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Phase I study of the safety and pharmacokinetics of trabectedin with docetaxel in patients with advanced malignancies

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Abstract

Purpose—Combination therapy with trabectedin and docetaxel was evaluated in patients with advanced malignancies.

Methods—In this open-label phase 1 study, docetaxel (60 or 75 mg/m²; 1-h intravenous infusion) was given on day 1 of a 21-day cycle in combination with escalating doses of trabectedin (0.4–1.3 mg/m² by 3-h intravenous infusion, 1 h after docetaxel) and prophylactic granulocyte colony-

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stimulating factor (G-CSF). Maximum tolerated dose (MTD) as primary objective and safety, plasma pharmacokinetics, and antitumor activity as secondary objectives were assessed.

Results—Patients ($N = 49$) received a median of four cycles of treatment. MTD was 1.3 mg/m² trabectedin and 60 mg/m² docetaxel for patients with limited and 1.1 mg/m² trabectedin and 60 mg/m² docetaxel for patients with unlimited prior chemotherapy. Dose-limiting toxicities (during cycle 1) included elevated alanine aminotransferase (ALT) and fatigue in patients with limited prior chemotherapy and elevated ALT and febrile neutropenia in those with unlimited prior chemotherapy. The most common drug-related adverse events were nausea (65 %), fatigue (63 %), and neutropenia (53 %). One patient achieved a complete response. Thirty patients had stable disease, and 11 had stable disease for 6 months. Pharmacokinetic results for trabectedin plus docetaxel were similar to those previously reported for the single agents.

Conclusion—In patients with previously treated, advanced malignancies, the combination of therapeutic doses of trabectedin and docetaxel showed clinical activity and was tolerable with prophylactic G-CSF, with no evidence of clinically important drug interactions.

Keywords

Advanced malignancies; Combination chemotherapy; Docetaxel; Ovarian cancer; Sarcoma; Trabectedin

Introduction

Trabectedin (Yondelis[®], ET-743; PharmaMar, Madrid, Spain/Centocor Ortho Biotech Products, LP, Horsham, PA, USA), a first-in-class anticancer DNA-binding agent, is approved by the European Commission for advanced soft tissue sarcoma (STS) and for relapsed platinum-sensitive ovarian cancer in combination with pegylated liposomal doxorubicin [1]. Trabectedin covalently binds the DNA minor groove, causing a bend in the major groove [2], alterations in transcription factor function and DNA repair processes, cell cycle arrest, and subsequent cell death [3–6].

Trabectedin is active in osteosarcoma [7], breast cancer [8, 9], STS [10], and ovarian cancer [11, 12]. Its unique mechanism of action and favorable toxicity profile offers opportunities for combination therapy [13–16]. Trabectedin plus docetaxel showed additive cytotoxicity in vitro and with paclitaxel had synergistic activity in STS and breast cancer cell lines [13, 14, 17]. Because trabectedin and docetaxel act by different mechanisms, have activity against multiple cancers, and use similar dosing schedules, we evaluated this combination in advanced cancer patients.

The primary objective of this study was to determine the maximum tolerated dose (MTD) of trabectedin plus docetaxel in patients with advanced malignancies who had received limited (1 combination or 2 single-agent regimens) or unlimited prior cytotoxic chemotherapy. Secondary objectives included safety, pharmacokinetics, and tumor response.

Materials and methods

Patients

Eligible patients were ≥18 years of age, had advanced, treatment-refractory cancer, an Eastern Cooperative Oncology Group performance status of 0–1, and adequate hematologic, hepatic, and renal function. Key exclusion criteria included prior trabectedin, grade ≥2 peripheral neuropathy, <4 weeks since radiation therapy or last dose of systemic therapy, known central nervous system metastasis, and chronic liver disease.

Study design

The study protocol and amendments were reviewed and approved by the Fox Chase Cancer Center Institutional Review Board. The study was conducted in accordance with accepted ethical principles having their origin in the Declaration of Helsinki and Good Clinical Practice guidelines and all applicable regulatory requirements. All patients provided written informed consent.

On day 1 of each 3-week cycle, docetaxel 60 or 75 mg/m² was infused intravenous (IV) over 1 h. After 1-h observation, trabectedin was infused IV over 3 h at one of six dose levels (0.4, 0.6, 0.75, 0.9, 1.1, or 1.3 mg/m²). Treatment was continued until disease progression or unacceptable toxicity. Dose escalation using a conventional 3 + 3 scheme was based on toxicities in cycle 1. All patients received oral dexamethasone 8 mg twice daily on days –1, 0, and 1 of each cycle except for a single IV dose before docetaxel infusion. After dose-limiting neutropenia in the first two cohorts, the protocol was amended to allow primary prophylaxis with granulocyte colony-stimulating factor (G-CSF; filgrastim). No intra-patient dose escalation occurred.

Dose reductions were instituted for toxicities attributed to one or both agents. For absolute neutrophil count (ANC) <500/μL with fever or infection, ANC <500/μL for >5 days, or platelet count <25,000/μL, trabectedin was decreased by one level and docetaxel was decreased from 60 to 50 mg/m² or from 75 to 60 mg/m². Subsequent cycles were delayed for up to 3 weeks if any of the following were not met: platelet count ≥100,000/μL, ANC ≥1500/μL, bilirubin and alkaline phosphatase ≤upper limit of normal, liver transaminases grade ≤1, and other nonhematologic drug-related effects grade ≤2. Trabectedin was decreased by one level for grade ≥3 nausea or vomiting despite adequate prophylaxis, grade ≥1 nonosseous alkaline phosphatase elevation, grade ≥3 transaminase elevation with recovery to grade ≤1 or conjugated bilirubin greater than upper limit of normal, or any other grade ≥3 nonhematologic toxicity. For grade ≥3 transaminase elevation without recovery to grade ≤1, trabectedin was decreased by one level for patients with clinical benefit or discontinued. Dose reductions for docetaxel and trabectedin were limited to one and ≥2, respectively.

Toxicity assessment

Dose-limiting toxicity (DLT) was defined as ≥1 of the following in cycle 1: ANC < 500 μL for >5 days or with fever or sepsis; platelet count <25 000 μL; any grade 3/4 nonhematologic toxicity except nausea or vomiting despite appropriate prophylaxis; grade 3 transaminitis

lasting >1 week; or cycle delay >3 weeks. The MTD was defined as the highest dose at which less than one-third of patients experienced DLT in cycle 1. Prophylaxis with G-CSF was added at dose levels 2. After the MTD with G-CSF in patients with limited chemotherapy had been determined, additional patients with unlimited prior chemotherapy were enrolled at the corresponding dose level, which was subsequently de-escalated until the MTD with G-CSF for this population was established. At least six patients were treated at each MTD.

Pharmacokinetic assessment

Pharmacokinetic analysis with data from three or more patients at each dose level was performed in cycle 1 using validated methods [18]. Peripheral venous blood was obtained before and 30 min after initiating docetaxel; 10 min before and 10, 30, and 60 min after completing docetaxel; before trabectedin; 30 and 90 min after initiating trabectedin; and 10 min before and at prespecified time points after completing trabectedin. Pharmacokinetic parameters were calculated by noncompartmental analysis using individual plasma concentration–time data.

Safety and antitumor assessments

Treatment-emergent adverse events (AEs) were graded according to the National Cancer Institute Common Terminology Criteria, version 2. Clinical laboratory tests, vital signs, and physical examinations were evaluated throughout the study and at treatment termination. Tumor response was assessed by Response Evaluation Criteria In Solid Tumors (RECIST) [19] after every two cycles and at treatment termination. A complete response (CR) or a partial response (PR) required confirmation 4 weeks later.

Statistical analyses

Analyses were carried out with the Statistical Analysis System (SAS®), version 9.1 (SAS Institute Inc., Cary, NC, USA). Safety and efficacy analyses sets included all patients who received one or more dose(s) of trabectedin. Pharmacokinetic analyses sets included all patients from whom blood samples were obtained for pharmacokinetics. Descriptive statistics were provided by dose level for plasma concentrations of each study drug at each sampling time.

Results

Patient characteristics

The majority of patients were men (55 %), were white (90 %), and had an Eastern Cooperative Oncology Group (ECOG) status of 1 (67 %). Forty-nine patients received one or more doses of trabectedin (Table 1), of which 47 had documented disease progression before study entry. Patients received trabectedin for a median of 12.1 weeks (range 3–118) and a median of four cycles (range 1–38) across all cohorts. The median number of cycles was highest for the 1.3/75 mg/m² (trabectedin/docetaxel doses) limited prior chemotherapy cohort (10 cycles; range 2–18 cycles). Median dose intensity per 3 weeks across all cohorts was 0.8 mg/m² (range 0.3–1.3 mg/m²) for trabectedin and 56 mg/m² (range 10–75 mg/m²) for docetaxel. Median cumulative trabectedin dose at the MTD for patients with unlimited

prior chemotherapy (1.1 mg/m² trabectedin/60 mg/m² docetaxel, $n = 6$) was 4.1 mg/m² (range 1.1–5.5 mg/m²) and for those with limited prior chemotherapy (1.3 mg/m² trabectedin/60 mg/m² docetaxel, $n = 8$) was 6.0 mg/m² (range 2.4–20.7 mg/m²). The corresponding values for docetaxel were 230 mg/m² and 275 mg/m².

Treatment and principal toxicities

Trabectedin was escalated from 0.4 to 1.3 mg/m² in combination with docetaxel 60 mg/m² (Table 2). Patients in the first two cohorts had no restrictions on prior chemotherapies and received no prophylactic G-CSF. At 0.4 and 0.6 mg/m² trabectedin with 60 mg/m² docetaxel dose levels, 5/6 and 4/4 patients, respectively, had grade 3 or 4 neutropenia. To allow for escalation above trabectedin 0.6 mg/m² and docetaxel 60 mg/m², the protocol was amended limiting prior therapy. Of the eight patients with limited prior therapy subsequently accrued to dose level 2, six experienced grade 3 or 4 neutropenia. Prophylactic G-CSF was added to allow for further dose increases in this patient population; only a single patient with limited prior therapy experienced grade 3 neutropenia, and none experienced grade 4 neutropenia until the MTD (trabectedin 1.3 mg/m² and docetaxel 60 mg/m²) was reached. The limited prior therapy MTD was then used as a starting dose to determine the MTD with G-CSF in patients with unlimited prior therapy (Table 2).

A total of 9/10 patients without G-CSF at the initial two dose levels had grade 3 or 4 neutropenia, while 5/8 patients with multiple prior therapies had grade 3–4 neutropenia at 1.1 and/or 1.3 mg/m² trabectedin with 60 mg/m² docetaxel and G-CSF. In contrast, 5/23 patients with limited prior treatment who received G-CSF experienced grade 3–4 neutropenia over all treatment cycles, including 3/6 patients at the DLT dose level.

Dose-limiting toxicities

The DLTs in patients with unlimited prior chemotherapy treated with 1.3 mg/m² trabectedin/60 mg/m² docetaxel plus G-CSF were grade 3 elevated alanine aminotransferase (ALT; $n = 1$) and grade 4 febrile neutropenia ($n = 1$). DLTs in patients with limited prior chemotherapy at the 1.3 mg/m² trabectedin/75 mg/m² docetaxel dose level were grade 3 elevated ALT ($n = 1$) and fatigue ($n = 1$). Based on these results, the MTD was 1.1 mg/m² trabectedin/60 mg/m² docetaxel for patients with unlimited prior chemotherapy and 1.3 mg/m² trabectedin/60 mg/m² docetaxel for those with limited prior chemotherapy.

The most frequently reported drug-related AEs of any grade were nausea (65 %), fatigue (63 %), neutropenia (53 %), anemia (45 %), and increased ALT (45 %). Drug-related grade 3 and 4 AEs occurred in 71 % of all patients (Table 2). In cycle 1, the only drug-related grade 4 AE was neutropenia, which was more common in patients with unlimited prior chemotherapy. The median time to grade 4 ANC nadir in cycle 1 was 9 days (range 7–13 days); the median time to grade 3 or 4 neutropenia across all cycles was 8 days (range 6–86 days). The addition of G-CSF mitigated the occurrence of neutropenia.

No drug-related grade 3 or 4 nausea or vomiting was observed. The AE incidence did not increase with dose escalation, except for nausea, diarrhea, and elevations of transaminases and AP. No unexpected serious AEs were reported. One patient, a 49-year-old man in the 1.1/60 mg/m² cohort with osteogenic sarcoma of the left leg received a single dose on day 1,

and after developing sepsis on day 38, the patient died on day 39. His death was considered not related to study medication.

Twenty patients (41 %) required one or more trabectedin dose adjustments: 19 due to drug-related AEs, particularly neutropenia ($n = 8$; 16 %). Most trabectedin dose adjustments occurred in cycle 2. Docetaxel dose reductions occurred in 19 (39 %) patients, also primarily due to drug-related neutropenia ($n = 6$; 12 %). At least one cycle delay occurred in 18 (37 %) patients; approximately one-third of cycle delays lasted 6–12 days. No trabectedin dose interruption occurred. Two patients discontinued the study for drug-related AEs (grade 4 febrile neutropenia, gastric, and duodenal ulcers).

Pharmacokinetics

After initiation of trabectedin infusion, mean time to maximum plasma concentration was 1.5–3 h (Table 3). After infusion, mean plasma trabectedin concentrations declined in a multi-exponential fashion (Fig. 1). Mean maximum plasma concentrations generally increased with increasing dose (Table 3), from 3.46 to 8.91 ng/mL (limited prior chemotherapy) and from 1.54 to 10.3 ng/mL (unlimited prior chemotherapy). A similar trend was observed for the area under the concentration–time curve. In general, mean plasma clearance values decreased and mean volume of distribution at steady state increased with increasing dose. Terminal trabectedin half-life estimates ranged from 62.6 to 160 h; the value for the 0.4/60 mg/m² dose group was deemed unreliable because trabectedin plasma concentrations at the end of infusion in many patients were below the lower limit of quantification.

Mean plasma concentrations of docetaxel peaked between 0.5 and 1 h after the start of infusion and declined in a multi-exponential manner after cessation of infusion. Terminal half-life values ranged from 23.1 to 34.7 h. In general, no clear differences between or consistent trends across cohorts were apparent for mean plasma clearance, volume of distribution at steady state, or terminal half-life of docetaxel. Mean maximum concentrations of docetaxel ranged from 1717 to 2695 ng/mL across the 60 mg/m² cohorts. Mean plasma concentration of docetaxel in the single docetaxel 75 mg/m² cohort was 2218 ng/mL. Mean plasma clearance among the different cohorts ranged from 34.8 to 59.9 L/h.

Tumor response

Tumor response data are shown in Table 4. Disease progression occurred in 15 patients at cycle 2 or earlier. The disease control rate (CR + PR + stable disease) was 63 %. The CR occurred in a female patient (0.6/60 mg/m² cohort) with primary peritoneal papillary serous carcinoma, who had undergone debulking surgery followed by adjuvant carboplatin, paclitaxel, and pegylated doxorubicin, but had progressive disease, 9 months later. She achieved CR after four cycles of trabectedin with docetaxel and was without disease progression for 7 months.

A total of 30 patients (61 %) achieved stable disease, lasting 6 months in 11 patients: endometrial stromal sarcoma (7 months), gastric cancer (8 months), liposarcoma (6 and 27 months), prostate cancer (9 and 13 months), extraskeletal myxoid chondrosarcoma (15 months), chondrosarcoma (12 months), small cell lung cancer (7 months), spindle cell

sarcoma NOS (10 months), leiomyosarcoma (15 months), myxofibrosarcoma (16 months), and alveolar soft part sarcoma (6 months). All but the patient with small cell lung cancer had evidence of increasing tumor volume on baseline scans. The prostate cancer patients were hormone refractory and had not received prior chemotherapy. Of the nine patients with sarcoma, five had not received prior chemotherapy. All of the remaining patients had received one prior therapy, except one patient who had received two prior therapies.

Discussion

Results of this phase 1 trial demonstrate that the combination of trabectedin and docetaxel is tolerable and has clinical activity in some patients with advanced, clinically progressive malignancies. The doses of each drug were in the therapeutic range for the respective single agents. A high rate of disease control was achieved (63 %), primarily manifested as stable disease (61 %), which lasted 6 months in approximately one-third of patients.

The pharmacokinetic profiles of trabectedin and docetaxel were consistent with those previously reported [20–22]. No unexpected serious toxicities occurred, suggesting no clinically significant drug interactions between the two agents. The combination did not lead to excess hepatic toxicity, but was associated with a relatively high incidence of hematologic toxicities, especially prolonged and febrile neutropenia. Thus, this regimen may be best suited for patients with limited prior therapy who receive concomitant G-CSF support.

Other combinations with trabectedin have been evaluated in phase 1 trials of patients with advanced malignancies, including trabectedin/pegylated liposomal doxorubicin ($n = 36$; median 4 cycles) [23] and trabectedin/gemcitabine ($n = 15$; median 2 cycles) [24]. Both combinations had antitumor activity and were tolerable, with no evidence of pharmacokinetic interactions [23, 24]. The MTDs determined in the present study may potentially be improved by combinations with alternate taxane schedules such as weekly administration [25]. The combination of paclitaxel and trabectedin is attractive given less severe myelosuppression with paclitaxel compared with docetaxel [26].

We observed antitumor activity in diverse cancer types. Activity in prostate [27, 28], small cell lung [29, 30], and gastric cancer [31] is not surprising given their known sensitivity to docetaxel, although most of the patients in our study received a relatively low dose of docetaxel (60 mg/m²). The observed activity in STS is of greater interest given previous reports of no or poor response of STS to docetaxel [32–34]. Single-agent trabectedin for STS in the second-line setting also has a low objective response rate [35–37].

In our study, response durations in patients with leiomyosarcoma and liposarcoma, sarcoma subtypes most responsive to trabectedin, ranged from 6 to 27 months. Unlike gemcitabine/docetaxel [38], trabectedin/docetaxel yielded no objective responses, but we did observe prolonged stable disease in subtypes not known to be sensitive to trabectedin or docetaxel alone (i.e., alveolar soft part sarcoma, chondrosarcoma, myxoid chondrosarcoma, and endometrial stromal sarcoma).

Docetaxel is active in gynecologic epithelial carcinomas [39, 40], with response rates of 40 and 22.4 % in chemotherapy-naïve and chemotherapy-refractory settings, respectively, while

trabectedin is active in ovarian cancer as a single agent and with pegylated doxorubicin [11, 12, 41–43]. The CR in a patient who had received prior therapy with carboplatin, paclitaxel, and liposomal doxorubicin is notable.

In conclusion, the results of this phase 1 study show that clinically active dose combinations of trabectedin and docetaxel generally were well tolerated when given with prophylactic G-CSF, with no evidence of cumulative toxicity after prolonged treatment. There was preliminary evidence of antitumor activity. Further evaluation of trabectedin plus docetaxel is warranted, particularly in patients with refractory ovarian cancer and in patients with chemotherapy-naïve as well as chemotherapy-refractory STS.

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References

1. European Medicines Agency. [Accessed 15 Oct 2014] Yondelis: Product Information. http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000773/human_med_001165.jsp&murl=menus/medicines/medicines.jsp&jsenabled=true
2. Zewail-Foote M, Hurley LH. Ecteinascidin 743: a minor groove alkylator that bends DNA toward the major groove. *J Med Chem.* 1999; 42:2493–2497. DOI: 10.1021/jm9902411 [PubMed: 10411470]
3. Minuzzo M, Marchini S, Broggini M, et al. Interference of transcriptional activation by the antineoplastic drug ecteinascidin-743. *Proc Natl Acad Sci USA.* 2000; 97:6780–6784. DOI: 10.1073/pnas.97.12.6780 [PubMed: 10841573]
4. Takebayashi Y, Pourquier P, Zimonjic DB, et al. Antiproliferative activity of ecteinascidin 743 is dependent upon transcription-coupled nucleotide-excision repair. *Nat Med.* 2001; 7:961–966. DOI: 10.1038/91008 [PubMed: 11479630]
5. Martinez EJ, Corey EJ, Owa T. Antitumor activity- and gene expression-based profiling of ecteinascidin Et 743 and phthalascidin Pt 650. *Chem Biol.* 2001; 8:1151–1160. DOI: 10.1016/S1074-5521(01)00082-5 [PubMed: 11755394]
6. Erba E, Bergamaschi D, Bassano L, et al. Ecteinascidin-743 (ET-743), a natural marine compound, with a unique mechanism of action. *Eur J Cancer.* 2001; 37:97–105. DOI: 10.1016/S0959-8049(00)00357-9 [PubMed: 11165136]
7. Laverdiere C, Kolb EA, Supko JG, et al. Phase II study of ecteinascidin 743 in heavily pretreated patients with recurrent osteosarcoma. *Cancer.* 2003; 98:832–840. DOI: 10.1002/cncr.11563 [PubMed: 12910529]
8. Zelek L, Yovine A, Brain E, et al. A phase II study of Yondelis (trabectedin, ET-743) as a 24-h continuous intravenous infusion in pretreated advanced breast cancer. *Br J Cancer.* 2006; 94:1610–1614. DOI: 10.1038/sj.bjc.6603142 [PubMed: 16736024]
9. Gurtler JS, Goldstein L, Delprete S, et al. Trabectedin in third line breast cancer: a multicenter, randomized, phase II study comparing two administration regimens. *J Clin Oncol.* 2005; 23:34s. Abstract 625.

10. Cesne AL, Judson I, Maki R, et al. Trabectedin is a feasible treatment for soft tissue sarcoma patients regardless of patient age: a retrospective pooled analysis of five phase II trials. *Br J Cancer*. 2013; 109:1717–1724. DOI: 10.1038/bjc.2013.524 [PubMed: 24022187]
11. Krasner CN, McMeekin DS, Chan S, et al. A Phase II study of trabectedin single agent in patients with recurrent ovarian cancer previously treated with platinum-based regimens. *Br J Cancer*. 2007; 97:1618–1624. DOI: 10.1038/sj.bjc.6604088 [PubMed: 18000504]
12. Sessa C, De Braud F, Perotti A, et al. Trabectedin for women with ovarian carcinoma after treatment with platinum and taxanes fails. *J Clin Oncol*. 2005; 23:1867–1874. DOI: 10.1200/JCO.2005.09.032 [PubMed: 15774779]
13. Takahashi N, Li WW, Banerjee D, et al. Sequence-dependent enhancement of cytotoxicity produced by ecteinascidin 743 (ET-743) with doxorubicin or paclitaxel in soft tissue sarcoma cells. *Clin Cancer Res*. 2001; 7:3251–3257. [PubMed: 11595721]
14. Takahashi N, Li W, Banerjee D, et al. Sequence-dependent synergistic cytotoxicity of ecteinascidin-743 and paclitaxel in human breast cancer cell lines in vitro and in vivo. *Cancer Res*. 2002; 62:6909–6915. [PubMed: 12460906]
15. Scotlandi K, Perdichizzi S, Manara MC, et al. Effectiveness of Ecteinascidin-743 against drug-sensitive and -resistant bone tumor cells. *Clin Cancer Res*. 2002; 8:3893–3903. [PubMed: 12473605]
16. Meco D, Colombo T, Ubezio P, et al. Effective combination of ET-743 and doxorubicin in sarcoma: preclinical studies. *Cancer Chemother Pharmacol*. 2003; 52:131–138. DOI: 10.1007/s00280-003-0636-6 [PubMed: 12783202]
17. Barrera H, Moore R, Jimeno J, et al. Interaction of ET-743 and standard cytotoxic agents against a panel of human tumor cell lines. *Proc Am Assoc Cancer Res*. 1999; 40:591. Abstract 3896.
18. Blay JY, von Mehren M, Samuels BL, et al. Phase I combination study of trabectedin and doxorubicin in patients with soft-tissue sarcoma. *Clin Cancer Res*. 2008; 14:6656–6662. DOI: 10.1158/1078-0432.CCR-08-0336 [PubMed: 18927308]
19. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst*. 2000; 92:205–216. DOI: 10.1093/jnci/92.3.205 [PubMed: 10655437]
20. Villalona-Calero MA, Eckhardt SG, Weiss G, et al. A phase I and pharmacokinetic study of ecteinascidin-743 on a daily $\times$ 5 schedule in patients with solid malignancies. *Clin Cancer Res*. 2002; 8:75–85. [PubMed: 11801542]
21. Baker SD, Zhao M, Lee CK, et al. Comparative pharmacokinetics of weekly and every-three-weeks docetaxel. *Clin Cancer Res*. 2004; 10:1976–1983. DOI: 10.1158/1078-0432.CCR-0842-03 [PubMed: 15041715]
22. Bruno R, Vivier N, Vergniol JC, et al. A population pharmacokinetic model for docetaxel (Taxotere): model building and validation. *J Pharmacokinet Biopharm*. 1996; 24:153–172. [PubMed: 8875345]
23. von Mehren M, Schilder RJ, Cheng JD, et al. A phase I study of the safety and pharmacokinetics of trabectedin in combination with pegylated liposomal doxorubicin in patients with advanced malignancies. *Ann Oncol*. 2008; 19:1802–1809. DOI: 10.1093/annonc/mdn363 [PubMed: 18497430]
24. Messersmith WA, Jimeno A, Ettinger D, et al. Phase I trial of weekly trabectedin (ET-743) and gemcitabine in patients with advanced solid tumors. *Cancer Chemother Pharmacol*. 2008; 63:181–188. DOI: 10.1007/s00280-008-0733-7 [PubMed: 18379785]
25. Mauri D, Kamposioras K, Tsali L, et al. Overall survival benefit for weekly vs. three-weekly taxanes regimens in advanced breast cancer: a meta-analysis. *Cancer Treat Rev*. 2010; 36:69–74. DOI: 10.1016/j.ctrv.2009.10.006 [PubMed: 19945225]
26. Vasey PA, Jayson GC, Gordon A, et al. Phase III randomized trial of docetaxel-carboplatin versus paclitaxel-carboplatin as first-line chemotherapy for ovarian carcinoma. *J Natl Cancer Inst*. 2004; 96:1682–1691. DOI: 10.1093/jnci/djh323 [PubMed: 15547181]

27. Eymard JC, Priou F, Zannetti A, et al. Randomized phase II study of docetaxel plus estramustine and single-agent docetaxel in patients with metastatic hormone-refractory prostate cancer. *Ann Oncol.* 2007; 18:1064–1070. DOI: 10.1093/annonc/mdm083 [PubMed: 17434899]
28. Caffo O, Sava T, Comploj E, et al. Docetaxel, with or without estramustine phosphate, as first-line chemotherapy for hormone-refractory prostate cancer: results of a multi-centre, randomized phase II trial. *BJU Int.* 2008; 102:1080–1085. DOI: 10.1111/j.1464-410X.2008.07779.x [PubMed: 18485028]
29. Hesketh PJ, Crowley JJ, Burris HA 3rd, et al. Evaluation of docetaxel in previously untreated extensive-stage small cell lung cancer: a Southwest Oncology Group phase II trial. *Cancer J Sci Am.* 1999; 5:237–241. [PubMed: 10439170]
30. Yokoyama A, Kurita Y, Watanabe K, et al. Early phase II clinical study of RP56976 (docetaxel) in patients with primary pulmonary cancer. Docetaxel Cooperative Study Group for Lung Cancer. *Gan To Kagaku Ryoho.* 1994; 21:2609–2616. [PubMed: 7979421]
31. Ajani JA. Optimizing docetaxel chemotherapy in patients with cancer of the gastric and gastroesophageal junction: evolution of the docetaxel, cisplatin, and 5-fluorouracil regimen. *Cancer.* 2008; 113:945–955. DOI: 10.1002/cncr.23661 [PubMed: 18623382]
32. van Hoesel QG, Verweij J, Catimel G, et al. Phase II study with docetaxel (Taxotere) in advanced soft tissue sarcomas of the adult. EORTC Soft Tissue and Bone Sarcoma Group. *Ann Oncol.* 1994; 5(6):539–542. [PubMed: 7918126]
33. Verweij J, Catimel G, Sulkes A, et al. Phase II studies of docetaxel in the treatment of various solid tumours. EORTC Early Clinical Trials Group and the EORTC Soft Tissue and Bone Sarcoma Group. *Eur J Cancer.* 1995; 31A(Suppl 4):S21–S24. DOI: 10.1016/0959-8049(95)00362-M [PubMed: 7577101]
34. Edmonson JH, Ebbert LP, Nascimento AG, et al. Phase II study of docetaxel in advanced soft tissue sarcomas. *Am J Clin Oncol.* 1996; 19:574–576. [PubMed: 8931674]
35. Morgan JA, Le Cesne A, Chawla S, et al. Randomized phase II study of trabectedin in patients with liposarcoma and leiomyosarcoma (L-sarcomas) after failure of prior anthracyclines (A) and ifosfamide (I). *J Clin Oncol.* 2007; 25:559s. Abstract 10060.
36. Le Cesne A, Blay JY, Judson I, et al. Phase II study of ET-743 in advanced soft tissue sarcomas: a European Organisation for the Research and Treatment of Cancer (EORTC) soft tissue and bone sarcoma group trial. *J Clin Oncol.* 2005; 23:576–584. DOI: 10.1200/JCO.2005.01.180 [PubMed: 15659504]
37. Yovine A, Riofrio M, Blay JY, et al. Phase II study of ecteinascidin-743 in advanced pretreated soft tissue sarcoma patients. *J Clin Oncol.* 2004; 22:890–899. DOI: 10.1200/JCO.2004.05.210 [PubMed: 14990645]
38. Hensley ML, Maki R, Venkatraman E, et al. Gemcitabine and docetaxel in patients with unresectable leiomyosarcoma: results of a phase II trial. *J Clin Oncol.* 2002; 20:2824–2831. DOI: 10.1200/JCO.2002.11.050 [PubMed: 12065559]
39. Kavanagh JJ, Kudelka AP, de Leon CG, et al. Phase II study of docetaxel in patients with epithelial ovarian carcinoma refractory to platinum. *Clin Cancer Res.* 1996; 2:837–842. [PubMed: 9816238]
40. Rose PG, Blessing JA, Ball HG, et al. A phase II study of docetaxel in paclitaxel-resistant ovarian and peritoneal carcinoma: a Gynecologic Oncology Group study. *Gynecol Oncol.* 2003; 88:130–135. DOI: 10.1016/S0090-8258(02)00091-4 [PubMed: 12586591]
41. Del Campo J, Roszak A, Ciuleanu T, et al. Phase II open-label, randomized study of trabectedin (T) given as two different dosing schedules in women with platinum-sensitive, recurrent ovarian carcinoma: preliminary results. *J Clin Oncol.* 2006; 24:263s. Abstract 5031.
42. McMeekin DS, Krasner C, Chan S, et al. Final results of a phase II study of weekly trabectedin in second/third line ovarian carcinoma. *J Clin Oncol.* 2005; 23:457s. Abstract 5011.
43. Monk BJ, Herzog T, Kaye S, et al. A randomized phase III study of trabectedin with pegylated liposomal doxorubicin (PLD) versus PLD in relapsed, recurrent ovarian cancer. *Ann Oncol.* 2008; 19:viii2. Abstract LBA4.

Fig. 1.

Mean plasma concentrations of trabectedin (3-h IV infusion) in patients 1 h after docetaxel (1-h infusion)

Table 1

Patient demographic and baseline characteristic

Characteristic	Dose cohort Trabectedin (mg/m ²)/docetaxel (mg/m ²)									
	Unlimited prior therapy (mg/m ²)					Limited prior therapy (mg/m ²)				
	0.4/60 (n = 6)	0.6/60 (n = 12)	1.1/60 (n = 6)	1.3/60 (n = 2)	0.75/60 (n = 3)	0.9/60 (n = 3)	1.1/60 (n = 3)	1.3/60 (n = 8)	1.3/75 (n = 6)	Total (N = 49)
Age, median (years)	46.5	56	65	64.5	66	60	42	62.5	62	60
Range	31–72	41–71	49–70	60–69	63–66	35–68	41–43	50–70	32–67	31–72
Gender, n (%)										
Women	2 (33)	7 (58)	4 (67)	2 (100)	0	2 (67)	1 (33)	3 (38)	1 (17)	22 (45)
Men	4 (67)	5 (42)	2 (33)	0	3 (100)	1 (33)	2 (67)	5 (63)	5 (83)	27 (55)
Race, n (%)										
Asian	0	0	0	0	0	0	0	1 (13)	0	1 (2)
Black	0	0	0	0	0	1 (33)	0	2 (25)	0	3 (6)
Hispanic	0	0	0	0	0	0	1 (33)	0	0	1 (2)
White	6 (100)	12 (100)	6 (100)	2 (100)	3 (100)	2 (67)	2 (67)	5 (63)	6 (100)	44 (90)
ECOG PS, n (%)										
0	0	4 (33)	1 (17)	0	2 (67)	0	2 (67)	4 (50)	3 (50)	16 (33)
1	6 (100)	8 (67)	5 (83)	2 (100)	1 (33)	3 (100)	1 (33)	4 (50)	3 (50)	33 (67)
Prior treatment, n (%)										
Chemotherapy	6 (100)	10 (83)	6 (100)	2 (100)	1 (33)	1 (33)	2 (67)	5 (63)	2 (33)	35 (71)
Surgery	5 (83)	10 (83)	6 (100)	2 (100)	2 (67)	2 (67)	2 (67)	8 (100)	4 (67)	41 (84)
Radiotherapy	4 (67)	8 (67)	2 (33)	1 (50)	1 (33)	1 (33)	1 (33)	3 (38)	3 (50)	24 (49)

Diagnoses included

Sarcoma: 21 patients (5 liposarcoma, 4 leiomyosarcoma, 3 chondrosarcoma, 2 alveolar soft part sarcoma, 2 spindle cell sarcoma NOS, 2 osteogenic sarcoma, 1 endometrial stromal sarcoma, 1 fibrosarcoma, and 1 myxofibrosarcoma)

Lung cancer; 5 patients (3 small cell lung cancer and 2 nonsmall cell lung cancer)

Pleural mesothelioma: 1 patient

Gynecologic malignancy; 5 patients (2 papillary serous ovarian; 1 each of adenocarcinoma, fallopian tube carcinoma, and primary peritoneal carcinoma)

Adenocarcinoma of the gastrointestinal tract; 5 patients (colon, gallbladder, stomach, ampulla of Vater, and appendix)

Prostate cancer; 4 patients

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Renal cell carcinoma; 2 patients
Salivary adenoid cystic carcinoma; 1 patient
Squamous cell carcinoma of the esophagus; 1 patient
Head and neck carcinoma; 1 patient
Urothelial carcinoma; 1 patient
Carcinoma of parotid gland; 1 patient
ECOG Eastern Cooperative Oncology Group, *PS* performance status

Table 2

Drug-related grade 3 and 4 adverse events (safety analysis set)

Adverse event, <i>n</i> (%)	Dose cohort Trabectedin (mg/m ²)/docetaxel (mg/m ²)										
	Unlimited prior therapy (mg/m ²)					Limited prior therapy (mg/m ²)					
	0.4/60 ^a (<i>n</i> = 6)	0.6/60 ^a (<i>n</i> = 12)	1.1/60 ^b (<i>n</i> = 6)	1.3/60 (<i>n</i> = 2)	1.1/60 (<i>n</i> = 3)	0.75/60 (<i>n</i> = 3)	0.9/60 (<i>n</i> = 3)	1.1/60 (<i>n</i> = 3)	1.3/60 ^b (<i>n</i> = 8)	1.3/75 (<i>n</i> = 6)	Total (<i>N</i> = 49)
All drug-related grade 3 and 4 adverse events	5 (83)	10 (83)	4 (67)	2 (100)	2 (67)	1 (33)	0	0	6 (75)	5 (83)	35 (71)
Hematologic											
Neutropenia	5 (83)	10 ^c (83)	3 (50)	1 (50)	1 (33)	0	0	0	3 (38)	3 (50)	26 (53)
Leukopenia	0	5 (42)	3 (50)	0	1 (33)	0	0	0	0	3 (50)	12 (24)
Anemia	0	1 (8)	1 (17)	0	0	0	0	0	1 (13)	0	3 (6)
Thrombocytopenia	0	0	3 (50)	0	0	0	0	0	0	0	3 (6)
Febrile neutropenia	1 ^d (17)	0	0	1 (50)	0	0	0	0	0	0	2 (4)
Nonhematologic											
ALT elevation	0	0	1 (17)	1 ^c (50)	1 (33)	1 (33)	0	0	2 (25)	3 ^e (50)	9 (18)
AST elevation	0	0	1 (17)	1 (50)	1 (33)	0	0	0	0	0	3 (6)
CPK elevation	0	0	0	0	0	0	0	0	1 (13)	0	1 (2)
GGT elevation	0	0	0	0	1 (33)	0	0	0	0	0	1 (2)
Weight decreased	0	0	0	0	1 (33)	0	0	0	0	0	1 (2)
Fatigue	0	0	0	0	0	0	0	0	2 ^e (25)	1 ^d (17)	3 (6)
Diarrhea	0	0	1 (17)	0	0	0	0	0	0	0	1 (2)
Duodenal ulcer											
Hemorrhage	0	0	0	0	0	1 (33)	0	0	0	0	1 (2)
Gastric ulcer	0	0	0	0	0	1 (33)	0	0	0	0	1 (2)
Infection	0	0	0	1 (50)	0	0	0	0	0	1 (17)	2 (4)
Anorexia	0	0	0	1 (50)	0	0	0	0	0	0	1 (2)

ALT alanine aminotransferase, AST aspartate aminotransferase, CPK creatine phosphokinase, GGT gamma-glutamyltransferase

^aNo restriction on the number of prior chemotherapies

^bMaximum tolerated dose

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c Four patients had dose-limiting toxicities of low absolute neutrophil count and drug-related neutropenia and pyrexia

d Dose-limiting toxicity

e Dose-limiting toxicity in one patient

Table 3

Mean pharmacokinetic parameters of trabectedin (pharmacokinetic analysis set)

Parameters	Dose cohort Trabectedin (mg/m ²)/docetaxel (mg/m ²)									
	Unlimited prior therapy (mg/m ²)					Limited prior therapy (mg/m ²)				
	0.4/60 (n = 6)	0.6/60 (n = 9)	1.1/60 (n = 6)	1.3/60 (n = 2)	0.75/60 (n = 3)	0.9/60 (n = 2)	1.1/60 (n = 2)	1.3/60 (n = 7)	1.3/75 (n = 6)	
<i>T</i> _{max} (h)	1.98	2.53	NA	2.84	1.61	2.21	2.83	2.44 ^a	NA	
<i>C</i> _{max} (ng/mL)	1.54	2.4	NA	10.3	3.46	5.78	5.66	8.91 ^a	NA	
AUC _{last} (ng h/mL)	5.89	12	NA	59.4	23.1	31.5	32.7	49.4 ^a	NA	
AUC _∞ (ng h/mL)	6.64	14.9	NA	75.6	34.7 ^b	41.2	39	62.6	NA	
CL (L/h)	130	90.1	NA	30.4	41.7 ^b	40	54.3	40.8	NA	
<i>V</i> _{ss} (L)	832	2775	NA	3213	5737 ^b	1741	4011	2805	NA	
<i>t</i> _{1/2} (h)	14.7	62.6 ^c	92	111	160	64.7 ^d	70.4 ^d	90.3	130	

AUC area under plasma concentration–time curve, CL clearance, *C*_{max} peak plasma concentration, NA not assessable because of missing samples, *t*_{1/2} half-life, *T*_{max} time to *C*_{max}, *V*_{ss} volume of distribution at steady state

^a *n* = 8,

^b *n* = 2,

^c *n* = 12,

^d *n* = 3

Table 4

Best overall response

Response, n (%)	Dose cohort		Trabectedin (mg/m ²)/docetaxel (mg/m ²)									
	Unlimited prior therapy (mg/m ²)		Limited prior therapy (mg/m ²)									
	0.4/60 (n = 6)	0.6/60 (n = 12)	1.1/60 (n = 6)	1.3/60 (n = 2)	0.75/60 (n = 3)	0.9/60 (n = 3)	1.1/60 (n = 3)	1.3/60 (n = 8)	1.3/75 (n = 6)	Total (N = 49)		
Overall response rate	0	1	0	0	0	0	0	0	0	1 (2)		
Complete response	0	1	0	0	0	0	0	0	0	1 (2)		
Partial response	0	0	0	0	0	0	0	0	0	0		
Stable disease	3	5	5	1	2	1	1	7	5	30 (61)		
6 months	0	2	0	0	1	1	1	2	4	11 (22)		
Progressive disease	1	6	1	1	1	1	2	1	1	15 (31)		
Not evaluable	2 ^a	0	0	0	0	1 ^b	0	0	0	3 (6)		

^aTwo patients were terminated from the study because of toxicity after they received only one cycle of therapy

^bOne patient had clinical progression after one cycle of therapy without radiographic progression