Published in final edited form as:
Cancer Invest. 2011 November ; 29(9): 617–625. doi:10.3109/07357907.2011.621912.

A Phase I Multicenter Study of Continuous Oral Administration of Lonafarnib (SCH 66336) and Intravenous Gemcitabine in Patients with Advanced Cancer

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Abstract

We conducted a phase I study to assess safety, pharmacokinetics, pharmacodynamics and activity of lonafarnib plus gemcitabine. Subjects received oral lonafarnib twice daily and gemcitabine on days 1, 8 and 15 every 28 days; multiple dose levels were explored. Lonafarnib had no apparent effect on gemcitabine PK. Mean lonafarnib half-life ranged from 4 to 7 hours; median T_{max} values ranged from 4 to 8 hours. Two patients had partial response; 7 patients had stable disease ≥6 months. Oral lonafarnib at 150 mg AM/100 mg PM plus gemcitabine at 1000 mg/m^2 is the maximum tolerated dose with acceptable safety and tolerability.

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Declaration of Interest

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The following authors report declaration of interest:
David Cutler: 1) Employment: Merck (formerly Schering-Plough); 2) Stock ownership: Merck (formerly Schering-Plough)
Scott Kaufmann: 1) Research Funding: Merck (formerly Schering-Plough 2) Advisory Board: Merck (formerly Schering-Plough)
Michael Meyers: 1) Stock Ownership: Merck (formerly Schering Plough); 2) Honoraria: Merck (formerly Schering-Plough; 3) Other Renumeration: Merck (formerly Schering-Plough)

Keywords

Lonafarnib; Gemcitabine; Phase I; Advanced Cancer

Introduction

Protein prenylation is the process of post-translational lipid modification via the covalent addition of a hydrophobic isoprenoid residue, either farnesyl pyrophosphate or geranylgeranyl pyrophosphate, to the carboxyl terminus[1, 2]. This process is mediated by three enzymes, farnesyl transferase and geranylgeranyl transferase I and II. Prenylation is critical for the proper membrane localization and function of many proteins involved in a wide variety of cellular functions[3, 4].

Interest in protein prenylation intensified in the 1980s with the discovery that Ras proteins undergo farnesylation[3, 5]. Ras proteins serve as molecular switches that transmit cell surface signals to the nucleus and belong to the small guanosine triphosphate binding protein (G protein) superfamily[6]. Activating point mutations in *RAS* genes are found in 30% of human cancers, including 90% of pancreatic cancers and 50% of colon and thyroid cancers[7, 8]. Preclinical studies have demonstrated that farnesylation is essential for the transforming properties of activated Ras, making this step a promising target for anti-neoplastic drug development[9–11].

Lonafarnib (Sarasar, Merck & Company, formerly Schering Plough Research Institute, Kenilworth, NJ, USA, previously known as SCH 66336) is a potent and specific orally bioavailable tricyclic non-peptide farnesyl transferase inhibitor (FTI). In vitro, lonafarnib inhibits H-Ras processing in whole cells and blocks the anchorage independent growth properties of fibroblasts and human tumor cell lines expressing activated K-Ras proteins[12, 13]. In the nude mouse, lonafarnib potently inhibits growth of a wide array human tumor xenograft models[14, 15]. Multiple single agent Phase I studies with lonafarnib indicate the drug is well-tolerated and exhibits clinical activity[16–19].

Gemcitabine is a nucleoside analog that, after metabolic activation, inhibits DNA synthesis, thereby leading to cell cycle-specific cytotoxicity in S phase and blockade of cell cycle progression through the G1/S phase boundary. Gemcitabine is indicated for the treatment of advanced breast, lung, pancreatic and ovarian cancer.

Preclinical data suggests the clinical activity of FTIs combined with gemcitabine may be augmented when compared to each agent alone[20]. In addition, gemcitabine demonstrates non-overlapping mechanism of action and toxicities with lonafarnib. For these reasons, we performed a phase I dose escalation study to determine the maximum tolerated dose (MTD), pharmacokinetics and to preliminarily evaluate the clinical activity of lonafarnib plus gemcitabine in advanced solid tumors.

Materials and Methods

Patient Eligibility

Eligibility criteria included histologically confirmed solid malignancy refractory to standard therapy; presence of measurable disease; age ≥ 18; World Health Organization Performance Status of 0, 1 or 2; baseline toxicity grade ≤ 1; adequate end organ function assessed within 14 days prior to commencement of therapy [absolute neutrophil count (ANC) > 1.5×10^9/L, platelet count ≥ 100×10^9/L, hemoglobin ≥ 10 g/dL, serum creatinine ≤ 1.5 times the upper limit of normal (ULN), bilirubin ≤ 2.0 mg/dL, alanine aminotransaminase or aspartate aminotranaminase ≤ 3 times ULN (5 fold if elevations are due to liver metastases)]; willingness to comply with treatment and follow-up; and life expectancy ≥ 12 weeks. Exclusion criteria included hematological malignancies; poorly controlled systemic illness or infection; inability to take oral medication; chemotherapy, radiation or biologic or investigational therapy concurrently or within four weeks prior to administration of lonafarnib (6 weeks for mitomycin C or nitrosourea); previous wide field radiation therapy to ≥25% of bone marrow such as pelvic radiation; prior bone marrow or peripheral stem cell transplantation; pregnancy or lactation; HIV positivity or AIDS-related illness; and active central nervous system metastasis. Men or women of childbearing potential were required to use an effective contraception throughout the study period, and women of childbearing potential were required to have a negative urine or serum pregnancy test within 24 hours prior to first administration of lonafarnib. The study protocol was approved by the institutional review boards of the respective study centers and followed the guidelines of the Helsinki Declaration. Written informed consent was obtained prior to study-related procedures. The study was conducted from October 1998 to August 2001.

Treatment

This was an open-label, dose-escalation, multiple-dose study. Lonafarnib was administered twice daily with food continuously, and gemcitabine was dosed as a 30 minute intravenous infusion on days 1, 8, and 15. Both drugs were given on 28 day cycles. The dose escalation scheme is outlined in Table 1. The starting dose for lonafarnib was 150 mg orally twice daily, 75% of the established continuous monotherapy dose[21]. The starting dose of weekly gemcitabine was 750 mg/m2.

Cycles were repeated until unacceptable toxicities or disease progression. Patients with stable disease or disease response ≥ 8 months were given the option of discontinuing gemcitabine and continuing lonafarnib monotherapy. The use of concomitant colony stimulating factors including erythropoietin was prohibited.

Patient Monitoring

History, physical examination, performance status, laboratory tests and urinalysis were performed at baseline and every 28 days. Electrocardiography was performed at baseline and every 28 days to monitor for QTc abnormalities. Because of documented retinal toxicity with high dose lonafarnib in animal studies, direct ophthalmoscopy, visual acuity and color vision testing were performed by an ophthalmologist at baseline, end of cycle 1 and end of study. Retinal photography was obtained at baseline and as clinically indicated.

Adverse events were assessed using National Cancer Institute Common Toxicity Criteria (NCI CTC) version 2.0. Lonafarnib was held for ANC $<0.5 \times 10^9$/L or platelet count $<50{,}000 \times 10^9$/L and restarted one dose level lower when ANC $>0.5 \times 10^9$/L and platelet count $>50 \times 10^9$/L. Lonafarnib was held for serum creatinine ≥2X ULN (twice baseline level if serum creatinine elevated at baseline) and resumed at the next lower dose level when serum creatinine returned to baseline. If QTc increased to >500 msec and to >130% of baseline QTc, the dose of lonafarnib was decreased by one level.

Gemcitabine was administered at full dose if ANC $\geq 1.0 \times 10^9$/L and platelet count $\geq 100 \times 10^9$/L; at 75% dose if ANC ≥ 0.5–1.0×10^9/L or platelet ≥ 50–100×10^9/L; and held if ANC $<0.5 \times 10^9$/L or platelet count $< 50 \times 10^9$/L. In the event that dose reduction or holding was required, gemcitabine was administered at one dose level lower for the following cycle. Lonafarnib was decreased by one dose level for occurrence of grade 3 nausea, vomiting or diarrhea despite optimal supportive therapy. If grade 3 diarrhea persisted longer than 48 hours despite lonafarnib dose reduction, gemcitabine dose was reduced by 25%.

Tumor evaluation by computed tomography or magnetic resonance imaging was performed at baseline and every 2 cycles. Clinically evaluable lesions were measured every cycle. Evaluation of tumor response was performed using modified World Health Organization reporting of response criteria.

Dose Escalation

A rule-based traditional 3+3 dose escalation design was used to enroll a maximum of 6 patients per dose level and a total of 6 patients at the MTD level[22]. The MTD was determined as the dose level where 0 or 1 out of 6 patients experienced DLT and at least 2 patients experienced DLT at the next higher level (DLT dose level). With the design and the sample size used for this study, doses with high toxicity rates (>40%) had a high probability >0.70 of being declared as DLT. Patients who withdrew from study prior to completion of cycle 1 other than for serious adverse events or dose limiting toxicity were replaced.

DLTs were defined as ANC $<0.5 \times 10^9$/L for longer than 5 days; ANC $<0.5 \times 10^9$/L with fever (≥38.3°C); platelets $<25 \times 10^9$/L; hemoglobin <6.5 g/dL; any treatment-emergent grade ≥3 non-hematologic toxicity; grade ≥3 nausea/vomiting while receiving an optimal anti-emetic regimen for prophylaxis and management (i.e., consisting of a 5-HT3 antagonist on an optimal dose-schedule); grade ≥3 diarrhea while receiving an optimal anti-diarrheal regimen; or treatment delay for toxicity lasting greater than 2 weeks.

Protocol amendments were carried out during the course of the trial to facilitate the evaluation of doses intermediate to the initial scheme in order to define more accurately the recommended phase II dose.

Endpoints

The primary objective of this study was to characterize the safety, tolerability, maximum tolerated dose (MTD) and dose-limiting toxicity (DLT) of lonafarnib when administered orally in combination with gemcitabine in subjects with advanced malignancy. Secondary objectives of this study were to characterize the multiple-dose pharmacokinetics of oral

lonafarnib; to characterize the pharmacokinetics of gemcitabine when administered in combination with lonafarnib; preliminary evaluation of the anti-tumor activity of lonafarnib in combination with gemcitabine; and preliminary evaluation of prelamin A as a marker of farnesyl transferase inhibition.

Pharmacokinetic studies

At each dose level, multi-dose pharmacokinetic evaluation of lonafarnib was performed on day 15 in cycles 1 and 2. Blood samples for lonafarnib concentration were collected just prior to the morning dose (0 hr) and at 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 16, 20 and 24 hours. On day 14, evening doses of lonafarnib were withheld to evaluate pharmacokinetics over 24 hours. In addition, a single blood sample was drawn prior to each infusion of gemcitabine.

Gemcitabine pharmacokinetics were determined on cycle 1 days 1 and 15. Blood samples for gemcitabine concentration were collected just prior to infusion, at 15 minutes, end of infusion (30 minutes), 45 minutes, 1 hour, 1.5, 2, 3, 4, 6, 8, 10 and 12 hours after the beginning of the infusion from the arm opposite the infusion. On cycle 1 day 1, the morning dose of lonafarnib was withheld to evaluate gemcitabine pharmacokinetics.

Plasma lonafarnib and gemcitabine concentrations were determined using validated liquid chromatography with tandem mass spectrometric detection (LC-MS/MS) assays. The lower limits of quantitation were 5.00 and 10.1 ng/mL for lonafarnib and gemcitabine, respectively. The corresponding linear concentration ranges were 5.00–2500 ng/mL and 10.1–2535 ng/mL, respectively. The analyses for lonafarnib were performed at Taylor Technology, Princeton, NJ; the analyses for gemcitabine were performed at MDS Pharma Services, Inc., Saint-Laurent, Quebec, Canada.

Individual plasma lonafarnib and gemcitabine concentrations were analyzed using model-independent methods. The maximum plasma concentration (C_{max}) and time of maximum plasma concentration (T_{max}) were the observed values. The terminal phase rate constant (k) was calculated as the negative slope of the log:linear terminal portion of the plasma concentration-time curve using linear regression. The terminal phase half-life, t½, was calculated as 0.693/k. The area under the plasma concentration-time curve during the 12 hour dosing interval, AUC(τ), and from time 0 to the time of final quantifiable sample, AUC(tf), were calculated using the linear trapezoidal method.

Total body clearance (CL/F) for lonafarnib following multiple-dose oral administration was calculated by the following equation: CL/F= Dose/AUC(τ).

Apparent volume of distribution (Vdarea/F) for lonafarnib following multiple-dose oral administration was calculated as: Vdarea/F = [Dose/AUC(τ)]/k.

Pharmacodynamics

Prelamin A is a polypeptide dependent on farnesylation for processing; its accumulation in buccal mucosal cells serves as an in-vivo marker of farnesyl transferase inhibition. Buccal swabs were obtained on cycle 1 days 1 and 15 and fixed with acetone. Double label immunohistochemistry using mouse-anti-lamin A and rabbit anti-prelamin A antibodies

followed by fluorochrome-labeled secondary antibodies was performed as previously described[16].

Results

Patient Demographics

Twenty-five subjects were enrolled in the present study. Baseline demographic and clinical characteristics are summarized in Table 2. The median age was 56 years (range 26–74). The majority of patients had performance status 0–1. Ten patients had received 2 or more prior lines of systemic chemotherapy for advanced disease.

Dose Escalation and MTD

The dose escalation schedule and DLTs are summarized in Table 1.

Two patients in dose level 1 (lonafarnib 150 mg BID, gemcitabine 750 mg/m^2) developed DLTs consisting of grade 3 anorexia, diarrhea, dehydration, and fatigue; and grade 3 headache, anorexia, nausea, and vomiting, respectively. Four patients recruited to the next dose level lower (dose level -1: lonafarnib 100 mg BID, gemcitabine 750 mg/m^2) completed cycle 1 without DLT. Because it was felt that both lonafarnib and gemcitabine could potentially be subtherapeutic at dose level -1, intermediate doses A (lonafarnib 100 mg BID) and B (lonafarnib 150 mg AM and 100 mg PM) were then examined (Table 1). Intermediate level C was also added to explore full dose lonafarnib 200 mg BID with low dose gemcitabine 600 mg/m^2. Hence, intermediate cohorts A, B and C provided further guidance with regard to drug dosing, safety and tolerability. No DLTs were observed at intermediate levels A and C. One of 7 patients developed dose limiting grade 4 neutropenia and thrombocytopenia at intermediate level B. The MTD was thus determined to be lonafarnib 150 mg AM and, 100 mg PM with gemcitabine 1000 mg/m^2 on days 1, 8 and 15 every 28 days. This was also the RPTD given the tolerability profile and clinically relevant dose of gemcitabine.

Safety

The incidence of treatment-related toxicities by dose level is shown in Table 3.

Considering cycle 1 only, treatment-emergent adverse events (AE) were reported by 92% (23/25) of patients. The most commonly reported (≥33% incidence) events were: anorexia (72%), fatigue (72%), nausea (72%), diarrhea (52%), neutropenia (48%), vomiting (48%), and headache (40%). Grade 3 and 4 AEs were reported by 36% (9/25) of patients, most commonly (≥10% incidence) anorexia (12%), fatigue (12%), and neutropenia (12%).

Considering all cycles, treatment-related AEs were reported by 96% (24/25) of patients. The most commonly reported (≥33% incidence) events were fatigue (96%), nausea (88%), anorexia (80%), vomiting (60%), diarrhea (60%), neutropenia (60%), headache (56%), anemia (52%), thrombocytopenia (48%), and weight decrease (36%). Grade 3 or 4 AEs occurred in 68% (17/25) of patients, most commonly (≥10% incidence) neutropenia (24%), fatigue (20%), thrombocytopenia (16%), anorexia (12%), headache (12%), and diarrhea

(12%). There were two on-study deaths resulting from disease progression and deemed unrelated to the study treatment; there were no deaths attributed to study treatment.

Efficacy

Twenty-five patients were evaluable for efficacy. There were no complete responses. Two patients experienced partial responses: a 37-year old female with sarcoma (response duration of 22 months), and a 56-year old male with pancreatic adenocarcinoma (response duration of 2 months). Four patients had stable disease for over a year (13, 14, 16, and 20 months, respectively), and eight additional subjects had stable disease ranging from 3 months to 10 months (Table 4). Only one patient had known prior gemcitabine treatment.

Lonafarnib Pharmacokinetics

Lonafarnib was slowly absorbed following oral administration with food. Median T_{max} values ranged from 4 to 8 hours. Following twice daily multiple doses of lonafarnib in combination with weekly gemcitabine, mean half-life ($t_{1/2}$) ranged from 4 to 7 hours, and mean total body clearance (CL/F) was 163–594 mL/min. Dose dependency in systemic exposure was confounded by high inter-subject variability in total body clearance. Nonetheless, the greatest AUC and C_{max} values were observed at the highest dose level (Table 5).

There was no apparent difference in AUC(τ) values between Cycle 1 Day 15 and Cycle 2 Day 15 based on log-transformed data. The point estimate was 105% when comparing Cycle 2 Day 15 to Cycle 1 Day 15. The 90% confidence interval for the point estimate was 76.2–145%, which suggests that steady state was attained by Cycle 1 Day 15.

A total of 65 pre-dose plasma samples from 7 patients were collected during Cycles 3–24. Mean pre-dose plasma lonafarnib concentrations ranged from 340 to 2355 ng/mL. The intra-subject variability in pre-dose plasma lonafarnib concentrations ranged from 25 to 118%.

Gemcitabine Pharmacokinetics

Plasma gemcitabine concentrations and derived pharmacokinetic parameters following administration of gemcitabine alone (Day 1) were similar to those in combination with lonafarnib (Day 15; Table 5). There was no statistically significant difference (p=0.363) in AUC(tf) values between Day 1 and Day 15 based on log-transformed data. The point estimate was 109% when comparing Day 15 to Day 1 and the 95% confidence interval for the point estimate was 93.2%–127%. AUC(tf) was used because AUC(I) values could not be determined in this study. Additionally, the distribution of individual AUC(tf) values following administration of gemcitabine in combination with 100 mg lonafarnib encompassed the same range as those in combination with 150 mg lonafarnib. Thus, multiple doses of lonafarnib had no important effect on the pharmacokinetics of gemcitabine.

Pharmacodynamics

Of those buccal mucosal swabs available for prelamin A testing, 10 of 17 samples (59%) showed prelamin A accumulation after treatment with lonafarnib, indicating farnesyl

transferase inhibition. Some degree of inhibition was seen across all dosing cohorts except level 1. At dose level 1, buccal cells where not found in 2 out of 4 patients, no post treatment specimen was available in the third patient, and no prelamin accumulation was demonstrated in the fourth patient. Figure 1A illustrates the accumulation of prelamin A. There was no apparent relationship between pre-dose plasma lonafarnib concentration on day 15 or AUC(τ) and prelamin A accumulation in buccal smears (data not shown).

Discussion

In this open-label, dose escalation, multiple-dose study of twice daily oral lonafarnib in combination with weekly intravenous gemcitabine given on days 1, 8 and 15 every 28 days, the MTD and recommended phase II dose for this regimen was determined to be lonafarnib 150 mg AM, 100 mg PM and gemcitabine 1000 mg/m^2. At the recommended phase II dose, this regimen was well tolerated. However, in combination with full dose gemcitabine, lonafarnib needed to be given at reduced doses compared to its monotherapy dose. The adverse event profile of this combination consisted primarily of myelosuppression and gastrointestinal toxicities, which are overlapping toxicities of each agent.

The lonafarnib pharmacokinetic parameter estimates reflected high inter-subject variability, as also previously noted[23, 24]. There was no difference in plasma lonafarnib concentrations between cycle 1 day 15 and cycle 2 day 15. The Cmax and AUC values obtained in this study when either 100 or 200 mg lonafarnib was administered with gemcitabine were similar to those in previous phase I studies when lonafarnib was administered alone[23, 24] which suggest that gemcitabine had no apparent effect on the pharmacokinetics of lonafarnib and is consistent with prior studies[25]. Similarly, evaluation of gemcitabine pharmacokinetics on the first day of lonafarnib compared to after 15 days of dosing revealed no pharmacokinetic interaction between the drugs.

Modest clinical activity was seen in this generally heavily pretreated population (Table 4). Two subjects achieved a partial response and 7 patients had prolonged stable disease lasting longer than 6 months; most patients with clinical activity were gemcitabine naive. There appeared to be no relationship between the presence of prelamin A accumulation and pre-dose plasma concentrations of lonafarnib on the day of sampling, or with AUC(τ), suggesting the absence of any dose effect on this one marker of farnesylation at least in the evaluated dose ranges.

The clinical development of FTIs has been hampered by the limited activity of these agents at tolerable doses. In a variety of solid tumor settings, FTIs have shown limited activity as monotherapy, with response rates ranging between 0–13%[26–34]. In addition, no survival benefit was demonstrated in a randomized phase III study of best supportive care with or without tipifarnib in chemo-refractory colorectal cancer[35]. In combination studies of FTI plus chemotherapy, several phase I and II trials have shown mixed results regarding safety and activity[25, 36–45]. In addition, randomized phase III studies to date have not been able to demonstrate clinically meaningful benefit from the addition of FTIs to chemotherapy in solid tumors[46, 47].

FTIs continue to be evaluated in the field of hematologic malignancies, where promising phase II activity has been demonstrated[48–53]. In addition, research is ongoing to elucidate the exact mechanisms of FTI action and resistance. It is now known that refractoriness to FTIs can result from alternate prenylation of K-Ras and N-Ras by geranylgeranyl transferase I[54–57]; and that the anti-neoplastic effects of FTIs may also involve inhibition of other prenylated proteins such as RHOB, RHEB and centromeric proteins[58–61]. Importantly, biomarkers to identify suitable tumor types and patients for FTI therapy are lacking as *RAS* mutations are not predictive of response[62].

Acknowledgments

This work was supported by Merck & Company, formerly known as Schering-Plough Research Institute. We gratefully acknowledge the invaluable contributions of the patients who participated in this study and their families. We also gratefully acknowledge the research clinical teams and health care providers at Duke, UCLA and Mayo clinic who participated in this clinical study.

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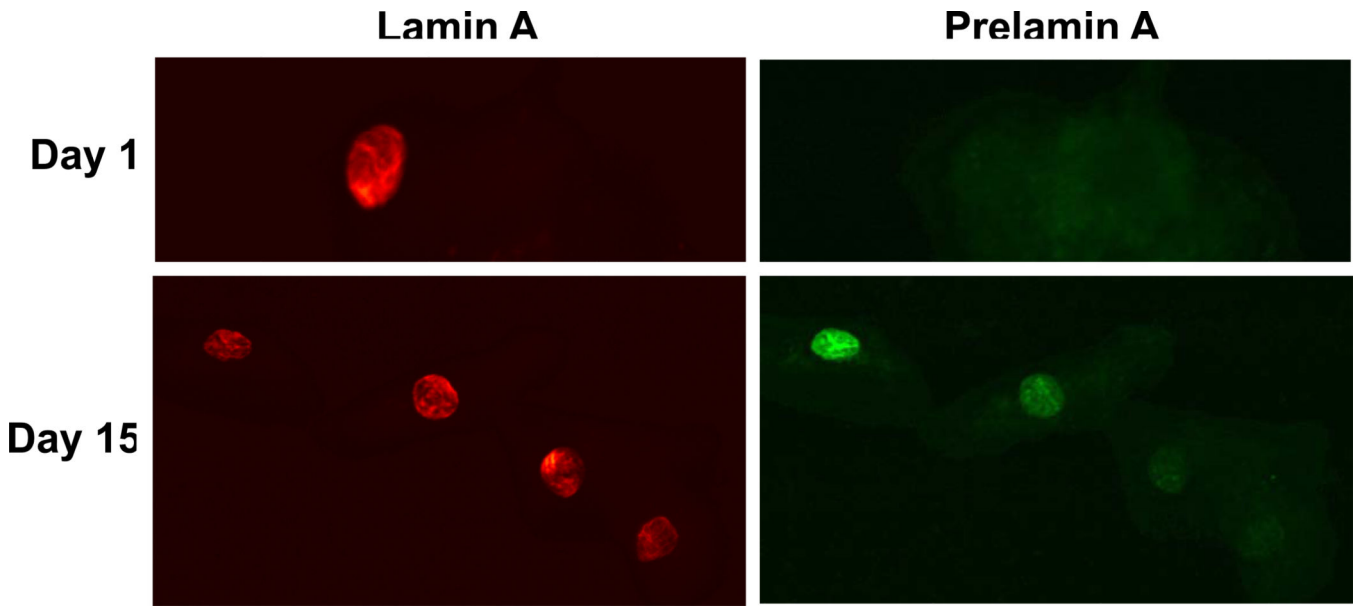

Figure 1.

Prelamin A accumulation after treatment with Lonafarnib. A.) Buccal cells were reacted with anti-rabbit prelamin A and mouse anti-lamin followed by fluorochrome-labeled secondary antibodies.

Table 1

Dose escalation scheme and cycle 1 dose-limiting events (DLTs).

Dose Level	Lonafarnib	Gemcitabine*	No. Patients	No. Patients with DLTs	DLT events
−1	100 mg BID	750 mg/m^2	4	0	-
1	150 mg BID	750 mg/m^2	4	2	Grade 3 headache, anorexia, nausea, and vomiting. Grade 3 anorexia, diarrhea, dehydration, and fatigue
Intermediate					
A	100 mg BID	1000 mg/m^2	3	0	-
B	150 mg AM, 100 mg PM	1000 mg/m^2	7	1	Grade 4 neutropenia and thrombocytopenia
C	200 mg BID	600 mg/m^2	7	0	-

* Intravenously days 1, 8, 15 every 28 days

Cancer Invest. Author manuscript; available in PMC 2014 July 17.

Table 2

Baseline Clinical and Demographic Characteristics

	Patients (N=25)	
Characteristics	**No.**	**%**
Gender		
Female	12	48
Male	13	52
Ethnicity		
White	23	92
Asian	1	4
Native American Indian	1	4
Age, years		
Median	56	
Range	26–74	
ECOG performance status		
0	1	4
1	22	88
2	2	8
Primary tumor		
Pancreatic adenocarcinoma	8	32
Non-small cell lung cancer	6	24
Renal cell carcinoma	2	8
Sarcoma	2	8
Others[#]	7	28
Prior chemotherapy		
0	9	36
1	5	20
2	8	32
≥3	2	8
unknown	1	4

ECOG: Eastern Cooperative Group

[*] one each of adenocarcinoma unknown primary, adenoid cystic carcinoma, ampullary carcinoma, hepatocellular carcinoma, mesothlioma, small cell lung cancer, squamous cell carcinoma ethmoid sinus

Table 3

Common Treatment Related Toxicities

Toxicity	Total	Level -1 (100+750)	Level 1 (150+750)	Intermediate A (100+1000)	Intermediate B (150/100+1000)	Intermediate C (200+600)
	(N=25)	(N=4)	(N=4)	(N=3)	(N=7)	(N=7)
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
Anemia						
Grade 1–2	12 (48)	2 (50)	3 (75)	1 (33)	4 (57)	2 (29)
Grade 3–4	3 (12)	0	0	1 (33)	2 (29)	0
Anorexia						
Grade 1–2	17 (68)	4 (100)	1 (25)	3 (100)	4 (57)	5 (71)
Grade 3–4	3 (12)	0	3 (75)	0	0	0
Diarrhea						
Grade 1–2	12 (48)	2 (50)	2 (50)	2 (67)	4 (57)	2 (29)
Grade 3–4	3 (12)	1 (25)	1 (25)	0	0	1 (14)
Fatigue						
Grade 1–2	19 (76)	3 (75)	3(75)	2 (67)	5 (71)	6 (86)
Grade 3–4	5 (20)	1 (25)	1 (25)	1 (33)	1 (14)	1 (14)
Headache						
Grade 1–2	11 (44)	1 (25)	2 (50)	1 (33)	5 (71)	2 (29)
Grade 3–4	3 (12)	0	2 (50)	1 (33)	0	0
Nausea						
Grade 1–2	20 (80)	3 (75)	2 (50)	3 (100)	5 (71)	7 (100)
Grade 3–4	2 (8)	0	2 (50)	0	0	0
Neutropenia						
Grade 1–2	9 (36)	1 (25)	2 (50)	1 (33)	2 (29)	3 (43)
Grade 3–4	6 (24)	1 (25)	1 (25)	0	3 (43)	1 (14)
Thrombocytopenia						
Grade 1–2	9 (36)	0	2 (50)	1 (33)	2 (29)	4 (57)
Grade 3–4	4 (16)	0	0	1 (33)	2 (29)	1 (14)
Vomiting						

Toxicity	Total (N=25) No. (%)	Level -1 (100+750) (N=4) No. (%)	Level 1 (150+750) (N=4) No. (%)	Intermediate A (100+1000) (N=3) No. (%)	Intermediate B (150/100+1000) (N=7) No. (%)	Intermediate C (200+600) (N=7) No. (%)
Grade 1–2	13 (52)	0	3 (75)	3 (100)	3 (43)	4 (57)
Grade 3–4	2 (8)	1 (25)	1 (25)	0	0	0
Weight Loss						
Grade 1–2	9 (36)	2 (50)	1 (25)	0	2 (29)	4 (57)
Grade 3–4	0	0	0	0	0	0

Table 4

Characteristics of Patients with Partial Response and Prolonged Stable Disease ≥ 6 months

Age/Sex	Lonafarnib + Gemcitabine Dose	Primary Tumor	Response	Duration (Months)	Prior Treatment
F/37	150/100+1000	Sarcoma	PR	22	Ifosphamide, MAID, radiotherapy
M/56	100+1000	Pancreatic adenocarcinoma	PR	2	Not available
F/34	150+750	Pancreatic cancer	SD	20	Gemcitabine, 5 FU, SU5416, immunotherapy
F/73	150/100+1000	Non small cell lung cancer	SD	16	Paclitaxel carboplatin, vinorelbine
M/48	200+600	Adenocarcinoma unknown primary	SD	14	Radiotherapy
F/69	150/100+1000	Malignant mesothelioma	SD	13	Gene therapy
F/55	200+600	Small cell lung cancer	SD	10	Etoposide carboplatin, topotecan
F/63	150+750	Non small cell lung cancer	SD	8	Paclitaxel carboplatin, Vinorelbine, thalidomide
M/70	150+750	Renal cell carcinoma	SD	8	IL-2, interferon, 5-FU, KW2189, Radiotherapy

F= Female; M= Male PR= Partial response;
SD= Stable disease
5-FU= 5-Fluorouracil; KW2189 = Duocamycin B2 Analog, MAID= Mesna, Adriamycin, Ifosphamide, Dacarbazine; SU5418 = Semaxanib

Table 5

Lonafarnib plus Gemcitabine Pharmacokinetic Parameter Estimates

Lonafarnib							
Lonafarnib+Gemcitabine Dose	**Cycle**	**No. of subjects**	**C_{max} (ng/mL)**	**T_{max}*** (hour)**	**AUC (τ) (ng*hr/mL)**	**CL/F (nL/min)**	**T½ (hour)**
100+750	1	4	717	5.0	5995	504	5.21
	2	3	757	4.0	6033	571	3.50
100+1000	1	3	1007	4.0	8201	577	3.80
	2	2	645	5.5	5945	370	3.79
150+750	1	2	779	5.5	5790	437	3.67
	2	1	1500	8.0	15325	163	6.68
150/100**+1000	1	6	1078	6.0	8947	413	5.57
	2	6	736	5.0	5634	440	4.68
200+600	1	5	2044	6.0	16812	594	5.32
	2	4	1885	5.0	14544	261	4.78

Gemcitabine					
Lonafarnib+Gemcitabine Dose	**Day**	**No. of subjects**	**C_{max} (ng/mL)**	**T_{max}*** (hour)**	**AUC (τ) (ng*hr/mL)**
100+750	1	4	11307	0.50	5382
	15	4	14953	0.50	7889
100+1000	1	2	10163	0.38	5075
	15	3	9797	0.25	5064
150+750	1	2	12495	0.25	5948
	15	2	11653	0.50	8005
150/100**+1000	1	7	15083	0.50	8801
	15	6	17471	0.50	10111
200+600	1	6	7934	0.38	4141
	15	7	11191	0.25	4966

C_{max}, peak plasma concentration, T_{max}, time to peak concentration, AUC(τ), area under the plasma concentration - time curve over the dosing interval (12 hours), CL/F, apparent total body clearance

*Lonafarnib dose (mg) BID + gemcitabine dose (mg/m2)

** Lonafarnib dose 150 mg AM, 100 mg PM

*** Median values