Assessment of Safety and Efficacy of Combined Trabectedin and Low-Dose Radiotherapy for Patients With Metastatic Soft-Tissue Sarcomas A Nonrandomized Phase 1/2 Clinical Trial

Javier Martin-Broto, MD, PhD; Nadia Hindi, MD; Antonio Lopez-Pousa, MD; Javier Peinado-Serrano, MD; Rosa Alvarez, MD; Ana Alvarez-Gonzalez, MD; Antoine Italiano, MD; Paul Sargos, MD; Josefina Cruz-Jurado, MD; Josep Isern-Verdum, MD; Maria Carmen Dolado, MD; Inmaculada Rincon-Perez, MD; Paloma Sanchez-Bustos, MSc; Antonio Gutierrez, MD, PhD; Cleofe Romagosa, MD, PhD; Carlo Morosi, MD; Giovanni Grignani, MD; Marco Gatti, MD; Pablo Luna, MD; Ignacio Alastuey, MD; Andres Redondo, MD, PhD; Belen Belinchon, MD; Jordi Martinez-Serra, PhD; Marie-Pierre Sunyach, MD; Jean-Michel Coindre, MD, PhD; Angelo P. Dei Tos, MD, PhD; Jesus Romero, MD, PhD; Alessandro Gronchi, MD; Jean-Yves Blay, MD, PhD; David S. Moura, PhD

**IMPORTANCE**
Active therapeutic combinations, such as trabectedin and radiotherapy, offer potentially higher dimensional response in second-line treatment of advanced soft-tissue sarcomas. Dimensional response can be relevant both for symptom relief and for survival.

**OBJECTIVE**
To assess the combined use of trabectedin and radiotherapy in treating patients with progressing metastatic soft-tissue sarcomas.

**DESIGN, SETTING, AND PARTICIPANTS**
Phase 1 of this nonrandomized clinical trial followed the classic 3 + 3 design, with planned radiotherapy at a fixed dose of 30 Gy (3 Gy/d for 10 days) and infusion of trabectedin at 1.3 mg/m² as the starting dose, 1.5 mg/m² as dose level +1, and 1.1 mg/m² as dose level –1. Phase 2 followed the Simon optimal 2-stage design. Allowing for type I and II errors of 10%, treatment success was defined as an overall response rate of 35%. This study was conducted in 9 sarcoma referral centers in Spain, France, and Italy from April 13, 2015, to November 20, 2018. Adult patients with progressing metastatic soft-tissue sarcoma and having undergone at least 1 previous line of systemic therapy were enrolled. In phase 2, patients fitting inclusion criteria and receiving at least 1 cycle of trabectedin and the radiotherapy regimen constituted the per-protocol population; those receiving at least 1 cycle of trabectedin, the safety population.

**INTERVENTIONS**
Trabectedin was administered every 3 weeks in a 24-hour infusion. Radiotherapy was required to start within 1 hour after completion of the first trabectedin infusion (cycle 1, day 2).

**MAIN OUTCOMES AND MEASURES**
The dose-limiting toxic effects of trabectedin (phase 1) and the overall response rate (phase 2) with use of trabectedin plus irradiation in metastatic soft-tissue sarcomas.

**RESULTS**
Eighteen patients (11 of whom were male) were enrolled in phase 1, and 27 other patients (14 of whom were female) were enrolled in phase 2. The median ages of those enrolled in phases 1 and 2 were 42 (range, 23-74) years and 51 (range, 27-73) years, respectively. In phase 1, dose-limiting toxic effects included grade 4 neutropenia lasting more than 5 days in 1 patient at the starting dose level and a grade 4 alanine aminotransferase level increase in 1 of 6 patients at the +1 dose level. In phase 2, among 25 patients with evaluable data, the overall response rate was 72% (95% CI, 53%-91%) for local assessment and 60% (95% CI, 39%-81%) for central assessment.

**CONCLUSIONS AND RELEVANCE**
The findings of this study suggest that the recommended dose of trabectedin for use in combination with this irradiation regimen is 1.5 mg/m². The trial met its primary end point, with a high overall response rate that indicates the potential of this combination therapy for achieving substantial tumor shrinkage beyond first-line systemic therapy in patients with metastatic, progressing soft-tissue sarcomas.

**TRIAL REGISTRATION**
ClinicalTrials.gov Identifier: NCT02275286

First-line systemic treatment for metastatic soft-tissue sarcomas (STSs) has hardly improved over 40 years, doxorubicin being the standard approach; no significant overall survival (OS) benefit has been demonstrated with combination schemes.\(^1\)\(^5\) Nevertheless, anthracycline-based polychemotherapy regimens can be recommended if the aim is surgical resection or fast palliation, since they offer a significantly higher probability of tumor shrinkage.\(^6\)

In second and further lines of treatment, the therapeutic aim is to offer disease control at the lowest possible toxicity level. All second-line drugs approved for use in STSs exhibited an overall response rate (ORR) lower than 10% in pivotal trials: 9.9%, 6.0%, and 4.0% for trabectedin,\(^7\) pazopanib,\(^8\) and eribulin,\(^9\) respectively. To date, tumor-volume response is therefore an unmet need in second-line therapies of advanced STS, with a few exceptions, such as high-dose ifosfamide in synovial sarcoma.\(^10\)

Concurrent exposures to trabectedin and radiotherapy (RT) appeared to be synergistic in preclinical experiments. Trabectedin has been argued to exert radiosensitization action through interference with the DNA repair mechanisms\(^11\) or by inducing arrest in the G2/M phase of the cell cycle, which is the most sensitive to RT.\(^12\) Supported by these data and by observations in the context of clinical palliation, we designed a phase 1/2 trial of trabectedin plus low-dose external RT for patients with metastatic, nonresectable STS. We expected that trabectedin, when used in this combination, would enhance the activity of RT in the irradiated nodules, preserving the tumor control for all metastatic lesions. Two additional cohorts are being conducted in the same study to address the same concept among patients with localized myxoid liposarcoma\(^13\) and retroperitoneal sarcomas.

### Methods

The TRASTS (Trabectedin and Radiotherapy in Soft-Tissue Sarcoma) study was conducted from April 13, 2015, to November 20, 2018, at 9 sarcoma referral centers: 6 in Spain (Santa Creu i Sant Pau Hospital, Barcelona; Gregorio Marañon University Hospital and University Hospital La Paz, Madrid; University Hospital Son Espases, Mallorca; University Hospital Virgen del Rocío, Sevilla; and University Hospital of the Canary Islands, Tenerife); 2 in France (Institut Bergonié, Bordeaux; Centre Léon Bérard, Lyon, France); and 1 in Italy (Candiolo Cancer Institute, Turin). The study protocol for this phase 1/2 nonrandomized clinical trial was approved by the ethics committees at all participating centers, and procedures were performed in accordance with each center’s Ethics Committee guidelines and in compliance with the Declaration of Helsinki.\(^14\) All patients signed a written informed consent form to participate in the study. The full trial protocol appears in Supplement 1. Translational and preclinical studies also were performed and are described in eMethods in Supplement 2.

### Patients

A total of 45 patients older than 18 years and with a diagnosis of metastatic STS, progressing at least after 1 line of chemotheraphy, were enrolled. Other relevant inclusion/exclusion criteria and the baseline assessments are described in eMethods in Supplement 2.

Patients fitting inclusion criteria and receiving at least 1 cycle of trabectedin combined with the RT regimen constituted the per-protocol population for phase 2 of the study; those who received at least 1 cycle of trabectedin, the safety population.

### Phase 1 Design

Phase 1 followed the classic 3 + 3 design. Two dose levels for trabectedin escalation were planned: 1.3 mg/m\(^2\) as the starting dose (level 0), and 1.5 mg/m\(^2\) as an escalated dose (level +1). To allow a better assessment of cardiotoxic effects, the starting dose level was expanded if no predefined dose-limiting cardiotoxic effects were observed at level 0. In addition, a de-escalated dose (level -1) was foreseen at 1.1 mg/m\(^2\) if the starting dose level was associated with at least 2 dose-limiting toxic events.

### Phase 2 Design

The main end point of phase 2 was ORR according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1. The Simon 1-sample, 2-stage optimal design\(^15\) was applied, with an ORR of 35% or greater considered to support the hypothesis that the treatment was effective, and with an ORR of 10% or less considered to support the null hypothesis. For type I and II errors of 10%, at least 2 of the first 11 patients had to have objective RECIST response to complete the required sample with 19 accrued patients. Because synchronization between chemotherapy and RT was crucial, an accrual of 5 additional patients was estimated to be necessary so as to ensure a sample of at least 19 patients for the per-protocol stage.

### Treatments

Trabectedin (Yondelis; Pharma Mar SA) was administered every 3 weeks in a 24-hour infusion, following manufacturer’s instructions. An RT regimen delivering a total dose of 30 Gy
Safety and Efficacy of Combined Trabectedin and Radiotherapy for Metastatic Soft-Tissue Sarcomas

Original Investigation Research

in 10 fractions of 3 Gy per day was selected to allow the inclusion of several lesions in the irradiation field while also including bulky lesions and fitting with normal tissue dosimetric constraints. Radiotherapy had to start within 1 hour after completion of the first trabectedin infusion (cycle 1, day 2). Central review was planned for confirmation of the pathological findings, RT planning, and radiological assessment of disease response.

Objectives
The main end point of phase 1 was to determine the recommended dose of trabectedin for use in combination with low-dose RT. Data on adverse events were collected by following the CTCAE (Common Terminology Criteria for Adverse Events), version 4.03. Secondary end points included quality of life and the post hoc determination of the predictive value of HMG (the high-mobility group gene) in blood.

The main end point for phase 2 was ORR according to RECIST, version 1.1. Progression-free survival (PFS) and OS were secondary objectives.

Statistical Analysis
Statistical analysis was performed from September 12 to September 23, 2019 by using SPSS Statistics, version 20 (IBM Corporation). Time-to-event variables were measured from the start of treatment and were estimated according to the Kaplan-Meier method. Comparisons between the variables of interest were done by the log-rank test.

Variables following binomial distributions were expressed as frequencies, percentages, and/or 95% CIs. Comparisons between quantitative and qualitative variables were performed through nonparametric tests (Mann-Whitney or Kruskal-Wallis). All P values reported were 2-sided, and statistical significance was defined by P ≤ .05.

Results
From April 2015 to November 2018, a total of 45 patients (24 [53%] male and 21 [47%] female; median age of 50 [range of 23-74] years) with progressing metastatic STS were enrolled in the study: 18 patients were enrolled in phase 1, and 27 other patients were enrolled in phase 2. Eleven of the 18 (61%) enrolled in phase 1 were male, and 14 of the 27 (52%) in phase 2 were female. The median age (range) was 42 (23-74) years for those in phase 1, and 51 (27-73) years for those in phase 2. Demographic and baseline clinical characteristics are shown in the Table.

A total of 90 three-week cycles of trabectedin were given to the 18 patients in phase 1, and 17 of the 18 completed the scheduled protocol for RT without any delay. One patient received just 1 cycle of trabectedin at the initial dose level because of early aggressive progression with a hemothorax, which occurred on day 1 of cycle 1. A total of 277 three-week cycles of trabectedin were administered in phase 2. Twenty-five of the 27 patients who received at least 1 cycle of trabectedin followed by the RT regimen (phase 2, per-protocol population) were included in the analysis. One patient (phase 2, safety population) died of septic shock during the first week and was included in the safety population; another patient, who was unable to be in a supine position (and consequently unable to receive RT) because of rapidly progressive disease, was excluded from participation in phase 2 because of an ECOG (Eastern Cooperative Oncology Group) performance status score of 2 (Figure 1). (ECOG scores range from 0, indicating no impairment, to 4, indicating complete inability to carry out any self-care, and confinement to a bed.)

Table. Demographic and Clinical Characteristics of Participants in Phases 1 and 2

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Phase 1</th>
<th>Phase 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 18</td>
<td>n = 27</td>
</tr>
<tr>
<td>Age, median (range), y</td>
<td>42 (23-74)</td>
<td>51 (27-73)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>7 (39)</td>
<td>14 (52)</td>
</tr>
<tr>
<td>Male</td>
<td>11 (61)</td>
<td>13 (48)</td>
</tr>
<tr>
<td>ECOG score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>12 (67)</td>
<td>19 (70)</td>
</tr>
<tr>
<td>1</td>
<td>6 (33)</td>
<td>8 (30)</td>
</tr>
<tr>
<td>Sarcoma subtype</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leiomyosarcoma</td>
<td>1 (6)</td>
<td>7 (26)</td>
</tr>
<tr>
<td>Synovial</td>
<td>10 (56)</td>
<td>6 (22)</td>
</tr>
<tr>
<td>Liposarcoma</td>
<td>2 (11)</td>
<td>4 (15)</td>
</tr>
<tr>
<td>Dedifferentiated</td>
<td>1 (6)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Myxoid</td>
<td>1 (6)</td>
<td>3 (11)</td>
</tr>
<tr>
<td>Undifferentiated pleomorphic sarcoma</td>
<td>3 (16)</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Rhabdomyosarcoma</td>
<td>0</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Pleomorphic</td>
<td>0</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Sclerosing</td>
<td>0</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Otherab</td>
<td>2 (11)</td>
<td>6 (22)</td>
</tr>
<tr>
<td>Metastasis-free interval, median (range), mo</td>
<td>10 (0-93)</td>
<td>9 (0-123)</td>
</tr>
<tr>
<td>Previous lines of systemic therapy, median (range)</td>
<td>1 (1-2)</td>
<td>2 (1-6)</td>
</tr>
<tr>
<td>Patients with previous metastasectomies</td>
<td>8 (44)</td>
<td>6 (22)</td>
</tr>
<tr>
<td>Nodule sites</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lungs only</td>
<td>18 (100)</td>
<td>15 (56)</td>
</tr>
<tr>
<td>Lungs and extrapulmonary</td>
<td>0</td>
<td>8 (30)</td>
</tr>
<tr>
<td>Extrapulmonary only</td>
<td>0</td>
<td>4 (15)</td>
</tr>
<tr>
<td>Irradiated nodule sites</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lungs only</td>
<td>18 (100)</td>
<td>18 (67)</td>
</tr>
<tr>
<td>Lungs and extrapulmonary</td>
<td>0</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Extrapulmonary only</td>
<td>0</td>
<td>7 (26)</td>
</tr>
<tr>
<td>Pelvis</td>
<td>0</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Abdominal cavity</td>
<td>0</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Soft tissue</td>
<td>0</td>
<td>4 (15)</td>
</tr>
</tbody>
</table>

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

a ECOG scores range from 0 to 4, with the highest score indicating complete inability to carry out any self-care.

b Other includes the following subtypes: 3 unspecified sarcomas, 2 malignant peripheral nerve sheath tumors, 1 malignant phyllodes tumor, 1 malignant myoepithelioma, and 1 myxofibrosarcoma.

c Refers to the interval between initial sarcoma diagnosis and the appearance of metastases. For patients with metastatic spread at initial diagnosis, the interval is 0.

Downloaded From: https://jamanetwork.com/ on 09/16/2023
The median baseline numbers of pulmonary nodules per patient enrolled in study phases 1 and 2, respectively, were 7 (range, 1-22) and 4 (range, 1-83), and the median numbers of irradiated nodules per patient were 3 (range, 1-6) and 1 (range, 1-4). For nodule counts per patient, see eTable 1 in Supplement 2.

**Phase 1**
All 18 patients had values of forced expiratory volume in the first second greater than 1.0 L, with a median value of 2.1 L (range, 1.3-3.6 L) (higher values indicate better pulmonary function), and the median percentage of the predicted normal forced expiratory volume in the first second was 76% (range, 50%-97%). Likewise, the diffusing capacity of lung for carbon monoxide was greater than 40% in all patients, with a median of 50% (range, 45%-97%).

 Twelve patients were enrolled at an initial trabectedin dose level of 1.3 mg/m² to allow better assessment of cardiotoxic effects. The expansion from 6 to 12 patients was recommended by the trial steering committee after detecting a grade 2 decrease in the left ventricular ejection fraction (LVEF) in the first 2 patients who received trabectedin at the 1.3 mg/m² dose level (LVEF, 49% and 45%, respectively). No additional cardiotoxic effects were observed in the remaining patients at initial dose level (n = 10) or in patients at the 1.5 mg/m² level (n = 6). Both patients who experienced a decrease in LVEF had received a substantial cumulative dose of previous doxorubicin (>750 mg/m²). There was no difference between the LVEF values at baseline (median, 62% [range, 54%-68%]) and before cycle 3 (median, 61% [range, 45%-68%]) (P = .45).

Dose-limiting toxic effects were reported as follows: grade 4 neutropenia lasting more than 5 days was seen in 1 patient at the initial dose level, and a transient grade 4 increase in alanine aminotransferase levels was observed among the 6 patients enrolled at the escalated dose level (+1 dose level). Thus, the recommended dose of trabectedin in combination with the RT regimen was 1.5 mg/m² for phase 2 of the study.

The toxicity profile of this combination therapy was the same as that expected for trabectedin alone (eTable 2 in Supplement 2), with the exception of 1 case of grade 3 pneumonitis coincident with disease progression.

**Phase 2**
The clinical cutoff for final data analyses was August 31, 2019. At that time, 7 of 26 patients (27%) were still receiving treatment, while 19 (73%) had discontinued trabectedin therapy: 13 (69%) because of progression, 4 (21%) because of toxic effects, 1 (5%) because of consent withdrawal, and 1 (5%) because of death associated with septic shock in the context of neutropenia.

For the 25 evaluable patients, the RECIST-based ORR was 72% (95% CI, 53%-91%) in local radiological assessment: 2 patients experienced a complete response; 16, partial response; 4, stable disease; and 3, progression. The RECIST-based ORR was 60% (95% CI, 39%-81%) in central radiological assessment: 2 patients experienced complete response; 13, partial response; 5, stable disease; and 5, progression (Figure 2). Moreover, the median of dimensional reduction in irradiated nodules was −44% (range, +16% to −100%); in 6 of 25 patients (24%), the irradiated nodules progressed at the time of RECIST progression (eTable 1 in Supplement 2).

With a median follow-up interval of 14.0 months (range, 5.0-21.0 months), the median PFS was 9.9 months (95% CI, 7.0-12.7 months) (eFigure 1 in Supplement 2), and the 12-month PFS rate was 44% (95% CI, 23%-65%). Note, if only irradiated nodules are considered, the median PFS was not reached, while the 12-month PFS rate was 65% (95% CI, 45%-88%). The median of OS (eFigure 1 in Supplement 2) was not reached, and the 18-month OS rate was 86% (95% CI, 71%-100%). In the univariate analysis, only the metastasis-free interval and the RECIST-based response had a significant prognostic role in survival (eTable 3 in Supplement 2). Grade 3 pneumonitis was observed in 3 patients (eTable 4 in Supplement 2).

Global health status analyses and RT central review data, along with HMGs as potential prognostic biomarkers (eTable 5 in Supplement 2) and preclinical results, are described in the eResults in Supplement 2.

**Discussion**
In this phase 1/2 trial of trabectedin and RT, the recommended dose of trabectedin was 1.5 mg/m². In phase 2, ORR for trabectedin and RT was 72% according to RECIST, and thus, the trial met its primary end point.

Toxic effects of this combination therapy were comparable with data published for trabectedin alone, the only exception being pneumonitis: summing our data from phases 1 and 2, a total of 4 patients had grade 3 pneumonitis. In 3 of these 4 patients, pneumonitis proved reversible; in the fourth patient, recovery was impeded by cancer progression.
Safety and Efficacy of Combined Trabectedin and Radiotherapy for Metastatic Soft-Tissue Sarcomas

Original Investigation Research

or small lesions, nor requiring irradiation of all lesions). Furthermore, the 12-month PFS rate of 44% and the 18-month OS rate of 86% constitute good survival in second or further lines of treatment in metastatic STS. To our knowledge, results like these have never previously been reported in this setting.

Of note, trabectedin induced G2/M accumulation in our preclinical experiments, which has been reported as a likely mechanism of radiosensitization.13,29 Nevertheless, trabectedin also increases FAS-dependent cell death,30 a mechanism that may play a role in the activity of this therapy combination, since FAS upregulation has also been reported after RT.31

Limitations

This study has the inherent limitations of all phase 1 and single-arm phase 2 trials: the lack of a comparative cohort, and a low number of cases. Encouraged by these results, a randomized phase 2 trial was designed, aiming to demonstrate the potential superiority of the combination of trabectedin and low-dose RT, not only in terms of ORR but also regarding benefits of survival and quality of life among patients with symptoms related to tumor volume.

Conclusions

This study’s findings suggest that the combination of trabectedin plus low-dose RT may allow substantial shrinkage of target lesions in a high proportion of patients with previously treated metastatic STS, enabling more effective symptom palliation and more durable tumor control than can be achieved with systemic therapy alone.
Efficacy and safety of trabectedin and radicabazine for first-line treatment of advanced or metastatic soft-tissue sarcoma


Conflict of Interest Disclosures: The authors thank the Spanish, Italian, and French national sarcoma research groups (GEIS, ISG, and FSG, respectively) for supporting the administrative activation procedures for the study. GEIS also supported data management, monitoring, drug labeling, insurance, shipping, data analyses, pharmacovigilance, translational research, and meetings. Melissa Fernandez Pinto, MSc, project manager in the GEIS data center, Madrid, Spain, and Patricio Ledesma, BEng, head of clinical operations of Softpromed Investigación Clínica, Palma, Spain, contributed data management; these persons did not receive any compensation. Vivienne Birch, BA, verified the English-language manuscript and was compensated for her work.

REFERENCES


