tal of 117+ cycles (median 2, mean 3.2, range 1-14+) were administered at 99% of the specified dose intensity. All patients had failed prior therapy with paclitaxel and platinum. 20/36 (55%) had failed one to three additional salvage therapies, including 12/36 (33%) Doxil, 10/36 (28%) topotecan, 4/36 (11%) gemcitabine, and 1/36 (3%) docetaxel therapy. The most common possibly drug-related toxicities (< Grade 2) were: fatigue, nausea, and anemia. There were no Grade 4 toxicities, no Grade 3 myelosuppression or thrombocytopenia and no cumulative toxicities. At interim analysis, ORR was seen in 4/31 patients (13%), 1 CR (3%), 3 PRs (10%), 12 SDs (39%) and 15 PDs (48%). The ORR was 15% in 2nd-line patients. The disease stabilization rate (CR+PR+SD) was 52% (16/31). The longest duration of therapy is in the CR patient, progression-free for 14+ cycles (12+ months). Tumor responses have been accompanied by declines in CA125 and symptom improvement. Three patients have died due to disease progression. Median survival exceeds 10 months.

**Conclusions:** TLK286 has significant single-agent antitumor activity in platinum and paclitaxel refractory or resistant ovarian cancer and is well tolerated. Median survival has not yet been reached but exceeds 10 months. Patient follow-up for response and survival is ongoing. Objective tumor responses including a durable complete response in bulky disease and improved survival in this heavily pretreated population are encouraging and warrant future studies of TLK286 in ovarian cancer.

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### Phase II Study of TLK286 (Glutathione Analog Activated by GST P1-1) in refractory colorectal cancer

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**Introduction:** TLK286 is a novel glutathione analog, activated by the enzyme glutathione-S transferase P1-1 (GST P1-1). GST P1-1 is overexpressed in many types of human malignancies and is implicated in resistance to several classes of anticancer therapies. Following activation of TLK286 by GST P1-1, apoptosis is induced through the stress response pathway.

**Methods:** Up to 75 evaluable patients with colorectal cancer who had failed prior 5-fluorouracil, leucovorin and irinotecan chemotherapy and any amount of cytostatic agents were to be enrolled in this multicenter, open label, single arm study. TLK286 was administered at 1000 mg/m$^2$ every 3 weeks until tumor progression or unacceptable toxicities. Objective response rate (ORR) was determined by RECIST criteria. Time to progression (TTP) and survival were estimated by Kaplan-Meier analysis. Adverse events (AEs) were graded by the NCI-CTC.

**Results:** 73 patients (35 M/22F) median age 66 (range 29-81), ECOG median 1 (range 0-1), median number of prior chemotherapy regimens 2 (range 1-5) were treated with a total of 196+ TLK286 treatments (median 2, mean 2.7, range 1-8+). The target dose of TLK286 was maintained in 94% of cycles. Most frequent AEs were (Grade 1-2): fatigue (24%), nausea (15%), vomiting (7%), hematuria (9%), urinary frequency (9%) and anemia (9%). There was one Grade 4 AE reported at day 21 (ANC 476/mm3) in a patient with progressive disease and underlying bone marrow disorder. Grade 3 AEs were infrequent (7% of patients). As of interim analysis, 36 of 73 patients were evaluable for tumor response. Five patients (14%) had stable disease (SD) as best response. Median duration of SD was 167 days (range 120-219+ days). In patients with SD there were declines in the CEA tumor marker (median decrease 42%, range 6-70%) These CEA declines have not translated into objective responses. There have been 19 deaths reported due to progressive disease. At interim analysis, estimated median survival (Kaplan-Meier) was 172 days (range 30-219+ days).

**Conclusions:** TLK286 was well tolerated in heavily pre-treated patients with refractory colorectal cancer. There were no objective tumor responses in advanced colorectal cancer when TLK286 was administered as a single agent once every 3 weeks. Analysis of subpopulations suggests that investigation of a more intensive dose schedule or use of TLK286 in combination therapy in colorectal cancer is warranted.

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### Enhanced antitumor activity of TLK286 in combination with carboplatin, doxorubicin and docetaxel in human ovarian and breast cancer cell lines

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TLK286 is a novel glutathione analog that is activated by the enzyme glutathione-S transferase P1-1 (GST P1-1). GST P1-1 is constitutively expressed in many cancers and overexpressed following treatment with chemotherapeutic agents. Following activation of TLK286 by GST P1-1, apoptosis is induced through the stress response signaling pathway. TLK286 is being evaluated in phase 2 clinical trials in ovarian, breast, non-small cell lung and colorectal cancers and has shown significant single agent antitumor activity and improvement in survival in patients with lung and ovarian cancers. Since the side effect profile observed with TLK286 is non-overlapping with standard chemotherapeutics, we have tested TLK286 *in vitro* in combination with docetaxel, doxorubicin and carboplatin, respectively. Ovarian cancer cell line OVCAR3 was incubated with TLK286 alone and in combination with doxorubicin or carboplatin for approximately three cell doublings and viability was determined using the Wst-1 assay. In various study designs (fixed and variable ratios), we have consistently observed marked enhancement of cytotoxicity when TLK286 was combined with either doxorubicin or carboplatin compared to either agent alone. The results are particularly significant for TLK286 and carboplatin, with maximum or near maximum activity observed under all conditions examined. TLK286 was tested in combination with docetaxel in the breast cancer cell line MCF-7. MCF-7 cells were treated with the single drugs or in combination for approximately 1 doubling time, and the cells were then labeled with BrdU overnight. The incorporation of BrdU, which reflects the extent of cell proliferation, was determined using ELISA. The drug combination, at various concentrations and ratios, was more effective at inhibiting cell proliferation than the single drugs. Analyses using the combination index method indicate synergies between low concentrations of carboplatin, doxorubicin or docetaxel and variable concentrations of TLK286. The results suggest that TLK286 shows enhanced cytotoxicity towards ovarian and breast cancer cells when used in combination with carboplatin, doxorubicin or docetaxel.

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### Ethanolatoamine platinum chelates as prodrugs which are selectively activated in slightly acidic environment

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Dichloroplatinum(II) and tetrachloroplatinum(IV) complexes with two hydroxyethylamine ligands in cis-configuration undergo intramolecular ligand exchange reactions in aqueous solution. NMR studies have shown that the hydroxyethylamine ligands are able to chelate platinum, thereby forming cyclic ethanolatoamine platinum species under proton and chloride abstraction in a pH-dependent equilibrium reaction (Fig. 1).

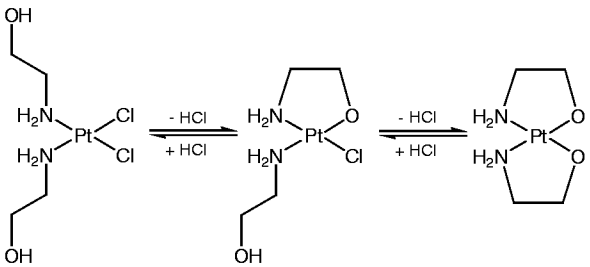


Figure 1. Intramolecular ligand exchange reactions of dichlorobis(2-hydroxyethylamine) platinum(II) (left) resulting in ethanolatoamine chelates.

The chelates are stable in slightly basic solution, whereas in acidic solution the rings open by protonization of ethanolate oxygen. Since rupture of the ethanolatoamine rings increases the reactivity towards biological targets, it should be possible to administer the less reactive chelates as prodrugs, which are then selectively activated within the acidic microenvironment found in many solid tumors. In order to evaluate this concept both ring-closed and ring-opened dichloroplatinum(II) and tetrachloroplatinum(IV)