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## Phase I Trial of Tipifarnib in Patients With Recurrent Malignant Glioma Taking Enzyme-Inducing Antiepileptic Drugs: A North American Brain Tumor Consortium Study

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### A B S T R A C T

#### Purpose

To determine the maximum-tolerated dose (MTD), toxicities, and clinical effect of tipifarnib, a farnesyltransferase (FTase) inhibitor, in patients with recurrent malignant glioma taking enzyme-inducing antiepileptic drugs (EIAEDs). This study compares the pharmacokinetics and pharmacodynamics of tipifarnib at MTD in patients on and off EIAEDs.

#### Patients and Methods

Recurrent malignant glioma patients were treated with tipifarnib using an interpatient dose-escalation scheme. Pharmacokinetics and pharmacodynamics were assessed.

#### Results

Twenty-three assessable patients taking EIAEDs received tipifarnib in escalating doses from 300 to 700 mg bid for 21 of 28 days. The dose-limiting toxicity was rash, and the MTD was 600 mg bid. There were significant differences in pharmacokinetic parameters at 300 mg bid between patients on and not on EIAEDs. When patients on EIAEDs and not on EIAEDs were treated at MTD (600 and 300 mg bid, respectively), the area under the plasma concentration-time curve (AUC)<sub>0-12 hours</sub> was approximately two-fold lower in patients on EIAEDs. Farnesyltransferase inhibition was noted at all tipifarnib dose levels, as measured in peripheral-blood mononuclear cells (PBMC).

#### Conclusion

Toxicities and pharmacokinetics differ significantly when comparing patients on or off EIAEDs. EIAEDs significantly decreased the maximum concentration, AUC<sub>0-12 hours</sub>, and predose trough concentrations of tipifarnib. Even in the presence of EIAEDs, the levels of tipifarnib were still sufficient to potently inhibit FTase activity in patient PBMCs. The relevance of these important findings to clinical activity will be determined in ongoing studies with larger numbers of patients.

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### INTRODUCTION

Treatment of malignant glioma remains a major therapeutic challenge. Conventional chemotherapy adds little to surgical resection and radiotherapy. After primary treatment, patients with glioblastoma multiforme (GBM)

achieve a median survival of approximately 10 months,<sup>1</sup> with similarly limited response rates and relatively short durations of response in patients with recurrent GBM.<sup>2,3</sup> Only approximately 15% to 20% of patients seem to benefit from chemotherapy.<sup>4,5</sup> Neither single nor combination chemotherapy

for malignant glioma has been successful (see reviews of current treatment modalities).<sup>1,4,6,7</sup>

The heterogeneity of molecular pathways and control steps in glioma pathology make the neoplasia difficult to treat.<sup>8</sup> However, our enhanced understanding of the biology of malignant gliomas provides a new opportunity to investigate agents that target the disrupted cellular mechanisms of the malignant glial cell.

A logical therapeutic target for malignant glioma is the enzyme farnesyltransferase (FTase). Farnesylated proteins are active in numerous signaling pathways that lead to division of normal cells and to malignant transformation of cancer cells.<sup>9</sup> Many signal transduction proteins associated with tumorigenesis require FTase-mediated post-translational modifications.<sup>10</sup> FTase inhibitors (FTIs) were developed to target abnormal signaling pathways commonly activated in neoplasia. Inhibitory mechanisms include antiproliferative, antiangiogenic, and pro-apoptotic effects.

One protein involved in malignant transformation that requires farnesylation for activation of its signaling pathways is Ras, a small guanosine triphosphatase (GTPase).<sup>11</sup> Many human cancers, including those of brain origin, overexpress several growth factor receptors that depend on Ras signaling.<sup>11</sup> Indeed, amplification of epidermal growth factor receptor and the angiogenic factor vascular endothelial growth factor can lead to downstream Ras activation. These factors are implicated in the pathogenesis of malignant astrocytomas.<sup>11-13</sup>

Although FTIs were originally developed to target those human cancers that depend on Ras for malignancy, subsequent studies showed that FTIs act via both Ras-dependent and Ras-independent mechanisms. Several studies showed that FTIs decreased proliferation in some tumor cell lines that harbor wild-type Ras with no mutations including glioma.<sup>14-16</sup> Moreover, FTIs proved not only to be cytostatic but also, under some circumstances, to cause tumor regression.<sup>15,17,18</sup> Thus, FTIs seem to act against a wide variety of both *ras* and non-*ras* tumor types. Recent evidence indicates that more than 60% of human tumor cell lines demonstrate some sensitivity to FTIs.<sup>15</sup>

FTIs present a new therapeutic modality. They possess a unique mechanism of action, can affect multiple tumor-promoting pathways, and have shown efficacy in *in vivo* animal models with human brain tumors implanted intracranially.<sup>19,20</sup> Tipifarnib (R115777, Zarnestra; Johnson & Johnson Pharmaceutical Research & Development LLC, Titusville, NJ) is a potent and selective nonpeptidomimetic FTI. In pharmacokinetic studies, tipifarnib has demonstrated oral bioavailability with dose-proportional pharmacokinetics.<sup>21,22</sup> Investigations are currently underway to determine the ability of tipifarnib to cross the blood-brain barrier. However, the blood-brain barrier is often altered in patients with malignant glioma, and it is likely that this small molecule could penetrate it, at least in this circumstance.<sup>23</sup>

In phase I and II clinical trials, tipifarnib has demonstrated single-agent responses in a variety of malignancies.<sup>24-29</sup> In addition to displaying antitumor activity, the drug was generally well tolerated.

Tipifarnib undergoes both phase I (oxidative) and phase II (conjugative) metabolism in the liver. The principle metabolite in humans is tipifarnib glucuronide.<sup>30</sup> Biliary excretion and fecal elimination is the main route of elimination of tipifarnib and metabolites.<sup>30</sup> Less than 17% of the oral tipifarnib dose is excreted in the urine as the glucuronide conjugate, and less than 0.1% is excreted unchanged.<sup>21</sup> A large majority of glioma patients are treated with enzyme-inducing antiepileptic drugs (EIAEDs), which can induce the activity of uridine diphosphate–glucuronosyltransferases (UGT) and cytochrome P450 mixed-function oxidase in the liver<sup>31</sup> and GI tract,<sup>32</sup> as well as other tumors.<sup>33</sup> Consequently, patients receiving EIAEDs show decreased plasma levels of several chemotherapeutic drugs administered at conventional doses.<sup>34-36</sup> Induction of hepatic enzymes can alter the pharmacokinetics of these agents, which may lead to ineffective dosing.<sup>37-39</sup> Notably, EIAEDs reduced the area under the plasma concentration–time curve (AUC) values of irinotecan by 1.5-fold compared with those values obtained in malignant glioma patients not taking EIAEDs.<sup>40</sup>

The well-known drug-drug interactions attributable to EIAEDs and the resultant alterations in the pharmacokinetics of several anticancer agents were the basis for this clinical study. The investigation of tipifarnib interaction with EIAEDs in the treatment of glioma patients was a key focus of this trial.

A phase I study was performed to determine the dose-limiting toxicity (DLT), the maximum-tolerated dose (MTD), and the pharmacokinetic and pharmacodynamic parameters of oral administration of tipifarnib twice a day in patients taking EIAEDs. Because EIAEDs are known to affect metabolic enzymes that are known to act on tipifarnib, it was predicted that the plasma levels of the metabolic enzymes would be affected. Whether this affects the ability of tipifarnib to inhibit its target FTase and the DLT of tipifarnib is critical. Additionally, the pharmacokinetic and pharmacodynamic data were compared with the data of a companion study in patients not receiving EIAEDs who were administered a fixed dose of tipifarnib 300 mg bid for the first 21 days of each 28-day cycle.

## PATIENTS AND METHODS

### Patient Population

Eligible patients were  $\geq 18$  years of age with confirmed diagnosis of progressive or recurrent malignant glioma with measurable imaging disease. Typical limitations<sup>41</sup> were used regarding number of prior therapies, time elapsed since last prior therapy, Karnofsky performance status, and laboratory values. Patients

were excluded from the study if they had significant existing medical problems, were pregnant or breast feeding, or were taking proton pump inhibitors.

The protocol and informed consent were approved by the local institutional review board at each participating institution. All patients reviewed, signed, and provided written informed consent before enrollment.

**Stratification**

All phase I patients were considered in group B and were taking one or more of the following EIAEDs: carbamazepine, oxcarbazepine, phenytoin, fosphenytoin, phenobarbital, or primidone. Patients in group B received an EIAED while on protocol. Patients who switched from a non-EIAED to an EIAED before enrollment had to receive the EIAED for a minimum of 2 weeks (Table 1).

**Study Design**

This phase I trial was designed to establish the MTD for tipifarnib in patients taking EIAEDs, define the safety and pharmacokinetic profile of tipifarnib twice a day in the patient population, assess antitumor activity against recurrent or progressive malignant glioma, and assess FTase inhibition in peripheral-blood monocytes as a biomarker of effective biologic activity.

**Dosing**

Tipifarnib was supplied by the National Cancer Institute (Bethesda, MD) as 100-, 200-, and 300-mg tablets. On day 1 (course 1 only), all patients received a single oral dose of tipifarnib immediately after a meal, followed from day 2 through day 21 by the appropriate dose twice daily. Patients taking EIAEDs (group B) participated in the dose-escalation component of the study for determination of MTD and DLT. Dose escalation was performed in cohorts of three patients beginning at a starting dose of tipifarnib 300 mg bid for 21 days followed by 7 days off the drug. This cycle was repeated every 28 days. If the first group of three patients did not experience DLT, a subsequent group of three additional patients was enrolled, and the dose was increased by 100 mg bid. If one patient experienced DLT, three more patients were added at that dose. The MTD was defined as the dose at which  $\leq$  one in six patients experienced a DLT and at which the next higher dose exceeded that limit. DLT was determined over the first 4 weeks of treatment. The pharmacokinetic and pharmacodynamic data

from these patients were compared with pharmacokinetic and pharmacodynamic data obtained from a separate group of patients not taking EIAEDs who received a fixed dose of tipifarnib 300 mg bid for the first 21 days of each 28-day cycle.

**Patient Evaluation**

Pretreatment evaluation included a medical history and physical examination. Baseline tumor measurements by magnetic resonance imaging (MRI)/computed tomography were obtained within 14 days before study entry. Baseline hematology and chemistries were obtained within 7 days of initiation of therapy and before the start of each cycle. Complete physical examinations were performed at each cycle. Hematology tests were obtained weekly throughout the course of treatment. Serum chemistries were obtained before each cycle, and MRI was performed every other cycle to assess response.

Patients with stable or responding disease received the same dose of tipifarnib at the next cycle or a reduced dose if adverse events were observed in the current cycle. If a patient experienced a DLT, the dose on the subsequent cycle was reduced by one dose level (ie, by 100 mg bid).

DLT was evaluated according to the National Cancer Institute Common Toxicity Criteria version 2. DLT was defined as any grade 4 hematologic toxicity, any nonhematologic grade 3 toxicity, or failure to recover from toxicities within 2 weeks from the last dose of study drug (ie, patient became ineligible for re-treatment with the study drug within 2 weeks of the last dose).

Patients assigned to a treatment cohort remained at the assigned dose level until tumor progression, or unacceptable toxicity, or patient request. Patients were removed from the study if MRI determination indicated tumor progression. Progression was defined as a 25% increase in the sum of the products of all measurable disease over the smallest sum observed, clear worsening of any assessable disease, or the appearance of any new lesion. Failure to return for evaluation because of death or deteriorating condition was considered to represent progression.

Complete response was defined as the complete disappearance of all measurable and assessable disease. Complete responders could not be taking corticosteroids, except as needed for physiologic maintenance. Patients demonstrating a partial response received the same or decreasing doses of dexamethasone and showed stable or improved neurologic examinations. A  $\geq$  50% decrease compared with baseline in the sum of the products of perpendicular diameters of all measurable lesions was considered a partial response. An assessment of stable disease or no response was given to those patients with a tumor status that did not qualify for complete response, partial response, or progression for a minimum of 12 weeks.

**Pharmacokinetic Evaluation**

Blood samples (5 mL) were collected in heparin (Na or Li) –containing, nonseparator tubes by venipuncture (heparin lock) or by central venous catheter, if in place. At the time of sampling, the first 1 mL of blood was discarded before drawing the 5-mL sample. Samples were obtained before administration of tipifarnib and at 0.5, 1, 1.5, 2, 3, 5, 8, 12, and 24 hours after administration of a single oral dose immediately after a meal on day 1 of cycle 1. Blood samples for trough levels were also drawn on days 8 and 22.

Blood samples were kept on ice and centrifuged within 30 minutes at 3,000 rpm for 10 to 15 minutes. Plasma was frozen and shipped to Johnson & Johnson Pharmaceutical Research and Development (Beerse, Belgium). Quantitative analyses were performed using a validated liquid chromatography method with

**Table 1.** Study Schema

Group A
Not taking EIAEDs
Fixed dose: tipifarnib 300 mg bid
Determination of PFS at 6 months
Considered part of phase II component of current trial
Group B
Taking EIAEDs
Escalating doses of tipifarnib starting at 300 mg bid
Determination of DLT
Determination of MTD
Patients receiving MTD dose considered part of phase II component of current trial
Abbreviations: DLT, dose-limiting toxicity; EIAEDs, enzyme-inducing antiepileptic drugs; MTD, maximum-tolerated dose; PFS, progression-free survival.

tandem mass spectrometry (lower limit of quantification, < 2 ng/mL), as previously published.<sup>21</sup>

The pharmacokinetic parameters for tipifarnib were characterized by standard noncompartmental methods. The time intervals relative to the oral administration of tipifarnib and the actual sample times were used for the determination of time to peak concentration and the AUC. Peak concentrations ( $C_{max}$ ) were determined by inspection of each individual's plasma concentration versus time curve. Trough levels represent concentrations obtained just before oral administration on days 8 and 22. Elimination rate constants were estimated by linear regression of the last three to four data points on the terminal log linear portion of the concentration-time curve. Elimination half-lives were calculated by dividing 0.693 by the elimination rate constants. The  $AUC_{0-12 \text{ hours}}$  was calculated using the linear trapezoidal rule. The  $AUC_{0-\infty}$  was calculated by trapezoidal summation to the last measurable data point and then extrapolated to infinity.

Pharmacokinetic parameters are reported as mean values  $\pm$  standard deviations. The relationship between the administered dose of tipifarnib and AUCs was analyzed by Spearman's correlation coefficient and linear regression analysis. Differences in the kinetic parameters between groups A and B at tipifarnib 300 mg were evaluated by an unpaired two-tailed *t* test. Two-tailed probability values of  $P \leq .05$  were regarded as statistically significant.

### Laboratory Correlative Studies

Blood samples (8 mL) for determination of FTase activity were collected in Becton Dickinson (Mountain View, CA) mononuclear-cell preparation tubes provided before dosing on days 1, 8, and 21. S.M.S. (H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL) was responsible for the analyses. Peripheral-blood mononuclear cells (PBMCs) were separated and prepared for Western blotting. Postmicrosomal supernatants were collected and assayed for FTase and the closely related enzyme geranylgeranyltransferase (GGTase I) activity. The ability of FTase and GGTase I to transfer [<sup>3</sup>H]farnesyl and [<sup>3</sup>H]geranylgeranyl from [<sup>3</sup>H]farnesyl pyrophosphate (FPP) and [<sup>3</sup>H]geranylgeranyl pyrophosphate (GGPP) to recombinant H-Ras-CVLS and H-Ras-CVIL, respectively, was determined as described previously.<sup>28,42</sup> To determine the effects of tipifarnib on protein prenylation, membranes were probed with an antibody (MS-225; Lab-Vision Corp/Neomarkers Inc, Fremont, CA) against HDJ-2, an exclusively farnesylated protein, or with an antibody (SC-65; Santa Cruz Biotechnology, Santa Cruz, CA) against Rap1, a protein that is only geranylgeranylated.

### Statistical Considerations

The primary end points for the tipifarnib dose-escalation phase I study were toxicity and pharmacokinetics, which were then used to define a recommended phase II dose. The dose for patients receiving EIAEDs was escalated as described, and DLT, MTD, and safety were evaluated.

Using the dose-escalation scheme described, the probabilities of escalating to the next dose level, based on the true rate of DLT at the current dose, are listed in Table 2. Thus, if the true underlying

Probability	True Toxicity at a Given Dose Level					
	10%	20%	30%	40%	50%	60%
Probability of escalating	0.91	0.71	0.49	0.31	0.17	0.08

proportion of DLTs was 50% at the current dose, there was a 17% chance of escalating to the next dose.

## RESULTS

### Patient Characteristics

A total of 25 patients taking EIAEDs, including phenobarbital, phenytoin, and carbamazepine, were enrolled onto the study from June 2000 to April 2001 (group B). Patient characteristics are listed in Table 3. The safety population ( $n = 23$ ), which comprised 15 men and eight women, had a median age of 46 years (range, 24 to 74 years) and a median Karnofsky performance score of 80 (range, 60 to 90). The majority of assessable patients (13 of 23 patients) had a diagnosis of recurrent GBM at enrollment. Of the other 10 patients, there were six with anaplastic astrocytoma, two with anaplastic oligodendroglioma, one with gliosarcoma, and one with mixed glioma. All patients had prior surgery and radiation therapy. One or more prior chemotherapy regimens were used in 21 patients; nine patients received one prior regimen, and 12 patients received two prior regimens. The two remaining patients in the safety population had received no prior chemotherapy.

**Table 3.** Patient Characteristics for Patients Taking EIAEDs (group B)

Baseline Characteristic	No. of Patients (N = 25)	%
<b>Age, years</b>		
Median	46	
Range	23-73	
<b>Assessability status</b>		
Nonassessable*	2	8
Toxicity only	4	16
Response and toxicity	19	76
<b>Sex</b>		
Male	8	34.8
Female	15	65.2
<b>Performance score</b>		
90	10	43.5
80	5	21.7
70	6	26.2
60	2	8.7
<b>Histology</b>		
Anaplastic astrocytoma	6	26.1
Anaplastic oligodendroglioma	2	8.7
Mixed glioma, anaplastic	1	4.3
Glioblastoma multiforme	13	56.5
Gliosarcoma	1	4.3
<b>Prior chemotherapy</b>		
1 regimen	9	
2 regimens	12	
No prior therapy	2	

Abbreviation: EIAEDs, enzyme-inducing antiepileptic drugs.

\*Patients enrolled but not treated with study drug.

**Table 4.** Cycle 1 Adverse Events for Patients Taking EIAEDs (group B)

Adverse Event	No. of Adverse Events by Grade			No. of Adverse Events
	Grade 1	Grade 2	Grade 3	
<b>Hematologic</b>				
Anemia	9			9
Granulocytopenia	4	3		7
Leukopenia	4	3		7
Lymphocytopenia		1		1
Thrombocytopenia	5			5
<b>Nonhematologic</b>				
Abdominal pain	1			1
Anorexia		1		1
Consciousness level depressed	1			1
Constipation		1		1
Diarrhea	9			9
Euphoria	3			3
Fatigue	5	3		8
Headache	2	1	1	4
Hiccups	1			1
Hyperglycemia	1			1
Insomnia	1			1
Muscle weakness	1			1
Nausea alone	5	3		8
Sensory	1			1
Skin rash	1	2	4	7
Vomiting	2	1		3

Abbreviation: EIAEDs, enzyme-inducing antiepileptic drugs.

Of the 25 patients on EIAEDs, two received no study drug, and four were not assessable for response with MRI (two patients had DLT, one refused further therapy, and

one had an intercurrent illness) but were assessable for toxicity. The other 19 patients were assessable for both response and toxicity.

**Toxicity**

Tipifarnib doses for group B ranged from 300 to 700 mg bid. Hematologic toxicity within this dose range was mild to moderate, consisting primarily of grade 1 and 2 anemia, granulocytopenia, leukopenia, and thrombocytopenia. Grade 3 toxicities were nonhematologic and consisted of skin rash, headache, and fatigue. Grade 3 rash occurred in two of six patients receiving tipifarnib 700 mg bid and in one of six patients receiving tipifarnib 600 mg bid. No other grade 3 toxicity attributable to study drug was seen, and there were no grade 4 toxicities. The measles-like rash, which was similar to that observed with phenytoin, was the DLT. The MTD for patients receiving EIAEDs was defined as 600 mg bid. Table 4 lists all adverse events observed during cycle 1 of therapy that were considered possibly, probably, or likely related to tipifarnib treatment. Because of the limited number of adverse events, determining the correlation of drug pharmacokinetics with toxicities was not possible.

**Response**

Although the primary objectives of this study did not include evaluation of response, response to tipifarnib therapy was determined. At the time of this report, all assessable patients had progressed, and only one patient has survived. No objective responses were seen in the phase I component of this trial. Two patients had stable disease for more than 6 months (anaplastic oligodendroglioma and GBM), and one patient had GBM for more than 1 year. The median

**Table 5.** Pharmacokinetic Parameters

Pharmacokinetic Parameters of Tipifarnib (day 1 single dose)	Group A,		Group B									
	300 mg*		300 mg		400 mg		500 mg		600 mg		700 mg	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
No. of patients	24		4		3		4		6		6	
t <sub>max</sub> , hours	2.34	1.16	2.50	0.58	2.17	0.76	2.75	1.71	2.25	1.54	2.00	0.55
C <sub>max</sub> , ng/mL	634	374	143	74.8	448	230	342	342	451	143	377	160
t <sub>1/2</sub> , hours†	3.66	1.18	3.03	1.77	3.61	0.70	2.49	0.75	3.08	1.47	3.50	1.73
AUC <sub>0-12hr</sub> , µg · h/mL	3.35	1.85	0.55	0.21	1.23	0.53	1.29	1.00	1.73	0.75	1.44	0.56
AUC, µg · h/mL	3.8	2.17	0.66	0.30	1.32	0.54	1.46	1.29	1.98	0.43	1.55	0.60
Cl/F, L/h	109	64.2	564	337	343	150	561	390	316	80	547	312
Day 8 trough, ng/mL												
Mean	110		12		36		20		55		32	
Range	3-434		7-15		5-69		11-27		27-125		23-43	
Day 22 trough, ng/mL												
Mean	112		11		25		30		49		31	
Range	8-670		8-17		10-49		3-71		14-103		28-33	

Abbreviations: AUC, area under the plasma concentration-time curve; Cl/F, relative clearance; C<sub>max</sub>, maximum drug concentration; t<sub>1/2</sub>, half-life; t<sub>max</sub>, time to peak concentration; SD, standard deviation.

\*Group A comprises patients not receiving enzyme-inducing antiepileptic drugs.

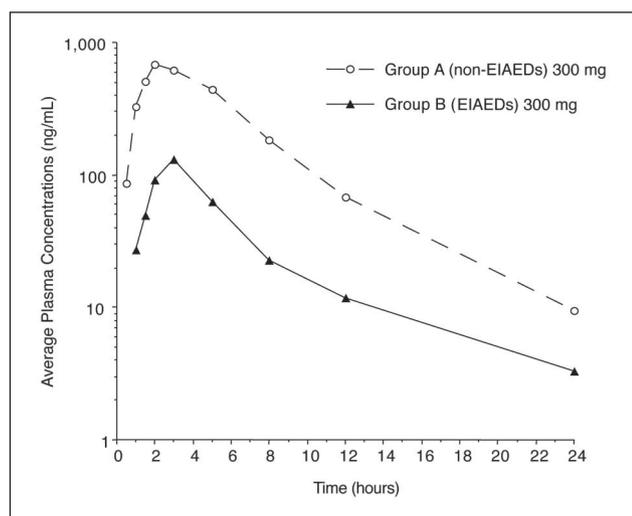
†Harmonic mean.

progression-free survival time for assessable patients was 7 weeks.

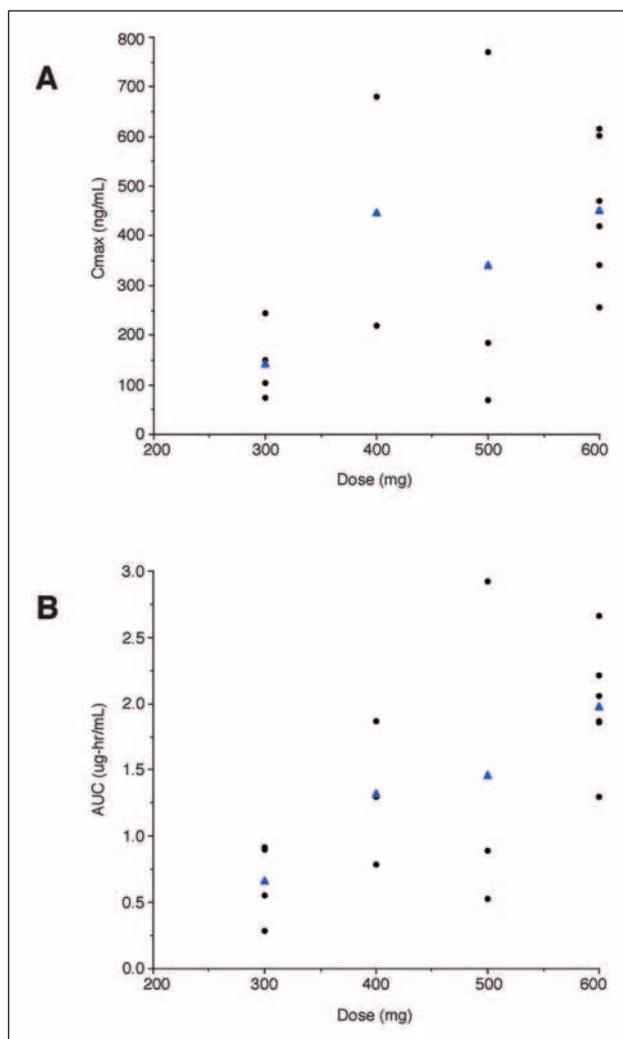
### Pharmacokinetic Results

The pharmacokinetic parameters at day 1 for patients in groups A and B receiving a single dose of tipifarnib 300 mg are listed in Table 5. No differences in time to peak concentration or mean harmonic half-lives were seen ( $P > .05$ ).  $C_{max}$  values were 4.4-fold lower in group B (ie, patients taking EIAEDs) than in group A patients ( $P < .05$ ). Trough concentrations differed significantly as well. Predose trough concentrations obtained on days 8 and 22 were nine- and 10-fold lower, respectively, in patients taking EIAEDs ( $P < .05$ ). Figure 1 compares representative mean plasma  $C_{max}$  versus time for four randomly selected group A patients and the four group B patients who received tipifarnib 300 mg. The plasma  $C_{max}$  at each time point were lower in group B compared with group A.

The  $AUC_{0-12 \text{ hours}}$  and AUC values between the two patient groups also differed significantly. Patients in group B had  $AUC_{0-12 \text{ hours}}$  and AUC values approximately six-fold lower than group A patients. Pharmacokinetic parameters also differed at the MTD. At 600 mg bid, the  $AUC_{0-12 \text{ hours}}$  for group B patients was approximately two-fold lower than the  $AUC_{0-12 \text{ hours}}$  at the 300-mg dose level in group A patients. Dose-proportional increases in  $C_{max}$  and AUC values of tipifarnib for the group B patients were observed from 300 to 600 mg (Fig 2). However, there was a wide interpatient variation for the  $C_{max}$  and AUC values for both group A and B patients. At the 600-mg dose level (MTD, group B patients), there was a 5.8- and 2.4-fold difference in the range for  $C_{max}$  (0.43 to 2.51 ng/mL) and  $AUC_{0-12 \text{ hours}}$  (255 to 615  $\mu\text{g} \cdot \text{hr/mL}$ ), respectively. There was no apparent relationship between dose (300 to 700 mg) and tipifarnib



**Fig 1.** Tipifarnib mean plasma concentrations versus time curve for group A (○) and group B (▲) patients at the 300-mg dose level. EIAEDs, enzyme-inducing antiepileptic drugs. Ave, average.

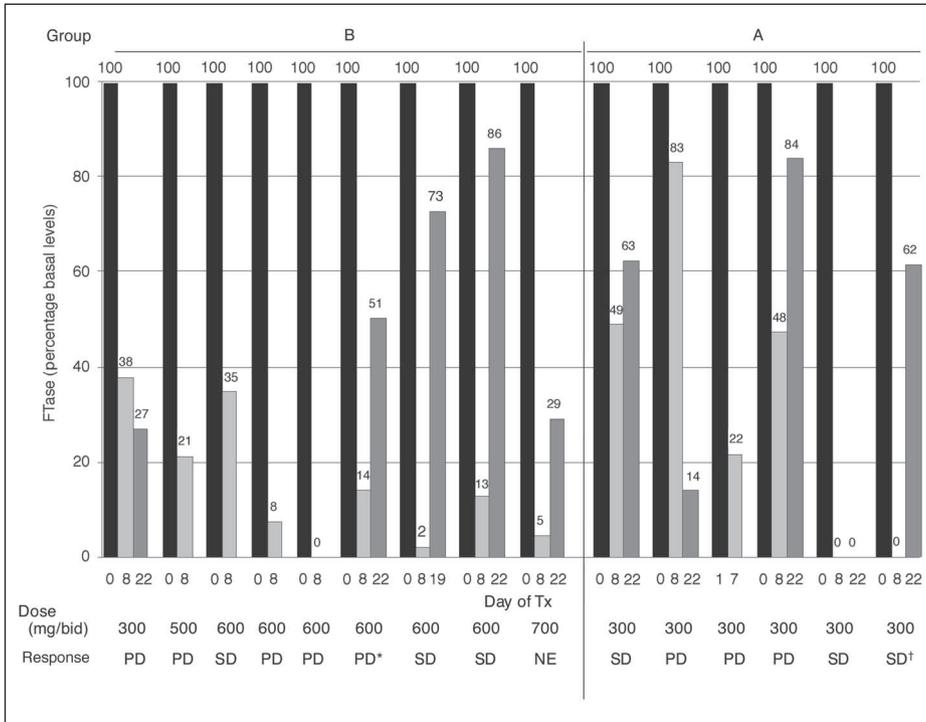


**Fig 2.** Relationship between dose of tipifarnib and (A) peak concentration ( $C_{max}$ ) and (B) area under the plasma concentration-time curve (AUC) in patients receiving enzyme-inducing antiepileptic drugs. Day 1 individual values (○) and mean values (▲) after oral administration of tipifarnib over the dose range of 300 to 600 mg are shown.

clearance ( $P > .20$ ). Inpatient variation in predose trough concentrations on days 8 and 22 was minimal.

### Analysis of FTase Enzyme Activity

Because EIAEDs significantly decreased  $C_{max}$ ,  $AUC_{0-12 \text{ hours}}$ , and predose trough concentrations, we sought to determine whether this decrease translated into a decrease in the ability of tipifarnib to inhibit its biochemical target. To this end, PBMCs were prepared from the blood of patients before tipifarnib treatment as well as on days 8 and 22 after treatment initiation. Figure 3 shows that treatment with tipifarnib resulted in potent (up to 100%) inhibition of FTase enzymatic activity. In most patients, the percentage of inhibition of FTase on day 22 (the first day of the off week) was lower than on day 8 after initiation of treatment, indicating that inhibition of FTase is reversible. It is important to note



**Fig 3.** Farnesyltransferase (FTase) inhibition and relationships to dose and response. FTase activity was potently inhibited in patients with progressive disease (PD; \*) and patients with stable disease (SD; †). Inhibition was observed at all doses. Similar inhibition levels were seen with patients both on and off enzyme-inducing antiepileptic drugs. NE, not assessable; Tx, treatment.

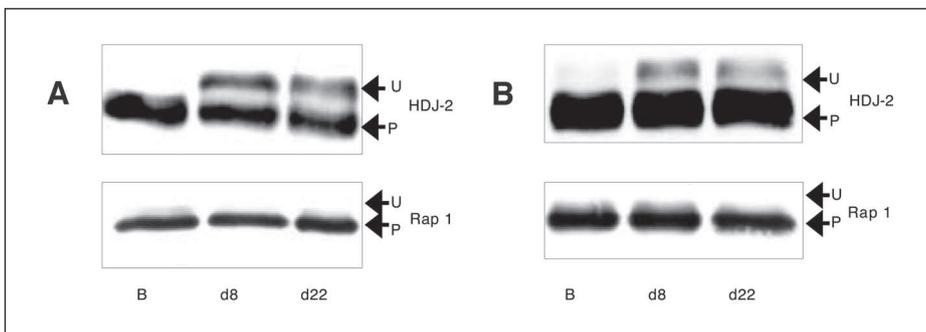
that, although EIAEDs decreased the AUC<sub>0-12 hours</sub> by two-fold in patients receiving tipifarnib 600 mg bid compared with patients receiving 300 mg bid (without EIAEDs), tipifarnib was still able to inhibit FTase activity potently in both groups. Furthermore, there was no apparent correlation between FTase inhibition and tipifarnib clinical activity; enzyme activity was potently inhibited in patients who progressed as well as in patients who had stable disease (Fig 3). Tipifarnib treatment had little effect on GGTase I activity (data not shown).

To determine whether inhibition of the FTase enzymatic activity resulted in inhibition of farnesylation of proteins selectively, we evaluated the ability of tipifarnib to inhibit HDJ-2 protein farnesylation and Rap1 geranylgeranylation in PBMCs. As a result, PBMCs from patients were processed for HDJ-2 and Rap1 prenylation by Western blotting, as described in Patients and Methods. Figure 4 shows that HDJ-2 farnesylation, but not Rap1 geranylgeranylation, was inhibited by tipifarnib (Fig 4). Before tipifarnib treatment at baseline, HDJ-2 protein from PBMCs migrated as a single band, whereas, in post-treatment samples, farnesylated HDJ-2 was distinguishable from the more slowly migrating nonfarnesylated protein. In contrast, tipifarnib treatment did not inhibit Rap1 geranylgeranylation.

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## DISCUSSION

In this study, EIAEDs altered the pharmacokinetics of tipifarnib. These agents significantly reduced tipifarnib peak/trough concentrations and exposure, as evidenced by reduced AUC. Hepatic metabolism and biliary secretion of tipifarnib and its metabolites is complex and involves many enzymes. A mass balance study confirmed that tipifarnib is extensively metabolized and is excreted in feces. Glucuronidation seems to



**Fig 4.** Inhibition of farnesylation of HDJ-2 but not geranylgeranylation of Rap1. Pre-treated HDJ-2 migrates as a single band, and farnesylase-treated HDJ-2 migrates as double bands. Rap1 protein migrates as a single band both before and after treatment. Tipifarnib 600 mg bid (maximum-tolerated dose for group B) inhibits HDJ-2 farnesylation in patients receiving enzyme-inducing antiepileptic drugs (EIAEDs) to a comparable degree as tipifarnib 300 mg bid in patients not on EIAEDs (group A). B, d8, and d22 bands designate basal cell level and 8 days and 22 days after tipifarnib treatment, respectively. U, unprocessed protein; P, processed protein.

be the major route of disposition.<sup>30</sup> Furthermore, antiepileptic drugs, such as phenytoin and phenobarbital, can induce the UGT activity.<sup>31</sup> Reportedly, UGT1A4 is the predominate UGT enzyme responsible for the glucuronidation of tipifarnib.<sup>43</sup> Because glucuronidation of tipifarnib was not measured in this study, it is only speculation that glucuronidation activity is sufficiently enhanced by EIAEDs to explain the decrease in systemic exposure. The transporter(s) that mediates biliary excretion of tipifarnib and its metabolites is also unknown. Preliminary evidence from tissue culture experiments suggests that tipifarnib is not a substrate for multidrug-resistance transporter (PgP-170ABC1), which, therefore, is unlikely to account for reduced tipifarnib accumulation.<sup>44</sup> However, Sparreboom et al<sup>45</sup> observed a trend for higher tipifarnib AUCs with the homozygous T allele of ABCB1\*8 (1236C > T). In addition, tipifarnib is also metabolized through the cytochrome P450 enzyme system, which is another pathway induced by EIAEDs.

Comparison of pharmacokinetic parameters between studies can provide meaningful insight despite the problematic considerations that sometimes confound statistical comparisons, notably, potential differences in the bioavailability and bioequivalence of the formulations. Several studies have reported the pharmacokinetics of tipifarnib after oral administration of the liquid,<sup>21</sup> capsule,<sup>25</sup> or tablet formulation.<sup>46</sup> Bioequivalency between the capsule and the tablet has been demonstrated,<sup>47</sup> and the bioavailability of the tablet used in this study was estimated to be 33%.<sup>46</sup> Along with other published reports,<sup>21,25,48</sup> we observed substantial interindividual variability in the oral bioavailability of tipifarnib. The previously defined MTD for tipifarnib in patients with advanced solid malignancies (300 mg bid)<sup>48</sup> was used as the starting point for the phase I dose-escalation component of this trial and as the maintenance dose for the phase II portion. Pharmacokinetic values observed in the comparator patient group not taking EIAEDs and receiving tipifarnib 300 mg bid were similar to published results.<sup>49</sup> However, for patients taking both tipifarnib and EIAEDs, the MTD was 600 mg bid, and pharmacoki-

netic parameter values were reduced. These results are listed in Table 6. Comparatively, there is a 5.3-fold difference in the AUC<sub>0-12 hours</sub> for group B patients versus the historical control group at the 600-mg bid dose level. The clinical significance of the lower exposure to tipifarnib in this group of patients awaits the completion of our phase II study and biologic correlations.

Tipifarnib treatment selectively inhibits FTase enzymatic activity in PBMCs from patients with recurrent malignant glioma. Furthermore, tipifarnib inhibited processing of farnesylated HDJ-2 but not of geranylgeranylated Rap1. These results were independent of dose and clinical response. Although EIAEDs significantly reduced the levels of tipifarnib, these levels were still sufficient to inhibit FTase activity. This is consistent with other reports that have shown that doses as low as 100 mg bid are effective at inhibiting FTase<sup>25,27</sup> (Sebti and Kurzrock, unpublished results). These findings provide additional support for the potential use of FTase enzymatic activity and HDJ-2 farnesylation as biomarkers for tipifarnib and other putative FTIs. However, the optimal dose can only be established by randomized, controlled, dose-ranging trials in which biomarker changes can be correlated with clinical or surrogate end points, such as response or time to progression.

DLTs were different between the two patient groups. Rash was the DLT for patients taking EIAEDs but was uncommon in the other group. The reasons for these differences remain to be explored. Other investigators have reported myelosuppression as the principal DLT of tipifarnib in patients not taking EIAEDs.<sup>21,22,48</sup>

Rash as a toxicity of tipifarnib has been previously reported.<sup>28,29,46,48</sup> Its manifestation has been exanthema, a generalized irregular red coloring, with slight cutaneous edema and itching.<sup>48</sup> Dose-related and reversible rashes are not unusual drug reactions. In this study, the rash typically occurred in the first treatment cycle. The relevance and etiology of this toxicity is unknown, and its appearance does not seem to correlate with response to tipifarnib treatment. In the current study, the rash could have been the result of a

**Table 6.** Pharmacokinetic Comparison With Historical Controls

Pharmacokinetic Parameter	Dose of Tipifarnib			
	300 mg bid		600 mg bid	
	Capsules (n = 5)*	Tablets† (n = 24)	Capsules (n = 8)*	Tablets‡ (n = 6)
t <sub>max</sub> , hours	2.5	2.5	2.9	2.3
C <sub>max</sub> , ng/mL	882	634	1728	451
t <sub>1/2</sub> , hours	2.4	3.7	3.3	3.1
AUC <sub>0-12hr</sub> , μg · hr/mL	3.76	3.35	8.90	1.73

Abbreviations: AUC, area under the plasma concentration-time curve; C<sub>max</sub>, maximum drug concentration; t<sub>1/2</sub>, half-life; t<sub>max</sub>, time to peak concentration.

\*Data from Karp et al.<sup>25</sup>

†Group A: patients not receiving enzyme-inducing antiepileptic drugs.

‡Group B: patients receiving enzyme-inducing antiepileptic drugs.

metabolite generated in the setting of EIAEDs or an interaction with these drugs. Although MTD was defined as the statistical analysis originally set out to accomplish, rash was an unusual and unexpected DLT. Future studies using agents affected by EIAEDs might consider a more thorough study of metabolites. Additionally, the substantial interindividual variability of pharmacokinetic results found in this study might give credence to dose-finding approaches that integrate pharmacokinetic and toxicity evaluations.

This study showed that the toxicities and pharmacokinetics differ significantly when comparing patients on or off EIAEDs who were treated at MTD with tipifarnib. Although FTase and HDJ-2 protein farnesylation was potently inhibited at the drug levels examined in the presence of EIAED, it is not clear whether these levels are adequate to inhibit the farnesylation of proteins in brain tumors. Preliminary re-

sults from the phase II trial of tipifarnib in patients with recurrent GBM who were not receiving EIAED and who were treated at MTD demonstrate clinical responses and disease stabilization, which implies accessibility of drug to tumor in the brain at these doses.<sup>50</sup> The ongoing phase II study will evaluate whether responses to tipifarnib are similar in patients receiving and not receiving EIAEDs. In addition to clinic outcomes, pharmacodynamic studies involving tumor may provide more critical data regarding effective biologic dosing of tipifarnib.

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**Authors' Disclosures of Potential Conflicts of Interest**

Although all authors completed the disclosure declaration, the following authors or their immediate family members 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. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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