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Feasibility Study of Intra-patient Sorafenib Dose-Escalation or Re-Escalation in Patients with Previously Treated Advanced Solid Tumors

Thomas J. Semrad, MD, MAS^{1,2}, Courtney Eddings, BS¹, Chong-Xian Pan, MD, PhD^{1,2}, Derick H. Lau, MD, PhD^{1,2}, David Gandara, MD¹, Laurel Beckett, PhD³, and Primo N. Lara Jr., MD^{1,2}

¹Division of Hematology/Oncology, Department of Internal Medicine, University of California, Davis, Sacramento, California

²Section of Hematology/Oncology, The Department of Veterans Affairs Northern California Health Care System, Sacramento, California

³Division of Biostatistics, Department of Public Health Sciences, University of California, Davis, Davis, California.

Abstract

Purpose—To determine if intra-patient dose escalation of the multi-targeted kinase inhibitor sorafenib is feasible in patients with advanced pretreated solid malignancies.

Methods—An intra-patient dose escalation scheme starting at 400 mg BID was employed in this prospective trial. Doses were escalated to 600 mg BID for the second cycle and to 800 mg BID for the third cycle in the absence of grade 3+ adverse events. In the event of grade 3+ adverse events during cycle 1, doses were reduced to 400 mg daily through cycle 2. Dose re-escalation for cycle 3 was allowed in the absence of grade 3+ adverse events during cycle 2. Further dose escalation was prohibited. The primary endpoint was the overall percentage of patients tolerating dose escalation to 600 mg BID through cycle 2 or tolerating re-escalation to 400 mg BID through cycle 3.

Results—Fifty eligible patients with various solid tumors and a median of 3 prior therapies were enrolled. Eleven patients (22%) tolerated primary dose escalation or re-escalation. Only 14 patients (28%) completed cycle 1 without dose modification or discontinuing treatment. Seven of 13 patients tolerated primary dose escalation through cycle 2. Four of 5 patients tolerated dose re-escalation through cycle 3. Reasons for escalation failure included tumor progression (42%) and adverse events (26%). Common grade 3+ adverse events included hand-foot skin reaction, hypertension, and hypophosphatemia.

Conclusions—Intra-patient dose escalation and/or re-escalation of sorafenib were not feasible in pretreated solid tumor patients. Sorafenib dose escalation remains an investigational approach.

Address correspondence to: Thomas J. Semrad MD, MAS Division of Hematology/Oncology Department of Internal Medicine University of California Davis Cancer Center 4501 X Street, Suite 3016 Sacramento, CA 95817 Phone: (916) 734-3771; Fax: (916) 734-7946 thomas.semrad@ucdmc.ucdavis.edu.

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Keywords

dose escalation; dose re-escalation; dose-toxicity relationship; maximum tolerated dose; sorafenib

INTRODUCTION

Sorafenib is an oral small-molecule multi-kinase inhibitor originally developed as a serine/threonine Raf kinase inhibitor. It also inhibits other kinases including the vascular endothelial growth factor receptor (VEGFR) and the rearranged during transfection (RET) receptor, amongst others [1]. Four separate phase I dose-escalation trials of sorafenib using different dose schedules were performed in refractory advanced solid tumors [2-5]. Based on the development of dose limiting skin toxicity, diarrhea, and fatigue at higher doses, 400 mg twice daily was selected for further study [6]. Common toxicities observed in phase III trials with sorafenib included skin rash, hand-foot skin reaction, hypertension, and diarrhea [7,8]. While the approved dosing schedule of 400 mg orally twice daily is now widely used, it has been suggested that the dose and schedule of sorafenib can still be optimized for individual patients [9].

Many patients taking sorafenib remain on chronic therapy with stable or responding disease and tolerable toxicities. Indeed, many patients do not develop significant toxicity at the approved dose [6-8]. Although there are limited data regarding the cumulative toxicities of prolonged sorafenib therapy, there is anecdotal experience that some patients appear to have diminished toxicity with continued exposure [10]. However, the rate of development of tachyphylaxis to sorafenib's early toxicities is incompletely explored. It is also unclear whether there is clinical value to re-escalating the dose of sorafenib back to its prior level in patients who subsequently tolerate a reduced dose.

In 2007, the first results of an intra-patient sorafenib dose escalation trial in advanced renal cell cancer were presented [11]. Efficacy data were presented for 44 evaluable patients treated with 400 mg twice daily of sorafenib on days 1 through 28, followed by 600 mg twice daily (days 29 through 56) and 800 mg twice daily on days 57 and beyond. Ninety-one percent of patients were escalated to total daily doses of 1,200 mg or 1,600 mg. An unprecedented eight patients (18%) had a complete radiographic response, while 14 patients (32%) had partial responses and another 14 patients had stable disease for 3 months or longer. Similar results were presented from an expanded cohort and in a similar but separate small phase II clinical trial in renal cell carcinoma [12,13]. To date, there are no data exploring the possibility of whether the intra-patient dose escalation of sorafenib increases its efficacy in other solid tumors.

In patients with refractory advanced solid tumors, we designed this study to test the feasibility of 1) escalating the dose of sorafenib in patients who tolerate the FDA-approved dose for four weeks (primary intra-patient dose escalation) and 2) re-escalating the dose back to the original dose of 400 mg twice daily in those who required a dose reduction due to toxicity but tolerated the reduced dose for at least four weeks (dose re-escalation).

PATIENTS AND METHODS

Patients

Patients aged 18 years and older with refractory solid tumors were eligible. Patients with measurable or non-measurable disease on imaging studies performed within 28 days of registration were eligible and were required to have an Eastern Cooperative Oncology Group (ECOG) performance status of 0-2. Any number of prior treatments was allowed, as long as treatment was completed at least two weeks prior to registration and all toxicities had resolved to grade 1 or less. Further inclusion criteria included ability to give informed consent, ability to take oral medication, and acceptable end-organ function defined by an absolute neutrophil count $1,500/\text{mm}^3$, hemoglobin 9.0g/dl , platelet count $100,000/\text{mm}^3$, total bilirubin 1.5 times the upper limit of normal (ULN), ALT and AST 2.5 times the ULN ($5 \times$ ULN for patients with liver involvement), and creatinine 1.5 times ULN. Patients on warfarin or low molecular-weight heparin treatment were allowed provided they were on a stable dose and had no evidence of bleeding.

Exclusion criteria included any prior treatment with sorafenib or sunitinib and treatment with bevacizumab within the prior 3 months. Patients were excluded for significant cardiac comorbidities including uncontrolled hypertension defined as systolic blood pressure > 150 mmHg or diastolic blood pressure > 90 mmHg despite optimal medical management, New York Heart Association class II or greater congestive heart failure, recent (within past 6 months) myocardial infarction, unstable angina, or ventricular arrhythmia requiring anti-arrhythmic therapy. Further exclusion criteria included thrombotic or embolic events within the past 6 months and evidence of bleeding diathesis or coagulopathy. Patients with Common Terminology Criteria for Adverse Events (CTCAE) grade 2 or higher bleeding events, major surgery, open biopsy, or significant traumatic injury within the prior 4 weeks were also excluded, as were patients with non-healing wound, ulcer, or bone fracture or clinically serious active infection. Due to the death of a patient from pulmonary hemorrhage, the protocol was amended after 18 patients to exclude non-small cell lung cancer with any component of squamous cell carcinoma.

The study protocol was reviewed and approved by the institutional review board of the University of California, Davis. All patients gave written informed consent before treatment.

Study Procedures

Prior to registration, patients underwent a history and physical examination that including assessment of height, weight, ECOG performance status, vital signs, and a pregnancy test for all females of child-bearing potential. Although measurable disease was not required, radiographic tumor assessment was required within 4 weeks of registration. Tumor measurements were subsequently performed every 2 cycles, and responses were evaluated using Response Evaluation Criteria in Solid Tumors (RECIST) criteria [14]. History and physical examination were performed by the treating physician every 4 weeks. Blood pressure was measured weekly and toxicity was monitored continuously through the trial using the CTCAE version 3.0.

Treatment Plan

Eligible patients initiated treatment with sorafenib at 400 mg orally twice daily for the first 28-day cycle. Doses were escalated to 600 mg twice daily for the second and 800 mg twice daily for the third cycle if there were no CTCAE grade 3 or higher adverse events in the preceding cycle. If grade 3 or higher toxicity developed at any point in cycle 1, the dose was reduced to 400 mg daily once toxicity had resolved to grade 1 or less and given for the duration of cycle 1 and throughout cycle 2. If no further grade 3 or higher toxicities were observed, the patient was re-escalated to 400 mg twice daily for cycle 3. After cycle 3, no further dose escalation was allowed and dose modification in the maintenance phase followed the package insert. The study design is summarized graphically in **Figure 1**. Because a secondary intention of the trial was to explore whether intra-patient dose escalation or re-escalation might result in enhanced activity, patients could continue on treatment until progression of target tumor dimensions of up to 100% over baseline or the development of new lesions.

Statistical Analysis

The primary endpoint of the trial was an estimate of the overall percentage of patients tolerating a dose escalation to 600 mg twice daily for 28 days plus the percentage tolerating a re-escalation to 400 mg twice daily in cycle 3. We assumed that a dose escalation/re-escalation rate of 70% would be worthy of further study and that a dose escalation/re-escalation rate of 50% or less would not be worthy of further investigation. At a planned sample size of 51 patients and 5% significance, this study had 90% power to differentiate a dose escalation/re-escalation rate of 70% versus 50%. The secondary endpoints of the trial were toxicities, overall response rate (complete or partial response) according to RECIST criteria, and progression free survival (PFS). Numbers and types of toxicities are summarized descriptively. PFS is summarized by life-table based estimates of median times. All patients who received at least one dose of sorafenib were included in these analyses.

RESULTS

Baseline Characteristics

Between December 2008 and October 2009, fifty-one patients with a variety of advanced solid tumors were enrolled. Fifty patients who were eligible to begin treatment and took at least one dose of study drug were included in this analysis. Patients had been treated with a median of 3 prior lines of systemic treatment but had preserved performance status (ECOG 0 or 1 in 84%). Thirty-one (62%) patients were female. The most common tumor types were non-small cell lung cancer (30%) and colorectal cancer (14%). Detailed demographic and clinical characteristics are provided in **Table 1**.

Dose Escalation

The primary endpoint of the trial was reached by eleven patients (22%). Completion and tolerance for each treatment cohort is summarized in **Table 2**. During cycle 1 at a dose of 400 mg twice daily, 28 patients required a dose reduction or treatment discontinuation for grade 3 or higher toxicity, 5 patients developed early progression and 3 patients withdrew

(**Figure 2**). Only fourteen patients (28%) were able to complete cycle 1 without the development of dose modifying toxicity or discontinuing study treatment. Seven of thirteen patients (54%) who were treated at an escalated dose of sorafenib (600 mg twice daily) in cycle 2 tolerated it for 4 weeks. All four patients who were subsequently treated with 800 mg twice daily in cycle 3 tolerated that dose.

Fifty-nine percent of the 22 patients treated at the reduced dose of 400 mg daily during cycle 2 completed this cycle of treatment without further grade 3 or higher toxicity or early progression. However, only 5 of these 13 patients were subsequently re-escalated to 400 mg twice daily in cycle 3. The primary reason for this lower rate is disease progression observed on repeat imaging performed after cycle 2. Nevertheless, 4 of these 5 (80%) patients tolerated dose re-escalation back to the 400 mg twice daily dose level.

For the entire trial population, the most common reasons for failure of protocol treatment were progression (42%) and adverse events (26%) (**Table 3**). Seven of the 18 patients (39%) who attempted dose escalation or re-escalation did not tolerate it, primarily due to adverse events at the escalated doses.

Efficacy

Treatment efficacy was exploratory in this mixed population of advanced solid tumors. Of the 34 patients who were evaluable for treatment response by RECIST, no responses were observed. Two patients with head and neck squamous cell cancers had evidence of tumor necrosis by radiographic studies and by physical examination. The best overall response was stable disease in 38% of evaluable patients. The development of new lesions was the reason for progression in 11 patients. The median progression free survival in this mixed refractory solid tumor cohort was 4.7 months (95% C.I. 4.3 – 6.1 months).

Toxicity

All fifty treated patients were eligible for toxicity assessment. Toxicity data are summarized in **Table 4**. Grade 3 or higher adverse events were observed in 64% of the patients. The principal grade 3 or higher non-hematologic treatment-related toxicities were hand-foot skin reaction in eleven patients (22%), hypophosphatemia in four patients (8%), hypertension in four patients (8%), and anorexia in three patients (6%). Common grade 1 or 2 non hematologic treatment-related toxicities were fatigue (34%), hand-foot skin reaction (32%), rash (28%), hypertension (26%), diarrhea (26%) and anorexia (20%). Hematologic toxicities were generally mild. A possibly attributable grade 5 pulmonary hemorrhage developed during cycle 2 of treatment in one patient with extensive endobronchial metastasis from adenoid cystic carcinoma being treated at 400 mg daily.

DISCUSSION

In this study of patients with heavily pre-treated advanced solid tumors, primary intra-patient dose escalation or dose re-escalation following a dose reduction was not feasible for the majority of patients. We observed substantial toxicity at the recommended dose and this severely limited the population eligible for dose escalation. Due to a combination of rapid disease progression and toxicities at standard doses, a very small percentage of patients

enrolled were eligible for dose escalation or re-escalation. However, primary intra-patient dose escalation or dose re-escalation was successful in over half of those in whom it was attempted. Further research into the determinants of sorafenib-associated toxicities is needed to allow for the identification of patients who may potentially benefit from this strategy.

The spectrum of toxicities associated with sorafenib observed on this trial was generally consistent with those seen with the use of sorafenib in other settings; however, the frequency of grade 3 or higher toxicities was increased. For example, grade 3 hand-foot skin reactions were observed in 22% of patients in this study compared with 12% of patients in phase III TARGETs study of sorafenib in advanced RCC and 8% in the phase III SHARP trial in advanced HCC [7,8]. The high rate of severe toxicity at the recommended dose of sorafenib observed in our trial may be related to the fact that these patients had been heavily treated prior to enrollment into this trial. It is also consistent with several observational studies of sorafenib-associated toxicities in general clinical practice. Of 58 patients with advanced RCC treated in an expanded access nonrandomized treatment protocol at the Princess Margaret Hospital for a median of 7 months, CTCAE grade 3 adverse events were observed in 64% of patients with 62% requiring interruption of sorafenib dosing for toxicity [15]. Additionally, in a retrospective analysis of 24 unselected patients treated with sorafenib at the Medical College of Georgia, treatment interruption was required by 63% at a median of 2 weeks of initiation of treatment [16]. However, 38% of these sorafenib-treated patients in that cohort were successfully re-escalated to the starting dose at a median of 7 weeks from starting treatment.

Our results differ from preliminary results of intra-patient sorafenib dose escalation trials in patients with metastatic renal cell cancer [11-13]. The more homogeneous patient populations treated in those trials had been treated with a maximum of one prior regimen and tolerance of the FDA-approved regimen was excellent. While untreated patients with renal cell or hepatocellular carcinoma were eligible for this study, the majority of enrolled patients in this current trial had advanced solid tumors with several lines of previous treatment. Although we selected patients with preserved performance status and organ function and did not observe a difference in tolerance based on number of prior treatment regimens (data not shown), reduced tolerance to sorafenib as a result of prior therapy could explain the higher rates of toxicity observed in this trial. Moreover, the low tolerance of the starting dose of sorafenib in this trial limits comparison to prior dose escalation trials in metastatic renal cell cancer.

There are several other limitations of our study design. Drug levels were not measured as part of this study and therefore could not be correlated to drug tolerance; however, a clear relationship between drug exposure, dose, and drug-related adverse events was not observed in sorafenib's phase I testing [6,17]. Furthermore, while patients could continue with escalation or re-escalation with evidence of progression (up to 100% tumor growth, but no new lesions), the number of patients eligible for dose re-escalation was diminished by progression beyond these bounds. The efficacy of sorafenib as a single agent in this unselected population was minimal.

As in prior intra-patient dose escalation trials, we chose to start sorafenib at the current recommended dose, but in this trial we observed unexpected rates of toxicity during the first cycle of treatment. Whether initiating escalation after starting at a lower dose or waiting a longer period of time prior to escalation would be components of a more effective strategy is not known. Of note, a significant fraction of patients tolerated the higher dose when intra-patient dose escalation or re-escalation to a higher dose was attempted. Indeed, several patients tolerated the highest dose of sorafenib on this trial (1600 mg per day) without significant adverse events. Future studies should measure serum drug concentrations and search for biomarkers to select patients for dose escalation strategies. Our study does not exclude the possibility of success and benefit for this approach in carefully selected patients.

In conclusion, we did not meet our definition of feasibility for sorafenib dose escalation or dose re-escalation in this population of patients with refractory advanced solid tumors. The toxicities observed at standard doses in fit but pretreated patients were substantial. Future studies of this strategy should seek selection biomarkers and alternative study populations. Intra-patient sorafenib dose escalation and re-escalation after a toxicity-related dose reduction remain experimental approaches.

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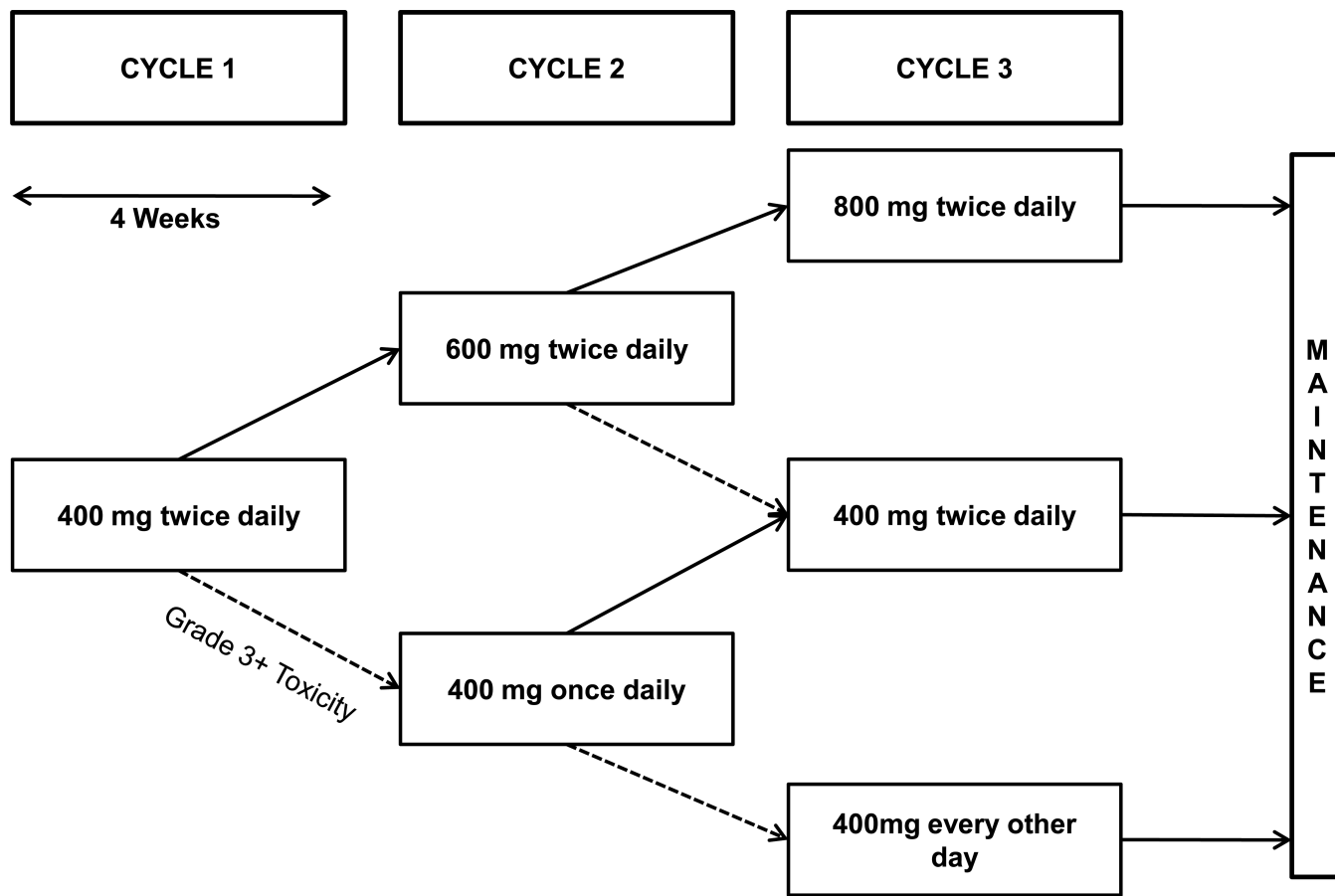


Fig. 1. Study Schema. Patients were treated at the dose levels described with cycle length defined as four weeks. Dashed arrows refer to dose de-escalation as the result of grade 3 or higher toxicity. Solid arrows refer to dose escalation which was performed during the first 3 cycles if a patient tolerated a dose level for 28 or more days without grade 3 or higher toxicity

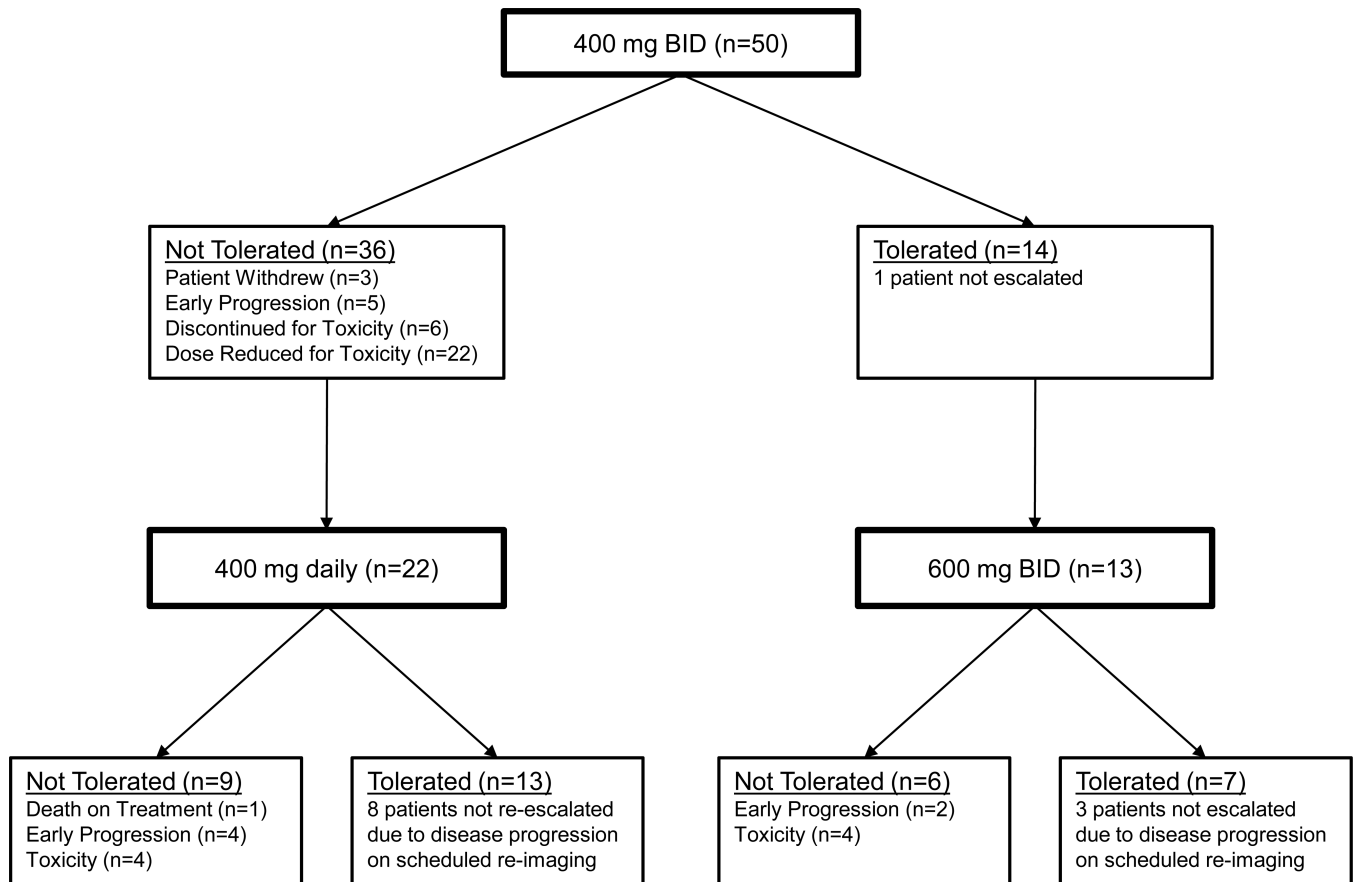


Fig. 2. Flow of patients through the first two cycles of treatment on the study. Reasons for treatment failure at a given dose level are noted

Table 1

Patient Demographic and Clinical Characteristics (n = 50)

Characteristic	n (%)
Age, years	
Median (range)	61 (25-88)
Prior Lines of Therapy, n	
Median (range)	3 (0-6)
ECOG Performance Status	
0	14 (28)
1	28 (56)
2	8 (16)
Gender	
Female	31 (62)
Male	19 (38)
Race/Ethnicity	
White	36 (72)
Asian	7 (14)
Hispanic	5 (10)
Black	2 (4)
Tumor Site	
Non-small cell lung cancer	15 (30)
Colorectal Cancer	7 (14)
Head and neck cancer	4 (8)
Pancreatic cancer	3 (6)
Soft tissue sarcoma	3 (6)
Hepatocellular cancer	2 (4)
Differentiated thyroid cancer	2 (4)
Gastric cancer	2 (4)
Adenoid cystic carcinoma	2 (4)
Prostate cancer	2 (4)
Renal cell cancer	1 (2)
Breast cancer	1 (2)
Testicular cancer	1 (2)
Mesothelioma	1 (2)
Bladder cancer	1 (2)
Melanoma	1 (2)
Thymic carcinoma	1 (2)
Ovarian cancer	1 (2)

Table 2

Dose Escalation Results by Treatment Cohort

Treatment Cohort	<u>Cohort Total</u>	<u>Tolerated</u>
	n	n (row %)
Cycle 1: 400 mg twice daily	50	14 (28%)
Cycle 2: 600 mg twice daily	13	7 (54%) ^I
Cycle 2: 400 mg once daily	22	13 (59%)
Cycle 3: 800 mg twice daily	4	4 (100%)
Cycle 3: 400 mg twice daily	5	4 (80%) ^I

^ITolerance of treatment by patients in these cohorts was the primary endpoint of this trial.

Table 3

Reasons for Escalation Failure

Category	Entire Population (n=50)	Escalation Attempted (n=18)
	n (%)	n (%)
Disease Progression	21 (42)	2 (11)
Adverse Events (Total)	13 (26)	5 (28)
Adverse Events at Escalated Dose	5 (10)	5 (28)
Withdrawal	5 (10)	0 (0)
Overall	39 (78)	7 (39)

Table 4

Major Treatment-Related Toxicities.

Adverse Event	<u>Any Grade¹</u>		<u>Grade 3-5²</u>	
	N	%	N	%
Any	42	84	32	64
Blood/Bone Marrow				
Hemoglobin	10	20	0	0
Leukopenia	7	14	0	0
Lymphopenia	11	22	3	6
Thrombocytopenia	3	6	0	0
Cardiac				
Hypertension	13	26	4	8
Constitutional				
Fever	5	10	0	0
Fatigue	17	34	1	2
Weight Loss	7	14	0	0
Dermatologic/Skin				
Dry Skin	5	10	0	0
Hand-foot skin reaction	16	32	11	22
Pruritis	3	6	0	0
Rash	14	28	2	4
Gastrointestinal				
Anorexia	10	20	3	6
Constipation	4	8	1	2
Diarrhea	13	26	2	4
Mucositis	6	12	1	2
Nausea	8	16	1	2
Hemorrhage/Bleeding				
Pulmonary/Upper				
Respiratory	2	4	2	4
Lymphatics				
Edema	3	6	0	0
Metabolic/Laboratory				
Hypoalbuminemia	4	8	2	4
Alkaline phosphatase	7	14	0	0
AST	5	10	0	0
Bicarbonate, serum – low	4	8	0	0
Hyperbilirubinemia	3	6	0	0
Hyperkalemia	3	6	1	2
Hypokalemia	7	14	2	4
Hyponatremia	5	10	1	2
Hypophosphatemia	9	18	4	8

Adverse Event	<u>Any Grade</u> ¹		<u>Grade 3-5</u> ²	
	N	%	N	%
Musculoskeletal/Soft Tissue				
Muscle Weakness	2	4	2	4
Neurology				
Mood alteration	4	8	0	0
Pain				
Abdomen	5	10	0	0
Headache	3	6	0	0
Musculoskeletal	5	10	1	2
Other	5	10	2	4
Pulmonary/Upper Respiratory				
Voice changes	3	6	0	0

¹Toxicities of any grade occurring in 3 or more individuals

²Grade 3-5 toxicities occurring in 2 or more individuals