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ORIGINAL REPORT

Carboplatin and Paclitaxel in Combination With Either Vorinostat or Placebo for First-Line Therapy of Advanced Non–Small-Cell Lung Cancer

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ABSTRACT

Purpose
Vorinostat, a histone deacetylase inhibitor, exerts anticancer effects by both histone and nonhistone–mediated mechanisms. It also enhances the anticancer effects of platinum compounds and taxanes in non–small-cell lung cancer (NSCLC) cell lines. This phase II randomized, double-blinded, placebo-controlled study evaluated the efficacy of vorinostat in combination with carboplatin and paclitaxel in patients with advanced-stage NSCLC.

Patients and Methods
Patients with previously untreated stage IIIB (ie, wet) or IV NSCLC were randomly assigned (2:1) to carboplatin (area under the curve, 6 mg/mL × min) and paclitaxel (200 mg/m^2 day 3) with either vorinostat (400 mg by mouth daily) or placebo. Vorinostat or placebo was given on days 1 through 14 of each 3-week cycle to a maximum of six cycles. The primary end point was comparison of the response rate.

Results
Ninety-four patients initiated protocol therapy. Baseline patient characteristics were similar between the two arms. The median number of cycles was four for both treatment arms. The confirmed response rate was 34% with vorinostat versus 12.5% with placebo ($P = .02$). There was a trend toward improvement in median progression-free survival (6.0 months *v* 4.1 months; $P = .48$) and overall survival (13.0 months *v* 9.7 months; $P = .17$) in the vorinostat arm. Grade 4 platelet toxicity was more common with vorinostat (18% *v* 3%; $P < .05$). Nausea, emesis, fatigue, dehydration, and hyponatremia also were more frequent with vorinostat.

Conclusion
Vorinostat enhances the efficacy of carboplatin and paclitaxel in patients with advanced NSCLC. HDAC inhibition is a promising therapeutic strategy for treatment of NSCLC.

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INTRODUCTION

Platinum-based chemotherapy remains the cornerstone of treatment of advanced non–small-cell lung cancer (NSCLC).[1] For patients with a good performance status, improvements in both survival and quality of life have been noted with combination chemotherapy.[2] Though the addition of targeted agents, such as bevacizumab and cetuximab, to chemotherapy has resulted in improvement in outcomes for patients with advanced NSCLC, the benefits are modest.[3-5] Therefore, there is a continued need to develop novel strategies to improve the efficacy of systemic therapy in NSCLC.

Histone deacetylase (HDAC) inhibitors are members of a novel class of anticancer agents that act by regulating chromatin structure and function.[6] They induce acetylation of histones, the core proteins around which the nucleic acids are wound, and they render the DNA more open for transcription, which results in increased expression of several genes that are often silenced in cancer, such as tumor suppressor genes. Acetylation of regulatory proteins, such as heat shock protein 90, hypoxia-inducing factor α, and α tubulin, also may contribute to the anticancer effects of HDAC inhibitors.[7-10] These molecular events ultimately result in induction of apoptosis and cell cycle arrest, modulate anticancer immunity, and inhibit angiogenesis.[8,11-14]

Vorinostat, a hydroxamic acid derivative that inhibits class I and II HDACs, has been approved by the US Food and Drug Administration for the

treatment of patients with cutaneous T-cell lymphoma.[15] It is administered orally on either a continuous daily or intermittent schedule. The common adverse effects of vorinostat include nausea, emesis, fatigue, and thrombocytopenia.[16] In preclinical studies, vorinostat exhibits synergistic anticancer effects when given in combination with taxanes and platinum compounds.[17-19] It induces tubulin acetylation in a synergistic manner when given in combination with paclitaxel, which leads to induction of apoptosis. Vorinostat also enhances DNA fragmentation induced by platinum compounds. This is thought to be caused by the higher degree of platinum-adduct formation when the chromatin is rendered to a more open configuration.

In early-phase clinical trials, HDAC inhibitors have demonstrated anticancer activity in a variety of solid-organ malignancies, primarily in the form of disease stabilization.[20-23] In a phase II study, vorinostat monotherapy was associated with disease stabilization in eight of 16 patients with refractory NSCLC.[24] Given that several patients in this study had experienced progression with multiple prior systemic therapy regimens, the efficacy of vorinostat was clinically relevant to pursue in combination regimens rather than as monotherapy. Earlier, we conducted a phase I clinical study to determine the optimal doses for the combination of the vorinostat, carboplatin, and paclitaxel and to assess the safety and feasibility of administration of this regimen.[25] Partial responses were observed in 10 of 19 patients with advanced-stage NSCLC and an additional four patients had disease stabilization. There were no major drug-drug pharmacokinetic interactions between vorinostat and paclitaxel. These promising preclinical and clinical data led to the present randomized, phase II, placebo-controlled study.

PATIENTS AND METHODS

Patient Eligibility

Patients (age $\geq$ 18 years) with cytologic or histologic confirmation of NSCLC, stage IIIB (with malignant pleural effusion) or IV disease, performance status (PS) of 0 or 1 on the Eastern Cooperative Oncology Group (ECOG) scale, and no prior therapy for advanced-stage disease were eligible. Presence of measurable disease was required. Qualifying laboratory criteria were as follows: leukocytes $\geq$ 3,000/μL, absolute neutrophil count (ANC) $\geq$ 1,500/μL, platelets $\geq$ 100,000/μL, serum total bilirubin less than or equal to the institutional upper limit of normal (ULN), serum transminases $\leq$ 2.5 $\times$ ULN, and serum creatinine less than or equal to the ULN. Patients with serum creatinine levels at or greater than the ULN were eligible if the estimated creatinine clearance was $\geq$ 60 mL/min/1.73 m^2. Patients with brain metastasis should have received appropriate local therapy and should have had no evidence of progression in the brain for at least 3 weeks. Those who received prior radiotherapy should have recovered from all treatment-related adverse events. Patients with history of allergic reactions to paclitaxel, prior therapy with a known HDAC inhibitor, peripheral neuropathy greater than grade 1, and inability to take oral medications were ineligible. Those with serious, intercurrent illness that interfered with the ability to administer combination chemotherapy were excluded. Pregnant women were excluded, and those with reproductive potential were required to use contraception. Human immunodeficiency virus–positive patients on antiretroviral therapy were excluded because of the potential for unfavorable drug-drug interactions. All patients provided written informed consent. The study was approved by the institutional review board at each institution (CONSORT diagram, Fig 1).

Treatment Plan

Patients were randomly assigned to treatment with carboplatin and paclitaxel combined with either vorinostat or placebo. Carboplatin and paclitaxel were administered on day 3 of each treatment cycle. On the days of chemotherapy administration, vorinostat was administered in the clinic, after which paclitaxel 200 mg/m^2, diluted in 500 mL of 5% dextrose, was given as a 3-hour intravenous (IV) infusion. Premedications for paclitaxel included dexamethasone (20 mg oral doses at 12 hours and 6 hours before the paclitaxel), diphenhydramine (50 mg IV), and a histamine receptor–2 antagonist (ranitidine 50 mg or cimetidine 300 mg IV). Appropriate substitutions for premedications were allowed to follow local institutional guidelines. After the paclitaxel infusion, carboplatin, dosed to achieve an area under the concentration versus time curve (AUC) of 6 mg/mL $\times$ min, dissolved in 100 mL of 5% dextrose or 0.9% saline, was administered as a 30-minute IV infusion. The carboplatin dose was calculated by using the Calvert formula.[26] Vorinostat and placebo were provided by the Cancer Therapy Evaluation Program (CTEP) of the National Cancer Institute (NCI; Bethesda, MD). Vorinostat 400 mg or a matching placebo was given on days 1 through 14 of each treatment cycle. The sequence of vorinostat first and followed by chemotherapy on day 3 were derived from the favorable preclinical data with this schedule.[17] Patients were required to maintain a calendar to document intake of the vorinostat. Missed doses were not to be made up. Treatment cycles were repeated every 3 weeks. Treatment was continued until disease progression, unacceptable toxicity, or withdrawal of consent occurred, to a maximum of six cycles. Crossover from the experimental to the control arm was not allowed. Granulocyte colony-stimulating factor was not allowed during the first cycle of therapy, but it was allowed as secondary prophylaxis for subsequent cycles according to standard guidelines.

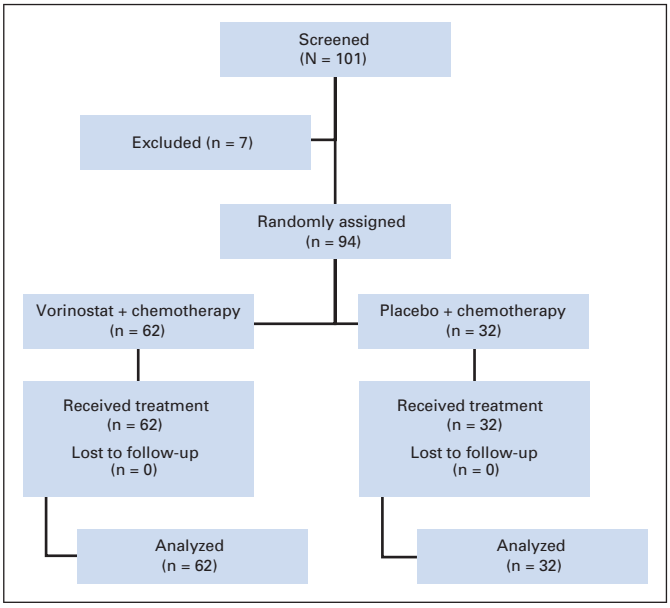

Fig 1. CONSORT diagram.

Toxicity was graded by the NCI Common Terminology Criteria version 3.0. All treatment-related toxicities (except neuropathy and alopecia) were required to be grade 1 or fewer before initiation of a new treatment cycle. Dose modifications were performed for grade 3 or 4 toxicities. Patients who experienced grade 3 or 4 toxicities attributable to vorinostat had dose reductions by 100 mg/d in subsequent cycles. Paclitaxel and carboplatin doses were reduced by 25 mg/m^2 and an AUC of 1, respectively, on the basis of adverse effects attributed to either drug. Patients who required more than two dose reductions were removed from the study. Reduction in the dose of two drugs at the same time was considered one dose reduction. For grade 4 neutropenia, the dose of paclitaxel was reduced for the first episode. For the second episode of grade 4 neutropenia or grades 3 to 4 neutropenia associated with fever, the doses of both paclitaxel and vorinostat were reduced. For grade 3 platelets, the dose of carboplatin was reduced for the first episode, and the dose of vorinostat was reduced for the second episode. For grade 4 platelets, the doses of both

carboplatin and vorinostat were reduced. For nonhematologic toxicities, including clinically significant laboratory abnormalities, the dose of the relevant agent was reduced.

Patient Evaluations

Pretreatment evaluations were as follows: history and physical examination (H&P), assessment of PS, CBC, and hepatic and renal function tests. An ECG was obtained if clinically indicated. Women of reproductive age underwent a serum pregnancy test. CBC and hepatic and renal function tests were done weekly during cycle 1. From cycle 2 onward, only the CBC was checked weekly, and the rest of the laboratory tests were done before initiation of each cycle of therapy. Radiologic studies were performed after every two cycles of therapy. H&P and assessment of PS were done before initiation of each cycle. Responses were assessed by the treating physician by RECIST (Response Evaluation Criteria in Solid Tumors).[27]

Statistical Methods

The primary end point of this double-blinded, placebo-controlled study was to compare the response rate associated with the addition of vorinostat to the regimen of carboplatin and paclitaxel. A planned sample size of 93 randomly assigned (2:1) patients provided 80% power to detect an improvement in response rate from 25% in the control arm to 50% in the experimental arm, with a one-sided type-I error of 10%. This calculation was carried out by using nQueryAdvisor 5.0 software on the basis of methods given for Fisher's exact power calculation with a one-sided α.[28] Patients were stratified on the basis of sex and presence or absence of brain metastasis. The projected accrual rate was seven patients per month, and the actual accrual was eight patients per month. Secondary end points included assessment of the safety profile and evaluation of progression-free survival and overall survival for both treatment arms. All treated patients were included in the analysis of efficacy and safety. The toxicities were tabulated by organ system. Time to disease progression and overall survival were evaluated by using the Kaplan-Meier method. Differences between the two treatment arms with respect to survival end points were evaluated by using the log-rank test, and the hazard ratio was calculated by using Cox regression in *S*-Plus. Statistical tests were two sided, except for the exact tests that were one sided, as per the preplanned analysis.

Table 1. Patient Baseline Demographic and Clinical Characteristics

Characteristic	Treatment Group: Carboplatin + Paclitaxel + Vorinostat No.	%	Carboplatin + Paclitaxel + Placebo No.	%
No. of patients	62		32	
Male sex	38	61	20	63
Age, years				
Median	64		66.5	
Range	32-83		48-85	
< 65	34	55	11	34
65-70	11	18	11	34
> 70	17	27	10	31
Ethnicity				
White	53	85	27	84
African American	5	8	4	13
Other	4	7	1	3
Brain metastasis	10	16	5	16
ECOG performance status				
0	24	39	13	41
1	38	61	19	59
Stage				
IIIB	5	8	1	3
IV	57	92	31	97
Histology				
NSCLC NOS	27	44	13	41
Adenocarcinoma	18	29	11	34
Squamous cell carcinoma	12	19	6	19
Large-cell carcinoma	2	3	1	3
Other	3	5	1	3

Abbreviations: ECOG, Eastern Cooperative Oncology Group; NSCLC, non–small-cell lung cancer; NOS, not otherwise specified.

RESULTS

Patient Characteristics

A total of 101 patients signed consent, and 94 patients completed registration and initiated treatment. Patients were enrolled between May 2007 and June 2008; 62 of these patients were treated in the vorinostat arm, and 32 were treated in the placebo arm. The median ages of patients were 64 and 66.5 years, respectively, for the two treatment arms (Table 1). Patients older than 70 years accounted for 27% and 31% of the vorinostat and placebo arms, respectively. NSCLC not otherwise specified (NOS) accounted for approximately 40% of patients entered, and an equal proportion of patients with squamous histology were in the two treatment arms. Brain metastasis was present in 16% of the patients in both arms of the study. One patient in the placebo arm was removed from study after only 3 days of entry because of detection of brain metastasis. Overall, there were no clinically or statistically significant differences in baseline characteristics between the two treatment arms.

Treatment

A median of four cycles of therapy were given to patients in both arms of the study (range, one to six cycles). Sixteen patients (26%) discontinued treatment in the vorinostat arm after just one cycle of therapy compared with five patients (16%) in the placebo arm. Patient refusal (n = 4) and toxicity (n = 5) were the most common reasons for early discontinuation of therapy (before second cycle) with vorinostat. Fifty-three percent of patients completed at least four cycles of therapy with vorinostat compared with 56% with placebo. The proportions of patients who completed all six cycles of therapy were 29% and 41%, respectively, for the vorinostat and placebo arms. Disease progression was the most common reason for treatment discontinuation on the placebo arm, at 34%, compared with 18% on the vorinostat arm (Table 2).

Safety

Grade 4 thrombocytopenia was more common with the addition of vorinostat to chemotherapy (18% *v* 3%; $P < .05$). This was not associated with any grade 3 or 4 hemorrhage. Two patients experienced fever associated with grade 3 neutropenia on the vorinostat arm. Grade 2 or 3 nausea, vomiting, diarrhea, dehydration, fatigue, and hyponatremia were more frequent in the vorinostat arm compared with chemotherapy and placebo, though these differences were not statistically significant. There were two treatment-related deaths, both in the vorinostat arm. One patient died as a result of infection with grade 3 neutropenia, and the cause of death in the other patient was undetermined. The toxicity data are summarized in Tables 3 and 4.

Efficacy

The confirmed response rate was 34% (95% CI, 22% to 47%) among patients who received vorinostat in combination with chemotherapy compared with 12.5% (95% CI, 4% to 29%) among patients

Table 2. Reasons for Treatment Discontinuation

Reason	Treatment Group: Carboplatin + Paclitaxel + Vorinostat No.	%	Carboplatin + Paclitaxel + Placebo No.	%
Progression of disease	11	18	11	34
Toxicity	15	24	3	9
Early death	5	8	3	9
Intercurrent illness	1	2	—	—
Patient refusal	7	11	1	3
Treatment completed per protocol	20	32	12	38
Information not available	1	2	—	—
Received other treatment	2	3	1	3
Other*	—	—	1	3

*Patient was removed from study after only 3 days of entry due to detection of brain metastasis.

who received placebo and chemotherapy ($P = .02$, one-sided Fisher's exact method). One patient experienced a complete response with vorinostat. Among patients with squamous histology, four (33%) of 12 patients experienced partial response with vorinostat compared with none of six patients with placebo. Objective responses were noted in 17 (34%) of 50 patients with nonsquamous histology in the vorinostat arm compared with four (16%) of 26 patients in the placebo arm. During median follow-ups (of alive patients) of 10.3 months in the vorinostat arm and 11.3 months in the placebo arm, there was a favorable trend toward improvement in median progression-free survival and overall survival with the addition of vorinostat to chemotherapy (Fig 2). The median progression-free survival durations were 6.0 months (95% CI, 4.3 to 6.9 months) and 4.1 months (95% CI, 1.9 to 5.5 months) for the vorinostat and placebo arms, respectively (hazard ratio, 0.84; $P = .48$, adjusted for stratification factors). The median overall survivals were 13.0 months (95% CI, 9.7 to not reached) and 9.7 months (95% CI, 6.0 to 13.0 months) for the vorinostat and placebo arms, respectively (hazard ratio, 0.68; $P = .17$). The 1-year overall survival rate also was more favorable with vorinostat at 51% compared with 33% with placebo.

DISCUSSION

Systemic therapy has become integral to the treatment of all stages of NSCLC, with the exception of stage IA disease.[29-31] Platinum-based combinations have demonstrated survival benefits in advanced-stage and early-stage NSCLC. However, a plateau has been observed with the existing agents that have necessitated the evaluation of novel strategies to improve the efficacy of platinum-based, two-drug regimens. HDAC inhibitors constitute a novel class of agents that have demonstrated efficacy in the treatment of hematologic malignancies, either as monotherapy or in combination regimens. The mechanisms by which HDAC inhibitors exert anticancer effects appear to be disease dependent and target dependent.[32] This study was prompted by promising activity noted in our phase I study with this combination. To understand the mechanisms behind the favorable interaction, we first conducted a series of preclinical studies of vorinostat in combination with carboplatin and paclitaxel in various NSCLC cell lines.[17] Synergy was noted among the three agents and was more pronounced when the administration of vorinostat preceded carboplatin and paclitaxel. This sequence subsequently was utilized for this clinical trial. Our experiments also documented a dose-dependent enhancement of DNA fragmentation with the addition of vorinostat to carboplatin, and this effect was independent of the p53 gene status.

Paclitaxel binds to tubulin and alters the dynamic equilibrium between microtubule polymerization and depolymerization. HDAC 6, located in the cytoplasm, deacetylates tubulin by binding to the microtubule motor complex.[33] Preclinical studies have documented synergistic tubulin acetylation and subsequent mitotic arrest when cells were exposed to paclitaxel in combination with tubacin, a specific inhibitor of HDAC 6.[34] Our preclinical studies demonstrated synergistic enhancement of tubulin acetylation and induction of apoptosis with associated poly (ADP-ribose) polymerase cleavage on exposure to vorinostat and paclitaxel in various NSCLC cell lines.[17] The results of the randomized, phase II study reported here have confirmed the preclinical observations of improved anticancer activity and the promising data noted in our earlier, phase I study.

The primary end point of objective response rate was approximately three-fold higher with the addition of vorinostat to the regimen of carboplatin and paclitaxel. There was also an overall improvement in median progression-free survival and overall survival with the vorinostat combination regimen. The outcomes for the control arm of

Table 3. Grades 3 and 4 Hematologic Toxicity

Toxicity	Treatment Group by Grade: Carboplatin + Paclitaxel + Vorinostat 3 No.	%	4 No.	%	Carboplatin + Paclitaxel + Placebo 3 No.	%	4 No.	%
Hemoglobin	7	11	—	—	3	9	—	—
Leukocytes	10	16	6	10	3	9	3	9
Neutrophils	4	6	23	37	6	19	9	28
Platelets	9	15	11	18	4	13	1	3
Fever with grades 3 to 4 neutrophils	2	3	—	—	—	—	—	—

NOTE. These data represent toxicity by worst grade experienced per patient during the course of study therapy.

Table 4. Nonhematologic Toxicity

Toxicity	No. of Patients by Treatment Group and Grade					
	Carboplatin + Paclitaxel + Vorinostat			Carboplatin + Paclitaxel + Placebo		
	2	3	4	2	3	4
Albumin	3	0	0	2	0	0
Alopecia	14	0	0	8	0	0
Anorexia	9	1	0	3	0	0
AST/ALT/alkaline phosphatase	2	1	0	—	—	—
Atrial fibrillation/flutter	1	1	0	—	—	—
Serum bilirubin, high	1	0	0	1	0	0
Serum calcium, low	6	0	0	1	0	0
Confusion/personality/behavior	1	1	0	1	0	1
Creatinine	0	1	0	—	—	—
Constipation	3	0	0	3	1	0
Dehydration	1	6	0	0	2	0
Diarrhea	6	3	0	3	0	0
Dizziness	2	0	0	—	—	—
Dyspnea	1	1	1	0	2	1
Fatigue	20	8	0	7	1	0
Serum glucose, high	8	2	1	1	1	0
Hiccoughs	—	—	—	0	1	0
Hypotension	3	2	0	1	2	0
Hypertension	0	1	0	—	—	—
Infection	3	3	0*	0	1	1
Insomnia	2	0	0	2	0	0
Nausea/vomiting	13	3	0	4	0	0
Neuropathy	10	0	0	5	1	0
Serum magnesium, low	2	0	0	—	—	—
Muscle weakness	4	2	0	—	—	—
Myalgia	4	2	0	2	1	0
Pain, other	9	1	0	7	1	0
Phlebitis	1	0	0	1	0	0
Serum phosphate, low	1	6	0	1	1	0
Serum potassium, low	0	8	2	1	2	0
Rash	1	0	0	1	0	0
Serum sodium, high	0	1	0	—	—	—
Serum sodium, low	0	11	1	0	3	0
Thrombosis/pulmonary embolism	0	1	2	1	0	0

NOTE. These data represent toxicities by worst grade experienced, attributed as possible, probable, or definitely related to study therapy, and they exclude toxicities with a maximum grade of 2 that occur in only one patient.
*One patient had grade 5 infection.

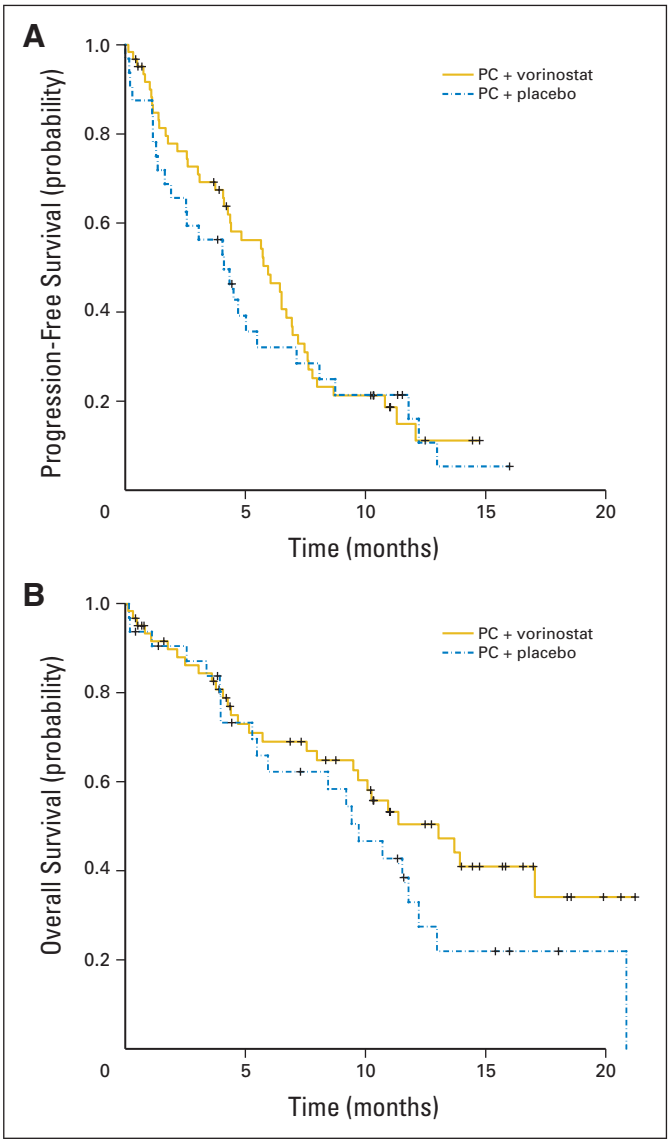

Fig 2. (A) Kaplan-Meier curve for progression-free survival. (B) Kaplan-Meier curve for overall survival. PC, paclitaxel and carboplatin.

carboplatin and paclitaxel, both in terms of efficacy and safety, are consistent with other randomized studies with this combination.[3,29,35] Comparable anticancer effects were noted with the vorinostat-based regimen in both squamous and nonsquamous histologic subtypes, which suggests the regimen has wider applicability in all patients with NSCLC. However, certain toxicities, such as nausea, vomiting, fatigue, hyponatremia, and thrombocytopenia, were common in the vorinostat arm and probably were the reason for early discontinuation in 26% of patients. Though the median number of cycles of treatment administered (ie, four) in both arms was similar, the proportion of patients that completed six cycles of therapy was higher in the chemotherapy than in the placebo arm (41% *v* 29%).

Although this study suggests that vorinostat may improve efficacy of carboplatin and paclitaxel, this comes at the cost of increased toxicity. Efforts to improve the therapeutic index of this regimen are warranted before testing in a large, randomized, phase III study. Because the proposed mechanism of synergy is the enhancement of efficacy of chemotherapy by vorinostat, we intend to evaluate a shorter schedule of vorinostat in this combination. This notion is supported by the results of a phase I study of vorinostat in combination with cisplatin and gemcitabine by Tredaniel et al.[36] Their study administered vorinostat on days 1 through 10 of each 3-week treatment cycle. This was tolerated well and also was associated with promising anticancer effects in previously untreated patients with advanced-stage NSCLC. Of 31 evaluable patients, 11 had a partial response and 15 had disease stabilization, which accounted for an overall disease control rate of 84%. Although these data are aligned with the results of our study, another recent, randomized study that evaluated the addition of vorinostat to chemotherapy in patients with advanced NSCLC was closed early for futility by the Data and Safety Monitoring committee, and the results are awaited. This study utilized a different schedule and

slightly different eligibility criteria. Vorinostat was given on days 1 through 14 on each cycle, and carboplatin and paclitaxel were administered on day 5 of cycle 1 only and on day 1 of each subsequent cycle. In addition, only patients who were ineligible to receive bevacizumab, or those that did not have access to bevacizumab, were included. To what extent these differences contributed to the divergent results from our study are unclear.

The favorable preclinical interactions; the promising results of our phase I study; and the documentation of enhanced activity in this placebo-controlled, randomized study provide the rationale for additional evaluation of this strategy, not only in NSCLC but potentially in other tumor types that are treated with the combination of a platinum compound and taxanes. HDAC inhibition, thus, is a promising therapeutic strategy for treatment of NSCLC and other solid malignancies.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. 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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