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A Phase I study of AT-101 with Cisplatin and Etoposide in patients with advanced solid tumors with an Expanded Cohort in Extensive-Stage Small Cell Lung Cancer

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Abstract

Background—A phase I, dose-escalation study of AT-101 with cisplatin and etoposide was conducted to determine the maximum tolerated dose (MTD)/recommended phase 2 dose (RP2D), safety and pharmacokinetics in patients with advanced solid tumors, with an expanded cohort in patients with extensive-stage small cell lung cancer (ES-SCLC) to assess preliminary activity.

Methods—In the dose escalation portion, increasing doses of AT-101 were administered orally BID on days 1–3 along with cisplatin on day 1 and etoposide on days 1–3 of a 21 day cycle. At the RP2D, an additional 7 patients with untreated ES-SCLC were enrolled.

Results—Twenty patients were enrolled in the dose-escalation cohort, and 7 patients with ES-SCLC were enrolled in the expanded cohort. The MTD/RP2D was established at AT-101 40 mg BID days 1–3 with cisplatin 60 mg/m² and etoposide 120 mg/m² on day 1 of a 21 day cycle with pegfilgrastim support. Two DLTs of neutropenic fever were seen at dose level 1. After the addition of pegfilgrastim, no additional DLTs were observed. Grade 3/4 treatment-related toxicities included: diarrhea, increased AST, neutropenia, hypophosphatemia, hyponatremia, myocardial infarction and pulmonary embolism. No apparent PK interactions were observed between the agents. Preliminary activity was observed with PRs in patients with ES-SCLC, high-grade neuroendocrine tumor, esophageal cancer and NSCLC.

Conclusions—AT-101 with cisplatin and etoposide is well tolerated with growth factor support. Anti-tumor activity was observed in a variety of cancers including ES-SCLC, supporting further investigation with BH-3 mimetics in combination with standard chemotherapy for ES-SCLC.

Keywords

AT-101; cisplatin; etoposide; phase I; extensive-stage small cell lung cancer

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

INTRODUCTION

Lung cancer is the most common cancer worldwide and is the leading cause of cancer-related mortality in the United States [1, 2]. Small cell lung cancer (SCLC) represents 13% of all lung cancers [3], and the majority of patients with SCLC present with extensive stage disease. Front line therapy for ES-SCLC typically involves a platinum doublet with good response rates [4]; however, the disease usually recurs and response to second line treatment is limited [3].

Bcl-2 is over-expressed in 83–90% of SCLC [5] and is associated with resistance to chemotherapy in SCLC cell lines [6]. The BCL-2 family of proteins is involved in tumorigenesis and tumor survival. Anti-apoptotic members such as Bcl-2 may contribute to cancer cell pathogenesis and resistance to cytotoxic therapy by binding to BH3 domains of pro-apoptotic family members, leading to sequestration and inhibition of their ability to promote cell death [7–9]. Agents that alter the expression of or interaction between pro- and anti-apoptotic Bcl-2 proteins influence cell growth and survival [10, 11].

AT-101 [R(–)-gossypol acetic acid], the levorotatory enantiomer of gossypol, is an orally administered BH-3 mimetic that interferes with heterodimerization of Bcl-2, Bcl-xL, Bcl-w, and Mcl-1, up-regulates pro-apoptotic proteins NOXA and PUMA and inhibits angiogenesis (AT-101 Brochure, Ascenta Therapeutics, Malvern, PA) [12]. An *in vitro* study using a SCLC cell line demonstrated synergistic cytotoxic effects following treatment with cisplatin and etoposide and anti-sense Bcl-2 therapy [13]. In the NCI-H446 SCLC xenograft model, anti-tumor activity was also observed with AT-101 alone and synergistic activity was seen with the combination of AT-101 and topotecan [14].

Clinically, AT-101 has been studied as a single agent in the phase I/II setting and has antitumor activity in CLL, castrate resistant prostate cancer (CRPC) and glioblastoma multiforme (GBM) with acceptable side effects [15–17]. Based on the rationale that inhibition of bcl-2 may increase the sensitivity of tumor cells to apoptosis induced by cytotoxic agents, we conducted a phase I trial of AT101, cisplatin and etoposide in solid tumors, followed by a dose expansion cohort at the MTD in patients with untreated ES-SCLC.

Materials and methods

Patients

Patients with histologically documented, advanced solid malignancy refractory to standard therapy or for which no curative standard therapy was available were considered eligible for the dose escalation cohort. In the expanded cohort, patients with histologically or cytologically confirmed extensive-stage small cell lung cancer without any prior treatment were enrolled. Patients with a history of limited stage-SCLC were permitted to have prior definitive chemoradiotherapy and prophylactic cranial irradiation if recurrence was > 6 month from definitive therapy. Other key eligibility criteria included: 18 years, Eastern Cooperative Oncology Group performance status of 0 to 2, adequate hematologic, hepatic and renal functions (WBC 3,000/μl, absolute neutrophil count 1,500/μl, platelets 100,000/μl, total bilirubin <1.5 mg/dL, AST/ALT 2.5 × the institutional upper limit of normal, creatinine <1.5 × institutional upper limit of normal or measured creatinine clearance 45 ml/min/1.73m² for patients with creatinine levels above institutional normal); and life expectancy greater than 12 weeks.

Patients were excluded if they had untreated brain metastasis, were treated within 4 weeks with chemotherapy or radiation therapy, received prior racemic gossypol or AT-101 or BH3

mimetic or had a history of allergic reactions attributed to compounds of similar chemical or biologic composition to AT-101.

All patients signed written informed consent, and the study was approved by the Health Sciences Institutional Review Board at the University of Wisconsin-Madison.

Study Design

This was an open label, dose escalation, phase I study of AT-101 in combination with cisplatin and etoposide followed by an expanded cohort in ES-SCLC at the MTD. In the dose escalation cohort, AT-101 was administered orally twice daily on days 1–3, with the requirement of fasting 1 hour before and after dosing, followed by cisplatin on day 1 and escalating doses of etoposide on days 1–3 (see Table 2 for dose escalation schema). Cycle length was 21 days. Cisplatin and etoposide were administered on day 2 of cycle 1 for PK analysis. Based on prior phase I data of AT-101 as a single agent, the starting dose of AT-101 was 30 mg twice a day [15, 18, 19]. A standard 3+3 dose-escalation design was used for the dose escalation portion of the study, and MTD was defined as the dose at which fewer than one-third of patients experienced a DLT to AT-101 in combination with cisplatin and etoposide. In the dose escalation, the MTD was based on assessment of DLT during the first 21 days of treatment. Due to early hematologic toxicity, the protocol was amended to include administration of filgastrim 6 mg subcutaneously on day 5 of cycle 1 and on day 4 of all subsequent cycles starting at dose level 1a. At the MTD/RP2D level, an additional 7 patients with ES-SCLC were enrolled to evaluate preliminary activity.

Safety Assessment

Dose limiting toxicities (DLT) based on Common Terminology Criteria for Adverse Events, version 3.0/4.0 (effective August 1, 2010), included grade 4 neutropenia lasting ≥ 7 days, grade 4 neutropenia and fever, grade 3 neutropenia with grade 3 infection, any grade thrombocytopenia associated with clinically significant bleeding, grade 4 thrombocytopenia, any non-hematologic grade 3 or higher toxicity (excluding alopecia, nausea, vomiting, or diarrhea). In addition, grade 3 or 4 nausea, vomiting, or diarrhea not controlled by medical therapy, and grade 3 or higher ileus or small bowel obstruction were considered DLTs.

All patients who completed at least one treatment course followed by 2 weeks of observation were considered evaluable. The determination of antitumor efficacy was based on objective tumor assessments made according to the Response and Evaluation Criteria in Solid Tumors (RECIST) criteria [20]. Baseline imaging-based tumor assessments were performed within 28 days prior to the start of treatment, and all tumor assessments were re-evaluated every 6 weeks thereafter. All patients with responding tumors (complete response (CR) and partial response (PR)) were required to have response confirmed 4 weeks after the first documented response.

Duration of Study

In the dose-escalation portion of the study, patients received a maximum of 6 cycles of cisplatin and etoposide in combination with AT-101. Treatment was stopped at the time of best response or disease progression. In the expanded cohort with ES-SCLC, patients who achieved a complete or partial response or stable disease continued AT-101 in combination with cisplatin and etoposide until evidence of disease progression or to a maximum of 4 cycles. The decision to administer an additional 2 cycles of therapy was left to the discretion of the attending physician.

Pharmacokinetic Analysis

AT-101—Plasma samples for the analysis of AT-101 were collected at baseline, 0.5, 1, 1.5, 2, 3, 4, 8, 12 and 24 hours after AT-101 administration on C1D1 and C2D1. An HPLC assay for the analysis of gossypol enantiomers was developed and validated. Following ether extraction, samples were suspended in 2ml R-2-amino-1-propanol (297682-5g, Aldrich) and analyzed with a Thermospectrum Separation System with UV detection. The standard curve linear was linear from 0.078 to 10 µg/ml, $r^2 = 0.9998$, with an intraday variability of 1.37% and 1.79% for (+)- gossypol and (–)- gossypol respectively for high standard (10 µg/ml), $n=3$ and 6.57% and 8.89% for (+)-gossypol and (–)- gossypol respectively for low standard (0.078 µg/ml), $n = 3$. Inter-day variability was 12.37% and 13.16% for (+)-gossypol and (–)-gossypol respectively for low standard (0.156 µg/ml), $n=11$ and 4.59% and 0.32% for (+)-gossypol and (–)- gossypol respectively for high standard (10 µg/ml), $n = 11$ over 30 days. LOD 0.0195 µg/ml and LLOQ 0.078 µg/ml for both. Recovery was based on standard addition: 82.93–100.84% for high standard of (+)-gossypol (10 µg/ml, average 98.5%, $n = 11$), 99.6–100.7% for high standard of (–)-gossypol (10 µg/ml, average 100.1%, $n = 11$), and 88.2–119.3% for low standard of (+)- gossypol (0.156 µg/ml, average 108.88%, $n = 11$), 83.84–106.88% for low standard of (–)- gossypol (0.156 µg/ml, average 95.01%, $n = 11$).

Cisplatin and Etoposide—Plasma samples for the analysis of cisplatin and etoposide were collected at baseline, 2, 2.5, 3, 4, and 8 hours after AT-101 administration on C2D1 and analyzed as previously described [21, 22].

Statistical Analysis

Baseline characteristics were summarized across all enrolled patients. Safety variables were summarized by descriptive statistics. Adverse events were described in terms of incidence and severity. AT-101, cisplatin and etoposide serum concentration data were analyzed by standard non-compartmental methods using the program WinNonLin Professional, version 5.2 (Pharsight Corporation). Data were summarized using means $\pm$ standard deviations and are depicted in tabular form. The primary outcome measure of this study was assessment of toxicity. The number of treatment anti-tumor responses served as the secondary outcome measure. Treatment efficacy was summarized by simple descriptive summary statistics delineating complete and partial responses as well as stable and progressive disease.

RESULTS

Patient Characteristics

Twenty-seven patients were enrolled between October 2007 and January 2012, including twenty patients in the dose escalation cohort and seven in the ES-SCLC dose expansion cohort (Table 1). Accrual to the dose expansion cohort halted after Ascenta Therapeutics stopped providing AT-101.

Dose Escalation and Toxicity

All 20 patients in the dose escalation cohort were evaluable for assessment of DLTs (Table 2). Two DLTs of neutropenic fever were observed in dose level 1. Three additional patients were then enrolled in dose level-1 with no DLTs observed. Given that the first two DLTs were limited to febrile neutropenia, the protocol was amended to include treatment with filgrastim 6 mg once on day 5 of cycle 1 and day of 4 of each subsequent cycle. Dose escalation then resumed at dose level 1a, and no additional DLTs were observed to the pre-determined dose escalation to dose level 3a. The MTD/RP2D was established at AT-101 40 mg, days 1–3, cisplatin 60mg/m², day 1, etoposide 120mg/m², days 1–3, and filgrastim 6 mg

on day 4. No unanticipated toxicities were observed in the 7 patients enrolled in the ES-SCLC dose expansion cohort.

Safety

All 27 patients were evaluable for assessments of toxicity and safety. The most frequent (10%) cycle 1 adverse events of all grades, and those grade 3 or higher, separated by dose levels and of at least possible attribution, are described in Table 3. The most common adverse events at least possibly related to treatment included myelosuppression, nausea, emesis, anorexia, diarrhea, fatigue, headache and alopecia, although the majority of the non-hematologic toxicities were grade 2 or less. There was no evidence of cumulative toxicity with AT-101. A high incidence of grade 3–4 neutropenia and leukopenia was seen at dose level 1 and -1, which improved significantly after the protocol was amended to include filgrastim. Despite this, however, 3 (42%) patients in the RP2D expansion cohort experienced grade 4 neutropenia, including one episode of febrile neutropenia requiring the dose reductions. These patients subsequently completed treatment without any additional complications.

Serious adverse events (SAEs) that required hospitalization, regardless of attribution, were documented in 9 (33%) patients throughout the study (5 in dose escalation cohort and 4 in the RP2D expansion cohort). The most commonly reported serious adverse events were grade 4 neutropenia, leukopenia and grade 3 febrile neutropenia seen in three patients (2 at DL1 (DLTs), and 1 in the RP2D expansion cohort). All other serious adverse events were seen in single patients and included: grade 4 non-ST elevation myocardial infarction (NSTEMI), atrial fibrillation with rapid ventricular rate, troponin elevation, pulmonary embolus, hyponatremia, grade 3 abdominal pain, chest pain, dyspnea, acute kidney injury with creatinine elevation. All patients, with the exception of two patients (one who experienced the NSTEMI and the other with elevated creatinine), went on to receive additional cycles of therapy per protocol.

Treatment delay and dose modification related to myelosuppression occurred in 2 (28.5%) patients in the RP2D cohort, however both patients subsequently completed therapy on protocol. Six patients in the dose escalation cohort received the maximum number of cycles allowed on protocol. Seven patients came off study at the discretion of their primary provider mainly due to unacceptable toxicities; in one case it was felt that the patient had derived maximum benefit from 4 cycles and one patient had symptoms suggestive of disease progression. In the RP2D expansion cohort, five patients received the maximum number of cycles on protocol. One was taken off study at the discretion of their primary provider as it was felt that this patient had derived maximum benefit from therapy. Lastly, there was one death on study that occurred in a 62 year old patient with ES-SCLC enrolled in the RP2D expansion cohort. She was anticoagulated for a mitral valve prosthesis, but had no additional prior cardiac history. During her cisplatin infusion on cycle 2 day 1, she experienced atrial fibrillation with rapid ventricular response. During her admission she also experienced a grade 1 stroke involving the left internal carotid artery. Despite a remarkable recovery from this stroke, she had a witnessed fatal PEA arrest on day 10 of the hospitalization.

Antitumor Activity

Eighteen out of 20 patients in the dose escalation cohort were assessable for response (Table 4). Confirmed partial responses were seen in 4 patients (1, each, with esophageal, high-grade neuroendocrine, non-small cell lung cancer and 1 with untreated ES-SCLC). Ten patients (3 with NSCLC, 2 with prostate, 1, each, with ES-SCLC, esophageal, adrenocortical, small cell urethral and gallbladder) attained stable disease. Four patients (1, each, with NSCLC, head and neck, unknown primary and neuroendocrine) experienced progressive disease.

In the ES-SCLC dose expansion cohort, six out of seven patients were assessable for response (Table 4). The 7th patient came off study prior to the end of cycle 2 due to death from cardiac arrest. Five patients (83.3%) had a confirmed partial response to therapy, while 1 patient (16.7%) had an unconfirmed partial response after 6 cycles. On repeat imaging this patient was noted to have disease progression.

Pharmacokinetics

The primary endpoint of this analysis was to compare AT-101 pharmacokinetic parameters on C1D1 (AT-101 alone) to those on C2D1 (AT-101 administered with cisplatin and etoposide). AT-101 pharmacokinetic parameters by dose level and cycle are described in Tables 5. The mean half-life of AT-101 was 3.32 hours (range 2.86–3.94). AUC and C_{max} are generally linear with dose and there are no significant differences between C1D1 and CD2, suggesting no interaction between AT-101 and standard chemotherapy. Of note, no (+)-gossypol was detected, suggesting no interconversion between the enantiomers occurs when AT-101 ((-)-gossypol) is administered. T_{max} occurred at approximately 3 hours, suggesting slow absorption. Etoposide and cisplatin pharmacokinetic parameters are in Table 6, and are similar to previous reports.[23, 24]

DISCUSSION

This phase I study was designed to determine the MTD/RP2D of AT-101 in combination with cisplatin and etoposide and to assess the therapeutic role of this regimen in patients with previously untreated ES-SCLC. The dose escalation portion of the study was complicated by early DLTs of febrile neutropenia seen at dose level 1, which was mitigated after the protocol was amended to include filgastrim and allowed dose escalation to proceed to the target dose (AT-101 40 mg; Cisplatin 60mg/m²; Etoposide 120mg/m²). The data on hematologic toxicity associated with AT-101 are conflicting and appear to possibly be dependent on the associated combination regimen. In the single agent phase I/II studies, AT-101 did not appear to cause significant hematologic toxicity [15–17, 25]. In the combination setting, exacerbation of hematologic toxicity was observed when AT-101 was added to docetaxel and prednisone in patients with metastatic castrate resistant prostate cancer [26]. On the other hand, no additional hematologic toxicity was attributed to AT-101 when it was combined with topotecan or docetaxel to treat lung cancer (SCLC and NSCLC, respectively) [27, 28]. Following the addition of filgastrim in our study, the incidence of hematologic toxicity resolved to that seen with EP alone when used to treat SCLC [29–31], suggesting that any additional marrow suppression caused by AT-101 in this combination can be effectively reduced by growth factor support.

We also observed a considerable rate of GI toxicities, which have been noted with AT-101, both as a single agent and in combination with other cytotoxic chemotherapy [15–17, 25, 26]. When compared to expected rates of GI toxicities with EP, our results suggest that AT-101 exacerbates the incidence of at least grade 1–2 events, including abdominal pain and diarrhea. A patient enrolled on dose level 1 experienced an NSTEMI associated with troponin elevations during cycle 1. Also, one patient with metastatic castrate resistant prostate cancer developed bilateral pulmonary emboli after cycle 4 on dose level 3a. Cardiac toxicities including elevated troponins and syncope, and thrombotic complications have also been reported with AT-101 [15, 26, 32]. Given the high rate of thrombotic complications that occur in the setting of advanced cancer, attribution of these events to AT-101 is challenging.

No significant interactions were observed in the AT-101 concentration after the addition of cisplatin and etoposide in cycle 2. Cisplatin and etoposide pharmacokinetics were similar to previously published reports, and although we did not evaluate them in the presence and

absence of AT-101, pharmacokinetic drug interactions resulting in increased toxicity is unlikely.

The clinical experience of AT-101 in ES-SCLC has been somewhat disappointing. Baggstrom et. al reported the use of AT-101 as a single agent in patients with recurrent, sensitive ES-SCLC; however, no responses to therapy was seen in this setting [25]. In a report by Heist et. al of AT-101 with topotecan in patients with relapsed and treatment refractory SCLC, the combination was well tolerated but poor response rates were seen [27]. However, our preliminary efficacy data of AT-101 added to cisplatin and etoposide are encouraging, albeit limited by our small number of patients. For example, in the dose expansion cohort, 5 of 7 patients attained a confirmed partial response. This rate exceeds expected antitumor response rates of 40% – 50% seen in this setting with EP alone [30, 31]. We hypothesize that any efficacy gains from AT-101 potentially derive from the role it may play in delaying and/or overcoming chemotherapy resistance and, as such, it would yield optimal results in the setting of combination cytotoxic therapy. Recent data from a randomized study in patients with advanced NSCLC, which combined AT-101 with docetaxel, also suggested a slight survival advantage in the second line setting [28].

SCLC is characterized by the rapid development of chemotherapy resistance resulting in poor overall survival [33, 34]. Bcl-2, overexpressed in a majority of small cell lung cancers, promotes resistance to therapy [5, 6]. While our results are limited by our small number of patients, they support suppression of Bcl-2 and related family members in the treatment of SCLC [13]. Further studies with AT-101 or similar BH-3 mimetics in combination with chemotherapy regimens in patients with previously untreated, treated or treatment refractory ES-SCLC, are warranted to evaluate if treatment with BH-3 mimetics extend survival rates.

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Table 1

Patient Characteristics

Dose Escalation Cohort	
Total	20
Median age, years (range)	60 (37-77)
Gender	
Male	14
Female	6
ECOG Performance Status	
0	6
1	13
2	1
Primary tumor type	
Lung - NSCLC	7
Lung - ES SCLC	1
Esophagus	2
Head & Neck	1
Prostate	3
Neuroendocrine	3
Unknown Primary (Squamous cell carcinoma)	1
Adrenal	1
Gall bladder	1
No. of prior chemotherapy regimens	
0	4
1	3
2	4
3 or more	9
RP2D Expansion Cohort in patients with ES-SCLC	
Total	7
Median Age, years (range)	64 (58-67)
Gender	
Male	3
Female	4
ECOG Performance Status	
0	1
1	4
2	2

Table 2

Dose Levels and Frequency of DLTs

Dose Level	N	Dose of AT-101 (mg)	Dose of Cisplatin (mg/m ²)	Dose of Etoposide (mg/m ²)	No. of Patients with DLTs	Description of DLTs
-1	3	20	60	100	0	
1	5	30	60	100	2	Febrile Neutropenia
1a	3	30	60	100	0	
2a	3	30	60	120	0	
3a	6	40	60	120	0	
RP2D Expansion Cohort	7	40	60	120	0	

Common Adverse Events during Cycle 1

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Dose Level	1A			2A			3A			RP2D Expansion		
Dose	AT-- 101 20 mg Cisplatin 60 mg/m ² Etoposide 100 mg/m ²			AT-- 101 30 mg Cisplatin 60 mg/m ² Etoposide 100 mg/m ²			AT-- 101 40 mg Cisplatin 60 mg/m ² Etoposide 120 mg/m ²			AT-- 101 40 mg Cisplatin 60 mg/m ² Etoposide 120 mg/m ²		
No. of Patients	3			5			3			6		
Grade	1-- 2	3	4	1-- 2	3	4	1-- 2	3	4	1-- 2	3	4
Pneumonia											1	
Dermatologic												
Alopecia	1			1				1		2		
Other												
Weakness	2			1								
Headache							1			1		
Urinary frequency										1		
Cardiac												
Cardiac Ischemia						1						
Elevated troponin						1						
Hypotension											1	

Table 4**Anti-Tumor Activity**

Dose Escalation	
Outcome	% Patients (n=18)
Confirmed Partial Response (PR)	22% (4)
Stable Disease (SD)	55.5% (10)
Progressive Disease (PD)	22% (4)
Dose Expansion	
Outcome	% Patients (n=6)
Confirmed Partial Response (PR)	83.3% (5)
Unconfirmed partial response (PR)	16.7% (1)
Stable Disease (SD)	0
Progressive Disease (PD)	0

Table 5AT-101 PK Parameters (Mean $\pm$ SD) by Cycle and Dose

		C _{max} (μ g/mL)	T _{max} (Hours)	Half-life (Hours)	AUC (hr $\cdot$ μ g/mL)	Cl/F (L/hr)	V/F (L)
Cycle	Dose AT101 (n)						
1	20mg (3)	1.01 $\pm$ 0.51	3.00 $\pm$ 1.00	3.46 $\pm$ 1.09	6.69 $\pm$ 3.59	3.91 $\pm$ 2.66	19.56 $\pm$ 2.66
	30mg (11)	1.93 $\pm$ 0.63	3.09 $\pm$ 0.54	2.98 $\pm$ 0.63	11.47 $\pm$ 3.22	2.80 $\pm$ 0.75	12.27 $\pm$ 0.75
	40mg (7)	1.67 $\pm$ 0.79	3.43 $\pm$ 0.53	3.44 $\pm$ 1.00	10.33 $\pm$ 5.32	5.02 $\pm$ 2.95	27.34 $\pm$ 2.95
2	20mg (3)	1.02 $\pm$ 0.64	3.67 $\pm$ 0.58	3.94 $\pm$ 1.23	6.97 $\pm$ 3.99	3.63 $\pm$ 2.11	22.95 $\pm$ 2.11
	30mg (8)	1.88 $\pm$ 0.56	3.63 $\pm$.52	2.86 $\pm$ 0.52	11.33 $\pm$ 3.58	2.93 $\pm$ 1.07	11.88 $\pm$ 1.07
	40mg (6)	1.96 $\pm$ 0.66	3.34 $\pm$ 0.81	3.26 $\pm$ 1.47	12.17 $\pm$ 3.18	3.53 $\pm$ 1.13	16.93 $\pm$.13

Table 6

Cisplatin and Etoposide PK Parameters by Cycle and Dose

	Day	C _{max} (µg/mL)	T _{max} (hr)	Half-life (hrs)	AUC (hr*µg/mL)	Cl (L/hr/m ²)	V (L/m ²)
Cisplatin (n=16)	C2D1	5.97±0.99	2.25±0.20	0.70±0.31	11.38±2.25	5.36±0.99	5.23±2.26
Etoposide 75mg/m ² (n=2)	C2D1	17.52±3.25	2.72±0.01	4.93±1.36	95.32±4.70	0.79±0.04	5.63±1.83
Etoposide 100 mg/m ² (n=6)	C2D1	22.61±5.11	2.97±0.13	5.95±1.07	148.18±36.65	0.70±0.14	5.89±0.63
Etoposide 120 mg/m ² (n=8)	C2D1	26.09±3.46	2.98±0.23	5.07±0.62	149.33±23.31	0.82±0.12	5.99±1.14