Published in final edited form as:

Invest New Drugs. 2011 April ; 29(2): 316–322. doi:10.1007/s10637-009-9364-z.

PHASE I TRIAL OF MOTEXAFIN GADOLINIUM AND DOXORUBICIN IN THE TREATMENT OF ADVANCED MALIGNANCIES

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Abstract

Purpose—To assess the safety, maximum-tolerated dose (MTD), and dose-limiting toxicities (DLT), of motexafin gadolinium (MGd), given in combination with doxorubicin, in patients with advanced solid tumors.

Study Design—The combination of MGd and doxorubicin was administered every 28 days (cycle 1) and then every 21 days (subsequent cycles). The dose of MGd, given daily for 3 days, was escalated from 1.0 mg/kg/d to 3.3 mg/kg/d, while the dose of doxorubicin was held at 30 mg/m².

Results—Fifteen patients received 37 cycles of treatment, for a median of 2 cycles per patient (range 0 – 6 cycles). Three patients (20%) completed 6 cycles of therapy. The MTD was identified as MGd, 2 mg/kg/day and doxorubicin, 30 mg/m². Dose limiting toxicities included grade 3 hypertension, pneumonia, bacteremia, and elevated GGT. Serious adverse events also included pulmonary embolism and urinary tract infection requiring hospitalization. There was no exacerbation of cardiac toxicity. No patients attained a response to treatment. Six patients (54%) had stable disease. The median time to disease progression, or to last assessment, was 49 days (range 8-195 days).

Conclusions—The combination of MGd and doxorubicin was fairly well tolerated. However, due to emerging preclinical data suggesting that MGd inhibits ribonucleotide reductase, further development of the combination of MGd plus doxorubicin is not recommended.

Keywords

Phase I; ribonucleotide reductase; motexafin gadolinium; oxidation-reduction; doxorubicin

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INTRODUCTION

Redox metabolism, the homeostasis of reactive oxygen species (ROS), including superoxide and hydrogen peroxide, and their detoxification, is critical in cell signaling and the regulation of apoptosis [1]. Reactive oxygen species damage cellular DNA through oxidative stress-induced destruction of pyrimidine and purine bases and via oxidation of protein thiols and lipids, ultimately triggering apoptosis [2]. Reducing metabolites, including thioredoxin, glutathione, and nicotinamide dinucleotide phosphate (NADPH), are responsible for protecting cells from toxic oxidant damage by maintaining the proper redox balance. The generation of ROS, and the depletion of reducing metabolites, is also an essential mechanism of action of numerous chemotherapeutic agents, such as cisplatin, etoposide, procarbazine, and doxorubicin [3].

Motexafin gadolinium (MGd) is a redox-active porphyrin-like texaphyrin that has strong electron affinity, such that it is more easily reduced than molecular oxygen. It has multiple mechanisms of action, including participation in futile redox cycling, in which MGd catalyses the transfer of electrons from the reducing metabolites to molecular oxygen, producing ROS, with the resultant consumption of NADPH [1,2,4]. In addition, MGd induced up-regulation of metallothionein and zinc transporter genes in A549 cells, disrupting zinc ion homeostasis and inducing oxidative stress [5]. Lastly, recent preclinical work at the Karolinska Institute demonstrated that MGd complexes with and inhibits the R1 subunit of ribonucleotide reductase [6,7]. Motexafin gadolinium has enhanced the efficacy of radiation and cytotoxic chemotherapeutics in multiple preclinical models, likely due to the lowering of the apoptotic threshold in cancer cells following MGd-induced redox imbalance [8-10].

The safety profile of MGd has been described in combination studies with radiation. Overall, MGd is well tolerated, with reversible hepatotoxicity identified as the dose limiting toxicity (DLT) [11]. Grade 3 and 4 adverse events have included elevations in liver function tests (seen in approximately 5% of patients), infusion-related hypertension (4%), and asthenia (4%). Additional adverse events have included a dose dependent transient and reversible olive-green discoloration of skin, urine, and sclera, due to the dark green color of MGd, and paresthesias, blisters, or a vesicular rash of the fingertips consistent with pseudo-porphyrria [3,4]. Single agent activity has been observed in hematologic malignancies, renal cell cancer, and in NSCLC, while the addition of MGd to whole brain radiotherapy in NSCLC patients with brain metastases delayed time to neurologic progression and improved memory and executive function [3,4,12,13].

Doxorubicin is a redox-cycling anthracycline that generates cytotoxic ROS through interactions with trace metals [14]. In the presence of reducing metabolites, it undergoes reduction and generates free radicals that can damage mitochondrial membranes [8]. Miller et al. found that treatment of EMT6 mammary sarcoma xenografts with the combination of doxorubicin and MGd resulted in statistically significantly enhanced tumor growth inhibition. Pharmacokinetic studies in Sprague Dawley rats showed no drug-drug interactions following exposure to this combination [8].

Clinical studies using magnetic resonance imaging, which detects the paramagnetic gadolinium ion of MGd, have confirmed that MGd selectively accumulates in tumor cells. Increasing oxidative stress may serve as a final common pathway for induction of apoptosis in cancer cells, and this threshold may be lowered by MGd. We herein report the results of a multicenter phase I clinical trial of MGd combined with doxorubicin. In doing so, we hoped to explore the potential clinical use of MGd as a chemotherapy enhancing compound.

PATIENTS AND METHODS

Patient selection

Eligible patients were at least 18 years of age and had a histologically documented, advanced stage solid tumor that was refractory to standard therapy or for which no curative standard therapy was available. Other inclusion criteria included: Eastern Cooperative Oncology Group (ECOG) performance status of 0-2; absolute neutrophil count $\geq 1,500/\text{mm}^3$, platelet count $\geq 100,000/\mu\text{L}$; total bilirubin $< 1.5 \text{ mg/dL}$; aspartate transaminase (AST) and alanine aminotransferase (ALT) $\leq 2 \times$ the institutional upper limit of normal; serum creatinine $\leq 2.0 \text{ mg/dL}$; adequate left ventricular function ($> 45\%$ at rest); and willingness and ability to provide written informed consent.

Exclusion criteria included: lifetime cumulative doxorubicin exposure $> 300 \text{ mg/m}^2$; history of myocardial infarction, congestive heart failure, or clinically significant ventricular arrhythmias; ≤ 4 weeks since prior chemotherapy or radiation therapy; enrollment in a clinical trial using another anti-neoplastic or investigational agent given during the planned course of doxorubicin and MGd; pregnant or lactating women; history of porphyria (testing not required at screening); history of glucose-6-phosphate dehydrogenase (G6PD) deficiency (testing required at screening unless a prior test result was available); ≤ 14 days since ingesting multidrug resistant modulating drugs, such as cyclosporine; or an inability to complete specified follow-up assessments.

Each patient gave written informed consent, according to institutional and federal guidelines. The protocol was approved by the Institutional Review Boards at the University of Wisconsin, Madison, and at the University of Pittsburgh.

Study design

This was a multicenter single arm phase 1 trial designed to determine the effect of combining MGd and doxorubicin in patients with advanced malignancies. A paired-course design, in which every patient was treated with doxorubicin alone, with MGd alone, and with the combination, was chosen in order to compare the safety of each treatment and to assess whether MGd increased the toxicity of doxorubicin. Each patient served as their own control. Cycle 1 lasted 28 days, while subsequent cycles lasted 21 days. Six cycles of treatment, or treatment up to a lifetime cumulative dose of 450 mg/m^2 doxorubicin, were planned.

As shown in the Figure, all patients received a single dose of MGd on day 1 of cycle 1 and doxorubicin on day 8 of cycle 1. Patients were divided into two groups (Groups A and B) after meeting eligibility criteria and prior to the initiation of therapy. Assignment to Groups A or B alternated between consecutive patients enrolled at a single center. Patients in Group A received 3 daily doses of MGd on days 8, 9, and 10 of cycle 1. The cycle 1 day 8 dose of MGd was given 4 hours after the start of the doxorubicin administration. Patients assigned to Group B received doxorubicin alone on day 8 of cycle 1. If no dose limiting toxicities (DLTs) occurred in cycle 1, then cycle 2 started on day 29. Treatments in cycle 2 were reversed. All patients received doxorubicin on day 1 of cycle 2. Patients in Group B then received 3 daily doses of MGd on days 1, 2, and 3 of cycle 2. The cycle 2, day 1 dose of MGd was given 4 hours after the start of the doxorubicin administration. Patients in Group A received only doxorubicin on day 1 of cycle 2. For all subsequent cycles (cycles 3 – 6), all patients (Groups A and B) received doxorubicin on day 1, followed by 3 daily doses of MGd on days 1, 2, and 3, with MGd given 4 hours after the start of the doxorubicin administration on day 1.

Adverse events were evaluated using the National Cancer Center (NCI) Common Toxicity Criteria (CTC), version 2.0.

Drug administration

Motexafin gadolinium was supplied by Pharmacyclics, Inc. (Sunnyvale, CA) in a solution containing 2.5 mg/mL MGd in 5% mannitol, USP. It was administered undiluted, at a volume calculated to supply the correct dosage, intravenously (IV) over 30 minutes, and within 8 hours after being drawn from the vial since it was formulated without preservatives. Injection was supplied in 50 mL vials. Doxorubicin hydrochloride for injection was supplied commercially, and was stored and prepared according to the manufacturer's instructions. It was infused IV over 15 minutes. Patients were premedicated with standard antiemetics according to institutional guidelines and practice.

Dose escalation

All blood counts must have met treatment criteria, and all significant adverse events must have resolved or adequately improved to grade 1 or less prior to proceeding to the next cycle of treatment. Cohorts of 3 to 6 patients were treated until the maximum tolerated dose (MTD) was established or until the highest intended dose level was treated. Cohorts of 3 patients were expanded to 6 upon the identification of a DLT. Further dose escalation could occur if no more DLTs were observed. Patients were evaluable for determination of DLTs only after they had received doxorubicin and at least one dose of MGd in combination treatment. The DLT assessment period extended through 21 days after the patient received the combination doxorubicin and MGd treatment (cycle 1 day 29 for Group A patients, and cycle 2 day 22 for Group B patients). The MTD was defined as the highest dose level at which 0 or 1 out of 6 evaluable patients experienced DLTs. Patients terminated from treatment for toxicity other than a defined DLT were replaced.

Dose limiting toxicities were judged to be related to protocol treatment and included: any grade 4 hematologic toxicity lasting ≥ 7 days, non-hematologic toxicity $\geq$ grade 3, other than nausea or vomiting; or $\geq$ grade 3 nausea or vomiting unresponsive to antiemetic therapy.

Patients were removed from protocol treatment for the occurrence of a DLT; disease progression; treatment delay ≥ 2 weeks for $\text{ANC} \leq 1500/\text{mm}^3$ or platelet count $\leq 100,000/\mu\text{L}$; the finding of left ventricular ejection fraction at rest below 45% and decreased 10% (absolute change) compared with screening ejection fraction, or 15% decreased (absolute change) compared with screening ejection fraction if it was still within the normal range ($> 45\%$); cumulative lifetime doxorubicin dose $\geq 450 \text{ mg/m}^2$, or investigator's discretion. Dose delays were specified in the protocol. Participants were followed for a minimum of 8 weeks following their termination from study treatment.

Pretreatment and follow-up studies

History, physical examination, weight, assessment of ECOG performance status, listing of concurrent medications, CBC, PT/INR, PTT, total bilirubin, AST, ALT, and serum creatinine were obtained from all patients at baseline to determine eligibility. Additional pre-registration studies included measurement of height, serum pregnancy testing for women of childbearing age, an ECG, G6PD determination, and a urinalysis. Patients with measurable disease had their tumor measurements assessed by RECIST criteria at baseline and at the end of every even-numbered cycle of treatment. All patients with responding tumors were required to have response confirmed with imaging 4 weeks after the first documented response. Patients also underwent assessment of left ventricular function at rest per MUGA scanning at baseline, after cycles 2 and 4 of treatment, and 2 months after the completion of

cycle 6. A CBC and serum chemistries (ALT, AST, GGT, albumin, alkaline phosphatase, BUN, calcium, bicarbonate, chloride, potassium, sodium, glucose, lactate dehydrogenase, phosphorus, serum creatinine, total bilirubin, total cholesterol, total protein, and uric acid) were obtained on weekly (days 1, 8, and 15) through every cycle of treatment, on day 22 of cycle 1, and at follow-up visits at 1 and 2 months following completion of therapy. Additionally, serum troponin-I was drawn on days 1, 8, and 22 of cycle 1 and on days 1 and 15 of all subsequent cycles. Lastly, an ECG, serum troponin-I, and a urinalysis were obtained 2 months after completing protocol treatment.

Statistical methods

All patients who received MGd were included in the safety analyses, which included extent of drug exposure, detailed summaries of deaths by time to death using Kaplan-Meier methods and by cause of death, detailed examination of adverse events, laboratory test results, and physical examination findings.

The primary objectives of this trial were to evaluate the safety and tolerability of MGd and doxorubicin in combination when administered to patients with advanced malignancies, and to determine the MTD and DLTs of this combination. Assessing the antitumor response rate using RECIST criteria served as a secondary objective.

The algorithm-based “3 by 3” design was chosen due to its practical simplicity. A dose level was considered intolerable if any of the following scenarios of DLT occurrences were observed: 2 or 3 of the first 3 patients experienced DLTs, or 1 of the first 3 patients experienced a DLT and so did 1 or more of the second 3 patients enrolled in that dose level. Probabilities for declaring a dose level intolerable, given various true occurrence rates of DLTs, were then calculated. For example, given a true DLT occurrence rate of 15%, the probability of declaring that dose level intolerable was 18.62%.

RESULTS

Patient characteristics and treatment

Fifteen patients enrolled between April 2002 and June 2004, 8 in Group A and 7 in Group B. Pretreatment characteristics are outlined in Table 1. The patient population included a very broad range of tumor types. All patients were assessable for safety and efficacy. Thirty-seven cycles of treatment were administered, for a median of 2 cycles per patient (range 0 – 6 cycles). Nine of 15 (60%) patients completed 2 cycles of treatment. Three patients (20%) completed the maximum of 6 cycles of therapy. The median cumulative dose of MGd administered to patients was 13.2 mg/kg, (range 1-41 mg/kg), while the median cumulative dose of doxorubicin was 60 mg/m², (range 0-180 mg/m²).

Dose escalation and toxicity

Thirteen of the 15 patients were evaluable for assessment of DLTs; 2 were not evaluable since they did not receive combination treatment with MGd and doxorubicin. The starting dose (level 1) was MGd, 1 mg/kg/day, and doxorubicin, 30 mg/m². No DLTs were observed in this cohort, and subsequent doses were escalated according to Table 2. At dose level 3 (MGd, 3.3 mg/kg/day, and doxorubicin, 30 mg/m²), a 62 year old male patient with esophageal cancer was removed from the study after completing cycle 1 due to grade 3 hypertension, related to his infusion of MGd. This cohort was expanded due to this DLT. A second DLT then occurred when a 54 year old female patient with colon cancer was hospitalized upon completing cycle 1, due to grade 3 non-neutropenic pneumonia, bacteremia, and elevated GGT, deemed possibly related to MGd. As such, accrual was

stopped and dose level 2 (MGd, 2 mg/kg/day and doxorubicin, 30 mg/m²) was identified as the MTD for this combination.

Safety

All 15 patients were evaluable for safety. The combination of MGd and doxorubicin was tolerated fairly well overall. There were no deaths on study.

A 66 year old male patient with bladder cancer, enrolled in dose level 3, died from unknown causes 29 days after receiving his final dose of MGd on cycle 1, day 8. This patient was taken off study due to progressive disease prior to the completion of cycle 1, and he expired in an in-patient Hospice 2 weeks after being diagnosed with new brain metastases. His total treatment consisted of MGd, at 3.3 mg/kg/day, on days 1 and 8 of cycle 1, and 1 dose of doxorubicin, at 30 mg/m², on cycle 1, day 8. During his 8 days on study, he experienced grade 3 dyspnea, hypoxia, syncope, and a grade 3 urinary tract infection (for which he was hospitalized), all judged unrelated to study medications. Grade 3 anemia was present at enrollment, and deteriorated to grade 4.

Serious adverse events occurred in 3 patients. A 65 year old female patient with esophageal cancer enrolled in dose level 1 developed a grade 4 pulmonary embolism after completing cycle 1 (Group B, MGd alone followed by doxorubicin alone). She was not evaluable for DLT since she did not receive the combination of MGd and doxorubicin. In addition, 2 patients were hospitalized, including the 66 year old male patient with bladder cancer and a urinary tract infection, and the 54 year old female patient with colon who developed pneumonia, bacteremia, and elevated GGT. (Both these latter 2 patients are described above.)

The 2 patients who experienced DLTs discontinued their treatment due to toxicity. Dose modifications were not permitted in this protocol. Two patients had delays in treatment due to toxicity: cycle 2 was delayed 2 weeks in a 26 year old female patient with adenoid cystic carcinoma enrolled in dose level 3 due to neutropenia, while a 71 year old male patient with hepatocellular carcinoma had cycles 2, 3, and 4 each delayed 1 week due to grade 3 hypophosphatemia that developed during treatment in dose level 1.

Grade 3 and 4 hematologic toxicities are listed in Table 3a. There were no cases of febrile neutropenia. All patients experienced at least grade 3 anemia on study. However, 10 patients had grade 3 anemia at study entry, while the remaining 5 patients enrolled with a hemoglobin between 8 and 9 g/dL. There were 2 cases of grade 1 and 2 stomatitis, but no occurrences of abnormal bleeding, thrombocytopenia, or coagulopathy. Myelosuppression was not increased in patients enrolled in Group A compared to Group B during cycles 1 and 2, therefore ruling out an obvious exacerbation of marrow toxicity in patients who received both MGd plus doxorubicin, compared to MGd alone.

Grade 3 and 4 non-hematologic toxicities at least possibly related to study treatment are listed in Table 3b. The occurrence of grade 3 fatigue in a 51 year old male patient with pancreas cancer enrolled in dose level 2 (MGd, 2.0 mg/kg/day, and doxorubicin, 30 mg/m²) was not considered a DLT since that patient had not received combination treatment with both MGd and doxorubicin. In addition, the cases of grade 3 hypophosphatemia and hypoglycemia were not considered DLTs since they occurred after the DLT evaluation period. Again, the frequency and severity of non-hematologic toxicities encountered by patients enrolled in Group A compared to Group B during cycles 1 and 2 did not differ.

All patients experienced 1 or more adverse events, the majority of which were grade 1 and 2. Adverse events reported in at least 3 patients (20%) included fatigue (87%), nausea

(53%), diarrhea (33%), vomiting (33%), dyspnea (27%), headache (27%), fever (27%), rigors (20%), anorexia (20%), insomnia (20%), productive cough (20%), and alopecia (20%). There was no evidence of cumulative toxicity. Three episodes of reversible olive-green discoloration occurred, including 2 cases of grade 1 skin discoloration and 1 case of grade 1 discoloration of the urine. Only 1 patient developed liver function test abnormalities (grade 3 elevation of GGT). No changes in ECGs, left ventricular function, or serum troponin levels were detected during this study.

Three patients completed the maximum of 6 cycles of treatment. Six patients were removed from study treatment due to progressive disease. Two patients came off study due to the participant's decision; both of these patients successfully completed at least 1 cycle of therapy. Two discontinued treatment due to the investigator's decision: 1 patient experienced grade 3 fatigue during cycle 1, and the other patient experienced a decline in performance status by the end of cycle 2. Finally, 2 patients were removed from study due to toxicity: 1 patient with grade 3 hypertension after cycle 1 and 1 patient who was hospitalized with pneumonia and bacteremia after completing cycle 1.

Efficacy

Fifteen patients were eligible for efficacy analyses. No patients attained a PR or CR. Six patients (54%) had stable disease. The median time to disease progression, or to last assessment, was 49 days (range 8-195 days).

DISCUSSION

We identified an MTD of MGd, 2 mg/kg/day, and doxorubicin, at 30 mg/m², when dosed on days 1 and 8 every 21 days in patients with advanced malignancies. This schedule proved moderately well-tolerated, with the majority of patients completing 2 cycles of treatment. Most of the observed toxicities were expected, including the DLTs of infusion-related HTN of MGd and the elevation of GGT, as were the less severe adverse effects of fatigue, nausea and vomiting, diarrhea, and olive-green discoloration of skin and urine. The tolerability of MGd in this population appeared commensurate with that noted in other studies [3,4,11].

Although formal pharmacokinetic analyses were not performed in this study, the absence of significantly unexpected toxicities suggests a lack of meaningful drug-drug interactions between MGd and doxorubicin. Neither hematologic nor non-hematologic toxicities appeared to be worsened by administration of both drugs in combination, compared to receiving either drug alone. Specifically, no worsening of doxorubicin-induced cardiac toxicity was encountered in this population (although only 3 of our patients received a cumulative doxorubicin dose of at least 180 mg/m²). The single unexpected toxicity of this combination was the universal occurrence of at least grade 3 anemia. Although not heavily pretreated, this population was unusually anemic at study entry, with all 15 patients initiating treatment with a hemoglobin less than 9 g/dL. Additional hematologic toxicity was not noteworthy in this study, and there were no occurrences of abnormal bleeding. Although doxorubicin has been noted to induce long-lasting hematopoietic injury that can manifest as chronic anemia, the high prevalence of severe anemia in this population was likely related to the chance enrollment of significantly anemic patients at treatment outset [15].

Ribonucleotide reductase converts ribonucleoside diphosphates to deoxyribonucleoside diphosphates, the rate limiting step in the synthesis of DNA precursors. It is a tetramer composed of 2 non-identical homodimers designated hRRM1 (R1) and hRRM2 (R2). The 17- kDa R1 dimer contains a catalytic site, binding sites for allosteric effectors, and a redox-active disulfide that participates in the reduction of substrates [16]. Cancer cells have much higher concentrations of active RR, compared to normal cells, due to the need for

deoxyribonucleotides. Inhibitors of RR that have been investigated as cancer therapeutics include hydroxyurea, 3-aminopyridine-2-carboxaldehyde thiosemicarbazone (Triapine®) and gemcitabine [7]. Hashemy et al. have demonstrated that MGd inhibits recombinant mouse RR [6]. This group recently used fluorescence correlation spectroscopy to show that MGd bound directly to the R1 subunit, and that R1 enzymatic activity was inhibited by both hydrogen peroxide and directly by MGd [7]. These intriguing data suggest that MGd may act on tumor cells by disrupting DNA repair via inhibition of RR. Therefore, combination studies with other RR inhibitors, especially the well-tolerated chemotherapeutic gemcitabine, are warranted.

In summary, we identified an MTD of this combination of MGd, 2 mg/kg/day, and doxorubicin, 30 mg/m², when dosed on days 1 and 8 every 21 days. This regimen was fairly well tolerated. Nonetheless, emerging documentation that MGd inhibits RR raises the potential that combination studies with RR inhibitors that have a more favorable toxicity profile, such as gemcitabine, may lead to regimens with a wider therapeutic index. As such, further evaluation of MGd plus doxorubicin is not recommended.

Acknowledgments

The authors acknowledge our patients, their families, and our clinic and research staff in the completion of this trial. The authors would like to thank Minesh P. Mehta, MBChB, for his thoughtful review of this manuscript. Melinda Baker assisted with preparation of this manuscript.

Financial and Grant Support: Pharmacyclics, Incorporated, Sunnyvale, CA

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Figure.
Treatment of Patients in Groups A and B

Table 1

Patient demographics

	N
Number of patients	15
Median age (range)	58 (26-73)
Sex	
Male	9
Female	6
Performance status	
0	5
1	10
Primary tumor type	
Esophagus	3
Sarcoma	1
Breast	1
Pancreas	1
Non-small cell lung	1
Renal	1
Thyroid, differentiated	1
Adenoid cystic carcinoma	1
Bladder	1
Hepatocellular	1
Prostate	1
Stomach	1
Colon	1
Prior lines of cytotoxic chemotherapy	
0	4
1	3
2	4
3	3
4	1
Prior radiotherapy*	
Yes	7
No	8

Table 2

Dose escalation schema with number of patients and cycles

Dose Levels	Motexafin Gadolinium (mg/kg/day)	Doxorubicin (mg/m ²)	Number of Patients	Number of Cycles
1	1.0	30	4	15
2	2.0	30	4	5
3	3.3	30	7	17

Table 3a

Grade 3 and 4 hematologic toxicity

Dose level	Neutropenia Grade		Anemia Grade		Anemia Grade [*]	
	3	4	3	4	3	4
1	2		1			3
2				1	1	2
3	1		3		2	2 [#]

^{*} Anemia occurring on study in the 10 patients who enrolled with grade 3 anemia

[#] Did not meet criteria for DLT due to improving to $\leq$ grade 3 within 7 days

Table 3b

Grade 3 and 4 non-hematologic toxicity **

Description	Dose Level 1	Dose Level 2	Dose Level 3
Fatigue		1	1
Nausea			1
Pulmonary embolism	1		
Hypertension			1 [#]
Hypophosphatemia	1		1
Hypoglycemia			1
Pneumonia			1 [#]
Bacteremia			1 [#]
Elevated GGT			1 [#]

** Includes all grade 3 and 4 non-hematologic toxicity that was considered at least *possibly* related to study treatment.

[#] Includes single event that met criteria for DLT.

Abbreviations: GGT (gamma-glutamyl transferase)