Patient-Reported Neuropathy and Taxane-Associated Symptoms in a Phase 3 Trial of *nab*-Paclitaxel Plus Carboplatin versus Solvent-Based Paclitaxel Plus Carboplatin for Advanced Non–Small-Cell Lung Cancer

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Introduction: *nab*-Paclitaxel (*nab*-P) is approved, in the United States, in combination with carboplatin for the first-line treatment of advanced non–small-cell lung cancer, based on a randomized phase 3 trial of *nab*-P plus carboplatin (*nab*-P/C) versus solvent-based paclitaxel plus carboplatin (sb-P/C). This trial revealed a higher overall response rate (33% versus 25%; $p = 0.005$) and longer, but not statistically significant, overall and progression-free survival for *nab*-P/C versus sb-P/C. In addition, *nab*-P/C demonstrated lower rates of grade 3 or higher peripheral neuropathy, myalgia, arthralgia, and neutropenia but higher rates of anemia and thrombocytopenia. This report analyzes patient and physician assessment of symptoms within this trial.

Methods: Patients completed the taxane subscale of the Functional Assessment of Cancer Therapy questionnaire, which focuses on taxane toxicity, including peripheral neuropathy and neurotoxicity. Mean baseline scores and changes from baseline are reported. Physicians also graded the severity of neuropathy at each patient visit using National Cancer Institute Common Toxicity Criteria.

Results: Patients receiving *nab*-P/C reported significantly less worsening of peripheral neuropathy ($p < 0.001$), pain ($p < 0.001$), and hearing loss ($p = 0.002$). Patient-reported edema was similar between the two treatment arms. In agreement with patient-reported symptoms, the results of a per-treatment cycle physician assessment of peripheral neuropathy also favored *nab*-P/C over sb-P/C ($p < 0.001$).

Conclusion: In this trial of patients receiving first-line treatment for advanced non–small-cell lung cancer, *nab*-P/C was associated with statistically and clinically significant reductions in patient-reported neuropathy, neuropathic pain in the hands and feet, and hearing loss compared with sb-P/C.

Key Words: *nab*-Paclitaxel, Solvent-based paclitaxel, Functional Assessment of Cancer Therapy-Taxane, Non–small-cell lung cancer, Peripheral neuropathy.

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The goals of therapy for advanced non–small-cell lung cancer (NSCLC) are to prolong survival and manage symptoms associated with the disease.[1] Because survival times for patients with advanced NSCLC are relatively short, symptom control is an important consideration.[2] Treatment can affect a patient's well-being through both symptom control and treatment-related toxicity.[3] Therefore, treatments that can help limit tumor growth (achieve a tumor response)[4] while limiting toxicity are of paramount importance in this population.[3]

Underscoring the value of symptom control to patients, an analysis of patient preference with respect to chemotherapy for advanced NSCLC found that 68% of those interviewed would accept chemotherapy if it would substantially reduce symptoms, even in the absence of a survival benefit.[5]

Worsening symptoms may decrease a patient's independence, rendering him or her more dependent on caregivers, including family. A number of reports have revealed that many patients with terminal cancer are concerned about becoming a burden to loved ones at the end of life.[6–8] This phenomenon, known as self-perceived burden, may be experienced at minimal to mild levels by 35% of patients and at moderate to extreme levels by another 28% of patients according to one study.[6] This perception of being a burden to loved ones may affect a patient's preference of treatment.[8]

Symptom management is an important component of care in advanced NSCLC because the majority of patients

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present with disease-related symptoms.[2] Symptom control can be achieved with tumor response, but it can also be achieved in the absence of an objective response, possibly through tumor shrinkage that does not meet the criteria to be considered a partial response.[2] The effect of tumor response on disease-related symptoms is an area of active research, with some but not all studies suggesting a link between tumor response and symptoms such as cough, dyspnea, chest pain, and systemic symptoms (fever, anorexia, and weight loss).[9–11] Therefore, tumor shrinkage is an important consideration because it may relate to both the goals of treatment and the patient's well-being.

Platinum-based regimens are recommended therapy for advanced NSCLC in patients with good performance status (PS).[1,12] Different platinum doublets offer similar overall response rates (ORRs) and overall survival values; therefore, the selection of the proper combination partner should be individually tailored by clinicians to their patients.[12] Solvent-based paclitaxel (sb-paclitaxel) is among the recommended platinum combination partners.[1,12] However, toxicities such as peripheral neuropathy, arthralgia, and myalgia are known taxane-associated side effects.[3,13] *nab*-Paclitaxel was developed to improve the therapeutic index of paclitaxel therapy.[14] Compared with sb-paclitaxel, *nab*-paclitaxel reaches a 10-fold higher peak concentration of free paclitaxel in patients, delivers 33% more drug to tumors in preclinical models, and crosses endothelial cells more efficiently.[15,16] Furthermore, *nab*-paclitaxel has shown superior ORR and time to progression/progression-free survival and favorable safety versus sb-paclitaxel and docetaxel in trials of metastatic breast cancer (MBC).[14,17]

nab-Paclitaxel, either as monotherapy or in combination with carboplatin (*nab*-P/C) has demonstrated promising efficacy in NSCLC in a number of clinical trials.[18–20] These findings were recently confirmed in a phase 3 trial in which *nab*-P/C was compared with sb-paclitaxel plus carboplatin (sb-P/C) as first-line treatment for patients with advanced NSCLC.[21] The dose and schedule of *nab*-P/C was chosen based on the findings of a phase 2 dose-finding study,[20] whereas the sb-P/C regimen was selected because it represents an established standard against which to compare *nab*-P/C.[22,23] Compared with sb-P/C, *nab*-P/C produced a significantly higher ORR (33% versus 25%, respectively; $p = 0.005$) and a nonsignificant 1-month longer median overall survival versus sb-P/C (12.1 versus 11.2 months, respectively; $p = 0.271$).[21] In addition, the safety profile revealed lower rates of physician-assessed grade 3 or higher sensory neuropathy, neutropenia, myalgia, and arthralgia for *nab*-P/C but lower rates of grade 3 or higher anemia and thrombocytopenia for sb-P/C. On the basis of these findings, the U.S. Food and Drug Administration approved *nab*-P/C for locally advanced or metastatic NSCLC as first-line treatment in patients who are not candidates for curative surgery or radiation therapy.[24]

The Functional Assessment of Cancer Therapy (FACT)-General questionnaire is a reliable and validated tool to measure symptoms and quality of life (QoL) from the perspective of a patient with cancer.[25] The tool consists of subscales that measure physical well-being, social/family well-being, emotional well-being, functional well-being, and patient perception of his or her relationship with the physician.[25] Subsequently, the developers of the FACT-General questionnaire created FACT-Taxane, a more specific tool to assess QoL in patients receiving taxanes.[3] FACT-Taxane consists of both FACT-General and an added taxane subscale. The subscale has 16 items (Table 1), including an 11-item neurotoxicity subscale and five additional taxane-specific questions related to the effects of arthralgia, myalgia, and skin changes. The tool was found to be reliable and sensitive to changes in symptoms over time.[3] In a study of patients with NSCLC receiving treatment with sb-P/C, the impact on QoL of lung cancer symptom improvement because of treatment equaled the impact of treatment-related toxicities on total QoL, as measured by the FACT-Taxane tool. However, with respect to patients' global rating of QoL by using the single item "I am content with the quality of my life right now," improvements in disease-related symptoms outweighed concerns about treatment-related toxicity.[3]

In the trial of *nab*-P/C versus sb-P/C described above, the taxane subscale of the FACT-Taxane questionnaire was selected as a methodical instrument to gauge patient perception of how treatment-related symptoms affected QoL.[3,21] In addition to assessing sensory neuropathy during study treatment by established grading criteria, the investigators also evaluated the degree of sensory neuropathy on a visit-by-visit basis. This analysis explores patient- and physician-assessed symptoms related to treatment with *nab*-P/C versus sb-P/C in patients with advanced NSCLC who participated in the phase 3 study.

PATIENTS AND METHODS

This international, multicenter, randomized phase 3 study in patients with advanced NSCLC compared the efficacy and safety of *nab*-P/C versus sb-P/C.[21] Patients in the *nab*-P/C arm received *nab*-paclitaxel 100 mg/m^2 on days 1, 8, and 15, administered as a 30-minute infusion, followed by

TABLE 1. The 16-Item Taxane Subscale of FACT-Taxane (Adapted from the Study by Cella et al., 2003)[3]

Category	Statement
Neurotoxicity component	I have numbness or tingling in my hands
	I have numbness or tingling in my feet
	I feel discomfort in my hands
	I feel discomfort in my feet
	I have joint pain or muscle cramps
	I feel weak all over
	I have trouble hearing
	I get a ringing or buzzing in my ears
	I have trouble buttoning buttons
	I have trouble feeling the shape of small objects when they are in my hand
	I have trouble walking
Taxane component	I feel bloated
	My hands are swollen
	My legs or feet are swollen
	I have pain in my fingertips
	I feel discomfort in my feet

FACT, Functional Assessment of Cancer Therapy.