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Repetitively Dosed Docetaxel and ¹⁵³Samarium-EDTMP as an Anti-Tumor Strategy for Metastatic Castration-Resistant Prostate Cancer

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Abstract

Background—Beta-emitting bone-seeking radiopharmaceuticals have historically been administered for pain palliation while docetaxel prolongs life in metastatic castration-resistant prostate cancer (mCRPC). In combination, these agents simultaneously target the bone stroma and cancer cell to optimize anti-tumor effects. The toxicity and efficacy when each agent is combined at full, recommended doses, in a repetitive fashion is not well established.

Methods—Patients with progressive mCRPC and ≥ 3 bone lesions received ¹⁵³Sm-EDTMP 1.0 mCi/kg every 9 weeks and docetaxel 75mg/m² every 3 weeks. In the absence of unacceptable toxicity, patients were allowed to continue additional cycles, defined by 9 weeks of treatment, until intolerance or biochemical/radiographic progression.

Results—Of 30 patients treated, 50% were taxane-naïve, 36.7% taxane-refractory, and 13.3% previously exposed to taxanes but not considered refractory. Patients received on average 2.5 cycles: 6.5 doses of docetaxel and 2.5 doses of ¹⁵³Sm-EDTMP. Twelve (40%) demonstrated decline in prostate-specific antigen of ≥ 50%. Median progression-free survival (biochemical or radiographic) was 7.0 months and overall survival was 14.3 months. Nine patients (30%) did not recover platelet counts above 100 K/mm³ after a median of 3 cycles to allow for additional treatment, with four experiencing prolonged thrombocytopenia. The most common reasons for trial discontinuation were progressive disease and hematologic toxicity.

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Conflicts of interest: HIS: consultancy for Amgen, Bristol-Meyers Squibb, Dendreon, EndoPharmaceuticals, Millenium, Novartis, Ortho Biotech Oncology Research, Santofi-Aventis, and Senior Scientific LLC. MJM: consultancy for Millennium Pharmaceuticals, Cytogen, Inc., and Sanofi Aventis. KAA, NPT, JAC, RDS, SFS, DER, CH, GH, SML have no conflicts of interest to report.

Discussion—¹⁵³Sm-EDTMP can be safely combined with docetaxel at full doses on an ongoing basis. Thrombocytopenia limited therapy for some patients; preliminary efficacy supports the strategy of combining a radiopharmaceutical with chemotherapy, an appealing strategy given the anticipated availability of alpha emitters that can prolong survival.

Keywords

prostate cancer; ¹⁵³Sm-EDTMP; docetaxel; chemotherapy; radiopharmaceutical

INTRODUCTION

Metastatic castration-resistant prostate cancer (mCRPC) has a strong predilection for bone, and therefore strategies utilizing bone seeking radiopharmaceuticals that target the bone microenvironment are scientifically relevant, but clinically remain underutilized. Concerns for myelosuppression, lack of a demonstrated survival benefit of beta-emitters, and the need for collaboration with nuclear medicine have all contributed to their limited use. Furthermore, although beta-emitting radiopharmaceuticals have long been approved for the treatment of bone pain, they have not been developed as anti-tumor agents either alone or in combination with other agents.

Combining a radiopharmaceutical such as samarium-153 ethylenediaminetetramethylenephosphonate (¹⁵³Sm-EDTMP), known to palliate bone pain, with first line chemotherapy with docetaxel, an agent known to prolong survival in patients with bone and soft tissue/visceral mCRPC, may enhance chemotherapeutic response and improve clinical outcomes. Each agent may offer independent effects that in combination provide additive benefit to the patient.

Trials have systematically combined these agents, but typically have limited either the dose or number of cycles of the beta radiopharmaceutical. For such reasons, we previously conducted a dose-escalation trial exploring a repetitively dosed regimen of ¹⁵³Sm-EDTMP and docetaxel.¹ ¹⁵³Sm-EDTMP was given every 6-9 weeks and docetaxel was given every 3 weeks in 28 patients with mCRPC. The maximum tolerated dose (MTD), based on cycle 1 toxicity, was not reached in this study providing rationale for utilizing the full U.S. Food and Drug Administration (FDA) approved doses of each agent (1 mCi/kg of ¹⁵³Sm-EDTMP and 75 mg/m² of docetaxel) as ongoing therapy. To facilitate our understanding of the toxicity profile, explore preliminary efficacy and duration of effect, and create a reference database by which combinations of alphaemitting radiopharmaceuticals and docetaxel could be compared, we present data on the 30 patients treated at full doses of docetaxel and ¹⁵³Sm-EDTMP repetitively through a preplanned expansion cohort until they experienced toxicity or progression.

METHODS

Study Design

Patients were treated at full FDA approved doses of docetaxel (75 mg/m² every 3 weeks) and ¹⁵³Sm-EDTMP (1.0 mCi/kg every 9 weeks). The protocol was approved by the Memorial Sloan-Kettering Cancer Center institutional review board and all patients provided written informed consent.

Patients

Eligible patients had histologic evidence of prostate adenocarcinoma, castrate levels of testosterone (< 50 ng/dL), and biochemical or radiographic progression as previously

described.¹ All patients had to have at least 3 bone metastases on bone scintigraphy. Visceral metastases or symptomatic lymphadenopathy were allowed provided there was also bone disease.

Adequate hematologic function was defined as white blood cells ≥ 3.0 K/mm³, absolute neutrophil count (ANC) ≥ 1.5 K/mm³, platelets ≥ 100 K/mm³, and hemoglobin ≥ 10 mg/dL. Adequate hepatic function required bilirubin levels of less than the upper limit of normal (ULN) and alanine aminotransferase and aspartate aminotransferase (ALT/AST) levels $\leq 1.5 \times$ ULN. Adequate renal function was defined as serum creatinine ≤ 2.0 mg/dL. Karnofsky Performance Status ≥ 60 was required.

Patients who had more than 1 course of external beam radiation targeted to bone, circumferential or transcortical pathologic long bone fractures, or spinal cord compression were excluded.

Treatment

Cycles consisted of ¹⁵³Sm-EDTMP administered on day 1 of each cycle, with docetaxel administered on days 1, 22, and 43, as seen in Figure 1. All patients received prednisone 5 mg twice daily throughout the cycle, and dexamethasone 4 mg twice daily on the day before, day of, and day after docetaxel. On day 1, patients were treated with 1.0 mCi/kg of ¹⁵³Sm-EDTMP followed by 75 mg/m² of docetaxel between 6 and 30 hours later. Docetaxel was administered again on days 22 and 43 in the absence of grade 3 or 4 toxicity. Treatment was permitted to be held for 1 week for toxicity recovery, with retreatment permitted in the absence of grade 3 or 4 toxicity. Patients were eligible to receive additional cycles in the presence of grade 0 to 1 neutropenia, platelet count $\geq 100,000$ K/mm³, or grade 2 nonhematologic toxicity. Recycling was allowed to be held for up to 2 weeks to allow for recovery of toxicity to permitted levels.

Patients were tested for hematologic parameters on day 1 and every 7 days thereafter. Prophylactic granulocyte colony stimulating factor (GCSF) was added following each docetaxel treatment for persistent grade 4 neutropenia lasting ≥ 1 week, or in the event of neutropenic fever. A dose reduction to 60 mg/m² of docetaxel and 0.5 mCi/kg² of ¹⁵³Sm-EDTMP was allowed for grade 4 thrombocytopenia. For other serious nonhematologic toxicity, dose reduction of both drugs by 25% for grade 2 toxicity and 50% for grade 3 toxicity was allowed.

Study Endpoints

Safety—The primary endpoint was safety with chronic dosing. Dose-limiting toxicity (DLT) for the first six patients, as pre-specified by the protocol, was defined as any neutropenic fever, grade 3 or higher nonhematologic toxicity, grade 3 neutropenia that lasted for 7 or more days despite growth factor support, grade 3 or higher anemia or thrombocytopenia that lasted for 5 or more days, or failure of count recovery to allow for therapy, in cycle 1. Any DLT in the first six patients was considered grounds for discontinuation. For the subsequent twenty-four patients, the definition of DLT was specifically liberalized in order to test the tolerance of the regimen given repetitively. Therefore, DLT was not defined by cycle 1 toxicity, but failure to meet criteria to allow for re-cycling as described above in the treatment section. Details of toxicities and adverse events were assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) v3.0 for all patients at all cycles.² Complete blood counts were performed weekly, and physical exam, vital signs, serum chemistry, and adverse event inquiries were performed once every 3 weeks. All patients who received at least 1 dose of study drug were included in the analysis.

Antitumor effects—Progression-free survival (PFS) was defined as the time between the start of treatment and the first documented progression or death. Progression was indicated by meeting at least 1 of 3 criteria: biochemical progression, soft-tissue progression, or a combination of a new bone lesion(s) with a rising PSA or worsening bone pain. PSA was drawn at baseline and every 3 weeks. Biochemical progression was defined as a 50% increase in PSA over nadir in patients who had experienced a 50% decline in PSA on study. In patients with a < 50% decline in PSA, progression was defined as a 25% increase over nadir or baseline, whichever was lower.

Radiographic assessments were performed at baseline and every 12 weeks. Soft-tissue response was assessed by Response Evaluation Criteria in Solid Tumors (RECIST) 1.0.³ The appearance of 1 or more new bone lesions in the setting of rising PSA or worsening bone pain (based on clinical judgment) was also considered progression.

Bone marker analyses—Indices of bone deposition (bone-specific alkaline phosphatase, osteocalcin) and bone resorption (serum and urine N-telopeptide) were assessed every 3 weeks.

Statistical Methods

The dose-escalations in this trial were conducted based on the probabilistic calculation that if the true risk of toxicity was 0.10, 0.20, 0.30, 0.40, 0.50, 0.60 then the probability of escalation was 0.91, 0.71, 0.49, 0.31, 0.17, and 0.08, respectively. It was on this basis that doses were escalated to the full FDA approved doses of each drug, as no MTD was reached on the basis of cycle 1 toxicity as previously reported.¹ The last six patients of the dose-escalation cohort were included in the expansion cohort analyses, in which 24 additional patients were treated. All 30 patients were treated to progression or toxicity, to confirm that the dose selected based on the above probabilities was in fact clinically safe. Progression free and overall survival were computed using the Kaplan-Meier estimator.

FINDINGS

Patients

Thirty-one patients were enrolled. One patient developed spinal cord compression after registration but before treatment and was excluded from the analysis. The first six patients were part of the published dose escalation portion of this trial, and included in this manuscript as they received the same dose/schedule as the remaining patients reported herein (part of the expansion cohort of this same trial). Table 1 provides baseline patient characteristics. Fifteen patients (50%) were taxane-naïve, eleven (36.7%) were taxane-refractory, and four (13.3%) had previous exposure to taxanes but were not considered refractory at the time of discontinuing docetaxel as they were responding to treatment. For purposes of this study, taxane refractoriness was defined as definitive disease progression biochemically and/or radiographically, while on first-line taxane therapy. No patient received fewer than three cycles of docetaxel (225 mg/m²) who met the study definition of taxane-refractory. Cabazitaxel was not approved at the time this study was conducted and therefore a more contemporary definition of taxane refractoriness (i.e., refractoriness in both the first and second line setting) was not implemented.

Treatment

Patients received a median of 2.5 doses of ¹⁵³Sm-EDTMP (range, 1–10 doses) and 6.5 doses of docetaxel (range, 1–32 doses) (Figure 2a and 2b). Taxane-naïve patients (*n*=15) received a median cumulative exposure of 3.0 mCi/kg of ¹⁵³Sm-EDTMP over 3 doses (range, 1–10) and 675 mg/m² of docetaxel over 9 doses (range, 1–29). The four patients who were taxane-

exposed but not taxane-refractory received a median cumulative exposure of 3.0 mCi/kg of ^{153}Sm -EDTMP over 3 doses (range, 1–6) and 600 mg/m² of docetaxel over 8 doses (range, 2–18). Taxane-refractory patients ($n = 11$) received a median cumulative exposure of 2.0 mCi/kg of ^{153}Sm -EDTMP over 2 doses (range, 1–4), and 375 mg/m² of docetaxel over 5 doses (range, 1–12). One patient in the taxane-exposed group had the dose of both drugs reduced by 25% mid-cycle because of grade 2 fatigue. No other dose reductions occurred.

Ten patients failed to recycle on the basis of hematologic toxicity (DLT). Thrombocytopenia was the most common hematologic reason ($n = 9$), and one patient experienced neutropenic fever in the first cycle. Disease progression accounted for 10 patients discontinuation of treatment. The remainder came off study for comorbid conditions, patient request for a treatment break, or closure of the trial.

Safety

Table 2 and 3 report adverse events from cycle 1 and all cycles. Neutropenia and thrombocytopenia were the predominant toxicities, as reviewed below and in Table 4.

Neutropenia—Grade 3 to 4 neutropenia occurred in 96% of patients. All patients recovered ANC to allow for recycling (Table 4). One patient experienced an uncomplicated neutropenic fever and recovered without sequelae but was taken off study as the protocol considered this grounds for discontinuation in the first six patients. Six other patients experienced a neutropenic fever, recovered their counts in time for recycling, and were permitted to stay on study per protocol. 18 patients received GCSF prophylaxis.

Thrombocytopenia—Eight patients (27%) experienced grade 3 to 4 thrombocytopenia. Five were taxane-naïve, one was previously exposed to taxanes, and two were taxane-refractory. Median platelet nadir in cycle 1 was 97 K/mm³ (range, 39–172 K/mm³) and the all-cycle median nadir was 64 K/mm³ (range, 19–172 K/mm³). Nine patients (30%) did not recover platelet counts sufficient to allow for recycling: two occurred in cycle 1; two in cycle 2; three in cycle 3; one in cycle 5; and one in cycle 6. Four of the nine patients who did not recover platelets to allow for recycling (13% of the total) experienced prolonged thrombocytopenia (87–177 days) that failed to recover to 100 K/mm³ after 1 or 2 cycles. One of these patients was taxane-naïve, one had prior taxane exposure, and two were taxane-refractory. Three of these four patients showed new lesions on bone scintigraphy with the onset of thrombocytopenia and went on to receive external beam radiation to bone. The fourth patient did not have a bone scan performed; MRI showed stable disease, but pain increased.

Antitumor Effects

Best-response PSA waterfall plots are presented in Figure 3. Overall, 24 patients (80%) had a decline in PSA, 12 of whom (40%) had a decline of at least 50%. Of the 10 patients with measurable soft-tissue disease, 2 (20%) achieved a partial response and 4 (40%) had stable disease.

The median PFS was 7.0 months (95% CI: 3.7–8.8) and OS was 14.3 months (95% CI: 10.3–24.0) (Figure 4). The longest PFS and OS was seen in the taxane-naïve group, with a median PFS of 8.2 months (95% CI: 5.7–13.7) and OS of 23.4 months (95% CI: 13.8–42.7). Taxane-exposed patients had a median PFS of 7.0 months (95% CI: 3.2–11.5) and OS of 19.4 months (95% CI: 5.6–30.3). The taxane-refractory group had a median PFS of 3.5 months (95% CI: 0.7–8.0) and OS of 9.6 months (95% CI: 4.8–13.5).

Bone Markers

Eighteen patients (60%) received zoledronic acid during the trial and one (3%) received alendronate. The median percentage change from baseline to week 3 was -14.1% for urinary N-telopeptide, -17.6% for serum N-telopeptide, -82.1% for osteocalcin and -6.25% for bone-specific alkaline phosphatase (Figure 5).

DISCUSSION

Beta-emitting radiopharmaceuticals have long been a part of the armamentarium for treating bone pain in mCRPC. However, there is growing evidence to support the development of bone seeking radiopharmaceuticals as anti-tumor agents to confer benefit beyond palliation. The most definitive evidence arises from the large, randomized phase 3 study of the alpha-emitter, radium-223, that demonstrated a 2.8 month prolongation in survival in comparison to placebo.⁴ Other strategies aimed at developing radiopharmaceuticals as anti-tumor agents have utilized combination beta-emitting radiopharmaceuticals with chemotherapy known to prolong survival. These earlier phase studies, however, have typically limited the dose and number of cycles of the beta-emitting radiopharmaceutical, primarily for concern of hematologic toxicity.⁵⁻⁸

The current trial defines the hematologic toxicity profile in the largest published cohort to date using repetitive, full dosing of each agent and in combination. Neutropenia rarely limited therapy and returned to acceptable levels at a median of 7 days from nadir, although 60% of patients received GCSF. Neutropenic fever was seen in 23% of patients and did not recur after GCSF prophylaxis; all patients recovered ANC in time for recycling.

Thrombocytopenia was a greater limitation, as recycling was precluded in nine patients (30%) after a median of 3 cycles. Four patients did not recover their platelet count to above 100 K/mm³ after a median of 1.5 cycles. These findings are consistent with those of Tu and colleagues, in which 28% of patients experienced grade 3 hematologic toxicity after 2 cycles of combination therapy.⁶ In our study, three of the four patients who never recovered a platelet count over 100 K/mm³ had signs of bone-based radiographic progression, suggesting disease status as a possible contributor. In another study, marrow failure occurred in 9 of 43 responders to induction with weekly docetaxel 20 mg/m² and estramustine who then underwent consolidation with single dose ¹⁵³Sm-EDTMP and continued weekly docetaxel.⁵ Involvement of prostate cancer in the bone marrow was the most common finding in these patients. Marrow involvement is common in terminal stages of CRPC, making the distinction between drug effect and progressive disease challenging when considering a heavily pretreated population.

The use of ¹⁵³Sm-EDTMP did not appear to limit the dose of docetaxel administered in this trial when compared to reference chemotherapy trials in mCRPC.^{9,10} Chemotherapy naïve patients received the same number of cycles of chemotherapy receiving both drugs as patients receiving docetaxel alone in previous trials. Even patients who were previously treated with docetaxel (but not refractory) received only 1 cycle less of docetaxel as chemotherapy naïve patients. The addition of ¹⁵³Sm-EDTMP therefore did not limit the duration of treatment or total chemotherapy exposure of docetaxel, and perhaps allowed for additional treatment by enhancing response in chemotherapy exposed or resistant patients.

Preliminary efficacy was demonstrated in this trial in both chemotherapy naïve and previously treated patients. Overall, 40% of patients had a PSA decline ≥50%. It appears that the use of a radiopharmaceutical in the present study was able to re-sensitize previously refractory patients to the effects of docetaxel.

The future use of bone seeking radiopharmaceuticals will likely emphasize alpha-emitting rather than beta-emitting radiopharmaceuticals. Alpha-emitting radiopharmaceuticals such as radium-223 deliver energy with lesser tissue penetration than beta-emitters, and subsequently have less hematologic toxicity. Radium-223 was developed as an anti-tumor agent, and has demonstrated a survival advantage.⁴ Therefore, we will not pursue ¹⁵³Sm-EDTMP and docetaxel in efficacy-based studies, despite the tolerability and preliminary promising efficacy data seen. Rather, the design, safety, and efficacy data from this study of ¹⁵³Sm-EDTMP and docetaxel has resulted in a presently ongoing multicenter study combining radium-223 and docetaxel (NCT01106352).¹¹ The rationale underlying that trial is that the combination involves two known life-prolonging therapies, each with favorable toxicity profiles when given as monotherapy that can target both tumor and bone. This report is among the largest safety and efficacy comparison datasets for interpreting the results of trials combining chemotherapy with alpha-emitting radiopharmaceuticals.⁸

In conclusion, full doses of ¹⁵³Sm-EDTMP and docetaxel can be given together as ongoing therapy in both chemotherapy naïve, exposed, and refractory patients. This study provides encouraging preliminary efficacy to support the development of combination strategies of bone-seeking radiopharmaceuticals with chemotherapy. Although the hematologic toxicity seen in this study was manageable, the anticipated availability of radium-223 that has been shown to be minimally toxic to the bone marrow provides even greater enthusiasm for combination regimens targeting both the tumor and the bone stroma.

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Figure 1.
Treatment schedule for expansion cohort. ¹⁵³Sm-EDTMP 1 mCi/kg and docetaxel 75mg/m².

Figure 2 a and 2b.

Taxane-naïve patients received the most ¹⁵³Sm-EDTMP and docetaxel with comparable rates among men with prior taxane exposure who were not considered refractory. Patients considered taxane-refractory prior to trial entry received the fewest cycles of therapy.

Figure 3. Waterfall graphs of best PSA response stratified by prior taxane exposure. Although PSA declined for all groups, the largest degree of change was seen in taxane-naïve patients.

Figure 4. Overall Survival and Progression-Free Survival (defined by PSA, imaging, or death). The median overall PFS was 7.0 months and OS was 14.3 months.

Figure 5.

Waterfall plots of bone markers at week 3 following the first dose of ^{153}Sm -EDTMP 1.0 mCi/kg and docetaxel 75 mg/m². Median value labelled in green. Serum and urine N-telopeptide (NTx) declined in the majority of patients. The largest declines were seen with osteocalcin; there was a variable effect on bone-specific alkaline phosphatase (BSAP).

Table 1

Patient characteristics at baseline

Characteristic	(<i>n</i> = 30)
Median age, years (range)	67 (52–89)
Extent of disease	
Bone only disease	20
Both soft tissue and bone disease	10
Prior treatment	
Taxane naïve	15
Prior exposure to taxane, but still taxane sensitive	4
Prior q3w taxane (<i>n</i> = 2):	
Median number of cycles (range)	7.5 (6–9)
Taxane schedule not documented	2 *
Taxane refractory	11
Prior weekly taxane (<i>n</i> = 1):	
Median number of cycles (range)	5 (5)
Prior q3w taxane (<i>n</i> = 10):	
Median number of cycles (range)	8 (3–17)
Median number of prior hormonal regimens (range)	4 (1–6)
Prior radiation therapy	21
Radiotherapy to primary tumor	16
Radiotherapy to metastatic sites	13
Spine	9
Pelvis	3
Skull	1
Radiotherapy to primary and metastatic sites	8
Median Karnofsky Performance Status (range)	80 (70–90)
Median Gleason (<i>n</i> = 22) (range)	8 (6–10)
Median PSA level (ng/mL) (range)	149.9 (4.95–2531.2)
Median Hemoglobin (g/dl) (range)	12.25 (9.9–14.7)
Median Alkaline phosphatase (U/L) (range)	223.5 (42–1254)

* One patient received docetaxel and one patient received paclitaxel.

q3w = every 3 weeks, PSA = prostate-specific antigen.

Table 2Adverse events – Cycle 1 only (*n* = 30 pts)

Body system	Adverse event ^a	Grade 1 No. of pts (%)	Grade 2 No. of pts (%)	Grade 3 No. of pts (%)	Grade 4 No. of pts (%)
Blood/bone marrow	Lymphopenia	0 (0)	0 (0)	18 (60)	0 (0)
	Hemoglobin	18 (60)	11 (37)	1 (3)	0 (0)
	Leukocytes	1 (3)	3 (10)	17 (57)	8 (27)
	Neutrophils	0 (0)	2 (7)	14 (47)	13 (43)
	Platelets	24 (80)	1 (3)	3 (10)	0 (0)
Constitutional	Fatigue	10 (33)	5 (17)	0 (0)	0 (0)
Cardiac	Atrial fibrillation	0 (0)	0 (0)	1 (3)	0 (0)
	Atrial tachycardia	0 (0)	0 (0)	1 (3)	0 (0)
Coagulation	INR	1 (3)	1 (3)	1 (3)	0 (0)
Dermatology/skin	Hair loss/alopecia	8 (27)	0 (0)	0 (0)	0 (0)
Gastrointestinal	Diarrhea	5 (17)	0 (0)	1 (3)	0 (0)
Infection	Febrile neutropenia	0 (0)	0 (0)	4 (13)	0 (0)
Metabolic/laboratory	Albumin, low	8 (27)	0 (0)	0 (0)	0 (0)
	Alkaline phosphatase	6 (20)	8 (27)	7 (23)	0 (0)
	ALT, SGPT	8 (27)	0 (0)	0 (0)	0 (0)
	Glucose, high	14 (47)	15 (50)	1 (3)	0 (0)
	Phosphate, low	0 (0)	0 (0)	2 (7)	0 (0)
Musculoskeletal	Fracture	0 (0)	0 (0)	1 (3)	0 (0)
	Muscle weakness– whole body/general	2 (7)	0 (0)	1 (3)	0 (0)
Pulmonary	Dyspnea	4 (13)	6 (20)	0 (0)	0 (0)
	Thrombosis/embolism	0 (0)	0 (0)	0 (0)	1 (3)

^aEvents grade 2 are reported if they occurred in 25% of patients, unless grade 3 or 4 toxicity was noted. All grade 3 or 4 events are included.

pts = patients, INR = international normalized ratio, ALT = alanine transaminase, SGPT = serum glutamate pyruvate transaminase

Table 3Adverse events – all cycles ($n = 30$ pts)

Body system	Adverse event ^a	Grade 1 No. of pts (%)	Grade 2 No. of pts (%)	Grade 3 No. of pts (%)	Grade 4 No. of pts (%)
Blood/bone marrow	Lymphopenia	0 (0)	0 (0)	18 (60)	5 (17)
	Hemoglobin	8 (27)	14 (47)	7 (23)	1 (3)
	Leukocytes	1 (3)	3 (10)	14 (47)	12 (40)
	Neutrophils	0 (0)	1 (3)	7 (23)	22 (73)
	Platelets	14 (47)	8 (27)	6 (20)	2 (7)
Constitutional	Fatigue	8 (27)	10 (33)	0 (0)	0 (0)
Cardiac	Atrial fibrillation	0 (0)	0 (0)	2 (7)	0 (0)
	Atrial tachycardia	0 (0)	0 (0)	1 (3)	0 (0)
Coagulation	INR	5 (17)	2 (7)	2 (7)	0 (0)
Dermatology/skin	Hair loss	8 (27)	0 (0)	0 (0)	0 (0)
Gastrointestinal	Anorexia	8 (27)	1 (3)	0 (0)	0 (0)
	Constipation	8 (27)	2 (7)	0 (0)	0 (0)
	Diarrhea	12 (40)	1 (3)	1 (3)	0 (0)
Hemorrhage/bleeding	Hemorrhage, bladder	0 (0)	0 (0)	1 (3)	0 (0)
Hepatobiliary	Cholecystitis	0 (0)	0 (0)	1 (3)	0 (0)
Infection	Febrile neutropenia	0 (0)	0 (0)	7 (23)	0 (0)
	Urinary tract NOS	0 (0)	0 (0)	1 (3)	0 (0)
Lymphatics	Edema – limb	14 (47)	1 (3)	0 (0)	0 (0)
Metabolic/laboratory	Albumin, low	14 (47)	1 (3)	1 (3)	0 (0)
	Alkaline phosphatase, high	8 (27)	7 (23)	8 (27)	0 (0)
	ALT, SGPT, high	14 (47)	0 (0)	0 (0)	0 (0)
	AST, SGOT, high	11 (37)	1 (3)	0 (0)	0 (0)
	Bilirubin, high	5 (17)	3 (10)	0 (0)	0 (0)
	Creatinine, high	6 (20)	2 (7)	1 (3)	0 (0)
	Glucose, high	10 (33)	15 (50)	5 (17)	0 (0)
	Phosphate, low	0 (0)	0 (0)	3 (10)	0 (0)
	Potassium, low	5 (17)	0 (0)	1 (3)	0 (0)
	Sodium, high	11 (37)	0 (0)	0 (0)	0 (0)
Musculoskeletal	Sodium, low	8 (27)	0 (0)	1 (3)	0 (0)
	Fracture	0 (0)	2 (7)	1 (3)	0 (0)
	Muscle weakness – whole body/general	6 (20)	0 (0)	1 (3)	0 (0)
Neurology	Neuropathy – sensory	10 (33)	0 (0)	0 (0)	0 (0)
	Syncope	0 (0)	0 (0)	2 (7)	0 (0)
Pain	Pain – various sites	9 (30)	3 (10)	2 (7)	0 (0)
Pulmonary	Cough	9 (30)	0 (0)	0 (0)	0 (0)
	Dyspnea	2 (7)	16 (53)	0 (0)	0 (0)
Genitourinary	Renal failure	0 (0)	0 (0)	1 (3)	0 (0)

Body system	Adverse event ^a	Grade 1 No. of pts (%)	Grade 2 No. of pts (%)	Grade 3 No. of pts (%)	Grade 4 No. of pts (%)
Vascular	Thrombosis/embolism (vascular access-related)	0 (0)	0 (0)	0 (0)	1 (3)
	Thrombosis/embolism	0 (0)	0 (0)	1 (3)	1 (3)

^aEvents grade 2 are reported if they occurred in ≥25% of patients, unless grade 3 or 4 toxicity was noted. All grade 3 or 4 events are included.

pts = patients, ALT = alanine transaminase, SGPT = serum glutamate pyruvate transaminase, AST = aspartate aminotransferase, SGOT = serum glutamic-oxaloacetic transaminase

Table 4Hematologic Adverse Events ($n = 30$ patients)

	Cycle 1 ($n=30$ patients; 30 cycles)	All Cycles ($n=30$ patients; 93 cycles)
Median nadir PLT, range (K/mm ³)	97 (39-172)	64 (19-172)
Median days to PLT recovery of patients, range	8 (2-87)	13 (2-177)
Pts who did not recover PLT to allow recycling ($>100\text{K/mm}^3$)	2/30	9 ^a /30
Median ANC nadir (K/mcL), range	0.45 (0.02–1.4)	0.3 (0-1.4)
Median days to ANC recovery of pts with nadir ANC grade 3, range	7 (2-15)	7 (2-23)
Number of patients who did not recover ANC to allow recycling	0/30	0/30
Number of patients with nadir HGB grade 3	1/30	8/30

^a 4 patients never recovered platelet count to 100K/mm^3 after 1-2 cycles and experienced prolonged thrombocytopenia (87-177 days).