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A phase 1 study of KOS-862 (Epothilone D) co-administered with carboplatin (Paraplatin®) in patients with advanced solid tumors

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Summary

Purpose—To determine the maximally tolerated dose (MTD) and pharmacokinetics of carboplatin plus KOS-862 (Epothilone D) a novel cytotoxic macrolide capable of causing mitotic arrest, in patients with advanced solid malignancies.

Experimental Design—Patients who have progressed on standard regimens were treated at four different levels of KOS-862(mg/m²)/Carboplatin(AUC): 50/5, 75/5, 75/6 and 100/6 in a “3+3” phase I study design to determine MTD. Patients received KOS-862 on Days 1 and 8, and carboplatin on day 1, of 3-week cycles. Pharmacokinetics of KOS-862 and Carboplatin were studied.

Results—Twenty-seven patients enrolled in the study. At the top dose level, 2 out of the 9 patients experienced Dose Limiting Toxicity. (grade 3 peripheral motor neuropathy in both patients) Twenty-seven patients had sufficient plasma data points for pharmacokinetic analysis

Both the parent drug, KOS-862, and the major inactive metabolite Seco-D KOS-862 (KOS-1965) were quantified in plasma. Kinetics of KOS-862 were the same as seen in monotherapy studies using the same route and time of administration. Two patients had tumor response after study treatment. Ten of 20 evaluable patients had stable disease after 2 cycles of study treatment. The MTD in the present study was KOS-862 100 mg/m² + carboplatin AUC=6.

Conclusions—The pharmacokinetics of KOS-862 were similar in this combination study to those seen in previous monotherapy studies using the same route and time of administration. We have described the MTD of this schedule. The neurotoxicity seen with this regimen should be considered prior to its administration in unselected populations.

Keywords

Epothilone D; Phase I; Carboplatin

Introduction

KOS-862 (Epothilone D; 12,13-desoxyepothilone B) belongs to a class of cytotoxic macrolides capable of causing mitotic arrest by stabilizing tubulin polymerization [1, 2]. Since microtubules are essential for mitosis, motility, secretion, and proliferation, the observed antitumor effects of epothilones have been attributed to their ability to initiate cell death by inhibiting such processes. KOS-862 has demonstrated in vitro cytotoxic activity in a panel of human cell lines, equipotent to that of paclitaxel. KOS-862 is more potent than paclitaxel in p-glycoprotein overexpressing cell lines that demonstrate multiple drug resistant properties [3, 4]. KOS-862 compares favorably with parent compound epothilone B [5, 6]. The compound differs from epothilone A and B which are classified as epoxides because of an epoxide moiety at C(12) to C(13) on the macrolide structure. KOS-862 is classified as an olefin (as is Epothilone C) and does not contain the epoxide moiety [7]. While having the epoxide moiety was predictive of increasing potency in the parent compounds, epothilone D retained potent biological activity similar to the epoxide containing parent compounds [8, 9]. The dose-limiting toxicity (DLT) for KOS-862 on all phase 1 schedules was primarily neurologic. In addition, individual patients have also experienced DLT consisting of atypical chest pain, nausea/vomiting/diarrhea leading to dehydration, and small-bowel obstruction.

Carboplatin (diamine [1,1-cyclobutane-dicarboxylato(2-)-O,O']-platinum) is a platinum-containing antineoplastic that exhibits potent antitumor activity. The drug is commercially available and has broad-spectrum activity against a variety of malignancies and a generally favorable toxicity profile. After intravenous (IV) delivery, activated platinum moieties are believed to lead to irreversible DNA or protein adducts. Carboplatin is administered by IV infusion, with doses calculated on a milligram-per-square-meter basis or using Calvert's formula that takes into account gender and renal function [10]. Doses have been calculated using a variety of formulae to estimate the glomerular filtration rate (GFR), including Cockcroft and Gault, and Jelliffe. For this study, the formula of Cockcroft and Gault was used to define the creatinine clearance rate.

The rationale for combining KOS-862 and carboplatin in part is due to their non-overlapping toxicities and different mechanisms of antineoplastic activity. The potential for complementary activity led to this phase I study. Co-administration of KOS-862 and carboplatin using human lung cancer cell lines did not reveal any sequence dependant action. Therefore the sequence of administration was empirically chosen with KOS-862 preceding carboplatin

The primary purpose of this phase I study was to establish the maximum tolerated dose (MTD), safety and pharmacokinetics of KOS-862 delivered days 1 and 8 plus carboplatin day 1 in 3 week cycles.

Patients and methods

Patient population

Patients with histologically confirmed advanced solid malignancies refractory to standard therapy or for whom no effective therapy existed were candidates for this study. Other eligibility criteria included: Age ≥ 18 years, Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, adequate hematopoietic (ANC $1.5 \times 10^9/L$, HGB 8.0 g/dL , Platelet count $75 \times 10^9/L$), hepatic {Aspartate aminotransferase (AST) $2.5 \times$ upper limit of normal (ULN) ($<5 \times$ ULN if liver metastases)} and renal (serum creatinine 2.0 mg/dL) functions, a minimum of 3 weeks must have elapsed between last receipt of chemotherapy, surgery, or radiotherapy and the first administration of KOS-862 and carboplatin;

Patients were excluded if they had: pre-existing neuropathy of Common Terminology Criteria for Adverse Events of the National Cancer Institute version 3 (CTCAE) Grade ≥ 2 due to any cause; prior significant toxicity to carboplatin therapy that would preclude retreatment with this agent (such as clinically symptomatic Grade 4 myelosuppression); documented hypersensitivity reaction of CTCAE Grade ≥ 3 to prior therapy containing Cremophor®; pregnant or breast-feeding women; known central nervous system (CNS) metastases requiring corticosteroids; patients with personal or family history of congenital long QT syndrome, or patients with mean QTc interval $>450 \text{ msec}$ (males) or $>470 \text{ msec}$ (females) identified on screening electrocardiograms (ECGs); prior malignancies unless free of recurrence for at least 5 years, except cured basal cell carcinoma of the skin, carcinoma-in-situ of either the cervix, breast or urinary bladder or stage T1 or T2 prostate cancer in patients whose prostate-specific antigen (PSA) level was $<2 \text{ ng/mL}$.

The Institutional Review Boards of the participating centers approved the protocol and all patients were required to give written informed consent before entry.

Treatment schedule

This was a Phase 1, open-label, dose-escalation trial. Patients received KOS-862 on Days 1 and 8, plus carboplatin on day 1, of 3-week cycles. On Day 1 of each cycle, patients were premedicated with antihistamines (H_1 and H_2 receptor antagonists) and corticosteroids, followed 30 min later by KOS-862 administered via intravenous infusion over 90 min. Carboplatin was then administered via IV infusion over 30 min at doses based on the estimated area under the plasma concentration versus time curve (AUC in $\text{mg/mL} \times \text{min}$).

On Day 8 of each cycle, therapy consisted of premedications followed 30 min later by IV infusion of KOS-862 only. Dose escalation was as follows (KOS-862 mg/m²/Carboplatin mg/mL x min): 50/5, 75/5, 75/6, 100/6.

Dose escalation decisions were based on 3 evaluable patients per cohort. An “evaluable” patient was one who received at least 2 treatments within 3 weeks during Cycle 1 and underwent at least one repeat safety assessment. If a patient withdrew from Cycle 1 for toxicity (DLT or otherwise), this patient was considered evaluable for dose escalation decisions. For the purpose of this study, the dose-limiting toxicity (DLT) was defined as any of the following clinical toxicities observed during the first treatment cycle, using the NCI CTCAE version 3.0: ANC <500/ μ L lasting more than 7 consecutive days or febrile neutropenia (ANC <1.0 $\times$ 10⁹/L, fever $\geq$ 38.5°C); grade 4 thrombocytopenia (platelets <25.0 $\times$ 10⁹/L or a bleeding episode requiring platelet transfusion); grade 4 anemia (hemoglobin <6.5 g/dL); non-hematological toxicity including: any grade $\geq$ 3 non-hematologic toxicity (except grade 3 injection site reaction, alopecia, anorexia, fatigue, or vomiting), nausea and/or vomiting of grade $\geq$ 3 despite the use of maximal medical intervention and/or prophylaxis; treatment delay of more than 3 weeks due to prolonged recovery from a drug-related toxicity

If no DLT was observed in a cohort of 3 evaluable patients, then the next dose level was to be evaluated. If one patient experienced a DLT, then the cohort was to be expanded to 6 evaluable patients. If 2 or more of 6 evaluable patients entered in a cohort experienced a DLT, then the MTD was exceeded and all further accrual was to be at the previous dose level. If no more than one of the 6 patients experienced a DLT, then the next dose level was to be evaluated. Once the MTD was defined, an additional 12 patients were to be enrolled at the MTD level. Consideration was to be given to enrolling a majority of lung and ovarian cancer patients in this group.

Efficacy assessments: therapeutic response

The purpose of this Phase 1 study was to establish the MTD, safety, and pharmacokinetics of KOS-862 and carboplatin when co-administered in 3-week cycles. Toxic effects were thus the primary study endpoint and were assessed continuously. Response information was obtained if patients had disease that could readily be measured and re-assessed. Response assessments were made every 3 cycles (approximately every 9 weeks) by Response Evaluation Criteria in Solid Tumors (RECIST).

Computed tomography (CT) and magnetic resonance imaging (MRI) were the preferred methods for tumor assessments.

At baseline, tumor lesions were categorized by the Investigator as measurable or non-measurable by the RECIST criteria.

Pharmacokinetic analysis/plasma sampling

Blood samples for pharmacokinetic analysis of KOS-862 and Seco-D metabolite were obtained on day 1 of cycle 1 and cycle 2 prior to the infusion, and at 60 min after the start of

the infusion, just before the end of the infusion and 5, 15, 30 min and 1.0, 2.0, 4.0 and 25.5 h following the infusion. Plasma was separated from the heparinized blood and stored at -70°C pending analysis. Blood samples for pharmacokinetic analysis of carboplatin were obtained on Day 1 of cycle 1 and cycle 2 prior to the start of the KOS-862 infusion, prior to the end of the carboplatin infusion and exactly 24 h following the end of the carboplatin infusion. A fourth sample for carboplatin was added in Amendment #2 at 2.75 h following the end of the infusion. All carboplatin samples were collected into heavy metal-free containers with EDTA as anticoagulant.

Plasma concentrations of KOS-862 (RO4598715) and Seco-D metabolite (RO4654366) were measured at Prevalere Life Sciences Inc, Whitesboro, N.Y 13492, using an assay developed by Kosan Biosciences Inc. Hayward CA94545, and Hoffman La-Roche, Nutley NJ 07110. Plasma samples were thawed on ice, and 25 μL was aliquotted into 96 deep-well block sitting on ice. 75 μL of a phosphate buffer solution pH 7.0 containing 100 ng/mL deuterated internal standard, RO4598715 ($\text{M} + 4$)/RO4654366 ($\text{M} + 4$) was added and mixed followed by 500 μL methyl-*t*-butyl ether. The block was covered, mixed and centrifuged for 10 min at 10°C . 300 μL of the supernatants were transferred to a 96 well injection block and evaporated to dryness using a Turbovac at room temperature. Samples were reconstituted in 100 μL methanol/water/0.088% formic acid (85:15:0.088, v/v).

The LC:MS:MS system consisted of a Liquid Chromatograph with Shimadzu SCL-10A controller, an Armor Advantage C8 5 μL column (30 $\times$ 2.1 mm) and gradient mobile phase based on 0.088% formic acid in water and 0.088% formic acid in methanol. Flow rate was 0.3–0.4 mL/min and the autosampler was set at 7°C . The Mass Spectrometer was either a Micromass Quattro Ultima with Electrospray (positive ion) or Sciex API 3000 with positive ion turbospray. Mass transitions monitored were: Channel 1 reaction 496 $\rightarrow$ 308 and Channel 2 reaction 493 $\rightarrow$ 304. These conditions gave run time of 5.5 min and cycle 9.0 min with approximate retention times for KOS-862 at 4.0 min and the Seco-D metabolite at 3.8 min.

Plasma samples for Carboplatin and free carboplatin were assayed by National Medical Services, Willow Grove, PA19090. The assay was fully validated and was part of the list of analytical methods offered by this commercial laboratory. Analysis for Total platinum and free platinum was performed in the Inductively Coupled Plasma Mass Spectrometer (ICPMS).

A non-compartmental intravenous model was fitted to the KOS-862 and Seco-D metabolite concentration-time data using Kinetica[®] (Thermo Electron Corporation, Philadelphia, PA19103). Area under the concentration-time curve was calculated by the log-linear rule and the terminal rate constant λ_z from at least three points on the elimination curve. C_{max} and T_{max} were determined directly from the concentration-time data.

Carboplatin AUC was calculated from the formula developed by Calvert [10]. Free Carboplatin AUC ($\text{mg/mL} \cdot \text{min}$) = $24 \text{ h Pt } (\mu\text{M}) + 0.3/0.82$

Where the 24 h Platinum is the total plasma platinum concentration collected at 24 h after the end of the carboplatin administration.

Data analysis

Descriptive statistics were used in summarizing all baseline patient characteristics, treatment administration, safety variables, and efficacy variables. No hypothesis testing was performed. Plasma concentrations and PK data were analyzed separately.

Results

General

Twenty seven patients, whose characteristics are detailed in (Table 1), received a total of 152 infusions of KOS-862 and 80 infusions of carboplatin for a total of 76 cycles of treatment. All patients had an ECOG performance status of either 0 or 1. All patients had had at least one prior line of cytotoxic treatment. Patients were treated in four different cohorts: 6 patients at 50 mg/m²+5 AUC, 8 patients at 75 mg/m²+5 AUC, 4 patients at 75 mg/m²+6 AUC, and 9 patients at 100 mg/m²+6 AUC. The first cohort was expanded to six after one of the first three individuals developed DLT (febrile neutropenia). No further DLT was seen. The second cohort was expanded to a total of eight patients as a result of two deaths that occurred. Both deaths were considered unrelated to treatment and are further described below in the next section. Four patients were enrolled in cohort number 3 without DLT seen. The additional patient was allowed in this cohort because there were two patients assigned nearly simultaneously in both participating medical centers. In the fourth cohort nine patients were enrolled with two DLTs seen. The two patients that experienced DLT were in the expanded portion of the study as no DLT was seen in the first three patients of this cohort. The accrual in this cohort was discontinued after nine patients instead of the planned 12. Fourteen patients (51%) discontinued as a result of insufficient response, 8 patients (30%) discontinued secondary to adverse events, 2 patients (7%) experienced infusion reactions related to carboplatin administration, 2 patients (7%) died, and 1 patient (4%) had a treatment delay that was considered a protocol violation. Fifteen patients (56%) completed at least 2 treatment cycles, including 5 patients (83%) in the 50/5 group, 4 patients (50%) in the 75/5 group, 2 patients (50%) in the 75/6 group, and 4 patients (44%) in the 100/6 group.

Toxicity

Two deaths occurred on this study, both in the 75/5 dose group. The first patient's death was attributed to cardiorespiratory failure secondary to sepsis and was considered unrelated to study drug because the sepsis occurred in the setting of a normal leukocyte count and differential. The patient received only one infusion of KOS-862, 3 days prior to death. The second death was attributed to hepatic encephalopathy resulting from progressive metastatic lung cancer, and was considered remotely related to study drug. This patient received only one infusion of KOS-862, 21 days prior to death. Although these two deaths were not considered related to study drug, the cohort was expanded to 8 patients to ensure the safety of this dose level.

Twenty-three patients (85%) experienced at least one grade 3 or 4 toxicity. (Table 2) The overall incidence of these AEs increased slightly with the carboplatin dose level; affecting 83% of the 50/5 group, 63% of the 75/5 group, and 100% of the 75/6 and 100/6 groups. The

most common grade 3/4 toxicity included neutropenia and fatigue, each in 4 patients (15%), and thrombocytopenia, hypersensitivity (to carboplatin), and dyspnea, each in 3 patients (11%). Severe or life-threatening decreased neutrophil count was also reported in 2 patients (7%), and decreased platelet count in 1 patient (4%). The only other severe or life-threatening AEs reported in more than one patient were hypoesthesia and grade 3 peripheral motor neuropathy each occurring in 2 patients (7%). The incidence of severe nervous system disorders in general and peripheral motor neuropathy in particular increased with the dose level of KOS-862. Of the 3 severe nervous system disorders, 2 occurred in the 100/6 group, and both severe toxic events of peripheral motor neuropathy occurred in the 100/6 group.

Dose limiting toxicity

Eight (32%) of the 25 evaluable patients developed DLT at any time point, and 3 patients (12%) experienced DLT during Cycle 1. (Table 3) After 1 patient in the first cohort had a DLT (severe neutropenia), the 50/5 group was expanded to 6 patients without the occurrence of an additional DLT. Dose escalation continued until 2 of the 9 patients enrolled in the 100/6 group experienced DLT during Cycle 1. Both of these patients were enrolled in the preplanned expansion of this final cohort after no DLT was seen in the first 3. Patient 011.404 with ovarian cancer had severe peripheral motor neuropathy, with impaired gait and difficulty walking, 8 days after receiving the first dose of study drug. The patient was unable to elevate her right great toe. The patient developed additional neuropathies including hypoesthesia, paresthesia, neuropathic pain, and restless legs syndrome. The peripheral motor neuropathy of the great toe was ongoing at the time of trial discontinuation. Patient 011.409 with ovarian cancer had two DLTs: severe peripheral motor neuropathy with onset the day after receiving the Cycle 1, Day 1 dose, and severe hypoesthesia in the toes with onset 13 days after the Cycle 1, Day 8 dose. On the same day as the hypoesthesia, the patient also developed a severe carboplatin hypersensitivity reaction. Both conditions were ongoing at the time of discontinuation. The incidence of DLTs was greater (3 of 7 patients [43%]) among patients with ovarian cancer, compared with those with other cancers (5 of 18 [28%]).

Efficacy

This study was designed primarily to evaluate safety and dose-limiting toxicity rather than efficacy. Because of the dose-escalation design, the small number of patients in each group, and lack of a control group, relatively little information about efficacy could be obtained. Two patients had objective overall tumor response after study treatment. One patient in the 50/5 group (44-year-old female with epithelial ovarian cancer, whose prior therapy included: Taxol/carboplatin x 6 cycles, IP cisplatin for 4 cycles) had a new 1.7×1.7 cm cystic mass anterior to right psoas suspicious for tumor implant prior to enrollment. Following one cycle of treatment the was not visualized; in parallel, the CA125 declined from 43 to 6. The patient is considered an unconfirmed complete response, as she withdrew from study due to prolonged neutropenia. In addition, one patient in the 75/6 group, who had non-small cell lung carcinoma, had an overall partial response during the study, beginning at Cycle 3 and confirmed at the final visit. Remarkable stability and toleration of this regimen was demonstrated in a 37-year-old patient with metastatic colorectal cancer with lung and liver

involvement. He was heavily pretreated. (7 prior regimens including FOLFIRI, FOLFOX, FOLFOX + Avastin, CALGB vaccine trial, bortezomib/paclitaxel; capecitabine/oxaliplatin; capecitabine alone, radiofrequency ablation and multiple hepatic artery embolizations) He achieved a mixed response. (The longest diameters the chest lesions shrank ~ 50% and the abdominal lesions increased ~10%). He maintained a performance status of 0 over 11 cycles of therapy and experienced Grade 1-2 peripheral sensory neuropathy.

Pharmacokinetics

Of the 27 patients entered into the study all completed the first PK sampling period and 18 completed Cycle 2 Day 1. Plasma concentration decay profiles demonstrate a biphasic decay with rapid distribution phase (Fig. 1). The Seco-D metabolite reached equal plasma concentration with parent drug at approximately 3 h post infusion.

Coefficients of variation for KOS-862 PK parameters were consistent across all dose cohorts and there was no dose dependency demonstrated for clearance or distributive volumes, (Table 4). The drug was cleared from the plasma at 8.2 ± 3.5 L/h/m² and the half-life was 7.6 ± 1.3 h with similar half-life for the metabolite. All PK parameters were in keeping with results from monotherapy studies. Exposure to KOS-862 showed overlapping values for the 50–100 mg/m² dose levels, (Fig. 2). Exposure to the Seco-D Metabolite also showed wide variation between patients. The ratio AUC_{tot} Seco-D metabolite to AUC_{tot} KOS-862 was determined for all patients. Mean ratio was 0.57 ± 0.33 , range 0.20 to 1.85; the maximum ratio, 1.85 was found in a patient with extremely high parent drug AUC_{tot} which suggests that the conversion to the Seco-D Metabolite is essential for metabolic elimination of KOS-862.

Patients who were dosed with a Carboplatin target AUC=5 averaged 5.32 ± 2.05 mg/mL*min; patients who were dosed with a target AUC=6 averaged 7.21 ± 1.1 mg/mL*min. There should not be any free platinum in the plasma at 24 h post carboplatin infusion, it should all be completely bound to proteins except in patients with impaired renal function.

Conclusion

The primary dose-limiting toxicity of KOS-862 combined with carboplatin was neurotoxicity. Three patients treated with the highest dose combination (100/6) developed peripheral (motor) neuropathy at some time point in treatment. Lower grades of neurotoxicity were seen in most patients. Twenty of the remaining 24 other patients had evidence of nervous system toxicity, including dizziness, hypoesthesia, paresthesia, or peripheral sensory neuropathy.

The MTD in the present study was KOS-862 100 mg/m² + carboplatin AUC=6, administered on Days 1 and 8 (KOS-862 only) of 21-day treatment cycles. In this small cohort of patients we suspect the occurrence of grade 3 neurotoxicity in patients with ovarian cancer is likely related to prior exposure to chemotherapy with known potential for neurotoxicity [11]. With improved selection, the MTD may have been higher.

Neurotoxicity is a class effect of microtubule targeting agents [12]. Sensory neuropathy is more prevalent but motor neuropathy and central nervous system toxicity have been reported. Direct comparison between the newer epothilones and older agents is not possible given the relatively small experience with epothilones. Significant neurotoxicity has been reported in a group of men with castrate resistant prostate cancer treated with KOS-862 after previously receiving docetaxel [13]. This level of neurological toxicity was not seen in the phase I experience or from prior phase 2 single agent trials in metastatic breast and lung cancer [14, 15]. A recent review of the literature indicated that the incidence rates of grade 3/4 sensory and motor neuropathy in patients treated with epothilones were similar to those in patients with breast cancer treated with taxanes [16].

Non-compartmental pharmacokinetic analysis of the plasma concentration, time data found no difference in the kinetics of KOS-862 compared to the previous studies using the same administration route and time. Carboplatin was administered after the KOS-862 infusion and appeared to have no effect on the clearance of KOS-862. At the highest dose administered, 100 mg/m², AUC_{tot} ranged from 6281 to 23616 ng.mL*h. The amount of extrapolation required to extend the AUC_{last} (the last measured time point) data to infinity was small, mean for all patients 6.9±3.1% indicating that the assay has appropriate sensitivity and that the blood collection to 24 h post-infusion was reasonable to estimate the elimination phase of KOS-862. Inter-patient variation in this study was four-fold, considerably less than seen in the NSCLC study in which the variation in AUC_{tot} was 17-fold. Clearance showed an overall RSD 43.0% with a range of clearances from 2.44 to 28.6 L/h/m² demonstrating the significant inter-patient variation. Several studies of the metabolism of KOS-862 have been undertaken. Metabolite profiling of the human plasma in a previous study indicated some 29 metabolites (MDS Pharma Services Study # 020278 dated July 2002). The study of the metabolic fate of KOS-862 in human microsomes produced 22 metabolites (MDS Pharma Services Project # 020295; Determination of the Ki Values Associated with the Inhibition of Human Liver Microsomes by Epothilone-D). Results of these studies indicate that KOS-862 is a substrate for CYP3A4, 2C9, 2C19 and 2B6 as well as a moderate competitive inhibitor of CYP3A4 at 6 micromolar and weak competitive inhibitor of CYP2C9 at 38–60 micromolar (this latter value is unlikely to be physiologically relevant). Inhibition of the formation of metabolites was also demonstrated using known chemical inhibitors for cytochromes 2B6, 2C9, 2C19, 3A4 and 3A4/5. It appears that multiple pathways for the elimination of KOS-862 exist; several of them are subsequent to the formation of *seco-D*-Epothilone metabolite produced by esterases. Although the drug is therefore unlikely to have a single metabolic pathway or be reliant upon one cytochrome, formal analyses of potential drug-drug interactions are not complete.

Calculation of the carboplatin AUC, based upon analysis of one blood sample collected 24 h post infusion, confirmed that, in most cases, the drug was administered at the appropriate dose. The two patients who demonstrated high results were both developing renal impairment, one with a raised BUN and the other a marginally elevated creatinine.

We have identified the MTD of the combination of KOS-862 and carboplatin. Kinetics of KOS-862 were similar to those seen in previous monotherapy studies using the same route and time of administration. The neurotoxicity seen in this trial is concerning and may be

related to our patient's prior treatment. Alternatively with activity seen in dose levels below the MTD perhaps a lower dose can provide similar efficacy with less toxicity. Ultimately with patient selection, this combination is worthy of further study.

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Fig. 1.
Log linear Concentration:time curves for 4 dose groups, KOS-862 only

Fig. 2.
KOS-862 AUC_{tot} (ng/mL*h) vs Dose (mg/m²)

Table 1

Patient characteristics

Characteristic	No. of patients
Total no. of patients	27
Sex (male:female)	12:15
Median age (range)	58(37–78)
ECOG ^a performance status	
0, 1	27
Previous treatment (percentage)	
1–2 Regimens	9(33)
3–5 Regimens	14(52)
6+ Regimens	4(15)
Prior Taxane	24(89)
Tumor Types (percentage)	
Non-small cell lung	6(22%)
Ovary	5(19%)
Other	4(15%)
Peritoneal	2(7%)
Small cell lung	2(7%)
Prostate	2(7%)
Colorectum	2(7%)
Sarcoma	2(7%)
Head and neck	1(4%)
Hepatocellular	1(4%)
Unknown primary	1(4%)
Bladder	1(4%)
Pancreas	1(4%)
Stomach	1(4%)

^aEastern Cooperative Oncology Group

Table 2

Grade 3/4 toxicity per cohort

KOS-862	50 mg/m²	75 mg/m²	75 mg/m²	100 mg/m²	Total
Carboplatin	5 AUC N=6	5 AUC N=8	6 AUC N=4	6 AUC N=9	Patients N=27
Hematologic toxicity					
Anemia	0	1 (13%)	0	0	1 (4%)
Neutropenia	3 (50%)	0	0	1 (11%)	4 (15%)
Thrombocytopenia	0	0	1 (25%)	2 (22%)	3 (11%)
Non hematologic toxicity					
Diarrhea	0	1 (13%)	0	0	1 (4%)
Fatigue	0	0	1 (25%)	3 (33%)	4 (15%)
Infections ^a	1 (17%)	1 (13%)	3 (75%)	1 (11%)	6 (22%)
Peripheral motor neuropathy	0	0	0	2 (22%)	2 (7%)
Peripheral sensory neuropathy	0	1 (13%)	0	1 (11%)	2 (7%)
Thromboembolic episode	0	0	2 (50%)	0	2 (7%)

Toxicity over multiple courses. DLT assessed in first course.

^b bacteremia, pneumonia, sepsis, upper respiratory tract infection, urinary tract infection

Table 3

Summary of solid tumor dosing cohorts and dose-limiting toxicity events

Dose Level	Patients with DLT/ Patients treated at dose level	Description of DLT events
Dose Level 1: K 50 mg/m ² + C AUC 5	1/6	- prolonged neutropenia
Dose Level 2: K 75 mg/m ² + C AUC 5	0/8	- 2 deaths occurred that were unrelated to treatment but led to the expansion of this cohort.
Dose Level 3: K 75 mg/m ² + C AUC 6	0/4	
Dose Level 4: K 100 mg/m ² + C AUC 6	2/9	-Grade 3 peripheral motor neuropathy in both and grade 3 peripheral sensory neuropathy in one.

K KOSAN-862; *C* carboplatin; *DLT* dose-limiting toxicity

Table 4

KOS-862 Pharmacokinetic parameters

Dose level (mg/m ²)	50/5			75/5			75/6			100/6		
	Mean	SD	%RSD	Mean	SD	%RSD	Mean	SD	%RSD	Mean	SD	%RSD
KOS-862/carboplatin												
C _{max} (ng/mL)	2536	1115	43.97	3491	859	24.62	3195	435	13.61	4483	1371	30.6
AUC _{last} (ng/mL* <i>h</i>)	8167	4891	59.88	10385	4012	38.64	8792	1524	17.3	11616	5216	44.90
AUC _{tot} (ng/mL* <i>h</i>)	8972	5634	62.80	11153	4450	39.90	9222	1656	18.0	12410	5430	43.76
L _z (l/h)	0.0903	0.0103	11.38	0.0969	0.0177	18.22	0.1079	0.0148	13.68	0.0930	0.0175	18.76
Half-life (h)	7.77	0.92	11.85	7.97	1.47	18.46	6.54	1.01	15.45	7.70	1.45	18.87
CL (L/h/m ²)	7.89	4.81	61.02	7.02	2.78	39.59	8.39	1.69	20.08	9.40	3.67	39.08
V _z (L/m ²)	87.30	53.86	61.69	80.25	32.07	39.97	78.13	12.95	16.57	106.72	50.18	47.02
V _{ss} (L/m ²)	70.65	42.09	59.58	59.54	22.12	37.16	57.10	9.55	16.72	74.06	35.19	47.52