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Original Article

Multicenter Phase 2 Study of Patupilone for Recurrent or Progressive Brain Metastases From Non–Small Cell Lung Cancer

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BACKGROUND: Treatment options for patients with non–small cell lung cancer (NSCLC) with brain metastases are limited. Patupilone (EPO906), a blood-brain barrier–penetrating, microtubule-targeting, cytotoxic agent, has shown clinical activity in phase 1/2 studies in patients with NSCLC. This study evaluates the efficacy, pharmacokinetics, and safety of patupilone in NSCLC brain metastases. **METHODS:** Adult patients with NSCLC and confirmed progressive brain metastases received patupilone intravenously at 10 mg/m^2 every 3 weeks. The primary endpoint of this multinomial 2-stage study combined early progression (EP; death or progression within 3 weeks) and progression-free survival at 9 weeks (PFS9w) to determine drug activity. **RESULTS:** Fifty patients with a median age of 60 years (range, 33-74 years) were enrolled; the majority were men (58%), and most had received prior therapy for brain metastases (98%). The PFS9w rate was 36%, and the EP rate was 26%. Patupilone blood pharmacokinetic analyses showed mean areas under the concentration-time curve from time zero to 504 hours for cycles 1 and 3 of 1544 and 1978 ng h/mL, respectively, and a mean steady state distribution volume of 755 L/m^2. Grade 3/4 adverse events (AEs), regardless of their relation with the study drug, included diarrhea (24%), pulmonary embolisms (8%), convulsions (4%), and peripheral neuropathy (4%). All patients discontinued the study drug: 31 (62%) for disease progression and 13 (26%) for AEs. Twenty-five of 32 deaths were due to brain metastases. The median time to progression and the overall survival were 3.2 and 8.8 months, respectively. **CONCLUSIONS:** This is the first prospective study of chemotherapy for recurrent brain metastases from NSCLC. In this population, patupilone demonstrated activity in heavily treated patients. ***Cancer* 2015;000:000–000**. © *2015 American Cancer Society*.

KEYWORDS: brain metastases, chemotherapy, non–small cell lung cancer, patupilone, recurrent metastases.

INTRODUCTION

Brain metastases are the most common form of adult central nervous system tumors and significantly outnumber primary brain tumors, with the majority (40%-56%) originating from lung cancer, especially non–small cell lung cancer (NSCLC).[1,2] Brain metastases from NSCLC are common at the initial diagnosis or within a year of presentation, but they can occur at any time during the course of the disease.[3] Standard therapies for brain metastases include symptomatic

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The last 3 authors contributed equally to this article.

This study was presented in part at the 2008 Annual Meeting of the American Society of Clinical Oncology, June 2008, Chicago, IL; the 2013 Annual Meeting of the American Academy of Neurology, March 2013, San Diego, CA; and the 2013 Annual Meeting of the Society for NeuroOncology, November 2013, San Francisco, CA.

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treatments (eg, corticosteroids to reduce peritumoral edema and anticonvulsants to control seizures), surgery, whole-brain radiotherapy, stereotactic radiosurgery, and chemotherapy.[4,5] Despite aggressive treatment, the prognosis is poor with a median overall survival (OS) of approximately 7 months after the diagnosis[6] and 4 to 5 months after brain metastasis recurrence.[7-9]

Although most anticancer agents are ineffective in treating brain tumors because of an inability to cross the blood-brain barrier, some chemotherapeutic and targeted therapies have demonstrated modest activity in patients with recurrent brain metastases in clinical trials.[10-12] Epothilones are blood-brain barrier–penetrating compounds that act as antimicrotubule cytotoxic agents by promoting tubulin polymerization and inducing mitotic cell cycle arrest and apoptosis in human cancer cells.[13,14] Similar to taxanes, epothilones bind β-tubulin; however, epothilones have a higher binding affinity to this molecular target than paclitaxel or docetaxel.[15] Unlike taxanes, epothilones are not substrates for the blood-brain barrier–associated multidrug transporter P-glycoprotein, and they have been demonstrated to cross the intact blood-brain barrier in rodents.[16,17]

Patupilone (EPO906) is a naturally occurring epothilone B that has shown growth inhibition of intracranial human lung tumors in preclinical studies.[18] In a phase 1/2 surgical study of recurrent glioblastoma, patients were treated with patupilone 1 week before surgical resection, and the concentration of patupilone was found to be 30 times higher in tumor tissue versus plasma; this clearly demonstrated adequate tumor/brain penetration.[19]

Patupilone has shown some clinical activity in phase 1/2 studies in previously treated patients with metastatic ovarian cancer, prostate cancer, and NSCLC.[20-22] The purpose of this phase 2 study was to evaluate the activity of patupilone in patients with NSCLC with brain metastases who had progressed after chemotherapy, surgery, and/or radiation to the brain.

MATERIALS AND METHODS

Study Design

This phase 2, open-label, single-arm, 2-stage, multicenter study evaluated the safety and efficacy of patupilone in patients with NSCLC with progressive brain metastases. The protocol and all amendments were reviewed by each site's institutional review board. A multinomial stopping rule was used for 2-stage enrollment, with 25 patients expected to be enrolled during stage 1 and an additional 25 patients enrolled during stage 2.[23] The decision to proceed to stage 2 was based on both progression-free survival at 9 weeks (PFS9w; also called response in the protocol) and early progression (EP) as described later.

Patients

Patients who were 18 years old or older, had a World Health Organization performance status ≤ 2 and radiographically confirmed parenchymal brain metastases from histologically confirmed NSCLC, and had progressed after radiotherapy, surgery, and/or chemotherapy were eligible for this study. Patients were required to have at least 1 recurrent bidimensionally measurable intracranial lesion $\geq$ 1 cm and to be on stable doses of corticosteroids and anticonvulsant agents for at least 1 week before baseline magnetic resonance imaging and/or at least 1 week before the initiation of treatment. All patients were required to have adequate hematologic and metabolic function. Patients with leptomeningeal disease, extracranial disease in more than 3 organ sites, grade 1 or higher peripheral neuropathy, diarrhea of any grade, severe cardiac insufficiency (New York Heart Association III or IV), any serious medical condition, or previous exposure to epothilones were not eligible. Patients were required to stop treatment with any investigational agent within 4 weeks before study enrollment or with radiotherapy, chemotherapy, and/or intracranial surgery at least 3 to 6 weeks before study entry. All patients provided written informed consent.

Treatment and Evaluation

Patients received patupilone intravenously at 10 mg/m^2 as a 20-minute intravenous infusion once every 3 weeks (21-day cycle) until disease progression, a satisfactory therapeutic response (at the treating investigator's discretion), withdrawal of consent, loss to follow-up, or unacceptable toxicity occurred. Patupilone was held for grade 3 and 4 hematologic (except anemia) and nonhematologic toxicities until they were resolved to grade 1 or lower, and the dose of treatment was reduced by 25%. It was held for diarrhea of any grade and grade 2 or higher neuropathy, and the dose was reduced by 25% when the event was resolved. Patients were discontinued from the study for toxicity or a study interruption > 3 weeks beyond the next scheduled dose.

Brain metastases were assessed for overall response as defined by the Neuro-Oncology Criteria of Tumor Response for Central Nervous System Tumors: the response was evaluated by an assessment of target (up to 5 bidimensional, measurable, enhancing brain tumor lesions) and nontarget lesions (additional measurable and evaluable brain and extracranial lesions), the appearance of new lesions, a neurologic examination scale (with scores

TABLE 1. Evaluation of Responses With the Neuro-Oncology Criteria of Tumor Response for Central Nervous System Tumors

Overall Response	Target Lesion (up to 5 Measurable Lesions)	Nontarget Lesion	New Lesion	Neurologic Examination Scale[a]	Corticosteroid Use
Complete response	None	None	No	+2, +1, 0, −1	No
Partial response	≥−50%	Nonenhancing, improved, unchanged	No	+2, +1, 0, −1	Stable (<25% increase from baseline)
Progression	≥+25%	Worsened	Yes	−2	Increase (>25% increase from baseline)
Stable disease[b]					

[a] The scale is scored as follows: +2, definitely better; +1, possibly better; 0, unchanged; −1, possibly worse; and −2, definitely worse.
[b] Any other disease status not meeting the criteria for a complete response, a partial response, or progression.

ranging from +2 to –2), and corticosteroid use (Table 1). Tumors were assessed at the completion of every 3-week cycle for the first 4 cycles, at every second cycle beyond cycle 4, and at the end of the study by contrast-enhanced brain magnetic resonance imaging and computed tomography (CT) scans of the chest, abdomen, and pelvis.

Adverse events (AEs) were recorded with the National Cancer Institute's Common Terminology Criteria for Adverse Events (version 3.0).

Pharmacokinetic Assessments

Blood samples were collected on day 1 immediately before and after patupilone infusion and at 1, 2, 4, 8, 24, 72, 168, 336, and 504 hours (immediately before the next patupilone dose) during cycle 1 and cycle 3. A pharmacokinetic analysis of patupilone was performed with a noncompartmental model. The estimated pharmacokinetic parameters included the peak and minimum drug concentrations after infusion, the area under the concentration-time curve from time 0 to infinity, the area under the concentration-time curve from time 0 to 504 hours ($AUC_{0\text{-}\tau}$), the half-life of the terminal elimination phase, the clearance of the drug in the blood, the drug accumulation ($AUC_{0\text{-}\tau\ \text{cycle}\ 3}/AUC_{0\text{-}\tau\ \text{cycle}\ 1}$), and the apparent volume of the distribution in the body.

Statistical Methods

The primary endpoint was to determine the activity of patupilone with respect to EP and PFS9w for enrolled patients. The EP rate was defined as the proportion of patients suffering progression or death within the first 3 weeks of the study (cycle 1). PFS9w (also called response in the protocol) was defined as the proportion of patients alive without progression after 9 or more weeks of study treatment (day 1 of cycle 4 and beyond). The phase 2 multinomial stopping rule was applied to the primary endpoint to determine measures of inactivity (response or PFS9w rate $\leq$ 10%, EP rate $\geq$ 60%) and activity (response or PFS9w rate $\geq$ 20%, EP rate $\leq$ 40%) at the end of stage 1.[23] In particular, the criteria for considering the drug effective and stopping after stage 1 (and rejecting the inactivity hypothesis) were as follows: 2 to 4 responses and 10 or fewer EPs, 5 responses and 11 or fewer EPs, or 6 or more responses and 14 or fewer EPs.

A sample size of 25 patients for each of the 2 stages (total n = 50) would yield a target power of 85% with a 10% target level of significance.

Because of the poor prognosis of these patients, 9 weeks of progression-free survival was chosen as a measure of response, and the EP rate was given equal importance in the multinomial approach; this limited the number of patients required for this study.

Secondary endpoints included the overall response rate (complete and partial responses), the time to disease progression (TTP) and duration of stable disease of brain metastases, OS, safety and tolerability, and patupilone blood pharmacokinetics. TTP and OS were measured from the start of study treatment until disease progression and death, respectively. Kaplan-Meier estimate was used for survival analysis.

RESULTS

Patient Characteristics

A total of 50 patients (25 during stage 1 and 25 during stage 2) were enrolled in this study from November 2005 through July 2009 (Table 2). The median age was 60 years (range, 33-74 years), and 58% were men. A majority of the patients had a World Health Organization performance status of 0 or 1 (90%). The time since the initial diagnosis of brain metastases was <3 years for 78% of the patients. All patients had received prior therapy for NSCLC, and 49 of 50 patients had received treatment for brain metastases (Table 2).

Treatment

Patients were treated with a median of 2 cycles of the study drug (range, 1-13 cycles) and remained on

treatment for a median of 8 weeks (range, 3-42 weeks). All patients discontinued the study drug: 62% for disease progression, 26% for AEs, 8% for withdrawal of consent due to patient preference (eg, reasons other AEs), 2% for administrative issues, and 2% for abnormal test results. Forty-six percent of the patients required a dose adjustment or interruption for AEs, including grade 1 to 3 diarrhea (28%), grade 2 peripheral neuropathy (4%), and grade 2 dehydration (4%).

Pharmacokinetics

The pharmacokinetics was assessed for 28 patients at cycle 1 and for 11 patients at cycle 3 (Table 3). Patupilone blood concentration–time profiles declined rapidly after the 10 mg/m^2 dose (Fig. 1). The mean $AUC_{0\text{-}\tau}$ values for cycles 1 and 3 were 1544 and 1978 L/m^2, respectively, and the mean steady-state volume of distribution was 755 L/m^2; this suggested an extensive distribution of patupilone to tissues. The low mean blood clearance of patupilone of approximately 7 L/h/m^2, coupled with the large steady-state volume of distribution, was consistent with the long mean half-life of the terminal elimination phase for patupilone of approximately 103 hours. The mean ratio of the areas under the curve (cycle 3/cycle 1) was approximately 0.97, and this indicated a lack of patupilone accumulation with this dosing schedule.

TABLE 2. Patient Demographic and Baseline Characteristics (n = 50)

Characteristic	Value
Age, median (range), y	60 (33-74)
Sex: men/women, No. (%)	29 (58)/21 (42)
WHO performance status, No. (%)	
0	16 (32)
1	29 (58)
2	5 (10)
Time since initial diagnosis of lung cancer, No. (%)	
<1 y	13 (26)
1-3 y	23 (46)
≥3 y	13 (26)
Missing	1 (2)
Time since initial diagnosis of brain metastases, No. (%)	
<1 y	21 (42)
1–3 y	18 (36)
≥3 y	7 (14)
Missing	4 (8)
Prior antineoplastic therapy for brain metastases, No. (%)	
Radiotherapy	49 (98)
Surgery	22 (44)
Chemotherapy	16 (32)

Abbreviation: WHO, World Health Organization.

Response

The primary endpoint was evaluated at the end of stage 1. Among 25 patients, there were 7 (28%) who were progression-free at 9 weeks, 8 (32%) with EP (progressive disease within the first cycle), and 8 with neither PFS9w nor EP. In 2 patients, an assessment could not be made. This result met the statistical criteria to stop the study at stage 1 for activity. Because there were only moderate numbers of patients without progression at 9 weeks (28%) and early progressors (32%), the decision was made to continue the trial to stage 2 to obtain more information regarding the activity of patupilone in this population of NSCLC patients with brain metastases. Overall results for stage 1 and stage 2 showed that 18 patients were progression-free at 9 weeks (36%; 95% confidence interval [CI], 20%-50%), and 13 (26%) had EP (95% CI, 10%-40%; Table 4). Because the statistical boundary for activity was crossed at the end of stage 1, there was no intention to use formal success criteria at the end of stage 2. Nevertheless, the result at the end of stage 2 also crossed the statistical boundary for activity defined in the

TABLE 3. Patupilone Pharmacokinetic Parameters in Cycles 1 and 3

	Cycle 1			Cycle 3		
Pharmacokinetic Parameter	No.	Mean	Mean CV (%)[a]	No.	Mean	Mean CV (%)[a]
C_{max} (ng/mL)	27	160.66	144.19	11	198.27	183.41
C_{min} (ng/mL)	9	0.376	91.50	8	0.342	105.13
$AUC_{0\text{-}\infty}$ (ng h/mL)	27	1415.57	73.87	—	—	—
$AUC_{0\text{-}\tau}$ (ng h/mL)	28	1543.83	63.80	11	1977.76	100.14
Clearance (L/h/m^2)	28	6.857	74.78	—	—	—
V_{ss} (L/m^2)	28	754.97	88.33	—	—	—
$t_{1/2}$ (h)	28	102.69	42.11	10	108.08	23.46
R	—	—	—	11	0.970	6.11

Abbreviations: $AUC_{0\text{-}\infty}$, area under the concentration-time curve from time 0 to infinity; $AUC_{0\text{-}\tau}$, area under the concentration-time curve from time 0 to 504 hours; C_{max}, peak drug concentration after infusion; C_{min}, minimum drug concentration after infusion; CV, coefficient of variation; R, drug accumulation ($AUC_{0\text{-}\tau\ cycle\ 3}/AUC_{0\text{-}\tau\ cycle\ 1}$); $t_{1/2}$, half-life of the terminal elimination phase; V_{ss}, steady-state volume of distribution.

[a] Mean CV (%) = square root[exp(variance for log-transformed data) − 1] × 100

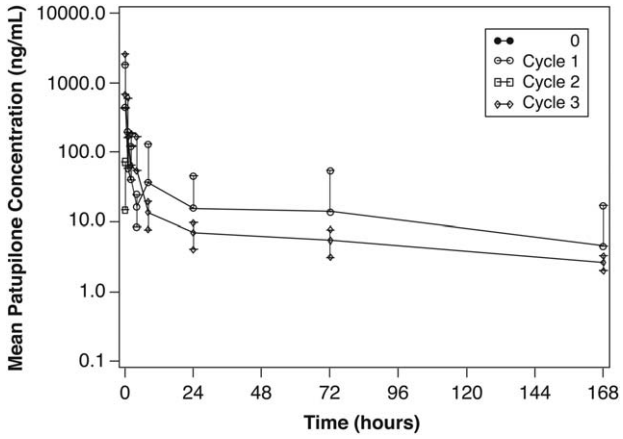

Figure 1. Mean blood concentration–time profiles for patupilone for cycles 0 to 3 (28 patients). Cycles 0 and 2 have only 1 data point at time 0. Error bars represent standard deviations.

TABLE 4. Overall Stage 1 and Stage 2 Tumor Early Progression and Response (n = 50)

Primary Endpoint	No. (%)	95% CI
EP	13 (26)	10–40
PFS9w	18 (36)	20–50
Neither EP nor PFS9w	19 (38)	

Abbreviations: CI, confidence interval; EP, early progression (ie, disease progression or death within the first 3 weeks [cycle 1]); PFS9w, progression-free survival at 9 weeks (ie, survival without progression up to day 1 of cycle 4 and beyond).

protocol. These results indicated that patupilone is active in patients with brain metastases from NSCLC. Thirty-one patients eventually suffered disease progression in the brain; 7 of these patients (23%) had systemic progression, and 13 (42%) were stable systemically. The status of systemic disease at the time of progressive disease in the brain was unknown for 11 patients. The median duration of stable disease in the brain was 72 days (range, 20-301 days).

Survival

The median follow-up was 163 days (5.4 months). The median OS was 264 days (8.8 months; 95% CI, 158-386 days) with a 6-month OS rate of 65% (95% CI, 48%-77%; Fig. 2A). The median TTP was 96 days (3.2 months; 95% CI, 42-125 days) with a 6-month TTP rate of 21% (95% CI, 8%-37%; Fig. 2B). Thirty-two patients died: 25 from brain metastases, 4 from systemic disease, 2 from infections, and 1 from unknown causes.

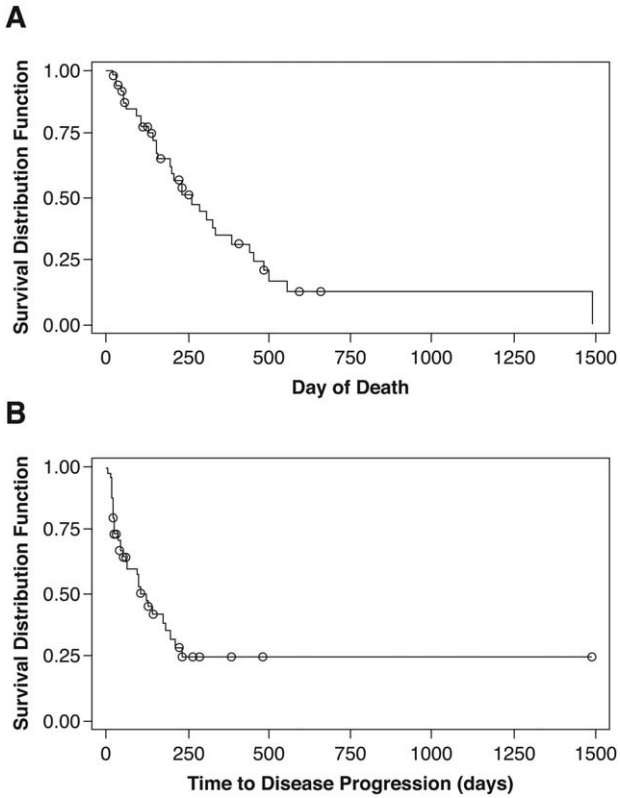

Figure 2. (A) Overall survival and (B) time to disease progression (50 patients). Circles indicate censored events.

Safety and AEs

All patients experienced at least 1 AE during the study (Table 5), and 88% of the reported AEs were suspected to be treatment-related. The most common drug-related AEs (all grades) included diarrhea (76%), fatigue (26%), peripheral neuropathy (20%), nausea (20%), and dehydration (10%). Grade 3/4 AEs were reported for 60% of the patients, and they most frequently included diarrhea (24%), hypokalemia (8%), pulmonary embolisms (8%), dehydration (8%), and peripheral neuropathy (4%). No patient had grade 4 diarrhea or peripheral neuropathy. Hematologic and liver function abnormalities were mostly grade 1 events, and no grade 4 events were noted.

Serious AEs were experienced by 25 patients (50%), of whom 20 had grade 3/4 AEs, including diarrhea (20%), dehydration (10%), pulmonary embolisms (8%), and convulsions (6%). The majority of the serious AEs, other than diarrhea, were thought to be unrelated to the study drug.

Three patients died within 28 days of the last dose of the study drug, and these deaths were unrelated to the

TABLE 5. Incidence of Adverse Events (>10% of All Grades), Regardless of the Study Drug Relation

Adverse Event	Grade 3/4, No. (%)	All Grades, No. (%)
Any	30 (60)	50 (100)
Diarrhea	12 (24)	38 (76)
Fatigue	1 (2)	25 (50)
Neuropathy, peripheral	2 (4)	14 (28)
Nausea	0	14 (28)
Headache	1 (2)	11 (22)
Constipation	0	9 (18)
Muscular weakness	0	8 (16)
Dehydration	3 (6)	7 (14)
Insomnia	0	7 (14)
Vomiting	0	7 (14)
Convulsion	2 (4)	6 (12)
Edema, peripheral	1 (2)	6 (12)
Dyspnea	0	6 (12)
Rash	0	6 (12)

treatment: 1 was due to brain metastases, and 2 were due to peritonitis and pneumonia. There were no study drug–related deaths.

Salvage Treatment

Twenty-nine of the 50 patients received no further treatment. The various salvage regimens used were pemetrexed (4), temozolomide (3), radiation (3), surgical resection (1), topotecan (1), erlotinib (1), irinotecan and bevacizumab (1), bevacizumab (1), and gemcitabine and carboplatin (1). There were no available data on salvage treatment for 5 patients.

DISCUSSION

This study is the largest prospective trial of chemotherapy for recurrent brain metastasis reported to date and is the only study solely focusing on NSCLC. It serves as a benchmark and provides reliable historical controls for future trials in unselected NSCLC.

Patupilone, an epothilone B with good blood-brain barrier penetration, was found to have some activity in a heavily pretreated population of NSCLC patients with brain metastases. However, it was relatively poorly tolerated, with a fourth of the patients discontinuing the drug because of AEs. The toxicities were similar to those demonstrated in a recently published breast cancer brain metastasis phase 2 trial, which did not meet its primary endpoint of 35% 3-month central nervous system progression-free survival.[24] Although the patients in our study had relatively favorable prognostic factors in terms of age and performance status, the majority had recurrent brain metastases within <3 months. They did poorly overall with a median OS of 8.8 months, which is similar to the results of other studies.[6] We did not have information on the number of brain metastases or extracranial metastases at the time of treatment initiation, but the majority died of progressive brain metastases and not systemic disease. This highlights the fact that in addition to brain-penetrating properties, there is a need to develop agents that have improved antitumor activity. A limiting factor other than central nervous system penetration is the difference in blood-tumor barrier permeability. Although the blood-tumor barrier is thought to be compromised in brain metastases, the extent and magnitude are heterogeneous.[25] This leads to variable uptake of the drug, which may not reach cytotoxic concentrations within brain metastases. In general, the blood pharmacokinetic data for patupilone were similar to those seen in a previously published phase 1 study.[26]

Several chemotherapeutic agents such as cisplatin, carboplatin, vinorelbine, etoposide, and pemetrexed in various combinations have been tried as first-line treatments in patients with brain metastases from NSCLC with response rates of 23% to 50%, with the best results observed in synchronous brain metastases in chemotherapy-naive patients.[27-30] However, traditional chemotherapy has been found to be less effective in patients who are pretreated with chemotherapy or radiotherapy,[30] and only small, rare studies of NSCLC brain metastases are available. Most of the reported experience is derived from studies grouping recurrent brain metastases from all histologies, with outcomes of NSCLC described as a subgroup.[7,8] Temozolomide, both as a single agent and in combination, has been the most studied agent in this setting and is associated with poor objective response rates of 0% to 10% in patients and a TTP of up to 3.6 months, although some studies have shown higher rates of disease control (including stable disease)[7-10,31]; a single-agent study specifically focusing on NSCLC that allowed enrollment of brain metastasis patients was terminated early because of a lack of efficacy.[31] Comparison with our results is challenging because of the varying response criteria[32,33] and small sample sizes of previous studies.

Molecularly targeted agents are increasingly used for NSCLC harboring specific genetic alterations. Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors such as erlotinib and gefitinib have demonstrated high response rates of more than 74% to 88% in previously untreated patients with brain metastases from EGFR-mutant NSCLC.[12,34,35] A prospective trial of gefitinib in pretreated patients achieved disease control of 27% and median progression-free survival of 3 months.[11] Pulsatile high-dose weekly erlotinib led to an objective response

rate of 67% with a median TTP of 2.7 months in patients with EGFR-mutant lung cancers, the majority of whom had been previously treated.[36] In a retrospective pooled analysis of phase 2 and 3 trials with crizotinib (an anaplastic lymphoma kinase [ALK] tyrosine kinase inhibitor) designed to evaluate outcomes of ALK-rearranged NSCLC patients with asymptomatic, untreated brain metastases, 9% of patients were found to have an objective response, and another 70% had stable disease.[37] A more recent phase 1/2 study of alectinib in crizotinib-resistant, ALK-positive NSCLC demonstrated an objective response rate of 52% in 21 patients with brain metastases.[38] Overall, the use of this targeted therapy is limited to the 5% to 20% of NSCLC patients with EGFR-mutant or ALK-positive tumors, but clearly in pretreated individuals, the median TTP is not more than 3 months.[39] However, median progression-free survival of 8 months has been seen with a combination of erlotinib and whole-brain radiotherapy, and the initial results with alectinib appear promising.[38-40]

This study had several limitations. We did not have uniform data on the status of systemic disease in several patients. Cerebrospinal fluid pharmacokinetics would have been helpful for determining whether cytotoxic concentrations of patupilone were attained. We did not have information on the molecular subtypes of the patients to identify whether a certain group of patients fared better than others.

In conclusion, patupilone was found to have activity in patients with brain metastases from NSCLC, but it was poorly tolerated. Further development of this drug for any indication was discontinued after a recent phase 3 study did not meet its primary endpoint of improved OS in platinum-refractory or -resistant patients with recurrent epithelial ovarian cancer, primary fallopian tube cancer, or primary peritoneal cancer, although the overall response rate was higher in the patupilone arm.[41]

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CONFLICT OF INTEREST DISCLOSURES

Lakshmi Nayak reports personal compensation from Amgen (Advisory board) outside of submitted work. Lisa M. DeAngelis reports funding from Novartis during the conduct of the study and personal fees from BMJ Publishing Group, CarThera, Celgene, Juno Therapeutics, and Pharmaco-Kinesis Corporation outside the submitted work. Ramaswamy Govindan reports personal fees from Celgene, Bayer, Roche, Clovis Oncology, Helsinn Healthcare, Boehringer Ingelheim, AbbVie, GlaxoSmithKline, GeneCentric, Pfizer, Merck, and Genentech outside the submitted work. Shirish Gadgeel reports personal compensation from Novartis for activities outside the submitted work. David M. Peereboom reports research support from Pfizer and research funding from Novartis for activities outside the submitted work. Ming Zheng and Patrick Urban are employees of Novartis. Lauren E. Abrey is an employee of Roche. Antonio Omuro reports personal fees from Novartis, Bristol-Myers Squibb, Juno Therapeutics, and Stemline for activities outside the submitted work. Patrick Y. Wen reports research support from Novartis for the submitted work; he also reports research support from AbbVie, Agios, AngioChem, Astra Zeneca, Cubist, Exelixis, Genentech/Roche, GlaxoSmithKline, Karyopharm, Merck, Novartis, Regeneron Pharmaceuticals, Sanofi-Aventis, and Vascular Biogenics and working on advisory boards for AbbVie, Cavion, Celldex, Genentech/Roche, Momenta, Novocure, Sigma Tau, Midatech, Novacure, and Vascular Biogenics and for a speakers bureau for Merck.

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