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Stromal Caveolin-1 Is Associated With Response and Survival in a Phase II Trial of *nab*-Paclitaxel With Carboplatin for Advanced NSCLC Patients

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Abstract

In this phase II trial, carboplatin with nanoparticle albumin-bound (nab)-paclitaxel as first-line therapy for advanced non-small-cell lung cancer (NSCLC) was evaluated. Most patients had squamous cell histology. Tumor-associated stromal caveolin-1 (Cav-1) expression was correlated with improved response rate and survival in NSCLC patients who received nab-paclitaxel in this phase II trial. These results suggest Cav-1 might serve as a potential biomarker in this patient population.

Background—The combination of bevacizumab with platinum-based chemotherapy results in greater response rate (RR) and overall survival (OS) in advanced non-small-cell lung cancer (NSCLC). Bevacizumab is contraindicated in patients with squamous histology or hemoptysis. Nanoparticle albumin-bound (nab)-paclitaxel is a novel formulation of paclitaxel with greater dose tolerance and improved efficacy. We hypothesized that nab-paclitaxel and carboplatin would be superior to alternative doublets in advanced NSCLC patients ineligible for bevacizumab.

Patients and Methods—We conducted a single-arm phase II trial (NCT00729612) with carboplatin and nab-paclitaxel on day 1 of a 21-day cycle to evaluate RR (primary end point),

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Disclosure

The authors have stated that they have no conflicts of interest.

Supplemental Data

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safety, toxicity, and OS. Eligibility included: squamous histology, hemoptysis, or ongoing anticoagulation. Correlative studies included immunohistochemistry for secreted protein acid rich in cysteine (SPARC) and caveolin-1 (Cav-1).

Results—Sixty-three patients were enrolled. Most patients had squamous cell carcinoma (n = 48); other reasons for eligibility included hemoptysis (n = 11) and anticoagulation (n = 2). Toxicity Grade 3/4 included neuropathy, cytopenias, and fatigue. RR was 38% (24 partial response/0 complete response); 20 patients had stable disease (32%). Median progression-free survival was 5 months and median OS was 9.7 months. Immunohistochemistry for SPARC and Cav-1 was performed in 38 and 37 patients respectively. Although no association was found for SPARC expression in tumor or stroma with RR or OS, we found that higher Cav-1 levels in tumor-associated stroma was associated with improved RR and OS.

Conclusion—Carboplatin and nab-paclitaxel every 21 days demonstrated promising efficacy with tolerable toxicity in NSCLC patients ineligible for bevacizumab therapy. Further analysis and validation of Cav-1 and SPARC expression in tumor and stromal compartments as prognostic and/or predictive biomarkers of NSCLC or nab-paclitaxel treatment is warranted.

Keywords

Caveolin-1; Clinical Trial; nab-paclitaxel; Sensory neuropathy; SPARC

Introduction

Non-small-cell lung cancer (NSCLC) remains one of the most common cancers and the leading cause of cancer death around the world. Five-year overall survival (OS) for lung cancer has changed little over the past 30 years (from approximately 12% to 16%)¹ and chemotherapy remains the primary treatment for advanced disease.

The current standard approach in advanced NSCLC includes doublet platinum-based chemotherapy,^{2–4} with incorporation of targeted therapy if possible. In a pivotal phase III trial headed by the Eastern Cooperative Oncology Group (ECOG), ECOG 4599, the efficacy of chemotherapy (paclitaxel and carboplatin) with or without bevacizumab was compared. The combination of bevacizumab improved survival (OS and progression-free [PFS]) and response rates.⁵ This study, however, excluded a significant subset of patients, particularly those with squamous cell carcinoma, and raised questions about the optimal approach to chemotherapy for patients ineligible for bevacizumab.

A novel formulation of paclitaxel—nanoparticle albumin-bound (*nab*)-paclitaxel—has been approved by the Food and Drug Administration for use in NSCLC because of improved response rates compared with solvent-based paclitaxel.⁶ *nab*-Paclitaxel is composed of 130 nm-sized albumin bound to paclitaxel particles. The albumin functions as an interactive carrier of lipophilic drugs; albumin binds to a cell surface gp60 receptor (albondin) and enters into cells through caveolae-mediated endothelial transport.

A secreted protein acid rich in cysteine (SPARC), and caveolin-1 (Cav-1), a major component of caveolae, are both potential biomarkers for *nab*-paclitaxel. SPARC is commonly overexpressed in tumors; it binds albumin and any drugs bound to it, which

might facilitate caveolae-mediated endocytosis.^{7,8} This is reflected in the preclinical finding of a 30% to 40% greater intratumor concentration of *nab*-paclitaxel in murine tumors with a high rate of SPARC expression.⁹ In addition, stromal SPARC expression correlated with improved survival in a phase II trial with gemcitabine and *nab*-paclitaxel in advanced pancreatic cancer.¹⁰ Cav-1 has been investigated in NSCLC primarily as a driver of tumorigenesis and potential prognostic biomarker. Previous studies suggest that Cav-1 tumoral expression is associated with poor response to gemcitabine-based chemotherapy and worse survival.^{11,12}

Several clinical trials have evaluated *nab*-paclitaxel in NSCLC. Two early phase trials evaluated single agent *nab*-paclitaxel for previously untreated, advanced NSCLC either weekly or every 3 weeks with response rates of 16% to 30% and median survival of 11 months in both trials.^{13,14} In a pivotal randomized phase III trial carboplatin with either *nab*-paclitaxel weekly or solvent-based (sb) paclitaxel every 3 weeks in NSCLC were compared. This trial was open to all NSCLC histologies—squamous cell carcinoma accounted for 43% of the patient population. In this trial an overall response rate of 33% with *nab*-paclitaxel (vs. 25% for sb-paclitaxel; $P = .005$) was demonstrated in all patients with a response rate of 41% (vs. 24% for sb-paclitaxel; $P < .001$) in the squamous cell carcinoma subset of patients. The median PFS was 6.3 months and OS 12.1 months with the *nab*-paclitaxel regimen (compared with 5.8 months PFS and 11.2 months OS in the sb paclitaxel arm; $P = .214$ and $P = .271$, respectively).⁶

In our phase II trial we evaluated the clinical activity of carboplatin and *nab*-paclitaxel as first-line chemotherapy in NSCLC. The primary end point was response rate with secondary end points for survival and toxicity. In correlative studies we evaluated SPARC and Cav-1 expression in tumor and stromal tissue and evaluated their relationship to response and survival.

Patients and Methods

Patients

Between September 2008 and December 2011, we conducted a single-arm, single-institution phase II trial that included 63 patients with advanced or recurrent NSCLC (including malignant pleural effusion). Eligible patients included patients with contraindications to bevacizumab therapy, including squamous cell histology, hemoptysis, thromboembolic disease, requirement for therapeutic anticoagulation, or cavitary lung lesions. Brain metastases were permitted provided the patient had controlled disease after appropriate treatment and was able to be weaned from steroid therapy. All patients were required to have measurable disease, ECOG performance status of 0 to 2, and no known hepatitis (B or C) or HIV. Women of child-bearing age were required to have a negative serum pregnancy test within 7 days before enrollment. Adequate organ function and bone marrow reserve was required (absolute neutrophil count > 1500 , platelets $> 100,000$, total bilirubin < 1.5 mg/dL, alanine aminotransferase/aspartate aminotransferase ≤ 2.5 times the upper limit of normal, and creatinine < 1.5 mg/dL (or creatinine clearance > 50 mL/min).

Exclusion criteria included major surgery, open biopsy or significant traumatic injury within 4 weeks of receipt of first study drug, significant psychiatric illness that would impair adequate informed consent, baseline peripheral neuropathy Grade 2, pregnancy, or uncontrolled brain metastases (or leptomeningeal disease). Previous chemotherapy for stage IIIB, stage IV, or recurrent NSCLC (American Joint Committee on Cancer version 6) was not permitted; however, previous adjuvant chemotherapy or definitive chemoradiation for locally advanced disease were permitted. A 14-day break was required between palliative radiation therapy and study enrollment.

Study Design/Treatment Plan

The study was designed as a 2-stage Simon model based on response rates; 27 patients were enrolled in the first stage and 36 patients in the second stage. Interim analysis was performed to analyze response rate after the enrollment of the initial 27 patients. In the 2-stage design, if 4 patients responded of the first 27 patients, accrual was to be halted, however if 5 responded, accrual would continue to the planned total of 63 patients.

Chemotherapy included *nab*-paclitaxel (300 mg/m² for the first 40 patients—dose reduced to 260 mg/m² in the remaining 23 patients) followed by carboplatin area under the curve 6 administered as an intravenous infusion on day 1 of a 21-day cycle. No premedications were administered prophylactically for allergic reactions unless the patient had specific symptoms during a previous cycle. An antiemetic regimen of ondansetron 16 mg orally or 8 mg intravenously was administered before the chemotherapy. The use of prophylactic growth factors such as erythropoietin, granulocyte-colony stimulating factor, or granulocyte macrophage-colony stimulating factor was not permitted during the first cycle. If a patient suffered febrile neutropenia or > 7 days of Grade 4 neutropenia that required dose reduction, granulocyte-colony stimulating factor (filgrastim or pegfilgrastim) was used in subsequent cycles in place of a dose reduction at the discretion of the treating physician. For Grade 3 peripheral neuropathy, *nab*-paclitaxel was held until toxicity improved to at least Grade 1 and then restarted with a dose reduction (200 mg/m²). Grade 4 peripheral neuropathy also required holding *nab*-paclitaxel—treatment could be restarted with a reduction to 175 mg/m² if neuropathy improved to at least Grade 1. Patients were permitted to receive up to 6 cycles of treatment.

Clinical Benefit Evaluation

Measurable disease was required for study enrollment. Baseline computed tomography scans were done within 4 weeks of starting chemotherapy in all patients and repeated after every 2 cycles. Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0 was used for assessment of tumor response. All patients who responded were required to have their response confirmed 4 to 6 weeks after the first documentation of response. PFS and OS were calculated from the date of the first chemotherapy infusion.

Correlative Analysis

For immunohistochemistry, archival tissue was requested from all enrolled patients, and there was tissue available for 44 patients. Slides were deparaffinized in xylene (3 changes of 2 minutes each) and then rehydrated through graduated alcohols of 2 minutes each (100%,

95%, and 70%) and ended with distilled water. The slides were placed in a 3% peroxidase block for 5 minutes, then steam-retrieved for 25 minutes in pH 6.0 citrate buffer, cooled, and washed in running water. After rinsing in tris buffered saline, slides were incubated with a primary antibody for Cav-1 (rabbit monoclonal antibody, N-20, Santa Cruz, sc-894) at 1:200 or SPARC (osteonectin, mouse monoclonal antibody, ON1-1, Invitrogen, 33-5500) at 1:400 for 60 minutes in a Biocare Medical Intellipath Autostainer. After primary antibody incubation the slides were rinsed and incubated with an horseradish peroxidase polymer 2-step system conjugated antirabbit or mouse for 20 minutes. Slides were rinsed again in tris buffered saline, incubated with DAB+ (Dako) for 5 minutes, rinsed, and counterstained with hematoxylin for 10 seconds. Slides were then rinsed in ammonia water and dehydrated following the opposite order (70%, 95%, and 100% alcohol) that ended in xylene, then mounted, and coverslipped.

Immunohistochemical staining was evaluated by a board certified pathologist (K.S.) blinded to patient data. Cav-1 and SPARC expression was assessed in tumor tissue for staining intensity (0–3) and percentage (0–100%) which was used to derive an H-score ranging from 0 to 300, and in stroma tissue for staining intensity (0–3).¹⁵

Statistical Analysis

The primary end point was the response rate defined according to RECIST version 1.0 criteria. We expected that if the response rate was < 20% then this combination would not be considered worthy of further study. If the response rate was at least 35% (at least 16 of the 63 patients), then we would consider this combination of interest. The Simon 2-stage design criteria were an $\alpha = .10$, $\beta = .10$, $P_0 = .20$, and $P_1 = .35$. Sample size was based on an intent to treat analysis with no dropouts because of nonevaluable patients. Patients lost to follow-up or lacking protocol-specified disease evaluations were considered to have disease progression on the date of last contact. The 95% confidence interval (CI) for the overall response rate was estimated using exact binomial methods and median PFS and OS were estimated using Kaplan–Meier methods. All analyses were run using Stata 12.1 (Stata Corporation, College Station, TX). For the correlative study, patients were dichotomized into 2 groups based on Cav-1 or SPARC expression levels: for tumor H-score, high (median or greater) versus low (less than median); for stroma intensity score: high (2 and 3) versus low (0 and 1). The survival probabilities between groups were compared using a log-rank test. The analyses were conducted using SAS 9.3 (SAS, Inc; Cary, NC).

Results

Patient Characteristics

Between September 2008 and December 2011, 63 patients with an average age of 63 years (range, 36–82 years) were enrolled in the trial. The most common histology was squamous cell carcinoma (48 patients), followed by adenocarcinoma (9 patients), adenosquamous (2 patients), and poorly differentiated carcinoma/NSCLC not otherwise specified (4 patients). Demographic information is detailed in Table 1.

Treatment

The first 40 patients treated in the trial received *nab*-paclitaxel 300 mg/m². Because of observed toxicity (primarily sensory neuropathy), the dose was reduced to 260 mg/m². Patients received a median of 4 cycles (range, 1–7 cycles). Sixteen patients required dose reduction; most dose reductions occurred in the 40 patients treated at the higher dose of *nab*-paclitaxel (12 of 16 patients).

Response Rate and Survival

Of the enrolled patients, 54 patients were considered evaluable for response. Reasons for nonevaluation are detailed in Figure 1. One patient enrolled but died before receipt of any chemotherapy. Three patients died after cycle 1, 1 patient died before completion of cycle 2, and 2 patients withdrew after cycle 1. Partial response was the best response observed in 24 patients (38.1%; 95% CI, 26.1–51.2). No complete responses were demonstrated. Stable disease was demonstrated in 20 patients (32%). Ten patients (16%) had progressive disease. Overall response rate was 38.1%; the disease control rate (partial response + stable disease) was 70%. Secondary end points of the trial included evaluation of survival. A median PFS of 5.0 months (95% CI, 4.3–6.4) was observed with a median OS of 9.7 months (95% CI, 8.4–13.2; Figure 2).

Toxicity

All toxicities were assessed using Common Terminology for Adverse Events version 3.0. Expected toxicities were observed and were primarily Grades 1 and 2. Grade 3 or 4 toxicities that occurred in 5% of patients included cytopenias (anemia, thrombocytopenia, neutropenia), sensory neuropathy, neutropenic fever, infection, hyponatremia, hypoxia, dyspnea, dehydration, and fatigue. Other less common Grade 3 or 4 toxicities included motor neuropathy, seizure, confusion, muscle weakness, metabolic changes (alkalosis, hypokalemia, hypophosphatemia, hyperglycemia, hypermagnesemia), respiratory changes (respiratory failure, pulmonary hemorrhage, bronchospasm), hypotension, diarrhea, nausea, mucositis, renal failure, and anorexia.

Sensory neuropathy was particularly problematic in the patients who received *nab*-paclitaxel 300 mg/m²—16 patients of the first 40 treated (40%) experienced Grade 3 neuropathy and Grade 3 neuropathy was only observed in 3 patients (13%) after an amendment to change the starting dose to 260 mg/m². A total of 51 of the 63 patients developed neuropathy of any grade: 15 patients with Grade 1 neuropathy, 17 patients with Grade 2 neuropathy, and 19 patients with Grade 3 neuropathy. Six patients discontinued treatment because of Grade 3 sensory neuropathy; these patients received 3 to 5 cycles of treatment. Among patients who developed Grade 3 neuropathy, 15 patients (78%) received 4 cycles and only 4 patients received > 4 cycles. For patients with Grades 1 or 2 neuropathy, 15 patients received 4 cycles and 17 patients received > 4 cycles. Two patients also demonstrated Grade 3 motor neuropathy (1 at each dose level)—1 of these patients discontinued treatment after 3 cycles because of foot drop. Two Grade 5 toxicities possibly related to treatment were observed (dehydration and death not otherwise specified). Toxicities are detailed in Table 2.

Correlative Tissue Biomarker Studies

Tissue was requested from all enrolled patients before therapy, and there was archival tissue identified for 44 patients. The tissue sites were lung (70%), lymph nodes (11%), bone (4.5%), pleura (4.5%), and other metastases (10%, including pericardium, neck, subcutaneous tissue, and liver). After assessment of suitable tissue for immunohistochemistry, there were 38 and 37 patients for Cav-1 and SPARC staining, respectively. Of these patients, lack of response or clinical outcomes data resulted in only 31 and 33 patients available for response correlation, 25 and 26 patients for PFS correlation, and 31 and 33 patients for OS correlations for Cav-1 and SPARC, respectively.

In tumor or stromal tissue, SPARC levels were not significantly associated with altered response rates, or clinical outcomes (PFS or OS; see Supplemental Tables 1 and 2, and Supplemental Figures 1–4 in the online version). For Cav-1 levels in tumor tissue, higher Cav-1 levels were not significantly associated with altered response or clinical outcomes (see Supplemental Table 3, and Supplemental Figures 5–7 in the online version). However, higher Cav-1 levels in the stroma were significantly correlated with improved partial response rates (9 of 18 patients or 50%, vs. 3 of 15 patients or 20%; $P = .036$, Fisher exact test). Furthermore, a significantly improved OS was noted for patients with greater stromal Cav-1 expression (Figure 3A, log-rank $P = .008$). Of the 44 patients with available tissue, only 38 patients had tissue suitable for Cav-1 stromal staining. Of those, 31 patients had squamous histology and 7 patients had nonsquamous histology (1 adenosquamous, 5 adenocarcinoma, and 1 NSCLC not otherwise specified). Stromal Cav-1 expression was observed in squamous and nonsquamous histologies, with no significant differences detected in the expression of the 2 groups.

Discussion

In this phase II trial of *nab*-paclitaxel and carboplatin efficacy similar to previously reported doublet chemotherapy regimens was demonstrated including in the phase III trial by Socinski et al,⁶ who used weekly *nab*-paclitaxel: a significant improvement in response rates for squamous cell lung cancer patients compared with the patients with nonsquamous cell lung cancer—an overall response rate of 33% with *nab*-paclitaxel in all NSCLC patients with a response rate of 41% in the squamous cell carcinoma subset. The phase III trial also demonstrated numerically longer OS (all histologies 12.1 months, squamous cell histology 10.7 months) with the weekly *nab*-paclitaxel regimen than demonstrated in our trial (OS, 9.7 months).^{6,16} As a single-arm trial, however, we were limited by lack of comparison with standard paclitaxel.

Results of our trial suggest that dose density might be an important factor to enhance efficacy of *nab*-paclitaxel, particularly in the squamous cell population. Use of *nab*-paclitaxel every 3 weeks required an overall lower dose per cycle (260 mg/m² vs. 100 mg/m² weekly for 3 weeks [300 mg/m²]) because of toxicity. In the first 40 patients, dose reductions were required in 30% of patients; after empiric dose reduction of *nab*-paclitaxel dose this decreased to 17%. The phase III trial required dose reductions in 46% of treated patients, primarily because of cytopenias.⁶

Toxicity differences between the dosing schedules were also notable. Our trial also supports the reported data on neurotoxicity with taxanes; we observed a significant rate of peripheral neuropathy with every 3 weeks dosing which seems to be alleviated with weekly dosing. We observed Grade 3 sensory neuropathy in 30% of patients; in contrast, Socinski et al reported an incidence of only 3%.⁶ Dose reductions for sensory neuropathy were only performed in 2% of *nab*-paclitaxel patients when administered on the weekly schedule. The rates of cytopenias (anemia, neutropenia, and thrombocytopenia), however, were much lower with our dosing schedule (7.9%-9.5% vs. 13%–33%).⁶

Our trial also evaluated SPARC and Cav-1 expression in the tumor and stromal compartments as the primary correlative study. This portion of the trial had several key limitations; tissue collection was attempted for all patients but new biopsies were not required. Using archival samples limited availability; < 55% of the 63 patients enrolled had suitable tissue with available response or outcomes data. In addition, no new tissue samples were obtained to evaluate effect of treatment on SPARC or Cav-1 expression. In future trials mandatory biopsies might be considered to obtain more complete samples.

In our biomarker studies, SPARC expression in tumor or stromal tissue was not found to be associated with response or outcomes, consistent with other studies. The relationship between *nab*-paclitaxel and SPARC expression has not been clearly delineated. At least 1 animal model (pancreatic cancer) demonstrated saturation of SPARC and no relationship between SPARC expression and intratumoral *nab*-paclitaxel levels.¹⁷ This is in contrast with correlative studies in humans suggestive of a potential relationship and use of SPARC as a prognostic biomarker in NSCLC and/or predictive biomarker in other diseases.^{10,18,19} Our negative results could be because of our limited data set, although our results also support the concept that SPARC might not be related to *nab*-paclitaxel efficacy. In support of this, Hidalgo et al recently presented data that SPARC expression in the tumor or stroma was not prognostic or predictive of clinical outcomes in patients with pancreatic cancer treated with *nab*-paclitaxel and gemcitabine in the phase III Metastatic Pancreatic Adenocarcinoma Clinical Trial (MPACT) that established superiority of *nab*-paclitaxel and gemcitabine over gemcitabine alone.^{20,21}

This study is the first to demonstrate a role for stromal Cav-1 in NSCLC as a prognostic (and potentially predictive) biomarker. The possibility that stromal Cav-1 staining could serve as a predictive biomarker to *nab*-paclitaxel is supported by preclinical data for a role for Cav-1 in albumin-mediated endocytosis, through a gp60-dependent mechanism.^{22,23} Although we did not find that Cav-1 levels in tumor directly correlated with improved response or survival, stromal Cav-1 levels did significantly correlate with objective and partial response rates and OS. Others have shown that higher Cav-1 levels in the tumor are associated with worse outcome in NSCLC, potentially by promoting more aggressive tumor characteristics.^{11,12,24,25} Perhaps the reason for the lack of association between higher tumor Cav-1 levels and outcome is that the potential increased albumin-binding and higher tumor intracellular concentrations of *nab*-paclitaxel that lead to improved efficacy were counterbalanced by the tumor-promoting functions of Cav-1 in tumor cells. One possible explanation for the observed finding is that higher stromal Cav-1 levels allow for increased *nab*-paclitaxel uptake in stromal tissue, which subsequently exposes adjacent tumor tissues

to higher concentrations of *nab*-paclitaxel in the tumor microenvironment. Conversely, higher Cav-1 levels in stroma might also have tumor-suppressive properties, as has been shown in other studies.^{26–29} Regardless, additional validation of stromal Cav-1 as a prognostic biomarker in NSCLC and/or predictive biomarker for *nab*-paclitaxel therapy is warranted.

Conclusion

In our trial we demonstrated results similar to the larger phase III study and confirmed the activity of *nab*-paclitaxel combined with carboplatin, particularly in squamous NSCLC. In addition, we explored SPARC and Cav-1 expression as markers for response to *nab*-paclitaxel and demonstrated a correlation between stromal Cav-1 and clinical outcomes. Although every 3 weeks dosing remains an option, our trial confirmed that weekly dosing appears less toxic and might be more efficacious. Future directions might include the combination of *nab*-paclitaxel with targeted therapy for squamous cell lung cancer such as fibroblast growth factor receptor-targeted drugs. Because of the synergy between paclitaxel and bevacizumab, combinations with these other antiangiogenic agents might be attractive. In addition, further evaluation of stromal Cav-1 as a biomarker is indicated.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Clinical Practice Points

- In this phase II trial, *nab*-paclitaxel with carboplatin was evaluated in NSCLC patients ineligible for bevacizumab, primarily those with squamous cell carcinoma.
- Since completion of this trial, additional phase II and a phase III trial have also evaluated the role of first-line treatment with *nab*-paclitaxel.
- In the pivotal phase III trial, carboplatin in combination with either *nab*-paclitaxel weekly or sb paclitaxel every 3 weeks was compared.
- Results of the phase III trial demonstrated a statistically significant improved response rate with *nab*-paclitaxel, and a nonsignificant improvement in survival. In particular, subset analysis suggested clinical benefit was more significant in squamous cell carcinoma.
- We used *nab*-paclitaxel every 3 weeks in our phase II trial.
- Our results demonstrated that dosing *nab*-paclitaxel every 3 weeks had a response rate comparable with weekly dosing.
- Different toxicities were observed. Neuropathy was a dose-limiting toxicity for dosing *nab*-paclitaxel every 3 weeks. Fewer cytopenias were observed than in the phase III trial of weekly *nab*-paclitaxel dosing.
- Stromal Cav-1 levels were also evaluated and demonstrated correlation with response rate and survival.
- Results of this trial support the role of *nab*-paclitaxel in first-line therapy for patients with NSCLC, and particularly for those with squamous cell histology.
- Results also suggest that we might be able to better identify patients more likely to have clinical benefit from the *nab*-paclitaxel formulation based on stromal expression of biomarkers.

Figure 1.
Patient Enrollment and Responses

Figure 2.
Kaplan–Meier Plots of (A) Progression-Free Survival (PFS) and (B) Overall Survival

Figure 3.

(A) Kaplan–Meier Plot Demonstrating That Patients With Higher Cav-1 Expression in the Stroma ($n = 18$) Had Improved Overall Survival Compared With Patients With Low Cav-1 Expression in Stromal Tissue ($n = 15$) (Log-Rank $P = .008$). (B) Representative Immunohistochemistry Images for a Patient Whose Tumor Exhibited High Intensity (3) Tumor Staining for Cav-1 but Virtually Absent Stromal Staining (0) (Left Panel), and

Another Patient With Low Tumor Cav-1 Staining Intensity (0), but High Stromal Staining (3) (Right Panel)

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Table 1

Patient Demographic Characteristics

Characteristic	Value
Patients, n	63
Men, n (%)	42 (66.7)
Women, n (%)	21 (33.3)
Age (Minimum/Maximum), Years	63.3 (36/82)
Mean Tobacco Pack-Years (Minimum/Maximum)	50.3 (1/150)
Current/Former Smokers, n	57
Never Smokers, n	6
Previous Therapy, n	
Radiation (including photodynamic therapy)	21
Surgery	10
Chemotherapy	10
No previous therapy	33
Histology, n	
Squamous cell carcinoma	48
Adenocarcinoma	9
Adenosquamous carcinoma	2
Poorly differentiated NSCLC or NOS	4
Eligibility Criteria, n	
Histology (squamous or adenosquamous)	50
Hemoptysis	11
Thrombosis	2

Abbreviations: NOS = not otherwise specified; NSCLC = non–small-cell lung cancer.

Table 2

Treatment-Related Toxicity Grade 3

Toxicity	Grade 3, n	Grade 4, n	Grade 5, n
Hematologic			
Anemia	6	1	0
Neutropenia	5	7	0
Thrombocytopenia	6	1	0
Leukopenia/lymphopenia	12	1	0
Febrile neutropenia	2	2	0
Infection (nonneutropenic)	2	0	0
Neurologic			
Sensory neuropathy	19	0	0
Motor neuropathy	2	0	0
Gastrointestinal			
Nausea	1	0	0
Anorexia	1	0	0
Colitis	1	0	0
Dehydration	1	2	1
Dyspnea	2	0	0
General			
Fatigue	14	0	0
Hyponatremia	4	0	0
Hypokalemia	1	0	0
Back pain	1	0	0
Insomnia	1	0	0
Death NOS (possibly related)	0	0	1

Abbreviation: NOS = not otherwise specified.