Phase I Combination Study of Trabectedin and Doxorubicin in Patients with Soft-Tissue Sarcoma

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Abstract

Purpose: To determine the dose of trabectedin plus doxorubicin with granulocyte colony-stimulating factor support associated with manageable neutropenia and acceptable dose-limiting toxicities (DLT) in patients with recurrent or persistent soft-tissue sarcoma.

Methods: In this phase I, open-label, multicenter trial, patients previously treated with 0-1 prior chemotherapy regimens excluding doxorubicin, an Eastern Cooperative Oncology Group performance status 0-1, and adequate organ function received a 10- to 15-min i.v. infusion of doxorubicin 60 mg/m² immediately followed by a 3-h i.v. infusion of trabectedin 0.9 to 1.3 mg/m² on day 1 of a 3-week cycle. Because four of the first six patients experienced DLT-defining neutropenia during cycle 1, all subsequent patients received primary prophylactic granulocyte colony-stimulating factor. The maximum tolerated dose was the highest dose level with six or more patients in which less than one-third of the patients experienced severe neutropenia or DLT. Blood was collected during cycle 1 for pharmacokinetic analyses. Adverse events, tumor response, and survival were assessed.

Results: Patients (N = 41) received a median of six cycles of treatment (range, 2-13). The maximum tolerated dose was trabectedin 1.1 mg/m² and doxorubicin 60 mg/m². Common grade 3/4 treatment-emergent adverse events were neutropenia (71%), alanine aminotransferase increase (46%), and thrombocytopenia (37%). Overall, 5 (12%) patients achieved a partial response and 34 (83%) maintained stable disease. Median progression-free survival was 9.2 months. Doxorubicin and trabectedin pharmacokinetics were not altered substantially with concomitant administration.

Conclusion: The combination of doxorubicin 60 mg/m² followed by trabectedin 1.1 mg/m² every 21 days is safe and active in patients with soft-tissue sarcoma.

Soft-tissue sarcoma (STS) is a rare type of cancer that is difficult to treat. The established standard of care for unresectable STS is doxorubicin-based chemotherapy, with typical response rates of 10% to 30% and only limited options for those who relapse or develop resistance (1–4). Progression-free survival (PFS) and overall survival (OS) rarely exceeds 6 months and 1 year, respectively. New management strategies should be developed (5).

Trabectedin (YONDELIS, ET-743; Johnson & Johnson Pharmaceutical Research & Development; PharmaMar) is a tetrahydroisoquinoline alkaloid isolated from Ecteinascidia turbinata, a marine ascidian. Its complex mechanism involves binding to the minor groove of double-stranded DNA and subsequent bending of DNA toward the major groove (6–8), resulting in inhibition of gene activation and of nucleotide excision repair and in induction of DNA strand breaks and cell cycle arrest in S and G2 phases (9–12). In vitro, trabectedin has shown potent cytotoxic activity against a variety of cell lines, including human STS (13, 14), and antitumor activity against a variety of human xenografts, including sarcomas (15). Moreover, there appears to be no cross-resistance between trabectedin and other chemotherapy (15).

In clinical trials, single-agent trabectedin has shown activity in a variety of tumor types, including osteosarcoma, liposarcoma, leiomyosarcoma, fibrosarcoma, synovial sarcoma, breast cancer, and ovarian cancer (16–27). The clinical activity of single-agent trabectedin has been shown in heavily pretreated patients with advanced STS, with a median duration of response of ~9 to 12 months and 6-month PFS rates of 24% to 29% (19, 21, 23, 24). Trabectedin (1.5 mg/m² every 3 weeks)
was also evaluated in 35 chemotherapy-naive patients with advanced STS, with a clinical benefit rate of 20% and median duration of response of 16.5 months (25). It was recently approved in the European Union for patients with advanced STS after failure of anthracyclines or ifosfamide or for those who are unsuited to receive such agents.

The cytotoxicity of trabectedin and doxorubicin was investigated in vitro in two STS cell lines, which showed a synergistic antitumor effect mediated via apoptosis in both cell lines (14). Further analysis in preclinical studies in human sarcoma-bearing mice suggested a synergistic effect (28). Prior unpublished phase I studies combining trabectedin and doxorubicin in patients with STS have also shown increased efficacy but with greater myelotoxicity in the absence of growth factor support. More recent results of a clinical trial evaluating trabectedin and pegylated liposomal doxorubicin in 30 heavily pretreated patients with advanced malignancies suggested that it was well tolerated at nearly full single-agent doses. Further, the trial showed a response rate of 20% and stable disease rate of 47% (29). Given the above results showing increased efficacy with trabectedin combined with doxorubicin or pegylated liposomal doxorubicin but greater myelotoxicity, it was of interest to study the combination of trabectedin and doxorubicin in patients with advanced STS with hematopoietic growth factor support.

The primary objective of this trial was to determine the doses of trabectedin and doxorubicin that could be safely delivered with granulocyte colony-stimulating factor (G-CSF) support and with a clinically acceptable incidence of dose-limiting toxicities (DLT), including neutropenia, in patients with recurrent or persistent STS. Secondary objectives were to evaluate the pharmacokinetics and safety profile of trabectedin and doxorubicin.

### Materials and Methods

**Patients.** Patients were eligible if they were ages ≥18 years with a diagnosis of STS (any histology, metastatic disease, or recurrent/persistent disease after initial therapy), an Eastern Cooperative Oncology Group performance status of 0-1, a left ventricular ejection fraction within normal limits, and adequate organ function. To continue treatment, patients had to meet the following criteria on day 1 of each cycle: platelets ≥100,000/μL; absolute neutrophil count ≥1,500/μL; direct bilirubin ≤ upper limit of normal; transaminase elevation grade ≤2; and alkaline phosphatase elevation, other non-hematologic drug-related effects, and creatinine phosphokinase elevation grade ≤1.

Patients were excluded if they had received >1 prior chemotherapy regimen (including adjuvant), were pregnant or lactating or planning to become pregnant during or for 1 year after therapy, had been exposed previously to anthracyclines or trabectedin, had received radiation therapy <4 weeks from study entry or had radiotherapy to >20% of the bone marrow, or had known central nervous system metastasis. All patients provided written informed consent.

**Study design.** This was a phase 1, open-label study conducted at five sites (three in the United States and two in France). A patient who completed at least six cycles was considered to have completed the study. The protocol was approved by the institutional review board of the study centers, and the trial was done in accordance with the Declaration of Helsinki and International Conference on Harmonization/Good Clinical Practice guidelines.

Sequential escalating doses of doxorubicin with trabectedin were tested as outlined in Table 1; dose level -1 was prespecified if dose level 1 was associated with an unacceptable rate of DLTs as described below. G-CSF was administered to all patients who experienced grade 4 neutropenia in cycle 1; these patients were given the option to receive secondary prophylactic G-CSF for subsequent cycles. If two or more of the first six patients experienced severe neutropenia during cycle 1, they were to be excluded from all future enrollment decisions and from determination of selected dose, and all subsequently enrolled patients were to receive primary prophylactic G-CSF (G-CSF with the first cycle of chemotherapy). Dose escalation continued, provided that less than one-third of patients at a dose level experienced severe neutropenia or other DLT. If more than one-third but less than two-thirds of patients experienced severe neutropenia or other DLT, three additional patients were enrolled at that same dose level. If two-thirds or more of patients at a dose level experienced severe neutropenia or other DLT, the dose was considered unacceptable, and the next group of patients was enrolled at the next lower dose level. Maximum tolerated dose (MTD) was defined as the highest dose level with at least six patients enrolled and at which less than one-third of patients experienced severe neutropenia or other DLT.

**Treatment administration.** On day 1 of each cycle, all patients received an i.v. infusion of dexamethasone (20 mg). Within 1 h of treatment, dexamethasone, doxorubicin was given i.v. over 10 to 15 min. Immediately after the doxorubicin infusion, trabectedin was given as a 3-h i.v. infusion. If two or more of the first six patients experienced severe neutropenia during cycle 1, all subsequently enrolled patients would receive primary prophylactic G-CSF (filgrastim 5 μg/kg/d, day 3 for ≥10 days or until absolute neutrophil count >1,000/μL after nadir or pegfilgrastim according to the manufacturer’s recommendations). In addition, patients received prophylactic and therapeutic antimetics as needed. Other supportive care, including transfusions, hematopoietic growth factors, antibiotics, analgesics, and antiemetics, was permitted throughout the trial.

**Safety.** DLT was defined as any of the following: severe neutropenia, defined as grade 4 event lasting ≥7 days despite G-CSF, grade 4 event of any duration with fever ≥38.5°C, or event of any grade associated with sepsis or documented infection; platelet <25,000/μL; delay in therapy >3 weeks due to drug-related adverse events; or any grade 3/4 toxicity that was severe, unexpected, and deemed related to the combination (except nausea/vomiting despite appropriate antimetic prophylaxis or grade 3/4 transaminitis lasting >7 days). Absolute neutrophil count was monitored biweekly. Adverse events were recorded, and toxicity was graded using the National Cancer Institute Common Toxicity Criteria version 3.0 (30). Doxorubicin therapy was discontinued if the left ventricular ejection fraction decreased to <45% or if other cardiac symptoms occurred. If six or more cycles were administered (cumulative doxorubicin dose, 360 mg/m²), patients underwent a multiple-gated acquisition scan or

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**Table 1. Dose escalation schedule**

<table>
<thead>
<tr>
<th>Dose level</th>
<th>Doxorubicin dose (mg/m²)</th>
<th>Trabectedin dose (mg/m²)</th>
<th>n*</th>
</tr>
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<tbody>
<tr>
<td>-1</td>
<td>50</td>
<td>0.9</td>
<td>0</td>
</tr>
<tr>
<td>1A</td>
<td>60</td>
<td>0.9</td>
<td>4</td>
</tr>
<tr>
<td>1</td>
<td>60</td>
<td>0.9</td>
<td>18</td>
</tr>
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<td>2</td>
<td>60</td>
<td>1.1</td>
<td>13</td>
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<tr>
<td>3</td>
<td>60</td>
<td>1.3</td>
<td>6</td>
</tr>
<tr>
<td>4</td>
<td>75</td>
<td>1.3</td>
<td>0</td>
</tr>
</tbody>
</table>

*Dose escalation/de-escalation and dose modification schedules as specified in Materials and Methods.

† Patients who had severe neutropenia in cycle 1 but without prophylactic G-CSF use.

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Response to therapy and survival. Best overall response was determined by the investigator. Disease status was confirmed by repeated assessments at least every 4 weeks after the criteria for response were first met based on the Response Evaluation Criteria in Solid Tumors guidelines (31). Survival data were collected during the follow-up phase (every 8 weeks for the first 2 years and every 3 months thereafter).

Pharmacokinetic analysis. Before dosing and at various times after dosing in cycle 1, whole blood samples were obtained for pharmacokinetic analysis. Plasma trabectedin concentrations were measured by validated liquid chromatography-tandem mass spectrometry (validated concentration range, 0.025-2.5 ng/mL) at the Slotervaart Hospital in samples collected pre-dose and at 1 h 15 min, 3 h 5 min, 3 h 45 min, 5 h, 9 h, 24 h, 51 h, 75 h, 147 h, and 219 h. Plasma doxorubicin and doxorubicinol concentrations were measured by validated liquid chromatography-tandem mass spectrometry (validated concentration range for both, 1-500 ng/mL) at Pharma Bio-Research in samples collected pre-dose and at 15 min, 1 h 15 min, 3 h 5 min, 3 h 45 min, 5 h, 9 h, 24 h, and 51 h. Pharmacokinetic variables \[\text{C}_{\text{max}}\], \[\text{t}_{\text{max}}\], terminal rate constant, \[\lambda_{z}\], terminal half-life, \[\text{AUC}_{\text{inf}}\], area under the plasma concentration-time curve (AUC) from time 0 to the last quantifiable point, \[\text{AUC}_{\text{last}}\], and apparent volume of distribution at steady state, \[V_{\text{ss}}\] were estimated by noncompartmental methods.

Statistical analysis. A maximum sample size of 58 was based on the assumption that up to 48 patients would be enrolled. The recommended combination dose was based on the DLT rate observed in cycle 1 only. Because this study was limited to patients with STS and only a few planned dose levels, a larger than usual sample size was planned for each dose level to better investigate the safety profile of the combination. The larger sample size for each dose level guaranteed a 95% confidence interval of the DLT rate at the MTD below 33%.

All patients who received one or more doses of trabectedin were included in the safety analysis. Adverse events were summarized for each dose level and by severity. OS and PFS were summarized with Kaplan-Meier curves. Descriptive statistics were calculated for the plasma concentrations of trabectedin, doxorubicin, and doxorubicinol at each sampling time by dose level.

Table 2. Demographic and clinical characteristics

<table>
<thead>
<tr>
<th>Sex</th>
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<td>Female</td>
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<tr>
<td>Male</td>
<td>26</td>
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<tr>
<td>Age, y</td>
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<td>18 to &lt;65</td>
<td>33</td>
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<tr>
<td>≥65</td>
<td>8</td>
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<tr>
<td>Median (range)</td>
<td>56.0 (29-75)</td>
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Eastern Cooperative Oncology Group status

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Histology

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<td>Liposarcoma</td>
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<td>Other</td>
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Primary tumor site

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<td>Abdomen/pelvis</td>
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<tr>
<td>Abdomen/pelvic wall</td>
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<tr>
<td>Chest wall</td>
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</tr>
<tr>
<td>Chest, other</td>
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</tr>
<tr>
<td>Face</td>
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<td>Lower extremity</td>
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<tr>
<td>Neck</td>
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<td>Retropertioneal</td>
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<td>Uterus</td>
<td>1</td>
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Previaous therapy

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<tr>
<td>Systemic*</td>
<td>7</td>
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<tr>
<td>Surgery</td>
<td>39</td>
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<tr>
<td>Radiotherapy</td>
<td>15</td>
</tr>
</tbody>
</table>

*Previous systemic therapies included gemcitabine, carboplatin, cisplatin, docetaxel, doxorubicin, etoposide, fluorouracil, imatinib mesylate, melphalan, and tumor necrosis factor receptor IgG1.

two-dimensional echocardiogram that was repeated every two cycles thereafter or they were permitted to discontinue doxorubicin. Patients who discontinued doxorubicin could continue receiving single-agent trabectedin 1.3 mg/m².

Table 3. Grade 3/4 treatment-emergent adverse events

<table>
<thead>
<tr>
<th>Event</th>
<th>Level 1A* (n = 4)</th>
<th>Level 1 (n = 18)</th>
<th>Level 2 (n = 13)</th>
<th>Level 3 (n = 6)</th>
<th>Total (N = 41)</th>
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<tbody>
<tr>
<td></td>
<td>No. patients (%)</td>
<td>No. patients</td>
<td>No. patients</td>
<td>No. patients</td>
<td>No. patients</td>
</tr>
<tr>
<td>Total with grade 3/4 events</td>
<td>4 (93)</td>
<td>17 (94)</td>
<td>12 (92)</td>
<td>5 (83)</td>
<td>38 (93)</td>
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<tr>
<td>Neutropenia</td>
<td>4 (93)</td>
<td>13 (72)</td>
<td>9 (69)</td>
<td>3 (50)</td>
<td>29 (71)</td>
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<tr>
<td>ALT increased</td>
<td>2 (41)</td>
<td>8 (44)</td>
<td>7 (53)</td>
<td>2 (33)</td>
<td>19 (46)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>3 (61)</td>
<td>6 (33)</td>
<td>5 (38)</td>
<td>1 (17)</td>
<td>15 (37)</td>
</tr>
<tr>
<td>AST increased</td>
<td>2 (41)</td>
<td>4 (22)</td>
<td>3 (23)</td>
<td>1 (17)</td>
<td>10 (24)</td>
</tr>
<tr>
<td>Anemia</td>
<td>3 (61)</td>
<td>3 (17)</td>
<td>3 (23)</td>
<td>0 (0)</td>
<td>9 (22)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>2 (41)</td>
<td>4 (22)</td>
<td>1 (7)</td>
<td>1 (17)</td>
<td>8 (20)</td>
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<tr>
<td>Febrile neutropenia</td>
<td>4 (80)</td>
<td>2 (11)</td>
<td>1 (7)</td>
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<td>7 (17)</td>
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<tr>
<td>Vomiting</td>
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<td>5 (28)</td>
<td>1 (7)</td>
<td>0 (0)</td>
<td>6 (15)</td>
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<td>Asthenia</td>
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<td>3 (17)</td>
<td>1 (7)</td>
<td>0 (0)</td>
<td>5 (12)</td>
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<tr>
<td>Stomatitis</td>
<td>1 (20)</td>
<td>1 (5)</td>
<td>1 (7)</td>
<td>0 (0)</td>
<td>3 (7)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>2 (15)</td>
<td>1 (17)</td>
<td>3 (7)</td>
</tr>
<tr>
<td>Nausea</td>
<td>0 (0)</td>
<td>1 (6)</td>
<td>0 (0)</td>
<td>1 (17)</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>2 (15)</td>
<td>0 (0)</td>
<td>2 (5)</td>
</tr>
</tbody>
</table>

NOTE: Adverse events reported at any time from first treatment dose to within 30 d of last treatment dose are included. Drug-related means possible, probable, or very likely. Toxicity grade: National Cancer Institute Common Toxicity Criteria version 3.0.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase.

*Patients with severe neutropenia in cycle 1 but without prophylactic G-CSF use.
Patient population. This study was conducted between June 2005 and August 2006, and 41 patients were enrolled. Each received one or more doses of study medication and was included in the analysis. Demographic and clinical characteristics are summarized in Table 2. Men constituted 63% of the population, and the median age was 56 years (range, 29-75). Most of the population (59%) had an Eastern Cooperative Oncology Group performance status of 1, almost half (49%) had liposarcoma, and almost all (95%) had undergone previous surgery.

Safety. Patients received a median of six cycles of treatment (range, 2-13). Median duration of treatment was 18.1 weeks.

Table 4. Best overall response by Response Evaluation Criteria in Solid Tumors

<table>
<thead>
<tr>
<th>No. patients</th>
<th>Level 1A* (n = 4)</th>
<th>Level 1 (n = 18)</th>
<th>Level 2 (n = 13)</th>
<th>Level 3 (n = 6)</th>
<th>Total (N = 41)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partial response</td>
<td>0</td>
<td>4</td>
<td>1</td>
<td>0</td>
<td>5 (12)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>4</td>
<td>14</td>
<td>10</td>
<td>5</td>
<td>33 (80)</td>
</tr>
<tr>
<td>≥6 mo</td>
<td>4</td>
<td>9</td>
<td>2</td>
<td>0</td>
<td>15 (37)</td>
</tr>
<tr>
<td>&lt;6 mo</td>
<td>0</td>
<td>5</td>
<td>4</td>
<td>2</td>
<td>11 (27)</td>
</tr>
<tr>
<td>Unknown †</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td>3</td>
<td>7 (17)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Other ‡</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>2 (5)</td>
</tr>
</tbody>
</table>

*Patients with severe neutropenia in cycle 1 but without prophylactic G-CSF use.
† Follow-up <6 mo and without disease progression.
‡ Not enough data to establish response type.

Results

Patient population. This study was conducted between June 2005 and August 2006, and 41 patients were enrolled. Each received one or more doses of study medication and was included in the analysis. Demographic and clinical characteristics are summarized in Table 2. Men constituted ~63% of the population, and the median age was 56 years (range, 29-75). Most of the population (59%) had an Eastern Cooperative Oncology Group performance status of 1, almost half (49%) had liposarcoma, and almost all (95%) had undergone previous surgery.

Safety. Patients received a median of six cycles of treatment (range, 2-13). Median duration of treatment was 18.1 weeks.

Fig. 1. A, Kaplan-Meier curve for PFS for all treatment groups. B, Kaplan-Meier curve for OS for all treatment groups.
(range, 6-44), and median administered cumulative doses were trabectedin 5.39 mg/m² (range, 1.9-13.7) and doxorubicin 350.0 mg/m² (range, 88-543). Median cumulative dose intensity was 0.89 mg/m² per 3 weeks (range, 0.5-1.3) for trabectedin and 54.7 mg/m² per 3 weeks (range, 25-60) for doxorubicin. At dose level 1, before the institution of prophylactic G-CSF, four of the first six patients experienced severe neutropenia during the first treatment cycle; this group is referred to as dose level 1A. Consequently, all subsequent patients, including four additional patients enrolled at level 1, received primary prophylactic G-CSF.

No DLTs were observed at dose level 1; dose level 2 was truncated to 13 patients after no DLTs were observed. Two patients at dose level 3 experienced DLTs, which were grade 4 neutropenia (n = 1) and grade 4 thrombocytopenia (n = 2), making this dose level unacceptable.

Dose modifications/reductions were required for trabectedin in 51% of patients and for doxorubicin in 27% of patients. Hyperbilirubinemia and thrombocytopenia were the most frequently occurring adverse events to lead to trabectedin dose reduction; thrombocytopenia was the most frequent event leading to doxorubicin dose reduction. Fifty-one percent of all patients had to delay treatment for one or more cycles. Neutropenia was the most frequent reason for cycle delays. The most common grade 3/4 treatment-emergent adverse events were neutropenia (71%), alanine aminotransferase increase (46%), and thrombocytopenia (37%; Table 3). The most common drug-related adverse events of any severity were nausea (83%), neutropenia (80%), and alopecia (71%). One death occurred within 30 days of last dose at dose level 3 possibly related to chest wall radiation-induced lung fibrosis; however, a causal relationship to study drug could not be positively excluded.

**Response to therapy and survival.** Best response to treatment is shown in Table 4. Five patients achieved a partial response (3 with liposarcoma including two myxoid type, 1 with leiomyosarcoma of unknown site of origin, and 1 with sarcomatoid carcinoma), and of the 33 patients who maintained stable disease, 15 (37%) did so for ≥6 months. Median PFS was 9.2 months (Fig. 1A). Three-, 6-, and 12-month PFS rates were 85.4% (95% confidence interval, 70.3-93.1), 58.5% (95% confidence interval, 42.0-71.8), and 43.8% (95% confidence interval, 28.4-58.1), respectively. Median OS across all dose levels is shown in Fig. 1B. Median OS for dose levels 1A, 1, and 2 had not been reached at clinical cutoff, with a median follow-up of 21 months; median OS for dose level 3 was 14.8 months.

**Pharmacokinetic analysis.** The relatively small sample size and between-patient variability precluded comparison of pharmacokinetic variables of trabectedin among dose levels; however, clinically relevant differences among mean values were not readily apparent. Pharmacokinetic variables of trabectedin were similar to historical control values for single-agent trabectedin. An increase in mean $C_{\text{max}}$ and $AUC_8$ of doxorubicin was observed with increasing doses of trabectedin; however, minimal differences and no clear trend were observed when mean plasma concentrations at each time point from 1.25 to 51 h were compared. Minimal differences in $t_{1/2}$ values of doxorubicin were observed among dose levels. For doxorubicinol, an increase in mean $C_{\text{max}}$ and $AUC_8$ of doxorubicin was observed with increasing doses of trabectedin; however, minimal differences and no clear trend were observed when mean plasma concentrations at each time point from 1.25 to 51 h were compared. Minimal differences in $t_{1/2}$ values of doxorubicin were observed among dose levels. For doxorubicinol, an increase in mean $C_{\text{max}}$ was observed with increasing doses of trabectedin. Minimal differences and no clear trend were observed when mean plasma $AUC_8$ and $t_{1/2}$ values were compared (Table 5).

### Table 5. Mean (SD) pharmacokinetic variables of trabectedin, doxorubicin, and doxorubicinol in patients coadministered single doses of trabectedin and doxorubicin

<table>
<thead>
<tr>
<th>Variable</th>
<th>Level 1 (n = 3)</th>
<th>Level 2 (n = 5)</th>
<th>Level 3 (n = 5)</th>
<th>Level 1 (n = 3)</th>
<th>Level 2 (n = 5)</th>
<th>Level 3 (n = 5)</th>
<th>Level 1 (n = 3)</th>
<th>Level 2 (n = 5)</th>
<th>Level 3 (n = 5)</th>
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<tbody>
<tr>
<td>$C_{\text{max}}$, ng/mL</td>
<td>5.97 (0.92)</td>
<td>8.44 (2.74)</td>
<td>8.91 (3.38)</td>
<td>1750 (453)*</td>
<td>2452 (286)</td>
<td>3596 (1972)</td>
<td>21.0 (3.17)</td>
<td>25.4 (8.96)</td>
<td>31.1 (13.5)</td>
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<td>$t_{1/2}$, h</td>
<td>2.75 (0.92)</td>
<td>1.00 (1.28)</td>
<td>2.83 (2.97)</td>
<td>2000 (187)*</td>
<td>2505 (88)</td>
<td>3187 (1273)</td>
<td>1.25 (58.2)</td>
<td>1.25 (1548)</td>
<td>1.27 (1566)</td>
</tr>
<tr>
<td>$AUC_{\text{last}}$, ng h/mL</td>
<td>3.63 (1.14)</td>
<td>51.1 (26.9)</td>
<td>59.9 (26.9)</td>
<td>2406 (187)</td>
<td>2781 (1273)</td>
<td>3499 (276)</td>
<td>607 (928)</td>
<td>680 (293)</td>
<td>799 (648)</td>
</tr>
<tr>
<td>$AUC_{\text{tr}}$, ng h/mL</td>
<td>36.3 (6.86)</td>
<td>57.3 (15.3)</td>
<td>72.2 (12.6)</td>
<td>29.2 (111)</td>
<td>24.1 (1206)</td>
<td>27.2 (1010)</td>
<td>65.4 (928)</td>
<td>53.6 (293)</td>
<td>52.7 (648)</td>
</tr>
<tr>
<td>$t_{1/2}$, h</td>
<td>0.89 (0.28)</td>
<td>85.4 (17.8)</td>
<td>90.9 (17.8)</td>
<td>29.2 (3.62)</td>
<td>24.1 (8.66)</td>
<td>27.2 (15.3)</td>
<td>65.4 (44.6)</td>
<td>53.6 (15.3)</td>
<td>52.7 (12.6)</td>
</tr>
<tr>
<td>$\lambda_v$, h⁻¹</td>
<td>0.0105 (0.000286)</td>
<td>0.00880 (0.000305)</td>
<td>0.00786 (0.000158)</td>
<td>0.0239 (0.00295)</td>
<td>0.0290 (0.00293)</td>
<td>0.0279 (0.00969)</td>
<td>0.0137 (0.00701)</td>
<td>0.0138 (0.00378)</td>
<td>0.0136 (0.00304)</td>
</tr>
<tr>
<td>$C_L$, L/h</td>
<td>2.163 (7.69)</td>
<td>2574 (9.10)</td>
<td>3028 (17.4)</td>
<td>42.5 (6.86)</td>
<td>40.1 (5.12)</td>
<td>33.5 (7.79)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>$V_{ss}$, L</td>
<td>197 (197)</td>
<td>2574 (197)</td>
<td>3028 (181)</td>
<td>956 (474)*</td>
<td>561 (124)</td>
<td>495 (318)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

Abbreviation: NR, not reported.

* n = 2.
† Median (range).
‡ n = 4.
§ n = 3.
Discussion

This phase I, dose-finding trial of trabectedin and doxorubicin in patients with STS was prompted by evidence that the two agents were active as single agents in STS, had synergistic effects on STS cells in vitro (14), showed synergistic responses in STS preclinical studies (28), and showed activity in patients with STS, although with myelotoxicity in the absence of growth factor support. Previously, it was determined that the recommended dose of single-agent trabectedin was 1.5 mg/m² when given as a 24-h infusion in 3-week cycles (16) and 1 and 1.3 mg/m² when given as a 3-h infusion in 3-week cycles (26, 32, 33). A randomized phase II study using two different treatment schedules given every 3 weeks either over a 3- or 24-h infusion has been explored (34–36). Safety and efficacy were not substantially different, although less myelosuppression was found with the 3-h infusion schedule. In addition, the dose intensity did not differ significantly between both schedules, and the 3-h regimen provided a greater convenience. Therefore, based on prior experience, the 3-h regimen was considered an appropriate schedule for combination regimens. Commonly used doses of single-agent doxorubicin when given in 3-week cycles are 60 to 75 mg/m² (3, 4). Because neutropenia was expected to be the most severe toxicity, we incorporated G-CSF treatment into the design as primary prophylaxis.

We found that the MTD of trabectedin and doxorubicin given in 3-week cycles was trabectedin 1.1 mg/m² plus doxorubicin 60 mg/m². Thus, these data indicate that, with the proper usage of primary prophylactic G-CSF, trabectedin and doxorubicin can be combined at nearly full single-agent doses for the treatment of patients with recurrent or persistent STS. After institution of primary G-CSF prophylaxis, no DLTs were observed with doses up to trabectedin 1.1 mg/m² plus doxorubicin 60 mg/m².

Doxorubicin and trabectedin pharmacokinetics were not altered substantially with concomitant administration based on comparisons of trial results with results of previous studies in which each was given as a single agent. These findings are consistent with results from preclinical studies of combination administration of doxorubicin and trabectedin in human STS tumor-bearing animals (28).

Although the primary goal of the study was not to measure response, findings of a partial response in 5 of 41 (12%) patients and stable disease in 34 of 41 (83%) patients [15 (37%) patients with stable disease ≥6 months] showed the benefit of this combination in STS; a clinical benefit rate of patients with recurrent or persistent STS. After institution of primary G-CSF prophylaxis, no DLTs were observed with doses up to trabectedin 1.1 mg/m² plus doxorubicin 60 mg/m².

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Finally, atypical lipomatous tumors have long PFS in the absence of response regardless of treatment, but this was not the diagnosis of any patients treated in this trial.

In conclusion, in patients with recurrent or persistent STS, the combination of trabectedin and doxorubicin with primary prophylactic G-CSF support is safe and generally well tolerated and shows antitumor activity. The MTD and recommended phase II dose of trabectedin is 1.1 mg/m² with doxorubicin 60 mg/m², both administered every 3 weeks. Because this combination may fulfill the need for a more active regimen to treat patients with STS, further investigation is warranted.

Disclosures of Potential Conflicts of Interest

JY Blay and Isabelle Ray-Coquard received a research grant from Johnson and Johnson for another trial.

Acknowledgments

We thank the clinical research teams who assisted in the care of these patients (Centre Léon Bérard: Laura Brousseau, Maria Chelgoum, and Arlette Dumortier; Fox Chase Cancer Center: Monica Davey, R.N.; and North Idaho Cancer Center: Sheryl Golden, R.N.) and Namit Ghiydal, Ph.D. (Johnson & Johnson Pharmaceutical Research & Development) and Lisa Shannon, PharmD (Scientific Connexions) for providing medical writing and editing services.

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Jean-Yves Blay, Margaret von Mehren, Brian L. Samuels, et al.


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