Phase I Study of the Farnesyltransferase Inhibitor BMS-214662 Given Weekly in Patients with Solid Tumors

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Abstract

Purpose: A phase I trial of BMS-214662, a selective farnesyltransferase inhibitor with significant preclinical antitumor activity in which drug was given as a weekly 1-hour infusion for four of six weeks, was conducted to evaluate the tolerability, pharmacokinetics, and pharmacodynamic effect on farnesyltransferase activity in peripheral blood mononuclear cells.

Experimental Design: BMS-214662 was given to 27 patients with solid tumors at 10 escalating dose levels (28-220 mg/m^2) allowing intrapatient dose escalation; pharmacokinetics and pharmacodynamics were done at the first seven dose levels.

Results: Grade 4 neutropenia (four patients) was the most common dose-limiting toxicity followed by aminotransferase elevation (grade 3 alanine aminotransferase and grade 4 aspartate aminotransferase) and grade 3 dehydration. Most frequent toxicities were neutropenia in 11 (14%), anemia in 15 (19%), fatigue in 9 (12%), and nausea and diarrhea in 6 (8%) of courses, respectively. One minor response lasting 18 weeks in a patient with non–small cell lung cancer, serum calcitonin level reduction accompanied by disease stabilization in two of four patients with medullary thyroid carcinoma, and stable disease in 16 of 25 evaluable patients was seen. No correlation was observed between dose and C_{max}, total body clearance (mean, 26.15 $\pm$ 10.88 L per hour per m^2), volume of distribution at steady state (mean, 39.51 $\pm$ 17.91 L/m^2), or half-life (mean, 2.63 $\pm$ 1.81 hours); a moderate correlation existed between dose given and systemic drug exposure (AUC). Substantial inhibition of peripheral blood mononuclear cell farnesyltransferase activity but near complete recovery by 24 hours was seen.

Conclusion: BMS-214667 was well tolerated as a weekly 1-hour i.v. infusion for four of six weeks with evidence of pharmacodynamic effect. The study was terminated before maximum tolerated dose was reached. Alternative schedules of drug administration might result in improved pharmacodynamic profile.

Ras proteins (H-ras, N-ras, K-ras4A, and K-ras4B) are small GTP-binding proteins that regulate signal transduction cascades leading to cellular growth, differentiation, apoptosis, cytoskeletal organization, and membrane trafficking (1, 2). Farnesyltransferase inhibitors were initially designed to target Ras. However, accumulating lines of evidence suggest that their antitumor activity cannot be ascribed simply to Ras inhibition.

The *Ras* family of oncogenes consisting of three ras isoforms, *H-ras*, *K-ras*, and *N-ras*, is mutated in ~30% of human cancers (3). Several studies have identified the presence of ras mutations as an indicator of a poor prognosis for patients with colon (4), lung (5, 6), pancreatic cancer (7), thyroid cancer (8), and acute myeloid leukemia (9).

Ras is initially synthesized as a biologically inactive cytoplasmic peptide and is converted to its active GTP-bound state by extracellular stimuli that activate cell surface receptors (10) followed by a series of post-translational modifications necessary for plasma membrane attachment catalyzed by the enzyme farnesyltransferase and geranylgeranyl-transferase I (11, 12).

The frequency and prognostic role of *Ras* mutations in human tumors along with its central role in regulation of basic cellular functions, prompted the development of farnesyltransferase inhibitors as a means to interrupt Ras signaling. Although farnesyltransferase inhibitors reverse alterations associated with the Ras-transformed phenotype in *Ras* mutation–bearing cells (13), they are also effective in tumors with wild-type Ras (14) and it seems that both geranylgeranyl-transferase I and farnesyltransferase inhibitors are required for inhibition of Ras prenylation (15). It is also clear that farnesylated proteins other than Ras might be responsible for the antitumor activity of farnesyltransferase inhibitors, such as the Ras superfamily of GTPases RHOB and RND as well as RHEB, a Ras-related protein

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which is an activator of the mammalian target of rapamycin/S6 kinase signaling pathway (12). Whereas the investigation for their precise mode of action is still in progress, farnesyltransferase inhibitors are being tested in clinical trials and show activity both as monotherapy and in combination with cytotoxic chemotherapy (16). BMS-214662, a potent and selective inhibitor of farnesyltransferase, showing single-digit nanomolar farnesyltransferase inhibitory potency and >1,000-fold selectivity for farnesyltransferase over geranylgeranyl-transferase, has been shown to possess significant preclinical antitumor activity both *in vitro* and *in vivo* (17–20). In the clinical setting, BMS-214662 has been investigated in phase I studies, given either orally or as an i.v. infusion. Oral dosing of the drug was not developed further because of dose-limiting gastrointestinal toxicity (i.e., nausea), not allowing dose escalation (21). Dosing schedules employed for the i.v. route include 1-hour infusion every 3 weeks (22), continuous weekly 1-hour infusion (23), and weekly 24-hour infusion for three of four weeks and a daily for five consecutive days i.v. infusion every 3 weeks (BMS-214662 Investigator Brochure). In those studies, tumor regression was observed in patients with colorectal, breast, and non–small cell lung cancers.

This phase I study was designed to establish the maximal tolerated dose (MTD) of BMS-214662 given as a weekly 1-hour infusion for four out of 6 weeks in patients with solid tumors. The study also aimed at characterizing the nature of dose-limiting toxicities and evaluating the pharmacokinetic and pharmacodynamic profile of the drug. This study provided the opportunity to explore the safety, pharmacokinetics, and pharmacodynamics of the drug using a weekly schedule that was already in the process of being explored but in the unique setting of lung and head and neck malignancy–bearing patient. In addition, this study provided the opportunity to explore the possibility that a higher MTD could be reached compared with the uninterrupted weekly schedule.

Patients and Methods

Eligibility. Previously treated and untreated patients with histologically confirmed malignancy for which no treatment known to prolong survival was available were allowed to participate. Patient eligibility also included the following criteria: at least 18 years of age; Karnofsky performance status of at least 70% (Zubrod 2); last dose of chemotherapy or radiation therapy at least 4 weeks before study entry (6 weeks for nitrosureas or mitomycin); adequate hematologic variables (WBC count of $\geq$3,000/mm^3, an absolute neutrophil count of $\geq$1,500/mm^3, a platelet count of $\geq 100 \times 10^9$ /L, and a hemoglobin level of $\geq$10 g/d); adequate hepatic function (normal bilirubin and alkaline phosphatase levels, baseline transaminase levels no greater than 1.5 times the upper limit of normal) and adequate renal function (serum creatinine levels $\leq$1.5 times the upper limit of normal or a measured 12-hour creatinine clearance time of $\geq$10 mL/min/1.73 m^2); and albumin level of $\geq$3.0 gm/dL. Patients should not have received more than three prior chemotherapeutic regimens and should have recovered from all treatment-related toxicities. Patients receiving concurrent therapy with drugs known to alter the metabolism of the CYP3A4 hepatic enzymatic system were not allowed to participate due to the possibility of interfering with the metabolism of BMS-214662. All patients signed a written informed consent approved by the Institutional Review Board at The University of Texas M.D. Anderson Cancer Center.

Patient evaluation. Pretreatment evaluation included complete medical history and physical examination, complete blood count with leukocyte differentials, serum chemistry, liver function tests, and urinalysis. Ophthalmologic examination and ECG were also obtained at baseline. Patients had a complete radiologic assessment, including chest X-ray and computerized tomography scans or magnetic resonance imaging scans of all measurable or valuable disease.

Interim testing during treatment included medical history every 2 weeks for the first cycle and every 6 weeks subsequently, physical examination every 2 weeks, complete blood count with differential, serum chemistry every week, and ophthalmologic evaluation every 3 months and at study termination. Chest X-ray and radiologic imaging studies for the assessment of tumor response were done every 12 weeks after an initial 4-week assessment.

Treatment plan. After the baseline evaluation, patients were started on BMS-214662 given as a 1-hour infusion weekly for 4 weeks. Three patients were enrolled at each dose level and treated with once weekly i.v. infusion of BMS-214662, with weekly assessment of toxicity during these first 4 weeks. Subsequently, the patients had a 2-week rest during which no treatment was received. Assessment of toxicity within each cohort was done once the third patient had completed 4 weeks of treatment and the following dose level for the next cohort was decided. Patients who experienced grade 0 or 1 toxicities had their dosage increased one dose level in the subsequent cycle. Intrapatient dose escalation occurred after each cycle until the patient encountered grade $\geq$2 toxicity. The first cycle at each new dose level was considered for dose-limiting toxicities. This resulted in several cohorts with more than three patients per dose level. After the first 4 weeks of treatment, patients were evaluated for response. Responders or patients with stable disease were maintained on the study drug until disease progression.

Dose escalation. The nine dose levels to be studied were 28, 36, 56, 102, 154, 168, 182, 196, 210, and 220 mg/m^2. Dose-limiting toxicity was defined as grade 3 and 4 nonhematologic (including grade $\geq$3 nausea and/or emesis despite the use of adequate medical intervention) and grade 4 hematologic (neutropenia and thrombocytopenia) toxicity. The goal of the trial was to determine the MTD, defined as the dose among the nine levels having toxicity rate closest to 33%. Dose escalation was done by empirical selection for the first three dose levels, based on existing clinical data from other ongoing trials. The continual reassessment method (24) was used starting at 102 mg per m^2 per week, with patients treated in cohorts of three at each successive dose level chosen by the continual reassessment method, using the safety modification that no dose level may be skipped when escalating. The exponential model with prior toxicity probabilities of 0.05, 0.10, 0.18, 0.33, 0.47, 0.60, 0.70, 0.76, and 0.80 was used; thus, the continual reassessment method was started at the dose that was a priori assumed to elicit the targeted toxicity rate. The robustness of this method was evaluated using simulation under four hypothetical "true" dose-toxicity response scenarios, including the a priori model, during the planning phase of the trial. According to the operating characteristics of this design under four dose-toxicity scenarios, the continual reassessment method treats fewer patients at low, potentially inefficacious doses and successfully identifies the MTD with much greater accuracy than the 3 + 3 method. A computer program for the conduct of the trial was available from the Department of Biostatistics at The University of Texas M.D. Anderson Cancer Center.

Toxicity and dose modifications. Adverse events were recorded and graded using the National Cancer Institute Common Toxicity Criteria and assessed by the investigator for any relationship with BMS-214662 treatment. Grade 1 to 3 myelosuppression did not require dose modification. Patients were retreated at weekly intervals if any toxicity considered related to BMS-214662 had recovered to baseline or grade 1 severity. Patients with grade 4 myelosuppression thought to derive clinical benefit from treatment were treated at a 25% lower dose in all subsequent cycles, whereas grade 4 nonhematologic toxicity warranted removal from the study. For patients who clinically benefited from treatment and developed drug-related toxicities (grade <4 nonhematologic), that could be alleviated by dose reduction and/or lengthening of dosing interval, modification of drug dosing was permitted at the discretion of the investigator. In consultation with the National Cancer

Institute, Cancer Therapy Evaluation Program, cases with >4 weeks delay, were removed from the study. Patients who withdrew from the study due to disease progression or due to serious adverse events (grade ≥3), deemed related to the study drug were not replaced. Patients who withdrew from the study before completion of the first cycle for reasons other than serious adverse events, unacceptable toxicity or disease progression were defined as dropouts and were replaced. All patients receiving any amount of drug treatment were evaluable for toxicity and patients receiving at least one course of therapy were evaluable for response assessment.

Clinical pharmacokinetics and pharmacodynamics. The pharmacokinetic profile of BMS-214662 was determined following the first dose for the patients who participated in the pharmacokinetics study. The ability of the drug to suppress constitutive peripheral blood mononuclear cells (PBMC) farnesyltransferase was also assessed following the first infusion to evaluate the pharmacodynamic properties of the drug. The participation in the pharmacokinetic and pharmacodynamic portion was optional according to the M.D. Anderson Institutional Review Board mandate.

Assessment of pharmacokinetic and pharmacodynamic effects of BMS-214662 was undertaken for dose levels ranging from 28 to 182 mg/m^2. No samples were processed for the patients at the three highest dose levels. Venous blood samples for the pharmacokinetic study were collected at the following time points: baseline (before dose), 1, 1.17, 1.33, 1.5, 1.75, 2, 3, 4, 6, 8, 12, and 24 hours after the start of the infusion. For each sample, 5 mL of blood was collected in ice-cold, tri-potassium EDTA Vaccutainer blood collection tube, and centrifuged at 1,000 × *g* at 5°C for 10 minutes. The plasma portion was transferred to polypropylene cryovials and stored at −20°C until analysis by the Drug Disposition and Bioanalytical Services Department at Bristol-Myers Squibb Pharmaceutical Research Institute, New Brunswick, NJ.

The concentration of BMS-214662 in plasma was determined by an analytic method involving reversed-phase high performance liquid chromatography with UV detection as described previously (22). BMS-214662 was separated from other plasma constituents by using a Luna C18 analytic column (4.6 × 150 mm, 5-μm particle size, Phenomenex, Torrance, CA).

Study samples were assayed together with a series of nine calibration standards of BMS-214462 in plasma at concentrations ranging from 4.3 to 4,000 ng/mL in terms of the free base form of the drug. The relationship between the chromatographic peak height and known drug concentration for each calibration standard was analyzed by linear regression using the reciprocal of the nominal concentration of the standards as the weighting factor. Values of the variables describing the best-fit line were used to calculate the BMS-214662 concentration in study samples. The lower limit of quantitation was 4.3 ng/mL. The relative SD for the interassay and intra-assay precision in these matrices was within 7% and the accuracy was >92%.

The pharmacokinetic variables were estimated from individual patient plasma concentration-time data using a noncompartmental model. The pharmacokinetics estimated variables included maximum plasma concentration (C_{max}), time to maximum plasma concentration (T_{max}), area under the plasma concentration/time curve from time 0 to infinity (AUC), plasma half-life ($t_{1/2}$), volume of distribution (V_d) and systemic clearance (CL) following the 1-hour i.v. administration of BMS-214662. All pharmacokinetics modelling was done using WinNonlin Version 2.1 software (Pharsight Corp., Palo Alto, CA). Pharmacokinetics data were reported as mean and SD.

The inhibition of constitutive farnesyltransferase activity in PBMCs was evaluated in blood samples (8 mL each) collected immediately before the fist dose and at 1, 6, 12, and 24 hours after the start of the infusion. The tubes remained at room temperature and were centrifuged for 30 minutes at 1,700 × *g* at 20°C within 20 minutes of collection. The PBMCs were then transferred to separate polypropylene tubes and washed twice with 10 mL of ice-cold PBS. Following each washing cells were separated by centrifugation at 1,700 × *g* for 10 minutes. The PBMC cellular pellet was stored at −70°C until analysis. Farnesyltransferase activity was determined by a radioenzyme assay done by the Clinical Pharmacodynamics Laboratory at Bristol-Myers Squibb Pharmaceutical Research Institute, Three Hamilton Health Place, Hamilton, NJ, as previously described (25).

Response assessment. Tumor measurements were assessed in accordance with the Response Evaluation Criteria in Solid Tumors at 4 weeks from treatment start and every 12 weeks thereafter and at withdrawal from study. Patients deriving clinical benefit were maintained on study until disease progression or unacceptable toxicity.

Results

Patient characteristics. Thirty patients were entered into this phase I study starting on May 2000 until July 2002. Three patients were enrolled but never received BMS-214662 due to drug unavailability. Two patients were evaluable only for toxicity assessment because they failed to complete the first treatment cycle. Patient characteristics are listed in Table 1.

Toxicity. A total of 78 courses were given to 27 patients at doses ranging from 28 to 220 mg/m^2. The median number of courses given per patient was 3 (range, 0.25-7 cycles).

Table 1. Patient characteristics

No. patients, *n* (%)	30 (100)
Age (y), median (range)	57 (18-75)
Gender	
Male	17 (57)
Female	13 (43)
Performance status	
0	2 (7)
1	26 (86)
2	2 (7)
Histology/tumor site	
Non – small cell lung cancer	8 (27)
Head and neck squamous cell cancer	6 (20)
Salivary gland cancer	4 (13)
Adenoid cystic	3
Acinic cell	1
Thyroid carcinoma	7 (23)
Papillary	2
Follicular (Hürthle cell)	1
Medullary	4
Adenocarcinoma paranasal sinus	1 (3)
Thymic carcinoma	2 (7)
Neurofibrosarcoma	1 (3)
Atypical carcinoid lung	1 (3)
Prior therapy	
Chemotherapy	21 (84)
Radiation therapy	22 (88)
Surgery	20 (80)
Prior chemotherapy regimens	
≤1	14 (56)
2	8 (32)
≥3	3 (12)
Evaluability status	
Inevaluable	3 (10)
Response and toxicity	25 (83)
Toxicity only	2 (7)

Grade 4 neutropenia was the most common dose-limiting toxicity observed. Specifically, one of four patients treated at 36 mg/m^2, one of six patients at 56 mg/m^2, one of four patients at 154 mg/m^2, and one of four patients treated at 168 mg/m^2, developed grade 4 neutropenia (Table 2). Three of these four episodes of neutropenia occurred acutely 3 to 4 days after infusion of the drug and all remained uncomplicated and resolved within 2 to 7 days. One patient treated at 196 mg/m^2 developed grade 3 dehydration as a result of diarrhea (grade 1), nausea and vomiting (grade 2) starting on day 1 of the first cycle and grade 3 and 4 transaminitis (alanine aminotransferase and aspartate aminotransferase, respectively). He was withdrawn from the study on the third day after treatment due to unacceptable toxicity. No dose-limiting toxicities were reported for the patients treated at the remaining (including >196 mg/m^2) dose levels. MTD was not reached in our study since dose escalation was halted at 220 mg/m^2.

Table 3 lists the most frequent grade 2, 3, and 4 toxicities, during all cycles by dose level. Neutropenia was the most common grade 3 and 4 hematologic toxicity reported in 11 (14%) of 78 cycles. One patient treated at dose level two (168 mg/m^2) presented with grade 3 neutropenic fever and neutropenic sepsis several hours after drug infusion, necessitating inpatient i.v. fluids and antibiotics but recovered uneventfully and was subsequently retreated. The onset of grade 3 and 4 neutropenia was observed within a range of days 2 to 36 of treatment (median, day 19) and was of a median duration of 5 days (range, 2-7 days). Most episodes occurred the 3 to 4 days following infusion of the drug. Grade 2 anemia occurred in 14 (18%) cycles, whereas no thrombocytopenia was seen.

Nonhematologic toxicity was generally mild. Grade 2 and 3 diarrhea was reported in six (8%) of courses. The only incident of grade 3 diarrhea was seen in a patient with metastatic medullary thyroid carcinoma, whose disease symptomatology included episodes of flushing and intermittent grade 3 diarrhea treated with tincture of opium. Although the episode was protracted, starting on day 9 of the second course and continuing until day 8 of course 3 it cannot be entirely ascribed to BMS214662. Based on this, no dose reduction was employed, and during the third cycle, the severity of diarrhea subsided to grade 1 in accordance with an improvement of the patient general clinical status, including her flushing episodes and bone pain. Other nonhematologic adverse events included grade 2 nausea and fatigue; 6 (8%) and 9 (12%) of courses respectively.

Table 2. Dose-limiting toxicity per dose level

Dose level (mg/m^2)	No. patients	Dose-limiting toxicity (*n*)
28	3	—
36	4	Grade 4 neutropenia (1)
56	6	Grade 4 neutropenia (1)
102	8	—
154	4	Grade 4 neutropenia (1)
168	4	Grade 4 neutropenia (1)
182	6	—
196	9	Grade 4 dehydration, grade 3 SGPT, and grade 4 SGOT elevation (1)
210	5	—
220	3	—

Efficacy. One patient with non–small cell lung cancer with bony metastases treated at 56 mg/m^2 experienced a minor response in the primary tumor on day 29 of cycle 2 which lasted for 18 weeks. Stable disease as best protocol response was reported in 16 (64%) of 25 patients who were evaluable for efficacy assessment. Of these, 15 experienced disease stabilization for a period longer than 12 weeks. Median duration of stable disease for the whole group of patients was 22 weeks (range, 6-72 weeks). Disease progression was documented in eight (32%) patients.

Seven patients with thyroid carcinoma were treated on the study, four with medullary, two with papillary, and one with follicular (Hürthle cell) carcinoma. A prolonged stabilization of disease was reported for all of them. Specifically, median duration of stable status was 32 weeks (range, 24-35 weeks).

In two of the four patients with medullary thyroid carcinoma, there was reduction of the serum calcitonin value as measured by a fully automated chemiluminescence assay for monomeric calcitonin (Nichols Advantage Calcitonin assay; normal values < 4.6 pg/mL). In the first patient, with a germ line codon 634 RET proto-oncogene mutation (26), there was a reduction in serum CT from 479,000 to 208,000 pg/mL with a return to a value of 401,000 pg/mL following discontinuation of therapy. In the second, a patient with a codon 918 germ line RET mutation (27), there was a reduction in the serum calctionin from 68,000 to 15,000 pg/mL during therapy with a value of 71,000 pg/mL following discontinuation of therapy and accompanied by a reduction in her baseline bone pain, flushing episodes, and diarrhea. The other two patients, one with a codon 918 somatic *RET* proto-oncogene mutation, had no change in their serum calcitonin values.

In one patient with metastatic papillary carcinoma, disease stabilization of 25 weeks was associated with a significant improvement in the disease-related symptoms and performance status. The reasons for study discontinuation for the 27 patients who received at least one cycle of therapy included disease progression (21), patient's choice (4), study drug toxicity (1), and drug being unavailable (1).

Pharmacokinetic and pharmacodynamic results. Participation in the pharmacokinetic and pharmacodynamic portions of this study was optional. Pharmacokinetic data were obtained from three patients each at 28, 36, 154, and 168 mg/m^2 dose levels, two patients each at 56 and 182 mg/m^2, and from four patients at 102 mg/m^2 dose levels. The 24-hour sample was available in only five patients for analysis. Pharmacokinetic variables of BMS-214662 were estimated by noncompartmental analysis of the individual patient data and a summary of these results is presented in Table 4. From 28 to 182 mg/m^2, the overall mean systemic clearance and half-life of BMS-214662 were 26.15 ± 10.88 L per hour per m^2 and 2.63 ± 1.81 hours, respectively. The overall mean residence time and volume of distribution at steady state were 1.58 ± 0.86 and 39.52 ± 197.91 L/m^2, respectively. The mean plasma concentration-time profiles of BMS-214662 are shown in Fig. 1. The mean maximum concentration (C_{max})

Table 3. Cumulative toxicity (all cycles): worst grade toxicity per patient per dose level

	Dose (mg/m^2) (Number of patients per dose level)									
Toxicity Grade 2/3/4	**28 (3)**	**36 (4)**	**56 (6)**	**102 (8)**	**154 (4)**	**168 (4)**	**182 (6)**	**196 (9)**	**210 (5)**	**220 (3)**
Hematologic anemia	2/0/0	1/0/0	1/0/0	–	1/0/0	1/0/0	1/0/0	2/0/0	–	–
Neutropenia	–	0/0/0	0/0/1	0/0/1	0/1/1	0/0/3	0/0/2	1/1/0	1/0/0	0/0/0
Neutropenic fever	–	–	–	–	–	0/1/0	–	–	–	–
Anorexia	1/0/0	–	–	–	1/0/0	–	–	1/0/0	–	–
Nausea	–	–	–	1/0/0	1/0/0	1/0/0	–	1/0/0	–	2/0/0
Vomiting	–	–	–	–	–	–	–	1/0/0	–	2/0/0
Diarrhea	–	–	–	1/0/0	1/0/0	1/0/1	–	–	–	–
Aspartate aminotransferase	–	–	–	–	–	–	–	0/0/1	–	–
Alanine aminotransferase	–	–	–	–	–	–	0/1/0	0/1/0	–	–
Headache	–	1/0/0	–	–	1/0/0	–	–	–	–	–
Fatigue	1/0/0	–	1/0/0/	1/0/0	1/0/0	–	–	1/0/0	–	–

NOTE: Dose levels at which no grade 2/3 or 4 toxicities were observed are marked by –.

of BMS-214662 from 28 to 182 mg/m^2 dose levels ranged from 2.27 ± 1.31 to 6.03 ± 3.26 μg/mL (mean ± SD). As shown in Fig. 2A (*top*), there were no correlation between dose and achieved C_{max} (r^2 = 0.03). There was a moderate correlation between dose given and the resultant AUC (r^2 = 0.45) as shown in Fig. 2B. The mean systemic exposure (AUC) of BMS-214662 ranged from 1.11 ± 0.60 to 7.70 ± 0.52 μg/mL hour (mean ± SD).

The ability of BMS-214662 to inhibit constitutive farnesyltransferase activity in PBMCs was determined by sampling from two to four patients for each dose level studied (a total of 21 patients). Mean (SD) baseline farnesyltransferase activity of PBMCs measured before the first dose was 27.5 (11.17) fmol per μg protein per hour. Inhibition of farnesyltransferase activity by 1 hour after the start of the infusion was observed across all dose levels studied although the degree of inhibition varied. Farnesyltransferase activity in PBMCs (expressed as a percentage of the pretreatment baseline activity) determined after administration of the first dose of BMS-214662 is presented in Table 5. Farnesyltransferase activity recovered gradually during the initial 6 hours after completion of the infusion and approached baseline values within 24 hours of dosing. The average farnesyltransferase activity decreased from 75.7 ± 76.7% to 14.6 ± 1.46 % of the baseline activity as the dose was increased from 28 to 182 mg/m^2 with the most substantial reductions occurring at the higher dose levels. Based on our data, a better relationship was shown between dose of BMS-214662 and AUC than with C_{max}; thus, in an attempt to describe the correlation between the inhibition farnesyltransferase activity in PBMCs and the $AUC_{0\text{-}\alpha}$, an inhibitory sigmoid maximal effect (E_{max}) model (WinNonlin version 2.1 software, Pharsight Corp., Palo Alto, CA) was used with data weighed (1/year). E_0 was fixed at 100% because the data was normalized to the individual baseline value. Figure 3 depicts the curve generated from this model. The estimated E_{50} was 0.250 μg/mL hour (CV = 140%) and γ = 0.597 (CV = 44.7%).

Discussion

We reported here the results of a phase I study of the farnesyltransferase inhibitor BMS-214667 given as a weekly 1-hour infusion for four of six weeks in patients with solid tumors. This study was done in parallel to five additional phase I studies of this agent.

BMS-214662 associated toxicity consisted primarily of myelosuppression (i.e., grade 3 and 4 neutropenia and grade 2 anemia). The median duration of the neutropenic episodes

Table 4. Pharmacokinetic variables of BMS-214662

Dose level (mg/m^2)	*n*	C_{max} (μg/mL)	$T_{1/2}$ (h)	$AUC_{0\text{-}\alpha}$ (μg/mL h)	CL_t (L/h/m2)	V_{ss} (L/m2)	MRT (h)
28	3	2.27 ± 1.31	4.00 ± 4.51	1.11 ± 0.60	29.39 ± 13.72	52.20 ± 20.85	2.34 ± 2.08
36	3	3.63 ± 4.26	1.62 ± 0.16	3.31 ± 4.03	15.25 ± 15.15	14.52 ± 16.75	0.80 ± 0.30
56	2	6.34 ± 2.57	3.76 ± 1.51	2.95 ± 0.56	19.57 ± 3.78	30.25 ± 10.75	1.52 ± 0.25
102	4	6.03 ± 3.77	1.97 ± 0.53	3.91 ± 1.23	29.10 ± 6.93	46.23 ± 14.04	1.56 ± 0.35
154	3	5.40 ± 2.12	2.94 ± 1.18	7.39 ± 4.29	25.20 ± 11.12	33.79 ± 8.70	1.49 ± 0.53
168	3	3.38 ± 0.73	2.37 ± 0.64	6.04 ± 3.01	33.22 ± 16.73	46.14 ± 26.93	1.42 ± 0.47
182	2	5.45 ± 0.88	2.25 ± 0.97	7.70 ± 0.52	23.69 ± 1.97	40.04 ± 0.04	1.69 ± 0.14

NOTE: Values are mean ± standard of deviation.
Abbreviation: MRT, mean residence time.

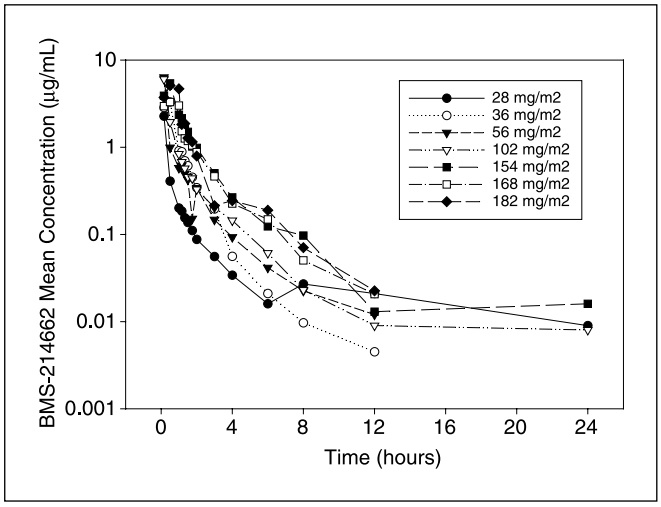

Fig. 1. Mean plasma concentration-time profiles of BMS-214662 from 0 to 24 hours after i.v. infusion over 1 hour at dose levels indicated in the text box. *Points,* geometric means of the observed plasma concentrations at each time point in the cohort of the patients evaluated at each dose level.

was short, the nature was acute as was previously observed by other investigators employing the weekly schedule (BMS Investigator's brochure) rather than cumulative. Moreover, only one episode of neutropenic fever occurring within 24 hours of infusion of the drug, was reported which was effectively treated with the usual supportive measures. Nonhematologic toxicity was mild with nausea, vomiting (ameliorated by standard antiemetic prophylaxis), self-limited diarrhea, and fatigue observed more frequently. Dose-limiting toxic effects consisted mainly of grade 4 neutropenia which was not strictly dose-related because it was observed only at the 2nd, 3rd, 5th, and 6th of 10 dose levels (36, 56, 154, and 168 mg/m^2, respectively). One episode of grade 3 dehydration due to diarrhea, nausea and vomiting accompanied with serious but transient and reversible increase in hepatic aminotransferases was also dose limiting at 196 mg/m^2, but no significant hepatic enzyme elevation was observed otherwise. This toxicity profile is consistent with the previous reports of dose-limiting side effects of BMS-214662 as a 1-hour infusion in three previous phase I studies employing three different schedules: once every 21 days; daily × 5 consecutive days, repeated every 21 days; and once weekly without scheduled dose interruption (22). The most clinically significant and dose-limiting toxicities from these studies consisted of nausea, vomiting, diarrhea, transient/reversible, and noncumulative increases in hepatic aminotransferases, increases in blood urea nitrogen and creatinine as a result of intravascular volume depletion and transient declines in the peripheral white cell count. Particularly, pertinent to our results are the results of the phase I study of BMS-214662 given as a 1-hour continuous weekly infusion in which the principal dose-limiting toxicity of therapy proved to be nausea, vomiting, diarrhea, and reversible increases in transaminases. Dose escalation in this study proceeded up to 278 mg/m^2 but was terminated at this level due to dose limiting diarrhea, nausea and vomiting. However, at the immediately lower dose level of 245 mg/m^2 apart from the common BMS-214662–associated toxicities, one patient developed acute abdominal pain, hyperamylasemia, metabolic acidosis, and disseminated intravascular coagulation, and died, 209 mg/m^2 remained as the recommended phase II dose for this schedule (23). In this phase study, the MTD was reported at 245 mg/m^2. Although the nature of dose-limiting toxicities is not different between the two studies, their frequency was higher in the aforementioned study. This might be due to the uninterrupted schedule of administration and/or to the higher doses employed in that study. Despite the fact that our schedule was better tolerated and the MTD was not reached, further dose escalation beyond 220 mg/m^2 was not deemed advisable. This decision to not dose escalate beyond the dose of 220 mg/m^2 was taken based on communications between the National Cancer Institute, Cancer Therapy Evaluation Program, Bristol Myers Squibb and the investigators at the M.D. Anderson Cancer Center. It was based on the observation of fatal pancreatitis occurring at the dose of 245 mg/m^2 in the weekly 1-hour infusion uninterrupted schedule phase I study which established an MTD of 209 mg/m^2 for this schedule.

No objective clinical responses were documented in this phase I trial. However, minor response was reported for a patient with non–small cell lung cancer. Moreover, a decrease in serum calcitonin levels was observed in medullary thyroid cancer in two patients, and one patient with papillary thyroid carcinoma experienced an improvement in her disease-related

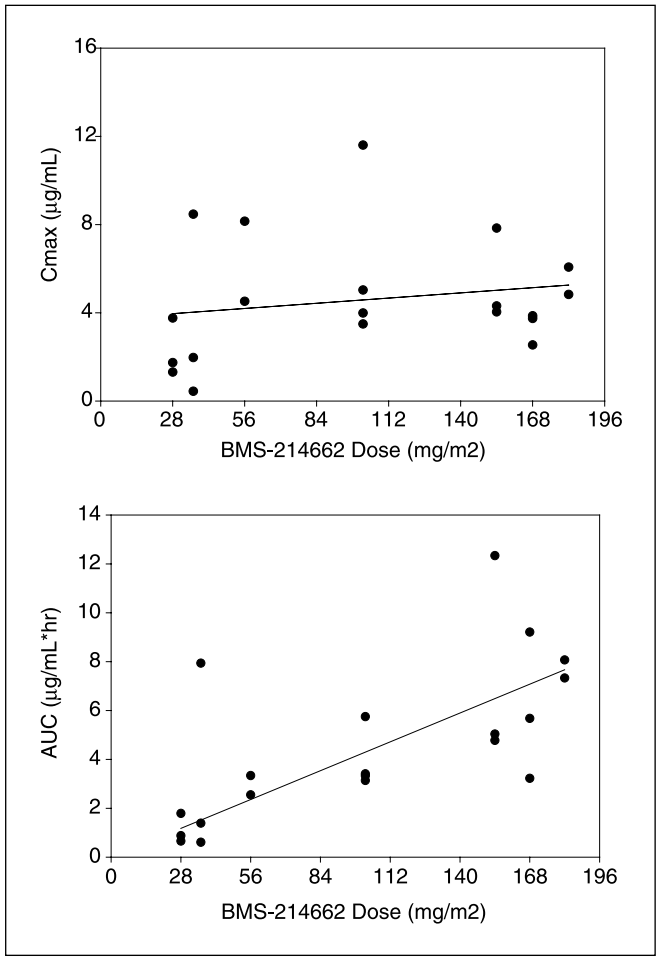

Fig. 2. Figures demonstrating the relationship between C_{max} (r^2 = 0.03, *top*) and AUC (r^2 = 0.45, *bottom*) and dose of BMS-214662, respectively.

Table 5. Inhibition of FT activity in PBMCs after treatment with BMS-214662

Dose (mg/m^2)	No. patients	Farnesyltransferase activity (% of baseline)				
		1 h	2 h	6 h	12 h	24 h
28	3	51.9 ± 25.1*	72.2 ± 24.2	94.8 ± 31.5	77.1 ± 47.7	79.4 ± 32.0
36	3	75.7 ± 76.7	46.2 ± 13.2	112.4 ± 66.2	89.9 ± 59.0	62.3†
56	3	16.4 ± 11.0	100.3†	41.9 ± 23.4	54.8 ± 25.7	88.0†
102	3	30.9 ± 11.8	63.7 ± 44.1	155.9 ± 148.3	72.6 ± 37.6	81.5 ± 36.1
159	4	70.9 ± 71.7	33.3 ± 15.3	75.7 ± 63.9	175.1 ± 113.6	147.9 ± 23.3
168	3	19.6 ± 11.6	15.4 ± 5.5	78.0 ± 21.0	86.1 ± 33.0	87.3 ± 47.5
182	2	14.6 ± 1.46	18.1 ± 4.8	79.4 ± 36.6	103.4 ± 24.0	78.8 ± 4.3

*Mean ± SD.
†Data available from only one patient. All time points are from the start of BMS-214662 infusion administered over 1 hour.

symptoms. The significance of the reduction in serum calcitonin in the two patients with medullary thyroid cancer is unclear. Activating mutations in the RET (28) proto-oncogene have been described in all forms of medullary thyroid cancer, including multiple endocrine neoplasia 2A and 2B (a hereditary medullary thyroid cancer syndrome) and familial medullary thyroid carcinoma (29–32). The Ret-MEN2B mutation causes specific potentiated phosphorylation of Tyr^{1062} (Y1062; ref. 27), which represents a binding site for the Src homology and collagen (protein) adaptor proteins (32). Thus, various signaling pathways are activated mainly via phosphorylation of Y1062 in RET, including the RAS/extracellular signal-regulated kinase pathway and c-*jun* NH_2-kinase pathway (33–36).

Each of the patients who had a reduction of calcitonin had an activating mutation of the RET tyrosine kinase receptor (27). It is possible that the activating mutations of the Ret kinase generate mitogen-activated protein kinase activity that is directly targeted by the effects of farnesyltransferase inhibitors on the RAS/mitogen-activated protein kinase pathway thus affecting secretion of calcitonin and the disease course in these patients. However, it is also possible that the farnesyltransferase inhibitor was directly inhibiting calcitonin synthesis or augmenting metabolism such that levels lowered independent of tumor effect.

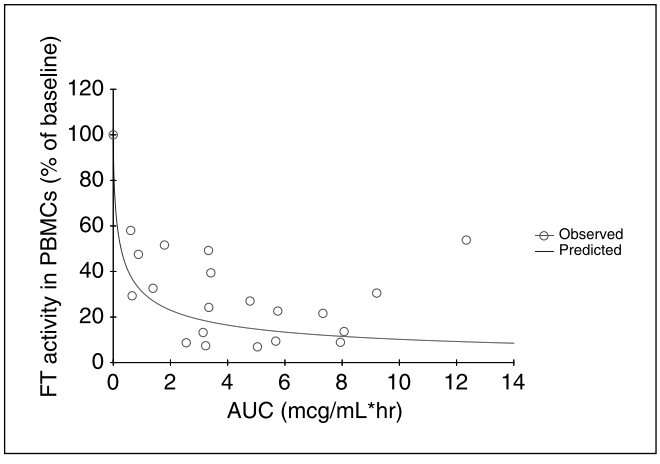

Fig. 3. Inhibitory sigmoidal maximum effect model in the relationship between farnesyltransferase (*FT*) activity in PBMCs (% of baseline) and the BMS-214662 $AUC_{0\text{-}\alpha}$; E_{50} = 0.250 μg/mL h (CV = 140%), γ = 0.597 (CV = 44.7%). Observed values (○) and predicted fit of the data (*solid line*).

There was no observed correlation between dose and achieved C_{max}; however, there was a moderate correlation between dose given and systemic exposure (AUC) to BMS-214662 from 28 to 182 mg/m^2 dose levels. This is in part due to the small number of patients per dose level. There was no relationship between dose of BMS-214662 given and total body clearance (CL_t), apparent volume of distribution at steady state (V_{ss}), or half-life ($t_{1/2}$) from 28 to 182 mg/m^2 dose levels. There was some degree of variability in the clearance of BMS-214662 with a mean of 26 L per hour per m^2 and a SD of nearly 40%. An explanation may be the unauthorized concomitant intake of medication(s) that shared the same substrate enzyme, cytochrome P450 3A4 (CYP3A4) as BMS-214662, although their use was not allowed in this study. Based on the pharmacokinetic findings of this study, this compound seems to have a suboptimal profile, especially as a molecularly targeted agent seen its relatively short circulating plasma half-life and limited volume of distribution. Indeed the profile of this drug when given in this schedule, even from the limited sampling available in this study, is more suggestive of a cytotoxic agent. However, because we do not actually have information on tumor cell kinetics and potential preferential uptake of the drug by tumor cells these statements are arguable.

BMS-214662 had been identified as the most potent proapoptotic farnesyltransferase inhibitor among the agents in this class, and the induction of apoptosis has been thought to be independent of the farnesyltransferase inhibition (20), and through activation of the c-*jun* NH_2-terminal kinase pathway. It was also shown that the minimal concentration required for BMS-214662–induced apoptosis was 370 nmol/L and did not differ appreciably for 24- and 48-hour exposures to the drug, suggesting a requirement for a certain threshold drug concentration. Apoptosis in these *in vitro* experiments was not detectable for the first 6 hours irrespective of high drug concentrations. As previously noted by others (22, 37), we observed that even at the highest dose level for which pharmacokinetics data were available the mean plasma concentration dropped below the apoptosis inducing level of 370 nmol/L (189 ng/mL) by 8 hours after administration

(mean observed at 8 hours 70 ± 56 SD ng/mL). These results also suggest that a longer infusion of the drug might result in higher and more sustainable plasma concentrations that are within the apoptosis-inducing range.

Regardless of dose level, BMS-214662 was effective in suppressing the PBMCs farnesyltransferase activity by 1 hour after the start of the infusion albeit the degree of inhibition varied. The degree and duration of inhibition of farnesyltransferase activity in PBMCs were relatively dependent on the dose and plasma concentration achieved with BMS-214662. The maximum level of inhibition was 14.6 % of the pretreatment activity occurring at the end of the infusion, recovering to a mean of 91% of baseline activity by 6 hours. From the E_{max} sigmoidal model, generated to correlate AUC with inhibition of farnesyltransferase activity, the E_{50} was 0.250 μg/mL hour with a high coefficient of variance at 140%. This value is substantially higher than the IC_{50} values for the *in vitro* inhibition of farnesylation. However, it is difficult to make any correlation without additional information regarding inhibition of farnesyltransferase at the tumor.

It is possible that a more sustained and substantial inhibition of farnesyltransferase activity is required for apoptosis inducing effects suggesting alternative schedules of administration, such as continuous infusion.

A critical issue that remains to be addressed is the identification of farnesyltransferase inhibitor targets. As more clinical and preclinical data emerges, it is increasingly clear that although the mechanism of action of farnesyltransferase inhibitors is indeed through inhibition of farnesyltransferase and Ras proteins are indeed substrates for this enzyme, the most frequently mutated *Ras* gene products in human cancer escape farnesyltransferase inhibitor inhibition. It is also clear that the differential activity of this class of agents is based on how critical yet unidentified farnesylated proteins are to the survival of certain tumors. None of the tumors in our clinical trial were sequenced for presence of H-ras, N-Ras, or K-Ras mutations. However, recent research in this area points to other potential candidates as critical determinants of sensitivity to these agents such as transforming growth factor-β precursors, serine/threonine kinase-11, and inositol-1,4,5-triphosphate 5-phosphatases (I and IV; ref. 38) the PRL family of protein tyrosine phosphatases that are farnesylated proteins with roles in transformation and invasion of epithelial cells (39), RND proteins (40), farnesylated members of the RHO family of small GTPases especially RHEB an activator of the mammalian target of rapamycin/S6 kinase signaling pathway (41–43) or the centromeric proteins that interact with microtubules and are necessary for completion of mitosis (44). The possibility exists that the cytotoxicity of farnesyltransferase inhibitors may be due to inhibition of farnesylation of several critical proteins. In addition, the possibility exists that farnesyltransferase inhibitors might exert their action through alternative mechanisms apart from protein prenylation, such as induction of wild-type p53, resulting in a p21-dependent G_1 block, or apoptotic cell death in cells with mutant p53 or p21 loss (45), or p53-independent apoptosis (46).

Several drugs in this class have been evaluated and clinical data suggest a similar profile for activity of these agents but overall disappointing activity as single agents in solid tumors (47–49). Currently, the focus of clinical trials is on hematologic malignancies such as refractory acute myeloid leukemia, chronic myelogenous leukemia, and MDS where activity has been shown (50–52) and selected solid tumors such as breast cancer and head and neck cancer. In our trial, we saw interesting biological activity with BMS214662 in thyroid cancer that might be taken in consideration for future development of this drug. Further studies with farnesyltransferase inhibitors alone or in combination with other agents, especially after careful elucidation of the protein targets, are warranted.

References

1. Barbacid M. Ras genes. Annu Rev Biochem 1987;56:779–827.
2. Boguski MS, McCormick F. Proteins regulating Ras and its relatives. Nature 1993;366:643–54.
3. Bos JL. Ras oncogenes in human cancer: a review. Cancer Res 1989;49:4682–9.
4. Andreyev HJ, Norman AR, Cunningham D, et al. Kirsten ras mutations in patients with colorectal cancer: the "RASCAL II" study. Br J Cancer 2001;85:692–6.
5. Slebos RJ, Kibbelaar RE, Dalesio O, et al. K-*ras* oncogene activation as a prognostic marker in adenocarcinoma of the lung. N Engl J Med 1990;323:561–5.
6. Broermann P, Junker K, Brandt BH, et al. Trimodality treatment in stage III nonsmall cell lung carcinoma: prognostic impact of K-*ras* mutations after neoadjuvant therapy. Cancer 2002;94:2055–62.
7. Malats N, Porta M, Corominas JM, Pinol JL, Rifa J, Real FX. Ki-ras mutations in exocrine pancreatic cancer: association with clinico-pathological characteristics and with tobacco and alcohol consumption. PANK-ras I Project Investigators. Int J Cancer 1997;70:661–7.
8. Garcia-Rostan G, Zhao H, Camp RL, et al. ras mutations are associated with aggressive tumor phenotypes and poor prognosis in thyroid cancer. J Clin Oncol 2003;21:3226–35.
9. Kiyoi H, Naoe T, Nakano Y, et al. Prognostic implication of FLT3 and N-RAS gene mutations in acute myeloid leukemia. Blood 1999;93:3074–80.
10. McCormick F. Activators and effectors of ras p21 proteins. Curr Opin Genet Dev 1994;4:71–6.
11. Rowinsky EK, Windle JJ, Von Hoff DD. Ras protein farnesyltransferase: a strategic target for anticancer therapeutic development. J Clin Oncol 1999;17:3631–52.
12. Sebti SM, Der CJ. Opinion: searching for the elusive targets of farnesyltransferase inhibitors. Nat Rev Cancer 2003;3:945–51.
13. Kohl NE, Mosser SD, deSolms SJ, et al. Selective inhibition of ras-dependent transformation by a farnesyltransferase inhibitor. Science 1993;260:1934–7.
14. Sepp-Lorenzino L, Ma Z, Rands E, et al. A peptidomimetic inhibitor of farnesyl: protein transferase blocks the anchorage-dependent and -independent growth of human tumor cell lines. Cancer Res 1995;55:5302–9.
15. Sun J, Qian Y, Hamilton AD, Sebti SM. Both farnesyltransferase and geranylgeranyltransferase I inhibitors are required for inhibition of oncogenic K-Ras prenylation but each alone is sufficient to suppress human tumor growth in nude mouse xenografts. Oncogene 1998;16:1467–73.
16. Haluska P, Dy GK, Adjei AA. Farnesyl transferase inhibitors as anticancer agents. Eur J Cancer 2002;38:1685–700.
17. Baum C, Kirschmeier P. Preclinical and clinical evaluation of farnesyltransferase inhibitors. Curr Oncol Rep 2003;5:99–107.
18. Manne V, Lee FY, Bol DK, et al. Apoptotic and cytostatic farnesyltransferase inhibitors have distinct pharmacology and efficacy profiles in tumor models. Cancer Res 2004;64:3974–80.
19. Hunt JT, Ding CZ, Batorsky R, et al. Discovery of (*R*)-7-cyano-2,3,4, 5-tetrahydro-1-(1*H*-imidazol-4-ylmethyl)-3- (phenylmethyl)-4-(2-thienylsulfonyl)-1*H*-1,4-benzodiazepine (BMS-214662), a farnesyltransferase inhibitor with potent preclinical antitumor activity. J Med Chem 2000;43:3587–95.
20. Rose WC, Lee FY, Fairchild CR, et al. Preclinical antitumor activity of BMS-214662, a highly apoptotic and novel farnesyltransferase inhibitor. Cancer Res 2001;61:7507–17.
21. Camacho LH, Soignet SL, Pezzulli S, et al. Dose escalation study of oral farnesyl transferase inhibitor (FTI) BMS-214662 in patients with solid tumors. Proc Am Soc Clin Oncol 2001;20:78a; Abstract 311.
22. Ryan DP, Eder JP Jr, Puchlaski T, et al. Phase I clinical trial of the farnesyltransferase inhibitor BMS-214662 given as a 1-hour intravenous infusion in patients with advanced solid tumors. Clin Cancer Res 2004;10:2222–30.
23. Voi M, Tabernero J, Cooper MR, et al. A phase I study of the farnesultransferase (FT) inhibitor BMS-214662 administered as a weekly 1-hour infusion in patients (Pts) with advanced solid tumors: clinical findings. Proc Am Soc Clin Oncol 2001;20:79a.
24. Goodman SN, Zahurak ML, Piantadosi S. Some practical improvements in the continual reassessment

method for phase I studies. Stat Med 1995;14:1149–61.

25. Dutta S, Matsumoto Y, Ebling WF. Is it possible to estimate the parameters of the sigmoid E_{max} model with truncated data typical of clinical studies? J Pharm Sci 1996;85:232–9.

26. Khorana S, Gagel RF, Cote GJ. Direct sequencing of PCR products in agarose gel slices. Nucleic Acids Res 1994;22:3425–6.

27. Yip L, Cote GJ, Shapiro SE, et al. Multiple endocrine neoplasia type 2: evaluation of the genotype-phenotype relationship. Arch Surg 2003;138:409–16; discussion 416.

28. Takahashi M, Buma Y, Iwamoto T, Inaguma Y, Ikeda H, Hiai H. Cloning and expression of the ret proto-oncogene encoding a tyrosine kinase with two potential transmembrane domains. Oncogene 1988;3:571–8.

29. Carlson KM, Dou S, Chi D, et al. Single missense mutation in the tyrosine kinase catalytic domain of the RET protooncogene is associated with multiple endocrine neoplasia type 2B. Proc Natl Acad Sci U S A 1994;91:1579–83; 1994 Feb 15.

30. Hofstra RM, Landsvater RM, Ceccherini I, et al. A mutation in the RET proto-oncogene associated with multiple endocrine neoplasia type 2B and sporadic medullary thyroid carcinoma [see comment]. Nature 1994;367:375–6.

31. Santoro M, Carlomagno F, Romano A, et al. Activation of RET as a dominant transforming gene by germline mutations of MEN2A and MEN2B. Science 1995;267:381–3.

32. Asai N, Murakami H, Iwashita T, Takahashi M. A mutation at tyrosine 1062 in MEN2A-Ret and MEN2B-Ret impairs their transforming activity and association with shc adaptor proteins. J Biol Chem 1996;271:17644–9.

33. Hayashi H, Ichihara M, Iwashita T, et al. Characterization of intracellular signals via tyrosine 1062 in RET activated by glial cell line-derived neurotrophic factor. Oncogene 2000;19:4469–75.

34. Besset V, Scott RP, Ibanez CF. Signaling complexes and protein-protein interactions involved in the activation of the Ras and phosphatidylinositol 3-kinase pathways by the c-Ret receptor tyrosine kinase. J Biol Chem 2000;275:39159–66.

35. Salvatore D, Melillo RM, Monaco C, et al. Increased *in vivo* phosphorylation of ret tyrosine 1062 is a potential pathogenetic mechanism of multiple endocrine neoplasia type 2B. Cancer Res 2001;61:1426–31.

36. Chiariello M, Visconti R, Carlomagno F, et al. Signalling of the Ret receptor tyrosine kinase through the c-Jun NH_2-terminal protein kinases (JNKS): evidence for a divergence of the ERKs and JNKs pathways induced by Ret. Oncogene 1998;16:2435–45.

37. Mackay HJ, Hoekstra R, Eskens FA, et al. A phase I pharmacokinetic and pharmacodynamic study of the farnesyl transferase inhibitor BMS-214662 in combination with cisplatin in patients with advanced solid tumors. Clin Cancer Res 2004;10:2636–44.

38. Fiordalisi JJ, Johnson RL II, Weinbaum CA, et al. High affinity for farnesyltransferase and alternative prenylation contribute individually to K-Ras4B resistance to farnesyltransferase inhibitors. J Biol Chem 2003;278:41718–27. Epub 2003 Jul 25.

39. Cates CA, Michael RL, Stayrook KR, et al. Prenylation of oncogenic human PTP(CAAX) protein tyrosine phosphatases. Cancer Lett 1996;110:49–55.

40. Hansen SH, Zegers MM, Woodrow M, et al. Induced expression of Rnd3 is associated with transformation of polarized epithelial cells by the Raf-MEK-extracellular signal-regulated kinase pathway. Mol Cell Biol 2000;20:9364–75.

41. Clark GJ, Kinch MS, Rogers-Graham K, Sebti SM, Hamilton AD, Der CJ. The Ras-related protein Rheb is farnesylated and antagonizes Ras signaling and transformation. J Biol Chem 1997;272:10608–15.

42. Garami A, Zwartkruis FJ, Nobukuni T, et al. Insulin activation of Rheb, a mediator of mTOR/S6K/4E-BP signaling, is inhibited by TSC1 and 2. Mol Cell 2003;11:1457–66.

43. Castro AF, Rebhun JF, Clark GJ, Quilliam LA. Rheb binds tuberous sclerosis complex 2 (TSC2) and promotes S6 kinase activation in a rapamycin- and farnesylation-dependent manner. J Biol Chem 2003;278:32493–6.

44. Ashar HR, James L, Gray K, et al. Farnesyl transferase inhibitors block the farnesylation of CENP-E and CENP-F and alter the association of CENP-E with the microtubules. J Biol Chem 2000;275:30451–7.

45. Sepp-Lorenzino L, Rosen N. A farnesyl-protein transferase inhibitor induces p21 expression and G_1 block in p53 wild type tumor cells. J Biol Chem 1998;273:20243–51.

46. Vitale M, Di Matola T, Rossi G, Laezza C, Fenzi G, Bifulco M. Prenyltransferase inhibitors induce apoptosis in proliferating thyroid cells through a p53-independent CrmA-sensitive, and caspase-3-like protease-dependent mechanism. Endocrinology 1999;140:698–704.

47. Adjei AA, Mauer A, Marks R, et al. A phase II study of the farnesyltransferase inhibitor R115777 in patients with advanced non-small cell lung cancer. Proc Am Soc Clin Oncol 2002;21:290a.

48. Heymach JV, De Porre PM, Devore RF, et al. Phase II study of the farnesyl transferase inhibitor (FT) R115777 (Zarnestra) in patients with relapsed small cell lung cancer (SCLC). Proc Am Soc Clin Oncol 2002;21:319a.

49. Van Cutsem E, Karasek P, Oettle H, et al. Phase III trial comparing gemcitabine + R115777 (Zarnestra) versus gemcitabine + placebo in advanced pancreatic cancer (PC). Proc Am Soc Clin Oncol 2002;21:130a.

50. Cortes J, Albitar M, Thomas D, et al. Efficacy of the farnesyl transferase inhibitor R115777 in chronic myeloid leukemia and other hematologic malignancies. Blood 2003;101:1692–7.

51. Kurzrock R, Kantarjian HM, Cortes JE, et al. Farnesyltransferase inhibitor R115777 in myelodysplastic syndrome: clinical and biologic activities in the phase 1 setting. Blood 2003;102:4527–34.

52. Kurzrock R, Albitar M, Cortes JE, et al. Phase II study of R115777, a farnesyl transferase inhibitor, in myelodysplastic syndrome. J Clin Oncol 2004;22:1287–92.