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CLINICAL TRIAL REPORT

# Phase I study of TZT-1027, a novel synthetic dolastatin 10 derivative, for the treatment of patients with non-small cell lung cancer

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**Abstract**
*Purpose* The purpose of this phase I study was to evaluate the maximum-tolerated dose (MTD), dose-limiting toxicity (DLT), the recommended dose for phase II study, pharmacokinetics, and antitumor activity of TZT-1027 (soblidotin) in patients with non-small cell lung cancer (NSCLC) when administered every 3–4 weeks.
*Methods* Eligible patients had the following characteristics: stage III/b or IV NSCLC that was refractory to conventional therapy or for which no standard therapy was available; Eastern Cooperative Oncology Group (ECOG) performance status (PS) $\leq$2; adequate organ function; and age $\geq$20 and <75 years. The patients were administered TZT-1027 in escalating doses from 0.5 to 5.6 mg/m$^2$. Pharmacokinetic samples were collected during each treatment course.
*Results* Forty-nine patients were enrolled. Three patients had DLTs, including neutropenia, neutropenia complicated by fever, myalgia, and neuropathic pain. The common toxicities included constipation, anorexia, alopecia, nausea, leukopenia, and neutropenia. One complete response and three partial responses were observed. The pharmacokinetic parameters (AUC and $C_{max}$) of TZT-1027 tended to increase linearly with dose.
*Conclusions* DLTs included neutropenia, neutropenia complicated by fever, myalgia, and neuropathic pain. The MTD was 4.8 mg/m$^2$. The recommended phase II study dose of TZT-1027 is 4.8 mg/m$^2$ administered every 3–4 weeks.

**Keywords** Dolastatin · Phase I study · Non-small cell lung cancer · TZT-1027

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## Introduction

The first cytotoxic drug that was derived from material obtained from the ocean was the synthetic nucleotide analogue cytarabine. This marine compound is frequently used in hematological proliferation disorders. Dolastatin 10 was isolated in 1987 from the Indian Ocean sea hare, *Dolabella auricularia* [18]. TZT-1027 ($N^2$-(*N*,*N*-dimethyl-L-valyl)-*N*-[(1*S*,2*R*)-2-methoxy-4-[(2*S*)-2-[(1*R*, 2*R*)-1-methoxy-2-methyl-3-oxo-3-[(2-phenylethyl)amino]propyl]-1-pyrrolidinyl]-1-[(*S*)-1-methylpropyl]-4-oxobutyl]-*N*-methyl-L-valinamide) is a newly synthesized dolastatin 10 derivative [12]. The chemical structure of TZT-1027 is shown in Fig. 1. TZT-1027 inhibits the polymerization of microtubule proteins by binding to tubulin. TZT-1027 appears to have two binding sites on tubulin, a high-affinity site and a low-affinity site, whereas vinblastine has only one binding site. Although the binding sites of TZT-1027 and vinblastine are not completely identical, TZT-1027 can interact with vinblastine when binding to tubulin [14]. Compared to other antitumor agents, TZT-1027 has the highest cytotoxic and apoptosis-inducing effects against a wide variety of human cancer cells. TZT-1027 can arrest cells at the G2/M phase and then induce apoptosis [26]. The antivascular activity of TZT-1027 is stronger than that of vincristine or

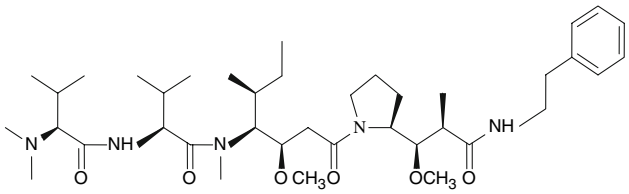

**Fig. 1** Chemical structure of TZT-1027

AC-7700, a combretastatin A-4 derivative [17]. TZT-1027 exerts its antitumor activity through direct cytotoxicity and selective blockade of tumor blood flow [4, 13, 17, 26, 27].

TZT-1027 has been shown to be active against P388 leukemia, Colon 26 adenocarcinoma, B16 melanoma, and M5076 sarcoma implanted in mice. The antitumor activity of TZT-1027 against these tumors was superior or comparable to dolastatin 10, cisplatin, vincristine, 5-fluorouracil, and E7010. TZT-1027 was also effective against human xenograft LX-1 lung and MX-1 breast carcinomas [7]. TZT-1027 exhibited potent antitumor activities in an in vivo model in which vincristine and docetaxel failed to show effectiveness [25].

In animals, TZT-1027 has no relevant neurotoxic potential compared to other antimicrotubule agents such as paclitaxel or vincristine, which induce peripheral neurotoxicity [16]. However, cardiotoxicity has been observed in rats and monkeys treated with TZT-1027.

Pharmacokinetic studies have shown that there was no accumulation of TZT-1027 in the plasma of rats administered repeated doses. TZT-1027 is bound predominantly to alpha1-acid glycoprotein (α1-AGP). CYP3A4 is the major P450 hepatic isoform responsible for the metabolism of TZT-1027. The primary route of excretion is fecal.

In Japan, the first single-dose, phase I study involving 23 patients was conducted using doses ranging from 0.15 to 1.35 mg/m$^2$. The major hematological toxicity was neutropenia (all patients ≤ grade 3). Non-hematological toxicities included anorexia, malaise, nausea, and alopecia. The maximum tolerated dose (MTD) was not determined. One patient with sarcoma had a partial response. Three patients with NSCLC had a >50% tumor reduction, though these patients did not achieve a partial response, since the duration of their response was short [15]. Subsequently, 40 Japanese patients were enrolled in a repeated-dose, phase I study in which TZT-1027 was administered on days 1, 8, and 15, at doses ranging from 0.3 to 2.1 mg/m$^2$. The dose-limiting toxicity (DLT) was neutropenia, and the MTD was determined to be less than 2.1 mg/m$^2$. Non-hematological toxicities included malaise, nausea, and alopecia. A partial response was observed in one patient with thymoma [28].

The results of the single-dose, phase I study suggested that TZT-1027 might have efficacy in NSCLC patients. The repeated-dose, phase I study (on days 1, 8, and 15) was ongoing at the time the present study began. Therefore, the present phase I study was done in NSCLC patients administered TZT-1027 every 3–4 weeks.

The primary objective of the present study was to determine the MTD, assess the DLTs, determine the recommended dose for phase II study, and evaluate the pharmacokinetics of TZT-1027 administered intravenously over 1 h every 3–4 weeks in NSCLC patients. The secondary objective was to evaluate the antitumor activity of TZT-1027.

## Patients and methods

### Study design

This open-label, dose-escalating, phase I study enrolled patients with NSCLC. A starting dose of 0.5 mg/m$^2$ was chosen based on the Japanese, single-dose, phase I study; this dose was the highest dose that had no effect on hematological function. Patients who failed to complete the first course for reasons other than DLT were replaced. Up to three courses of TZT-1027 were administered every 3–4 weeks; patients could receive up to three courses. At the end of the third course, two additional courses were administered to patients who showed efficacy without any drug-related serious adverse events. The protocol, investigator's brochure, and patient informed consent form were approved by the central and local ethics committee in Hungary. The study was conducted according to the Declaration of Helsinki and the ICH GCP guidelines.

### Patient eligibility

Eligible patients had a histologically or cytologically confirmed diagnosis of stage III/b or IV NSCLC that was refractory to conventional therapy or for which no standard therapy was available. Inclusion criteria also included the following: age ≥20 and <75 years; Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤2; estimated life expectancy ≥12 weeks at the time of entry; no prior chemotherapy or radiotherapy within 4 weeks; dimensionally measurable lung disease; adequate hematopoietic function (hemoglobin ≥6 mmol/L, white blood cell (WBC) count ≥4,000/mm$^3$, platelet count ≥100,000/mm$^3$); adequate hepatic function (bilirubin ≤ 24 μmol/L, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ rimes the upper limit of normal); adequate renal function (serum creatinine ≤ lower limit of normal); normal cardiac function; and a left ventricular ejection fraction (LVEF) measured by echocardiography or multi-gated acquisition scan (MUGA) >50%. All patients signed a written informed consent form. Exclusion criteria included the

presence of brain metastasis, history of a severe cardiac disorder (including severe atrial or ventricular arrhythmia or heart block), or pregnancy.

### Treatment and dose escalation

TZT-1027 was administered as an 1-h intravenous infusion every 3–4 weeks. The starting dose was 0.5 mg/m$^2$, and the dose was increased up to a dose of 2.4 mg/m$^2$ according to the modified Fibonacci method. Further dose-escalation was done with the agreement of the investigator and the sponsor, based on the toxicity at the prior dose level. At least three patients were entered at each dose level. If one of three patients experienced DLT during the first course, three additional patients were entered at that dose. The MTD was defined as one dose level below the dose that induced DLTs in at least two of six patients. DLT was defined as: grade 4 neutropenia lasting ≥5 days; neutropenia with fever (≥38.5°C); grade 4 thrombocytopenia; grade 3 or 4 vomiting with maximum supportive care; grade 3 or 4 non-hematological toxicity excluding nausea and vomiting; or inability to start a second course up to day 29. Treatment was resumed when all of the following criteria were met: WBC ≥ 3,000/mm$^3$, absolute neutrophil count (ANC) ≥1,500/mm$^3$, platelet count ≥100,000/mm$^3$, and non-hematological toxicities recovered to grade 0 or 1. Toxicities were evaluated according to the National Cancer Institute Common Toxicity Criteria, version 2.0.

### Drug administration

TZT-1027 was supplied by Teikoku Hormone Mfg. Co., Ltd. (now ASKA Pharmaceutical Co., Ltd) as a clear colorless aqueous solution in glass vials that were stored at room temperature. The required dose of TZT-1027 was diluted in 250 mL of 0.9% saline, and then administered over 1 h as an intravenous infusion. The actual dose was based on the body surface area that was calculated using the height and body weight before each course.

### Treatment assessment

A baseline assessment was done within 14 days prior to TZT-1027 treatment and included a medical history, physical examination, vital signs, concomitant medication, blood counts, biochemistry, alpha1-acid glycoprotein (α1-AGP), and urinalysis. Holter ECG monitoring was done on the day of each treatment. The LVEF was determined by MUGA scan before TZT-1027 administration and after the second and third courses. To assess the tumor, chest X-rays were taken before TZT-1027 administration and after each course, and computed tomography (CT) was done before TZT-1027 administration and after the second and third courses according to World Health Organization criteria [11]. In those patients who received two additional courses, the tumor was assessed on CT after the fourth and fifth courses. During treatment courses, physical examination, toxicity assessment, blood counts, biochemistry, and urinalysis were performed weekly.

### Pharmacokinetic sampling and assay

The pharmacokinetics was evaluated on the day of each treatment. Blood samples were collected before TZT-1027 was administered, at the end of the infusion, and 3, 6, and 24 h after infusion. Blood samples were centrifuged at 3,000 rpm for 10 min at 4°C. The separated plasma was frozen at −18°C or below until the time of analyses. The specimens were stored and shipped on dry ice to the central laboratory (Pharmacokinetic Research Department, Teikoku Hormone Mfg. Co., Ltd, Japan) for further analysis. Plasma concentrations were determined using the liquid chromatography mass spectrometry method.

### Pharmacokinetic and pharmacodynamic analyses

The following pharmacokinetic parameters were evaluated by non-compartmental analysis: area under the curve (AUC), maximum concentration ($C_{max}$), half-life ($T_{1/2}$), mean residence time (MRT), and total clearance ($Cl_{tot}$). The plasma α1-AGP level before TZT-1027 administration was measured. Pharmacokinetic variables are presented as the mean ± SD. The correlations between pharmacokinetic parameters (AUC or $C_{max}$) and dose, as well as between the plasma α1-AGP level and $Cl_{tot}$, were assessed. Correlations between the decrease in ANC from baseline (%) and pharmacokinetic parameters (AUC or $C_{max}$) were explored.

## Results

### Patient characteristics

The demographic characteristics of the patients are shown in Table 1. Forty-nine patients (40 males and 9 females) with a median age of 57 years were enrolled in this study. The most frequent histological diagnosis was adenocarcinoma. Forty-five patients were pretreated with a minimum of one chemotherapy regimen. All patients were assessed for safety. Pharmacokinetics and pharmacodynamics were assessed in 47 patients. Antitumor activity was assessed in 39 patients. The major reason that the patients could not be assessed for efficacy was the premature termination of study drug administration. As shown in Table 2, 12 different doses of TZT-1027, ranging from 0.5 to 5.6 mg/m$^2$, were administered. Three to six patients were treated at

**Table 1** Demographic characteristics

| Characteristics | Number of patients |
|---|---|
| Number of patients | 49 |
| Age, years; median (range) | 57 (31–73) |
| Gender | |
| Male | 40 |
| Female | 9 |
| Performance status (ECOG) | |
| 0 | 30 |
| 1 | 19 |
| Pretreatments | |
| Surgery | 23 |
| Radiotherapy | 27 |
| Chemotherapy | 45 |
| Histology | |
| Adenocarcinoma | 27 |
| Squamous | 15 |
| Large cell | 1 |
| Not specified | 6 |

**Table 2** Number of treatment courses

| Dose ($mg/m^2$) | Number of patients | Number of courses |
|---|---|---|
| 0.50 | 3 | 6 |
| 0.75 | 4 | 10 |
| 1.05 | 3 | 6 |
| 1.35 | 6 | 14 |
| 1.80 | 6 | 15 |
| 2.40 | 4 | 9 |
| 2.80 | 3 | 11 |
| 3.20 | 3 | 11 |
| 3.60 | 5 | 8 |
| 4.20 | 3 | 7 |
| 4.80 | 7 | 20 |
| 5.60 | 2 | 2 |
| Total | 49 | 119 |

each dose. A total of 119 treatment courses were administered. The median number of treatment courses per patient was three (range, 1–5). Twenty-four patients completed the study until the end of the third course, eleven patients completed the second course, and four patients completed the first course. Ten patients terminated the study prematurely; seven patients during the first course, two patients during the second course, and one patient during the third course. The reasons for premature discontinuation were: death (6 patients); protocol violation (1 patient); non-tolerable adverse event (1 patient); patient's request (1 patient); and lost to follow-up (1 patient).

### Dose-limiting toxicity

One patient experienced DLT at 1.8 $mg/m^2$; this 67-year-old male had squamous cell carcinoma and developed grade 4 neutropenia on day 6. Three additional patients were enrolled at that dose, and no further DLT was observed. Two patients received TZT-1027 treatment at 5.6 $mg/m^2$. DLT was observed in both patients. One patient, a 73-year-old male with squamous cell carcinoma, developed grade 3 myalgia and neuropathic pain on day 4. This patient died on day 7 due to acute myocardial infarction, which was unrelated to TZT-1027. Another patient, a 73-year-old male with adenocarcinoma, developed grade 4 neutropenia complicated by fever of 39.5°C on day 4. This patient died of bronchopneumonia on day 8, which was unrelated to TZT-1027. To confirm the MTD, three additional patients were treated at 4.8 $mg/m^2$; no DLTs were observed.

### Hematological toxicity

The hematological toxicities occurring during all courses are summarized in Table 3. The most common hematological toxicities were neutropenia and leukopenia; 13 patients had neutropenia and leukopenia. Grade 3 or 4 neutropenia was observed at doses $\geq$1.8 $mg/m^2$, and 2 of these 13 patients had a DLT. Five patients developed thrombocytopenia, and two patients developed anemia.

### Non-hematological toxicity

Table 4 shows drug-related, non-hematological toxicities occurring during all courses. The most frequent toxicities were constipation, anorexia, alopecia, and nausea. Drug-related adverse events were particularly more frequent in patients administered doses of $\geq$4.2 $mg/m^2$. Five patients had myalgia at doses $\geq$4.8 $mg/m^2$; one of them had DLT at 5.6 $mg/m^2$. One patient developed DLT 4 days after the first dose (grade 3 neuropathic pain) at 5.6 $mg/m^2$. Four patients had an injection site reaction; all of these events were grade 1 or 2. Cardiac disorders, such as grade 1 sinus tachycardia and grade 1 ventricular bigeminy, were observed. One patient treated with 1.35 $mg/m^2$ developed grade 1 sinus tachycardia during the study period, and another developed grade 1 ventricular bigeminy (couplets on the Holter ECG during the third TZT-1027 infusion) at the same dose. In 69% of patients, LVEF was assessed, usually at the end of the second treatment course. No patients had the LVEF decrease $\geq$20%, and there were no adverse events related to the LVEF decrease.

### Pharmacokinetics and pharmacodynamics

The pharmacokinetics of TZT-1027 was assessed on day 1 of each treatment course. Thirty-eight patients were

**Table 3** Hematological toxicities during all courses

| Dose ($mg/m^2$) | Number of patients | Neutropenia grade | | | | Leukopenia grade | | | | Thrombocytopenia grade | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 1 | 2 | 3 | 4 | 1 | 2 | 3 | 4 | 1 | 2 | 3 | 4 |
| 0.50 | 3 | | | | | | | | | | | | |
| 0.75 | 4 | | | | | | | | | | | | |
| 1.05 | 3 | | | | | | | | | | | | |
| 1.35 | 6 | | | | | | | | | | | | |
| 1.80 | 6 | | 1 | | 1 | | 1 | 1 | | 1 | | | |
| 2.40 | 4 | | | | 1 | | | | 1 | | | | |
| 2.80 | 3 | | | | | | | | | | | | |
| 3.20 | 3 | | | | | | | | | | | | |
| 3.60 | 5 | | | 1 | | | | 1 | | 1 | | | |
| 4.20 | 3 | 1 | | 1 | | | 2 | | | 1 | | | |
| 4.80 | 7 | | | 1 | 4 | | 1 | 3 | 1 | | | 1 | |
| 5.60 | 2 | | | | 2 | | | | 2 | | | 1 | |
| Total | 49 | 1 | 1 | 3 | 8 | | 4 | 5 | 4 | 3 | | 2 | |

**Table 4** Non-hematological toxicities during all courses drug-related adverse events (number of patients, 49)

| Adverse events | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|
| Constipation | 10 | 8 | | |
| Anorexia | 11 | 6 | | |
| Alopecia | 2 | 11 | | |
| Nausea | 3 | 3 | | |
| Myalgia | 2 | 2 | 1 | |
| Injection site reaction | 3 | 1 | | |
| Stomatitis | 3 | | | |
| Vomiting | 1 | 2 | | |
| Fatigue | 1 | 2 | | |
| Abdominal pain | 1 | | 1 | |
| Neuropathic pain | | | 1 | |
| Hypokalaemia | | | 1 | |
| Dyspnoea | | 1 | | |
| Hyperglycaemia | | 1 | | |
| Injection site pain | | 1 | | |
| Arthralgia | 1 | | | |
| Sinus tachycardia | 1 | | | |
| Ventricular bigeminy | 1 | | | |
| Visual disturbance | 1 | | | |
| Hyperaemia | 1 | | | |
| Flatulence | 1 | | | |

assessed on day 1 of the second treatment course, and 26 patients were assessed on day 1 of the third treatment course. The pharmacokinetic parameters determined during the first treatment course are shown in Table 5. The maximum plasma TZT-1027 concentration occurred at the end of the 1-h infusion. The plasma concentrations during the second and third treatment courses were almost the same as those during the first treatment course. Accumulation was not observed during the second and third treatment courses. The AUC and $C_{max}$ of TZT-1027 tended to increase linearly with dose. The correlations between pharmacokinetics (AUC and $C_{max}$) and hematological toxicity (ANC decrease % from baseline) showed that ANC tended to decrease as AUC and $C_{max}$ increased ($r = 0.56$ and 0.52, respectively). Figure 2 shows that $Cl_{tot}$ tended to decrease as the plasma α1-AGP level increased ($r = -0.48$).

### Antitumor activity

One patient achieved a complete response, and three patients had a partial response. A 69-year-old male with squamous cell carcinoma had a complete response at 2.8 $mg/m^2$; the duration of the complete response was confirmed to be >26 months. A 46-year-old female with adenosquamous carcinoma had a partial response at 3.2 $mg/m^2$; the partial response lasted for 61 days, at which time new bone metastasis appeared. A 61-year-old male with anaplastic carcinoma had a partial response at 4.8 $mg/m^2$; the length of response was 63 days. A 52-year-old male with adenocarcinoma had a partial response at 4.8 $mg/m^2$; disease progression was observed after 9 months. Furthermore, 20 patients had stable disease, and 15 patients had progressive disease.

## Discussion

Dolastatins with potent antitumor activity were isolated from *Dolabella auricularia* during the search for new physiologically active substances present in marine organisms. Subsequently, the research has been focused on dolastatin 10, which had the most potent antitumor activity among the dolastatins. Two phase I studies of dolastatin 10 administered

**Table 5** Pharmacokinetic parameters of TZT-1027 on day 1 of the first treatment course

| Dose ($mg/m^2$) | Number of patients | $C_{max}$ (ng/mL) Mean (SD) | $AUC_{0-t}$ (ng h/mL) Mean (SD) | $T_{1/2}$ (h) Mean (SD) | MRT (h) Mean (SD) | $Cl_{tot}$ ($L/h/m^2$) Mean (SD) |
|---|---|---|---|---|---|---|
| 0.50 | 3 | 51.26 (10.28) | 135.24 (33.97) | 2.69 (0.49) | 2.72 (0.31) | 3.56 (0.97) |
| 0.75 | 3 | 84.13 (26.04) | 297.77 (94.24) | 6.11 (1.96) | 5.06 (1.91) | 2.59 (0.82) |
| 1.05 | 3 | 128.98 (33.89) | 443.97 (141.91) | 5.44 (0.46) | 4.16 (0.59) | 2.52 (0.99) |
| 1.35 | 6 | 154.87 (59.94) | 515.76 (239.60) | 5.41 (1.33) | 4.08 (1.12) | 3.02 (1.33) |
| 1.80 | 6 | 149.22 (42.91) | 507.29 (138.20) | 6.46 (1.23) | 4.99 (1.46) | 3.66 (1.14) |
| 2.40 | 4 | 265.36 (62.35) | 873.63 (129.87) | 5.59 (0.47) | 4.16 (0.99) | 2.73 (0.43) |
| 2.80 | 3 | 121.48 (37.80) | 568.67 (139.90) | 5.44 (0.23) | 5.24 (1.14) | 4.96 (1.08) |
| 3.20 | 3 | 219.01 (79.47) | 856.56 (226.35) | 6.92 (1.07) | 5.74 (0.64) | 3.70 (0.89) |
| 3.60 | 5 | 306.91 (161.71) | 1157.81 (754.09) | 6.17 (1.51) | 5.05 (1.62) | 4.41 (3.42) |
| 4.20 | 3 | 453.39 (123.75) | 1692.72 (379.07) | 6.54 (1.12) | 5.40 (0.88) | 2.44 (0.45) |
| 4.80 | 6 | 516.66 (102.22) | 1935.15 (432.16) | 7.75 (1.00) | 6.28 (0.79) | 2.43 (0.55) |
| 5.60 | 2 | 933.90 (54.43) | 3748.38 (583.60) | 15.43 (0.83) | 15.09 (0.01) | 1.17 (0.18) |

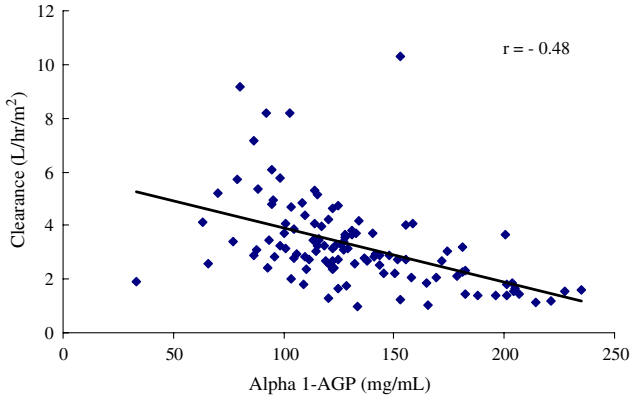


**Fig. 2** Correlation between α1-AGP and the clearance of TZT-1027

once every 3 weeks were conducted in patients with advanced solid tumors [9, 19]. In these studies, dolastatin 10 was well tolerated; the DLT was neutropenia, and non-hematological toxicities were mild [9, 19]. Six phase II studies were completed in patients with NSCLC, melanoma, prostate, colorectal, ovarian, and pancreaticobiliary cancers, including hepatocellular carcinomas and adenocarcinomas of the bile duct, gallbladder, and pancreas; however, no tumor response was observed in these studies [5, 6, 8, 10, 20, 24].

TZT-1027, a novel tubulin-binding dolastatin 10 derivative, was developed in order to obtain a more effective agent than the parent compound. In preclinical studies, TZT-1027 demonstrated not only a direct cytotoxic effect on cancer cell lines, but also antivascular activity [4, 13, 17, 26, 27]. TZT-1027 markedly increased survival when administered intermittently compared to single or consecutive doses.

The DLTs noted in the present study were neutropenia, neutropenia complicated by fever, myalgia, and neuropathic pain. Neutropenia was also identified as the DLT in the repeated-dose, phase I studies in Japan, Germany [21], and The Netherlands [1]; neutropenia was also the DLT for dolastatin 10. Myalgia and neuropathic pain were observed only at the highest dose, 5.6 $mg/m^2$; thus, they may have only been observed when the dose exceeded the MTD.

The most common hematological toxicities were neutropenia and leukopenia, but, in most patients, they were mild, short, and reversible. The neutropenia and leukopenia were complicated by fever in only one patient.

The most frequent drug-related non-hematological toxicities were constipation, anorexia, alopecia, and nausea; all of these are common adverse events of anticancer drugs.

In animals, TZT-1027 does not induce peripheral neurotoxicity at any dose [16]. In the present study, neurotoxicity occurred in only one patient who experienced neuropathic pain at the highest dose (5.6 $mg/m^2$). One of the major adverse events induced by antimicrotubule anticancer agents such as *Vinca* alkaloids and taxanes is peripheral neurotoxicity. In the phase I study of TZT-1027 done in Germany, two patients had neurotoxicity as the DLT at 3.0 $mg/m^2$, while the MTD of the study was 2.7 $mg/m^2$. These patients had colorectal cancer that had been pretreated with anticancer agents including oxaliplatin; peripheral neurotoxicity is known as the most frequent adverse event of oxaliplatin [21].

Although the MTD was 4.8 $mg/m^2$ in the present study and 2.7 $mg/m^2$ in the German phase I study [21], the administration schedules were similar in the two studies. One possible explanation of the difference in MTDs could be the number of prior chemotherapy regimens. In the present study, the median number of pretreatment regimens was 1, compared to 4 in the German phase I study. The fact that patients in this study had less pretreatment than those in the German phase I study may have allowed higher TZT-1027 doses to be used.

In the present study, a tumor response was observed in 4 of 49 patients (8.2%), including 1 complete response and 3 partial responses. All patients in this study had previously received treatment with radiotherapy or chemotherapy. Currently in the US, docetaxel, pemetrexed, and erlotinib are approved for NSCLC patients previously treated with chemotherapy. The approval of docetaxel was based on two phase III studies: TAX 317 [22], a phase III study of docetaxel versus best supportive care; and TAX 320 [2], a phase III study of docetaxel versus vinorelbine or ifosfamide in NSCLC patients previously treated with platinum-containing chemotherapy. In the TAX 317 study, the overall response rate of docetaxel was 7.1%, while in the TAX 320 study, the overall response rate of docetaxel was 6.7% [2, 22]. In a phase III study of pemetrexed versus docetaxel in NSCLC patients that were previously treated with chemotherapy, the overall response rates were 9.1 and 8.8% for pemetrexed and docetaxel, respectively [3]. In a phase III, placebo-controlled study of erlotinib in previously treated NSCLC patients, the overall response rate of erlotinib was 8.9% [23]. In the present study, TZT-1027 had a comparable response rate to these approved agents.

In conclusion, the present study showed that the recommended dose of TZT-1027 when administered every 3–4 weeks is 4.8 mg/m$^2$. TZT-1027 was well tolerated and had antitumor activity in previously treated NSCLC patients.

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