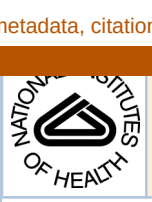

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Phase I and Pharmacokinetic Study of Pegylated Liposomal CKD-602 (S-CKD602) in Patients with Advanced Malignancies

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Abstract

Purpose—S-CKD602 is a pegylated liposomal formulation of CKD-602, a semi-synthetic camptothecin analogue. Pegylated (STEALTH®) liposomes can achieve extended drug exposure in plasma and tumor. Based on promising preclinical data, the first phase I study of S-CKD602 was performed in patients (pts) with refractory solid tumors.

Experimental Design—S-CKD602 was administered IV every 3 weeks. Modified Fibonacci escalation was used (3–6 pts/cohort), and dose levels ranged from 0.1 to 2.5 mg/m^2. Serial plasma samples were obtained over two weeks and total (lactone + hydroxyl acid) concentrations of

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STATEMENT OF CLINICAL RELEVANCE

This study of S-CKD602 is the first phase I study of a pegylated-liposomal formulation of a camptothecin analogue and first pharmacokinetic study evaluating the disposition of the liposomal encapsulated and released drug for a carrier formulation of a camptothecin analogue. Evaluation of the pharmacokinetic disposition of the liposomal encapsulated verses released drug is of the utmost importance because the liposomal encapsulated drug is an inactive prodrug. S-CKD602 showed manageable toxicity and promising antitumor activity, especially in platinum-refractory ovarian cancer. The prolonged plasma exposure of encapsulated and released CKD-602 over 1 to 2 weeks is consistent with STEALTH liposomes and provides extended exposure compared with non-liposomal CKD-602. S-CKD602 also has pharmacologic advantages over other liposomal camptothecin agents. There is significant inter-patient variability in the pharmacokinetic disposition of S-CKD602 and pharmacokinetic disposition of S-CKD is associated with saturable clearance. These pharmacokinetic characteristics may also be associated with all liposomal and nanoparticle carrier agents. The results of our current phase I study of S-CKD602 can be extrapolated to future clinical trials of S-CKD602 and other nanosomal and nanoparticle anticancer agents and can be used to determine if the carrier-mediated anticancer agents provide pharmacologic advantages.

encapsulated, released, and sum total (encapsulated + released) CKD602 measured by LC-MS/MS.

Results—45 pts (21 male) were treated: median age 62 years (range: 33–79 years); ECOG status: 0 to 1 (43 pts) and 2 (2 pts). Dose-limiting toxicities of grade 3 mucositis occurred in 1/6 pts at 0.3 mg/m^2, grade 3/4 bone marrow suppression in 2/3 pts at 2.5 mg/m^2, and grade 3 febrile neutropenia and anemia in 1/6 pts at 2.1 mg/m^2. The maximum tolerated dose was 2.1 mg/m^2. Partial responses occurred in 2 pts with refractory ovarian cancer (1.7 and 2.1 mg/m^2). High inter-patient variability occurred in the pharmacokinetic disposition of encapsulated and released CKD-602.

Conclusions—S-CKD602 represents a promising new liposomal camptothecin analogue with manageable toxicity and promising antitumor activity. Phase II studies of S-CKD602 at 2.1 mg/m^2 IV once every 3 weeks are planned. Prolonged plasma exposure over 1 to 2 wks is consistent with STEALTH® liposomes and provides extended exposure compared with single doses of non-liposomal camptothecins.

INTRODUCTION

S-CKD602 is a STEALTH® liposomal formulation of CKD-602, a camptothecin analogue which inhibits topoisomerase I (1–3). The STEALTH® liposomal formulation consists of phospholipids covalently bound to methoxypolyethylene glycol (mPEG) on the outside of the lipid bilayer. Non-liposomal CKD-602 administered IV at 0.5 mg/m^2/day for 5 consecutive days repeated every 21 days is approved in Korea for the treatment of newly diagnosed small cell lung cancer and relapsed ovarian cancer (4–7).

The development of STEALTH® liposomes was based on the discovery that incorporation of mPEG-lipids into liposomes yields preparations with prolonged plasma exposure and superior tumor delivery compared to conventional liposomes composed of natural phospholipids and non-liposomal agents (1,8,9). STEALTH® liposomal doxorubicin (Doxil®) is approved for the treatment of refractory ovarian cancer, Kaposi sarcoma, and multiple myeloma (10,11). Encapsulation of the CKD-602 in the acidic core of a STEALTH® liposome should also protect the active-lactone form of the drug from being converted to the inactive-hydroxy acid form in the blood and allow for release of the active-lactone form into the tumor over a protracted period of time, which is ideal for a cell cycle-specific drug (1–3,12–14). The clearance of non-pegylated and pegylated liposomes is via the reticuloendothelial system (RES) (1,8,9,15,16). Once the drug is released from the liposome the pharmacokinetic disposition will be the same as after administration of the non-liposomal formulation of the drug (1,8,9,15,16).

The plasma exposure of S-CKD602 at 1 mg/kg IV × 1 was approximately 25-fold greater than non-liposomal CKD-602 at 30 mg/kg IV × 1 in mice (3,6,15). In plasma, approximately 82% of CKD-602 was encapsulated inside of the liposome after administration of S-CKD602 (3). In mice bearing human tumor xenografts, the duration of exposure of CKD-602 in tumor was 3-fold longer for S-CKD602 compared with non-liposomal CKD-602 (3). In addition, the antitumor response and therapeutic index were greater for S-CKD602 compared with non-liposomal CKD-602 (3,6). These results are consistent with reports that the antitumor response to camptothecin analogues is related to the duration of time the drug concentration in tumor is above a critical threshold (3,6,12–14,17).

Therefore we conducted the first human phase I and pharmacokinetic study of S-CKD602. The objectives in this study were to determine the maximum tolerated dose (MTD) of S-CKD602, determine the toxicity profile of S-CKD602, and evaluate the pharmacokinetics disposition of encapsulated, released, and sum total (encapsulated + released) CKD-602.

PATIENTS AND METHODS

Patients

Patients ≥ 18 years of age with a histologically or cytologically confirmed malignancy for which no effective therapy was available were eligible for this study. Pertinent eligibility criteria included a Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2, adequate bone marrow, hepatic, and renal function as evidenced by the following: absolute neutrophil count (ANC) ≥ 1500/μL, platelets ≥ 100,000/μL, total bilirubin ≤ 1.5 x upper limit of the institutional normal range (ULN), aspartate aminotransferase (AST) ≤ 1.5 x the ULN if liver metastases were not present and ≤ 4 x the ULN if liver metastases were present, and absence of microscopic hematuria (18). Prior treatment with camptothecin analogues other than S-CKD602 or non-liposomal CKD-602 was permitted. Written informed consent, approved by the Institutional Review board of the University of Pittsburgh Medical Center, was obtained from all patients prior to study entry.

Dosage and Administration

S-CKD602 is a formulation of CKD-602 encapsulated in long-circulating STEALTH® liposomes. In S-CKD602, the STEALTH® liposome bilayer is composed of N-(carbonyl-methoxypolyethylene glycol 2000)-1,2-distearoyl-*sn*-glycero-phosphoethanolamine (MPEG-DSPE) and 1,2-distearoyl-*sn*-glycero-phosphocholine (DSPC) in a molar ratio of approximately 5:95. The mean particle diameter is approximately 100 nm, and CKD-602 encapsulation inside the liposomes exceeds 85%. S-CKD602 was supplied by ALZA Corporation in sterile 10 mL single-use amber vials as a clear to slightly opalescent suspension with a nominal total CKD-602 concentration of 0.1 mg/mL. S-CKD602 was diluted 3-fold in 5% dextrose prior to administration. No pre-medications were administered prior to S-CKD602.

S-CKD602 was administered IV over approximately 1 hour every 3 weeks. Doses administrated, expressed in mg of CKD-602 per m^2, were 0.10, 0.15, 0.20, 0.25, 0.30, 0.35, 0.40, 0.45, 0.50, 0.65, 0.85, 1.1, 1.7, 2.1, and 2.5 mg/m^2. This phase I study followed a standard dose escalation design with patients enrolled in cohorts of 3 initially, with the possibility of extending the cohort up to 6 patients depending on the number of dose-limiting toxicities (DLT) (18). No intra-patient dose escalation was permitted. The MTD was defined as the dose below the dose at which 2 out of up to 6 patients experienced a DLT. At the 2.5 mg/m^2 dose level, 2 patients out of 3 experienced a DLT. Since the next lower dose (1.7 mg/m^2) dose level was associated with minimal toxicity, an additional intermediate dose level of 2.1 mg/m^2 was investigated.

Patient Assessment

Radiological response was measured by the Response Evaluation Criteria in Solid Tumors (RECIST) every 2 cycles (19). Toxicity was assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.01 and by relationship to study drug. Dose limiting toxicities (DLT) were assessed during cycle 1. Hematologic DLT's were defined as: platelet count ≤25,000/mm^3, ANC < 500/mm^3 for ≥ 7 days, fever (≥ 38.5°C) accompanied by ANC < 1000/mm^3 and any other grade 3 or 4 hematologic event as listed in CTCAE version 3.0. Other DLTs included any non-hematologic grade 3 or 4 event that increased by ≥ 2 grades from baseline, with the exception of nausea, vomiting, alopecia, weight change, fatigue, and infusion reactions. Complete blood counts were obtained weekly and as medically indicated. The nadir and percentage decrease at nadir for the

[1]National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v3.0 Instructions and Guidelines (Updated August 9, 2006) Available from: http://www.fda.gov/cder/cancer/toxicityframe.htm.

absolute neutrophil count (ANC), platelets, red blood cells (RBC), and monocytes were estimated using standard methods (18,20,21).

Sample Collection, Processing, Analytical Studies, and Pharmacokinetic Analysis

Plasma samples for pharmacokinetic assessment were obtained from all patients. On cycle 1, blood (7 mL) was collected in EDTA (purple top) tubes prior to administration, at end of the infusion (approximately 1 h), and at 3 h, 5 h, 7 h, 24 h, 48 h, 72 h, 96 h, 168 h (day 8), and 336 h (day 15) after the start of the infusion. The blood samples were centrifuged at 1,380 x g for 6 min. The plasma for the determination of the encapsulated and released CKD-602 was processed via solid phase separation as described previously (3). Plasma for the determination of sum total (encapsulated + released) CKD-602 concentrations was placed in a polypropylene sscrew-top tube and stored at −80°C until processed by acetonitrile extraction as described previously (3). The encapsulated, released, and sum total CKD-602 concentrations were measured by a specific liquid chromatographic tandem mass spectrometric assay (LC-MS/MS) as previously described (3). The total (lactone + hydroxy acid) form of CKD-602 was measured for encapsulated, released, and sum total samples. The lower limit of quantitation (LLQ) of the total form encapsulated, released, and sum total CKD-602 were 2, 0.05, and 1 ng/mL, respectively.

The area under the encapsulated, released, and sum total CKD602 plasma concentration versus time curve of the total form of CKD-602 form 0 to last measurable sample ($AUC_{0\text{-}t}$) and 0 to infinity ($AUC_{0\text{-}\infty}$) were calculated using the log trapezoidal method (22). The ratio of released CKD-602 AUC to encapsulated CKD-602 AUC for each patient was calculated.

At doses of 1.7, 2.1, and 2.5 mg/m^2, plasma samples for sum total CKD-602 were also processed to measure the lactone and carboxylate forms of CKD-602 as previously described (12–14,17). The lactone and carboxylate concentrations of sum total CKD-602 were measured via LC-MS/MS and the LLQ was 1 ng/mL for both forms. The percentage CKD-602 lactone in each plasma sample was calculated as (lactone concentration divided by the lactone concentration plus the carboxylate concentration) × 100).

Statistical Analysis

Comparisons between the nadir and percent decrease at nadir for ANC, platelets, RBC, and monocytes on cycles 1, 2, 4, and 8 were performed using analysis of variance and multiple comparison t-test (22). The statistical analysis was performed using SAS software (Cary, NC).

RESULTS

Patient Characteristics

Patient characteristics are summarized in Table 1. Forty-five patients were enrolled on this study from September 29, 2003 to October 17, 2005 at University of Pittsburgh Cancer Institute. All patients received at least one dose of drug and were evaluable for toxicity. A total of 147 cycles were administered. The mean (range) number of cycles administered was 3.3 (1 to 12).

Toxicity

Drug-related toxicities are described in Table 2. Hematological toxicity was the most common adverse event [grade 3 or 4 neutropenia occurred in 8 patients (18%), grade 3 anemia occurred in 4 patients (9%), and grade 3 or 4 thrombocytopenia occurred in 4 patients each (9%)]. DLT occurred at the dose of 0.3 mg/m^2 (mucositis in 1 of 6 patients), 2.1 mg/m^2 (anemia, febrile neutropenia in 1 of 6 patients) and 2.5 mg/m^2 (neutropenia,

anemia and thrombocytopenia in 2 of 3 patients). The MTD was defined as 2.1 mg/m^2, due to 2 of 3 patients experiencing DLT at the dose of 2.5 mg/m^2. The relationship between encapsulated and released CKD-602 AUC and DLT is depicted in Figures 1a and 1b, respectively.

The cumulative toxicity of S-CKD602 as related to ANC, platelets, red blood cells (RBC), and monocytes was evaluated. The nadir and % decrease at nadir for ANC, platelets, RBC, and monocytes are presented in Table 3. The nadir and % decrease at nadir for ANC, platelets, RBC, and monocytes were similar on cycles 1, 2, 4, and 8 ($P > 0.05$).

Response

Partial responses were documented in 2 (at 1.7 and 2.1 mg/m^2) of 5 patients with ovarian cancer. The 3 patients with ovarian cancer who did not respond were treated at 0.3, 2.1, and 2.5 mg/m^2. The patients with ovarian cancer treated at 2.1 and 2.5 mg/m^2 developed DLT in cycle 1 and were not evaluated for response. Six patients (sarcoma (n = 3), hepato cellular (n = 1), prostate (n = 1), and thyroid cancer (n = 1)) had stable disease that lasted for ≥ 6 cycles. The relationship between encapsulated and released CKD-602 AUC and response is depicted in Figures 1a and 1b, respectively.

Pharmacokinetics

Pharmacokinetic sampling was initiated in all 45 patients enrolled on the study. The relationship between S-CKD602 dose and encapsulated CKD-602 AUC is presented in Figures 1a (log scale) and 2a (linear scale). There was significant variability in the encapsulated AUC at each dose of S-CKD602 and a limited linear relationship between dose and encapsulated AUC. At the MTD of 2.1 mg/m^2, there was a 13.3-fold range in encapsulated CKD-602 AUC. The encapsulated CKD-602 AUCs were similar from 0.1 to 1.1 mg/m^2 and from 1.7 to 2.5 mg/m^2; however from 1.1 to 1.7 mg/m^2 there was a 7.7-fold greater increase in the mean encapsulated AUC than in dose.

The relationship between S-CKD602 dose and released CKD-602 AUC is presented in Figures 1b (log scale) and 2b (linear scale). There was significant variability in the released AUC at each dose of S-CKD602 and a poor linear relationship between dose and released AUC. At the MTD of 2.1 mg/m^2, there was a 16.7-fold range in released CKD-602 AUC. There is significant variability in the released AUC at each dose of S-CKD602 and a poor linear relationship between dose and released AUC. The released CKD-602 AUCs were similar from 0.10 to 0.85 mg/m^2. However, the mean released CKD-602 AUC increased 2.1-fold from 0.85 to 1.1 mg/m^2 and 3.8-fold from 1.7 to 2.1 mg/m^2.

The encapsulated, released, and sum total CKD-602 AUCs and ratio of released AUC to encapsulated AUC at each S-CKD602 dose are presented in Table 4. The encapsulated CKD-602 AUC was similar to the sum total AUC at all doses. In addition, the encapsulated AUC were significantly greater than the released AUC at all doses > 0.50 mg/m^2. The ratio of released CKD-602 AUC to encapsulated CKD-602 AUC decreased as the dose of S-CKD602 was increased. The mean ratio of released CKD-602 AUC to encapsulated CKD-602 AUC at S-CKD602 doses of 0.10 to 0.40 mg/m^2, 0.50 to 1.10 mg/m^2, and from 1.70 to 2.5 mg/m^2 ranged from 0.14 to 0.71, 0.01 to 0.03, and 0.005 to 0.011, respectively. The mean ± SD percentage lactone of sum total CKD-602 in each plasma sample at doses of 1.7, 2.1, and 2.5 mg/m^2 were 97.4 ± 1.7 %, 97.9 ± 1.4 %, and 98.6 ± 0.7 %, respectively.

DISCUSSION

Major advances in the use of liposomes, conjugates, and nanoparticles as vehicles to deliver drugs have occurred the past 10 years (1,8,9). STEALTH® liposomal doxorubicin (Doxil®)

and albumin stabilized nanoparticle formulation of paclitaxel (Abraxane®) are now FDA approved (10,11,24). In addition, there are greater than 100 liposomal and nanoparticle formulations of anticancer agents currently in development (1). This is the first phase I and pharmacokinetic study of a pegylated-liposomal formulation of a camptothecin analogue and also the first to evaluate the pharmacokinetic disposition of the encapsulated and released drug after administration of a liposomal or nanoparticle carrier formulation of a camptothecin analogue (25,26,27). Evaluation of the pharmacokinetic disposition of the liposomal encapsulated verses released drug is of the utmost importance because the liposomal encapsulated drug is an inactive prodrug and thus only the released drug is active (1,3). The prolonged plasma exposure of encapsulated and released CKD-602 over 1 to 2 weeks for S-CKD602 is consistent with STEALTH® liposomes and provides extended exposure compared with non-liposomal CKD-602 and other liposomal formulations of camptothecins (1–3,25–27).

S-CKD602 was well tolerated, and the overall incidence of grade 3 or 4 toxicity compared favorably with other camptothecins (7,12,20,21,23,25–27). In contrast to irinotecan, patients treated with S-CKD602 did not have grade 3 or 4 diarrhea (12,20,28). The incidence of grade 3 or 4 neutropenia and neutropenic fever after administration of S-CKD602 compares favorably to topotecan (12,20,29). In addition, the hematologic toxicity associated with S-CKD602 was non-cumulative (12,20,29).

S-CKD602 exhibited promising antitumor activity with partial responses in two patients with platinum refractory ovarian cancer and stable disease in 6 other patients with refractory solid tumors. The two patients with platinum refractory ovarian cancer were treated at 1.7 and 2.1 mg/m^2. Both patients were heavily pretreated and had previously received STEALTH® liposomal doxorubicin (Doxil®) and the patient treated at 1.7 mg/m^2 had previously received topotecan. The patient treated at 1.7 mg/m^2 had a partial response confirmed after cycle 4 and was removed from the study after cycle 12 due to an increasing CA-125. This patient also received topotecan in addition to other agents. The patient treated at 2.1 mg/m^2 had a partial response confirmed after cycle 6 and was removed from the study after cycle 11 due to an increasing CA-125. Thus, studies of S-CKD602 in the treatment of patients with ovarian cancer that is platinum refractory or sensitive ovarian cancer and in patients with ovarian cancer who have failed Doxil and topotecan are warranted (28,30). There was no direct relationship between antitumor response and the exposure of encapsulated or released CKD-602. However, the two patients with partial responses had encapsulated and released CKD-602 AUCs that were greater than the mean AUC for that dose (Figures 1a and 1b). Moreover, four of the five evaluable patients with encapsulated CKD-602 AUC > 30,000 ng/mL•h had a partial response (n = 2) or stable disease (n = 2).

The pharmacokinetic disposition of S-CKD602 is consistent with the STEALTH® concept (1,8,9,15,16). After a single dose of S-CKD602 at the MTD of 2.1 mg/m^2, the plasma exposure of sum total CKD-602 was 68-fold higher compared with five daily doses of non-liposomal CKD-602 at the MTD of 0.5 mg/m^2/d (5,7). Patients treated at doses of S-CKD602 ≥ 1.7 mg/m^2 had quantifiable plasma concentrations of encapsulated and released CKD-602 from 1 to 2 weeks after administration of a single dose of S-CKD602. The encapsulated CKD-602 AUC was similar to the sum total AUC at all doses. In addition, the encapsulated AUC were significantly greater than the released AUC at all doses > 0.50 mg/m^2. At dose < 0.50 mg/m^2, the interpretation of encapsulated and released CKD-602 is complicated by the lower LLQ for released (0.05 ng/mL) compared with encapsulated (2 ng/mL) CKD-602 and that most concentrations of encapsulated and released drug were near or below the LLQ. At the MTD of 2.1 mg/m^2, the mean ± SD ratio of released CKD-602 AUC to encapsulated CKD-602 AUC was 0.011 ± 0.004. This data suggests that most of the CKD-602 remains encapsulated in the plasma after administration of S-CKD602. These

results are also consistent with our previous studies of S-CKD602 in mice (3). Encapsulation of the CKD-602 in the acidic core of the STEALTH® liposome also maintained CKD-602 in the active-lactone form with the mean percentage lactone of > 97%.

There was significant inter-patient variability in the pharmacokinetic disposition of encapsulated and released CKD-602 after administration of S-CKD602 (1,2). There was also a poor relationship between the dose of S-CKD602 and the AUC of encapsulated and released CKD-602. At low doses of S-CKD602 the variability of encapsulated CKD-602 were greater than at higher doses. At the MTD of 2.1 mg/m2, there was a 13-fold range in encapsulated CKD-602 AUC. There is greater pharmacokinetic variability in encapsulated CKD-602 compared with released CKD-602. This data suggests that the clearance of the STEALTH® liposomal carrier is more variable than the released drug and ultimately determines the overall exposure of drug in each patient (5,25–27). The high inter-patient variability in the pharmacokinetic disposition of S-CKD602 is consistent with other liposomal anticancer agents (5,25–27). Our data also suggests that S-CKD602 undergoes non-linear or saturable clearance at higher doses (1,3). The clinical significance of these differences and the factors associated with the pharmacokinetic variability need to be evaluated for S-CKD602 and other liposomal and nanoparticle anticancer agents (1). As most of the drug remains encapsulated in the pegylated liposome in plasma it appears that the overall pharmacokinetic variability is associated with the clearance of the liposomal carrier.

S-CKD602 exhibits all of the pharmacologic, antitumor, and cytotoxic advantages of a long acting, liposomal anticancer agent (1–3,12,14,31). Thus, based on our prior preclinical studies and the phase I study presented here, S-CKD602 warrants evaluation in phase II studies in camptothecin sensitive tumors, especially ovarian, gastric and small cell lung cancer, and potentially resistant tumors.

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References

1. Zamboni WC. Liposomal, nanoparticle, conjugated formulations of anticancer agents. Clin Cancer Res. 2005; 11:8230–4. [PubMed: 16322279]
2. Zamboni WC, Friedland DM, Ramalingam S, et al. Final results of a phase I and pharmacokinetic study of STEALTH liposomal CKD-602 (S-CKD602) in patients with advanced solid tumors. Proc of ASCO. 2006; 24:82s.
3. Zamboni WC, Strychor S, Joseph E, et al. Plasma, tumor, and tissue disposition of STEALTH liposomal CKD-602 (S-CKD602) and Non-liposomal CKD-602 in mice bearing A375 human melanoma xenografts. Clin Cancer Res. 2007; 13(23):7217–23. [PubMed: 18056203]
4. Crul M. CKD-602. Curr Opin Investig Drugs. 2003; 4:1455–9.
5. Lee JH, Lee JM, Lim KH, et al. Preclinical and phase I clinical studies with CKD-602, a novel camptothecin derivative. Ann N Y Acad Sci. 2000; 922:324-S. [PubMed: 11193913]
6. Yu NY, Conway CA, Pena RL, Chen JY. STEALTH liposomal CKD-602, a topoisomerase I inhibitor improves the therapeutic index in human tumor xenograft models. Anticancer Res. 2007; 27:2541–5. [PubMed: 17695551]
7. Lee D, Kim SW, Suh C, et al. Belotecan, new camptothecin analogue, is active in patients with small-cell lung cancer: results of a Multicenter early phase II study. Ann Oncol. 2007 Sept 6.

8. Papahadjopoulos D, Allen TM, Gabizon A, et al. Sterically stabilized liposomes: improvements in pharmacokinetics and antitumor therapeutic efficacy. Proc Natl Acad Sci USA. 1991; 88:11460–4. [PubMed: 1763060]
9. Maeda H, Wu J, Sawa T, Matsumura Y, Hori K. Tumor vascular permeability and the EPR effect in macromolecular therapeutics: a review. J Control Release. 2000; 65:271–84. [PubMed: 10699287]
10. Markman M, Gordon AN, McGuire WP, Muggia FM. Liposomal anthracycline treatment for ovarian cancer. Semin Oncol. 2004; 31:91–105. [PubMed: 15717739]
11. Krown SE, Northfelt DW, Osoba D, Stewart JS. Use of liposomal anthracyclines in Kaposi's sarcoma. Semin Oncol. 2004; 31:36–52. [PubMed: 15717737]
12. Sparreboom, A.; Zamboni, WC. Topoisomerase I Inhibitors. In: Chabner, BA.; Longo, DL., editors. Cancer Chemotherapy and Biotherapy: Principles and Practice. 4. Philadelphia, PA: Lippincott Williams & Wilkins; 2005. p. 371-413.
13. Zamboni WC, Stewart CF, Thompson J, et al. The relationship between topotecan systemic exposure and tumor response in human neuroblastoma xenografts. J Natl Cancer Inst. 1998; 90:505–11. [PubMed: 9539245]
14. Stewart CF, Zamboni WC, Crom WR, et al. Topoisomerase I interactive drugs in children with cancer. Invest New Drugs. 1996; 14:37–47. [PubMed: 8880392]
15. Zamboni WC, Eiseman JE, Strychor S, et al. Relationship between the plasma and tumor disposition of STEALTH liposomal CKD-602 and macrophages/dendritic cells (MDC) in mice bearing human tumor xenografts. Proc Annu Meet Am Assoc Cancer Res. 2006; 47(1280):#5449.
16. Maruca LJ, Ramanathan RK, Strychor S, et al. Age-related effects on the pharmacodynamic (PD) relationship between STEALTH liposomal CKD-602 (S-CKD602) and monocytes in patients with refractory solid tumors. Proceedings of ASCO. 2007:#2576.
17. Zamboni WC, Gajjar AJ, Houghton PJ, et al. A topotecan 4-hour intravenous infusion achieves cytotoxic exposure throughout the neuroaxis in the nonhuman primate model: implications for the treatment of children with metastatic medulloblastoma. Clin Cancer Res. 1998; 4:2537–44. [PubMed: 9796988]
18. Zamboni WC, Tonda ME. New designs of clinical trials. Highlights in Oncol Practice. 2000; 18:2–7.
19. Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. Cancer. 1981; 47:207–14. [PubMed: 7459811]
20. Rowinsky EK, Kaufmann SH, Baker SD, et al. A phase I and pharmacological study of topotecan infused over 30 minutes for five days in patients with refractory acute leukemia. Clin Cancer Res. 1996; 2:1921–30. [PubMed: 9816150]
21. Jung LL, Zamboni WC. Cellular, pharmacokinetic, and pharmacodynamic aspects of response to camptothecins: can we improve it? Drug Resist Update. 2001; 4:273–88.
22. Rowland, M.; Tozer, T. Clinical pharmacokinetics: concepts and applications. Philadelphia: Lea and Febiger; 1989. p. 9-32.
23. Rosner, G. Fundamentals of Biostatistics. 5. Pacific Grove, CA: Duxbury; 2000.
24. Gradishar WJ, Tjulandin S, Davidson N, et al. Phase II trial of nanoparticle albumin-bound paclitaxel compared with polyethylated castor oil-based paclitaxel in women with breast cancer. J Clin Oncol. 2005; 23:7768–71. [PubMed: 16204007]
25. Kraut EH, Fishman MN, LoRusso PM, et al. Final results of a phase I study of liposome encapsulated SN-38 (LE-SN38): safety, pharmacogenomics, pharmacokinetics, and tumor response. Proc Am Soc Clin Oncol. 2005; 23:139s–139s.
26. Giles FJ, Tallman MS, Garcia-Manero G, et al. Phase I and pharmacokinetic study of a low-clearance, unilamellar liposomal formulation of lurtotecan, a topoisomerase 1 inhibitor, in patients with advanced leukemia. Cancer. 2004; 100:1449–58. [PubMed: 15042679]
27. Gelmon K, Hirte H, Fisher B, et al. A phase 1 study of OSI-211 given as an intravenous infusion days 1, 2, and 3 every three weeks in patients with solid cancers. Invest New Drugs. 2004; 22:263–75. [PubMed: 15122073]
28. Rowinsky EK, Verweij J. Review of phase I clinical studies with topotecan. Semin Oncol. 1997; 24:S20.

29. Green AE, Rose PG. Pegylated liposomal doxorubicin in ovarian cancer. Int J Nanomedicine. 2006; 1:229–39. [PubMed: 17717964]

30. Innocenti F, Ratain MJ. Irinotecan treatment in cancer patients with UGT1A1 polymorphisms. Oncology. 2003; 17:52–5. [PubMed: 12800608]

31. Bookman MA. Developmental chemotherapy and management of recurrent ovarian cancer. J Clin Oncol. 2003; 21:149s–67s. [PubMed: 17633784]

Figure 1a

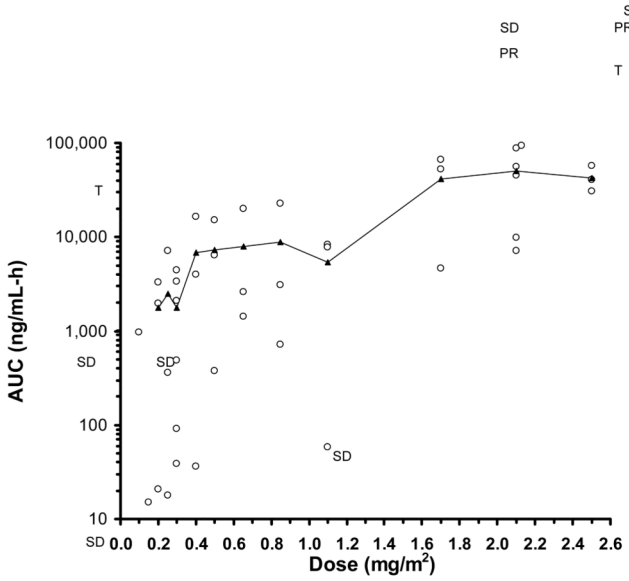

Figure 1b

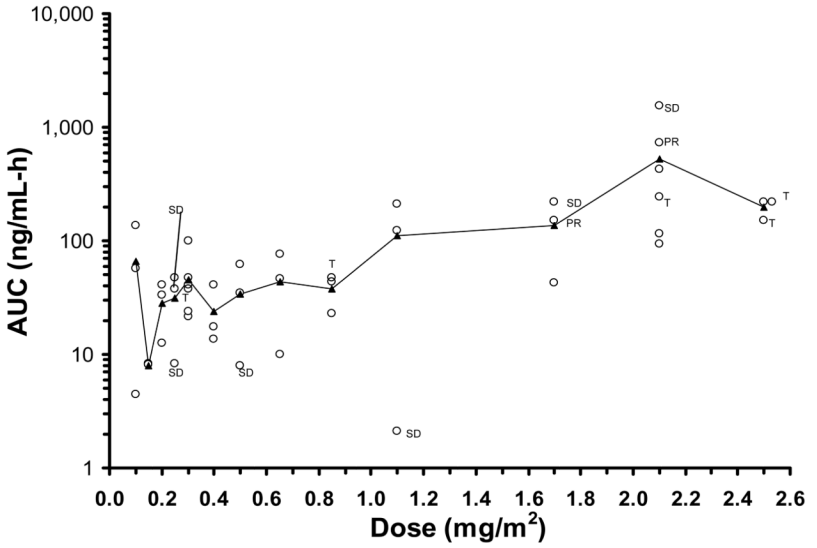

Figure 1.

Relationship between dose of S-CKD602 and encapsulated CKD-602 $AUC_{0-\infty}$. Figures 1a and 2a represent the encapsulated AUC on a log and linear scale, respectively. S-CKD602 was administered at 0.10, 0.15, 0.20, 0.25, 0.30, 0.40, 0.50, 0.65, 0.85, 1.10, 1.70, 2.10, and 2.50 mg/m^2. The patients with DLT are represented by the T. The patients with partial response are represented by the PR. The patients with stable disease are represented by SD. Two patients in each dose level treated at 0.10, 0.15, and 0.85 mg/m^2 had 1 to 2 detectable concentrations of encapsulated CKD-602 and thus an accurate encapsulated CKD-602 AUC could not be calculated for these patients. The patients treated at 2.5 mg/m^2 had limited pharmacokinetic sampling due to toxicity and logistical issues. The patients treated at 2.5 mg/m^2 with the highest, medium, and lowest AUCs were calculated from 0 to 96 h, 0 to 48 h, and 0 to 96 h, respectively.

Figure 2a

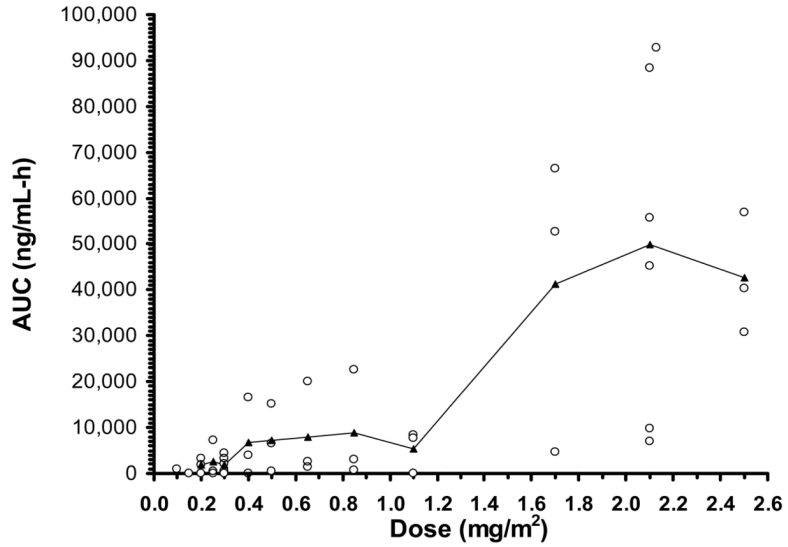

Figure 2b

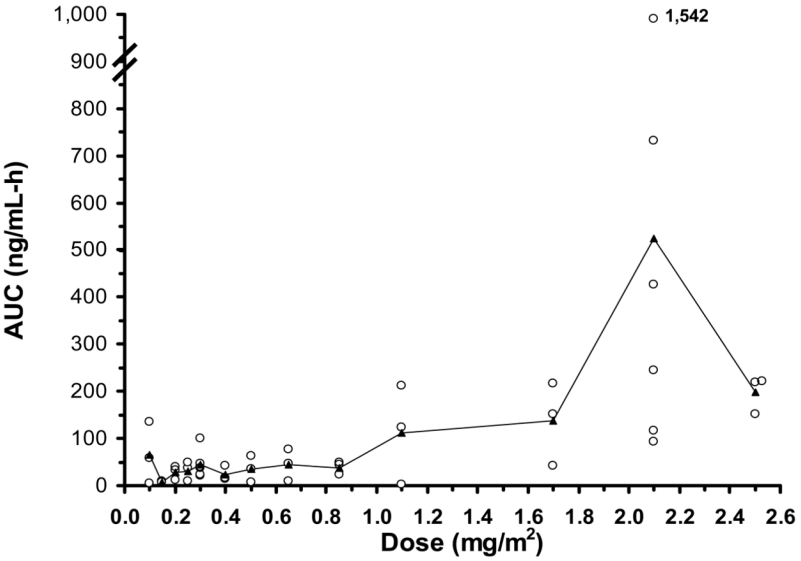

Figure 2.

Relationship between dose of S-CKD602 and released CKD-602 $AUC_{0-\infty}$. Figures 1b and 2b represent the released AUC on a log and linear scale, respectively. S-CKD602 was administered at 0.10, 0.15, 0.20, 0.25, 0.30, 0.40, 0.50, 0.65, 0.85, 1.10, 1.70, 2.10, and 2.50 mg/m^2. The patients with DLT are represented by the T. The patients with partial response are represented by the PR. The patients with stable disease are represented by SD. The patients treated at 2.5 mg/m^2 had limited pharmacokinetic sampling due to toxicity and logistical issues. The patients treated at 2.5 mg/m^2 with the highest, medium, and lowest AUCs were calculated from 0 to 96 h, 0 to 48 h, and 0 to 96 h, respectively.

Table 1

Patient Characteristics

Characteristics	
Male/Female Enrolled (n)	21/24
Male/Female Evaluable (n)	21/24
Age (yr)	
Median	62
Mean	60.6
Range	33 – 79
ECOG Performance Status (n)	
0	16
1	27
2	2
Tumor Type	
Colorectal Adenocarcinoma	17
Ovarian Cancer	5
Sarcoma	5
Non-Small Cell Lung Cancer	4
Pancreatic Adenocarcinoma	3
Hepatocellular Carcinoma	2
Prostate Carcinoma	2
Esophageal, Metastatic Breast, Mesothelioma, Renal Cell Carcinoma, Thyroid, Appendix, Unknown Primary	1 patient for each tumor type
Prior Treatments	
Median	3
Range	1 – 9

Table 2

Common Drug-Related Adverse Events by Maximal Severity for All Cycles

Adverse Events [a]	Grade 1	Grade 2	Grade 3	Grade 4
Anemia	3	6	4	0
Neutropenia	3	2	5	3
Thrombocytopenia	4	1	3	1
Diarrhea	12	0	0	0
Nausea	20	4	1	0
Vomiting	6	2	1	0
Anorexia	5	3	0	0
Fatigue	12	8	3	0
Pyrexia	3	2	0	0

[a] Patients were counted once per cycle for the most severe of multiple drug-related occurrences of a specific MedDRA preferred term.

Table 3

The Nadir and Percentage Decrease at Nadir in ANC, Platelets, RBC, and Monocytes on Cycles 1, 2, 4, and 8

	Cycle 1		Cycle 2		Cycle 4		Cycle 8	
	% Decrease Mean ± SD (Range) [n = 45]	**Nadir (cells × 10^3/μL) Mean ± SD (Range) [n = 45]**	**% Decrease Mean ± SD (Range) [n = 36]**	**Nadir (cells × 10^3/μL)Mean ± SD (Range) [n = 36]**	**% Decrease Mean ± SD (Range) [n = 12]**	**Nadir (cells × 10^3/μL)Mean ± SD (Range) [n = 12]**	**% Decrease Mean ± SD (Range) [n = 5]**	**Nadir (cells × 10^3/μL) Mean ± SD (Range) [n = 5]**
ANC	33.7 ± 28.4 (0.0 – 91.2)	3.0 ± 2.2 (0.0 – 8.7)	24.0 ± 25.3 (0.0 – 80.0)	2.6 ± 2.4 (0.0 – 8.0)	22.3 ± 32.8 (0.0 – 100.0)	2.2 ± 2.1 (0.0 – 6.1)	36.6 ± 42.3 (13.3 – 99.9)	2.7 ± 1.6 (1.4 – 5.2)
Platelets	22.4 ± 25.4 (0.0 – 93.9)	220.6 ± 119.8 (16.0 – 570.0)	25.8 ± 27.1 (0.0 – 90.9)	212.8 ± 97.4 (16.5 – 427.0)	20.6 ± 25.4 (0.0 – 83.3)	256.0 ± 86.8 (84.0 – 386.0)	36.7 ± 23.8 (17.9 – 76.5)	262.4 ± 79.7 (142.0–355.0)
RBC	11.0 ± 8.5 (0.0 – 33.0)	3.6 ± 0.57 (2.3 – 4.6)	8.1 ± 5.7 (0.0 – 22.9)	3.7 ±.47 (2.8 – 4.7)	5.9 ± 5.2 (0.0 – 16.7)	3.5 ±.68 (2.2 – 4.4)	6.4 ± 4.1 (2.9 – 11.8)	3.5 ±.39 (3.1 – 3.9)
Mono	43.6 ± 34.6 (0.0 – 97.4)	0.33 ± 0.28 (0.0 – 0.88)	40.4 ± 34.0 (0.0 – 96.7)	0.31 ±.26 (0.0 – 0.94)	39.8 ± 30.6 (0.0 – 89.4)	0.37 ±.29 (0.0 – 0.93)	67.3 ± 33.2 (18.2 – 90.8)	0.28 ±.37 (0.06 – 0.84)

Table 4

The Total Form of Encapsulated, Released, and Sum Total CKD-602 Area Under the Concentration Verses Time Curves (AUC) after Administration of S-CKD602 at Each Dose

Dose (mg/m2)	Patients	Sum Total [a,g] $AUC_{0-\infty}$ (ng/mL•h)	Encapsulated [g] $AUC_{0-\infty}$ (ng/mL•h)	Released [g] $AUC_{0-\infty}$ (ng/mL•h)	Ratio Released AUC to Encapsulated AUC [f]
0.10 [e]	3	180 ± 235 (29 – 451)	962 [b]	66 ± 66 (4 – 135)	0.141
0.15 [e]	3	49 ± 18 (36 – 70)	15 [b]	8 [h] 8	0.533
0.20 [e]	3	1,381 ± 1,203 (80 – 2,455)	3,306 [c] 1,972	28 ± 14 (12 – 40)	0.010 0.021
0.25 [e]	3	2,109 ± 3,203 (142 – 5,806)	2,516 ± 4,035 (17 – 7,171)	31 ± 20 (8 – 47)	0.710 ± 1.20 (0.007 – 2.10)
0.30 [e]	6	1,657 ± 1,546 (128 – 3,532)	1,756 ± 1,869 (38 – 4,479)	45 ± 28 (21 – 99)	0.160 ± 0.214 (0.009 – 0.552)
0.40 [e,i]	3	3,592 [i] 119 14,720	4,007 [i] 36 16,527	14 [i] 17 41	0.003 [i] 0.480 0.002
0.50	3	6,609 ± 5,820 (694 – 12,330)	7,315 ± 7,419 (380 – 15,139)	34 ± 26 (8 – 61)	0.010 ± 0.009 (0.004 – 0.021)
0.65	3	8,600 ± 9,153 (1,897 – 19,030)	8,007 ± 10,408 (1,434 – 20,008)	44 ± 33 (10 – 76)	0.013 ± 0.015 (0.002 – 0.030)
0.85	3	6,700 ± 8,179 (1,053 – 16,080)	8,810 ± 12,026 (718 – 22,630)	38 ± 13 (23 – 48)	0.016 ± 0.015 (0.002 – 0.032)
1.10	3	6,192 ± 5,137 (298 – 9,727)	5,382 ± 4,621 (58 – 8,360)	112 ± 105 (2 – 213)	0.026 ± 0.010 (0.016 – 0.036)
1.70	3	39,814 ± 29,960 (5,933 – 62,810)	41,271 ± 32,462 (4,646 – 66,498)	137 ± 88 (42 – 217)	0.005 ± 0.004 (0.003 – 0.009)
2.10	6	44,639 ± 32,859 (7,358 – 85,875)	49,837 ± 36,968 (7,055 – 92,871)	525 ± 551 (93 – 1542)	0.011 ± 0.004 (0.005 – 0.017)
2.50 [d]	3	57,126 ± 13,090 (43,300 – 69,330)	42,674 ± 13,212 (30,774 – 56,893)	197 ± 40 (151 – 222)	0.005 ± 0.002 (0.004 – 0.007)

[a] The sum total (encapsulated + released) CKD-602 AUC was based on measured concentrations in plasma and was not calculated based on adding the encapsulated + released concentrations.

[b] Two patients in each dose level treated at 0.10 and 0.15 mg/m^2 had 1 to 2 quantifiable concentrations of encapsulated CKD-602 and thus an accurate encapsulated CKD-602 AUC could not be calculated for these patients.

[c] One patient at 0.20 mg/m^2 had 2 quantifiable concentrations of encapsulated CKD-602 and thus an accurate encapsulated CKD-602 AUC could not be calculated for these patients.

[d] The patients treated at 2.5 mg/m^2 had limited pharmacokinetic sampling due to toxicity and logistical issues. The patients treated at 2.5 mg/m^2 with the highest, medium, and lowest AUCs were calculated from 0 to 96 h, 0 to 48 h, and 0 to 96 h, respectively.

[e] At dose < 0.50 mg/m^2, the interpretation of encapsulated and released CKD-602 is complicated by the lower LLQ for released (0.05 ng/mL) compared with encapsulated (2 ng/mL) CKD-602 and that most concentrations of encapsulated and released drug were near or below the LLQ.

[f] The ratio of released CKD-602 AUC to encapsulated CKD-602 AUC was calculated for individual patient values and not the mean of the cohort.

[g] The total (lactone + carboxylate) form of encapsulated, released, and sum total (encapsulated + released) CKD-602 AUCs are presented.

[h] One patient at 0.15 mg/m^2 had 2 quantifiable concentrations of released CKD-602 and thus an accurate encapsulated CKD-602 AUC could not be calculated for these patients.

[i] One patient at 0.40 mg/m^2 only had pharmacokinetic samples obtained from 0 to 24 h. Thus, the sum total, encapsulated, and released CKD-602 AUC for this patient is from 0 to 24 h because the percent of the AUC from 0 to infinity that was extrapolated was > 15%. The sum total, encapsulated, and released CKD-602 AUCs for the other two patients are from 0 to infinity.