# A Dose Finding Study of Weekly and Every-3-Week *nab*-Paclitaxel Followed by Carboplatin as First-Line Therapy in Patients with Advanced Non-small Cell Lung Cancer

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**Introduction:** This nonrandomized study aimed to identify the optimal dose of every-3-week (q3w) and weekly *nab*-paclitaxel plus q3w carboplatin as first-line therapy in patients with advanced non-small cell lung cancer (NSCLC) for a phase 3 trial.

**Methods:** Previously untreated patients with advanced NSCLC enrolled sequentially into seven cohorts (25 patients/cohort, $N = 175$). Cohorts 1 to 4 and 5 to 7 received *nab*-paclitaxel q3w and weekly, respectively. Patients were evaluated for efficacy and safety.

**Results:** The most common treatment-related ≥ grade 3 adverse events were neutropenia (60%), neuropathy (19%), fatigue (9%), and thrombocytopenia (29%) (no grade 4 neuropathy or fatigue). A 100 mg/m$^2$ weekly *nab*-paclitaxel produced less serious adverse events than other doses/schedules. Response rate (RR) was greater in the weekly versus q3w cohorts (47% vs. 30%). Median progression-free survival (PFS) ranged from 4.8 to 6.9 months, and overall survival (OS) ranged from 8.3 to 15.0 months (all cohorts). Patients receiving 100 mg/m$^2$ weekly *nab*-paclitaxel achieved 48% RR with 6.2 and 11.3 months of PFS and OS, respectively. In a retrospective analysis, patients with nonsquamous cell carcinoma receiving weekly *nab*-paclitaxel had significantly improved RR (59.4% vs. 23.5%, respectively, $p = 0.003$), and >2 months longer PFS and OS compared with q3w schedule. In patients with squamous cell carcinoma, the q3w schedule significantly increased PFS by 3 months ($p = 0.014$) and OS by >2 months (no difference in RR) compared with the weekly schedule.

**Conclusion:** *nab*-Paclitaxel plus carboplatin is an effective therapy for advanced NSCLC. Based on favorable efficacy and safety profiles, a phase 3, randomized, multicenter study comparing 100 mg/m$^2$ weekly *nab*-paclitaxel plus q3w carboplatin to solvent-based paclitaxel plus carboplatin has enrolled patients.

**Key Words:** *nab*-Paclitaxel, Abraxane, Taxane, NSCLC, Antitumor activity.

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The most commonly used taxane combination treatment for patients with advanced non-small cell lung cancer (NSCLC) is carboplatin plus solvent-based paclitaxel.[1,2] Solvent-based paclitaxel 175–225 mg/m$^2$ every-3-week (q3w) combined with every-3-week carboplatin area under the curve (AUC) = 6. q3w demonstrated a 17 to 32% overall response rate (ORR) in patients with advanced NSCLC.[3–6] However, the Cremophor EL excipient in solvent-based paclitaxel raises major safety and efficacy concerns. Emerging data indicated that Cremophor EL contributes to severe toxicities, including hypersensitivity reactions and peripheral neuropathy, and entraps paclitaxel in micelles, thus reducing its availability to tumor cells.[7,8] Despite several studies that compared various treatments of patients with advanced NSCLC, lung cancer is still the leading cause of cancer death, and the 5-year relative survival rate for stage IV NSCLC is only 2%.[9] Because of the safety and efficacy limitations of current therapy options, there is a critical need for safe chemotherapy agents with improved antitumor activity.

A novel paclitaxel formulation, nanoparticle albumin-bound (*nab*-) paclitaxel (Abraxane; Abraxis Bioscience, Los Angeles, CA) can be administered safely at higher doses than doses used for solvent-based paclitaxel,[10] and it produced excellent antitumor activity in taxane-refractory metastatic breast cancer patients.[11] In a phase 3 trial, q3w *nab*-paclitaxel showed increased efficacy compared with q3w solvent-based paclitaxel.[12] Consistent with these results, in a phase 2 study, *nab*-paclitaxel 260 mg/m$^2$ q3w demonstrated single-agent activity in first-line patients with advanced NSCLC, producing an ORR of 16% in 43 patients with median time to progression (TTP) and overall survival (OS) of 6 and 11

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months, respectively.[13] These efficacy results compared favorably with a phase 3 trial with solvent-based paclitaxel monotherapy (16% ORR, but only 3.9 and 6.8 months of TTP and OS, respectively),[14] or combination therapy with solvent-based paclitaxel plus carboplatin (17% ORR, and 3.1 and 8.1 months of median TTP and OS, respectively).[6] In addition, an outstanding safety profile of *nab*-paclitaxel was observed; no grade 4 toxicities were reported. Furthermore, *nab*-paclitaxel monotherapy (125 mg/m$^2$) administered weekly on days 1, 8, and 15 (3 of 4 weeks) as first-line treatment for patients with advanced NSCLC further increased efficacy compared with the q3w monotherapy study, producing 30% ORR with 5 and 11 months of median TTP and OS, respectively.[15]

Given the favorable efficacy and safety profile of n*ab*-paclitaxel compared with solvent-based paclitaxel, this study was conducted to identify the optimal dose of *nab*-paclitaxel plus carboplatin AUC = 6 q3w as first-line therapy in patients with advanced NSCLC. This phase 2 study was designed to provide sufficient efficacy and safety data to possibly permit the planning of a subsequent phase 3 trial. In addition, a retrospective histologic analysis was conducted to identify whether efficacy outcomes were different in nonsquamous (adenocarcinoma and large cell carcinoma) versus squamous cell carcinoma subtypes of NSCLC.

## PATIENTS AND METHODS

This study was conducted at 13 investigational centers in Russia, between March 15th, 2005, and June 1, 2007. The protocol and all related materials were approved by the Independent Ethics Committees of the participating medical institutions. This study was conducted in accordance with the World Medical Association Declaration of Helsinki and Good Clinical Practice, Guidelines of the International Conference on Harmonization. Written informed consent was obtained from all patients before study-related tests were carried out.

### Patients

Eligible patients included men and nonpregnant, nonlactating women, at least 18 years of age, with histologically or cytologically confirmed stage IIIB or IV NSCLC with pleural effusion or evidence of inoperable local recurrence or metastasis, and no other concurrent malignancy. Patients had measurable disease as defined by the RECIST guidelines.[16] Patients had no previous treatment for metastatic disease, had a life expectancy of more than 12 weeks, and an Eastern Cooperative Oncology Group performance status of 0 or 1. Patients were required to have adequate hematologic, hepatic, and renal function.

Patients were excluded from the study if they had evidence of active brain metastasis, any other clinically serious concurrent illness, or if they received radiotherapy or chemotherapy in the previous 4 weeks. Patients with peripheral neuropathy greater than grade 1 (defined according to the National Cancer Institute Common Terminology Criteria for Adverse Events v3.0) or a history of allergy or hypersensitivity to either of the study drugs were also excluded.

### Study Design

This multicenter, open-label, phase 2 study evaluated the safety and efficacy of q3w or weekly *nab*-paclitaxel followed by carboplatin AUC = 6 q3w in patients with advanced NSCLC. Patients were sequentially enrolled in four q3w cohorts and three weekly cohorts of increasing dose levels of *nab*-paclitaxel (25 patients per cohort) (Figure 1). This sample size ($n$ = 25 per cohort) was anticipated to provide sufficient data to characterize the safety and to assess the efficacy of the regimens at each dose level. Patients in cohorts 1 to 4 received *nab*-paclitaxel q3w at successively higher dose levels: 225 mg/m$^2$ (the highest dose typically used for solvent-based paclitaxel), 260 mg/m$^2$ (the dose of *nab*-paclitaxel approved for the treatment of patients with metastatic breast cancer), 300 mg/m$^2$ (the maximal tolerated dose of *nab*-paclitaxel in a q3w schedule), and 340 mg/m$^2$ (an approximately 50% increase over the highest used solvent-based paclitaxel dose of 225 mg/m$^2$). After the emergence of promising weekly data, three additional cohorts were added, in which patients received various weekly regimens of *nab*-paclitaxel. Patients in the first weekly regimens (cohort 5) received *nab*-paclitaxel 140 mg/m$^2$ weekly for 2 weeks (on days 1 and 8 of a 21-day cycle), followed by a week of rest. This schedule matched the dose intensity in an earlier study of *nab*-paclitaxel in NSCLC.[15] Cohort 6 received a lower weekly dose (100 mg/m$^2$) administered weekly without a break (on days 1, 8, and 15 of a 21-day cycle), providing a planned dose intensity (100.0 mg/m$^2$/wk) comparable with that of cohort 5 (93.3 mg/m$^2$/wk). Cohort 7 also received a weekly dose (125 mg/m$^2$) administered weekly without a break (on days 1, 8, and 15); the dose intensity (125 mg/m$^2$/wk) represented a 25% increase in planned dose intensity over cohort 6.

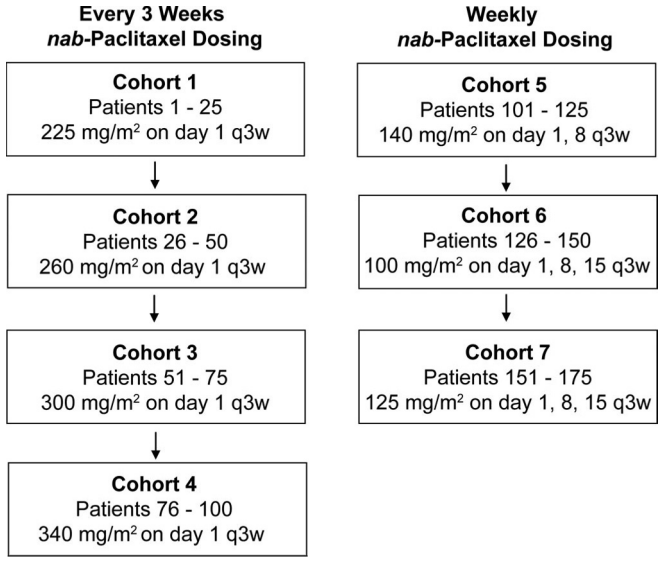


**FIGURE 1.** *nab*-Paclitaxel dosing schedule. All patients also received q3w carboplatin area under the curve = 6. *nab*-paclitaxel, nanoparticle albumin-bound paclitaxel; q3w, every-3-week.

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Patients received treatment on an outpatient basis. *nab*-Paclitaxel was given as a single 30-minute intravenous infusion, without premedication, followed by carboplatin as a 30-minute infusion at AUC = 6 calculated using the Calvert formula.[17] Patients continued receiving treatment in the absence of disease progression or unacceptable toxicity.

## Efficacy and Safety Endpoints

The primary efficacy endpoint of this study was the percentage of patients who achieved an objective confirmed complete or partial overall response (CR or PR, respectively). Secondary efficacy endpoints were to evaluate stable disease (SD) for ≥16 weeks, progression-free survival (PFS), and OS.

The safety endpoints were the incidence of treatment-related adverse events (AEs), laboratory abnormalities, serious AEs, and incidence of patients experiencing dose modifications, dose interruptions, and premature discontinuation of study drug.

## Assessments

All patients who received at least one dose of *nab*-paclitaxel and carboplatin (treated population) were evaluated for efficacy. Response assessments were performed every third cycle, that is, every 9 weeks. All measurable lesions up to a maximum of five lesions per organ and 10 lesions in total, representative of all involved organs, were identified as target lesions and measured and recorded at baseline. Response rates (RRs), SD ≥16 weeks, and PFS were evaluated based on RECIST. Phone follow-up or review of survival records were conducted monthly for 6 months and every 3 months thereafter for 18 months (total of 24 months).

Treatment-related AEs in the entire patient population were reported through the end of study or 30 days after the end of treatment, whichever was longer. Nonhematologic AEs were reported as treatment-related AEs graded using National Cancer Institute Common Terminology Criteria for Adverse Events v3.0. The median time to improvement of at least 1 grade level was determined for severe (≥ grade 3) peripheral neuropathy. Time to improvement was defined as the time from the first occurrence of grade 3 peripheral neuropathy to improvement of at least to grade 2. Laboratory analyses to determine complete blood counts and serum chemistries were performed in a central laboratory (Pivotal Laboratories Ltd., York, UK).

## Statistical Methods

The primary and secondary endpoints were summarized descriptively, and 2-sided 95% confidence intervals (CIs) are presented. Within histologic subtypes of NSCLC, differences between weekly and q3w treatments for RR and disease control rate (DCR; CR + PR + SD ≥16 weeks) were compared using $\chi^2$ test, and PFS and OS comparisons were analyzed using log-rank test.

# RESULTS

## Patients

A total of 175 patients were enrolled in the study in successive cohorts of 25 patients to each of seven treatment groups. Patient baseline characteristics are described in Table 1. The patient population was predominately men (81%), and all patients were whites.

## Patient Disposition

All enrolled patients received at least one dose of treatment and were evaluated for all of the study endpoints. All 175 (100%) patients have discontinued therapy, mostly due to progressive disease (45%), unacceptable toxicity without progressive disease (22%), patient discretion (22%), or other (11%), including AEs not related to study drug or investigator discretion. Treatment was permanently discontinued for unacceptable toxicity in 24% (cohort 1), 16% (cohort 2), 24% (cohort 3), and 44% (cohort 4) of patients in the q3w cohorts and in 24% (cohort 5), 8% (cohort 6), and 28% (cohort 7) of patients in the weekly cohorts. In particular, the most common AEs that led to treatment discontinuation were thrombocytopenia and peripheral neuropathy in the q3w cohorts, and thrombocytopenia and neutropenia in the weekly cohorts. Only patients in the q3w cohorts received prior chemotherapy; two (2%) patients had neoadjuvant, and one patient had adjuvant therapy. No patients received prior therapy for metastatic disease.

One hundred sixty-six of 175 treated patients had identified nonsquamous or squamous cell carcinoma histology (Table 1) and were included in the retrospective efficacy analysis (Table 3). Of the 100 patients receiving the q3w regimens, 31 (31%) patients had adenocarcinoma and 3 (3%) had large cell carcinoma (total of 34 [34%] patients with nonsquamous cell carcinoma), 59 (59%) patients had squamous cell carcinoma, and 7 (7%) patients had other (poorly differentiated or nondifferentiated) histology. Of the 75 patients receiving the weekly regimens, 32 (43%) patients had adenocarcinoma (no large cell carcinoma), 41 (55%) patients had squamous cell carcinoma, and 2 (3%) patients had other histology.

## Efficacy Results

### Primary Analysis

ORR ranged from 24 to 56% among the seven cohorts (Table 2). In general, there was a trend for improved RR in the weekly cohorts compared with the q3w cohorts. In the weekly cohorts, ORR ranged from 36% in the 125 mg/m$^2$ to 56% in the 140 mg/m$^2$ weekly cohort; in the q3w cohorts, ORR ranged from 24% in the 260 and 300 mg/m$^2$ cohorts to 40% in the 225 mg/m$^2$ cohort. There was no apparent direct dose proportional relationship observed in ORR across the q3w or weekly cohorts in terms of *nab*-paclitaxel dose. Similar to ORR, DCR showed a wide range among the seven dose cohorts spanning from 32 to 64%, but there was no difference between weekly (48–64%) and q3w treatments (32–60%).

Median PFS was similar between q3w and weekly treatments. Median PFS ranged from 4.8 to 6.9 months in the q3w cohorts and 5.6 to 6.4 months in the weekly cohorts (Table 2 and Figure 2). Median OS was also similar between the q3w and weekly cohorts, ranging from 8.3 to 14.6 months in the q3w cohorts and 11.3 to 15.0 months in the weekly cohorts (Table 2 and Figure 3).


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**TABLE 1.** Baseline Patient Demographics and Characteristics

| | ***nab*-Paclitaxel Doses and Schedule (n = 25 per C)** | | | | | | |
|---|---|---|---|---|---|---|---|
| | **q3w** | | | | **Weekly Days 1, 8** | **Weekly Days 1, 8, 15** | |
| | **C1 225 mg/m²** | **C2 260 mg/m²** | **C3 300 mg/m²** | **C4 340 mg/m²** | **C5 140 mg/m²** | **C6 100 mg/m²** | **C7 125 mg/m²** |
| Men, n (%) | 23 (92) | 18 (72) | 17 (68) | 20 (80) | 22 (88) | 21 (84) | 20 (80) |
| Age, mean yr | 59.7 | 63.1 | 60.1 | 61.3 | 61.6 | 59.9 | 58.8 |
| Range | 43–75 | 48–81 | 41–81 | 37–75 | 47–81 | 34–78 | 37–79 |
| Histology of malignancy at diagnosis, n (%) | | | | | | | |
| Nonsquamous cell | 9 (36) | 7 (28) | 9 (36) | 9 (36) | 10 (40) | 9 (36) | 13 (52) |
| Adenocarcinoma | 8 (32) | 7 (28) | 9 (36) | 7 (28) | 10 (40) | 9 (36) | 13 (52) |
| Large cell | 1 (4) | 0 | 0 | 2 (8) | | 0 | 0 |
| Squamous cell | 11 (44) | 18 (72) | 14 (56) | 16 (64) | 15 (60) | 16 (64) | 10 (40) |
| Other[a] | 5 (20) | 0 | 2 (8) | 0 | 0 | 0 | 2 (8) |
| Disease stage, n (%) | | | | | | | |
| IIIB | 10 (40) | 8 (32) | 4 (16) | 3 (12) | 4 (16) | 4 (16) | 7 (28) |
| IV | 15 (60) | 17 (68) | 21 (84) | 22 (88) | 21 (84) | 21 (84) | 18 (72) |
| ECOG PS, n (%) | | | | | | | |
| 0 | 1 (4) | 0 | 3 (12) | 7 (28) | 5 (20) | 4 (16) | 3 (12) |
| 1 | 24 (96) | 25 (100) | 22 (88) | 18 (72) | 20 (80) | 21 (84) | 22 (88) |
| Preexisting peripheral neuropathy, n (%) | | | | | | | |
| Grade 0 | 23 (92) | 23 (92) | 24 (96) | 21 (84) | 25 (100) | 24 (96) | 25 (100) |
| Grade 1 | 2 (8) | 2 (8) | 1 (4) | 4 (16) | 0 | 1 (4) | 0 |

[a] Poorly differentiated or nondifferentiated non-small cell lung cancer.
C, cohort; ECOG PS, Eastern Cooperative Oncology Group performance status; q3w, every-3-wk.

**TABLE 2.** Response Rates, Disease Control Rates, and Progression-Free and Overall Survival for All Treated Patients

| | ***nab*-Paclitaxel Doses and Schedule (n = 25 per C)** | | | | | | |
|---|---|---|---|---|---|---|---|
| | **q3w** | | | | **Weekly Days 1, 8** | **Weekly Days 1, 8, 15** | |
| | **C1 225 mg/m²** | **C2 260 mg/m²** | **C3 300 mg/m²** | **C4 340 mg/m²** | **C5 140 mg/m²** | **C6 100 mg/m²** | **C7 125 mg/m²** |
| Overall response rate, n (%) | 10 (40) | 6 (24) | 6 (24) | 8 (32) | 14 (56) | 12 (48) | 9 (36) |
| 95% CI | 20.8–59.2 | 7.3–40.7 | 7.3–40.7 | 13.7–50.3 | 36.5–75.5 | 28.4–67.6 | 17.2–54.8 |
| Complete response, n (%) | 0 | 1 (4) | 0 | 0 | 0 | 1 (4) | 1 (4) |
| Partial response, n (%) | 10 (40) | 5 (20) | 6 (24) | 8 (32) | 14 (56) | 11 (44) | 8 (32) |
| Stable disease ≥16 Wk, n (%) | 5 (20) | 8 (32) | 3 (12) | 0 | 2 (8) | 2 (8) | 3 (12) |
| Disease control rate,[a] n (%) | 15 (60) | 14 (56) | 9 (36) | 8 (32) | 16 (64) | 14 (56) | 12 (48) |
| 95% CI | 40.8–79.2 | 36.5–75.5 | 17.2–54.8 | 13.7–50.3 | 45.2–82.8 | 36.5–75.5 | 28.4–67.6 |
| Progression-free survival, mo | 6.9 | 6.5 | 5.3 | 4.8 | 5.6 | 6.2 | 6.4 |
| 95% CI | 4.2–9.6 | 4.3–9.1 | 2.2–8.5 | 3.9–7.8 | 3.9–7.7 | 4.2–9.7 | 4.2–7.9 |
| Overall survival, mo | 10.7 | 12.2 | 8.3 | 14.6 | 12.0 | 11.3 | 15.0 |
| 95% CI | 8.7–17.0 | 8.5–21.9 | 4.2–15.4 | 7.6–17.2 | 6.5–17.1 | 7.8–>20.1 | 10.0–>18.4 |

[a] Disease control rate = CR + PR + SD ≥16 wk.
C, cohort; CI, confidence interval; q3w, every-3-wk; CR, complete overall response; PR, partial overall response; SD, stable disease.

## Retrospective Histologic Analysis

Patients with histologic confirmation of nonsquamous cell carcinoma receiving weekly *nab*-paclitaxel (all adenocarcinoma cases) achieved better efficacy compared with the q3w schedule (mostly [91%] adenocarcinoma cases) (ORR: 59.4% vs. 23.5%, respectively, $p = 0.003$), and >2 months

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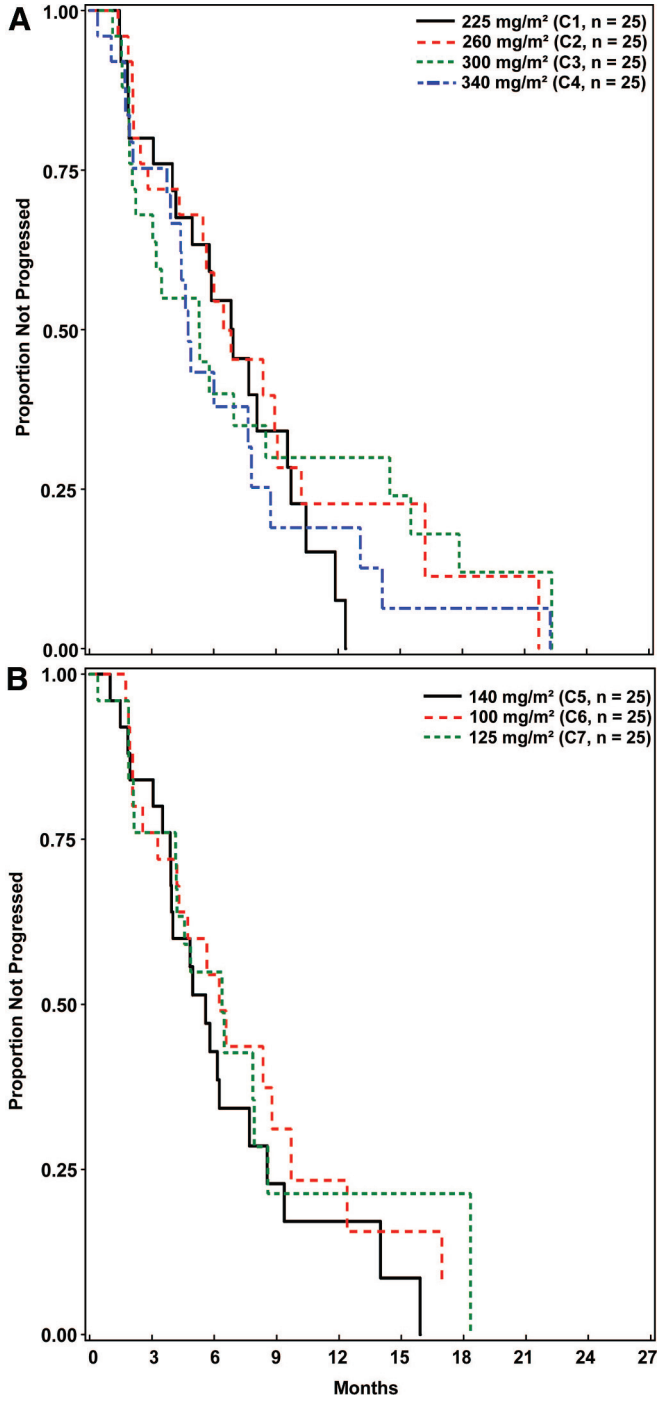


**FIGURE 2.** Progression-free survival. *A*, Cohort 1 to 4, every-3-week *nab*-paclitaxel dosing (top). *B*, Cohort 5 to 7, weekly *nab*-paclitaxel dosing (bottom). C, cohort.

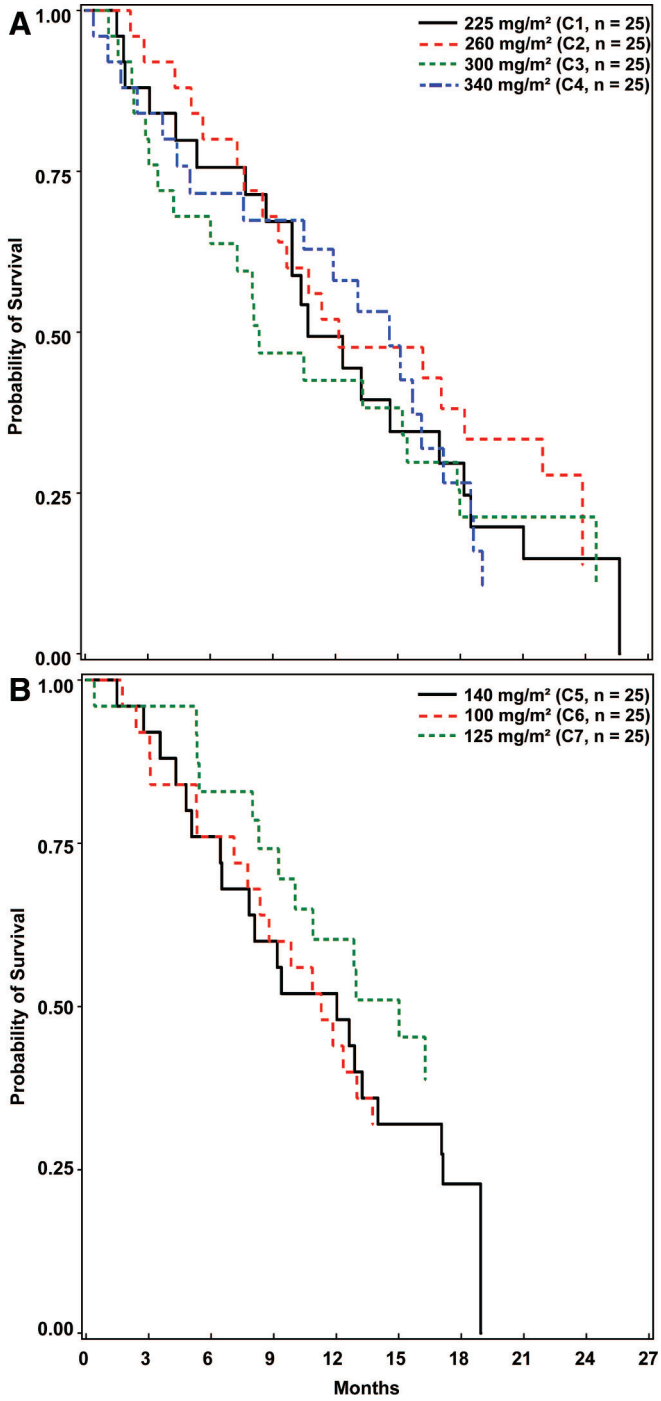


**FIGURE 3.** Overall survival. *A*, Cohort 1 to 4, every-3-week *nab*-paclitaxel dosing (top). *B*, Cohort 5 to 7, weekly *nab*-paclitaxel dosing (bottom). C, cohort.

longer PFS and OS compared with the q3w schedule (Figure 4*A*). Conversely, in patients with squamous cell carcinoma receiving q3w versus weekly *nab*-paclitaxel, PFS significantly increased by 3 months ($p = 0.014$) and OS increased by >2 months, with no difference in ORR (Figure 4*B*). In particular, of the 59 patients in the q3w cohorts with squamous cell carcinoma, 1 (2%) patient had CR, 20 (34%) patients had a PR, and 9 (15%) patients had SD for ≥16 weeks (Table 3). In the weekly cohorts of patients with squamous cell carcinoma (41 total), 16 (39%) patients had PR (no CR occurred) and 3 (7%) patients had SD for ≥16 weeks. Of the 34 patients in the q3w cohorts with nonsquamous cell


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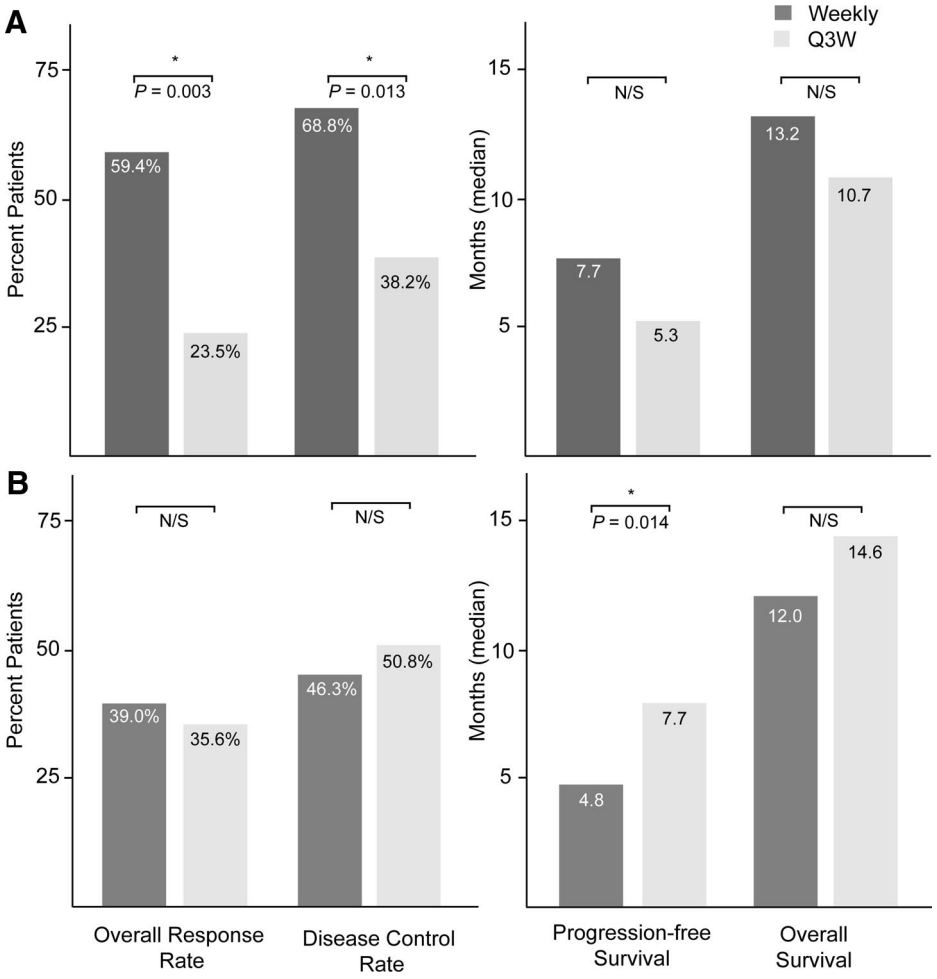


**FIGURE 4.** Efficacy results by histologic subtypes of NSCLC. *A,* Nonsquamous cell carcinoma (top). *B,* Squamous cell carcinoma (bottom). N/S, statistically nonsignificant; q3w, every-3-week; NSCLC, non-small cell lung cancer.

carcinoma, 8 (24%) patients had PR (no CR occurred) and 5 (15%) patients had SD for ≥16 weeks (Table 3). In the weekly cohorts of patients with nonsquamous cell carcinoma (32 total), 2 (6%) patients had CR, 17 (53%) patients had PR, and 3 (9%) patients had SD for ≥16 weeks.

## Treatment Exposure

In the q3w cohorts, the mean number of cycles administered was greater in the 225 mg/m$^2$ (6.5 cycles) and 260 mg/m$^2$ (6.7 cycles) cohorts than in the 300 mg/m$^2$ (4.5 cycles) and 340 mg/m$^2$ (4.6 cycles) cohorts. In the weekly cohorts, the greatest mean number of cycles was administered to the 140 mg/m$^2$ dose group (6.4 cycles) followed by the 100 mg/m$^2$ dose cohort (6.2 cycles), and the least mean number of cycles was administered to the 125 mg/m$^2$ dose group (5.0 cycles). The greatest mean cumulative dose of *nab*-paclitaxel was delivered in the 260 mg/m$^2$ q3w group (1685.8 mg/m$^2$), and the least mean cumulative dose delivered was in the 300 mg/m$^2$ q3w group (1290 mg/m$^2$).

The greatest mean dose intensity of *nab*-paclitaxel was delivered in the 340 mg/m$^2$ q3w group (95.99 mg/m$^2$/wk), and the least average dose intensity (mean value) of *nab*-paclitaxel was delivered in the 225 mg/m$^2$ q3w group (68.46 mg/m$^2$/wk). Although the planned dose intensity was the same in the 300 mg/m$^2$ q3w (cohort 3) and 100 mg/m$^2$ weekly (cohort 6) groups, the mean cumulative dose delivered was higher in cohort 6 (1541.8 mg/m$^2$) compared with cohort 3 (1290.0 mg/m$^2$).

## Safety Results

### Primary Analysis

In general, all seven cohorts showed comparable safety results, with the least severe AEs occurring in the 100 mg/m$^2$ weekly cohort (Table 4). Seven probably or possibly treatment-related deaths occurred: six in the q3w cohorts and one in the weekly cohorts. Treatment-related hematologic ≥ grade 3 AEs were neutropenia (60%), leukopenia (32%), thrombocytopenia (29%), and anemia (22%). In particular, with q3w treatment (cohorts 1–4), grade 3 and 4 neutropenia occurred in 33 and 22% of patients, respectively. With weekly treatment (cohorts 5–7), grade 3 and 4 neutropenia occurred in 32 and 35% of patients, respectively. No febrile neutropenia occurred during this study.

The most common treatment-related nonhematologic grade 3 AE was peripheral neuropathy (19%), and no grade 4 event occurred. Nineteen of 33 patients (58%) with grade 3 peripheral neuropathy improved to grade 2 or better: 15 of 25

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**TABLE 3.** Response Rates, Disease Control Rates, and Progression-Free and Overall Survival by Histologic Subtypes

| | *nab*-Paclitaxel Doses and Schedule (n = 25 per C) | | | | | | |
|---|---|---|---|---|---|---|---|
| | Q3w | | | | Weekly Days 1, 8 | Weekly Days 1, 8, 15 | |
| | C1 225 mg/m$^2$ | C2 260 mg/m$^2$ | C3 300 mg/m$^2$ | C4 340 mg/m$^2$ | C5 140 mg/m$^2$ | C6 100 mg/m$^2$ | C7 125 mg/m$^2$ |
| Squamous cell carcinoma histology | | | | | | | |
| Overall response rate, n (%) | 5 (45) | 5 (28) | 5 (36) | 6 (38) | 8 (53) | 5 (31) | 3 (30) |
| 95% CI | 16.8–76.6 | 9.7–53.5 | 12.8–64.9 | 13.8–61.2 | 28.1–78.6 | 11.0–58.7 | 6.7–65.2 |
| Complete response, n (%) | 0 | 1 (6) | 0 | 0 | 0 | 0 | 0 |
| Partial response, n (%) | 5 (45) | 4 (22) | 5 (36) | 6 (38) | 8 (53) | 5 (31) | 3 (30) |
| Stable disease ≥16 wk, n (%) | 2 (18) | 6 (33) | 1 (7) | 0 | 1 (7) | 1 (6) | 1 (10) |
| Disease control rate[a], n (%) | 7 (64) | 11 (61) | 6 (43) | 6 (37) | 9 (60) | 6 (38) | 4 (40) |
| 95% CI | 35.2–92.1 | 38.6–83.6 | 16.9–68.8 | 13.8–61.2 | 35.2–84.8 | 13.8–61.2 | 12.2–73.8 |
| Progression-free survival, mo | 8.1 | 8.4 | 5.3 | 6.0 | 5.0 | 4.5 | 4.2 |
| 95% CI | 4.2–10.4 | 5.7–21.7 | 1.9–15.5 | 4.4–7.8 | 3.9–6.1 | 2.1–9.7 | 4.1–7.9 |
| Overall survival, mo | 13.2 | 12.2 | 8.0 | 15.1 | 9.4 | 12.6 | 10.9 |
| 95% CI | 5.4–18.5 | 8.5–23.9 | 3.1–17.8 | 10.5–18.5 | 7.8–14.0 | 5.3–>18.8 | 9.2–16.3 |
| Nonsquamous cell carcinoma histology | | | | | | | |
| Overall response rate, n (%) | 4 (44) | 1 (14) | 1 (11) | 2 (22) | 6 (60) | 7 (78) | 6 (46) |
| 95% CI | 13.7–78.8 | 0.4–57.9 | 0.3–48.2 | 2.8–60.0 | 29.6–90.4 | 50.6–100.0 | 19.1–73.2 |
| Complete response, n (%) | 0 | 0 | 0 | 0 | 0 | 1 (11) | 1 (8) |
| Partial response, n (%) | 4 (44) | 1 (14) | 1 (11) | 2 (22) | 6 (60) | 6 (67) | 5 (38) |
| Stable disease ≥16 wk, n (%) | 1 (11) | 2 (29) | 2 (22) | 0 | 1 (10) | 1 (11) | 1 (8) |
| Disease control rate,[a] n (%) | 5 (56) | 3 (43) | 3 (33) | 2 (22) | 7 (70) | 8 (89) | 7 (54) |
| 95% CI | 21.2–86.3 | 9.9–81.6 | 7.5–70.1 | 2.8–60.0 | 41.6–98.4 | 68.4–100.0 | 26.8–80.1 |
| Progression-free survival, mo | 5.8 | 5.5 | 5.3 | 4.4 | 7.7 | 6.6 | 18.3 |
| 95% CI | 4.0–9.6 | 2.5–10.2 | 3.5–7.0 | 3.7–8.7 | 3.5–15.9 | 5.7–17.0 | 4.6–18.3 |
| Overall survival, mo | 12.4 | 10.7 | 10.5 | 11.9 | 13.1 | 9.8 | >18.4 |
| 95% CI | 10.3–21.0 | 7.3–>22.0 | 7.3–>25.1 | 4.4–>22.3 | 4.8–>18.4 | 7.8–11.3 | 15.0–>18.4 |

[a] Disease control rate = CR + PR + SD ≥16 wk.
C, cohort; CI, confidence interval; q3w, every-3-wk; CR, complete overall response; PR, partial overall response; SD, stable disease.

(60%) patients in the q3w cohorts and four of eight (50%) in the weekly cohorts. Both q3w and weekly *nab*-paclitaxel dosing produced a median time to peripheral neuropathy recovery of 18 days (q3w: 95% CI, 15–34 days; weekly: 95% CI, 8–>24 days) (Table 5).

Sixty-four (64%) and 49 (65%) patients in the q3w and weekly cohorts, respectively, had at least 1 cycle delay. Forty (40%) patients in the q3w cohorts and 38 (51%) patients in the weekly cohorts had at least 1 *nab*-paclitaxel dose reduction. Hematologic toxicity was the most common reason for *nab*-paclitaxel dose reductions (65 and 84% of patients with dose reduction in the q3w and weekly treatments, respectively). Six percentage and 16% of patients had a carboplatin dose reduction in the q3w and weekly cohorts, respectively. There were no *nab*-paclitaxel dose interruptions in the q3w and weekly cohorts, and two patients had carboplatin dose interruptions in the q3w cohorts because of hypersensitivity reaction.

## Retrospective Histologic Analysis

Consistent with the primary analysis, regardless of histology, all seven cohorts showed comparable safety results. Treatment-related hematologic ≥ grade 3 AEs in patients with nonsquamous cell carcinoma (66 total patients) and squamous cell carcinoma (100 total patients) were neutropenia (65 and 57%, respectively), leukopenia (38 and 28%), thrombocytopenia (38 and 24%), and ane-


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**TABLE 4.** Most Common Treatment-Related ≥ Grade 3 Adverse Events in ≥5% of Patients

| | *nab*-Paclitaxel Doses and Schedule (n = 25 per C) | | | | | | |
|---|---|---|---|---|---|---|---|
| | q3w | | | | Weekly Days 1, 8 | Weekly Days 1, 8, 15 | |
| Adverse Events, n (%) | C1 225 mg/m² | C2 260 mg/m² | C3 300 mg/m² | C4 340 mg/m² | C5 140 mg/m² | C6 100 mg/m² | C7 125 mg/m² |
| Neutropenia | | | | | | | |
| Grade 3 | 8 (32) | 9 (36) | 9 (36) | 7 (28) | 8 (32) | 9 (36) | 7 (28) |
| Grade 4 | 8 (32) | 6 (24) | 3 (12) | 5 (20) | 11 (44) | 7 (28) | 8 (32) |
| Leukocytopenia | | | | | | | |
| Grade 3 | 8 (32) | 6 (24) | 7 (28) | 9 (36) | 12 (48) | 6 (24) | 5 (20) |
| Grade 4 | 1 (4) | 0 | 0 | 1 (4) | 0 | 0 | 1 (4) |
| Peripheral neuropathy | | | | | | | |
| Grade 3 | 3 (12) | 4 (16) | 6 (24) | 12 (48) | 2 (8) | 2 (8) | 4 (16) |
| Grade 4 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Fatigue | | | | | | | |
| Grade 3 | 3 (12) | 1 (4) | 4 (16) | 3 (12) | 1 (4) | 0 | 4 (16) |
| Grade 4 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Thrombocytopenia | | | | | | | |
| Grade 3 | 7 (28) | 5 (20) | 5 (20) | 5 (20) | 5 (20) | 4 (16) | 5 (20) |
| Grade 4 | 3 (12) | 1 (4) | 2 (8) | 1 (4) | 3 (12) | 1 (4) | 4 (16) |
| Anemia | | | | | | | |
| Grade 3 | 4 (16) | 6 (24) | 3 (12) | 2 (8) | 4 (16) | 4 (16) | 10 (40) |
| Grade 4 | 1 (4) | 0 | 1 (4) | 1 (4) | 1 (4) | 0 | 1 (4) |
| Myalgia | | | | | | | |
| Grade 3 | 0 | 1 (4) | 1 (4) | 6 (24) | 0 | 0 | 0 |
| Grade 4 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Arthralgia | | | | | | | |
| Grade 3 | 0 | 1 (4) | 1 (4) | 2 (8) | 0 | 0 | 0 |
| Grade 4 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

C, cohort; q3w, every-3-wk.

**TABLE 5.** Time to Improvement of Peripheral Neuropathy

| | *nab*-Paclitaxel Doses and Schedule (n = 25 per C) | | | | | | |
|---|---|---|---|---|---|---|---|
| | q3w | | | | Weekly Days 1, 8 | Weekly Days 1, 8, 15 | |
| | C1 225 mg/m² | C2 260 mg/m² | C3 300 mg/m² | C4 340 mg/m² | C5 140 mg/m² | C6 100 mg/m² | C7 125 mg/m² |
| Improved to grade ≤2, n (%) | 2 (67) | 4 (100) | 2 (33) | 7 (58) | 1 (50) | 2 (100) | 1 (25) |
| Time to improvement, median days[a] | 15.0 | 14.5 | >48.0 | 23.0 | 8.0 | 15.5 | >24.0 |
| 95% CI | 9.0–>21.0 | 6.0–34.0 | 6.0–>48.0 | 17.0–>66.0 | — | 13.0–18.0 | 8.0–>24.0 |

[a] Time to improvement was defined as the time from the first occurrence of grade 3 peripheral neuropathy to improvement at least to a grade 2. Patients were followed up for 30 d from the time of the most recent occurrence.

C, cohort; CI, confidence interval; q3w, every-3-wk.

mia (21 and 23%). Seven (21%) and four (13%) patients with nonsquamous cell carcinoma in the q3w and weekly cohorts, respectively, had grade 3 peripheral neuropathy. In patients with squamous cell carcinoma, 16 (27%) in the q3w and 4 (10%) in the weekly cohorts had grade 3 peripheral neuropathy.

## DISCUSSION

In this study, the combination of *nab*-paclitaxel plus carboplatin AUC = 6 q3w demonstrated antitumor activity in all cohorts and was well tolerated. These results compare favorably with data reported in a phase 3 trial in patients with advanced NSCLC treated with the standard dose of solvent-based paclitaxel plus carboplatin.[6] In this study, patients receiving 140 mg/m² weekly *nab*-paclitaxel (cohort 5) achieved the highest DCR among all doses tested, but they also had more severe myelosuppression than those in other cohorts. The 100 mg/m² dose, although not showing the highest DCR of all doses tested, provided the best clinical benefit-risk ratio. Given the high cumulative dose delivered

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and the excellent safety and efficacy profile of cohort 6, the 100 mg/m$^2$ weekly *nab*-paclitaxel plus carboplatin AUC = 6 q3w combination was believed to be the optimal dosing and schedule for phase 3 comparison in patients with advanced NSCLC.

Although both q3w and weekly regimens were effective in patients with advanced NSCLC, weekly treatments with *nab*-paclitaxel seemed to be associated with improved clinical outcomes compared with q3w regimens. Patients who received a weekly schedule of *nab*-paclitaxel had greater ORR (range: 36–56%) than those who received q3w doses (range: 24–40%). Conversely, PFS was similar for q3w (range: 4.8–6.9 months) and weekly (range: 5.6–6.4 months) regimens. Similarly, OS was not different between q3w (range: 8.3–14.6 months) and weekly (range: 12.0–15.0 months) regimens.

Consistent with these results, a number of small studies have also reported antitumor activity with *nab*-paclitaxel combination therapy for the treatment of patients with NSCLC. A phase 1 study with *nab*-paclitaxel plus carboplatin administered to heavily pretreated patients with solid tumors, including NSCLC, demonstrated that this combination was active and well tolerated across a range of dosing schedules.[18] Furthermore, in a phase 2 open-label trial in patients with inoperable stage IIIB/IV NSCLC, first-line treatment of *nab*-paclitaxel 100 mg/m$^2$ weekly (3 of 4 weeks) plus carboplatin every 4 weeks was safe and demonstrated 50% ORR and 6.3 months median TTP.[19]

The antitumor activity of *nab*-paclitaxel plus carboplatin doublet therapy may, in part, be explained by the preferential intratumor paclitaxel accumulation through the novel albumin-bound paclitaxel formulation. In preclinical studies, not only higher intratumor concentration of *nab*-paclitaxel versus solvent-based paclitaxel was observed but also mice receiving *nab*-paclitaxel had increased CR, longer TTP, and prolonged OS.[20] An albumin-binding protein, secreted protein acidic and rich in cysteine (SPARC), is known to be overexpressed in lung cancer and is a poor prognostic factor.[21] Likely, the albumin-binding property of SPARC plays a role in the increased paclitaxel availability to tumor cells and may subsequently increase the efficacy of *nab*-paclitaxel. The role of SPARC in the efficacy of *nab*-paclitaxel is currently being evaluated in various clinical trials, including a phase 3 trial in patients with advanced NSCLC.

In addition to improved antitumor activity, *nab*-paclitaxel administered weekly was associated with less serious AEs than when administered q3w, with significant reductions in the incidence of peripheral neuropathy, myalgia, arthralgia, and alopecia. Even though this study combined *nab*-paclitaxel with carboplatin, time to improvement in peripheral neuropathy was comparable (median: 18 days) with that observed in a phase 3 study of monotherapy *nab*-paclitaxel in patients with metastatic breast cancer (median: 22 days).[12] Specifically, the incidence of peripheral neuropathy was lowest in the 100 and 140 mg/m$^2$ weekly cohorts, and in the 100 mg/m$^2$ cohort, all severe neuropathy cases improved to grade 2 or better within 16 days.

Novel targeted therapies and chemotherapeutic agents showed different efficacy in specific NSCLC subcategories, in particular, for squamous cell carcinoma and adenocarcinoma.[22] NSCLC subtypes not only arise from different anatomic locations but also have distinct embryologic origins[22] and, thus, are likely to have different drug transport capabilities. Therefore, histologic characterization of NSCLC has become increasingly important for targeted therapy to maximize benefits of therapeutic agents and avoid adverse side effects. In the present retrospective analysis, patients with either histologic subtype have responded to treatments. In particular, patients with histologic confirmation of nonsquamous cell carcinoma receiving weekly *nab*-paclitaxel (all adenocarcinoma cases) had improved efficacy outcomes compared with q3w schedule (mostly adenocarcinoma cases, 91%), in terms of ORR, PFS, and OS. Conversely, patients with squamous cell carcinoma receiving q3w *nab*-paclitaxel had improved efficacy outcomes (PFS and OS) compared with weekly schedule. The significance of these retrospective observations cannot be elucidated in the context of this study. In stage I to IIIA NSCLC tissues, squamous cell carcinomas express higher levels of cyclins (proteins regulating cellular proliferation) versus adenocarcinomas.[23] However, because of the scant information about the pharmacogenomic characterization of stage IIIB and IV NSCLC histologic subtypes, it is unclear which genes or proteins play a role in the differential efficacy outcome in this study. Future studies are needed to elucidate the pharmacogenomics of the histologic subtypes of advanced NSCLC.

In conclusion, this study demonstrated that *nab*-paclitaxel is an effective and safe therapy for NSCLC. In general, 100 mg/m$^2$ weekly *nab*-paclitaxel combined with carboplatin AUC = 6 q3w is an optimal dose and schedule for the treatments of advanced NSCLC. Based on the favorable safety profile and the excellent antitumor activity of the low weekly dose of 100 mg/m$^2$ *nab*-paclitaxel, a large (N = 1050) phase 3, randomized, multicenter study comparing 100 mg/m$^2$ *nab*-paclitaxel plus carboplatin AUC = 6 q3w with standard dose of solvent-based paclitaxel plus carboplatin has been initiated and completed enrollment.

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