Cancer Chemother Pharmacol (2004) 53: 513–518
DOI 10.1007/s00280-004-0764-7

ORIGINAL ARTICLE

**Steven J. Cohen · James Gallo · Nancy L. Lewis
R. Katherine Alpaugh · Louis Gentner · André Rogatko
Gwen Yeslow · Jessie Schol · Tom Verhaeghe
Peter Zannikos · Peter A. Palmer · Louis M. Weiner
Neal J. Meropol**

Phase I and pharmacokinetic study of the farnesyltransferase inhibitor R115777 in combination with irinotecan in patients with advanced cancer

Received: 28 August 2003 / Accepted: 17 December 2003 / Published online: 3 February 2004

Abstract *Purpose*: R115777 is a selective, nonpeptidomimetic inhibitor of farnesyltransferase (FTase), an enzyme responsible for the post-translational modification of several proteins, including Ras. Given the high frequency of *K-Ras* mutations in malignancies commonly treated with irinotecan, the broad preclinical antiproliferative activity of R115777 and its largely non-overlapping toxicity profile with irinotecan, this phase I study of the combination of R115777 and irinotecan in patients with advanced cancer was undertaken. *Patients and methods*: Enrolled onto the study were 14 patients (eight male, six female; median age 63 years, range 48–72 years). Five patients had an ECOG performance status (PS) of 0, eight patients PS 1, and one patient PS 2. The patients were treated with R115777 orally twice daily for 28 days and irinotecan 100 mg/m^2 as an intravenous infusion on days 1, 8, 15, and 22 of each 42-day cycle. Seven patients received R115777 100 mg twice daily and seven received R115777 200 mg twice daily. *Results*: Dose-limiting toxicity (DLT) was experienced by one of seven patients treated with R115777 100 mg (grade 3 fatigue), and two of seven patients treated with R115777 200 mg (grade 3 diarrhea, grade 4 neutropenia lasting >5 days). The maximum tolerated dose (MTD) was R115777 100 mg twice daily and irinotecan 100 mg/m^2 weekly. Non-DLTs were primarily rash, fatigue, diarrhea, and neutropenia. R115777 demonstrated linear pharmacokinetics without interaction with irinotecan and achieved serum levels required for antitumor activity in vitro. *Conclusions*: Serum levels of R115777 exceeded those necessary for FTase inhibition in vitro without evidence of interaction with irinotecan. However, the MTD of R115777 in this study was lower than that obtained with an alternate schedule. Thus, further development of this schedule is not recommended.

Keywords Irinotecan · R115777 · Phase I · Farnesyltransferase inhibitor · Pharmacokinetics

This work was supported by a grant from Johnson and Johnson Pharmaceutical Research and Development and NCI K12 CA01728.

S. J. Cohen (✉) · N. L. Lewis · R. K. Alpaugh
L. M. Weiner · N. J. Meropol
Department of Medical Oncology,
Fox Chase Cancer Center,
333 Cottman Avenue,
Philadelphia, PA 19111-2497, USA
E-mail: S_Cohen@fccc.edu
Tel.: +1-215-7282450
Fax: +1-215-7283639

J. Gallo
Department of Pharmacology,
Fox Chase Cancer Center,
Philadelphia, PA, USA

L. Gentner · P. Zannikos
Johnson and Johnson Pharmaceutical Research
and Development, Titusville, NJ, USA

A. Rogatko
Department of Biostatistics,
Fox Chase Cancer Center,
Philadelphia, PA, USA

G. Yeslow · J. Schol
Protocol Management Office,
Fox Chase Cancer Center,
Philadelphia, PA, USA

T. Verhaeghe · P. A. Palmer
Johnson and Johnson Pharmaceutical Research
and Development, Beerse, Belgium

Introduction

R115777 (ZARNESTRA, tipifarnib) is a selective, nonpeptidomimetic competitive inhibitor of farnesyltransferase (FTase), an enzyme responsible for post-translational modification of several proteins, including

Ras [8]. In vitro, R115777 inhibits farnesylation of lamin B and K-ras B peptide substrates at nanomolar concentrations, while demonstrating antiproliferative effects in colon and pancreatic cancer cell lines [8]. In vivo, R115777 suppresses tumor growth of human colon and pancreatic cancer xenografts [8]. Recent evidence suggests that the activity of R115777 may result from inhibition of multiple targets in addition to Ras [8].

Phase I studies of R115777 have demonstrated the tolerability of this orally administered compound in several delivery schedules. Hudes et al. evaluated a twice-daily schedule of R115777 given 21 days out of 28, with achievement of plasma levels required for FTase inhibition in vitro [12]. Dose-limiting toxicity (DLT) was primarily myelosuppression, with fatigue and hyperbilirubinemia observed. Alternative dosing has been explored. A study utilizing continuous twice daily dosing of R115777 has demonstrated myelosuppression and neurosensory toxicities as dose-limiting, and established 300 mg twice daily as the recommended phase II dose for chronic administration [5].

Irinotecan is a camptothecin derivative and topoisomerase-I inhibitor which has demonstrated a broad range of clinical antitumor activity. It results in improved survival when administered as both initial treatment of metastatic colorectal cancer in combination with 5-fluorouracil [19] and as salvage therapy after fluoropyrimidine therapy [6, 18]. Promising clinical activity has also been seen in a variety of other malignancies, including small-cell lung cancer and cancers of the upper gastrointestinal tract [2, 13, 17].

Given the broad preclinical antiproliferative activity of R115777, the different mechanisms of action of R115777 and irinotecan and their partially non-overlapping toxicity profiles, we hypothesized that both drugs could be safely combined with potential relevance in numerous clinical contexts. This phase I study was undertaken to determine the maximum tolerated dose (MTD) and DLT of the combination of weekly irinotecan and twice-daily R115777 administered for 28 days out of 42. Secondary objectives included assessment of pharmacokinetic interactions between R115777 and irinotecan and preliminary evaluation of antitumor activity.

Patients and methods

Patient eligibility

Patients enrolled onto this study were at least 18 years of age and had a pathologically confirmed malignancy for which no standard therapy existed. Additional inclusion criteria included: life expectancy of at least 3 months, at least 4 weeks elapsed since prior chemotherapy or radiotherapy (6 weeks for nitrosoureas or mitomycin C), Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2 (ambulatory at least 50% of waking hours), adequate hematologic function (absolute neutrophil count (ANC) $>1500/\mu l$, platelets $>100{,}000/\mu l$, hemoglobin $>9.0/dl$), adequate renal function (serum creatinine within normal limits), adequate hepatic function (ALT and AST not more than two times the upper limit of normal), and negative pregnancy test for women of childbearing potential. Exclusion criteria included prior bone marrow transplantation or high-dose chemotherapy, extensive prior radiation therapy (≥25% of bone marrow reserve), participation in another investigational treatment protocol within 30 days, known allergy to azole class of drugs or irinotecan, and concomitant use of proton pump inhibitors. Prior irinotecan was allowed. Patients provided written informed consent as per institutional and federal requirements, and the protocol was approved by the Institutional Review Board of Fox Chase Cancer Center.

Treatment plan and definition of MTD

This was a phase I, open label dose-escalation trial. R115777 was supplied by Johnson and Johnson Pharmaceutical Research and Development as 100-mg tablets and administered orally twice daily at 12-h intervals and within 30 min after meals for 28 consecutive days followed by a 2-week rest (42-day cycles). Irinotecan was given as a 90-min infusion on days 1, 8, 15, and 22 followed by a 2-week break. For cycle 1 only, R115777 dosing started on day 4 to allow pharmacokinetic assessment of irinotecan alone. Cycles were repeated every 42 days until evidence of disease progression or unacceptable toxicity. Three to six patients were to be enrolled at each dose level. If none of the first three patients experienced DLT within the first cycle, dose escalation would proceed. If one of three encountered DLT, three additional patients would be enrolled at that dose level. If DLT was not experienced in these additional three patients, dose escalation would proceed. The MTD was defined as the highest dose which did not cause DLT in two or three of three patients or in two or more of six patients (i.e. ≥33%) treated at that level during their first cycle of therapy.

The initial cohort of patients was treated with 100 mg twice daily of R115777 and 100 mg/m^2 of irinotecan weekly. In the absence of DLT, additional cohorts of patients would be treated with increasing doses of R115777 by increments of 100 mg twice daily. If a dose level exceeded the MTD, enrollment continued with a decrease in R115777 of 100 mg per dose.

A history and physical examination, and complete blood count (CBC), chemistries, liver function, coagulation studies, EKG, and radiographic evaluation of metastatic disease were performed within 14 days of initiation of therapy. Women of childbearing potential had urine or serum pregnancy tests prior to starting study medication. A CBC and chemistries were obtained weekly on study. Tumor response was evaluated with repeat radiographic assessment after two cycles of therapy or as clinically indicated using World Health Organization criteria [16].

Definition of DLT

Toxicity was graded according to the NCI Common Toxicity Criteria v 2.0 (http://ctep.info.nih.gov/reporting/ctc.html). DLT was defined as grade 3 or more non-hematologic toxicity (excluding rash, nausea, vomiting, or diarrhea responding to symptomatic management), grade 3 thrombocytopenia or grade 4 granulocytopenia lasting >5 days, any grade 4 thrombocytopenia or grade 4 neutropenia associated with fever or infection, omission of two or more doses of irinotecan in a cycle due to toxicity, or interruption of R115777 dosing for more than seven consecutive days due to drug-related toxicity.

Dose modification

Irinotecan

For ANC $<1500/\mu l$ but $\geq 1000/\mu l$ on the day of irinotecan therapy, the dose of irinotecan was reduced to 80 mg/m^2. For ANC $<1000/\mu l$, irinotecan was held and restarted upon neutrophil recovery with dose reduction to 80 mg/m^2. Further

necessity for dose reduction of irinotecan below 80 mg/m^2 mandated removal of the patient from study. For grade 2 or 3 diarrhea, irinotecan was reduced to 80 mg/m^2 with (grade 3) or without (grade 2) the omission of a dose. Grade 4 diarrhea would mandate dose reduction of irinotecan below 80 mg/m^2 and removal from study.

R115777

R115777 therapy was temporarily discontinued for grade 3 or more non-hematologic toxicity (excluding nausea/vomiting or diarrhea responding to symptomatic management), grade 4 neutropenia, grade 3 thrombocytopenia lasting >5 days, or grade 4 thrombocytopenia. R115777 was restarted when these toxicities resolved to grade 1 or less with a dose reduction of 100 mg twice daily.

Pharmacokinetic assessment

Blood samples (5 ml) were collected for pharmacokinetic evaluation on days 1 (irinotecan only), 6 or 7 (R115777 only), and 8 (R115777 and irinotecan). Irinotecan plasma levels were obtained on day 1 predosing, at 30 and 60 min into infusion, at the end of infusion, and at the following time-points (expressed as hours:minutes) after infusion: 0:10, 0:20, 0:30, 0:60, 0:90, 2:00, 3:00, 5:00, 6:00, 8:00, 10:00, 24:00, and 48:00. R115777 plasma levels were obtained predosing on day 6 or 7, and at 1, 2, 3, 5, 8, and 12 h after R115777 administration. On day 8, pharmacokinetic sampling was performed immediately prior to irinotecan infusion and R115777 administration, at 30 and 60 min into irinotecan infusion, at the end of infusion, and at the following time-points (expressed as hours:minutes) after infusion: 0:10, 0:20, 0:30, 0:60, 0:90, 2:00, 3:00, 5:00, 6:00, 8:00, 10:00, 24:00, and 48:00.

R115777 serum levels were measured by a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) assay in the range 2.00 to 5000 ng/ml. Briefly, samples for R115777 were analyzed in the following manner. To 0.1-ml aliquots of human plasma, 10 ng of a stable isotope-labeled internal standard was added. After adding 1 ml NaOH (0.1 *M*), the samples were extracted with 5 ml heptane containing 10% of isoamyl alcohol. The organic layer was evaporated under nitrogen at 65°C and the residue dissolved in 200 µl methanol, and 50 µl ammonium formate 0.002 *M* (pH 4) was added. The extracts were injected in 4-µl aliquots onto an API 3000 (Applied Biosystems) LC-MS/MS with a TurboIonspray interface, operated in the positive-ion mode. Separation was on a 5 cm × 4.6 mm chromatographic column, packed with 3 µm C18 BDS-Hypersil (Alltech). The mobile phase was 0.002 *M* ammonium formate/acetonitrile (40/60) at a flow rate of 1.5 ml/min. The total run time was 2.5 min. The mass spectrometer was operated in the MRM mode. The mass transitions monitored were m/z 489.1 to m/z 407.1 and m/z 492.1 to m/z 407.1 for R115777 and the internal standard, respectively.

Irinotecan and its metabolite SN-38 were measured by a validated HPLC fluorescence assay in the ranges of 5–1500 ng/ml and 0.5–100 ng/ml, respectively. Briefly, 200 µL acetonitrile/methanol (1:1, v/v) was added to human plasma (100 µl) to precipitate plasma proteins. After mixing, the sample was centrifuged at 23,000 *g* for 10 min. A volume of 75 µl of the supernatant was mixed with 75 µl 0.01 *M* sodium tetraborate (pH 9). After brief mixing, this solution was transferred to an autosampler vial and 25 µl was injected onto the HPLC column. Separation was on a 15 cm × 4.6 mm chromatographic column, packed with 3.5 µm Zorbax SB-C18 (Agilent Technologies). The mobile phase consisted of a mixture of 0.1 *M* ammonium acetate/acetonitrile/TEA (800/200/1), containing 5 m*M* tetrabutyl ammonium phosphate, pumped at a flow rate of 1.5 ml/min. The total run time was 10 min. Detection was by fluorescence with excitation and emission wavelengths of 385 nm and 525 nm, respectively.

Table 1 Patient characteristics ($n=14$)

Characteristic	Number
Age (years)	
Median	63
Range	48–72
Cycles of therapy	
Total	24
Median	1
Range	1–7
Sex (M/F)	8/6
Performance status	
0	5
1	8
2	1
Primary cancer	
Colorectal	8
Pancreas	2
GE junction	1
Hepatoma	1
Leiomyosarcoma	1
Cholangiocarcinoma	1
Two or more prior chemotherapy regimens	6
Prior irinotecan therapy	4

Results

Patient characteristics

Enrolled onto this study were 14 patients who received a total of 24 cycles of treatment (median 1, range 1–7). Patient characteristics are listed in Table 1. Of the 14 patients, 8 had colorectal cancer, and 13 had received prior chemotherapy (11 for metastatic disease), with 6 having received at least two prior regimens, and 4 having received prior irinotecan.

Toxicity

All enrolled patients received at least one dose of study drugs and were evaluable for toxicity. Of three patients treated at the initial dose level of R115777 100 mg twice daily and irinotecan 100 mg/m^2 weekly, one (a 69-year-old female with rectal cancer) experienced grade 3 hypophosphatemia. As this resolved without specific intervention within 4 days and grade 2 hypophosphatemia was present prior to enrollment on study, this was not considered a DLT and a decision was made to dose-escalate to cohort 2 (200 mg twice daily of R115777 with irinotecan 100 mg/m^2). As one of three initial patients at this dose level, a 61-year-old female with colon cancer, developed DLT (grade 3 diarrhea resulting in temporary suspension of therapy), accrual to cohort 2 was expanded. Of the next three patients treated with R115777 200 mg twice daily, one patient, a 73-year-old female with colon cancer, experienced grade 3 hypokalemia and grade 3 rash necessitating treatment discontinuation. As rash had not previously been described as a dose-related event with R115777 and the hypokalemia

Table 2 Maximum adverse event grade per patient ($n = 14$)

Toxicity	Cycle 1 (grade)				All cycles (grade)			
	1	2	3	4	1	2	3	4
Anemia	3	5	2	0	3	5	2	0
Anorexia	6	1	0	0	5	2	0	0
Diarrhea	7	3	1	0	6	4	1	0
Dry mouth	4	0	0	0	4	0	0	0
Elevated ALT/AST	1	0	0	0	1	0	1	0
Fatigue	7	1	1	0	8	1	1	0
Hyperbilirubinemia	0	1	0	0	0	1	1	0
Hypoalbuminemia	2	4	0	0	2	4	0	0
Hypokalemia	3	0	1	0	3	0	1	0
Hypophosphatemia	0	1	1	0	0	1	1	0
Leukopenia	3	3	0	0	3	3	0	0
Nausea	5	0	0	0	4	1	0	0
Neutropenia	1	1	3	2	2	1	3	2
Rash	1	2	1	0	1	2	1	0
Vomiting	3	0	0	0	4	1	0	0

was not considered clinically significant, this patient was not considered to have experienced DLT. The patient was replaced by one additional patient at the second dose level, a 63-year-old female with colon cancer who developed grade 4 neutropenia lasting for 12 days. As the MTD was exceeded at the second dose level, four additional patients were enrolled to the first cohort (R115777 100 mg twice daily and irinotecan 100 mg/m^2). Of these, a 70-year-old male with colon cancer developed grade 3 neutropenia lasting 8 days after the completion of cycle 1, and a 63-year-old male with colon cancer developed grade 3 fatigue lasting 25 days. The latter toxicity was considered a DLT. Thus, dose level 1 defined the MTD of this combination and schedule. Other toxicities are listed in Table 2. Grade 1 and 2 toxicities were primarily gastrointestinal (diarrhea, anorexia, nausea), fatigue, and myelosuppression. Rash was seen in four patients (three grade 1/2, one grade 3), associated with pruritus responsive to antihistamines, and typically located on the trunk. The rash was similar to that previously reported with R115777 [5]. No objective antitumor responses were observed.

Pharmacokinetics/pharmacodynamics

Pharmacokinetic parameters for days 7 and 8 R115777 dosing at 100 mg and 200 mg and for days 1 and 8 irinotecan and SN38 levels are summarized in Tables 3 and 4. All 14 patients provided samples for this analysis. The pharmacokinetic parameters for R115777 were evaluated as a function of dose (i.e. 100 mg and 200 mg) and time (i.e. day 7 and day 8). Values for R115777 Cmax (mean range from 408.1 to 1041.7 μg/l) and AUC (mean range from 1955.6 to 4316.8 μg·h/l) showed approximate dose proportional increases as a function of dose on both day 7 and day 8. The values for R115777 Tmax (mean range from 1.2 to 2.4 h) and T1/2 (harmonic mean range from 3 to 3.6 h) did not appreciably change as a function of either dose or time. Comparison of day 7 and day 8 pharmacokinetic parameters for R115777 revealed no significant differences. The pattern of changes in the pharmacokinetic parameters of R115777 is consistent with R115777 displaying linear pharmacokinetics.

The pharmacokinetic parameters from irinotecan and SN38 are in agreement with values reported previously [3]. There was no pharmacokinetic interaction between irinotecan and R115777, as the pharmacokinetic parameters for each drug were similar when given alone

Table 3 Pharmacokinetic parameters for R115777 ($n = 14$). Values are means ± SD except T1/2 values which are harmonic means and pseudo SD. Cmax and AUC differ only as a function of dose ($P < 0.05$); no differences were noted as a function of day (*Cmax* maximum plasma concentration, *Tmax* time to maximum plasma concentration, *AUC* area under the plasma concentration versus time curve, *T1/2* elimination half-life)

Day	Cmax (μg/l)		AUC (μg·h/l)		Tmax (h)		T1/2 (h)	
	100 mg	200 mg	100 mg	200 mg	100 mg	200 mg	100 mg	200 mg
7	472.1 ± 197.6	769.6 ± 340.8	2101.9 ± 539.0	3845.2 ± 1736.6	2.3 ± 1.0	2.3 ± 0.8	3.0 ± 0.5	3.4 ± 1.0
8	408.1 ± 215.4	1041.7 ± 556.2	1955.6 ± 758.2	4316.8 ± 2320.5	2.4 ± 1.1	1.2 ± 0.8	3.1 ± 0.8	3.6 ± 0.9

Table 4 Pharmacokinetic parameters for irinotecan and SN38 ($n = 14$). Values are means ± SD except T1/2 values which are harmonic means and pseudo SD (*Cmax* maximum plasma concentration, *Tmax* time to maximum plasma concentration, *AUC* area under the plasma concentration versus time curve, *T1/2* elimination half-life, *Cl* plasma clearance, *Vss* plasma volume at steady state, *NC* not calculated)

Day	Cmax (μg/l)		AUC (μg·h/l)		Tmax (h)		T1/2 (h)		Cl (l/h/m^2)	Vss (l/m^2)
	SN38	Irinotecan	SN38	Irinotecan	SN38	Irinotecan	SN38	Irinotecan	Irinotecan	Irinotecan
1	18.3 ± 7	1387 ± 312	239 ± 105	6956 ± 2319	2.25 ± 1.18	NC	19.8 ± 10.5	10.3 ± 3.1	15.7 ± 4.7	126.2 ± 33.4
8	17.2 ± 11.4	1550 ± 529	246 ± 116.7	7609 ± 2932	1.78 ± 0.61	NC	21.3 ± 9.95	10.7 ± 2.3	14.8 ± 5.1	128.1 ± 51.1

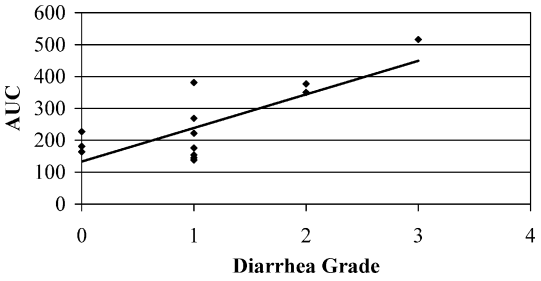

Fig. 1 Correlation between SN38 AUC on day 8 and worst grade of diarrhea in cycle 1 ($R = 0.75$, $P = 0.002$, Pearson correlation test)

(day 1 for irinotecan and day 7 for R115777) or in combination (day 8).

Pharmacodynamic assessment revealed a strong correlation between SN38 AUC and grade of diarrhea ($R = 0.75$, $P = 0.002$, Pearson correlation test; Fig. 1) but not between R115777 AUC values and grade of neutropenia or diarrhea (data not shown).

Discussion

This study defined the MTD of a combination of R115777 and irinotecan to be 100 mg twice daily of R115777 administered for 28 days with irinotecan 100 mg/m^2 administered days 1, 8, 15, and 22 of a 42-day cycle. Plasma levels of R115777 and irinotecan achieved were compatible with preclinical antitumor activity and phase I experiences [7, 8], without evidence of pharmacokinetic interaction.

The toxicities demonstrated in this phase I study are consistent with known side effect profiles of the two agents. Phase I studies of R115777 have predominantly shown myelosuppression as dose limiting [5, 12]. Diarrhea is common with weekly irinotecan therapy and is dose limiting [7]. Preliminary results of a phase I trial of an alternative administration schedule of these agents have been reported by Verweij and colleagues [20]. In that study, irinotecan was dosed once every 3 weeks and R115777 was given twice daily either continuously or intermittently for 14 out of 21 days. At the time of their report, treatment with intermittent R115777 at 200 mg twice daily with 350 mg/m^2 of irinotecan was well tolerated, and R115777 dose escalation was ongoing.

There are several non-mutually exclusive explanations for why the regimen explored in this study did not permit dose escalation of R115777. The recommended phase II dose and schedule of R115777 is 300 mg twice daily given for 21 days followed by a 1-week break. This dose has been well tolerated in patients with advanced prostate cancer [11], breast cancer [14], and acute leukemia [15], although patients with pancreatic and colon cancer do not tolerate it as well [4, 21]. In the current study, we extended the R115777 treatment duration to 28 days out of 42, which may have led to increased toxicity. This is supported by the observation that DLTs in our study were observed at a median of 21 days (range 14–29 days) from initiation of cycle 1 R115777 therapy. Presumably, some of this toxicity may have been prevented by a 14 out of 21-day R115777 schedule.

No evidence of a pharmacokinetic interaction was seen in either our study or that reported by Verweij and colleagues. The AUC reported by Verweij et al. for R115777 when measured with concurrent therapy is similar to our reported value (3588 ± 1555 vs 4317 ± 2321 h·ng/ml, mean ± SD) [20]. It is possible that our schedule has uncovered a pharmacodynamic interaction between irinotecan and R115777 that is independent of pharmacokinetic parameters. Alternatively, a small pharmacokinetic interaction may have been missed given the small number of patients in our study.

Irinotecan delivery scheduling may have contributed to the toxicity seen in our study. Although the weekly irinotecan schedule is more commonly utilized in North America, the every-3-week schedule frequently used in Europe is associated with decreased diarrhea and myelosuppression [9]. The average weekly AUC of SN38 received by patients was higher in our 4 out of 6 weekly irinotecan schedule than in the every-3-week irinotecan delivery utilized by Verweij and colleagues (164 vs 108 h·ng/ml). Thus, our schedule provided greater dose intensity of irinotecan, with SN38 AUC correlating strongly with grade of diarrhea.

Finally, patient characteristics may have accounted for some of the decreased tolerability in our study. Our patient population was predominantly comprised of pretreated patients with colorectal or pancreatic cancer. All but one of our patients received prior chemotherapy, with nearly half treated with at least two prior chemotherapy regimens.

R115777 has antitumor activity in several disease settings, including acute leukemia, breast cancer, and myeloproliferative disorders [10, 14, 15]. During the course of the current phase I study, it became apparent that R115777 does not demonstrate single-agent activity in gastrointestinal or lung cancers, diseases in which irinotecan has a standard role in management and *K-Ras* mutations are frequent. Our study in pancreatic cancer demonstrated no clinical responses in 20 treated patients [4], while only one antitumor response was seen in 51 patients with advanced colorectal cancer in the cooperative group setting [21]. No responses were seen with R115777 administered as a single agent in 44 previously untreated patients with non-small-cell lung cancer [1]. Thus, identification of a clinically relevant target disease for this combination awaits further investigation.

In conclusion, we defined the MTD of the combination of R115777 given for 28 days out of 42 and weekly irinotecan to be 100 mg twice daily and 100 mg/m^2, respectively. It is not possible to dose-escalate R115777 further on this delivery schedule. As this is only 33% of

the single agent MTD of R115777, with lower exposure than that achieved with the alternative schedule from Verweij et al. [20], we cannot recommend our schedule for further study.

References

1. Adjei AA, Mauer A, Bruzek L, Marks RS, Hillman S, Geyer S, Hanson LJ, Wright JJ, Erlichman C, Kaufmann SH, Vokes EE (2003) Phase II study of the farnesyl transferase inhibitor R115777 in patients with advanced non-small-cell lung cancer. J Clin Oncol 21:1760–1766
2. Ajani JA, Baker J, Pisters PW, Ho L, Mansfield PF, Feig BW, Charnsangavej C (2002) CPT-11 plus cisplatin in patients with advanced, untreated gastric or gastroesophageal junction carcinoma: results of a phase II study. Cancer 94:641–646
3. Chabot GG (1997) Clinical pharmacokinetics of irinotecan. Clin Pharmacokinetic 33:245–259
4. Cohen SJ, Ho L, Ranganathan S, Abbruzzese JL, Alpaugh RK, Beard M, Lewis NL, McLaughlin S, Rogatko A, Perez-Ruixo JJ, Thistle AM, Verhaeghe T, Wang H, Weiner LM, Wright JJ, Hudes GR, Meropol NJ (2003) Phase II and pharmacodynamic study of the farnesyltransferase inhibitor R115777 as initial therapy in patients with metastatic pancreatic adenocarcinoma. J Clin Oncol 21:1301–1306
5. Crul M, de Klerk GJ, Swart M, van't Veer LJ, de Jong D, Boerrigter L, Palmer PA, Bol CJ, Tan H, de Gast GC, Beijnen JH, Schellens JH (2002) Phase I clinical and pharmacologic study of chronic oral administration of the farnesyl protein transferase inhibitor R115777 in advanced cancer. J Clin Oncol 20:2726–2735
6. Cunningham D, Pyrhonen S, James RD, Punt CJ, Hickish TF, Heikkila R, Johannesen TB, Starkhammar H, Topham CA, Awad L, Jacques C, Herait P (1998) Randomised trial of irinotecan plus supportive care versus supportive care alone after fluorouracil failure for patients with metastatic colorectal cancer. Lancet 352:1413–1418
7. de Forni M, Bugat R, Chabot GG, Culine S, Extra JM, Gouyette A, Madelaine I, Marty ME, Mathieu-Boue A (1994) Phase I and pharmacokinetic study of the camptothecin derivative irinotecan, administered on a weekly schedule in cancer patients. Cancer Res 54:4347
8. End DW, Smets G, Todd AV, Applegate TL, Fuery CJ, Angibaud P, Venet M, Sanz G, Poignet H, Skrzat S, Devine A, Wouters W, Bowden C (2001) Characterization of the antitumor effects of the selective farnesyl transferase inhibitor R115777 in vivo and in vitro. Cancer Res 61:131–137
9. Fuchs CS, Moore MR, Harker G, Villa L, Rinaldi D, Hecht JR (2003) Phase III comparison of two irinotecan dosing regimens in second-line therapy of metastatic colorectal cancer. J Clin Oncol 21:807–814
10. Gotlib J, Dugan K, Katamneni U, Sridhar K, Wright J, Thibault A, Ryback ME, Greenberg PL (2002) Phase I/II study of farnesyltransferase inhibitor R115777 (Zarnestra) in patients with myeloproliferative disorders (MPDs): preliminary results (abstract 14). Proc Am Soc Clin Oncol 21:4a
11. Haas N, Peereboom D, Ranganathan S, Thistle A, Greenberg R, Ross E, Lewis N, Wright J, Hudes G (2002) Phase II trial of R115777, an inhibitor of farnesyltransferase, in patients with hormone refractory prostate cancer (abstract 721). Proc Am Soc Clin Oncol 21:181a
12. Hudes G, Schol J, Baab J, Rogatko A, Bol C, Horak I, Langer C, Goldstein LJ, Szarka C, Meropol NJ, Weiner L (1999) Phase I clinical and pharmacokinetic trial of the farnesyltransferase inhibitor R115777 on a 21 day dosing schedule (abstract 601). Proc Am Soc Clin Oncol 18:156a
13. Ilson DH, Saltz L, Enzinger P, Huang Y, Kornblith A, Gollub M, O'Reilly E, Schwartz G, DeGroff J, Gonzalez G, Kelsen DP (1999) Phase II trial of weekly irinotecan plus cisplatin in advanced esophageal cancer. J Clin Oncol 17:3270–3275
14. Johnston SR, Hickish T, Ellis P, Houston S, Kelland L, Dowsett M, Salter J, Michiels B, Perez-Ruixo JJ, Palmer P, Howes A (2003) Phase II study of the efficacy and tolerability of two dosing regimens of the farnesyl transferase inhibitor, R115777, in advanced breast cancer. J Clin Oncol 21: 2492–2499
15. Karp JE, Lancet JE, Kaufmann SH, End DW, Wright JJ, Bol K, Horak I, Tidwell ML, Liesveld J, Kottke TJ, Ange D, Buddharaju L, Gojo I, Highsmith WE, Belly RT, Hohl RJ, Rybak ME, Thibault A, Rosenblatt J (2001) Clinical and biologic activity of the farnesyltransferase inhibitor R115777 in adults with refractory and relapsed acute leukemias: a phase I clinical-laboratory correlative trial. Blood 97:3361–3369
16. Miller AB, Hogestraeten B, Staquet M, Winkler A (1981) Reporting results of cancer treatment. Cancer 47:207–214
17. Noda K, Nishiwaki Y, Kawahara M, Negoro S, Sugiura T, Yokoyama A, Fukuoka M, Mori K, Watanabe K, Tamura T, Yamamoto S, Saijo N; Japan Clinical Oncology Group (2002) Irinotecan plus cisplatin compared with etoposide plus cisplatin for extensive small-cell lung cancer. N Engl J Med 346:85–91
18. Rougier P, Van Cutsem E, Bajetta E, Niederle N, Possinger K, Labianca R, Navarro M, Morant R, Bleiberg H, Wils J, Awad L, Herait P, Jacques C (1998) Randomised trial of irinotecan versus fluorouracil by continuous infusion after fluorouracil failure in patients with metastatic colorectal cancer. Lancet 352:1407–1412
19. Saltz LB, Cox JV, Blanke C, Rosen LS, Fehrenbacher L, Moore MJ, Maroun JA, Ackland SP, Locker PK, Pirotta N, Elfring GL, Miller LL (2000) Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. Irinotecan Study Group. N Engl J Med 343:905–914
20. Verweij J, Kehrer DFS, Planting ASTh, de Jonge MJA, Eskens F, Klaren A, De Heus G, Palmer PA, Bol CJ, Sparreboom A (2001) Phase I trial of irinotecan in combination with the farnesyl transferase inhibitor (FTI) R115777 (abstract 319). Proc Am Soc Clin Oncol 20
21. Whitehead RP, McCoy S, MacDonald J, Rivkin SE, Neubauer M, Dakhil S, Lenz HJ, Tanaka M, Abbruzzese JL (2003) Phase II trial of R115777 (NSC #70818) in patients with advanced colorectal cancer: a Southwest Oncology Group study (abstract 1092). Proc Am Soc Clin Oncol 22