

# Effects of Patupilone on the Pharmacokinetics and Pharmacodynamics of Warfarin in Patients with Advanced Malignancies: A Phase I Clinical Trial

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## Abstract

Patupilone is a novel microtubule-targeting cytotoxic agent, which exerts its antitumor effect through microtubule stabilization. Pharmacokinetics, pharmacodynamics, and safety of warfarin when administered concomitantly with patupilone were investigated, and antitumor activity was assessed. This was a phase I, two-center, drug–drug interaction study. In the core phase of the study, treatment consisted of warfarin 20 mg orally (days 1 and 29) and patupilone 10 mg/m<sup>2</sup> i.v. (days 8 and 29). Patients benefiting from patupilone treatment continued treatment every 3 weeks (extension phase) until progression of disease, death, or unacceptable toxicity. Seventeen patients were treated (core phase, 17; extension, 9). The geometric mean ratios (comedication/monotherapy) for C<sub>max</sub> and area under the curve<sub>0–168</sub> of warfarin were near unity and their 90% confidence intervals were within the equivalence limits of 0.80 and 1.25. The half-life, plasma clearance, and International Normalized Ratio (INR) of warfarin were not affected by patupilone coadministration. The most common adverse events were diarrhea, nausea, vomiting, abdominal pain, anorexia, dehydration, asthenia, and peripheral neuropathy. Five (29.4%) patients experienced grade 3 study drug-related adverse events (diarrhea, 17.6%; increased INR, 11.8%; dehydration, 5.9%; and neutropenia, 5.9%). One patient with triple-negative breast cancer (estrogen receptor, progesterone receptor, and HER2/neu negative) had a partial response (35% decrease in tumor measurements by Response Evaluation Criteria in Solid Tumors), and 11 had stable disease for 6 weeks or more (≥12 weeks, 6 patients). The pharmacokinetics and pharmacodynamics of warfarin were not affected by patupilone coadministration, suggesting that patupilone has no clinically relevant effect on CYP2C9 metabolism. Patupilone showed antitumor activity in triple-negative breast cancer. *Mol Cancer Ther*; 10(1); 209–17. ©2011 AACR.

## Introduction

Patupilone is a novel microtubule-targeting cytotoxic agent, which exerts its antitumor effect through microtubule stabilization, eventually leading to apoptosis and cell death similar to taxanes (1, 2). However, patupilone is several times more potent than taxanes *in vitro* and appears to have a different  $\beta$ -tubulin-binding site than taxanes. Importantly, patupilone is not affected by com-

mon tumor resistance mechanisms, including  $\beta$ -tubulin mutation and overexpression of drug efflux pumps such as P-gp (3–5). Its antitumor activity has been shown in several clinical trials with various tumor types, including ovarian, prostate, lung, and colon cancer (6–11).

The metabolism of patupilone is characterized by both hydrolytic and oxidative steps, and carboxyl esterase-catalyzed hydrolysis appears to be the major metabolic pathway in humans. However, based on *in vitro* data, patupilone is a moderate inhibitor of the cytochrome P-450 isoenzymes CYP2C19 and CYP3A4/5 (IC<sub>50</sub> = 5  $\mu$ mol/L), and a weak inhibitor of CYP2C9 (IC<sub>50</sub> = 25  $\mu$ mol/L; unpublished data). This suggests that patupilone may inhibit the clearance of drugs metabolized through these enzymes such as the anticoagulant warfarin.

Thromboembolic events are common among cancer patients. We have previously reported that 18% of patients in phase I clinical trials have a history or new development of thromboembolic events, including deep venous thrombosis and pulmonary embolism (12). These events are associated with increased mortality and, therefore, require anticoagulation therapy (12). Because

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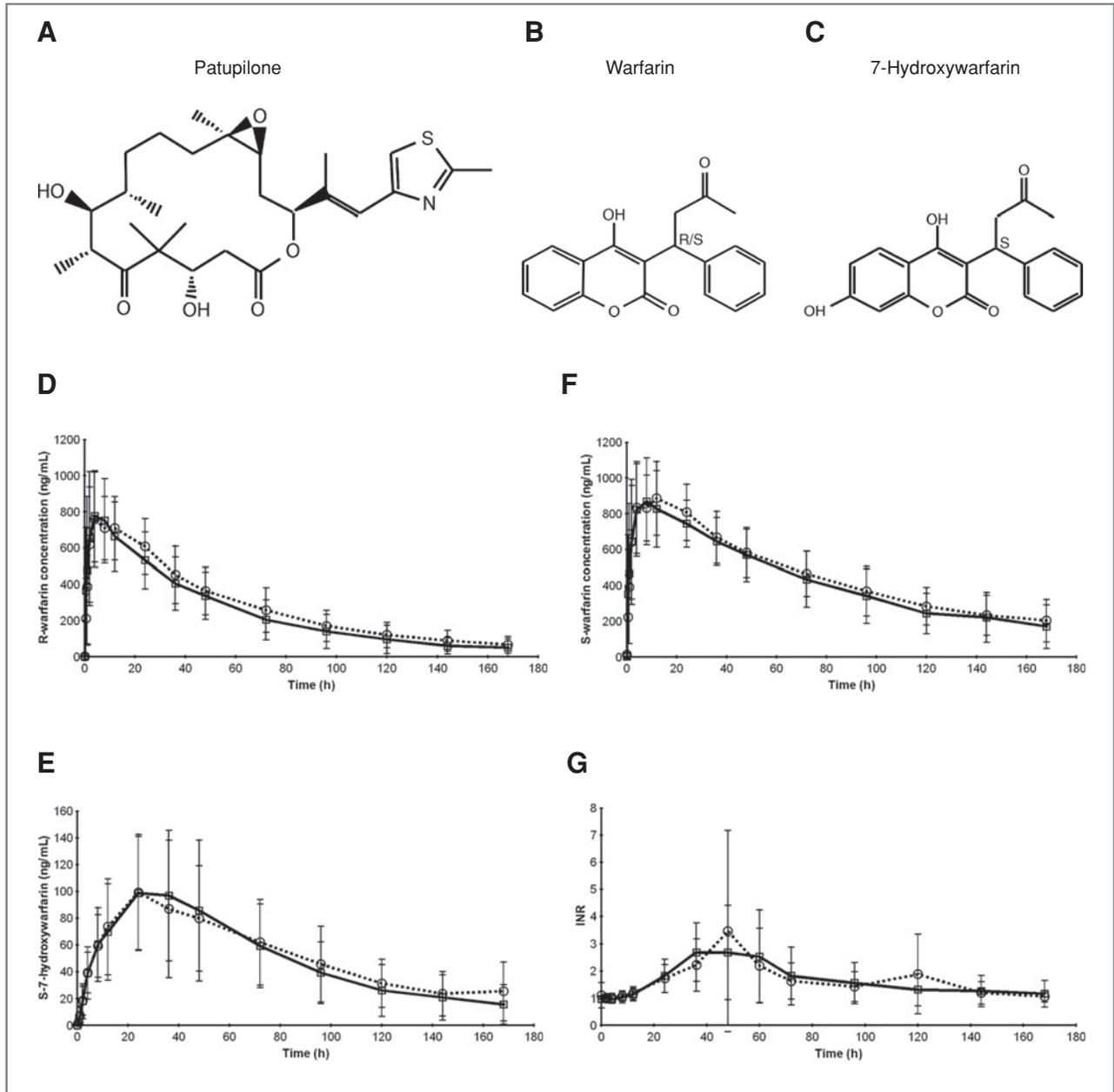
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vitamin K antagonists have been shown to be effective in the treatment and prophylaxis of thromboembolism (13), warfarin is frequently used by patients with cancer.

Warfarin is a racemic mixture of 2 enantiomers, *R*-warfarin and *S*-warfarin, in which the latter is more potent and responsible for most of its clinical activity. The enantiomers are metabolized through different cytochrome P-450 pathways: *R*-warfarin primarily by CYP1A2, CYP3A4, and CYP2C19; and *S*-warfarin exclusively through CYP2C9 into *S*-7-hydroxywarfarin (14, 15).

This study was designed to investigate the effect of patupilone 10 mg/m<sup>2</sup> administered once every 3 weeks (q3w) on the pharmacokinetics of warfarin in patients with advanced malignancies (primary objective).



**Figure 1.** A, structure of patupilone. B, structure of *R*-warfarin and *S*-warfarin. C, structure of *S*-7-hydroxywarfarin. D, mean *R*-warfarin plasma concentration–time profiles following oral administration of a single-dose warfarin 20 mg (monotherapy, solid line) or in combination (dotted line) with patupilone 10 mg/m<sup>2</sup> ( $n = 16$ ). E, mean *S*-warfarin plasma concentration–time profiles following p.o. administration of a single dose of warfarin 20 mg (monotherapy, solid line) or in combination (dotted line) with patupilone 10 mg/m<sup>2</sup> ( $n = 16$ ). F, mean *S*-7-hydroxywarfarin plasma concentration–time profiles following oral administration of a single dose of warfarin 20 mg (monotherapy, solid line) or in combination (dotted line) with patupilone 10 mg/m<sup>2</sup> ( $n = 16$ ). G, mean INR–time profiles following oral administration of a single dose warfarin 20 mg (monotherapy) or in combination (dotted line) with patupilone 10 mg/m<sup>2</sup> ( $n = 16$ ).

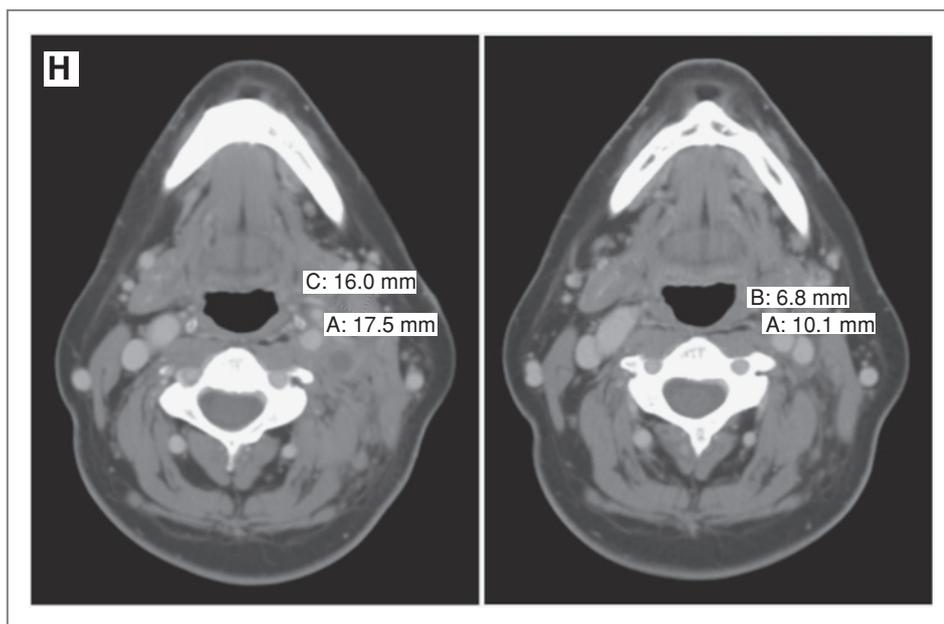


Figure 1 (Continued). H, computed tomographic images of the neck show a left carotid lymph node during a baseline scan of August 16, 2007 (left), measuring 16 × 18 mm with a subsequent decrease in size to 7 × 10 mm on a follow-up scan of October 10, 2007.

Secondary objectives included the evaluation of pharmacodynamics, the safety and tolerability of patupilone when administered concomitantly with warfarin (core phase), and potential antitumor activity.

## Patients and Methods

### Patient eligibility

Eligibility criteria included a documented advanced solid tumor that failed prior standard therapy or for which no standard therapy existed; age 18 years or older; World Health Organization (WHO) performance status 0 to 2; adequate coagulation profiles [International Normalized Ratio (INR)  $\leq$  1.4; bleeding and clotting time within upper limit of normal (ULN); partial thromboplastin time (PTT) within ULN, adequate bone marrow function (absolute neutrophil count  $\geq$   $1.5 \times 10^9$ /L, hemoglobin  $\geq$  10.0 g/dL, and platelet count  $\geq$   $100 \times 10^9$ /L); alkaline phosphatase (ALP)  $\leq$   $1.0 \times$  ULN; liver (alanine aminotransferase and aspartate aminotransferase)  $\leq$   $1 \times$  ULN; patients with bone metastases may have been included with ALP  $\geq$   $4 \times$  ULN if alanine aminotransferase, aspartate aminotransferase, and total bilirubin were within the normal range); total bilirubin, ULN or less; serum creatinine level  $< 2 \times$  ULN; and albumin  $\geq$  2.5 g/dL]. Main exclusion criteria were known history of or active bleeding disorders; hypersensitivity to warfarin or related compounds; use of vitamin K; central lines that required anticoagulant maintenance; use of warfarin or other agents containing warfarin and heparin.

Signed informed consent was obtained from all participants in accordance with institutional policy. The study was approved by the Institutional Review Boards and conducted in accordance with the principles of the Declaration of Helsinki and the International Conference

on Harmonization guidelines on Good Clinical Practice. Patients were recruited at The University of Texas MD Anderson Cancer Center [(MD Anderson) Houston, TX] and at the Cancer Therapy & Research Center, University of Texas Health Science Center (San Antonio, TX).

### Treatment plan

This was a phase I, 2-center, open-label, drug-drug interaction study. In the core phase of the study, patients were assigned to receive warfarin at 20 mg on day 1 and concomitantly with patupilone ( $10 \text{ mg/m}^2$  i.v. over 20 minutes) on day 29. In addition, patupilone was administered alone at  $10 \text{ mg/m}^2$  on day 8. Patients benefiting from patupilone treatment were allowed to continue to receive additional cycles of treatment every 3 weeks until progression of disease, death, or unacceptable toxicity occurred (extension phase).

### Pharmacokinetic sampling

Immediately prior to the administration of warfarin, 3 predose baseline blood samples were collected for both pharmacokinetic and pharmacodynamics analyses. After the administration of warfarin, serial blood samples (5 mL each) were collected at 0.5, 1, 2, 4, 8, 12, 24, 36, 48, 72, 96, 120, 144, and 168 hours post-warfarin dose on day 1 and day 29. Blood samples (4 mL each) for determination of blood patupilone concentrations were taken at 504 hours post-patupilone dose on day 8 and day 29.

### Analytical assays

Blood concentrations of patupilone (Fig. 1A) were determined using a liquid chromatography-mass spectrometry (LC/MS/MS) method (Avantix Laboratories, Inc.), as described previously (10). Plasma concentrations of *R*-warfarin, *S*-warfarin (Fig. 1B) and its

metabolite *S*-7-hydroxywarfarin (Fig. 1C) were also determined using the LC/MS/MS method. The lower limit of quantitation was 1.0 ng/mL and the linearity of the analytical methods in blood was validated (range, 1 to 1000 ng/mL). The internal standards for warfarin and *S*-7-hydroxywarfarin in these assays were phenyl-*D*<sub>5</sub>-warfarin and phenyl-*D*<sub>5</sub>-7-hydroxywarfarin, respectively. Within-study assay validation at nominal *R*-warfarin, *S*-warfarin, and *S*-7-hydroxywarfarin concentrations of 1, 2.5, 10, 100, and 1,000 ng/mL showed an assay precision (coefficient of variation) of 2.7% to 8.0% for *R*-warfarin, 3.3% to 7.5% for *S*-warfarin, and 1.3% to 8.6% for *S*-7-hydroxywarfarin. The bias was -10.4% to -4.4% for *R*-warfarin, -8.3% to -2.9% for *S*-warfarin, and -14.9% to 2.0% for *S*-7-hydroxywarfarin.

### Pharmacokinetic and pharmacodynamic parameters

Pharmacokinetics parameters determined for *R*-warfarin and *S*-warfarin and its metabolite *S*-7-hydroxywarfarin were area under the concentration-time curve from 0 to 168 hours ( $AUC_{0-168}$ ), time ( $T_{max}$ ) to reach the maximum plasma concentration ( $C_{max}$ ), apparent total plasma clearance of warfarin (CL/F) and the terminal half-life ( $T_{1/2}$ ). These pharmacokinetics parameters were calculated by standard noncompartmental analysis and a linear trapezoidal method using WinNonlin 5.2 (Pharsight). The pharmacokinetics parameter determined for patupilone was the blood concentration at 504 hours post-dose ( $C_{min}$ ).

The anticoagulant effect of warfarin was assessed by determining the prothrombin time (PT) from the blood samples taken from pre-dose to 168 hours post-dose. Measurements of PT were performed at the institutions where patients were treated following standard procedures in a laboratory certified by the Clinical Laboratory Improvement Amendments. The pharmacodynamic variable was the INR values of PT. The pharmacodynamic parameters determined for INR were area under the INR-time curve from 0 to 168 hours ( $AUC_{INR}$ ) and the maximum INR ( $INR_{max}$ ). The  $AUC_{INR}$  was calculated by a linear trapezoidal method using WinNonlin 5.2 and the  $INR_{max}$  was the observed value.

### Statistical analysis of pharmacokinetic/pharmacodynamic data

An intra-subject variability estimate (CV) of 11% was used for sample size calculation (16). A sample size of 12 subjects under a fixed sequence design was estimated to provide at least 90% power to show lack of drug-drug interaction for warfarin PK parameters, as indicated by the 90% confidence interval (CI) for the geometric mean ratio of warfarin + patupilone versus warfarin alone being completely contained within the range of 0.80 to 1.25. This calculation was based on a 2 one-sided test procedure with an overall type I error rate of 10%, assuming a true ratio of unity.

Statistical comparisons of log-transformed AUCs ( $AUC_{0-168}$  and  $AUC_{INR}$ ) and the maximum values ( $C_{max}$

and  $INR_{max}$ ) were performed via a linear mixed effects model using the SAS procedure PROC MIXED (SAS Institute Inc.). The ratio of geometric means for AUCs and the maximum values with associated 90% CI for coadministration of warfarin + patupilone compared with warfarin alone were determined using the aforementioned model.

### Safety and efficacy assessments

Patients were assessed at screening, prior to each administration of treatment (warfarin and/or patupilone) and at the end of study. Safety assessments consisted of monitoring and recording all adverse events, including serious adverse events; regular monitoring of hematology, coagulation profile, blood chemistry and urine; and vital signs, performance status and physical and neurological examination. The National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0) was used to grade toxicity.

Response was assessed using the Response Evaluation Criteria in Solid Tumors (RECIST; ref. 17). Tumor assessments were performed at baseline and subsequently every 2 cycles (1 cycle = 3 weeks).

## Results

### Patient demographics

From December 2006 to September 2007, 17 patients with advanced cancer were enrolled in the study (12 at MD Anderson and 5 in the Cancer Therapy & Research Center). Fifteen of the 17 patients completed the core study; another 9 patients continued into the extension phase. Details and reasons for discontinuation are shown in Table 1.

All patients were evaluable for safety analysis; 16 were further available for pharmacokinetics/pharmacodynamics analysis (1 patient in the core did not complete the protocol-defined warfarin and patupilone doses).

Patient characteristics are summarized in Table 2. The median age was 63 years and most patients (70.6%) had a WHO performance status of 1 at study entry. The median time from initial diagnosis was 59.5 months and 10 (58.8%) patients received 4 or more lines of prior systemic antineoplastic therapy.

### Pharmacokinetics of patupilone

This study determined only the trough (504 hours post-dose) concentrations of patupilone following a 20-minute i.v. infusion administered at 10 mg/m<sup>2</sup> every 3 weeks. The mean trough blood concentrations of patupilone in cycles 1 and 2 were 0.65 ± 0.61 and 0.89 ± 0.78 ng/mL, respectively.

### Pharmacokinetics of warfarin and its metabolite

The mean blood concentrations versus time profiles of *R*-warfarin and *S*-warfarin following oral administration of 20 mg warfarin (1 dose) in the presence and absence of

**Table 1.** Patient disposition

Disposition	Core (N = 17) <sup>a</sup>		Extension (N = 9) <sup>b</sup>	
	n	(%)	n	(%)
Entered	17	100	9	100
Completed	15	88.2	NA <sup>c</sup>	NA <sup>c</sup>
Discontinued	2	11.8	9	100
Adverse event	2	11.8	2	22.2
Disease progression	–	–	5	55.5
Consent withdrawal	–	–	2	22.2

<sup>a</sup>Core study: First 2 cycles with administration of warfarin (20 mg) on day 1, patupilone 10 mg/m<sup>2</sup> on day 8, and concomitant administration of warfarin (20 mg) with patupilone (10 mg/m<sup>2</sup>) on day 29.

<sup>b</sup>Extension study: cycle 3 onward when patupilone was administered at 10 mg/m<sup>2</sup> every 3 weeks.

<sup>c</sup>Patients were to continue treatment until disease progression, unacceptable toxicity or until the investigator/patient decided it was not in the best interest of the patient to continue participating in the clinical trial. NA, not applicable.

10 mg/m<sup>2</sup> patupilone are presented in Fig. 1D and E, respectively. Plasma concentrations of R-warfarin and S-warfarin were unchanged by coadministration of patupilone (10 mg/m<sup>2</sup>). The pharmacokinetic parameters of R-warfarin and S-warfarin are summarized in Table 3. Both C<sub>max</sub> and AUC<sub>0–168</sub> of R-warfarin and S-warfarin when coadministered with patupilone were similar to those of warfarin monotherapy. The geometric mean ratios for C<sub>max</sub> and AUC<sub>0–168</sub> of R-warfarin and S-warfarin were close to unity, and the 90% CIs for the geometric mean ratios for C<sub>max</sub> and AUC<sub>0–168</sub> were within the equivalence limits of 0.80 and 1.25 (Table 3). In addition, the oral clearance, volume of distribution, and terminal half-life of R-warfarin and S-warfarin during coadministration of warfarin and patupilone were similar to those of warfarin monotherapy.

The mean blood concentrations versus time profiles of the major metabolite of S-warfarin (S-7-hydroxywarfarin) are presented in Fig. 1F, and its plasma concentrations were unchanged by coadministration of patupilone. The geometric mean ratios for C<sub>max</sub> and AUC<sub>0–168</sub> for S-7-hydroxywarfarin were close to unity with the 90% CIs being contained within the equivalence limits of 0.80 and 1.25 for C<sub>max</sub> [geometric mean ratio of 1.08 (90% CIs of 0.96 to 1.21)] and AUC<sub>0–168</sub> [geometric mean ratio of 1.11 [(90% CIs of 1.01 to 1.22)].

### Pharmacodynamics of warfarin

The mean INR versus time profiles following oral administration of 20 mg warfarin in the presence and absence of 10 mg/m<sup>2</sup> patupilone are presented in Fig. 1G. The INR<sub>max</sub> and AUC<sub>INR</sub> were similar in the 2 groups (Table 4). The geometric mean ratios for INR<sub>max</sub> and AUC<sub>INR</sub> were close to unity, and the 90% CIs for the geometric mean ratios for AUC<sub>INR</sub> were within the equivalence limits of 0.80 and 1.25. However, the 90% CIs for the geometric mean ratios for INR<sub>max</sub> were larger

than the equivalence limits of 0.80 and 1.25, due to a large variability in these patients, as shown by the large coefficients of variation (62% to 98%; Table 4).

### Safety and tolerability

The most common adverse events related to study drug administration were gastrointestinal (diarrhea, nausea, vomiting, abdominal pain, anorexia, and dehydration), followed by asthenia and peripheral neuropathy (Table 5). Most of these events were grade 1 and 2. Five (29.4%) patients experienced grade 3 study drug-related adverse events (diarrhea, 17.6%; increased INR, 11.8%; dehydration, 5.9%; and neutropenia, 5.9%). The increased INR/PT occurred in the core phase and was likely related to warfarin coadministration. Three patients reported grade 4 events (neutropenia, pneumonia, and respiratory arrest); however, none of these were suspected to be related to study drug administration.

A total of 7 patients (41.2%) reported adverse events in the study, with diarrhea being the most common event by preferred term. Four of these 7 patients discontinued the study due to the event.

One death was reported in the study. The patient was a 68-year-old female with metastatic breast carcinoma involving the bone who had received multiple prior lines of hormone (n = 3) and chemotherapy (n = 7). The patient had received 1 dose of warfarin (cycle 1, day 1) and one dose of patupilone (cycle 1, day 8). She had a history of diabetes and herpes simplex virus. The patient was hospitalized 2 weeks after administration of the first dose of patupilone (cycle 1, day 22) due to diarrhea and *Clostridium difficile* gastroenteritis. She developed dehydration, hyponatremia, metabolic acidosis, and urinary tract infection, and she died on cycle 1, day 32 due to respiratory arrest. It was suspected that the patient also had diverticulitis.

**Table 2.** Patient characteristics

Characteristic	n	(%)
Age, median (range), y	63.0 (20–79)	
Sex		
Male	8	47.1
Female	9	52.9
Race		
Caucasian	14	82.4
Asian	1	5.9
Other	2	11.8
Baseline performance status (WHO)		
Missing	1	5.9
0	2	11.8
1	12	70.6
2	2	11.8
Primary site of cancer		
Bone sarcoma	1	5.9
Breast	2	11.8
Cervix	1	5.9
Colon	4	23.5
Head and neck	2	11.8
Lung	1	5.9
Esophagus	1	5.9
Ovary	1	5.9
Prostate	1	5.9
Other <sup>a</sup>	3	17.6
Months since initial diagnosis, median (range)	59.5 (9–137)	
Number of prior lines of therapy		
1	1	5.9
2	3	17.6
3	3	17.6
≥4	10	58.8

<sup>a</sup>One patient had each of the diagnoses: squamous cell carcinoma of the vulva; mucinous adenocarcinoma of the appendix and cancer of the thymus.

### Preliminary activity

Of the 17 patients enrolled in the trial, 1 (6%) patient had a partial response (35% decrease in tumor measurements by RECIST) at the first post-baseline tumor evaluation (day 51; Fig. 1H). This patient was a 46-year-old female with invasive breast cancer, who had 5 prior therapies, including adjuvant therapy with Adriamycin and cyclophosphamide; and salvage therapy with Taxotere, navelbine, gemcitabine, capecitabine, and CT2103 (paclitaxel combined with the protein poliglumex). The patient withdrew consent due to grade 2 peripheral neuropathy as well as intermittent abdominal cramps and intermittent grade 1 to 2 diarrhea. Eleven (65%) of 17 patients had stable disease for 6 weeks or more, including 6 patients whose disease was stable for 12 weeks or more. Three patients (17.6%) had progressive disease and response was unknown in 2 patients (1 patient discontinued due to diarrhea and another withdrew consent prior to the first post-baseline evaluation).

### Discussion

Warfarin is frequently used in the treatment and prevention of thrombosis and thromboembolic events, which are common in cancer patients. Warfarin has a narrow therapeutic index, and increases in plasma levels can lead to bleeding. Because patupilone has been shown to be a potential inhibitor of the metabolic pathway of warfarin *in vitro*, the main purpose of this study was to investigate the impact of patupilone on the pharmacokinetics of warfarin in humans. In addition, the pharmacodynamics of warfarin as well as the safety and preliminary antitumor activity of patupilone were evaluated.

This study was designed as previously described (18). Warfarin is administered as single agent at 20 mg on day 1 and concomitantly with patupilone on day 29, ensuring that baseline pharmacokinetic and pharmacodynamic effects are obtained for all patients. Further, it

**Table 3.** Pharmacokinetic parameters of *R*-warfarin and *S*-warfarin following oral administration of a single dose of warfarin 20 mg (monotherapy) or in combination with patupilone 10 mg/m<sup>2</sup> (*n* = 16)

Parameters	<i>R</i> -warfarin		<i>S</i> -warfarin	
	Warfarin alone	Warfarin + patupilone	Warfarin alone	Warfarin + patupilone
$C_{max}$ , ng/mL	951 ± 253	909 ± 259	997 ± 229	1023 ± 249
$T_{max}$ , h	4.0 (1.0–24) <sup>a</sup>	4.0 (0.8–12) <sup>a</sup>	4.0 (1.0–24) <sup>a</sup>	8.0 (1.0–24) <sup>a</sup>
AUC <sub>0–168</sub> , mg h/L	43.77 ± 15.41	47.54 ± 15.82	73.86 ± 23.44	77.66 ± 19.69
CL/F, L/h	0.49 ± 0.21	0.44 ± 0.21	0.28 ± 0.12	0.25 ± 0.06
$T_{1/2}$ , h	46.48 ± 19.69	49.95 ± 15.33	72.48 ± 33.75	75.31 ± 24.82
Ratio (comedication/monotherapy) of geometric means (90% CI):				
$C_{max}$	0.95 (0.85–1.06)		1.02 (0.94–1.11)	
AUC <sub>0–168</sub>	1.07 (0.93–1.23)		1.08 (0.97–1.20)	

<sup>a</sup>Median (range) for  $T_{max}$ .

has been shown that 20 mg of warfarin can be used without any significant safety issues: there was no significant bleeding or requirement for vitamin K rescue therapy, and the PT (INR) remained less than 2.0 in a study reported by Camidge and colleagues (18).

The mean trough concentration of patupilone during coadministration with warfarin was similar to that of the patupilone monotherapy at 10 mg/m<sup>2</sup> using every-3-week dosing schedule, and these trough concentrations were similar to those in previous phase I and II studies (10), supporting adequate exposure of patupilone in this study.

The *S*-warfarin and *R*-warfarin exposures, in terms of AUCs and  $C_{max}$ s, following coadministration with patupilone were equivalent to those of the control (warfarin monotherapy), suggesting that patupilone had no effect on warfarin pharmacokinetics in these patients with cancer. Because the potency of *S*-warfarin is significantly higher than that of *R*-warfarin, the pharmacologic effect of warfarin is highly dependent on the exposure of *S*-warfarin, which is predominately eliminated by CYP2C9 to form *S*-7-hydroxywarfarin (2, 3). The exposures of *S*-7-hydroxywarfarin, in terms of AUCs and

$C_{max}$ s, following coadministration of warfarin and patupilone were equivalent to those of the control, which further supported no *in vivo* CYP2C9 inhibition by patupilone. Thus, this study showed no drug–drug interactions with respect to the pharmacokinetics of warfarin when coadministered with patupilone in patients who had advanced malignancies. Based on these findings, other drugs metabolized by CYP2C9 in humans should not be affected by patupilone coadministration.

Because warfarin inhibits the synthesis of the vitamin K–dependent clotting factors II (prothombin), VII, IX, X, and proteins C and S, the pharmacodynamic effects of warfarin on INR were investigated. AUC<sub>INRS</sub> of warfarin alone or when coadministered with patupilone were equivalent suggesting that coagulation was not affected by patupilone in patients with advanced malignancies. The 90% CI for the geometric mean ratio of INR<sub>max</sub> included 1, suggesting a similarity in INR<sub>max</sub> between the treatment and control groups. However, the INR<sub>max</sub> constituted large variabilities (62% to 98% coefficient of variation) in these patients with cancer.

Overall, patupilone was generally well tolerated, with the gastrointestinal tract as the main target for toxicity

**Table 4.** Pharmacodynamic parameters (INR) following oral administration of a single dose of warfarin 20 mg (monotherapy) or in combination with patupilone 10 mg/m<sup>2</sup> (*n* = 16)

Parameters	Warfarin alone	Warfarin + patupilone
INR <sub>max</sub> , INR	3.13 ± 1.93 (62%)	3.79 ± 3.70 (98%)
AUC <sub>INR</sub> , INR h	282 ± 121 (43%)	283 ± 111 (39%)
Ratio (comedication/monotherapy) of geometric means (90% CI)		
INR <sub>max</sub>	1.07 (0.80–1.43)	
AUC <sub>INR</sub>	1.03 (0.93–1.15)	

<sup>a</sup>Arithmetic mean ± SD (percentage coefficient of variation).

**Table 5.** Study drug-related adverse events in core ( $n = 17$ ) and extension phase ( $n = 9$ )

Preferred term	Core ( $n = 17$ ) <sup>a</sup>		Extension ( $n = 9$ ) <sup>b</sup>		All patients ( $n = 17$ )	
	Any grade $n$ (%)	Grade 3	Any grade $n$ (%)	Grade 3	Any grade $n$ (%)	Grade 3
Any adverse event	17 (100.0)	4 (23.5)	9 (100.0)	2 (22.2)	17 (100.0)	5 (29.4)
Diarrhea	12 (70.6)	2 (11.8)	3 (33.3)	2 (22.2)	13 (76.5)	3 (17.6)
Asthenia/fatigue	7 (41.2)	0	3 (33.3)	0	8 (47.1)	0
Nausea	6 (35.3)	0	1 (11.1)	0	7 (41.2)	0
Peripheral neuropathy	4 (23.4)	0	3 (33.3)	0	6 (35.3)	0
Anorexia	3 (17.6)	0	2 (22.2)	0	5 (29.4)	0
Dehydration	5 (29.4)	1 (5.9)	0	0	5 (29.4)	1 (5.9)
Abdominal pain	2 (11.8)	0	1 (11.1)	0	3 (17.6)	0
Anemia	1 (5.9)	0	1 (11.1)	0	2 (11.8)	0
Dysgeusia	1 (5.9)	0	1 (11.1)	0	2 (11.8)	0
Increased INR/PT	2 (11.8)	2 (11.8)	0	0	2 (11.8)	2 (11.8)
Neutropenia	1 (5.9)	1 (5.9)	0	0	1 (5.9)	1 (5.9)
Vomiting	2 (11.8)	0	0	0	2 (11.8)	0
Arthralgia	1 (5.9)	0	0	0	1 (5.9)	0
Malaise	1 (5.9)	0	0	0	1 (5.9)	0
Myalgia	1 (5.9)	0	0	0	1 (5.9)	0
Weight decrease	1 (5.9)	0	0	0	1 (5.9)	0

NOTE: Results are reported in number of patients; no patient developed drug-related grade 4 adverse event.

<sup>a</sup>Core study: Includes data from first 2 cycles with administration of warfarin (20 mg) on day 1, patupilone 10 mg/m<sup>2</sup> on day 8, and concomitant administration of warfarin (20 mg) with patupilone (10 mg/m<sup>2</sup>) on day 29.

<sup>b</sup>Extension study, includes data from cycle 3 onward when patupilone was administered at 10 mg/m<sup>2</sup> every 3 weeks.

followed by asthenia and peripheral neuropathy. Cardiac, renal, and hepatic events were infrequent and not considered to be related to study drug. The few cases of increased INR (grade 3) in the core study were most likely attributable to concomitant administration of warfarin.

Taken together, the most frequent adverse events reported in this study were consistent with the safety profile of patupilone as described in previous studies. There were no new or unexpected findings. Moreover, the safety and tolerability profile of the combination of patupilone and warfarin in the core study was similar to patupilone monotherapy, as described previously, except for the expected warfarin-associated effects on coagulation.

An intriguing finding was that a patient with triple (estrogen receptor, progesterone receptor, and HER2/neu)-negative breast cancer had a partial response to patupilone, suggesting that the drug has antitumor activity in breast cancer. In addition, 65% of patients with heavily pretreated advanced solid tumors had stable disease according to RECIST criteria.

In conclusion, this study showed that the pharmacokinetics and pharmacodynamics of warfarin were not affected by patupilone coadministration in patients with advanced malignancies. The safety and tolerability following coadministration of patupilone and warfarin

were similar to those of patupilone monotherapy. These results demonstrate a lack of drug–drug interaction between the 2 drugs; thus, no dosage adjustment for warfarin or other drugs metabolized through the CYP2C9 pathway is required when used in patients treated with patupilone at 10 mg/m<sup>2</sup> every 3 weeks. More importantly, patupilone showed antitumor activity in triple-negative breast cancer.

#### Disclosure of Potential Conflicts of Interests

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