Phase II Trial of Nanoparticle Albumin-Bound Paclitaxel, Carboplatin, and Bevacizumab in First-line Patients with Advanced Nonsquamous Non-small Cell Lung Cancer

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Introduction: Carboplatin/paclitaxel chemotherapy with bevacizumab is an accepted standard treatment for advanced nonsquamous non-small cell lung cancer (NSCLC). The development of nanoparticle albumin-bound paclitaxel (*nab*-paclitaxel) has circumvented many of the infusion difficulties associated with standard solvent-based paclitaxel (in Cremophor) and offers theoretical advantages in efficacy. This trial evaluated the combination of *nab*-paclitaxel, carboplatin, and bevacizumab in advanced (stage IIIB/IV) nonsquamous NSCLC.

Methods: Fifty patients with stage IIIB/IV NSCLC were enrolled between October 2005 and April 2006; 48 were treated with *nab*-paclitaxel 300 mg/m^2, carboplatin area under the curve = 6, and bevacizumab 15 mg/kg every 21 days until progression or intolerable toxicity, up to 4 cycles; an additional 2 cycles could be administered to responding patients and the physician's discretion; maintenance bevacizumab was not administered. Patient demographics included: 56% female, median age 67 years (range, 32–83), performance status 0 (52%) or 1 (48%), adenocarcinoma 86%, and stage IV disease 82%. Responding patients received a minimum of 4 cycles. The primary end point was response rate.

Results: Response rate was 31% with a stable disease rate of 54%. No complete responses were observed. Median progression-free survival was 9.8 months (range, <1–22.3), and median survival was 16.8 months. Most frequent grades 3 and 4 treatment-related toxicities were neutropenia (54%) and fatigue (17%).

Conclusions: The combination of *nab*-paclitaxel, carboplatin, and bevacizumab was well tolerated with moderate neutropenia. Adverse events were manageable. Survival results are encouraging. These results indicate that this combination has promising activity as first-line therapy in patients with nonsquamous NSCLC.

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Platinum-based doublet chemotherapy is the standard initial treatment for advanced non-small cell lung cancer (NSCLC). Although chemotherapy improves quality of life (QOL) and survival in advanced NSCLC, progression-free survival (PFS) is <6 months, and overall survival is approximately 1 year with response rates of 20%.[1,2] Many currently used standard doublet chemotherapy regimens in advanced NSCLC share similar outcomes.[1] Eastern Cooperative Oncology Group (ECOG) 4599 evaluated the addition of bevacizumab to standard carboplatin/paclitaxel chemotherapy in nonsquamous NSCLC.[3] Entry criteria for ECOG 4599 have become standard for the use of bevacizumab in NSCLC and included nonsquamous histology, absence of brain metastasis or history of hemoptysis, and exclusion of patients on anticoagulation. Bevacizumab improved PFS (6.2 months versus 4.5 months, $p < 0.001$) and overall survival (12.3 months versus 10.3 months, $p = 0.003$) but increased the risk of bleeding complications, even in carefully selected patients (4.4% versus 0.7%, $p < 0.001$). In ECOG 4599,[4] patients continued maintenance bevacizumab until progression of disease. ECOG 4599 established bevacizumab in the treatment of advanced nonsquamous NSCLC, although the European AVAiL trial,[4] while demonstrating an improvement in PFS, failed to show a survival benefit for the addition of bevacizumab to gemcitabine/cisplatin chemotherapy in NSCLC.

Paclitaxel originally isolated from the bark of the Pacific yew (*Taxus brevifolia*) is one of the most widely used chemotherapeutic agents, demonstrating activity in a variety of tumor types. The standard formulation of paclitaxel (sP) consists of paclitaxel dissolved in a proprietary solvent, Cremophor EL (BASF Corp, Aktiengellschaft, Germany) and ethanol. In addition to its poor water solubility, sP has a number of other limitations: sP administration requires routine premedication with corticosteroids, diphenhydramine, and H_2 antagonists to reduce the incidence of potentially life-threatening hypersensitivity caused by a response to the formulation vehicle, Cremophor. Also, sP must be adminis-

tered over a period of 3 hours and requires the use of specialized non-DEHP containing infusion sets and in-line filters.[5]

Nanoparticle albumin-bound paclitaxel (*nab*-paclitaxel, Abraxane, Abraxis BioScience, Los Angeles, CA), a unique protein formulation of paclitaxel, was developed to reduce the toxicities associated with paclitaxel and the Cremophor/ethanol vehicle while maintaining or improving the chemotherapeutic effect of the drug. Preclinical studies have suggested that this formulation may improve drug delivery into tumor.[6,7] In phase I trials, the maximum tolerated dose of *nab*-paclitaxel was higher than the labeled dose for paclitaxel and the Cremophor/ethanol vehicle.[8] In phase II trials, antitumor activity was documented in metastatic breast cancer.[9,10] A phase III testing of n*ab*-paclitaxel in advanced breast cancer demonstrated significantly higher efficacy for *nab*-paclitaxel versus paclitaxel and the Cremophor/ethanol vehicle as measured by overall response rates (33% versus 19%, $p < 0.001$) and time to tumor progression (5.8 months versus 4.2 months, $p = 0.006$).[11] *nab*-Paclitaxel has been evaluated in NSCLC. Rizvi et al.[12] reported promising single agent results of weekly *nab*-paclitaxel with a response rate of 30%, time to progression of 5 months, and overall survival of 11 months in patients with advanced NSCLC. Green et al.[13] reported a response rate of 16% with *nab*-paclitaxel given as a single agent every 3 weeks in advanced NSCLC with a median survival of 11 months. *nab*-Paclitaxel has been evaluated in combination with carboplatin in the treatment of NSCLC utilizing both the weekly[14] and every 3-week[15] schedule of *nab*-paclitaxel. This phase II study was designed to evaluate the safety and antitumor activity of *nab*-paclitaxel combined with carboplatin and bevacizumab every 21 days in patients with advanced stage IIIB/IV NSCLC.

PATIENTS AND METHODS

Patients

Eligible patients had histologically or cytologically confirmed advanced stage IIIB (wet)/IV nonsquamous NSCLC with evidence of inoperable local recurrence or metastasis and had measurable disease by RECIST.[16] Patients could not have received previous chemotherapy for advanced disease but could have received previous radiation as long as the measurable disease was outside the radiation field or had progressed since completion of radiation. Other entry criteria included an ECOG performance status (PS) 0–1, age >18 years, and adequate hematologic, hepatic, and renal function. Exclusion criteria included pregnancy or breast feeding, preexisting peripheral neuropathy of National Cancer Institute grade ≥1, significant renal disease or proteinuria, active cardiac disease, history of seizure disorder, or another active malignancy. In addition, there were extensive exclusion standard criteria related to the administration of bevacizumab, similar to those used in ECOG 4599 study,[3] including the presence of central nervous system metastases, gross hemoptysis (>1/2 tsp of red blood), unstable angina, or the use of therapeutic anticoagulation. All patients signed an informed consent.

Study Design

This was an open-label, single arm phase II study. The protocol was approved by a central Institutional Review Board with jurisdiction over specific sites that registered patients on study.

Patients received intravenous *nab*-paclitaxel 300 mg/m^2, carboplatin intravenous (mg/mL min) area under the curve = 6, and bevacizumab 15 mg/kg on day 1 of each 21-day cycle. Patients did not receive maintenance bevacizumab after chemotherapy.

Patients were to receive a minimum of 4 cycles of treatment; however, patients who progressed or who developed an intolerable toxicity were taken off treatment. At the discretion of the treating physician, patients who achieved a complete response (CR) or partial response (PR) could receive an additional 2 cycles to a maximum of 6 cycles. Responses were evaluated between days 14 and 21 of cycles 2 and 4 (and 6 if applicable). Any additional treatment was at the discretion of the treating physician.

Therapy could continue in the absence of disease progression and unacceptable toxicity. All patients who received at least one dose of *nab*-paclitaxel, carboplatin, and bevacizumab were evaluable for response and toxicity.

Assessments

Verification that patients satisfied inclusion and exclusion criteria, review and signing of the informed consent, and a medical history were completed at baseline. A physical examination including vital signs, height and weight, assessment of the ECOG PS, complete blood count with differential and platelet count, disease assessment, and laboratory tests (total bilirubin, serum creatinine, aspartate transaminase, alanine transaminase, alkaline phosphatase, and serum calcium), and pregnancy test (when indicated) were also done at baseline. Toxicity was assessed at each patient visit and for 30 days after the last dose. Radiologic assessment of disease status was done every 6 weeks. Follow-up visit occurred at 3-month intervals for 2 years (measured from the start of treatment) to collect survival data and information about any additional therapy.

Response and progression were evaluated using the standardized international criteria proposed by the RECIST committee.[16]

Adverse events (AEs) were recorded throughout the trial. Toxicities and AEs were graded using the Common Terminology Criteria for Adverse Events Version 3.0.[17] The relationship of each event to treatment was assessed by the treating physician and recorded. Additional information about each event, such as treatment required, eventual outcome, and whether or not therapy had to be interrupted or dosages reduced, was also collected. AEs were recorded for up to 30 days following the last study treatment.

Statistical Analysis

The primary objective of this study was to determine antitumor activity of *nab*-paclitaxel/carboplatin/bevacizumab in patients with advanced NSCLC, based on RECIST criteria.[16] The secondary objectives of this study were to evaluate time to disease progression, determine the duration of re-