A Phase I Study Of The Combination Of TZT-1027 (Soblidotin) And Gemcitabine Administered On Day 1 And 8 Every Three Weeks To Patients With Advanced Or Metastatic Solid Tumors

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Citation

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Abstract

Background: TZT-1027 is a dolastatin 10 analog interfering with microtubule assembly, with increased antitumor activity when combined with gemcitabine in animal models.

Patients and Methods: Eligible patients with refractory solid tumors received gemcitabine followed by TZT-1027 on Days 1 and 8 every 21 days, with pharmacokinetic sampling during the first 24 hours.

Results: Fourteen patients received at least one course of study drug (10 at TZT-1027 dose 1.6 mg/m² and 4 at 2.0 mg/m²). There were 36% male, median age 59 years, median PS 0, median number of prior treatments 2. Reasons for withdrawal included: progression of disease (n=12) and adverse events (n=2). A total of 66 courses were administered. Of 12 instances of dose delay, 8 were due to neutropenia. Grade 3/4 adverse events included neutropenia (50%), thrombocytopenia (14%), fatigue (14%), and anorexia (7%). Cmax and AUICinf were 181 mcg/L (CV% 38.2) and 537 ng.h/mL (n=10 in cohort 1), and peaked at 1.05 hours after the end of TZT-1027 infusion, with a biphasic elimination. T1/2 was 5.12 h, clearance 3.9 L/h/m², and VSS 16.5 L/m².

Conclusions: The recommended phase II dose is 1.6 mg/m² of TZT and 800 mg/m² of gemcitabine. Pharmacokinetics are consistent between studies.

INTRODUCTION

DRUG

Dolastatin 10 was isolated in 1987 from the Indian Ocean marine mollusc, the sea hare (Dolabella auricularia) and was found to possess both in vitro and in vivo anti-tumor activity (1,2,3,4). TZT-1027 (Soblidotin), a synthetic tetrapeptide derivative of dolastatin 10, is a mitotic spindle poison that inhibit microtubule polymerization by interacting with tubulin in a similar domain as the vinca alkaloid binding region (1,2).

MECHANISM OF ACTION

TZT-1027 has a broader range of anti-tumor activity in vitro and in vivo against a variety of tumor types including those that are taxane-resistant and vincristine-resistant (5). This may be because TZT-1027 also inhibits monosodium glutamate-induced tubulin polymerization and thus implicates two binding sites, one of high affinity and the other of low affinity. TZT-1027 inhibits both guanosine 5'-triphosphate (GTP) binding to tubulin as well as GTP hydrolysis on tubulin while vinblastine only inhibits GTP hydrolysis. Thus, the binding sites are not completely
identical (6). The poisoning of microtubules causes cell cycle arrest at the G2/M transition phase resulting in apoptosis (7).

IN VITRO ACTIVITY
TZT-1027 is approximately 30 times more potent than vincristine and about 2,000 times more potent than cisplatin against 8 human tumor cell types. The cytotoxic action of TZT-1027 in tumor cells is time-dependent as activity is enhanced with longer exposure periods rather than by increases in concentration, with cytotoxicity peaking with exposures of 12 hours or more (8, 9). TZT-1027 cytotoxicity is less affected by the over-expression of multi-drug resistant proteins (e.g. P-glycoprotein, BCRP, MRP) compared to other tubulin inhibitors (vincristine, paclitaxel, or docetaxel).

IN VIVO ACTIVITY
Dose intensity is best achieved with repeat intermittent weekly dosing. Intravenous doses of TZT-1027 produce a greater than 80% tumor growth inhibitory response and increased the life span of syngeneic mice implanted with colon 26 adenocarcinoma, M5076 reticulum cell sarcoma, or B16 melanoma. TZT-1027 also showed significant anti-tumor activity against vincristine-resistant, cisplatin-resistant, and 5-FU-resistant P388 leukemia cells inoculated into mice (10).

CLINICAL STUDIES
Early Phase I clinical trials of TZT-1027 lead to the recommendation for Phase II studies of doses of 2.4 mg/m² on day 1 and day 8 every 21 days (11) or 2.7 mg/m² every 3 weeks (12). More recently, in combination with carboplatin area under the plasma concentration versus time curve (AUC) 5 on day 1, the recommended dose is 1.6 mg/m² on day 1 and 8 every 3 weeks. (13).

RATIONALE FOR THE STUDY
The reason to combine TZT-1027 with gemcitabine is based on non-overlapping mechanisms of action of the two drugs, their potential for broad activity, and the prolongation of survival seen in animal models (14). Based on the early Phase I studies, a weekly schedule with doses delivered on days 1 and 8, every 21-days of administration was selected for the combination of TZT-1027 and gemcitabine. Myelosuppression was anticipated to be the dose limiting toxicity (DLT) of this combination.

OBJECTIVES

PRIMARY OBJECTIVE
- To determine the maximum tolerated dose (MTD) and the DLTs of TZT-1027 and gemcitabine in combination on day 1 and day 8 of a 21-day course.

SECONDARY OBJECTIVES
- To determine the toxicity profile,
- To characterize possible pharmacokinetic interactions between the two drugs,
- To observe any anti-tumor activity.

PATIENTS AND METHODS
The study was approved by each local institutional review committee.

ELIGIBILITY
- Patients > 18 years old
- Histologically confirmed locally advanced or metastatic cancer
- ECOG performance status 0 - 2
- Life expectancy > 12 weeks
- Hematology: neutrophils >1.5 x 10³/mm³ and platelet counts >100 x 10³/mm³
- Chemistry: serum creatinine and a total bilirubin level of < 1.5 x upper limit of normal; a transaminase level of < 2.5 x upper limit of normal (< 5 in case of metastases in the liver)
- At least four weeks had elapsed since prior surgery, radiation or chemotherapy
- Minimally pretreated (MP), i.e., had received fewer than 6 courses of an alkylating agent-containing chemotherapy, six or fewer courses of carboplatin, fewer than 2 courses of mitomycin C or a nitrosourea as a part of a single regimen, and had not been treated with prior bone marrow transplantation or radiation therapy to >25% of hematopoietic reserves.
- Signed informed consent.
- No progression of disease during earlier treatment
with gemcitabine

- No concurrent radiotherapy, surgery or chemotherapy
- No women with the potential of becoming pregnant, unless utilizing birth control
- No symptomatic brain metastases
- No previous or current malignancies (except in situ carcinoma of the cervix or non-melanoma cancer of the skin)
- No mental disability or incompetence to give informed consent
- No concurrent life threatening illness
- No administration of any investigational drug within 28 days prior to receiving TZT-1027
- No history of hypersensitivity to gemcitabine
- No neuropathy at baseline ≥ grade 2
- No cardiac ejection fraction of < 40% by multiple gated acquisition cardiac scan (MUGA).

**SCHEDULE OF EVENTS**

**BEFORE ENTRY**

- Complete medical history
- Physical examination with height and weight, and a detailed neurologic exam
- Performance status
- Lesion measurement by RECIST criteria (15). Radiographic studies were reviewed by the principal investigators (CFV, HR, and CS).
- Complete blood cell count
- Relevant blood chemistries including coagulation studies and α 1-acid glycoprotein (α1-AGP)
- Urine analysis
- Pregnancy test
- Electrocardiogram (ECG)
- MUGA scan

- Chest x-ray and other indicated imaging studies

3 hours after completion of the TZT-1027 infusion

**ECG**

**WEEKLY**

- Complete blood cell counts

**BEFORE EACH COURSE**

- Medical history
- Physical examination with routine neurological examination, weight, vital signs, performance status
- Blood chemistry
- Adverse event collection. Adverse events were graded according to the National Cancer Institute Common Toxicity Criteria (NCI-CTCAE - Version 3.0, revised 2003).

**EVERY OTHER COURSE**

- Chest x-ray and other indicated imaging studies

**COMPLETION OF THE STUDY**

- MUGA scan
- Survival status

**TREATMENT**

**SUPPL:**

Gemcitabine was obtained from a commercial source. TZT-1027 Injection for parenteral use in clear glass vials containing 2.5 mg of TZT 1027 in 5 mL of sterile, clear, colorless, aqueous solution was supplied Daiichi Pharmaceutical Corporation.

**ADMINISTRATION**

The dose was administered in 250 mL 0.9% sodium chloride as an intravenous infusion over one hour into a peripheral vein or through a central venous catheter using a programmed peristaltic pump system. To allow optimal distribution of gemcitabine to the tumor, TZT-1027 which has an antivascular effect in animal models was administered after gemcitabine (\(t_{in}\)). One course consisted of a 30-minute infusion of gemcitabine followed by a 60-minute infusion of
TZT-1027 weekly for 2 consecutive weeks every 3 weeks. The starting dose of gemcitabine and TZT-1027 were 800 mg/m$^2$ and 1.6 mg/m$^2$, respectively. The TZT-1027 dose was chosen to be 2/3 of the dose determined in single agent phase I study (11). Increments of 0.4 mg/m$^2$ of TZT-1027 were planned into a 3+3 phase I design. Re-treatment on day 8 per protocol required neutrophils > 0.75 x 10$^3$/mm$^3$, platelet counts >75 x 10$^3$/mm$^3$, and for all non-hematologic toxicities to have recovered to baseline level or grade < 1, except alopecia. Treatment delays to allow recovery from toxic effects could not exceed 2 weeks. Reduction of doses to 1.2 mg/m$^2$ of TZT-1027 with gemcitabine 800 mg/m$^2$ was allowed if patients were being treated at dose level one). Dose re-escalation was not permitted. Continuation of treatment was dependent on the response and tolerance, usually until progression of disease occurred. Patients who experienced further DLTs despite dose delay or dose reduction were discontinued from therapy.

**DLT definition**: A 3+3 Simon design was utilized.

- Grade 4 neutropenia either lasting more than 5 days or with a fever above 38.5 o C, thrombocytopenia (< 25 x 10 3 /mm 3 )
- Grade 4 vomiting with maximum supportive care
- Grade 3 or 4 neurotoxicity
- Other grade 3 adverse events (excluding nausea and vomiting) requiring an adjustment of treatment administration, and inability to receive the second administration (Day 8) in the first course because of persistent toxicity or to start a second course of treatment after a 1 week delay (Day 29).

**MTD**

Doses of gemcitabine and TZT-1027, just below the dose level at which 2 patients of a cohort (of 3 or 6 patients) experience DLT during the first course. Additional patients were treated at the MTD.

**PHARMACOLOGY**

**TIME POINTS**

Blood samples were collected on day 1 during the first course of the study. Samples were taken before the start of the infusion, then post infusion at 30 minutes (end of gemcitabine infusion), at 1.0, 1.5 (end of TZT-1027 infusion), 2.0, 3.0, 5.5, 7.5, and 24 hours.

**METHODS**

Separate heparinized samples (5.0 ml/time point) were collected for analysis of gemcitabine, TZT-1027 and metabolites Ma (a hydroxyl TZT-1027 compound), and Mc (a demethylated TZT-1027 compound). For gemcitabine specimens, 50 µL of tetrahydrouridine was added to each heparinized 5 mL Vacutainer tube. All samples were centrifuged and plasma stored at -20ºC before shipping to MDS Pharma Services (Montreal, Canada).

Plasma levels of TZT-1027 and gemcitabine were measured by a validated high performance liquid chromatography (HPLC) method and mass spectrometric detection, with the lower limit of quantitation for TZT and gemcitabine being 0.250 mcg/L and 10.0 mcg/L, respectively (17, 18). The plasma collections were used to determine the pharmacokinetic parameters by non-compartmental analyses by using the computer program Kinetica (version 4.3) (19).

The pharmacokinetic parameter calculations were normalized with the individual body surface area measurements. The following parameters were evaluated: (maximum plasma concentration (C$_{max}$), time of maximum plasma concentration (T$_{max}$), AUC, elimination half-life (T$_{1/2}$), volume of distribution (Vd), and clearance (CL), and mean residence time (MRT). The linearity of the TZT-1027 and gemcitabine plasma kinetics in relation to dose and the relationship between toxicity and the pharmacokinetic parameters C$_{max}$, AUC, and CL were assessed.

In human plasma, TZT-1027 is predominantly bound to α1-AGP (20). The correlation between plasma α1-AGP concentrations and TZT-1027 clearance were measured by MDS Pharma Services Central Lab in Mississauga, Ontario, Canada.

**STATISTICAL ANALYSIS**

Patient characteristics were tabulated for safety and efficacy data.

PK parameters were summarized for each dose group and compared to other pharmacokinetics studies of TZT1027 administered alone (1027E-PRT001 (1027E-PRT001), 1027E-PRT002 (1027E-PRT002)) and 1027A-PRT009 (1027A-PRT009), and with published pharmacokinetics results for gemcitabine (21, 22). Analysis of variance (ANOVA) was performed using these studies as a fixed effect on the ln-transformed AUC$_{inf}$/Dose, Cmax/Dose,
CL and CL by body surface area (BSA) for TZT-1027. Each ANOVA included calculation of study least-squares means (LSM). The above statistical analyses were done using the SAS® general linear model (GLM) procedure.

For each patient, the observed α1-AGP values were plotted against TZT-1027 CL and the correlation between those values was investigated using linear regression, Emax and sigmoidal Emax models. The goodness of fit of the predicted values from each model was based on the Akaike information criterion methodology (23).

RESULTS

Patient Characteristics

Ten patients were treated at the first dose level (gemcitabine 800 mg/m² and TZT-1027 1.6 mg/m²). Four patients were treated at the second dose level (gemcitabine 800 mg/m² and TZT-1027 2.0 mg/m²). The median number of courses in cohort 1 was 4 (range 1-9). The number of courses administered in cohort 2 were 4, 4, 9, and 9. Reasons for withdrawal from study include progression of disease (n=12) and adverse events (n=2).

TOXICITY

All adverse events are summarized together because of the
small dose increment (25%) between cohort 1 and 2 and the small number of patients. A total of 66 courses were administered. Adverse events possibly related to drug administration are presented in the table.

**Figure 2**

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>NCI Grade</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood &amp; Lymphatic System Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>2 0 6 3 11</td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>1 0 1 0 2</td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>0 1 1 0 2</td>
<td></td>
</tr>
<tr>
<td>Gastroenterology Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>6 1 0 0 7</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0 2 0 0 2</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>2 2 0 0 4</td>
<td></td>
</tr>
<tr>
<td>General Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>2 4 2 0 8</td>
<td></td>
</tr>
<tr>
<td>Infusion Site Pain</td>
<td>3 0 0 0 3</td>
<td></td>
</tr>
<tr>
<td>Metabolism Disorders</td>
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<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>2 0 1 0 3</td>
<td></td>
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<tr>
<td>Nervous System Disorders</td>
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<td></td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>3 1 0 0 4</td>
<td></td>
</tr>
<tr>
<td>Neuropathy</td>
<td>3 0 0 0 3</td>
<td></td>
</tr>
<tr>
<td>Skin Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alopecia</td>
<td>3 1 - - 4</td>
<td></td>
</tr>
</tbody>
</table>

Most common drug-related adverse event observed during all courses in both cohorts. If a patient experienced multiple occurrences of an individual adverse event, it is counted only once, at the highest observed intensity.

There were 12 instances of dose delay, 8 were due to persistent neutropenia, to levels. No dose delay exceeded one week.

**FIRST COHORT (N=10):**

One patient developed a DLT of grade 4 neutropenia lasting >5 days. Another patient developed grade 3 fatigue which was attributed by the investigator to rapidly progressing disease. This patient was replaced. In all courses, grade 3 or 4 neutropenia was seen in a total of 6 patients (2 grade 4 and 4 grade 3). Grade 1 neutropenia was seen in 2 patients and grade 1 thrombocytopenia in 1 patient. Anemia was seen in 2 patients (1 grade 2 and 1 grade 3). Non-hematologic events included 3 instances of grade 2 fatigue, 2 instances of grade 2 diarrhea, 1 instance each of grade 1 and 2 emesis, and 2 and 1 instances of grade 1 and 2 nausea, respectively. There were two serious adverse events in course 1, including one patient hospitalized for an ileus unrelated to the treatment and the patient described above with grade 3 fatigue, who had progressive disease after the first course of treatment. Therefore, only 1 patient in this cohort experienced a DLT that was unequivocally related to TZT-1027.

**SECOND COHORT (N=4):**

There were 2 episodes of grade 3-4 neutropenia and one episode of grade 3 thrombocytopenia. The grade 4 neutropenia occurred in course 1 and was considered a DLT. Fatigue, nausea and vomiting were limited to grades 1-2. No diarrhea was reported at this dose level. The level of myelosuppression seen in cohort 2 made it clear that the weekly administration was not feasible at these doses. This cohort was not expanded because the sponsoring company decided to stop the development of this TZT-1027.

**PHARMACOLOGY**

Fourteen patients had a PK profile on day 1.
These results are consistent with previous PK reports of TzT-1027 demonstrating a linear behavior \((11, 12)\) as described in the table below which shows a comparison of pharmacokinetics parameters between 4 studies, in patients treated at similar doses. Each parameter is a function of the dose.

The p-values derived from the ANOVA did not show a statistically significant difference (p-value >0.05) between the ln-transformed PK parameters AUC\(_{0-\infty}\)/Dose, Cmax/Dose, CL and CL/BSA of TzT-1027 when given concomitantly with gemcitabine (this study) versus administered alone (Daichi 1027E-PRT001, 1027E-PRT002, and 1027E-PRT009 (course 1, day 8)). Furthermore, the PK of gemcitabine, as assessed by comparison of the PK parameters, CL and t\(_{1/2}\), to values previously reported in the literature, did not appear to be affected by the concurrent administration of TzT-1027.

Based on these results, the PK disposition of TzT-1027 and gemcitabine did not appear to be altered when they were coadministered as a single dose. As shown in the next table.

Mean (Range) Pharmacokinetic Parameters Unadjusted for

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BSA for Gemcitabine in Plasma – Course 1, Day 1 (with TZT-1027)

**Figure 5**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Number of Patients</th>
<th>Mean</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>AU/Cu (mcg/mL)</td>
<td>14</td>
<td>7226</td>
<td>2685 – 15,700</td>
</tr>
<tr>
<td>AU/Cu(mcg/mL)</td>
<td>10</td>
<td>6962</td>
<td>2654 – 11,275</td>
</tr>
<tr>
<td>Cmax (mcg/mL)</td>
<td>12</td>
<td>16955</td>
<td>4590 – 20,300</td>
</tr>
<tr>
<td>Tmax (h)</td>
<td>12</td>
<td>0.532</td>
<td>0.000 – 0.600</td>
</tr>
<tr>
<td>CL (L/h)</td>
<td>10</td>
<td>239</td>
<td>119 – 549</td>
</tr>
<tr>
<td>Vd (L)</td>
<td>10</td>
<td>85.4</td>
<td>46.9 – 218.1</td>
</tr>
<tr>
<td>t1/2 (h)</td>
<td>10</td>
<td>0.850</td>
<td>0.269 – 2.873</td>
</tr>
<tr>
<td>CU/BSPA (L/h/m²)</td>
<td>10</td>
<td>132</td>
<td>69 – 209</td>
</tr>
<tr>
<td>Vg/BSPA (L/m²)</td>
<td>10</td>
<td>47.5</td>
<td>27.1 – 117.9</td>
</tr>
</tbody>
</table>

Patient number varies depending on the sampling points in the terminal elimination phase, with some missing.

**RESPONSE**

One patient with transitional cell carcinoma of the bladder experienced a confirmed partial response. This patient was in cohort 1 (gemcitabine 800 mg/m² and TZT-1027 1.6 mg/m²). At baseline, this patient had 4 measurable lesions: 2 lymph nodes, 1 lung and 1 liver metastases. After the second course the total measurement of these lesions shrunk by 31%. This was confirmed after the fourth course. After the sixth course, the size of these lesions increased by 18% and the patient was removed from the study. The duration of partial response was 12 weeks. Stable disease was seen in patients with the following primary tumor types: non-small cell lung cancer (2 patients), breast (2 patients), rectum, adrenal, uterine, colon, ovarian, soft tissue sarcoma and unknown primary (1 patient in each). In the patient with colon cancer, the disease remained stable for 5.4 months and in the patient with uterine cancer, for 6.5 months. Two patients with pancreas and ovarian cancer had immediate progressive disease.

**DISCUSSION**

In this study, the MTD of the combination of TZT-1027 and gemcitabine was determined at 2.0 mg/m² of TZT-1027 and 800 mg/m² of gemcitabine. Therefore, the recommended Phase II dose is TZT-1027 1.6 mg/m² in combination with 800 mg/m² of gemcitabine. The most common dose limiting toxicity is neutropenia (See adverse event table). In four phase I studies testing single agent TZT-1027, the DLT is also reversible neutropenia (Liu, 2015, 2016). There were additional side effects of hepatic transaminase elevation, insomnia, phlebitis, skin reaction, dyspnea, hyperesthesia, myalgia, and interestingly reversible neurological toxicity in patients pretreated with oxaliplatin. A phase I study of weekly single agent TZT-1027 with a schedule of administration identical to the one used in this study (ie as a one-hour infusion weekly times two every three weeks) has been completed. Seventeen patients were enrolled at 4 dose levels (1.35, 1.8, 2.4 and 2.7 mg/m²). The stopping dose is 2.7 mg/m² and the MTD is established at 2.4 mg/m² as a single agent.

In our study, pharmacokinetic linearity could not be assessed with certainty because there were only two dose levels. More than 80% of TZT-1027 is eliminated by 48 hours and 90-100% by 168 hours. The predominant route of elimination is the feces, but only a small amount of unchanged TZT-1027 is recovered in the feces. The tissue distribution of TZT-1027 generally follows the circulatory blood pattern showing a rapid uptake into the major organs with little penetration in the brain. In vitro studies using liver microsomes obtained from rats, dogs, and monkeys have identified several hydroxylated and demethylated metabolites of TZT-1027 (Ma, Mb, Mc, Md and Mg). The first four have been identified using human liver microsomes. In this study, metabolites Ma and Mc were measured. Based on comparison to studies where TZT-1027 or gemcitabine were given alone (Liu, 2015, 2016), the PK disposition of either drug and the metabolites Ma and Mc did not appear to be altered when TZT-1027 was given in combination with gemcitabine, as there were no statistical significant difference in pharmacokinetics. Other in vitro studies show that the major human P450 isoform involved in the metabolism of TZT-1027 is CYP3A4 (with a small contribution by CYP3A5). Plasma protein binding of TZT-1027 is species-dependent and dose-independent. In vitro protein binding is approximately 50-60% in mice, 70-80% in rats, 70-80% in monkeys, 85% in dogs and 95% in human plasma. In human plasma, TZT-1027 is predominantly (>95%) bound to α1-AGP, which was also measured in this study. Values for α1-AGP and total TZT-1027 clearance were correlated and a linear model was found to provide the best fit to the data (Fig 2). An increase in α1-AGP levels is associated with a decrease in total
TZT-1027 clearance. This finding of decreased clearance with increased α1-AGP suggests that TZT-1027 is a flow-independent drug (e.g., CL = unbound intrinsic clearance). A good correlation between α1-AGP and total TZT-1027 clearance was also observed in previous internal studies (27,28,29). Pharmacokinetic data have been obtained from all Phase I studies. AUC and Cmax increase in relation to the administered dose.

**Figure 6**
Figure 1: Mean plasma concentration of TZT-1027 over time in 3 different studies: This study (at 1.6 and 2.0 mg/m²) and studies PRT001 (one-hour infusion, single dose once every three weeks ()), and PRT002 (one-hour infusion, weekly times two every three weeks ()).

T½, MRT and CL are dose independent. α1-AGP is the major plasma protein fraction that binds to TZT-1027 (>95%) and there is a good correlation between CL and α1-AGP plasma concentration.

**Figure 7**
Figure 2: Correlation between α1-AGP concentrations and TZT-1027 clearance in our study. α1-AGP is the main binding protein (>95%) for TZT-1027 in plasma. Figure 2 shows that an increase in α1-AGP levels is associated with a decrease in total TZT-1027 clearance. This finding of decreased clearance with increased α1-AGP suggests that TZT-1027 is a flow-independent drug. Values for α1-AGP and total TZT-1027 clearance were correlated and a linear model was found to provide the best fit to the data. The 95% confidence interval of the slope does not include zero, indicating a statistical significance (p<0.05). A good correlation between α1-AGP and total TZT-1027 clearance was also observed in previous studies (,,).

We observed minimal activity with one partial response in a patient with bladder cancer. The dose schedule of this combination needs be optimized to allow for better therapeutic dose intensity.

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