.

| Median (95% CI) | Advanced Sarcoma | PFS (Months) | PFS-3/6 (%) | OS (Months) | ORR (%) | SD (%) | DCR (%) |
|----------------|------------------|--------------|-------------|-------------|---------|--------|--------|
| Retrospective, Non-Interventional Studies | | | | | | | |
| French RetrospectYon database | Le Cesne et al., 2015 [19] | STS; n = 804 | 4.4 (3.9–4.9) | 59.0/40.0 | 12.2 (11.0–13.3) | 16.5 | 50.1 | 66.7 |
| | | L-sarcoma; n = 481 | 5.7 (4.9–6.5) | 64-69/NA | 15.0 (13.2–16.8) | 18.6 | 54.0 | 72.6 |
| TrObs study | Palmerini et al., 2021 [18] | STS; n = 512 | 5.1 (4.1–6.7) | NA/46.0 | 21.6 (19.3–25.0) | 13.7 (11.2–17.2) | 33.0 | 46.7 (43.2–51.9) |
| | | L-sarcoma; n = 348 | 8.3 (6.0–10.1) | NA/55.0 | 25.9 (22.4–33.4) | 16.6 | 37.4 | 53.4 |
| | | non-L-sarcoma; n = 164 | 2.4 (1.8–3.4) | NA/26.0 | 11.3 (8.1–16.3) | 9.0 | 23.8 | 32.3 |
| German retrospective study | Hoiczky M et al., 2013 [20] | STS; n = 101 | 2.1 | NA | NA | NA | NA |
| | | L-sarcoma; n = 46 | 3.1 | 51/38 | NA | NA | NA |
| | | non-L-sarcoma; n = 55 | 1.6 | 36/16 | NA | NA | NA |
| Prospective, Non-Interventional Studies | | | | | | | |
| Y-IMAGE study | Buonadonna et al., 2017 [17] | STS; n = 218 | 5.9 (4.9–7.8) | 70.0/49.0 | 21.3 (18.8–24.3) | 26.6 (20.9–33) | 39.0 | 65.6 (58.9–71.9) |
| YON-SAR study | Grunwald et al., 2022 | STS; n = 128 | 5.2 (3.3–6.7) | 60.7/44.5 | 15.2 (9.6–21.4) | 11.7 | 33.6 | 45.3 |

Results of time-to-event endpoints show median and 95% confidence intervals with available data. CI; confidence intervals; DCR, disease control rate; h, hour; L-sarcoma, liposarcoma or leiomyosarcoma; NA, not available; NR, not reached; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PFS-3/-6, PFS rate at 3/6 months; SD, stable disease; STS, soft tissue sarcoma.

YON-SAR reported a median OS of 15.2 months (95% CI: 9.6–21.4). Median OS in this observational study tended to be slightly longer than previously reported in phase II and III trials (12.4–13.9 months) [8,9,15,26] and observational study Retrospec-
However, other observational studies reported comparatively longer median OS of 21.3 months and 21.6 months [17,18] (Table 6). This variance in survival is likely explained by differences in patient populations. Several studies of trabectedin indicated that median OS is longer in L-sarcoma patients than in those with other histologies [29]. Conversely, the fraction of liposarcoma patients varied among studies (YON-SAR: 18.0%; Y-IMAGE: 23.4% [17]; TrObs: 30.3% [18]) and, thus, may contribute to differences in outcomes.

In our study, treatment duration was an important factor for long-term outcomes. Patients who received ≥6 trabectedin cycles obtained higher response rates than those who received <6 cycles (Table 3). This observation has been previously reported, and protracted trabectedin treatment beyond 6 cycles is supported both in retrospective [19,30] and prospective series, such as in phase II T-DIS study [26,31]. Clearly, a selection bias applies in this subgroup of patients, and contributing factors other than treatment duration cannot be excluded. However, our data indicate that patients who achieve disease control and tolerate trabectedin treatment can be safely treated beyond 6 cycles, until progression.

Furthermore, in our study nearly 60% of patients reported either improved or unchanged ECOG performance status during the study period. These data could indicate a low disease-related worsening during the treatment with trabectedin, and when the symptoms worsened, this was largely caused by the natural course of disease, since 60% of patients discontinued the treatment due to disease progression.

Although all enrolled patients were suitable to undergo treatment with trabectedin, we observed that therapy deviated from the approved label according to SmPC in 67 patients (52.3%). It is important to note that deviation from SmPC did not affect the efficacy of trabectedin in terms of PFS. As per investigator decision, trabectedin was given to 53 (41.4%) patients at a lower dose than that recommended (i.e., 1.5 mg/m²). Moreover, in the present study, median PFS and OS were similar between patients treated with reduced starting trabectedin dose and those with reduced dosing during the study; however, comparison of different trabectedin dosages was not the objective of this study. Although our data did not indicate major differences in outcomes among patients with reduced trabectedin doses, the putative effectiveness of full-dose trabectedin remains unknown in these patients. This regimen yielded more tumor shrinkage and superior time to progression compared to a weekly regimen. Although we believe it is imperative to use the recommended starting dose of trabectedin and consider treatment modifications only during therapy as specified in the SmPC, our data indicated that in selected cases, and always based on clinical judgment to optimize patient outcomes, reduced doses may be used.

Although aprepitant is not recommended as premedication for trabectedin, 10.9% of patients received aprepitant prior to the first cycle of trabectedin, and 4.4% to 20.0% of patients during therapy. Aprepitant was recognized to potentially increase trabectedin exposure and exert thereby an additional risk of toxicity if given concomitantly [32]. In such cases, close monitoring is required and appropriate dose adjustments should be applied in the event of toxicities.

The safety profile of trabectedin was in line with prior experience and reports, characterized by myelosuppression and hepatic toxicities [16]. In our study, trabectedin demonstrated a favorable safety profile over long-term treatment, as >40% of patients received ≥6 cycles of trabectedin and up to a maximum of 44 cycles of treatment. This is consistent with previous reports where comparable numbers of patients were treated with ≥6 cycles (e.g., RetrospectYon: 34.4%; TrObs: 36.5%; Y-IMAGE: 56.9% of patients) [17–19].

According to the non-interventional nature of this study, the exact time points and method of response assessment were not previously fixed but were determined according to the clinician’s discretion and with no central radiological review and response confirmation; thus, our data must be interpreted with caution. Moreover, missing or unavailable data can additionally hamper the interpretation of the results. Nevertheless, in spite of these limitations, our real-life study complements well the findings from the clinical trials with
trabectedin, as it provides information on unselected patient characteristics treated in routine treatment practices.

5. Conclusions

In conclusion, the findings of this non-interventional and prospective phase IV study in Germany consistently support that trabectedin is an active treatment in a routine clinical setting. The overall data observed in our study are in line with those observed in clinical and non-interventional studies and further support the use of trabectedin for patients with multiple sarcoma histotypes.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/cancers14215234/s1. Table S1. Characteristics of patients treated with prolonged trabectedin treatment (>24 cycles); Table S2. Best responses by patient and disease characteristics at baseline (post hoc analysis).

Author Contributions: Conceptualization, V.G., D.P. and B.D.R.; methodology, V.G., D.P. and B.D.R.; formal analysis and data curation, V.G., D.P. and B.D.R.; investigation, V.G., D.P., G.E., E.S., M.A., C.K.W.D., V.K., D.R., M.K., S.B., D.H. (Dirk Hempel), B.D.R., T.W. and P.I.; writing—original draft preparation, V.G., D.P. and B.D.R.; writing—review and editing, V.G., D.P., G.E., E.S., M.A., C.K.W.D., V.K., D.R., M.K., S.B., D.H. (Dirk Hahn), L.H.L., M.H., U.R., L.H.L., D.H. (Dirk Hempel), B.D.R., T.W. and P.I.; supervision, V.G. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by PharmaMar, S.A., Madrid, Spain.

Institutional Review Board Statement: All study procedures were carried out in accordance with the Declaration of Helsinki and its later amendments and local regulations on clinical trials, and were approved by the institutional review boards of each participating center (Landesärztekammer Baden-Württemberg, Ethik-Kommission, F-2013-044).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data underlying this article will be shared on reasonable request to the corresponding author.

Acknowledgments: This study was sponsored by PharmaMar, S.A., Madrid, Spain. The authors acknowledge Adnan Tanović for providing writing and editorial assistance for the manuscript (funded by PharmaMar, S.A.).

Conflicts of Interest: V.G. declares ownership interests in MSD, Bristol-Myers Squibb, AstraZeneca, Seagen, and Genmab, and Genmab, declares having received payment honoraria from Bristol-Myers Squibb, Pfizer, Novartis, Ipsen, Eisai, MSD, Merck Serono, Roche, AstraZeneca, EUSA Pharma, Janssen-Cilag, APOGEPHA, Nanobiotix, ClinSol, and Orno Pharmaceutical, fees from advisory boards from Bristol-Myers Squibb, Pfizer, Novartis, MSD, Ipsen, Janssen-Cilag, Onkowissen, CORE2ED, Eisai, and Debiopharm, and fees from speaker’s bureau from Novartis, Amgen, MSD, Bristol-Myers Squibb, Seattle Genetics, Ipsen, Bristol-Myers Squibb, Pfizer, and Astra Zeneca. D.P. declares fees from speaker’s bureau from Blueprint and PharmaMar and declares having received consulting fees and payment honoraria from Boehringer Ingelheim, PharmaMar, Roche, Advisory, Novartis, PharmaMar, Roche, Bristol-Myers Squibb, EUSA-Pharma, and Lilly. C.D., D.H. (Dennis Hahn), M.K. and V.K. declare fees from speaker’s bureau from PharmaMar. L.H. declares having received payment honoraria from Amgen, Astra Zeneca, Clovis, Eisai, GSK, MSD, Pharma Mar, and Roche. Beatriz De Rivas is an employee and stockholder of PharmaMar. The other authors indicated no financial relationships.

References
1. Lahat, G.; Lazar, A.; Lev, D. Sarcoma Epidemiology and Etiology: Potential Environmental and Genetic Factors. Surg. Clin. N. Am. 2008, 88, 451–481. [CrossRef] [PubMed]
2. Burningham, Z.; Hashibe, M.; Spector, L.; Schiffman, J.D. The Epidemiology of Sarcoma. Clin. Sarcoma Res. 2012, 2, 14. [CrossRef] [PubMed]
3. Montella, L.; Altucci, L.; Sarno, F.; Buonerba, C.; De Simone, S.; Facchini, B.; Franzese, E.; De Vita, F.; Tafuto, S.; Berretta, M.; et al. Toward a Personalized Therapy in Soft-Tissue Sarcomas: State of the Art and Future Directions. Cancers 2021, 13, 2359. [CrossRef] [PubMed]

4. Casali, P.G.; Abecassis, N.; Aro, H.T.; Bauer, S.; Biagini, R.; Bielack, S.; Bonvalot, S.; Boukouvina, I.; Bovee, J.V.M.G.; Brodowicz, T.; et al. Soft tissue and visceral sarcomas: ESMO-EURACAN Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann. Oncol. 2018, 29 (Suppl. S4), iv208–iv269. [CrossRef]

5. Larsen, A.K.; Galmiraini, C.M.; D'Incalci, M. Unique features of trabectedin mechanism of action. Cancer Chemother. Pharmacol. 2015, 77, 663–671. [CrossRef] [PubMed]

6. D'Incalci, M. Trabectedin mechanism of action: What's new? Future Oncol. 2013, 9 (Suppl. S12), 5–10. [CrossRef]

7. D'Incalci, M.; Galmiraini, C.M. A Review of Trabectedin (ET-743): A Unique Mechanism of Action. Mol. Cancer Ther. 2010, 9, 2157–2163. [CrossRef]

8. Demetri, G.D.; Chawla, S.P.; von Mehren, M.; Ritch, P.; Baker, L.H.; Blay, J.Y.; Hande, K.R.; Keohan, M.L.; Samuels, B.L.; Schuetze, S.; et al. Efficacy and safety of trabectedin in patients with advanced or metastatic liposarcoma or leiomyosarcoma after failure of prior anthracyclines and ifosfamide: Results of a randomized phase II study of two different schedules. J. Clin. Oncol. 2009, 27, 4188–4196. [CrossRef]

9. Demetri, G.D.; von Mehren, M.; Jones, R.L.; Hensley, M.L.; Schuetze, S.M.; Staddon, A.; Milhem, M.; Elias, A.; Ganjoo, K.; Tawbi, H.; et al. Efficacy and Safety of Trabectedin or Dacarbazine for Metastatic Liposarcoma or Leiomyosarcoma After Failure of Conventional Chemotherapy: Results of a Phase III Randomized Multicenter Clinical Trial. J. Clin. Oncol. 2016, 34, 786–793. [CrossRef]

10. Casali, P.G.; Blay, J.-Y. Soft tissue and visceral sarcomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann. Oncol. 2014, 25 (Suppl. S3), iii102–iii112.

11. De Sanctis, R.; Marrari, A.; Marchetti, S.; Mussi, C.; Balzarini, L.; Lutman, F.R.; Daolio, P.; Bastoni, S.; Bertuzzi, A.F.; Quaglìuolo, V.; et al. Efficacy of trabectedin in advanced soft tissue sarcoma: Beyond lipo- and leiomyosarcoma. Drug Des. Dev. Ther. 2015, 9, 5785–5791. [CrossRef] [PubMed]

12. Reichardt, P.; Grünwald, V.; Kasper, B.; Schuler, M.; Gelderblom, H. Efficacy of trabectedin in patients with some rare advanced soft tissue sarcoma subtypes other than liposarcoma and leiomyosarcoma. J. Med. Drug Rev. 2015, 5, 33–42.

13. Serdà, P.C.; Terès, R.; Sebio, A.; Bagué, S.; Orellana, R.; Moreno, M.E.; Riba, M.; López-Pousa, A. Single-Center Experience with Trabectedin for the Treatment of Non-L-sarcomas. Adv. Ther. 2022, 39, 1596–1610. [CrossRef] [PubMed]

14. Kawai, A.; Araki, N.; Sugiyama, H.; Ueda, T.; Yonemoto, T.; Takahashi, M.; Morioka, H.; Hiraga, H.; Hiruma, T.; Kunisada, T.; et al. Trabectedin monotherapy after standard chemotherapy versus best supportive care in patients with advanced, translocation-related sarcoma: A randomised, open-label, phase 2 study. Lancet Oncol. 2015, 16, 406–416. [CrossRef]

15. Le Cesne, A.; Blay, J.-Y.; Cupissol, D.; Italiano, A.; Delcambre, C.; Penel, N.; Isambert, N.; Chevreau, C.; Bonvalot, S.; Bertucci, A.F.; Schuetze, S.; et al. A randomized phase III trial comparing trabectedin to best supportive care in patients with pre-treated soft tissue sarcoma: T-SAR, a French Sarcoma Group trial. Ann. Oncol. 2021, 32, 1034–1044. [CrossRef]

16. Le Cesne, A.; Yovine, A.; Blay, J.-Y.; Delaloge, S.; Maki, R.G.; Misset, J.-L.; Frontelo, P.; Nieto, A.; Jiao, J.J.; Demetri, G.D. A retrospective pooled analysis of trabectedin safety in 1132 patients with solid tumors treated in phase II clinical trials. Invest. New Drugs 2012, 30, 1193–1202. [CrossRef]

17. Buonadonna, A.; Benson, C.; Casanova, J.; Kasper, B.; López Pousa, A.; Mazzeo, F.; Thomas, B.; Nicolas, P. A noninterventional, multicenter, prospective phase IV study of trabectedin in patients with ad-vaanced soft tissue sarcoma. Anticancer Drugs 2017, 28, 1157–1165. [CrossRef]

18. Palmerini, E.; Sanfilippo, R.; Grignani, G.; Buonadonna, A.; Romanini, A.; Badalamenti, G.; Ferraresi, V.; Vincenzi, B.; Comandone, A.; Pizzoloruso, A.; et al. Trabectedin for Patients with Advanced Soft Tissue Sarcoma: A Non-Interventional, Retrospective, Multicenter Study of the Italian Sarcoma Group. Cancers 2021, 13, 1053. [CrossRef]

19. Le Cesne, A.; Ray-Coquard, I.; Duffaud, F.; Chevreau, C.; Penel, N.; Nguyen, B.B.; Piperno-Neumann, S.; Delcambre, C.; Rios, M.; Chaigneau, L.; et al. Trabectedin in patients with advanced soft tissue sarcoma: A retrospective national analysis of the French Sarcoma Group. Eur. J. Cancer 2015, 51, 742–750. [CrossRef]

20. Hoiczky, M.; Grabellus, F.; Podleska, L.; Ahrens, M.; Schwindt, B.; Bäger, G.; Pöttgen, C.; Schuler, M.; Bauer, S. Trabectedin in metastatic soft tissue sarcomas: Role of pretreatment and age. Int. J. Oncol. 2013, 43, 23–28. [CrossRef]

21. Grünwald, V.; Pink, D.; Egerer, G.; Schalk, E.; Augustin, M.; Deinzer, C.; Kob, V.; Reichert, D.; Kebenko, M.; Brandl, S.; et al. 1496P Trabectedin for patients with advanced soft tissue sarcoma: A non-interventional, prospective, multicenter study. Ann. Oncol. 2022, 33 (Suppl. S7), S1231. [CrossRef]

22. Eisenhauer, E.A.; Therasse, P.; Bogaerts, J.; Schwartz, L.H.; Sargent, D.; Ford, R.; Dancey, J.; Arbuck, S.; Gwyther, S.; Mooney, M.; et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur. J. Cancer 2009, 45, 228–247. [CrossRef] [PubMed]

23. Choi, H.; Chamsangavej, C.; Faria, S.C.; Macapinlac, H.A.; Burgess, M.A.; Patel, S.R.; Chen, L.L.; Podoloff, D.A.; Benjamin, R.S. Correlation of computed tomography and positron emission tomography in patients with metastatic gas-trointestinal stromal tumor treated at a single institution with imatinib mesylate: Proposal of new computed tomography response criteria. J. Clin. Oncol. 2007, 25, 1753–1759. [CrossRef] [PubMed]
24. Mishra, D.; Vora, J. Non interventional drug studies in oncology: Why we need them? Perspect. Clin. Res. 2010, 1, 128–133. [CrossRef]

25. Van Glabbeke, M.; Van Oosterom, A.T.; Oosterhuis, J.W.; Mouridsen, H.; Crowther, D.; Somers, R.; Verweij, J.; Santoro, A.; Buesa, J.; Tursz, T. Prognostic factors for the outcome of chemotherapy in advanced soft tissue sarcoma: An analysis of 2,185 patients treated with anthracycline-containing first-line regimens—a European Organization for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group Study. J. Clin. Oncol. 1999, 17, 150–157.

26. Kantidakis, G.; Litière, S.; Neven, A.; Vinches, M.; Judson, I.; Blay, J.Y.; Wardelmann, E.; Stacchiotti, S.; D’Ambrosio, L.; Marrèaud, S.; et al. New benchmarks to design clinical trials with advanced or metastatic liposarcoma or synovial sarcoma patients: An EORTC-Soft Tissue and Bone Sarcoma Group (STBSG) meta-analysis based on a literature review for soft-tissue sarcomas. Eur. J. Cancer 2022, 174, 261–276. [CrossRef]

27. Le Cesne, A.; Blay, J.Y.; Domont, J.; Tresch-Bruneeel, E.; Chevreau, C.; Bertucci, F.; Delcambre, C.; Saada-Bouzid, E.; Piperno-Neumann, S.; Bay, J.-O.; et al. Interruption versus continuation of trabectedin in patients with soft-tissue sarcoma (T-DIS): A ran-domised phase 2 trial. Lancet Oncol. 2015, 16, 312–319. [CrossRef]

28. Patel, S.; von Mehren, M.; Reed, D.R.; Kaiser, P.; Charlson, J.; Ryan, C.W.; Rushing, D.; Livingston, M.; Singh, A.; Seth, R.; et al. Overall survival and histology-specific subgroup analyses from a phase 3, randomized controlled study of trabectedin or dacarbazine in patients with advanced liposarcoma or leiomyosarcoma. Cancer 2019, 125, 2610–2620. [CrossRef]

29. Le Cesne, A. Making the Best of Available Options for Optimal Sarcoma Treatment. Oncology 2018, 95 (Suppl. S1), 11–20. [CrossRef]

30. Blay, J.-Y.; Italiano, A.; Ray-Coquard, I.; Le Cesne, A.; Duffaud, F.; Rios, M.; Collard, O.; Bertucci, F.; Bompas, E.; Isambert, N.; et al. Long-term outcome and effect of maintenance therapy in patients with advanced sarcoma treated with trabectedin: An analysis of 181 patients of the French ATU compassionate use program. BMC Cancer 2013, 13, 64. [CrossRef]

31. Kotecki, N.; Le Cesne, A.; Tresch-Bruneeel, E.; Mir, O.; Chevreau, C.; Bertucci, F.; Delcambre, C.; Saada-Bouzid, E.; Piperno-Neumann, S.; Bay, J.-O.; et al. Update of the T-DIS randomized phase II trial: Trabectedin rechallenge versus continuation in patients (pts) with advanced soft tissue sarcoma (ASTS). Ann. Oncol. 2016, 27 (Suppl. S6), vi486. [CrossRef]

32. Yondelis Summary of Product Characteristics. Available online: https://www.ema.europa.eu/en/medicines/human/EPAR/yondelis#product-information-section (accessed on 1 October 2022).