Phase I Study of the Farnesyltransferase Inhibitor Lonafarnib with Weekly Paclitaxel in Patients with Solid Tumors

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Abstract

Purpose: To establish the maximum tolerated dose of the farnesyltransferase inhibitor lonafarnib (Sarasar, Schering-Plough Corp., Kenilworth, NJ) in combination with weekly paclitaxel in patients with solid tumors. Tolerability, pharmacokinetics, safety, and dose-limiting toxicity were characterized.

Experimental Design: Patients were enrolled from January 2000 to May 2001. Lonafarnib was administered continuously orally twice daily at doses of 100, 125, and 150 mg in combination with paclitaxel at doses of 40, 60, or 80 mg/m^2 i.v. over 1 h weekly in 28-day cycles in a phase I design. Plasma samples for determinations of lonafarnib and paclitaxel concentrations were collected at selected time points.

Results: Twenty-seven patients were enrolled. The maximum tolerated dose (the dose level below where dose-limiting toxicity occurred and the recommended phase II dose) was lonafarnib 125 mg/m^2 twice daily and paclitaxel 80 mg/m^2 weekly. Dose-limiting toxicity was neutropenia with or without fever, which occurred in two of three patients treated at the lonafarnib 150 mg twice daily dose level. Diarrhea was a common side effect of lonafarnib but usually was mild to moderate in severity and could be controlled with standard medication without lonafarnib dose adjustment. Other reported adverse events included nausea, vomiting, fatigue, and taste changes. These adverse events were neither more frequent nor more severe than would be expected with paclitaxel alone. There were no apparent pharmacokinetic interactions between weekly paclitaxel and continuous twice-daily lonafarnib.

Conclusions: The recommended dose of lonafarnib for phase II trials is 125 mg orally twice daily when combined with weekly paclitaxel 80 mg/m^2. The dose-limiting toxicity was neutropenia.

Prenylation is a posttranslational process through which proteins are modified by the addition of a 15-carbon farnesyl or a 20-carbon geranylgeranyl group (1). Several hundred proteins including potentially oncogenic proteins require posttranslational modification through prenylation to become functional. In the case of Ras for instance, prenylation increases the hydrophobicity of the protein and allows it to associate with the plasma membrane where it interacts with other molecules involved in cell signaling. Farnesyl protein transferase, geranylgeranyltransferase I, and geranylgeranyltransferase II are the only three known prenyltransferases. Inhibition of the critical prenyltransferase protein modification step has become a strategy in translational cancer research.

Lonafarnib (SCH 66336; Sarasar, Schering-Plough Corp., Kenilworth, NJ) is an oral, nonpeptide, tricyclic, specific inhibitor of farnesyl protein transferase. Lonafarnib was initially evaluated in clinical trials for cancers that frequently have *Ras* mutations because such mutations leading to constitutively activated Ras protein are found in many human cancers (2); the first step in postsynthesis processing of *Ras* gene products is catalyzed by farnesyl protein transferase (3); experiments have shown that inhibition of farnesylation by farnesyl transferase inhibitors prevents membrane localization and the activity of the Ras protein (3); and lonafarnib inhibits farnesyl protein transferase activity *in vitro* and blocks processing of H-Ras protein in whole cells (4). However, lonafarnib has shown activity against cell lines with mutated *K-Ras* or wild-type *Ras* (5). Phase II and III trials evaluating lonafarnib and other farnesyl transferase inhibitors as single agents or with chemotherapy have shown little activity in tumors that frequently contain mutated *Ras*. Ras protein can be processed to an active form by geranylgeranyltransferases as an alternative pathway to farnesyl protein transferase, and farnesyl protein transferase inhibition is relatively ineffective at blocking the geranylgeranyltransferase process (6).

There has been evidence for efficacy of lonafarnib and other farnesyl transferase inhibitors in breast cancer and acute myelogenous leukemia, malignancies that rarely have mutated *Ras* (7, 8). It is now thought that proteins that require

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prenylation other than Ras are the relevant targets for lonafarnib and other farnesyl transferase inhibitors that do not inhibit the geranylgeranyltransferases (9). Some of the other possible target proteins that require farnesylation for activation include the two centromeric proteins, CENP-E and CENP-F, which are preferentially expressed in mitotic cells and are direct substrates for farnesyl transferase inhibitors (10). The relevant target proteins of farnesyl transferase inhibitors in breast cancer and acute myelogenous leukemia are not known.

Lonafarnib has been shown to have a synergistic effect with paclitaxel in some human cell lines *in vitro* and enhances paclitaxel activity *in vivo* (11, 12). There is evidence that the combination of paclitaxel and lonafarnib is synergistic through enhancement of tubulin acetylation (13). A phase I trial of paclitaxel dosed every 3 weeks in combination with continuous twice-daily oral lonafarnib established a maximum tolerated dose of paclitaxel 175 mg/m^2 and lonafarnib 100 mg twice daily (14). Diarrhea was the most important grade 3 or 4 toxicity that was increased with the addition of lonafarnib to paclitaxel. There was no apparent effect of paclitaxel on lonafarnib pharmacokinetics or of lonafarnib on paclitaxel pharmacokinetics. Three patients who had received previous taxane therapy had a durable partial response to the combination of paclitaxel and lonafarnib.

Paclitaxel dosed at weekly intervals is well tolerated and provides dose-dense therapy. Weekly paclitaxel therapy has shown increased efficacy compared with paclitaxel every 3 weeks in some breast cancer trials (15, 16) and farnesyl transferase inhibitors have shown single-agent activity against metastatic breast cancer. The primary objective of this trial was to establish the maximum tolerated dose of weekly paclitaxel at a dose up to 80 mg/m^2/wk with continuous lonafarnib twice daily in 28-day cycles for patients with solid tumors. Secondary objectives were to characterize the tolerability, safety, and dose-limiting toxicities of the combination. The pharmacokinetics of paclitaxel and lonafarnib were also assessed during coadministration of weekly paclitaxel and twice daily lonafarnib.

Patients and Methods

This was a three-center phase I trial conducted through Schering-Plough Research Institute (Kenilworth, NJ). Patients were enrolled from January 2000 to May 2001. The primary end point of the study was to determine the maximum tolerated dose of continuously dosed, twice-daily lonafarnib when combined with paclitaxel up to 80 mg/m^2, administered weekly. Eligible patients were adults with previously treated or untreated solid tumors for which no curative treatment was available. All patients signed a written informed consent approved by the Institutional Review Board at the medical center where they received therapy.

Eligibility criteria included age >18 years, Karnofsky performance status of at least 50%, histologically confirmed cancer, measurable or evaluable disease, absolute neutrophil count $\geq 1.8 \times 10^9$/L, platelet count $\geq 100 \times 10^9$/L, hemoglobin $\geq$10 g/dL, serum creatinine $\leq$1.5 times upper limits of normal, transaminase $\leq$1.5 times upper limits of normal, total bilirubin $\leq$1.5 mg/dL, and albumin $\geq$3.0 g/dL. A history of malabsorption syndrome or surgery that might impair absorption of lonafarnib was not allowed. Women of childbearing potential were required to have a negative urine or serum pregnancy test. Men and women with reproductive potential must have been using an effective method of contraception. Patients with any of the following were excluded: more than two previous chemotherapy regimens, active comorbid medical problems, grade $\geq$2 nausea, grade $\geqq$1 vomiting, prior cancer therapy within 4 weeks, mitomycin or nitrosurea within the previous 6 weeks, previous radiation to $\geqq$25% bone marrow, pregnant or nursing status, active central nervous system metastases, prior bone marrow or stem cell transplant, known HIV positivity, known hypersensitivity to cremaphor, and QT_c >440 ms at baseline. Patients who were taking medications that might alter the metabolism of lonafarnib by the CYP3A4 hepatic enzyme system, such as systemic corticosteroids (except as pretreatment for paclitaxel administration), antiseizure drugs, azoles, rifampin, isoniazid, estrogens, macrolides, or cyclosporin, were excluded from the trial. Screening criteria were reviewed with the study monitor to confirm eligibility, and subjects were assigned to the appropriate dose level based on their enrollment sequence.

Lonafarnib capsules were administered orally, twice daily with food as 50-, 75-, and 100-mg formulations with paclitaxel administered i.v. over 1 h at 40, 60, or 80 mg/m^2 weekly in 28-day cycles. Dose levels for lonafarnib and paclitaxel are shown in Table 1. The first cohort of patients was treated at dose level 2. During cycle 1, paclitaxel was given on day 1 and lonafarnib begun on day 3. During subsequent cycles of therapy, lonafarnib and paclitaxel were both started on day 1. Premedications for paclitaxel included dexamethasone, diphenhydramine, antiemetics, and cimetidine or ranitidine. Although chronic corticosteroid administration was an exclusion criteria due to potential effects on CYP3A4 activity, transient (one-time) dosing of dexamethasone as required here should not alter CYP3A4 activity (17). Therapy for diarrhea was recommended at the discretion of the treating physician on the onset of grade 1 toxicity per standard practice. Colony-stimulating factors including erythropoietin and granulocyte colony-stimulating factor could not be used to prevent myelotoxicity; however, patients who developed febrile neutropenia could receive granulocyte colony-stimulating factor in accordance with standard medical care. Prophylactic antibiotics were prohibited. Radiation, biological therapy, other chemotherapy, or any other anticancer therapy was prohibited during the study.

Cohorts of three subjects each were assigned sequentially to increasing doses of lonafarnib and paclitaxel, beginning with lonafarnib 100 mg bid and paclitaxel 60 mg/m^2/wk (dose level 2). Enrollment of a new cohort of three patients or expansion of an ongoing dose-level cohort did not occur until three subjects had completed one cycle (28 days) of therapy and the results of day 29 laboratory tests were evaluated. Maximum tolerated dose and dose-limiting toxicity (for the purposes of dose escalation) were defined from the safety profile during the first 28-day cycle for each dose level. When dose-limiting toxicity occurred during the first cycle in one subject, a maximum of three additional subjects could be treated at that level (for a total of six subjects). The dose-limiting toxicity dose level was defined as the dose level at which a minimum of two subjects experienced dose-limiting toxicity.

Dose-limiting toxicity was defined as any of the following: absolute neutrophil count 500/μL for 7 days or longer; absolute neutrophil

Table 1. Dose escalation protocol for lonafarnib and paclitaxel

Dose level	Lonafarnib dose (mg twice daily)	Paclitaxel dose (mg/m^2/wk)	Patients (*n*)
1	100	60	7
2	100	80	7
3	125	80	10
4	150	80	3

NOTE: Lonafarnib was administered on days 3 to 28 in cycle 1 and on days 1 to 28 in all subsequent cycles. Paclitaxel was administered weekly during each cycle.

Table 2. Patient demographics

Subjects (*n*)	27
Age (y)	
Median	58
Range	27-74
Gender, *n* (%)	
Male	19 (70)
Female	8 (30)
Karnofsky performance status, *n* (%)	
70-<90	5 (19)
90-100	22 (81)
Histology (*n*)	
Non–small cell lung cancer	5
Colon	5
Renal	3
Pancreatic	3
Melanoma	3
Adrenal	2
Hepatobiliary	2
Unknown	2
Prostate	1
Sarcoma	1
Prior treatment, *n* (%)	
Chemotherapy	24 (89)
Taxane	6 (22)
Surgery	25 (93)
Radiation	13 (48)

count 500/μL with fever (≥38.3°C); platelets <25,000/μL (grade 4); grade 4 anemia (hemoglobin <6.5 g/dL); grade 3 to 4 nausea/vomiting while receiving an optimal antiemetic 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 antidiarrheal regimen, or any other treatment-related grade 3 nonhematologic toxicity; grade ≥2 neuropathy; dose modifications resulting in the subject's receiving <80% of the intended cumulative dose of paclitaxel; or treatment delay for toxicity lasting longer than 2 weeks. The maximum tolerated dose was defined as the dose level at which none of six or one of six subjects experienced dose-limiting toxicity during the first cycle when at least two subjects experienced dose-limiting toxicity at the next higher dose level.

Dose modification. Dosing was modified based on observed toxicity on the day of each planned dose of weekly paclitaxel. Lonafarnib was dosed without modification and paclitaxel was reduced by 50% for granulocytes <1,500/μL or platelets <100,000/μL. Lonafarnib was dosed without modification and paclitaxel was omitted for platelets <75,000/μL or granulocytes <500/μL for ≥7 days or with fever. A full paclitaxel dose was resumed following recovery. For platelet counts <50,000/μL, both paclitaxel and lonafarnib were omitted and continued at one lower dose level after recovery (Table 1). Paclitaxel dose was decreased by 50% for grade 2 neuropathy. Paclitaxel was omitted for grade 3 or 4 neuropathy and resumed at 50% the initial dose when neuropathy decreased to grade ≤2.

Lonafarnib was decreased by one dose level (Table 1) for grade ≥3 nausea or vomiting despite optimal antiemetic therapy on days when paclitaxel was not administered. Lonafarnib was decreased by one dose level for grade 3 diarrhea that was unresponsive to standard therapy. If the QT_c interval increased to >500 ms and was >130% of baseline QT_c, lonafarnib was held and resumed at one dose level lower after the QT_c normalized.

Pharmacokinetic methods. Blood samples (3 mL) for determination of plasma lonafarnib concentrations were collected before (0 h) and at 1, 2, 4, 6, 8, and 12 h after the morning dose on day 15 of cycle 1. Blood samples (5 mL) for determination of plasma paclitaxel concentrations were collected before (0 h) and at 0.5 h, 1 h, 1 h 5 min, and 1.5, 2, 4, 6, 8, 12, and 24 h after the beginning of the i.v. infusion on days 1 and 15 of cycle 1 and day 1 of cycle 2. Thus, the pharmacokinetics of paclitaxel was assessed once without (cycle 1 day 1) and twice with (cycle 1 day 15 and cycle 2 day 1) lonafarnib administration. Plasma was separated by centrifugation (4°C, 3,000 rpm for 15 min), divided into two aliquots, and stored frozen at −70°C until shipped to the analytic facility.

Plasma lonafarnib concentrations were determined using validated liquid chromatography with tandem mass spectrometry method (done at Taylor Technology, Princeton, NJ). The lower limit of quantitation was 5.00 ng/mL and the linear range was 5.00 to 2,500 ng/mL. Plasma paclitaxel concentrations were determined using a validated high-performance liquid chromatography method with a lower limit of quantitation of 10.0 ng/mL and a linear range of 10.0 to 2,500 ng/mL. The assay precision (percent coefficient of variation) and accuracy (percent bias) were <11% and <10%, respectively, for lonafarnib and <9% and <6%, respectively, for paclitaxel. Noninterference from the respective administered drug was shown and validated for both the lonafarnib and paclitaxel methods.

Individual plasma lonafarnib and paclitaxel concentrations were used for pharmacokinetic analysis 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 of the slope of the log-linear terminal portion of the plasma concentration-versus-time curve using linear regression. The terminal phase half-life ($t_{1/2}$) was calculated as $0.693/K$. The area under the plasma concentration-versus-time curve from time 0 to the final quantifiable sample [$AUC_{(tf)}$] and from time 0 to 12 h [$AUC_{(0\text{-}12\ h)}$] was calculated using the linear trapezoidal method. For paclitaxel, area under the plasma concentration-time curve from time 0 to infinity [$AUC_{(I)}$] was determined as follows: $AUC_{(I)} = AUC_{(tf)} + C_{est(tf)} / K$, where $C_{est(tf)}$ is the estimated concentration determined from linear regression at time t_f. Total body clearance (CL/F) for lonafarnib following multiple-dose oral administration was calculated by the following equation: CL/F = dose / $AUC_{(0\text{-}12\ h)}$. Total body clearance of paclitaxel following weekly i.v. infusion was calculated as follows: CL = dose / $AUC_{(I)}$.

Paclitaxel AUC values from patients who had samples collected on all three sampling days were pooled across all dose levels. An ANOVA model to extract effects due to dose, subject with dose, and day was applied on the log-transformed AUC data. The effect due to day was used to determine the effect of lonafarnib (i.e., cycle 1 day 15 and cycle 2 day 1 versus cycle 1 day 1) and sampling day (i.e., cycle 2 day 1 versus cycle 1 day 15) on paclitaxel pharmacokinetics.

Inhibition of HDJ-2 farnesylation. HDJ-2, a substrate of farnesyl protein transferase, was used as a marker of farnesyl protein transferase inhibition (16). When farnesylation is inhibited, HDJ-2 undergoes a mobility shift on SDS-PAGE, such that the unfarnesylated protein displays lower electrophoretic mobility. Levels of prenylated and unprenylated HDJ-2 were evaluated in peripheral blood mononuclear cell samples by immunoblot analysis and densitometric quantification. Biological assays for the inhibition of HDJ-2 farnesylation were done at Schering-Plough Research Institute.

Tumor response. Subjects were clinically evaluated for tumor response after the first cycle and every 28 days thereafter. Radiographic assessments were done every 8 weeks or more frequently if clinically indicated. Responses were to be confirmed 4 weeks after initial observations and criteria for determining partial or complete response had to be present for at least 4 weeks. Throughout the study, all lesions were measured by the same method, either similar radiographic study or physical examination, for consistent comparisons.

Results

Twenty-seven subjects were enrolled in this trial and 26 subjects received study medication (Table 1). Patient demographics are reported in Table 2. A total of 87 cycles of combination therapy were administered with a median of

three cycles. Seven subjects were treated in both dose levels 1 and 2, whereas 10 were treated at the maximum tolerated dose (Table 1). One subject was discontinued and replaced in each of dose levels 1 and 2 for protocol ineligibility and one subject in each of those dose levels had a dose-limiting toxicity, requiring treatment of an additional three subjects at each dose.

Among all dose level cohorts, 93% of subjects reported at least one treatment-related adverse reaction of any grade and 44% of subjects reported at least one grade 3/4 event (Table 3). The most common treatment-related adverse events of any grade were gastrointestinal and constitutional; diarrhea, nausea, and vomiting occurring in 22 of 27 (81%), 18 of 27 (67%), and 16 (59%) of subjects, respectively, and fatigue and anorexia occurring in 19 of 27 (70%) and 13 of 27 (48%) of subjects, respectively. The most common treatment-related grade 3/4 events were fatigue and vomiting, each occurring in 3 (11%) subjects, and anemia, neutropenia, anorexia, nausea, diarrhea, and dehydration, each occurring in 2 (7%) subjects. There was no dose relationship noted (Table 4B).

Gastrointestinal and constitutional symptoms were the most common nonhematologic toxicities reported, occurring in 25 of 27 (93%) and 24 of 27 (89%) of subjects, respectively. The most frequently reported nonhematologic adverse events overall were diarrhea (81%; grade 3/4, 7%), nausea (78%; grade 3/4, 7%), fatigue (70%; grade 3/4, 11%), vomiting (59%; grade 3/4, 11%), and dyspnea (56%; Table 3). No treatment-emergent hematologic adverse events were reported at rates of ≥25%. Nausea and neuropathy, which are adverse events associated with paclitaxel (17), as well as insomnia, rhinitis, and taste perversion, seemed to be potentially dose related, occurring more frequently in the 80-mg paclitaxel dosing groups (Table 3). At levels below the non-dose-limiting toxicity dose, the majority of adverse events were mild to moderate in severity.

Among all dose level cohorts, 46% (12 of 26) of treated subjects with baseline grade 0 to 2 hematologic laboratory data developed at least one treatment-emergent grade 3/4 hematologic toxicity, 30% within the first treatment cycle. Approximately 25% of subjects developed grade 3/4 neutropenia or leukopenia, 8% developed grade 3/4 thrombocytopenia, and 15% developed grade 3/4 anemia (Table 4A). The majority of these events were clinically asymptomatic and required no intervention. Hematologic toxicities observed with lonafarnib plus paclitaxel combination therapy were consistent with those that have been observed with paclitaxel, including weekly administration (12, 18). However, hematologic toxicity, particularly neutropenia, became dose-limiting at the highest dose level of the combination.

Grade 1 or 2 diarrhea was frequently associated with lonafarnib therapy but usually responded to standard antidiarrheal therapy; 22 subjects received short-term therapy with loperamide and 2 required additional therapy with diphenoxylate. Lonafarnib did not seem to increase the frequency or severity of the most common toxicities expected for weekly paclitaxel such as nausea, vomiting, fatigue, asthenia, peripheral neuropathy, and taste changes (Table 3).

There were no reductions in lonafarnib dose due to adverse events. The paclitaxel dose was reduced from 80 to 40 mg/m^2/wk due to adverse events in three subjects:

- 01/008 during cycle 4 for neuropathy
- 01/026 during cycle 3 and cycle 4 for neuropathy
- 04/009 during cycle 1 for gastrointestinal symptoms.

Six subjects discontinued the study due to adverse events, which included severe anorexia, fatigue, and vomiting.

Table 3. Summary of most frequent (>25%) treatment-emergent adverse events by dose level

										Total
Lonafarnib dose (mg twice daily)	100		100		125		150			
Paclitaxel dose (mg/m^2/wk)	60		80		80		80			
No. patients	7		7		10		3		27	
Adverse event rate*	Any severity	Grade 3/4	Any severity	Grade 3/4	Any severity	Grade 3/4	Any severity	Grade 3/4	Any severity	Grade 3/4
Diarrhea	7 (100)	2 (29)	6 (86)	0	7 (70)	0	2 (67)	0	22 (81)	2 (7)
Nausea	5 (71)	1 (14)	6 (86)	0	8 (80)	1 (10)	2 (67)	0	21 (78)	2 (7)
Fatigue	5 (71)	0	4 (57)	0	8 (80)	2 (20)	2 (67)	1 (33)	19 (70)	3 (11)
Vomiting	5 (71)	2 (29)	2 (29)	1 (14)	8 (80)	0	1 (33)	0	16 (59)	3 (11)
Dyspnea	5 (71)	1 (14)	3 (43)	0	6 (60)	1 (10)	1 (33)	0	15 (56)	2 (7)
Alopecia	6 (86)	0	3 (43)	0	5 (50)	0	0	0	14 (52)	0
Anorexia	4 (57)	0	2 (29)	0	5 (50)	1 (10)	2 (67)	1 (33)	13 (48)	2 (7)
Neuropathy	2 (29)	0	3 (43)	1 (14)	4 (40)	0	1 (33)	1 (33)	10 (37)	2 (7)
Abdominal pain	4 (57)	0	1 (14)	0	3 (30)	0	0	0	8 (30)	0
Coughing	3 (43)	0	1 (14)	0	3 (30)	0	1 (33)	0	8 (30)	0
Epistaxis	3 (43)	0	1 (14)	0	4 (40)	0	0	0	8 (30)	0
Dyspepsia	2 (29)	0	3 (43)	0	3 (30)	0	0	0	8 (30)	0
Fever	2 (29)	0	1 (14)	0	4 (40)	0	1 (33)	1 (33)	8 (30)	1 (4)
Constipation	1 (14)	0	2 (29)	0	5 (50)	0	0	0	8 (30)	0
Insomnia	1 (14)	0	3 (43)	0	3 (30)	0	1 (33)	0	8 (30)	0
Rhinitis	1 (14)	0	2 (29)	0	4 (40)	0	1 (33)	0	8 (30)	0
Taste perversion	1 (14)	0	2 (29)	0	3 (30)	0	1 (33)	0	7 (26)	0
Arthralgia	1 (14)	0	2 (29)	0	4 (40)	0	0	0	7 (26)	0

* Values expressed as n (%).

Table 4. Summary of treatment-related, treatment-emergent adverse events during the treatment period

(A) Hematologic laboratory parameters that changed from grade 0-2 to grade 3 or 4 abnormalities by dose

					Total
Lonafarnib dose (mg/twice daily)	100	100	125	150	
Paclitaxel dose (mg/m^2/wk)	60	80	80	80	
No. patients (*n*)	7	7	7	3	26
Hemoglobin	1 (14.3)	1 (14.3)	2 (22.2)	0	4 (15.4)
WBC	1 (14.3)	2 (28.6)	3 (33.3)	1 (33.3)	7 (26.9)
Neutrophils	0	1 (14.3)	4 (44.4)	1 (33.3)	6 (23.1)
Platelets	1 (14.3)	0	1 (11.1)	0	2 (7.7)

(B) Treatment-related, treatment-emergent, adverse events by descending frequency

									Total	
Lonafarnib dose (mg/twice daily)	100		100		125		150			
Paclitaxel dose (mg/m^2/wk)	60		80		80		80			
No. patients (*n*)	7		7		10		3		27	
Adverse event rate*	Any severity	Grade 3/4	Any severity	Grade 3/4	Any severity	Grade 3/4	Any severity	Grade 3/4	Any severity	Grade 3/4
Hematologic										
Neutropenia	0	0	0	0	0	0	2 (67)	2 (67)	2 (7)	2 (7)
Anemia	0	0	1 (14)	1 (14)	1 (10)	1 (10)	0	0	2 (7)	2 (7)
Nonhematologic										
Diarrhea	7 (100)	2 (29)	6 (86)	0	7 (70)	0	2 (67)	0	22 (81)	2 (7)
Vomiting	5 (71)	2 (29)	2 (29)	1 (14)	8 (80)	0	1 (33)	0	16 (59)	3 (11)
Dehydration	3 (43)	1 (14)	1 (14)	0	0	0	1 (33)	1 (33)	5 (19)	2 (7)
Heart block	1 (14)	1 (14)	0	0	0	0	0	0	1 (4)	1 (4)
Nausea	5 (71)	1 (14)	4 (57)	0	7 (70)	1 (10)	2 (67)	0	18 (67)	2 (7)
Anorexia	4 (47)	0	2 (29)	0	5 (50)	1 (10)	2 (67)	1 (33)	13 (48)	2 (7)
Cellulitis	0	0	0	0	0	0	1 (33)	1 (33)	1 (4)	1 (4)
Edema (legs)	1 (14)	0	2 (29)	0	0	0	2 (67)	1 (33)	5 (19)	1 (4)
Fatigue	5 (71)	0	4 (57)	0	8 (80)	2 (20)	2 (67)	1 (33)	19 (70)	3 (11)
Herpes zoster	0	0	0	0	1 (10)	1 (10)	0	0	1 (4)	1 (4)
Neuropathy	2 (29)	0	2 (29)	1 (14)	4 (40)	0	0	0	8 (30)	1 (4)
Rash	0	0	2 (29)	1 (14)	0	0	2 (67)	0	4 (15)	1 (4)

* Values expressed as n (%).

Life-threatening heart block and neutropenia also led to discontinuation. Two patients died during the study or within 30 days of study completion, both of disease progression.

Dose-limiting toxicity. The dose-limiting toxicity dose level was defined as the dose level at which at least two subjects experienced dose-limiting toxicity during the first treatment cycle. Four subjects experienced dose-limiting toxicities: one subject at dose level 2 with grade 4 heart block, one subject at dose level 3 with neutropenia, and two subjects at dose level 5 (one subject with grade 4 neutropenia and a second subject with febrile neutropenia). Neutropenia that occurred in two of three subjects, one in association with febrile neutropenia, was experienced at the dose-limiting toxicity dose level of paclitaxel 80 mg/m^2/wk and lonafarnib 150 mg twice daily continuously (dose level 4, Table 1). Therefore, the maximum tolerated dose was lonafarnib 125 mg twice daily given continuously with paclitaxel 80 mg/m^2/wk.

Tumor response. One subject with malignant melanoma experienced a partial response at cycle 2, which was maintained until cycle 5, when progressive disease was noted. This subject

Table 5. Mean (CV) pharmacokinetic parameters of lonafarnib when administered in combination with paclitaxel

Dose*	*n*	C_{max}, ng/mL	T_{max}, h†	$AUC_{(0\text{-}12\ h)}$, ng·h/mL	CL/*F*, mL/min	t_{f}, h	Predose, ng/mL
100 + 60	6	929 (77)	4 (0-6)	7,535 (93)	382 (74)	12 (0)	434 (100)
100 + 80	4	919 (61)	4 (2-12)	7,672 (71)	307 (59)	12 (0)	494 (78)
125 + 80	7	1,400 (30)	4 (2-6)	13,022 (32)	172 (30)	12 (0)	726 (38)
150 + 80	3	2,685 (NA)	5 (4-6)	19,729 (91)	203 (65)	12 (0)	1,723 (110)

Abbreviation: NA, not appropriate (sample size = 2).
*Lonafarnib dose (mg) twice daily + paclitaxel dose (mg/m^2) weekly.
†Median value (range).

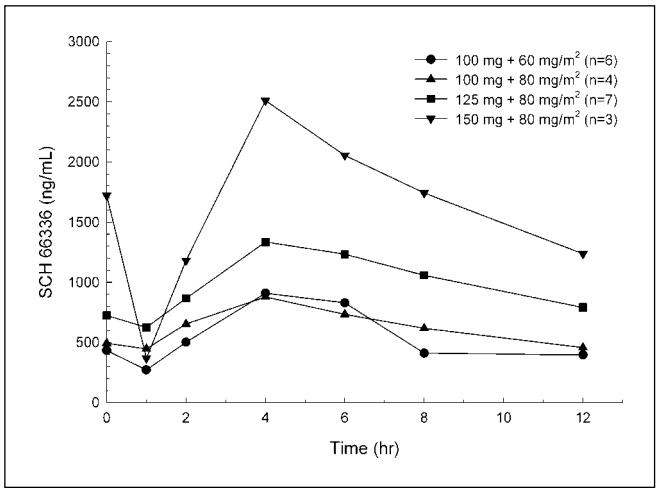

Fig. 1. Mean plasma lonafarnib concentration-versus-time profiles on day 15 of cycle 1 following twice-daily multiple-dose oral administration of lonafarnib in combination with weekly 1-h i.v. infusion of paclitaxel. Key indicates lonafarnib dose + paclitaxel dose.

had no prior taxane exposure. Stable disease was the best objective response in 16 subjects. Stable disease was maintained for four cycles in two subjects and for more than four cycles in six subjects. Among the six subjects with prior taxane exposure, four had stable disease documented at cycle 2. Prior taxane exposure had ranged from 2 to 5 months at doses ranging from 85 mg/m^2 administered weekly to 200 mg/m^2 every 3 weeks.

Pharmacokinetics of lonafarnib. Twenty patients had blood collected for pharmacokinetic evaluations. Increases in lonafarnib C_{max} and AUC values were dose related following oral administration of 100, 125, and 150 mg lonafarnib bid in combination with 80 mg/m^2 i.v. paclitaxel (Table 5). Lonafarnib was slowly absorbed following administration with food. Median T_{max} values ranged from 4 to 5 h. Half-life could not be estimated in this study due to lack of a definitive terminal phase in the plasma concentration-time profiles following twice-daily oral administration of lonafarnib with food. There was minimal fluctuation in plasma lonafarnib concentrations following multiple-dose administration (Fig. 1). The mean total body clearance ranged from 172 to 382 mL/min.

Mean lonafarnib C_{max} and AUC values obtained in this trial following 100 mg lonafarnib plus 60 and 80 mg/m^2 weekly paclitaxel are similar to those in a previous trial evaluating 100 mg lonafarnib plus 135 and 175 mg/m^2 paclitaxel once every 3 weeks (12), and to those in a previous phase I trial in which 100 mg lonafarnib was administered alone (ref. 19; Table 6). Thus, these results indicate that single dose of paclitaxel had no apparent effect on lonafarnib pharmacokinetics.

Pharmacokinetics of paclitaxel. There was no statistically significant difference ($P > 0.346$) in $AUC_{(tf)}$ values between cycle 1 day 1 (paclitaxel alone) and cycle 1 day 15 or cycle 2 day 1 (paclitaxel plus lonafarnib) based on log-transformed data (Table 6). The point estimates were 119% and 107% when comparing cycle 1 day 15 and cycle 2 day 1 to cycle 1 day 1, respectively. The corresponding 95% confidence intervals for these point estimates were 87% to 163% and 78% to 146%, respectively. $AUC_{(tf)}$ was used because $AUC_{(I)}$ values could not be determined for many subjects in this study. Additionally, the distribution of individual $AUC_{(tf)}$ values following administration of paclitaxel alone and in combination with either 100, 125, or 150 mg of lonafarnib encompassed the same range across pharmacokinetic evaluation days. These results suggest that multiple doses of lonafarnib had no effect on the pharmacokinetics of paclitaxel.

There was no statistically significant difference ($P = 0.559$) in the $AUC_{(tf)}$ values between cycle 1 day 15 and cycle 2 day 1 based on log-transformed data (Table 7). The point estimate was 90% when comparing cycle 2 day 1 to cycle 1 day 15. The 95% confidence interval for the point estimate was 66% to 123%, which suggests that sampling day had no effect on the pharmacokinetics of paclitaxel following once-weekly paclitaxel administration in combination with lonafarnib.

Plasma paclitaxel concentrations decreased rapidly after cessation of the 1-h infusion. This was followed by a prolonged terminal phase. Mean half-life ($t_{1/2}$) values ranged from 6 to 17 h and mean clearance ranged from 53 to 425 mL/min/m^2 (Table 8). There were no apparent differences in the mean $t_{1/2}$ or clearance values among cycle 1 day 1, cycle 1 day 15, and cycle 2 day 1 at each dose level.

HDJ-2 farnesylation. The prenylation status of HDJ-2 for baseline (pretreatment) and posttreatment peripheral blood mononuclear cell samples were available for 10 patients. Compared with pretreatment samples, increased levels of unprenylated HDJ-2 were detected in posttreatment samples from 6 of the 10 patients. In one of these patients, the maximum fraction of unprenylated HDJ-2 was only 8.5%. The fraction of unprenylated HDJ-2 in posttreatment samples from the other five patients ranged from 10.7% to 18.4%. These results are similar to those reported from posttreatment peripheral blood mononuclear cell samples in clinical studies with other farnesyl transferase inhibitors (20–22). Four of the 10 patients had no detectable increase in unprenylated HDJ-2 in peripheral blood mononuclear cells following treatment with lonafarnib. However, two of these patients had detectable levels of unprenylated HDJ-2 (20.6% and 16%, respectively) in pretreatment samples.

The reason for the relatively high frequency of baseline unprenylated HDJ-2 in this study is not known. Patients in whom an increase in posttreatment unprenylated HDJ-2 was observed were exposed to predose lonafarnib concentrations ranging from 204 to 1,310 ng/mL. However, given the small

Table 6. Comparisons of mean (CV) pharmacokinetic parameters of lonafarnib following multiple-dose administration of 100 mg lonafarnib alone in previous phase I studies (12, 19) or in combination with paclitaxel

Study	Dose*	*n*	C_{max}, ng/mL	$AUC_{(0\text{-}12\ h)}$, ng·h/mL
This study	100 + 60	6	929 (77)	7,535 (93)
This study	100 + 80	4	919 (61)	7,672 (71)
Khuri et al. (12)	100 + 135	3	760 (25)	5,550 (51)
Khuri et al. (12)	100 + 175	8	960 (40)	8,789 (32)†
Previous phase I (19)	100‡	6	1,012 (49)	8,773 (67)

*Lonafarnib dose (mg) twice daily + paclitaxel dose (mg/m^2).
†$n = 6$.
‡Lonafarnib alone dose (mg).

Table 7. Statistical comparisons of paclitaxel $AUC_{(tf)}$ values among three sampling days

Comparison	*P*	Point estimate* (%)	Confidence interval†
Cycle 1 day 1 vs cycle 1 day 15	0.346	119	87.2-163
Cycle 1 day 1 vs cycle 2 day 1	0.717	107	78.2-146
Cycle 1 day 1 vs cycle 1 day 15 and cycle 2 day 1	0.451	113	86.1-148
Cycle 1 day 15 vs cycle 2 day 1	0.559	89.7	65.6-123

*Expressed as a percentage ratio of cycle 1 day 15 or cycle 2 day 1 to cycle 1 day 1, and cycle 2 day 1 to cycle 1 day 15.
†95% confidence interval based on log-transformed data, $\alpha = 0.1$.

sample size and the detection of unprenylated HDJ-2 in two baseline samples, the relationship between unfarnesylated HDJ-2 and posttreatment plasma lonafarnib concentrations could not be assessed in this study.

Discussion

This multicenter phase I trial evaluated the maximum tolerated dose of the combination of weekly paclitaxel and continuous twice daily lonafarnib in subjects with advanced solid tumors. The dose of weekly paclitaxel was increased from 60 mg/m^2/wk to the maximum intended dose of 80 mg/m^2/wk in combination with lonafarnib without dose-limiting toxicity. The maximum tolerated dose, which is also the recommended dose for further phase II studies, was lonafarnib 125 mg twice daily in combination with paclitaxel 80 mg/m^2/wk in 28-day cycles.

The dose-limiting toxicity dose level was lonafarnib 150 mg twice daily in combination with paclitaxel 80 mg/m^2/wk. The toxicity that defined dose-limiting toxicity was neutropenia in two patients, one associated with febrile neutropenia. These findings contrast with a phase I trial evaluating the combination of paclitaxel every 3 weeks and lonafarnib, in which dose-limiting toxicities encountered at combinations that exceeded maximum tolerated dose were grade 4 diarrhea in three subjects and grade 4 neutropenia in one subject (14).

The nonhematologic adverse event profile of lonafarnib plus paclitaxel was similar to that observed for either agent alone (18, 19). The most frequent toxicity considered to be associated with lonafarnib was mild to moderate diarrhea and could be controlled with antidiarrheal therapy. No dose adjustments in lonafarnib were required for diarrhea. Other than this side effect, lonafarnib did not substantially contribute to the toxicity profile of paclitaxel.

Because paclitaxel is eliminated by the enzymes CYP2C8 and CYP3A4, and lonafarnib is a substrate primarily for CYP3A4 (17), the pharmacokinetics for both agents were evaluated in this study. No pharmacokinetic evidence was observed that either paclitaxel or lonafarnib altered the metabolism of the other agent. The $AUC_{(tf)}$ values of paclitaxel following administration of paclitaxel alone and paclitaxel in combination with lonafarnib were not significantly different ($P > 0.346$). In the phase I trial of paclitaxel every 3 weeks and continuous lonafarnib twice daily, lonafarnib was started 1 week before paclitaxel. Pharmacokinetic data for lonafarnib alone versus combination therapy showed that paclitaxel had no effect on lonafarnib levels (14). The C_{max} and AUC values for lonafarnib 100 mg twice daily in this trial were similar to those reported for lonafarnib alone at the same dose level (21, 22).

The maximum tolerated dose of single agent lonafarnib was 300 mg daily. Dose-limiting toxicities observed at lonafarnib 400 mg daily were diarrhea, asthenia, vomiting, and weight loss

Table 8. Mean (CV) pharmacokinetic parameters of paclitaxel

Dose*	Cycle (C), day (D)	*n*	C_{max}, ng/mL	T_{max}, h†	$AUC_{(I)}$, ng·h/mL	$AUC_{(tf)}$, ng·h/mL	$t_{1/2}$, h	CL, mL/min/m^2
	C1, D1	7	2,135 (46)	1.0 (0.5-1.083)	3,913 (28)‡	3,140 (41)	12.7 (33)§	270 (25)‡
100 + 60	C1, D15	6	3,043 (127)	0.75 (0.5-1.083)	2,526 (32)‡	3,188 (77)	13.1 (15)‡	425 (28)‡
	C2, D1	5	2,670 (31)‖	1.0 (1.0-1.083)	2,984 (38)¶	3,349 (48)	16.9 (17)‖	367 (36)¶
	C1, D1	6	3,494 (38)‡	1.0 (0.5-1.0)	5,695 (40)¶	4,346 (43)‡	9.76 (7)¶	260 (38)¶
100 + 80	C1, D15	4	12,638 (173)	1.0 (0.5-1.0)	3,465 (NA)**	10,537 (135)	7.70 (NA)**	386 (NA)**
	C2, D1	5	2,633 (31)‖	1.0 (0.5-1.0)	6,075 (56)¶	5,088 (50)	10.8 (24)¶	262 (44)¶
	C1, D1	9	6,528 (95)††	1.04 (0.5-1.5)	8,420‡‡	7,564 (98)	10.3 (20)‡‡	259 (50)‡‡
125 + 80	C1, D15	7	4,135 (117)§	1.0 (0.5-1.083)	7,711 (85)‡	6,041 (96)	12.3 (34)‡	240 (43)‡
	C2, D1	6	3,876 (18)‡	1.0 (1.0-1.083)	5,836 (25)‡	4,892 (33)	11.4 (37)‡	241 (28)‡
	C1, D1	3	5,127 (98)	1.0 (0.5-1.5)	8,953 (NA)**	7,039 (58)	9.34 (NA)**	167 (NA)**
150 + 80	C1, D15	3	5,080 (74)	1.0 (1.0-1.083)	8,410 (30)	8,635 (NA)**	7.78 (40)	167 (26)
	C2, D1	1	68,800 (NA)	1.083 (NA)	25,235 (NA)	25,113 (NA)	6.49 (NA)	52.8 (NA)

Abbreviation: NA, not appropriate (sample <3).
*Lonafarnib dose (mg) twice daily + paclitaxel dose (mg/m^2) weekly.
†Median value (range).
‡$n = 5$.
§$n = 6$.
‖$n = 4$.
¶$n = 3$.
**$n = 2$.
††$n = 8$.
‡‡$n = 7$.

(22). In a single-agent phase I trial of the farnesyl protein transferase inhibitor tipifarnib, dose-limiting toxicities were myelosuppression and grade 3 sensory neuropathy whereas mild to moderate diarrhea (32%) and fatigue (54%) were also reported (23). A phase I trial evaluating the combination of tipifarnib and gemcitabine reported myelosuppression as the principal dose limiting toxicity (24). A phase I trial of the farnesyl transferase inhibitor BMS-214662 with paclitaxel and carboplatin showed no apparent pharmacokinetic interaction between paclitaxel and the farnesyl transferase inhibitor, and the reported dose-limiting toxicities were neutropenia, thrombocytopenia, nausea, and vomiting (25).

One taxane-naïve patient with malignant melanoma had a durable partial response with progression of disease after five cycles. In addition, four patients who had previously received taxanes, including weekly paclitaxel, had stable disease or obtained minor objective responses (<50% of the sum of the perpendicular diameters of all measurable lesions).

The farnesyl protein transferase inhibitor tipifarnib has shown single-agent activity in acute myelogenous leukemia and breast cancer (7). Lonafarnib is currently being evaluated in clinical trials for metastatic breast cancer and myelogenous leukemias. The weekly dosing of paclitaxel has been more efficacious than paclitaxel every 3 weeks when combined with trastuzumab in Her2-positive metastatic breast cancer (16). It would be appropriate to consider phase II clinical trials combining weekly paclitaxel and lonafarnib in the setting of metastatic breast cancer.

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Phase I Study of the Farnesyltransferase Inhibitor Lonafarnib with Weekly Paclitaxel in Patients with Solid Tumors

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