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A Phase I Study of Cilengitide and Paclitaxel in Patients with Advanced Solid Tumors

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Abstract

Purpose: Cilengitide is a potent and selective inhibitor of the integrins αvβ3 and αvβ5. The primary objective of this phase I clinical trial was to establish the maximum tolerated dose and determine safety/tolerability of cilengitide in combination with paclitaxel in patients with advanced solid tumors. Secondary objectives included the evaluation of the preliminary clinical outcomes.

Patients and Methods: Patients with advanced solid tumors experiencing disease progression on standard treatment were assigned to two different dose levels of cilengitide (2000 mg intravenously once or twice weekly) in combination with fixed-dose, weekly paclitaxel (90 mg/m^2 intravenously).

Results: Twelve evaluable patients were treated per protocol. A single dose limiting toxicity (DLT) of grade 4 neutropenia was observed at the starting dose level of once weekly cilengitide. There were no grade ≥3 adverse events that occurred with >10% frequency. One patient achieved a partial response to therapy. Five patients experienced stable disease as best response, 3 of which discontinued study participation due to progressive, peripheral neuropathy.

Conclusions: Cilengitide in combination with paclitaxel was well-tolerated. Antitumor activity was observed. The recommended phase II dose is twice weekly cilengitide (2000 mg) with weekly paclitaxel (90 mg/m^2). Further studies evaluating drugs that target this pathway are warranted.

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Compliance with ethical standards:

Conflicts of Interest: Dr. Qin owns stock in Regeneron Pharmaceuticals. Dr. Goetz is a consultant for Eli Lilly.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institution and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent: Informed consent was obtained from all individual participants included in the study.

Keywords

Cilengitide; αvβ3 and αvβ5 integrins; paclitaxel; solid tumors

Introduction:

Integrins have diverse functions. They mediate cell attachment and migration, and they interact directly and indirectly with growth factor receptors to control passage through the cell cycle and to regulate survival of normal cells[[1–4]]. Furthermore, they support survival of transformed cells under stress due to hypoxia, chemotherapy, and radiation[[5–7]].

The integrins αvβ3 and αvβ5 appear to be particularly important in the process of angiogenesis, and they are expressed in a variety of malignancies, including melanoma, breast cancer, prostate cancer, colon cancer, and gliomas[[8, 9]]. Intratumoral expression of integrins has been associated with tumor progression and metastasis in melanoma, glioblastoma, breast cancer, and prostate cancer[[10–12]]. For example, αvβ3 is highly expressed on malignant breast tumor vasculature, and it is a prognostic indicator of relapse-free survival in breast cancer[[12–14]]. The critical role of integrins in angiogenesis and their association with tumor progression and metastases make them an attractive target for cancer therapy.

The expression and activities of αvβ3 integrin are integrally related to one of its ligands, Cyr61, a pro-angiogenic factor belonging to the CCN family[15]. Cyr61 is a cysteine-rich, heparin binding protein that is secreted and associated with the cell surface and extracellular matrix (ECM)[16]. In *in vitro* studies, Cyr61 has been reported to mediate cell adhesion and migration, foster cell survival, and enhance angiogenesis[17–19], in part by binding with v 3 integrin which mediates the cell-ECM interactions[20]. Studies from the Lupu laboratory have demonstrated that forced expression of Cyr61 promotes the upregulation of αvβ3 integrin expression.[21] They and others have furthermore demonstrated similar findings regarding the role of Cyr61 in tumor growth, angiogenesis, and metastasis *in vivo* [18, 22, 23]. In translational studies, Cyr61 expression in breast tumors has been shown to correlate with stage, tumour size and nodal status[17–19], and high levels of expression are furthermore associated with locoregional relapse, metastasis, and breast cancer mortality[20].

Cyr61 expression is also associated with tumor resistance to anti-neoplastic therapy. Overexpression of Cyr61 in luminal MCF-7 breast cancer cells induces anchorage-independent growth, estrogen receptor signaling independent of ligand binding, and resistance to endocrine therapy[18]. Breast carcinoma cell lines over-expressing Cyr61 have furthermore been found to be more resistant to paclitaxel-induced cytotoxicity; and in xenograft models, the use of αvβ3-antagonists resulted in tumor growth inhibition and synergy with paclitaxel (unpublished data, Ruth Lupu laboratory).

Cilengitide is a potent and selective antagonist of αvβ3 and αvβ5 integrin. It is a pentapeptide with a terminal half-life of ~3–5 hours. It is predominantly renally cleared, and the minimum washout is estimated to be 24 hours. In preclinical studies, cilengitide

is associated with anti-angiogenesis activity, suppression of tumor growth and progression, and enhancement of chemotherapy and radiotherapy efficacy[21–23]. As a single agent in a phase I trial, the maximum tolerated dose (MTD) was not reached[24]. In this study, we sought to combine cilengitide with paclitaxel in patients with locally advanced solid tumors who have experienced cancer progression with standard therapies.

Methods

Patients:

Eligible patients were aged ≥18 years and had histologically-confirmed metastatic, unresectable, solid tumor malignancy (excluding lymphoma) that had progressed on standard therapy; an Eastern Cooperative Oncology Group (ECOG) performance status ≤1; life expectancy of ≥12 weeks; and adequate hematologic, hepatic and renal function. All patients provided written informed consent.

Study design:

In this Phase I, open-label, single institution study, patients received cilengitide (2000 mg intravenously once or twice weekly according to dosing assignment), in combination with paclitaxel 90 mg/m^2 on day 1, 8 and 15 of each 21-day treatment cycle (Table 1). The standard cohort 3+3 design was applied to determine the maximum tolerated dose.

DLTs included the following study adverse events, attributed (definitely, probably, or possibly) to the study treatment, occurring during cycle 1: grade 4 anemia; febrile neutropenia; grade 3 neutrophil count decreased lasting ≥ 7 days; grade 4 neutrophil count decreased; grade 4 platelet count decreased; grade 3 platelet count decreased with bleeding; treatment delay of >2 weeks for any drug-related adverse event; any other grade 3 non-hematologic toxicities, except for grade 3 nausea, vomiting, or diarrhea with maximal supportive treatment(s).

The study was approved by the Mayo Clinic Institutional Review Board and performed in accordance with the Declaration of Helsinki and Good Clinical Practice.

Study endpoints and assessments:

The primary objective was to determine the safety and tolerability of cilengitide in combination with paclitaxel and to define the MTD for this treatment combination. Adverse events (AEs) and laboratory parameters were recorded and graded according to the National Cancer Institute CTCAE (version 4.0). Secondary objectives were to characterize the pharmacokinetics (PK) of cilengitide and paclitaxel with the proposed schedule, and to report the observed antitumor activity of cilengitide in combination with paclitaxel. As an exploratory objective, patient-reported outcomes (PRO) version of the CTCAE was piloted in this phase I study.

Tumor assessment was determined by CT and/or MRI scans at baseline and every 6 weeks thereafter. Tumor response and disease progression (PD) were defined by the modified Response Evaluation Criteria in Solid Tumors (RECIST) criteria (version 1.1). Up to 2 target lesions per organ and a total of 3 target lesions were permissible for tumor assessments.

Best tumor response is defined to be the best objective status (CR, PR, SD or PD) recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

Selected PRO-CTCAE items (21 items measuring 12 symptomatic adverse events) corresponding to the major adverse events required to be graded clinically were collected. PRO-CTCAE was administered in a paper booklet by a clinical research associate prior to treatment on days 1, 8 and 15 of each cycle during their regular clinical visits.

Statistical Analysis:

MTD was defined as the dose level below the lowest dose that induces DLT in at least one-third of patients (at least 2 of a maximum of 6 new patients).

The number and severity of all adverse events (overall, by dose-level, and by tumor group) were tabulated and summarized in this patient population. This provides an indication of the level of tolerance for this treatment combination in this patient group. The term toxicity is defined as adverse events that are classified as either possibly, probably, or definitely related to study treatment. The safety and tolerability will be assessed for all patients who receive at least one dose of the study medication.

Best tumor responses were summarized by simple descriptive summary statistics. A confirmed tumor response is defined to be a complete response (CR) or partial response (PR) noted as the objective status on 2 consecutive evaluations at least 6 weeks apart.

The PRO-CTCAE was not used for the determination of DLT or for dose-escalation. Instead, they measured toxicity from the patient point of view. The PRO-CTCAE data are summarized descriptively. Informal comparison and correlation of the PRO-CTCAE symptoms with their corresponding items in clinician reported CTCAE will be conducted in an exploratory manner.

Results

Study Population:

Thirteen patients enrolled between November 7, 2011, and August 22, 2012. Patient demographics and baseline characteristics are reported in Table 2. One patient was excluded from this analysis due to drop-out prior to receiving any treatment. Over half of the patients had either breast (n=4) or esophageal cancer (n=3), and the remaining 5 patients had other distinct solid tumor malignancies (lung, thyroid, bladder, neuroendocrine pancreas, sarcoma). Overall, 11 (91.7%) patients had visceral metastases (lung and/or liver). Nine of 12 (75.0%) patients had received prior taxane-based chemotherapy, and 5 of these 9 patients (55.6%) had experienced prior progression on taxane-based chemotherapy.

Dose-escalation and MTD determination:

Cilengitide dosing was started at 2000 mg intravenously once weekly (on day 1, 8, 15 every 21-day cycle) with standard weekly dosing of paclitaxel at 90 mg/m^2. Dose escalation was structured per Table 1. A single DLT was experienced by an individual in the first cohort

of 3 patients at the starting dose level (grade 4 neutrophil count decreased). There were no DLTs observed in the subsequent 9 evaluable patients. As such, the MTD for cilengitide when combined with standard weekly paclitaxel was not reached, and the recommended dose of cilengitide for subsequent study was determined to be 2000 mg twice weekly (on days 1, 2, 8, 9, 15, 16 every 21 days).

Paclitaxel dose reductions occurred in 5 patients. Two experienced their first dose reduction during the first 2 cycles of therapy, and 3 patients experienced their first dose reduction after the second cycle.

Safety:

The combination of cilengitide and paclitaxel was well tolerated (Table 3). The most commonly experienced adverse events (any grade, all cycles) were: nausea (75%), fatigue (66.7%), diarrhea (50%), alopecia (50%), sensory peripheral neuropathy (41.7%), neutropenia (33.3%), hypocalcemia (33.3%), and hyponatremia (33.3%). Of those, only nausea, fatigue, neutropenia, and alopecia occurred in one-third or more of patients in the first cycle of therapy.

Of the 5 patients with any grade chemotherapy-induced peripheral neuropathy (CIPN), only 2 had received taxane-based chemotherapy for prior treatment of their advanced malignancy. As it relates to grade 3 and 4 toxicities, for the 6 patients enrolled on dose level 1, there was one other grade 4 event (decreased lymphocytes), but it was considered unrelated to treatment. Grade 3 events from dose level 1 that were considered related to treatment, included: anemia (3 patients), decreased lymphocytes (1 patient), hyponatremia (1 patient), increased alkaline phosphatase (1 patient), and decreased neutrophil count (1 patient). Grade 3 neutropenia, lymphopenia, diarrhea, hyponatremia, and increased alkaline phosphatase all occurred in a single patient. Other grade 3 events considered unrelated to treatment include hypophosphatemia, decreased lymphocytes, headache, dizziness, and increased alkaline phosphatase. New onset brain metastasis requiring hospitalization occurred in 1 patient.

For the 6 patients enrolled on dose level 2, there were no grade 4 events. One patient experienced grade 3 diarrhea considered possibly related to treatment. Other grade 3 events considered unrelated to treatment include pruritus, rash, and allergic reaction.

Tumor Assessments:

All patients were evaluable for best response as determined by investigator review (Figure 1). One of 12 patients (8.3%) achieved a partial response (PR) to therapy, a young woman with newly diagnosed metastatic triple negative breast cancer who had prior receipt of adjuvant paclitaxel >1 year prior to enrollment. Five of 12 patients (41.7%) achieved a best response of stable disease (SD). Of these 6 patients with clinical benefit, 2 (33.3%) had experienced prior progression on taxane-based chemotherapy, including a patient with metastatic leiomyosarcoma who maintained SD for 11 cycles and discontinued treatment due to toxicity (CIPN). Three patients had SD at the time they terminated study participation due to intolerable CIPN attributed to the paclitaxel. Two of these patients had received 4–6 cycles of prior taxane-based chemotherapy and the other patient had no prior taxane exposure. Six of 12 (50%) patients had PD after the first 2 cycles of therapy.

PRO-CTCAE:

The PRO-CTCAE items were summarized descriptively in comparison to clinician-assessed CTCAE version 4.0 (NCI, 2009) during the first cycle. All but one patient completed weekly PRO-CTCAE. PRO-CTCAE captured most of the symptomatic adverse events reflected in clinician-assessed CTCAE. Some symptomatic adverse events were not reported clinically by CTCAE but were reported by patients by PRO-CTCAE. Overall, PRO-CTCAE items indicated slightly more severe degree of symptoms experienced by patients than those reported in CTCAE.

Discussion

The primary aim of this study was to determine the MTD of cilengitide administered concurrent with standard weekly paclitaxel so this combination could proceed to an expansion cohort in triple negative breast cancer and subsequent phase II trials. Standard 3+3 study design with dose escalation was utilized. As the MTD for single-agent cilengitide was not reached and there were no overlapping toxicities with paclitaxel, only 2 dose levels were planned for evaluation.

The MTD of cilengitide in combination with continuous, weekly paclitaxel (90mg/m^2) was not established. A single DLT of grade 4 neutropenia was observed in the first cohort of 3 patients on cycle 1 day 15, and it was managed by dose reduction. There were no further DLTs in the remaining 9 evaluable patients. A cilengitide dose of 2000 mg IV on days 1 and 2 every 7 days in combination with weekly paclitaxel was deemed tolerable and recommended for further evaluation in subsequent trials.

The only grade 3 AE attributed to therapy in more than one patient was anemia. The most common grade 1–2 AEs include nausea, diarrhea, alopecia, peripheral neuropathy, hypocalcemia and hyponatremia.

One objective response was observed in a patient with taxane-sensitive, triple negative breast cancer achieved a partial response to therapy that was maintained for 5 cycles. Disease stabilization at first tumor assessment (after 2 cycles of therapy) was achieved in 5 of 12 patients (41.7%). Of these 5 patients, 3 maintained SD beyond the second tumor assessment (after 4 cycles of therapy), including one patient with taxane-resistant leiomyosarcoma who received 11 cycles of therapy; unfortunately these 3 patients subsequently discontinued study treatment after a mean of 9 cycles (range 5–11) due to progressive CIPN and neuropathic pain.

The combination of paclitaxel and cilengitide was associated with clinical benefit (best response PR or SD) in 6 (50.0%) of the 12 evaluable patients. Notably, of the 5 patients who had experienced prior progression on taxane-based chemotherapy, 2 (40.0%) achieved clinical benefit. As this phase I trial included patients who were taxane-naïve and taxane-sensitive, a phase II single-arm study of the combination therapy in a taxane-resistant study population or a randomized study of paclitaxel alone or combined with cilengitide would be necessary to better define the clinical activity of cilengitide.

It is unlikely that prior cumulative exposure to taxane-based chemotherapy predisposed patients to the CIPN observed in this study given that 3 of 9 (33.3%) patients with prior taxane exposure developed any grade CIPN. The collective safety and clinical outcomes data suggest that an alternative dose and schedule for paclitaxel should be explored in combination with cilengitide to help mitigate the risk or early onset of CIPN. This may prevent early discontinuation and improve the overall tolerability of the combination therapy.

In March 2013, the results of the CENTRIC trial were released[25]. In this phase III study patients with a new diagnosis of glioblastoma were randomized to receive temozolomide chemoradiotherapy alone or combined with cilengitide. As the addition of cilengitide did not improve overall survival, further development of cilengitide as an anticancer drug was discontinued. As a result of this, the planned triple negative breast cancer dose expansion cohort did not open to enrollment, and the PK studies were not completed. The PRO-CTCAE findings will be reported separately.

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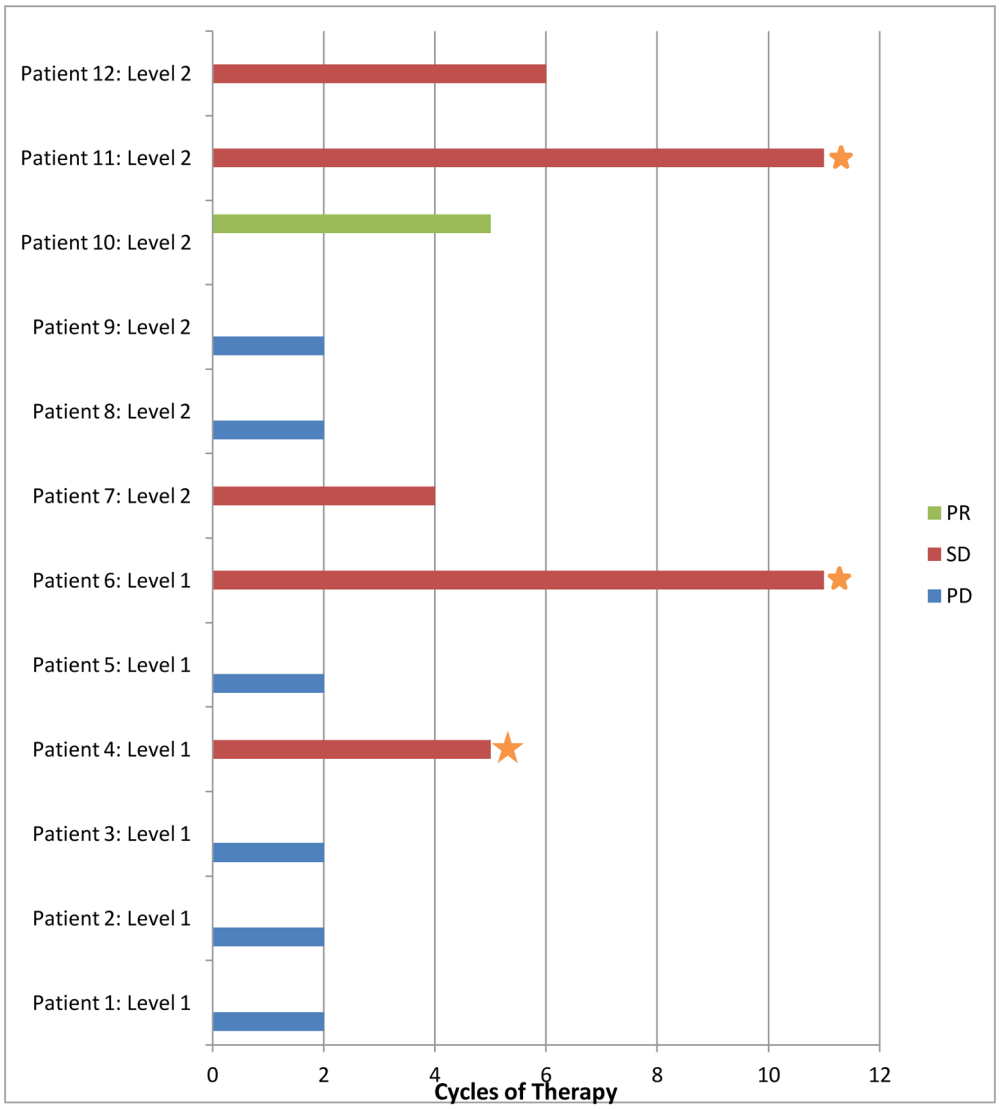

Figure 1: Duration of Therapy and Best Response

Treatment duration (in 21-day cycles) for patients exposed to standard weekly dose of paclitaxel (90 mg/m^2) in combination with cilengitide at two dose levels and corresponding best radiographic response to therapy (Partial Response, PR = Green; Stable Disease, SD = Red; Progressive Disease, PD = Blue). The star indicates those patients who discontinued therapy due to toxicities.

Table 1:
Study Drug Schedules and Dose Levels and for Cilengitide and Paclitaxel

Study drug dosing, route of administration, schedule, and retreatment interval.

Agent	Dose	Route	Schedule	Retreatment
Cilengitide	As assigned by Randomization Center	IV over 1 hour	Levels −4, −3, −2, −1, 1 *: Days 1, 8 and 15	Every 21 days +/− 3 days
			Level 2: Days 1, 2, 8, 9, 15, 16	
Paclitaxel	As assigned by Randomization Center	IV over 1 hour	Days 1, 8 and 15	Every 21 days +/− 3 days

Dose Level	Cilengitide (mg)		Paclitaxel (mg/m^2)
	Dose	Frequency	
−4	1500	Once weekly	60
−3	2000	Once weekly	60
−2	2000	Once weekly	70
−1	2000	Once weekly	80
1 *	2000	Once weekly	90
2	2000	Twice weekly	90

* Starting Dose Level

Table 2:

Patient Baseline Characteristics

The demographic, clinical, and pathologic characteristics for all evaluable patients at baseline are reported.

Baseline Characteristic	All Evaluable Patients (n=12)
Age, Median Years (Range)	56 (36, 67)
Gender	
Female	6 (50%)
Male	6 (50%)
Race	
White	10 (83.3%)
Black or African American	2 (16.7%)
Months Since Metastatic Diagnosis	27.5 (0, 98)
Median (Range)	
Performance Score	
0	2 (16.7%)
1	10 (83.3%)
Tumor Types	
Breast	4 (33.3%)
Esophageal	3 (25%)
Other solid tumor, misc.	5 (41.7%)
Sites of Metastasis	
Bone	3 (25%)
Liver	6 (50%)
Lung	7 (58.3%)
Lymph Node	5 (41.7%)
Pleura	3 (25%)
Skin	1 (8.3%)
Prior Treatments	
Chemotherapy	11 (91.7%)
Taxane-based chemotherapy	9 (75.0%)
Radiation Therapy	7 (58.3%)
Surgery	12 (100%)

Table 3:
Cycle 1 and All Cycles Adverse Events

Adverse Events (AEs), at least possibly related to treatment, are reported per CTCAE version 4.0 in all subjects at both dose levels. AEs that occurred in cycle 1 and in all cycles are further reported by severity.

Adverse Events n (% of dose level total)		Cycle 1		All Cycles	
		Any Grade	Grade ≥3	Any Grade	Grade ≥3
Body System	**Type**				
Hematology	**Anemia**	6 (50.0)	1 (8.3)	8 (66.7)	3 (25.0)
	Lymphocyte count decreased	1 (8.3)		2 (16.7)	1 (8.3)
	Neutrophil count decreased	4 (33.3)	1 (8.3)*	4 (33.3)	1 (8.3)
	White blood cell count decreased	2 (16.7)		3 (25.0)	
Hemorrhage	**Hemorrhage nasal**			1 (8.3)	
Hepatic	**Alanine aminotransferase increased**			2 (16.7)	
	Alkaline phosphatase increased			3 (25.0)	1 (8.3)
	Aspartate aminotransferase increased			3 (25.0)	
	Serum albumin decreased			1 (8.3)	
Lymphatics	**Edema limbs**			1 (8.3)	
Metabolic/Laboratory	**Serum calcium decreased**	1 (8.3)		4 (33.3)	
	Serum potassium decreased			3 (25.0)	
	Serum magnesium decreased			1 (8.3)	
	Serum sodium decreased			4 (33.3)	1 (8.3)
Neurology	**Dizziness**			1 (8.3)	
	Peripheral sensory neuropathy			5 (41.7)	
Pain	**Abdominal pain**			1 (8.3)	
	Joint pain	1 (8.3)		2 (16.7)	
	Bone pain			2 (16.7)	
	Myalgia	1 (8.3)		2 (16.7)	
	Pain	1 (8.3)		1 (8.3)	
	Pain in extremity	2 (16.7)		2 (16.7)	
Pulmonary	**Dyspnea**			3 (25.0)	
Renal/Genitourinary	**Creatinine increased**	1 (8.3)		2 (16.7)	
Cardiovascular	**Hypotension**			1 (8.3)	
	Sinus tachycardia			3 (25.0)	
Coagulation	**Activated partial thromboplastin time prolonged**			1 (8.3)	
Constitutional Symptoms	**Chills**			1 (8.3)	
	Fatigue	4 (33.3)		8 (66.7)	
	Fever	1 (8.3)		2 (16.7)	
	Weight gain			1 (8.3)	
Dermatology/Skin	**Alopecia**	4 (33.3)		6 (50.0)	
	Pruritus	1 (8.3)		2 (16.7)	

Adverse Events n (% of dose level total)		Cycle 1		All Cycles	
		Any Grade	Grade ≥3	Any Grade	Grade ≥3
	Rash acneiform			1 (8.3)	
Endocrine	**Hot flashes**	1 (8.3)		1 (8.3)	
	Hypothyroidism	1 (8.3)		1 (8.3)	
Gastrointestinal	**Anorexia**	3 (25.0)		3 (25.0)	
	Constipation	1 (8.3)		1 (8.3)	
	Dehydration			2 (16.7)	
	Diarrhea	3 (25.0)	1 (8.3)	6 (50.0)	1 (8.3)
	Mucositis oral	2 (16.7)		2 (16.7)	
	Nausea	9 (75.0)		9 (75.0)	
	Vomiting	2 (16.7)		3 (25.0)	

* Dose Limiting Toxicity