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Phase III Trial of Gemcitabine Plus Tipifarnib Compared With Gemcitabine Plus Placebo in Advanced Pancreatic Cancer

E. Van Cutsem, H. van de Velde, P. Karasek, H. Oettle, W.L. Vervenne, A. Szawlowski, P. Schoffski, S. Post, C. Verslype, H. Neumann, H. Safran, Y. Humblet, J. Perez Ruixo, Y. Ma, and D. Von Hoff

From the University Hospital Gasthuisberg, Leuven; St Luc University Hospital, Brussels, Belgium; Masarykuv Oncol, Brno, Czech Republic; Charite Campus Virchow-Klinikum, Berlin; Hannover Medical School, Hannover; Mannheim University Hospital, Mannheim, Germany; Academic Medical Center, Amsterdam, the Netherlands; Cancer Center, Warsaw, Poland; KH St Veit, Austria; Brown University, Providence, RI; Johnson & Johnson Pharmaceutical Research & Development, Beerse, Belgium and Titusville, NJ; and Arizona Cancer Center, Tucson, AZ.

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Address reprint requests to Eric Van Cutsem, MD, PhD, Department Internal Medicine, University Hospital Gasthuisberg, Herestraat 49, 3000 Leuven, Belgium; e-mail: Eric.VanCutsem@uz.kuleuven.ac.be.

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ABSTRACT

Purpose
To determine whether addition of the farnesyltransferase inhibitor tipifarnib (Zarnestra, R115777; Johnson and Johnson Pharmaceutical Research and Development, Beerse, Belgium) to standard gemcitabine therapy improves overall survival in advanced pancreatic cancer.

Patients and Methods
This randomized, double-blind, placebo-controlled study compared gemcitabine + tipifarnib versus gemcitabine + placebo in patients with advanced pancreatic adenocarcinoma previously untreated with systemic therapy. Tipifarnib was given at 200 mg bid orally continuously; gemcitabine was given at 1,000 mg/m^2 intravenously weekly × 7 for 8 weeks, then weekly × 3 every 4 weeks. The primary end point was overall survival; secondary end points included 6-month and 1-year survival rates, progression-free survival, response rate, safety, and quality of life.

Results
Six hundred eighty-eight patients were enrolled. Baseline characteristics were well balanced between the two treatment arms. No statistically significant differences in survival parameters were observed. The median overall survival for the experimental arm was 193 *v* 182 days for the control arm ($P = .75$); 6-month and 1-year survival rates were 53% and 27% *v* 49% and 24% for the control arm, respectively; median progression-free survival was 112 *v* 109 days for the control arm. Ten drug-related deaths were reported for the experimental arm and seven for the control arm. Neutropenia and thrombocytopenia grade ≥ 3 were observed in 40% and 15% in the experimental arm versus 30% and 12% in the control arm. Incidences of nonhematologic adverse events were similar in two groups.

Conclusion
The combination of gemcitabine and tipifarnib has an acceptable toxicity profile but does not prolong overall survival in advanced pancreatic cancer compared with single-agent gemcitabine.

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INTRODUCTION

Advanced pancreatic cancer has few therapeutic options and a dismal prognosis. The vast majority of patients (80% to 90%) present with advanced surgically nonresectable disease.[1,2] Less than 2% of patients with pancreatic cancer survive 5 years. Patients presenting with locally advanced pancreatic cancer are either treated with chemoradiotherapy, generally a fluorouracil (FU)- or gemcitabine-based regimen,[3] or with gemcitabine alone.[4] For tumors with distant metastases, gemcitabine has become the standard of care after a small randomized trial showed a statistically significant improvement in cancer-related symptoms (23.8% *v* 4.8% clinical benefit response) and a modest improvement in overall survival (5.6 *v* 4.4 months) compared with a regimen that was FU-based.[4,5]

R115777 (tipifarnib) belongs to the class of farnesyltransferase inhibitors. Farnesyltransferase inhibitors competitively inhibit the enzyme farnesyl protein transferase (FPT), which catalyzes the addition of a 15-

carbon farnesyl isoprenoid moiety to the cysteine residue of the C-terminal CAAX-box of a variety of intracellular proteins including the Ras proteins. Historically, the Ras oncoproteins have been considered the target substrate responsible for the antiproliferative effects of FPT inhibition, given that farnesylation is a critical step in the membrane anchorage of Ras proteins required for Ras activity.[6] Because K-*ras* mutations are responsible for permanent activation of the K-ras oncoprotein (if membrane bound) and are found in 70% to 90% of pancreatic adenocarcinomas, inhibition of K-*ras* gene function through inhibition of farnesyl protein transferase conceptually seemed a rational target in pancreatic cancer research at that time.[6,7]

In preclinical models, R115777 has antiproliferative effects against pancreatic cancer cell lines at clinically relevant concentrations (concentration that inhibits 50% growth [IC_{50}] from 9.5 to $>$ 500 nmol/L) and displayed marked growth inhibition and antiangiogenic effects in a pancreatic cancer xenograft model.[8] In clinical phase I and II single-agent studies, prolonged oral administration of tipifarnib was well tolerated.[9-11] A phase I combination study of tipifarnib with gemcitabine defined an oral dose of 200 mg bid of tipifarnib in combination with the standard weekly regimen of gemcitabine (1,000 mg/m^2/wk) as the recommended dose for additional testing.[12] Myelosuppression and fatigue were the dose-limiting toxicities of the combination, and antitumor activity in pancreatic cancer (partial response, prolonged disease stabilization) was observed. No pharmacokinetic drug-drug interaction between tipifarnib and gemcitabine was documented. Importantly, inhibition of farnesylation of the surrogate protein HDJ-2 was documented in peripheral-blood mononuclear cells at the 200-mg bid recommended dose. The concept of inhibiting ras function through FPT inhibition in a K-*ras*–driven tumor type, together with the preclinical and early clinical indications of antitumor activity of tipifarnib and the tolerability of the combination of tipifarnib and gemcitabine, led to the design of the randomized trial described in this article. The objective of this trial was to test in a double-blind, placebo-controlled fashion whether the addition of tipifarnib to gemcitabine would improve the overall survival of patients with advanced pancreatic cancer.

PATIENTS AND METHODS

Patient Population

The trial included patients with pathologically confirmed, locally advanced, unresectable or metastatic adenocarcinoma of the pancreas. Patients who had received chemotherapy or other systemic therapy for pancreatic cancer were not eligible. Prior irradiation or chemoradiotherapy with FU was allowed if the treatment-free interval had been at least 3 months. Patients with a potential for curative surgical resection or with nonmeasurable disease according to the Response Evaluation Criteria in Solid Tumors Group criteria were not eligible. Adequate baseline bone marrow function (absolute neutrophil count [ANC] $\geq$ 1,500/μL, platelet count $\geq$ 100,000/μL), adequate baseline hepatic function (serum bilirubin $\leq$ 2.0 mg/dL, transaminase $\leq$ 5 $\times$ the upper limit of institutional normal), and adequate renal function (creatinine $\leq$ 1.5 mg/dL) were required. Patients with poor performance status (Eastern Cooperative Oncology Group performance status [ECOG PS] 3 or 4) or with uncontrolled or severe cardiovascular disease were not eligible.

The protocol was approved by the institutional review boards at each institution.

Patient Assignment

Signed informed consent was obtained from each patient before study entry. Within 2 weeks before random assignment, patients underwent a screening visit including medical history and previous cancer therapy evaluation, physical examination, ECG, ophthalmologic examination, quality-of-life measurements, and laboratory tests. Baseline computed tomography or magnetic resonance imaging of the abdomen and any other anatomic area affected by pancreatic cancer was performed within 14 days before study entry.

Before the start of treatment patients were centrally randomly assigned to receive tipifarnib + gemcitabine or placebo + gemcitabine through a dynamic randomization procedure with stratification on the basis of three factors: presence or absence of metastatic disease, PS (ECOG 0 *v* 1 *v* 2), and investigator site.

Treatment

Tipifarnib and placebo tablets were supplied by Johnson & Johnson Pharmaceuticals Research and Development (Beerse, Belgium) as 100-mg film-coated tablets. The starting dose was 200 mg bid administered orally in a continuous daily dosing schedule. Tablets were to be taken after a meal. Temporary interruption of the oral medication was required in the event of grade 3 thrombocytopenia lasting more than 5 days; grade 3 neutropenia lasting more than 7 days; grade 4 neutropenia or thrombocytopenia of any duration; or grade 3 or 4 nonhematologic toxicity (excluding nausea and vomiting that responded to symptomatic management). Oral medication was restarted at a lower dose level on recovery of the toxicity to grade 0 to 1. In the event of development of grade 1 or 2 neuropathy lasting for more than 7 days, the oral study medication was interrupted and was restarted at a lower dose level at week 2 or 3 if stabilization or improvement of the grade 1 or 2 neuropathy occurred. Two dose reductions (100 mg AM, 200 mg PM; 100 mg bid) of oral study medication were permitted. Treatment was discontinued for patients developing unacceptable toxicity after two dose reductions.

Gemcitabine (Gemzar; Eli Lilly) was administered at a starting dose of 1,000 mg/m^2 intravenously during 30 minutes weekly for 7 consecutive weeks with 1 week rest. Thereafter, gemcitabine was administered once weekly at the same dose for 3 consecutive weeks, followed by 1 week of rest. During a cycle gemcitabine dose was reduced to 75% of previously administered dose if ANC was 750 to 999/μL or platelets were 50,000 to 99,999/μL. For ANC less than 750/μL or platelets less than 50,000/μL, the dose was withheld and on recovery (ANC $>$ 1,000/μL and platelets $>$ 100,000/μL), drug administration was restarted at 75% of the previous dose. For nonhematologic toxicity grade 2 to 4, the dose was withheld and on recovery to grade 0 to 1, drug administration was restarted at 75% of the previous dose (for grade 2) or at 50% of the previous dose (for grade 3 to 4). Dose adjustments at the start of a new cycle of therapy were based on the worst toxicity observed

during the previous cycle of therapy and were relative to the starting dose of gemcitabine received in the previous cycle: if nadir ANC was less than 500/μL, platelets were less than 50,000/μL, or nonhematologic toxicity grade 3 was observed, the next cycle was to be given at 75% of the starting dose of the previous cycle; if grade 4 nonhematologic toxicity occurred, the next cycle was to be given at 50% of the starting dose of the previous cycle. Discontinuation from the study for toxicity-related treatment delay exceeding 3 weeks was mandatory.

Efficacy Evaluation

Four hundred sixty-seven death events were required to detect a hazard ratio of 1.36 with 90% power for a two-sided test with an overall 5% significance level. The median survival was assumed to be 5.5 months in the control arm and 7.5 months in the tipifarnib + gemcitabine arm. Six hundred sixty patients were to be accrued over 13 months, with a follow-up period of 7 months. The significance levels were adjusted for the interim analysis, and were controlled at the conventional 5% level by adjusting the significance level at the final analysis. The efficacy analyses were based on all randomly assigned patients and are presented by treatment arm as randomized.

Overall survival was calculated for all randomly assigned patients from the date of randomization to the date of death (intent-to-treat analysis). All alive patients were censored at the date of last contact. Treatment comparison of survival time was performed using a two-sided stratified log-rank test with two stratification factors: PS (ECOG 0 ν 1 ν 2) and presence or absence of metastatic disease. The survival probabilities over time were based on Kaplan-Meier estimates. The hazard ratio of placebo + gemcitabine compared with tipifarnib + gemcitabine and its 95% CI were estimated by using the stratified Cox regression model with treatment as the covariate and with the two stratification factors.

Important factors were identified using a stepwise Cox regression model, stratified for ECOG PS and presence of metastatic disease. The influence of these important factors on survival was then assessed by a Cox proportional hazards regression model, stratified for the stratification factors and with treatment and the prognostic factors as covariates.

Radiologic disease assessments by computed tomography scan or magnetic resonance imaging were performed at baseline, after cycle 1, and then after every two cycles until disease progression. Tumor response was evaluated according to the Response Evaluation Criteria in Solid Tumors Group unidimensional response criteria.[13] The overall best response was defined as the best response recorded from the start of the treatment until disease progression, recurrence, or the start of new therapy. To be assigned a status of partial response or complete response, changes in tumor measurements had to be confirmed by repeat assessments performed no less than 4 weeks after the criteria for response were first met. Duration of overall response estimated for responders only was defined as the period from the first day the criteria for complete or partial response were met to the progression date. Tumor response evaluations were done separately by the investigators and a central radiology reviewer, and afterward were reconciled by the sponsor's medical reviewer.

Progression-free survival was calculated for all randomly assigned patients from the date of random assignment until the date progressive disease was initially documented. For patients who died before the assessment of progression of their disease, the date of death was considered as the date of progression. Patients who did not progress or die were censored at their last disease assessment date. Patients who discontinued study treatment and did not progress at the start date of the first subsequent anticancer therapy were censored at the date of the last objective disease assessment before or on the first day of the first subsequent anticancer therapy. Analysis of progression-free survival was based on the reconciled response assessment. Treatment comparison was performed using the same analysis method as for overall survival.

Patient Benefit

The Functional Assessment of Cancer Therapy—Pancreas (FACT-Pa) quality of life questionnaire was completed at screening and at the start of every treatment cycle. The trial outcome index (TOI), a selection of the most disease-specific categories of FACT-Pa, was analyzed over time. This selection contains the questions on physical well-being, functional well-being, and pancreatic cancer–specific questions. A longitudinal analysis, taking the patient dropout rate into account, was performed on TOI, using all randomly assigned patients with a baseline TOI value.

ECOG PS was determined at baseline and at the start of every cycle. Time to deterioration in PS was calculated for all randomly assigned patients. Deterioration was defined as a worsening by at least one ECOG PS level from the previous best score, with confirmation of worsening in the next visit or followed by death or withdrawal from treatment. Patients who did not have deterioration and who did not die during treatment were censored at the last PS assessment date. Best changes in PS versus baseline were classified as improved, unchanged, or worsened.

Safety Evaluation

Physical examinations and clinical chemistry (including electrolytes, liver, and renal function tests) were performed at screening, at the beginning of every new cycle, and at treatment termination. CBCs were obtained at screening, every week during treatment, and at treatment discontinuation. Screening and end-of-treatment ECG and ophthalmological tests (history, slit lamp, funduscopy) were performed. All clinically relevant abnormalities were reported by the investigator as adverse events and graded according to National Cancer Institute Common Toxicity Criteria, version 2.0.

Incidences of adverse events were calculated for the entire population of treated patients. Time to and duration of the first occurrence of grade 3 to 4 adverse events were calculated for all treated patients who had such events. Deaths during treatment or within 30 days from the last study treatment administration were tabulated, as well as the cause of death.

Pharmacokinetics

A sparse sampling procedure was followed to characterize the pharmacokinetics of R115777. Venous plasma samples (5 mL) were drawn at days 1, 8, and 15 of cycle 1. Determination of plasma R115777 concentration used a validated high-pressure liquid chromatography–ultraviolet (Johnson and Johnson Pharmaceutical Research and Development) detection method (lower limit of quantification of $<$ 1 ng/mL).[10] A Bayesian estimation of the individual pharmacokinetic parameters of R115777 was implemented in NONMEM software (Globomax, Hanover, MD), using the POSTHOC option. The results of a previous population pharmacokinetic analysis of R115777 using data from six phase I trials were used as prior information to describe the time course of R115777 after oral and intravenous administration.[14] The pharmacokinetic model is a three-compartment disposition model,

with first-order elimination from a central compartment and sequential zero-order to first-order absorption process and lag time.

RESULTS

Patient Disposition and Baseline Characteristics

A total of 688 patients entered onto this trial at 126 investigational sites in 14 countries in North America, Europe, and Asia between November 1999 and February 2001. The complete list of participating investigators and their affiliations is presented in the Appendix. Three hundred forty-one patients were assigned to tipifarnib + gemcitabine group and 347 were assigned to gemcitabine + placebo group. Of these patients, 15 (nine and six, respectively) did not receive treatment. At the final analysis cutoff date of September 15, 2001, 188 patients (92 and 96 patients, respectively) were still alive and 40 patients (12 and 28, respectively) were still receiving treatment. Twenty-three patients (3%) were ineligible because of absence of histologic confirmation of pancreatic adenocarcinoma (12 patients), abnormal hepatic or renal function (eight patients), and previous systemic therapy for pancreatic cancer (one patient).

Patient characteristics are shown in Table 1. Forty-three percent of patients were female and 88% were white. The median age was 62 years (range, 29 to 89 years). Stratification factors (PS, disease stage) were evenly distributed between the two groups; 85% of the patients had an ECOG PS of 0 or 1, and 76% had metastatic disease (involving the liver in 81% of these patients). Baseline tumor-related symptoms (weight loss, tumor pain, and history of jaundice) were also well balanced between the two groups. The majority of the patients had abdominal or back pain at trial entry (77%) and had experienced weight loss of at least 10% in the last 6 months (56%); a history of jaundice was noted in 37% of the patients. Median time from initial diagnosis to random assignment was 1 month (range, 0 to 78 months).

Eighty-six patients (13%) had previously been treated with surgery (Whipple procedure or total pancreatectomy) and 25 patients (4%) had received radiation treatment. Prior therapy with FU as radiosensitizer had been given to 18 patients (3%).

Table 1. Baseline Characteristics

Patient Characteristic	% of Patients: Tipifarnib + Gemcitabine (n = 341)	% of Patients: Placebo + Gemcitabine (n = 347)
Female	43	42
Age, years		
Median	61	62
Range	29-89	30-88
ECOG		
0	27	28
1	57	59
2	16	13
Metastatic		
Any site	76	77
Liver	63	60
Lung	14	12
Peritoneum	13	14
Histologic degree of differentiation		
Well	7	8
Moderate	27	32
Poor	26	22
Tumor-related symptoms		
Weight loss > 10%	56	56
Tumor pain	76	78
Jaundice in last 6 months	38	37
Time from diagnosis, months		
Median	1	1
Range	0-61	0-78
Previous therapy		
Whipple procedure or pancreatectomy	14	11
Radiotherapy	4	4
FU radiosensitization	3	3

Abbreviations: ECOG, Eastern Cooperative Oncology Group performance status; FU, fluorouracil.

Treatment Duration and Dose-Intensity

Median duration of treatment was slightly shorter in the tipifarnib + gemcitabine group (85 days) than in the gemcitabine + placebo group (98 days). Most common primary reasons for treatment termination were disease progression (48% and 54%, respectively), drug-related adverse events (17% and 10%, respectively), non–drug-related adverse events (7% and 9%, respectively), and death during treatment (7% and 6%, respectively).

The median dose-intensity for gemcitabine was slightly lower in the experimental arm than in the control arm (667 *v* 718 mg/m^2/wk). Sixteen percent of patients in both arms had at least one gemcitabine cycle delayed; 47% of patients in the experimental arm and 40% of the patients in the control arm had at least one gemcitabine dose reduction.

The median dose-intensity for the continuous oral study medication was 378 mg/d on the experimental arm. Five percent of patients required at least one dose reduction of the oral tipifarnib medication.

Efficacy Results

Overall survival. At the time of the clinical cutoff, 500 patients had died; 249 patients (73%) in the tipifarnib + gemcitabine arm and 251 patients (72%) in the placebo + gemcitabine arm. The median overall survival was 193 days (95% CI, 176 to 218) for the experimental arm and 182 days (95% CI, 155 to 206) for the control arm (Table 2). There was no statistically significant difference in overall survival between the two treatment groups (hazard ratio for tipifarnib + placebo arm, 1.03;

Table 2. Efficacy Parameters

Efficacy	Tipifarnib + Gemcitabine (n = 341)	Placebo + Gemcitabine (n = 347)	*P*
Overall survival			
Median, days	193	182	.75
95% CI	176 to 218	155 to 206	
6-month survival, %	53	49	
1-year survival, %	27	24	
Progression-free survival			
Median, days	112	109	.72
95% CI	105 to 119	101 to 118	
Best response reconciled, %			
CR or PR	6	8	
Stable disease	53	52	
Progression	28	30	
Not assessable	13	10	
Time to PS deterioration, days	142	125	.50
95% CI	121 to 176	107 to 144	

Abbreviations: CR, complete response; PR, partial response; PS, performance status.

Table 3. Adverse Events and Laboratory Abnormalities

Adverse Event	Tipifarnib + Gemcitabine (n = 331)		Placebo + Gemcitabine (n = 342)	
	All (%)	Grade 3 to 4 (%)	All (%)	Grade 3 to 4 (%)
Anemia	97	20	97	16
Thrombopenia	78	15	66	12
Neutropenia	73	40	63	30
Nausea	58	7	58	8
Fatigue	47	11	42	12
Vomiting	43	7	48	9
Diarrhea	37	4	25	3
Fever	31	2	37	4
Hypokalemia	23	11	13	5
Rash	18	2	15	1
Peripheral neuropathy	17	2	9	0
Dehydration	16	6	10	5
Dyspnea	15	4	20	7
Creatinine elevation	10	1	13	2
Jaundice	8	4	11	6
Deep thrombophlebitis	8	7	7	6
Myalgia	5	< 1	7	< 1
Cardiac failure	2	2	3	2

95% CI, 0.86 to 1.23; stratified log-rank $P = .75$). The 6-month survival and 1-year survival rates also were similar in the two groups (53% *v* 49% for 6-month survival rate and 27% *v* 24% for 1-year survival rate for the experimental and control arm, respectively).

The median survival time was similar for the two arms in each of the stratification groups. In the subgroup of locally advanced patients, the median survival time in the experimental arm was 335 days (95% CI, 278 to 500) versus 264 days (95% CI, 217 to 345; $P = .2$) at the time of study analysis (when 55% of patients in this subgroup had died). Updated survival analysis 5 months later (when 73% of patients in this subgroup had died) indicated a median survival time of 318 days (95% CI, 278 to 383) in the experimental arm versus 264 days (95% CI, 217 to 340; $P = .89$) in the control arm.

In the majority of patients, disease progression was the primary cause of death (65% and 61%, respectively). Drug-related deaths were reported in 10 patients (3%) in the experimental arm and in seven patients (2%) in the control arm (see Safety Results).

Progression-free survival and tumor response. At the time of the clinical cutoff, 572 patients (83%) were reported with disease progression or death. On the basis of the reconciled tumor response assessment, the median progression-free survival time was 112 days in the experimental arm and 109 days in the control arm (hazard ratio tipifarnib + placebo arm, 1.03; 95% CI, 0.87 to 1.22; stratified log-rank $P = .72$; Table 2). In the subgroup of locally advanced disease, the median progression-free survival time was 202 days (95% CI, 157 to 226) versus 136 days (95% CI, 107 to 217; $P = .15$).

On the basis of the reconciled tumor response assessment, overall response rate was 6% and 8%, respectively, and disease stabilization rate was 53% and 52%, respectively (Table 2). The median duration of response was 147 days in the tipifarnib + gemcitabine arm (95% CI, 116 to 223) and 127 days in the placebo + gemcitabine arm (95% CI, 114 to 344). The median duration of stable disease was 166 days for the experimental arm and 163 days for the control arm.

Quality of life. Ninety-four percent of patients had at least one postbaseline PS evaluation and 47% of patients had at least two cycles of quality-of-life (FACT-Pa) assessments completed. Deterioration in ECOG PS score was noted in 136 patients (43%) in the tipifarnib + gemcitabine group and in 161 patients (49%) in the placebo + gemcitabine group. The median time to deterioration was 142 and 125 days, respectively ($P = .5$). The intergroup difference in evolution over time in quality of life (TOI) was less than 5 at any measured time point, with a numerically higher value for TOI in the placebo arm during the first four cycles and a numerically higher value for TOI in the tipifarnib arm afterward. This TOI difference is not deemed clinically relevant.

Safety Results

Adverse events were reported in 326 (98%) patients in the tipifarnib + gemcitabine group and in 338 (99%) patients in the placebo + gemcitabine group.

The incidence of hematologic toxicity was higher in the tipifarnib arm (Table 3). Grade 3 to 4 neutropenia was reported in 40% and was complicated by fever or infection

in 14% of patients in the experimental arm versus 30% grade 3 to 4 neutropenia and a 6% fever or infection complication rate in patients in the control arm. Incidence of grade 3 to 4 thrombocytopenia and anemia were similar (15% *v* 12% and 20% *v* 16%, respectively).

The incidences of nonhematologic adverse events or laboratory abnormalities were evenly distributed throughout the two treatment groups (Table 3), with the exception of diarrhea, dehydration, hypokalemia, and peripheral neuropathy. The difference in incidence of diarrhea (37% *v* 25%) and dehydration (16% *v* 10%) mainly was due to grade 1 to 2 adverse events. Peripheral neuropathy, mostly grade 1 to 2, was observed in 17% of patients in the tipifarnib arm and in 9% of patients in the control arm. Isolated occurrences of hemolytic-uremic syndrome (two patients in the experimental arm and three patients in the control arm) and pneumonitis (five patients in the experimental arm and six patients in the control arm) were reported.

Ten patients in the tipifarnib arm (five infection, two diarrhea, one hepatic failure, one dyspnea, and one sudden death) and seven patients in the control arm (two gastrointestinal bleeding or thrombocytopenia, two infection, one aortic clot, one pericardial effusion, and one myocardial infarction) died as a result of drug-related adverse events.

Prognostic Factor Analysis

Baseline patient and tumor characteristics were tested for difference in overall survival to identify prognostic factors beyond the two stratification factors (PS and disease stage).

In univariate analysis, a significantly lower risk was found for death in well- or moderately differentiated tumors (versus poorly differentiated tumors), in patients with primary tumor location in the pancreatic head (versus in the body or tail of pancreas), in patients with baseline albumin level $\geq$ 3.5 g/dL (versus $<$ 3.5 g/dL), and in patients with baseline hemoglobin level $\geq$ 10 g/dL (versus $<$ 10 g/dL; Table 4). A higher risk of death was found in the presence of more than 10% weight loss within 6 months before enrollment and in the presence of abdominal or back pain at baseline. There was a trend toward better survival for those patients with one metastatic site versus those with more than one metastatic site ($P = .06$) and for those patients who had previously undergone a Whipple resection ($P = .09$). No significant difference for overall survival was found in age, sex, or occurrence of jaundice within 6 months before enrollment.

The variables with prognostic significance in the univariate analysis were subsequently included in a stepwise Cox regression model. In multivariate analysis of all patients (regardless of disease status or degree of differentiation of the primary tumor), the following characteristics remained important positive prognostic factors for survival: absence of more than 10% weight loss within 6 months before enrollment, absence of abdominal or back pain at baseline, baseline albumin level more than 3.5 g/dL, and location of the primary tumor in the head of the pancreas. In addition, in metastatic patients, presence of multiple sites of metastasis was an important negative prognostic factor for survival.

Table 4. Univariate Analysis of Potential Prognostic Factors Associated With Survival

Variable	No. of Patients	Median Survival (days)	*P*	Hazard Ratio
Overall	688	186		
ECOG performance status				
0	188	264	$<$ .001	0.53
1-2	500	159		
Stage				
Locally advanced	164	315	$<$ .001	0.51
Metastatic	524	170		
Differentiation				
Well or moderate	256	209	$<$ .001	0.63
Poor	165	147		
Albumin $\geq$ 3.5 g/dL				
Yes	420	225	$<$ .001	0.64
No	242	114		
Hemoglobin $\geq$ 10 g/dL				
Yes	630	194	.002	0.62
No	55	112		
Primary tumor site				
Head of pancreas	441	202	.005	0.76
Body or tail of pancreas	220	153		
Weight loss				
No	275	229	.01	0.78
Yes	387	161		
Abdominal or back pain				
No	155	238	.02	0.76
Yes	532	177		
Whipple procedure				
Yes	76	229	.09	0.77
No	612	185		
Metastatic sites				
1 site	367	178	.06	0.81
$>$ 1 site	157	137		
Jaundice $<$ 6 months				
No	425	184	.39	1.09
Yes	256	193		
Age, years				
$<$ 65	436	192	.51	0.94
$\geq$ 65	252	186		
Sex				
Male	394	188	.56	0.95
Female	194	186		

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

The treatment group comparison showed no difference ($P = .47$) using the Cox regression model adjusting for these factors and stratified by the PS and presence of metastatic disease.

Pharmacokinetic Analysis

Population pharmacokinetic analysis of tipifarnib was performed on the basis of 1,056 plasma samples obtained

from 307 patients in the tipifarnib + gemcitabine arm. The mean systemic clearance is 20.66 L/h (standard deviation [SD], 3.16 L/h), whereas the mean of the area under the curve during 24 hours is 5.36 mg · h/L (SD, 2.67 mg · h/L). In steady-state, the mean plasma concentration of tipifarnib, defined as the area under the curve during 24 hours divided by 24 hours, was 689.78 nmol/L (range, 95.08 to 3873 nmol/L), which is above or within the range of concentrations that inhibit 50% of growth at which antitumor activity was observed in preclinical models in various tumor types, including pancreatic cancer. A 15.3% variability in systemic clearance was observed. Baseline characteristics, including baseline liver function tests, did not significantly affect the pharmacokinetics of tipifarnib.

DISCUSSION

Advanced pancreatic cancer has a poor prognosis and therapeutic options are limited. Gemcitabine has become the standard first-line therapy.[4] Recent attempts in randomized controlled trials to improve overall survival by either combining gemcitabine with FU[15] or by replacing gemcitabine by BAY12-9566[16] or marimastat[17] have not been successful. Despite its reported antitumor activity in other treatment-resistant tumor types such as relapsed or refractory acute myelogenous leukemia (AML),[18,19] breast cancer,[11] and glioblastoma, the farnesyltransferase inhibitor tipifarnib did not improve the survival of gemcitabine-treated pancreatic cancer patients.

All patient characteristics and baseline tumor-related symptoms were well balanced between the two groups in this study. Not only was there a similar distribution of the stratification factors (PS and disease stage), but other potentially important baseline characteristics (sex, age, and time since initial diagnosis) and disease-related symptoms (prior weight loss and jaundice, or tumor-related pain) were well balanced. Baseline characteristics of the patient population in this trial (slight male predominance, median age older than 60 years, predominantly metastatic disease, and presence of liver metastases in 62% of patients) were similar to the characteristics in other randomized trials studying gemcitabine in this patient population.[4,15-17] Only the incidence of baseline abdominal or back pain in this trial (77%) was lower compared with the original gemcitabine study performed by Burris et al[4] in which presence of tumor-related pain was a requirement for study entry.

The efficacy data of the gemcitabine arm in this trial are within the range of what has been observed in other randomized trials studying gemcitabine treatment[4,15-17]: the median overall survival of 182 days, the median progression-free survival of 109 days, and a response rate of 8% are consistent with previously reported data (164 to 195 days, 67 to 107 days, and 5.4% to 16%, respectively).

The toxicity profile observed in the gemcitabine arm also is similar to that reported in previous studies of gemcitabine in this patient population, and mainly consisted of hematologic toxicity (30% grade 3 to 4 neutropenia, 12% grade 3 to 4 thrombocytopenia), fever (37%), fatigue, moderate gastrointestinal side effects (nausea or vomiting, diarrhea), fluid retention, and isolated occurrences of hemolytic-uremic syndrome and pneumonitis. The incidence of skin rash (15%) and peripheral neuropathy (9%) in gemcitabine-treated patients was higher in this double-blind, placebo-controlled trial than in previous open-label studies.[4,20]

The tipifarnib + gemcitabine combination was well tolerated and allowed patients to maintain their PS. Myelosuppression, mainly consisting of reversible neutropenia, was the predominant side effect, as was predicted by previous experience with this combination.[12] The incidences of nonhematologic adverse events or laboratory abnormalities were evenly distributed throughout the two treatment groups, with the exception of low-grade diarrhea, dehydration, peripheral neuropathy, and hypokalemia. The difference in incidence of diarrhea and dehydration mainly was due to grade 1 to 2 adverse events, and therefore only partially explains the observed difference in hypokalemia.

Although farnesyltransferase inhibitors clearly can inhibit Ras farnesylation in vitro, and pancreatic cancer is a tumor type harboring a high incidence of K-*ras* mutations, tipifarnib did not increase the antitumor activity of gemcitabine. A potential explanation for this negative result might be the advanced disease stage of the patient population studied, which might overshadow the *ras* mutation effect. Three fourths of the patients entered onto the trial had metastatic disease, and in one fourth of the patients, multiple organs were affected by metastatic spread. In the subgroup of patients with locally advanced disease, a difference in median survival time was noted in favor of the tipifarnib + gemcitabine arm, which might suggest a potential benefit in patients with low tumor burden.

Alternatively, one can hypothesize that the antitumor activity of farnesyltransferase inhibition occurs irrespective of *ras* mutation status. This hypothesis is currently supported by both clinical and laboratory observations. In phase I and II clinical trials of single-agent tipifarnib, antitumor activity has been observed in tumor types in which mutated *ras* plays a marginal role, if any. In relapsed or refractory AML, a 32% response rate (including two patients with a complete response) was noted in a phase I trial with tipifarnib monotherapy[18] and none of these patients were reported to have *ras* mutations; this activity has been confirmed by data of a phase II trial of patients with relapsed AML, reporting seven of 42 patients with a reduction in bone marrow blasts to less than 5%.[19] Responses and hematologic remissions have also been observed in chronic myelogenous leukemia, myelodysplastic syndromes, multiple myeloma, and myeloproliferative diseases.[21-24] In solid tu-

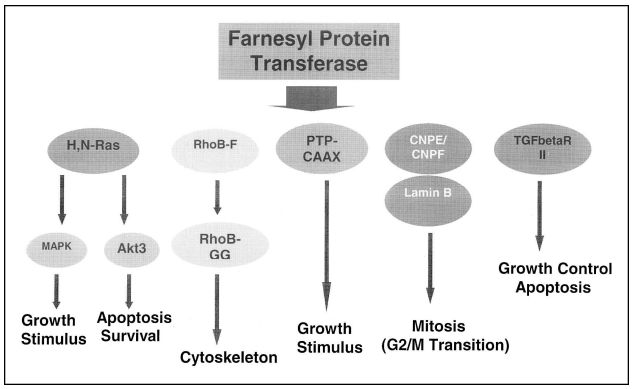

Fig 1. Multiple farnesylated intracellular proteins may contribute to the antiproliferative effects of farnesyl protein transferase inhibition. In addition to the Ras family of proteins, these targets include Rho-B and Rho-E, protein tyrosine phosphatase 4A (PTP4A)-1 and PTP4A-2, centromere-associated protein (CENP)-E and -F, and lamins. Inhibition of farnesylation of these different targets leads to different downstream effects. MAPK, mitogen-activated protein kinase; TGFbetaR, transforming growth factor beta receptor.

mors, single-agent antitumor activity in phase II has been seen in advanced breast cancer, with a 11% single-agent response rate and a 13% rate of disease stabilization for more than 6 months, irrespective of *ras* mutational status or of HER2 positivity, and in glioblastoma multiforme.[11]

Consistent with the observed ras-independent clinical activity of tipifarnib, alternative cellular targets of farnesyltransferase inhibition have been identified in preclinical experiments. Farnesylation inhibition of interesting candidate proteins might contribute to these observed antitumor properties; these proteins currently include RhoB, centromere-binding proteins E and F (CNP-E and CNP-F), lamin B, protein tyrosine phosphatase, and transforming growth factor beta receptor-II (Fig 1). Rho-B, a 21-kd G-protein that regulates receptor trafficking, has been implicated as the prenylated target of farnesyltransferase inhibitors by Prendergast et al.[25] RhoB can either be farnesylated or geranylgeranylated, and although farnesylated Rho-B promotes cellular transformation, geranylgeranylated Rho-B has the opposite effect. In the presence of farnesyltransferase inhibitors, RhoB would become exclusively geranylgeranylated and therefore be growth inhibitory. CENP-E and CENP-F are centromere-associated kinesin motors that play critical roles in mitosis; inhibition of farnesylation of CENPs would prevent their binding to microtubules and in this way contribute to the G_2/M arrest often observed with farnesyltransferase inhibitors. Other targets, including Rheb[26] and farnesylated proteins associated with the PI3-K/Akt-mediated cell survival pathway,[27] are also being investigated. There is a mounting volume of laboratory evidence that multiple relevant proteins beyond Ras determine the cellular responsiveness to farnesyltransferase inhibitors.

This 688-patient database constitutes one of the largest databases of clinical outcomes in advanced pancreatic cancer and therefore was further explored to identify relevant prognostic factors. The importance of PS and disease stage, already previously identified as prognostic factors in unresectable pancreatic cancer and used as stratification factors in this trial, was confirmed here.[28,29] In addition, weight loss, abdominal or back pain, baseline albumin level less than 3.5 g/dL, origin of primary tumor in body or tail of the pancreas, and multiple metastatic sites were identified as independent negative prognostic factors for survival. The worse prognosis of body or tail tumors had already been observed previously in the pancreatic cancer literature but was attributed to a lower likelihood of early diagnosis and resectability as a result of a later onset of obstructive jaundice or other clinical symptoms. In this advanced-disease trial, however, survival was calculated from the date of randomization, which occurred either when patients presented with unresectable disease or had a disease recurrence after previous surgery with curative intent. Therefore, alternative explanations can be hypothesized, such as a difference in tumor biology or a difference in metastatic spread pattern on the basis of the location of the primary tumor in the pancreas.

In conclusion, the combination of tipifarnib and gemcitabine is well tolerated but does not prolong overall survival in advanced pancreatic cancer compared with single-agent gemcitabine. In contrast, promising antitumor activity has been observed with this compound in AML, myelodysplastic syndromes, and breast cancer. Given the favorable toxicity profile as shown in this trial, additional development of tipifarnib in these tumor types seems warranted.

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Appendix

The appendix is included in the full-text version of this article, available on-line at www.jco.org. It is not included in the PDF (via Adobe® Acrobat Reader®) version.

Authors' Disclosures of Potential Conflicts of Interest

The following authors or their immediate family members have indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. Received more than $2,000 a year from a company for either of the last 2 years: H. van de Velde, J. Perez Ruixo, and Y. Ma, Johnson and Johnson Pharmaceutical and Research and Development.

REFERENCES

1. Rosewicz S, Wiedenmann B: Pancreatic carcinoma. Lancet 349:485-489, 1997

2. Cooperman AM: Pancreatic cancer: The bigger picture, in Cooperman AM, Chamberlain RS (eds): The Surgical Clinics of North America. Philadelphia, PA, Saunders, 2001, pp 557-574

3. Moertel CG, Frytak S, Hahn RG, et al: Therapy of locally unresectable pancreatic carcinoma: A randomized comparison of high dose (6000 rads) radiation alone, moderate dose radiation (4000 rads + 5-fluorouracil), and high dose radiation + 5-fluorouracil—The Gastrointestinal Tumor Study Group. Cancer 48:1705-1710, 1981

4. Burris HA III, Moore MJ, Andersen J, et al: Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: A randomized trial. J Clin Oncol 15:2403-2413, 1997

5. Van Cutsem E, Haustermans K, Van Steenbergen W: New treatment possibilities for pancreatic and biliary tumours. Ann Oncol 11: 165-169, 2000

6. Rowinsky EK, Windle JJ, Von Hoff DD: Ras protein farnesyltransferase: A strategic target for anticancer therapeutic development. J Clin Oncol 17:3631-3652, 1999

7. Butera J, Malachovsky M, Rathore R, et al: Novel approaches in development for the treatment of pancreatic cancer. Front Biosci 3:E226-E229, 1998

8. End DW, Smets G, Todd AV, et al: Characterization of the antitumor effects of the selective farnesyl protein transferase inhibitor R115777 in vivo and in vitro. Cancer Res 61:131-137, 2001

9. Zujewski J, Horak ID, Bol CJ, et al: Phase I and pharmacokinetic study of farnesyl protein transferase inhibitor R115777 in advanced cancer. J Clin Oncol 18:927-941, 2000

10. Crul M, De Klerk GJ, Swart M, et al: 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, 2002

11. Johnston SRD, Hickish S, Houston S, et al: Efficacy and tolerability of two dosing regimens of R115777 (Zarnestra), a farnesyl protein transferase inhibitor, in patients with advanced breast cancer. Proc Am Soc Clin Oncol 21:35a, 2002 (abstr 138)

12. Patnaik A, Eckhardt E, Itzbicka E, et al: A phase I and pharmacokinetic (Pk) study of the farnesyltransferase inhibitor, R115777 in combination with gemcitabine (Gem). Proc Am Soc Clin Oncol 19:2a, 2000 (abstr 5A)

13. Therasse P, Arbuck S, Eisenhauer E, et al: New guidelines to evaluate the response to treatment in solid tumors. J Natl Cancer Inst 92:205-216, 2000

14. Perez Ruixo J, Piotrovsky V, Cowan KH, et al: Population pharmacokinetic analysis of Zarnestra using data from phase I trials. Presented at XI Meeting of Population Approach Group in Paris, France, June 6-7, 2002

15. Berlin JD, Catalano P, Thomas JP, et al: Phase III study of gemcitabine in combination with fluorouracil versus gemcitabine alone in patients with advanced pancreatic cancer carcinoma: Eastern Cooperative Oncology Group Trial E2297. J Clin Oncol 20:3270-3275, 2002

16. Moore MJ, Hamm J, Dancey J, et al: Comparison of gemcitabine versus the matrix metalloproteinase inhibitor BAY 12-9566 in patients with advanced or metastatic adenocarcinoma of the pancreas: A phase III trial of the National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol 21:3296-3302, 2003

17. Bramhall SR, Schulz J, Nemunaitis J, et al: A double-blind placebo-controlled, randomised study comparing gemcitabine and marimastat with gemcitabine and placebo as first line therapy in patients with advanced pancreatic cancer. Br J Cancer 87:161-167, 2002

18. Karp JE, Lancet JE, Kaufmann SH, et al: Clinical and biologic activity of the farnesyltransferase inhibitor R115777 in adults with refractory and relapsed acute leukemias: A phase 1 clinical-laboratory correlative trial. Blood 97:3361-3369, 2001

19. Harousseau JL, Stone R, Thomas X, et al: Interim results from a phase II study of R115777 (Zarnestra) in patients with relapsed and refractory acute myelogenous leukemia. Proc Am Soc Clin Oncol 21:265a, 2002 (abstr 1056)

20. Storniolo AM, Enas NH, Brown CA, et al: An investigational new drug treatment program for patients with gemcitabine: Results for over 3000 patients with pancreatic carcinoma. Cancer 85:1261-1268, 1999

21. Cortes J, Albitar M, Thomas D, et al: Efficacy of the farnesyl transferase inhibitor R115777 in chronic myeloid leukemia and other hematologic malignancies. Blood 101:1692-1697, 2003

22. Kurzrock R, Cortes J, Kantarjian HM: Clinical development of farnesyltransferase inhibitors in leukemias and myelodysplastic syndrome. Semin Hematol 39:20-24, 2002

23. Gotlib J, Dugan U, Katamneni K, et al: Phase I/II study of farnesyltransferase inhibitor R115777 (Zarnestra) in patients with myeloproliferative disorders (MPDs): Preliminary results. Proc Am Soc Clin Oncol 21:4a, 2002 (abstr 14)

24. Alsina M, Overton R, Belle N, et al: Farnesyl transferase inhibitor FTI-R115777 is well tolerated, induces stabilization of disease and inhibits farnesylation and oncogenic/tumor survival pathways in patients with advanced multiple myeloma. Proc Am Assoc Cancer Res 43:1000, 2002 (abstr 4960)

25. Prendergast GC: Farnesyltransferase inhibitors define a role for RhoB in controlling neoplastic pathophysiology. Histol Histopathol 16:269-275, 2001

26. Tamanoi F, Kato-Stankiewicz J, Jiang C, et al: Farnesylated proteins and cell cycle progression. J Cell Biochem 37:64-70, 2001

27. Jiang K, Coppola D, Crespo NC, et al: The phosphoinositide 3-OH kinase/AKT2 pathway as a critical target for farnesyltransferase inhibitor-induced apoptosis. Mol Cell Biol 20:139-148, 2000

28. Cubiella J, Castells A, Fondevila C, et al: Prognostic factors in nonresectable pancreatic adenocarcinoma: A rationale to design therapeutic trials. Am J Gastroenterol 94:1271-1278, 1999

29. Ishii H, Okada S, Nose H, et al: Prognostic factors in patients with advanced pancreatic cancer treated with systemic chemotherapy. Pancreas 12:267-271, 1996