CLINICAL TRIAL REPORT

Phase I trial of weekly trabectedin (ET-743) and gemcitabine in patients with advanced solid tumors

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Abstract

Purpose To determine the maximum tolerated dose (MTD) of trabectedin plus gemcitabine administered on a weekly schedule in patients with advanced solid tumors.

Methods Patients with ECOG performance status 0–1 and adequate organ function were enrolled. On days 1, 8, and 15 of a 28-day cycle, patients received gemcitabine (starting dose, 800 mg/m^2) followed by trabectedin (starting dose, 0.3 mg/m^2). Strict liver function test treatment criteria were employed to avoid hepatic toxicity seen in previous trabectedin studies. Plasma samples were collected during cycles 1 and 2 for pharmacokinetic analyses.

Results Fifteen patients received ≥1 dose, with a median of two treatment cycles (range 1–10). The most common drug-related toxicity was hepatic. Dose reductions were required for trabectedin in four (27%) patients and gemcitabine in six (40%) patients. Cycle delays/dose holds were required in 11 (73%) patients and doses above trabectedin 0.4 mg/m^2 and gemcitabine 1,000 mg/m^2, which is the recommended phase II dose, were not feasible. Seven patients maintained stable disease after two cycles. Gemcitabine and trabectedin pharmacokinetics were not altered substantially with concomitant administration.

Conclusions Given the lack of pharmacokinetic interaction and potential efficacy of trabectedin and gemcitabine combination therapy, further study is warranted with alternate schedules.

Keywords Dose-finding · Phase I · Gemcitabine · Pharmacokinetics · Trabectedin

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Introduction

Most advanced solid tumor malignancies remain incurable, and the search for new cancer therapeutics with novel mechanisms of action has recently extended to marine organisms. Trabectedin (YONDELIS®, ET-743; Johnson & Johnson Pharmaceutical Research & Development, L.L.C., Raritan, NJ, USA; PharmaMar S.A.U., Madrid, Spain) is a tetrahydroisoquinolone alkaloid derivative originally isolated from the marine ascidian *Ecteinascidia turbinata* (sea squirt) and now produced synthetically. Trabectedin has a complex mechanism of action, involving DNA binding [25, 27], interference with transcription factor binding [24], and activation of the transcription-coupled nucleotide excision repair (NER) system to create lethal single-strand breaks in DNA [4, 35]. The cytotoxicity of trabectedin has been demonstrated in several in vitro and preclinical studies involving a variety of cancer types [12, 14, 18, 29, 37].

In clinical trials, single-agent trabectedin in a variety of administration schedules has achieved clinical responses in patients with a variety of tumor types, including ovarian cancer, osteosarcoma, soft tissue sarcoma, and breast cancer [7, 8, 11, 16, 17, 21, 30, 39, 40]. Recent data suggest that single-agent trabectedin may become a standard of care in advanced pre-treated sarcomas, with clinical benefit observed in patients with liposarcoma and leiomyosarcoma

following failure of all conventional treatment options [26]. Moreover, trabectedin was approved in the European Union in September 2007 for treatment of patients with advanced soft tissue sarcoma. The most common side effects have included cytopenias, which have been dose limiting, as well as nonhematologic toxicities such as hepatotoxicity manifesting as elevated transaminases, nausea/vomiting, and malaise. Hepatotoxicity has been reversible, rarely lasting >7 days, and noncumulative in patients with strict eligibility criteria including limited increases of total bilirubin, alkaline phosphatase (ALP), and aspartate (AST) and alanine aminotransferase (ALT). The mechanism of the transient transaminitis, or more rare cholangitis, is not known. Experience in patients with compromised liver function is limited to date. Interestingly, liver toxicity has been ameliorated by premedication with steroids in animal models [5]; dexamethasone has been employed as an antiemetic premedication in some phase II studies [7], and dexamethasone co-treatment has been associated with a decreased incidence of severe trabectedin-associated toxicities [28]. Phase I and II studies with trabectedin have evaluated a number of treatment schedules, the most extensive being every 3 weeks given over 3 or 24 h. The results of preclinical studies of trabectedin administered in combination with other agents suggested that additive or synergistic effects may be achieved [22, 33, 34].
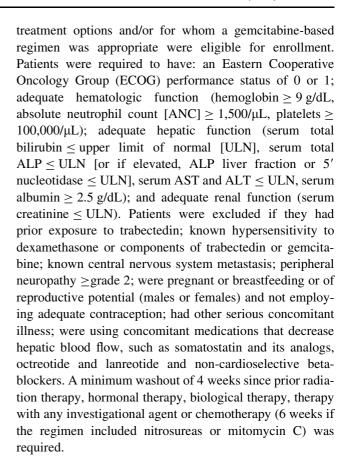
Gemcitabine (GEMZAR®, Eli Lilly and Company, Indianapolis, IN) is a nucleoside analog that is indicated for the treatment of: pancreatic cancer; non–small cell lung cancer (NSCLC), in combination with cisplatin; advanced ovarian cancer, in combination with carboplatin; and breast cancer, in combination with paclitaxel; and has shown promising efficacy either alone or combined with taxanes in patients with chemotherapy-resistant soft tissue sarcomas [13, 19, 20, 23]. Because trabectedin and gemcitabine act by different mechanisms, have activity against a variety of solid tumor types including soft tissue sarcomas [10], and are administered on weekly dosing schedules, it was of interest to study them in combination for the treatment of patients with advanced malignancies.

The primary objective of this study was to determine the maximum tolerated dose (MTD) of trabectedin administered in combination with gemcitabine once weekly for three consecutive weeks in a 4-week cycle. Secondary objectives included evaluating the safety and pharmacokinetics of the trabectedin/gemcitabine combination.

Methods

Patients

Patients ≥18 years of age with histologically confirmed advanced solid tumor malignancies refractory to standard treatment options and/or for whom a gemcitabine-based regimen was appropriate were eligible for enrollment. Patients were required to have: an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; adequate hematologic function (hemoglobin ≥ 9 g/dL, absolute neutrophil count [ANC] ≥ 1,500/μL, platelets ≥ 100,000/μL); adequate hepatic function (serum total bilirubin ≤ upper limit of normal [ULN], serum total ALP ≤ ULN [or if elevated, ALP liver fraction or 5′ nucleotidase ≤ ULN], serum AST and ALT ≤ ULN, serum albumin ≥ 2.5 g/dL); and adequate renal function (serum creatinine ≤ ULN). Patients were excluded if they had prior exposure to trabectedin; known hypersensitivity to dexamethasone or components of trabectedin or gemcitabine; known central nervous system metastasis; peripheral neuropathy ≥grade 2; were pregnant or breastfeeding or of reproductive potential (males or females) and not employing adequate contraception; had other serious concomitant illness; were using concomitant medications that decrease hepatic blood flow, such as somatostatin and its analogs, octreotide and lanreotide and non-cardioselective beta-blockers. A minimum washout of 4 weeks since prior radiation therapy, hormonal therapy, biological therapy, therapy with any investigational agent or chemotherapy (6 weeks if the regimen included nitrosureas or mitomycin C) was required.

Study design

This phase I, open-label, dose-finding combination study was conducted at a single site (Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD, USA). It included a screening visit a treatment phase, a treatment termination visit, and a follow-up phase of at least 30 days after treatment termination. The clinical protocol was approved by the Johns Hopkins Institutional Review Board, and all patients provided written informed consent prior to study drug administration.

Drug dosage and administration

Trabectedin and gemcitabine were administered by intravenous (IV) infusion on days 1, 8 and 15 of a 28-day cycle. Patients were premedicated with IV dexamethasone 10 mg prior to gemcitabine administration. Gemcitabine was given as a 30-min peripheral or central infusion, followed 30 min later by a 3-h central infusion of trabectedin. Planned dose levels were trabectedin 0.3, 0.4, 0.475, 0.535 and 0.58 mg/m^2 and gemcitabine 800 and 1,000 mg/m^2. A standard phase I "3 + 3" dose escalation design was used, with the recommended dose for phase II testing defined as the highest dose level at which no more than 1 of 6 patients experienced dose-limiting toxicity (DLT). No intrapatient dose escalation was

allowed. Use of colony-stimulating factor (CSF) according to institutional and American Society of Clinical Oncology (ASCO) guidelines was permitted after cycle 1.

Safety

Adverse events (AEs) were graded using the National Cancer Institute Common Toxicity Criteria (NCI-CTC), version 2.0. DLT was defined as any of the following during the first cycle: grade 4 neutropenia (ANC < 500/µL) for >5 days; febrile neutropenia (ANC < 500/µL with fever [body temperature $\geq$ 38.5°C] or sepsis); thrombocytopenia (platelets < 25,000/µL); any grade $\geq$3 nonhematologic toxicity (except nausea/vomiting and grade 3 transaminitis lasting <1 week); or delay of continuation of therapy >3 weeks. Dose reductions were not considered as DLTs.

Study drugs were administered if the following criteria for continuation of treatment were met: on day 1 of each cycle, ANC $\geq$ 1,500/µL, platelets $\geq$ 100,000/µL, total bilirubin $\leq$ ULN, and transaminases, creatine phosphokinase (CPK) and other nonhematologic drug-related effects < grade 2; on days 8 and 15 of each cycle, same as above, except ANC $\geq$ 1,000/µL and platelets $\geq$ 75,000/µL. If day 1 criteria were not met, the next dose of study drugs was delayed for 1 week and re-evaluated weekly; if day 8 or 15 criteria were not met, study drugs were not administered for that day. Missed day 8 or 15 doses were not substituted. A missed dose was designated a dose hold. A maximal cycle delay of 3 weeks was allowed for recovery from toxicity. If recovery took >3 weeks, the patient was discontinued from the protocol. Treatment continued until attaining unacceptable toxicity, disease progression or withdrawal of consent.

Dose reductions to the previous dose level for both agents were instituted for DLT in cycle 2 or later, as well as for total bilirubin > ULN at any time. No more than two dose reductions were allowed for each drug. The initial protocol included dose reductions for ALP > ULN and grade $\geq$ 3 ALT/AST elevation (patients did not receive study drug unless they had recovery to grade 1). Patients were to be discontinued from the study for DLT and if grade $\geq$ 3 ALT/AST elevations did not recover to grade 1 within 3 weeks. The protocol was subsequently amended (during dose level 1) so that dose reductions were not necessary for a grade 1 elevation of ALP nor transient (<1 week) grade 3 elevations of ALT/AST.

Assessments

AEs and toxicity were assessed weekly. Treatment responses were determined clinically and radiologically after every two cycles of therapy based on the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines [36].

Baseline evaluations were conducted within 14 days of study entry and included medical history, concurrent medications, vital signs, physical exam, urine pregnancy test (if applicable), electrocardiogram, complete blood count (CBC) with differential, and serum chemistry including albumin, ALP (liver fraction or 5′ nucleotidase if ALP > ULN), total bilirubin, ALT, AST, CPK and total protein. Radiologic evaluations were performed within 4 weeks of study entry. Vital signs were recorded on each treatment day, and CBCs and serum chemistries including liver function tests were performed weekly. Physical exams were repeated once per cycle. An off-study follow-up evaluation of toxicities and blood tests was performed.

Drug assay and pharmacokinetic analysis

Serial plasma samples for pharmacokinetic analyses were collected during cycles 1 and 2 at the following time points: immediately prior to treatment with gemcitabine, and at 20 min, 1, 1.5, 3, and 3 h; 50 min, 5, 6, and 9 h after the start of the gemcitabine infusion. The concentration of trabectedin was measured in plasma samples collected prior to dosing and at 30 min, 2, and 3 h, 50 min, 4, 5, 8, 11, 27, 51, and 168 h after the start of the trabectedin infusion. On cycle 1 days 8 and 15, and cycle 2 days 1, 8, and 15, samples were collected pre-dose, at 20 min (10 min prior to the end of the gemcitabine infusion), and 200 min (10 min prior to the end of the trabectedin infusion).

Plasma concentrations of trabectedin were determined with a validated liquid chromatography/mass spectrometry/ mass spectrometry (LC–MS/MS) method with a calibration range of 0.025–2.5 ng/mL. Gemcitabine and 2′-deoxy-2′,2′-difluorouridine (dFdU) plasma concentrations were quantified by a validated high performance liquid chromatography ultraviolet (HPLC–UV) method. The validated concentration range was 0.6–20 µg/mL and 1.35–90 µg/mL for gemcitabine and dFdU, respectively. For both assays, quality control samples spiked at three concentration levels in duplicate were used for batch acceptance criteria. At least four out of six quality control samples had to quantitate within 15% of nominal for a batch to be acceptable. All samples were analyzed at the bioanalytical laboratory of the Slotervaart hospital in Amsterdam, The Netherlands.

Pharmacokinetic parameters were to be estimated for trabectedin, gemcitabine, and dFdU using conventional noncompartmental methods, as implemented in WinNonlin, Version 5.1 (Pharsight).

Statistical considerations

All patients who received $\geq$1 dose of each study drug were included in the toxicity and efficacy analyses. For the pharmacokinetic analyses, parameters are presented as mean

values $\pm$ SD, and for all tests, the a priori cutoff for statistical significance was $P < 0.05$. Differences between pharmacokinetic parameters were compared by a paired Student's t test. Statistical calculations were performed with the Statistical Analysis System, Version 8.2 (SAS Institute, Cary, NC, USA).

Results

Patient population

This trial was conducted between March 2003 and April 2005. Fifteen patients received ≥ 1 dose of study medication and were included in the analysis population. The majority of patients in the analysis population had sarcoma ($n = 5$) or NSCLC ($n = 3$), and 67% had an ECOG performance status of 1. Relevant pretreatment characteristics of the analysis population are summarized in Table 1. Over half (10/15; 67%) of the patients terminated the study by the end of cycle 2; for the five who did not, terminations were at the end of cycles 3 ($n = 1$), 4 ($n = 1$), 6 ($n = 2$), and 10 ($n = 1$). Reasons for termination were disease progression ($n = 8$), AE [$n = 5$; 2 of which were considered possibly drug related (1 patient with nausea and peripheral edema and 1 with nausea and dehydration)], death ($n = 1$, a suicide deemed to be unrelated), and patient choice ($n = 1$).

Safety

The study was terminated due to an unacceptable frequency of adjustments to the weekly dosing schedule for hepatic toxicity. Only dose levels 1, 2, and 3 were evaluated. In all, 45 4-week cycles were administered. The median number of cycles was 2 (range 1–10), with median cumulative doses of trabectedin 1.79 mg/m^2 and gemcitabine 4,592 mg/m^2. Across the three dose cohorts, median cumulative dose intensity was 0.802 mg/m^2/4 weeks for trabectedin and 1841.02 mg/m^2/4 weeks for gemcitabine. Median relative dose intensity (actual/planned dose intensity) over all reported cycles ranged from 70% trabectedin and 67% gemcitabine at dose level 3 to 77 and 76%, respectively, at dose level 1. Dose reductions were required for trabectedin in four (27%) patients (all in cycle 2, with one patient requiring a second dose reduction in cycle 3) and for gemcitabine in six (40%) patients (five in cycle 2 and one in cycle 3). Cycle delays and dose holds due to AEs were required for 11 (73%) patients, predominantly within the first two cycles, and were most often related to liver toxicity.

No DLTs were seen in any of the cohorts (Table 2). Dose levels 1 and 3 were expanded to six patients due to cycle delays or dose reductions required in the first three patients. Since four of six patients at dose level 3 required

Table 1 Demographic and clinical characteristics of the analysis population

	Total ($N = 15$)
Sex	
Female	11
Male	4
Age	
18 to 65	11
> 65	4
Median	61.0
Range	26–78
ECOG performance status	
0	5
1	10
Histology	
Sarcoma	5
Leiomyosarcoma	3
Other	2
NSCLC	3
Colorectal	2
Renal	2
Anal	1
Salivary gland	1
Endometrial	1
Prior treatment	
Chemotherapy	
1 regimen	2
2 regimens	4
>2 regimens	8
Radiotherapy	4
Hormone therapy	3

ECOG Eastern Cooperative Oncology Group, *NSCLC* non-small cell lung cancer

dose holds/cycle delays (two required dose reductions), no further dose escalation was performed. Of the 25 total drug-related dose holds or reductions, 17 (68%) were due to elevated AST/ALT, 2 (8%) to elevated ALP, 4 (16%) to thrombocytopenia, and 1 (4%) each to congestive heart failure and pulmonary edema. The most frequently reported grade 3/4 drug-related AE was ALT increase (33%) (Table 3). Although a high frequency of hepatic toxicity was observed, no patient had cholestasis or liver failure. The most common drug-related AEs of any severity were ALT increase (80%), fatigue (73%), nausea (67%), AST increase (60%), vomiting (40%), neutropenia (33%) and anorexia (27%).

Efficacy

There were no complete or partial responses to therapy in this heavily pretreated patient population. Seven (47%) patients maintained stable disease for a duration of

Table 2 Dose cohorts analyzed and incidence of DLT

Dose level	Trabectedin (mg/m^2)	Gemcitabine (mg/m^2)	No. of patients	No. of cycles	No. of DLTs	No. of patients with dose reductions[a]		No. of patients with cycle delays or dose holds
						Trabectedin	Gemcitabine	
1	0.3	800	6	19	0	3	3	1
2	0.4	800	3	15	0	1	1	2
3	0.4	1,000	6	11	0	0	2	4

DLTs dose-limiting toxicities

[a] Although dose reductions were to involve both drugs, a few deviations from this procedure occurred in which only one of the two drugs was reduced

Table 3 Grade 3/4 drug-related adverse events

	Dose level 1 0.3/800 mg/m^2 trabectedin/gemcitabine ($n = 6$)	Dose level 2 0.4/800 mg/m^2 trabectedin/gemcitabine ($n = 3$)	Dose level 3 0.4/1000 mg/m^2 trabectedin/gemcitabine ($n = 6$)	Total [$N = 15$ (%)]
Total with grade 3/4 AE	3	2	3	8 (53)
ALT increased	1	2	2	5 (33)
Vomiting	2	1	1	4 (27)
Neutropenia	1	2	1	4 (27)
AST increased	1	1	1	3 (20)
Weight decreased	1	0	0	1 (7)
Cardiac failure	1	0	0	1 (7)
Acute prerenal failure	1	0	0	1 (7)
Leukopenia	0	0	1	1 (7)
Thrombocytopenia	0	0	1	1 (7)

AE adverse event, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase

Note: AEs reported at any time from first treatment dose to within 30 days of last treatment dose are included. Incidence is based on the number of patients. Drug-related means possible, probable, or very likely. Toxicity grade: NCI Common Toxicity Criteria, version 2.0

56–226 days: NSCLC ($n = 3$); colorectal cancer ($n = 2$); renal cancer and sarcoma ($n = 1$ each). Two of these seven patients maintained stable disease for at least 6 months.

Pharmacokinetic analysis

The pharmacokinetics of trabectedin in the present study were similar to those observed previously. Maximum plasma concentrations of trabectedin were typically observed between 2 and 3 h after the start of the 3-h infusion. Upon cessation of the infusion, the concentrations declined in a multiexponential manner. Trabectedin exhibited a high plasma clearance and relatively large distribution volume across the dose groups (Table 4). The mean terminal half-life of trabectedin in plasma ranged from 32.7 to 43.4 h. Interpatient variability in the plasma C_{max} and AUC_∞ values of trabectedin for the three treatment groups ranged from 14.8 to 118% (expressed as coefficient of variation). Plasma concentrations of gemcitabine (and dFdU) were not reported for dose level 1, because the plasma

samples were inadvertently collected in tubes that did not contain stabilizer, and were thus deemed unreliable. For gemcitabine, most samples collected from the second and third dose levels at 1 h after the end of infusion or later contained concentrations of gemcitabine that were below the limits of detection; therefore, plasma pharmacokinetic parameters of gemcitabine could not be calculated. Individual gemcitabine concentrations at 20 min after the start of the first dose in cycle 1 ranged from 2.88 to 20.5 μg/mL and from 7.03 to 21.9 μg/mL when gemcitabine 800 and 1,000 mg/m^2, respectively, was coadministered with trabectedin 0.4 mg/m^2. Maximum plasma concentrations of dFdU were typically observed at approximately 0.3–1 h after the start of the 30-min infusion (Table 4). Upon cessation of the infusion, the concentrations declined in a monoexponential manner. The mean terminal half-life values of dFdU in plasma were 6.82 and 4.79 h, respectively. Interpatient variability in the plasma C_{max} and AUC_∞ values of dFdU ranged from 11.4 to 61.3% (expressed as coefficient of variation).

Table 4 Mean (SD) pharmacokinetic parameters of trabectedin and dFdU in patients coadministered single doses of trabectedin and gemcitabine

Parameter	Trabectedin			dFdU		
	Dose level 1 $(n = 6)$	Dose level 2 $(n = 3)$	Dose level 3 $(n = 6)$	Dose level 1 $(n = 6)$	Dose level 2 $(n = 3)$	Dose level 3 $(n = 6)$
t_{max} (h)[a]	1.99 (0.5–3.00)	2.80 (2.00–2.83)	2.01 (2.00–2.80)	NA	0.98 (0.28–1.03)	0.97 (0.33–1.07)
C_{max} (ng/mL)[b]	1.96 (1.14)	1.79 (0.375)	3.35 (1.44)	NA	17.0 (10.4)	38.7 (4.4)
AUC_{∞} (ng h/mL)[c]	13 (15.3)	9.82 (1.46)	15.8 (6.61)	NA	119 (67.9)	225 (33.5)
$t_{\frac{1}{2}}$ (h)[d]	35.8 (51.9)	43.4 (36.1)	32.7 (14.1)	NA	6.82 (0.278)	4.79 (0.829)
CL (L/h)	73.0 (45.3)	79.6 (4.0)	49.9 (19.4)	NA	NR	NR
V_{ss} (L)	722 (591)	2527 (2774)	1089 (770)	NA	NR	NR

AUC area under the plasma concentration–time curve, C_{max} maximum plasma concentration, *CL* systemic clearance, *dFdU* 2′-deoxy-2′,2′-difluorouridine, *NA* not applicable, *NR* not reported, *SD* standard deviation, t_{max} time to C_{max}, $t_{1/2}$ terminal half-life, V_{ss} apparent volume of distribution at steady state

[a] Median (range)

[b] For dFdU, μg/mL

[c] For dFdU, μg h/mL

[d] For dFdU, $t_{1/2\lambda}$(h)

Discussion

In this phase I study, the combination of trabectedin and gemcitabine was evaluated to determine the MTD in patients with advanced malignancies. Due to hepatic toxicity observed in earlier trabectedin studies, strict liver function test criteria for treatment were implemented in this trial. Although no DLTs were observed in cycle 1 at any of the dose levels explored, a high frequency of dose adjustments (cycle delays, dose holds and dose reductions) in the weekly schedule precluded realistic determination of the MTD. The protocol was amended during exploration of the first dose level to liberalize the liver function test criteria, but further changes were not feasible due to safety concerns.

The pharmacokinetic parameters of trabectedin and gemcitabine were similar to those reported previously for single-agent studies of both drugs. However, due to the relatively small number of patients with available data, definitive conclusions regarding drug interactions could not be made. Efficacy of the trabectedin/gemcitabine combination, although not a primary endpoint of the study, was promising in that almost half (47%) of the patients analyzed maintained stable disease after two cycles.

In addition to its efficacy in approved combinations with cisplatin, carboplatin and paclitaxel, gemcitabine has shown activity and tolerability in phase I trials when given in combination with topotecan [32] and docetaxel [31]. Gemcitabine has also shown activity in phase II trials as a single agent and in combination with docetaxel in patients with advanced sarcomas, particularly leiomyosarcoma [13, 19, 20, 23]. Trabectedin has demonstrated efficacy as a single agent in patients with sarcoma [7, 8, 17, 26, 39] and has

shown promise in phase I trials against a variety of malignancies when given in combination with capecitabine [9], doxorubicin [1] or pegylated liposomal doxorubicin [3], but nearly all previous studies have used an every-3-week schedule. Although dose level 3 contained an approved gemcitabine dose of 1,000 mg/m² per week, the highest dose of trabectedin evaluated in combination with this gemcitabine dose was 0.4 mg/m² per week. This is slightly less than a third of the recommended dose of single-agent trabectedin as a 3-h infusion in 3-week cycles (1.3 mg/m²) [11, 30]. A single-agent study of trabectedin using a weekly schedule similar to this trial has been presented in abstract form, with a recommended dose of 0.610 mg/m² [2]. In that study, grade ≥3 AST/ALT elevations and grade ≥3 neutropenia were seen at all dose levels above 0.610 and 0.580 mg/m², respectively. It is possible that combination weekly schedules of trabectedin will be problematic due to hepatotoxicity, albeit transient and reversible, which prevents regular dosing. Moreover, the toxicity profiles of trabectedin and gemcitabine overlap, in particular with regard to myelosuppression and increases in transaminases. Trabectedin has also been tested in a daily ×5 schedule every 3 weeks [38], where the MTD was 0.325 mg/m² due to cytopenias. Interestingly, in that study hepatotoxicity was common in doses >0.216 mg/m², but this was not dose-limiting. A recently published pharmacokinetic/pharmacodynamic model of trabectidin using data from 711 patients in 14 studies with trabectidin confirmed the liver-protective effects of dexamethasone premedication, and there were no major differences between 3- and 24-h infusions [6].

Future studies of this combination could involve exploration of alterative dosing schedules, such as trabectedin day 1 and gemcitabine days 1 and 8 every 21 days. It

should be noted that gemcitabine 2,000 mg/m^2 has been dosed every 3 weeks in a combination trial with cisplatin for NSCLC [15], so an every-21-day schedule could be considered, but cytopenias, hepatotoxicity and other side effects may be prohibitive.

In conclusion, this study did not identify a DLT-defined recommended phase II dose, but rather a weekly feasible dose of trabectedin in combination with gemcitabine. The results obtained suggest a potentially manageable toxicity profile and no evidence of a significant pharmacokinetic interaction with the combination of trabectedin and gemcitabine for the treatment of advanced malignancies. This combination is particularly appealing for phase II testing in patients with soft tissue sarcomas in whom the two drugs as single agents have clinical activity. However, it must be noted that the dose of trabectedin that is tolerable is lower than that used as a single agent. Further study using different schedules may be warranted. This could include the 3-weekly dosing that is shown to be effective in soft tissue sarcoma.

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