**Abbreviation:** Abraxane® (ABI-007) is a novel 130-nm, albumin-bound (nab™) particle form of paclitaxel designed to utilize endogenous albumin pathways to increase intratumor concentrations of the active drug. This multicenter phase II study was designed to evaluate the efficacy and safety of Abraxane 260 mg/m² every 3 weeks in patients with non-small-cell lung cancer (NSCLC).

**Patients and Methods:** Patients with histologically confirmed, measurable NSCLC received Abraxane as first-line therapy.

**Results:** Forty-three patients were enrolled. The overall response rate was 16%; the disease control rate was 49%. Median time to progression was 6 months, and median survival was 11 months. The probability of not having progressed by 1 year was 13%; the probability of surviving 1 year was 45%. No severe hypersensitivity reactions were reported despite the lack of premedication; 95% of patients were treated without dose reduction. Two patients (5%) discontinued therapy because of treatment-related toxicities (neuropathy, fatigue [1 each]). No grade 4 treatment-related toxicity occurred.

**Conclusions:** Abraxane 260 mg/m² administered IV over 30 min without premedication was well tolerated. Significant tumor responses and prolonged disease control were documented in this group of patients with NSCLC. Exploration of higher doses of ABI-007 alone and in combination with other drugs active in NSCLC is warranted.

**Key words:** ABI-007, nab™, nanoparticle, nab-paclitaxel

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**Introduction**

Lung cancer is the most common malignancy in adults (men and women). The American Cancer Society estimates that more than 170 000 new cases of cancer of the lung or bronchus and more than 160 000 deaths due to this disease will be reported in the United States in 2005 [1]. Most of these patients will have non-small-cell lung cancer (NSCLC) that typically is categorized as advanced or metastatic at diagnosis.

Single-agent paclitaxel (Taxol®, Bristol-Myers Squibb Co., Princeton, New Jersey) plays a central role in the treatment of advanced NSCLC [2, 3]. Use of this drug is limited, however, by its poor solubility and by the toxicities associated with Cremophor® EL (polyoxyethylated castor oil), the lipid-based solvent used as a vehicle for Taxol and its generic equivalents. Cremophor is known to leach plasticizers from standard intravenous (IV) tubing and has been associated with histamine release, severe anaphylaxis, hyperlipidemia, abnormal lipoprotein patterns, aggregation of erythrocytes, and prolonged, sometimes irreversible sensory neuropathy [4–6]. Furthermore, administration of Taxol requires a long infusion period (typically 3–24 h), in-line filters, and premedication with steroids and antihistamines to minimize the risk of hypersensitivity reactions [2]. Despite these precautions, severe and sometimes fatal hypersensitivity reactions still occur [7]. In addition, Cremophor forms micelles that entrap paclitaxel in the plasma compartment, resulting in nonlinear pharmacokinetics for Taxol [8].

Abraxane® (paclitaxel protein-bound particles for injectable suspension) (albumin-bound), developed by American BioScience, Inc., Santa Monica, California, is a Cremophor-free, 130-nanometer particle form of paclitaxel that has been designed to address these limitations. This new formulation delivers paclitaxel as a suspension of albumin particles in saline, obviating the need for Cremophor and allowing a shorter infusion duration and use of standard infusion sets. The use of albumin as a vehicle eliminates the solvent-related toxicities and obviates the need for steroid and antihistamine...
premedication. Furthermore, albumin has the potential to increase drug delivery to tumors by initiating albumin receptor (gp60)-mediated transcytosis across endothelial cells [9] and accumulating drug in tumors due to binding of albumin to secreted protein, acidic and rich in cysteine (SPARC) [10].

A randomized, controlled, phase III trial recently compared 3-week cycles of Abraxane (260 mg/m² IV over 30 min without premedication) and Taxol (175 mg/m² IV over 3 h with premedication) in 454 patients with metastatic breast cancer [11]. Response rates and time to tumor progression (TTP) were significantly higher with Abraxane than with Taxol (33% versus 19% \[P = 0.001\] and 23.0 versus 16.9 weeks \[P = 0.006\], respectively). Furthermore, in an unplanned analysis, Abraxane improved survival in patients who received treatment as second-line or greater therapy. The incidence of grade 4 neutropenia (9%) in the phase III study was significantly lower with Abraxane despite a 49% higher paclitaxel dose. The incidence of grade 3 sensory neuropathy (10%) was greater with Abraxane (consistent with the higher dose), but these episodes improved rapidly with Abraxane and were easily managed with dose interruption and reduction.

Because of the limited efficacy and multiple toxicities associated with currently available treatments for NSCLC, the phase II study reported here explored the efficacy and safety of single-agent Abraxane at 260 mg/m² (the recently approved phase II study reported here explored the efficacy and safety associated with currently available treatments for NSCLC, the episodes improved rapidly with Abraxane and were easily managed with dose interruption and reduction.

Toxicity analyses. TTP and overall survival were summarized using Kaplan-Meier methods [13]. The number of objective responses plus the number of patients with SD ≥16 weeks (disease control) was also assessed.

patients and methods

The protocol and all related materials were approved by local institutional review boards or ethics committees. The study was conducted in compliance with Good Clinical Practice guidelines of the International Conference on Harmonisation and the Declaration of Helsinki. Written informed consent was required from all patients before participation.

patient population

Men and non-pregnant women (≥18 years of age) were eligible for inclusion in the study. Patients had histologically or cytologically confirmed NSCLC (at least 1 measurable [stage IIIb or IV] lesion) with evidence of inoperable local recurrence or metastasis, but no other active malignancy and no prior therapy for metastatic disease. Patients had an expected survival of ≥12 weeks with adequate hematologic, hepatic, and renal function. Patients were excluded from participation if they had clinical evidence of brain metastasis; serious concurrent illness; Eastern Cooperative Oncology Group (ECOG) performance status of ≥2; peripheral neuropathy (National Cancer Institute Common Toxicity Criteria for Adverse Events [NCI CTC] grade ≥2); or had received radiotherapy.

treatment

Abraxane was administered on an outpatient basis via 30-minute IV infusion at 260 mg/m² (paclitaxel dose) without steroid or antihistamine premedication, granulocyte colony-stimulating factor (G-CSF) support, special IV infusion sets, or in-line filters. Treatment was repeated every 3 weeks until disease progression or unacceptable toxicity occurred. Dose reductions (from 260 to 200 mg/m²) were permitted for grade 4 hematologic toxicity, neutropenic fever or sepsis, or grade 3 or 4 non-hematologic toxicity. If any of these adverse events (AEs) recurred after the initial resolution and reinitiation of Abraxane dosing, a second dose reduction (to 130 mg/m²) was recommended for all subsequent cycles. Patients who experienced a further recurrence of the dose-limiting AEs were withdrawn from the study.

assessments

Tumors were measured using Response Evaluation Criteria in Solid Tumors (RECIST) [12] at baseline and at the end of every third treatment cycle. The imaging method used for a given tumor at baseline was used consistently for that tumor throughout the study. Imaging for tumor re-evaluation was limited to sites of pre-existing metastasis identified at baseline or to new sites suspected to contain metastasis.

Response analyses were based on the investigator’s evaluation of radiologically and clinically detected target lesions. Tumor responses were categorized according to RECIST [12]: complete response (CR) = disappearance of all target lesions; partial response (PR) = ≥30% decrease in the sum of the longest diameters of target lesions; stable disease (SD) = not meeting the criteria for partial response or progressive disease; and progressive disease (PD) = an increase of ≥20% in the sum of the longest diameter of target lesions, unequivocal increase in the size of any lesion, or appearance of a new lesion. Responses to treatment were confirmed by restaging ≥24 weeks after the initial documentation of response. The actual date of death was assessed on a monthly basis for 6 months after study completion and every 3 months thereafter (total, 2 years).

Adverse events were graded according to the NCI CTC (v3.0), coded using the Medical Dictionary for Regulatory Activities, and then mapped to NCI CTC terms.

statistical methods

The primary efficacy endpoint was the percentage of patients in the treated population who achieved a confirmed CR or PR. All of the patients who received at least 1 dose of Abraxane were included in the response and toxicity analyses. TTP and overall survival were summarized using Kaplan-Meier methods [15]. The number of objective responses plus the number of patients with SD ≥16 weeks (disease control) was also assessed.

results

Between February 25, 2004 and June 21, 2004, 43 patients were enrolled at multiple sites in Russia. Patient demographic and other baseline characteristics are presented in Table 1. Most patients (84%) had visceral dominant disease; all (100%) had an ECOG performance status of 0 or 1.

efficacy

The ORR for Abraxane was 16.3% (95% CI: 5.24–27.31%) (Table 2); all seven responses were partial. The disease control rate was 48.8% (95% CI: 33.90–63.78%). As of the most recent update, 34 patients (79%) had progressed. Median TTP was 6 months (95% CI: 3.9–6.5) (Figure 1); median survival was 11 months (95% CI: 9.5–16.2) (Figure 2). The probability of not having progressed was 50% at 6 months and 13% at 1 year. The probability of surviving 1 year was 45%.

safety

Treatment was well tolerated, with 95% of patients receiving Abraxane at the protocol-specified dose. Almost all cycles (98%) were administered at the full dose. Patients received...
Disease control 43 21 (49%)
Confirmed overall response 43 7 (16%)

Table 2. Response rates, disease control, and survival

<table>
<thead>
<tr>
<th>Subgroup/variable</th>
<th>n (Baseline)</th>
<th>No. of responding patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall response (all partial responses)</td>
<td>43</td>
<td>7 (16%)</td>
</tr>
<tr>
<td>No. (%) of responders</td>
<td>43</td>
<td>5.24–27.31</td>
</tr>
<tr>
<td>95% CI</td>
<td>43</td>
<td></td>
</tr>
<tr>
<td>Response by Histology(^a)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Confirmed overall response</td>
<td>43</td>
<td>7 (16%)</td>
</tr>
<tr>
<td>Carcinoma/adeno carcinoma</td>
<td>11</td>
<td>1</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>29</td>
<td>5</td>
</tr>
<tr>
<td>Other</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Disease control(^b)</td>
<td>43</td>
<td>21 (49%)</td>
</tr>
<tr>
<td>Carcinoma/adeno carcinoma</td>
<td>11</td>
<td>5</td>
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<tr>
<td>Squamous cell carcinoma</td>
<td>29</td>
<td>14</td>
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<tr>
<td>Other</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Death</td>
<td>43</td>
<td>25 (53%)</td>
</tr>
<tr>
<td>Carcinoma/adeno carcinoma</td>
<td>11</td>
<td>5</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>29</td>
<td>16</td>
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<tr>
<td>Other</td>
<td>3</td>
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</tbody>
</table>

\(^a\)Other categories of non-small-cell lung cancer (NSCLC) include large-cell carcinoma, undifferentiated NSCLC, and mixed squamous and adeno carcinoma.

\(^b\)Includes responders + patients with stable disease ≥16 weeks.

The most frequently reported AEs were those expected for paclitaxel in this patient population. Treatment-related AEs that were reported in ≥10% of patients are presented in Table 3. No episodes of treatment-related grade 4 AEs (including neutropenia) were reported. Of the two patients who developed grade 3 peripheral neuropathy (neither of whom had peripheral neuropathy at baseline), one patient had treatment stopped for this side effect. The other patient experienced grade 3 neuropathy after six cycles; following a dose reduction to 200 mg/m², the neuropathy improved to grade 2 after seven cycles and to grade 1 after eight cycles. Other taxane-associated toxicities (e.g. nail changes and edema) were mostly mild to moderate; gastrointestinal AEs also were mostly mild to moderate and easily managed.

**Discussion**

Chemotherapy improves survival when compared to best supportive care (BSC) in chemotherapy-naive patients with advanced NSCLC [14, 15]. Selected second- and third-line treatment strategies, currently single-agent regimens, can further improve survival duration [16, 17]. A worldwide meta-analysis demonstrated that using 2-drug therapy produces superior survival compared to beginning with single-agent management [18, 19]. Recently released information suggests that adding the targeted therapy bevacizumab to first-line combination chemotherapy adds additional months to median survival [20]. However, although these advances are individually worthwhile and statistically significant, they have only moderate overall impact on survival. Additional therapies with differing mechanisms of action and/or toxicity profiles must be added to our therapeutic options. To gauge the potential utility of a new agent in treating patients with NSCLC, single-agent activity should be assessed. Some targeted therapies appear to act synergistically with cytotoxic chemotherapy while having no independent ability to induce tumor shrinkage. However, for traditional cytotoxic agents, a measurable single-agent response rate is a traditional *sine qua non* for further study.

The 1990s were a rich period for the emergence of new cytotoxic agents with activity against NSCLC. One class of particular interest was the antitubulin agents, including the taxanes paclitaxel and docetaxel (Taxotere\(^c\); Aventis Pharmaceutical Products, Inc., Bridgewater, New Jersey) [21]. Each has single-agent activity in the first-line setting and significantly improves overall survival in patients with advanced NSCLC when used as first-line therapy compared to BSC [22, 23]. In two phase III trials of first-line therapy conducted largely or completely in European centers, the single-agent response rates were 16.1% for paclitaxel [22] and
13.1% for docetaxel [23]. In the docetaxel-treated patients, an additional 31.4% experienced ‘disease stabilization’. In the paclitaxel versus BSC trial, median TTP with paclitaxel was 3.9 months compared to 0.5 months with BSC. Phase III trials with paclitaxel in patients with breast and ovarian cancer have not shown a dose–response or dose–survival relationship [24, 25]. In patients with lung cancer, docetaxel 100 mg/m² every 3 weeks is excessively toxic, and in North America and Europe, 75 mg/m² is the recommended dose for single-agent and combination regimens [21]. Japanese investigators often use 60 mg/m² [26].

The profile of taxane toxicity is well recognized. Grade 3/4 neutropenia is common. Recent data with docetaxel suggest that the risks of grade 3/4 neutropenia and febrile neutropenia increase with increasing age. Myelosuppression is reduced with weekly administration. Clinically relevant thrombocytopenia is rare. Using the traditional every-3-week schedule, the majority of patients experience alopecia. Myalgia, arthralgia, and some degree of peripheral neuropathy are common, especially with paclitaxel. Fatigue can be particularly prominent, especially with weekly docetaxel regimens. The frequency of severe hypersensitivity reactions (HSRs) with standard paclitaxel is significantly reduced by premedication with steroids and H₁ and H₂ blockers, and with an infusion duration ≥1 h. Steroid administration is recommended before, during, and after docetaxel administration to reduce cumulative fluid retention.

Paclitaxel has limited solubility in aqueous solutions. It is prepared in Cremophor and ethanol for administration. The Cremophor vehicle itself has substantial toxicity and is thought to be responsible for most of the HSRs seen with paclitaxel. Cremophor may also contribute to paclitaxel’s neurotoxicity [27]. The physical nature of the Cremophor-paclitaxel suspension may limit access of paclitaxel to tumor cells and contribute to the lack of a dose-response relationship [28]. Multiple strategies for eliminating Cremophor as the vehicle for administration of paclitaxel, such as liposomal encapsulation, binding to biodegradable polymers, and nanoparticle formulations, are being pursued.

Abraxane is a novel, albumin-stabilized, 130-nanometer particle form of paclitaxel. It does not utilize Cremophor for drug delivery. In a phase I study done at M.D. Anderson, the new formulation was safely administered as a short IV infusion without steroid or antihistamine premedication [29]. The MTD was 300 mg/m² given over 30 min once every 3 weeks. Alopecia occurred in all patients. Neurotoxicity and mucositis were dose limiting. Grade IV granulocytopenia and one episode of superficial keratopathy were seen at 375 mg/m². Pharmacokinetic parameters were linear over the clinically relevant dose range. The AUC for Abraxane was lower than that of the same dose of paclitaxel solubilized with Cremophor. This potentially reflects improved tissue distribution of albumin-based paclitaxel.

The current study of Abraxane provides the first phase II data concerning front-line use of a second-generation paclitaxel formulation in patients with advanced NSCLC who have good performance status. The sample size is moderate with an appropriate distribution of patient and disease characteristics except that only Caucasian patients were enrolled. All accrual came from Russian physicians through the coordination of an international contract research organization. Consistent with that demographic, 67% of patients had squamous cell tumors.

The primary study endpoints, antitumor activity and toxicity of Abraxane, were fully evaluated within the study population. The protocol allowed administration of chemotherapy until...
disease progression or unacceptable toxicity occurred. The overall intent-to-treat response rate was 16% (95% CI: 5.24–27.31%). This falls within the range of first-line response rates reported for first-generation taxanes. An additional 33% of patients experienced stable disease, rigorously defined as lasting ≥16 weeks. This combination of responses and prolonged stable disease are reflected in the current median TTP of 6 months (95% CI: 3.9–6.5). Thus far, 23 of 43 patients have died. The current estimated median survival time of 11 months is particularly notable for single-agent therapy, especially given the preponderance of males (77%) within the study population and the relatively limited availability of ‘evidence-based’ salvage therapy for many Russian patients with advanced NSCLC.

Abraxane produced minimal hematologic toxicity. Despite weekly monitoring, neither dose delays nor dose reductions were required because of myelosuppression. This observation supports the development of combination regimens containing clinically relevant doses of Abraxane. Non-hematologic toxicities similar to those associated with first-generation taxanes were more notable. Some degree of sensory neuropathy occurred in 28 patients (65%); however, it was grade 3 in only one patient (2%). Cardiopulmonary and gastrointestinal toxicities were infrequent and mild.

In this trial, 63% of patients received at least six cycles of treatment. This is a longer duration of treatment than is routinely used now in the non-protocol setting. It permitted evaluation of the potential for late emergence of cumulative toxicities. Some of the observed neurotoxicity and constitutional symptoms may be less relevant with a non-protocol regimen of four to six total cycles of first-line therapy followed by time off treatment.

These data demonstrate measurable single-agent activity and a favorable therapeutic index for Abraxane used as a 30-min IV infusion at 260 mg/m² every 3 weeks. The current TTP and estimated median survival data are closer to those seen with standard combination paclitaxel-carboplatin therapy than with paclitaxel alone [30]. Further monitoring of the survival experience of the treated cohort will be of substantial interest. Testing combinations of Abraxane plus a platinum or non-platinum partner as first-line therapy in patients with advanced NSCLC is warranted. Given the minimal myelosuppression, use of Abraxane may also facilitate administration of full-dose chemotherapy concurrently with radiation for the management of patients with stage III NSCLC. These strategies are currently under investigation.

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references