Docetaxel and Exisulind in Previously Treated Non-small Cell Lung Cancer (NSCLC) Patients: A Multicenter, Phase II Clinical Trial

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Purpose: This multicenter, phase II clinical trial was conducted to evaluate the activity of the combination of docetaxel and exisulind in advanced non-small cell lung cancer (NSCLC) patients who failed a prior platinum-containing regimen.

Patients and Methods: Patients with measurable disease and adequate organ function received exisulind (250 mg) given orally, twice daily, and docetaxel (36 mg/m²) administered intravenously on days 1, 8, and 15 of a 4-week cycle for up to six cycles. In the absence of disease progression or intolerable side effects, patients continued taking 250 mg of exisulind orally, twice daily.

Results: Thirty-three patients (median age 60 years; range 34–77; median performance status 1) were enrolled. There were no objective responses documented. Sixteen patients [48%, 95% confidence interval (CI): 31%–66%] had stable disease after 8 weeks of treatment. Median progression-free survival (PFS) was 2.1 months (95% CI: 1.5–3.2 months; median overall survival time was 8.0 months (range 0.2–25.9 months). Toxicity was moderate, with dose adjustment for adverse event/toxicity required for docetaxel or exisulind in 13 (39.3%) patients. Grade 3/4 lymphopenia, neutropenia, and anemia occurred in 48.5%, 12.1%, and 9.1% of patients, respectively. Grade 3 or greater toxicity was seen in 12.1%, 6.1%, and 3% of patients for nausea/vomiting, dyspnea, and abdominal pain, respectively.

Conclusions: Treatment with exisulind and weekly docetaxel was not active in NSCLC patients who failed a prior platinum-containing regimen. Further study of this combination does not seem warranted.

Key Words: Non-small cell lung cancer, Exisulind, Docetaxel, Chemotherapy.

(J Thorac Oncol. 2007;2: 933–938)

In 2006, an estimated 174,500 cases of lung cancer will be diagnosed, and an estimated 162,500 people will die from this disease.1 Approximately 87% will have non-small cell lung cancer (NSCLC) histology, and about two thirds of those will present with advanced, unresectable disease. Current American Society of Clinical Oncology guidelines recommend the first-line use of doublet platinum-based chemotherapy in advanced NSCLC and, alternatively, non–platinum-containing chemotherapy may be used.2 Second-line chemotherapy has prolonged survival in patients with advanced lung cancer. Two chemotherapy agents, docetaxel and pemetrexed, are U.S. Food and Drug Administration approved in this setting. In addition, the epidermal growth factor receptor inhibitor, erlotinib, showed a survival advantage over placebo in previously treated patients, and it has been approved for both second- and third-line treatment.

The induction of apoptosis in malignant cells is a common mechanism of therapeutic agents to destroy tumor cells. Nevertheless, most agents achieve apoptosis by indirect approaches. Thus, agents that could directly target the apoptotic pathway would be of additional value. Exisulind, a sulfone metabolite of the nonsteroidal anti-inflammatory drug (NSAID) sulindac, possesses proapoptotic properties. It inhibits cyclic GMP (cGMP) phosphodiesterases 2 and 5, which are often overexpressed in a variety of cancers (Figure 1). This inhibition leads to programmed cell death, as it causes sustained elevation of cGMP, leading to the activation of cGMP-dependent protein kinase G (PKG).3,4 The pathway to apoptosis continues with PKG activation promoting proteasomal degradation of β-catenin and activation of c-Jun NH₂-terminal kinase (JNK).2 Exisulind demonstrated in vitro tumor growth inhibition in breast5 and colon cancer6 cell lines and in vivo tumor growth inhibition of colon, bladder, breast, prostate, and lung cancers in rodent models.7,9 We previously have shown that exisulind produced synergistic growth inhibition when combined with docetaxel in vitro10 and in vivo when the combination significantly improved survival in an orthotopic lung cancer model.10,11

Initial clinical investigations involved the use of exisulind as a chemopreventative agent in familial adenomatous polyposis (FAP).12 Exisulind (250 mg, given orally, twice daily) was also studied in a randomized, double-blind, placebo-controlled trial of 96 high-risk men with increasing PSA
Patients and Methods

Patient Selection

Patients with confirmed advanced NSCLC that progressed or those who had received a platinum-based chemotherapy regimen in the past 6 months were eligible for this study. Other eligibility criteria included the following: (a) measurable disease; (b) age ≥18 years; (c) life expectancy ≥3 months; (d) Southwest Oncology Group performance status ≤2; (e) no prescription or over-the-counter NSAIDs for 2 weeks before enrollment (patients taking a cumulative monthly dose of aspirin of <3250 mg for cardiovascular prevention were not excluded from the study); (f) no chemotherapy or radiotherapy within 2 weeks or investigational agent within 4 weeks of study entry with full recovery from the acute effects of prior therapy; and (g) adequate hematopoietic, hepatic, and renal function.

Patients with uncontrolled or symptomatic brain metastases, significant medical conditions, peripheral neuropathy greater than grade 1, or known hypersensitivity to sulindac, taxanes, or other drugs formulated with polysorbate 80, were excluded. Women of child-bearing age were required to have a negative pregnancy test before study entry and were required to be on adequate birth control while on the study. Informed consent was obtained in accordance with federal and institutional guidelines.

Study Design

This was a two-center phase II trial of the combination of exisulind and docetaxel for advanced NSCLC patients who had failed a prior platinum-based chemotherapy regimen. Patients were enrolled prospectively at the University of Colorado and the University of Chicago. The primary endpoint of the study was objective response rate. Secondary endpoints included progression-free survival (PFS), median overall survival (OS), and toxicity.

Treatment

Docetaxel (36 mg/m²) was administered intravenously for 30 minutes on days 1, 8, and 15 for an every-28-days cycle for a maximum of six cycles. All patients received dexamethasone (8 mg, administered intravenously) before docetaxel infusion. The use of diphenhydramine was optional. Exisulind (250 mg, administered orally, twice daily) was started on day 1 through day 28 of each cycle and, after six cycles, was continued as a single agent until disease progression or intolerable toxicity.

Salicylates (except <3250 mg of aspirin for cardiovascular prevention) and NSAIDs (except ibuprofen or naproxen) were not allowed 2 weeks before enrollment and for the duration of the study.

Dose Modifications

Toxicities were graded according to the National Cancer Institute CTC, version 2.0. First- and second-reduction doses were as follows: exisulind (200 mg, administered orally, twice daily; and 150 mg, administered orally, twice daily), and docetaxel (30 and 25 mg/m², respectively, both administered intravenously). If an elevated bilirubin (grade 3

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or any elevation) or any grade 3 hepatotoxicity occurred, exisulind and docetaxel dosing was interrupted. When the patient had recovered to grade 1 toxicity, both drugs were restarted at their respective dose-reduction levels. Docetaxel was also reduced for an elevated alanine transferase (ALT) to 1.6 times the upper limit of normal (ULN), and by one dose level for any hematologic toxicity of grade or higher. Any patient requiring a dose-level reduction continued to receive the reduced dose for the remainder of the study. If there was a recurrence of grade 3 toxicity after two dose reductions, the patient could no longer receive that drug. If one drug was stopped for toxicity, the patient could continue the other drug at the discretion of the principal investigator.

Patients could not receive docetaxel unless their absolute neutrophil count (ANC) was ≥1500/ul and their platelet count was ≥100,000/ul. The use of colony stimulating support agents were to be used according to American Society of Clinical Oncology 2000 guidelines. Patients were removed from the study if they had intolerable toxicity or disease progression, or if they withdrew consent.

Exisulind was supplied by OSI Pharmaceuticals Inc., successor-in-interest to Cell Pathways, Inc. (Melville, NY), in 100- or 150-mg gelatin capsules. Docetaxel was commercially available from Sanofi-Aventis Pharmaceuticals, Inc.

Patient Assessment

Baseline assessment included a complete medical history, physical examination, assessment of performance status, complete blood count with a differential, comprehensive metabolic panel, plus phosphate, uric acid, and lactate dehydrogenase. A urinalysis and a serum pregnancy test (as appropriate) were performed before treatment. Pretreatment studies also included an electrocardiogram, and relevant radiographic studies to evaluate all measurable and assessable sites of disease. Patient adherence was monitored by pill counts and dosing diaries. Weekly blood counts were performed before docetaxel administration. Physical examination, toxicity evaluation, documentation of concurrent medications, complete laboratory analysis, and assessment of performance status were performed at each cycle.

Radiographic evaluations for disease status assessment were repeated after every other course, using the WHO criteria. A complete response was defined as the disappearance of all measurable and assessable disease for at least two measurements performed at least 4 weeks apart without worsening of disease-related symptoms or declining performance status. A partial response required at least a 50% reduction in the sum of the product of the bidimensional measurements of all lesions documented by at least two measurements separated by a minimum of 4 weeks. Any increase in the size of a lesion by ≥25% or the appearance of a new lesion was considered disease progression. Patients continued on treatment in the absence of disease progression or intolerable toxicity.

Statistical Analysis

Treatment success for an individual patient was defined as the occurrence of a complete or partial response. The smallest success proportion that would justify further study of the proposed regimen was 15%. A two-stage Fleming design was applied. This design uses 26 or 52 patients to test the null hypothesis that the true success proportion in a given patient population is, at most, 5%.

Stage 1: Enter 26 patients. If no successes are observed, accrual will be terminated and the regimen declared ineffective. If five or more successes are observed, accrual may be terminated and the trial declared a success. Otherwise, proceed to stage 2.

Stage 2: Enter an additional 26 patients. If five or fewer total successes are observed, the regimen will be declared ineffective. If six or more successes are observed, the trial will be declared a success.

This scheme provided an 81% power to conclude a success given a true response rate of 15%, and 4.6% probability of falsely concluding success given a true response rate of less than 5%.

Actuarial survival curves were generated using the Kaplan–Meier method.

RESULTS

Patient Characteristics

Between November 7, 2001 and January 14, 2004, 33 eligible patients were entered onto the study; their characteristics are listed in Table 1. There were 17 men and 16 women. The median age was 60 years (range 34–77), 84% had a performance status ≤1, and 70% were Caucasian. No patients had brain metastases. There were 26 patients evaluable for response, and all 33 patients were evaluable for toxicity. Thirty-three patients were enrolled in the trial to fulfill the

<table>
<thead>
<tr>
<th>TABLE 1. Patient Characteristics</th>
<th>No. of Patients</th>
<th>%</th>
</tr>
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<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>17</td>
<td>52</td>
</tr>
<tr>
<td>Female</td>
<td>16</td>
<td>48</td>
</tr>
<tr>
<td>Median age (range)</td>
<td>60 years (34–77)</td>
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<tr>
<td>Southwest Oncology Group status</td>
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<tr>
<td>0</td>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td>1</td>
<td>25</td>
<td>76</td>
</tr>
<tr>
<td>2</td>
<td>5</td>
<td>15</td>
</tr>
<tr>
<td>Race</td>
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<tr>
<td>Caucasian</td>
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<tr>
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<td>24</td>
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<tr>
<td>Asian</td>
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<td>6</td>
</tr>
<tr>
<td>Extralymphatic metastatic sites</td>
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<td></td>
</tr>
<tr>
<td>Liver</td>
<td>6</td>
<td>18</td>
</tr>
<tr>
<td>Bone</td>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td>Adrenal</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Time elapsed since prior chemotherapy</td>
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<td></td>
</tr>
<tr>
<td>&lt;3 months</td>
<td>24</td>
<td>73</td>
</tr>
<tr>
<td>3–6 months</td>
<td>8</td>
<td>24</td>
</tr>
<tr>
<td>&gt;6 months</td>
<td>1</td>
<td>3</td>
</tr>
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</table>
Fleming Stage 1 design; seven patients were removed from study before they were evaluable for response. These seven patients had progressive disease before radiologic assessment for efficacy could be determined according to protocol guidelines.

**Efficacy**

No objective responses were observed. Sixteen patients (48%, 95% confidence interval (CI): 31%–66%) had stable disease after treatment. Median PFS was 2.1 months (95% CI: 1.5–3.2 months). Median follow-up time was 8.0 months (range 0.2–25.9 months). Figure 2A shows the actuarial PFS curve for all patients. The median survival curve for the entire population is shown in Figure 2B. Median survival was 8.0 months, and the 1-year survival estimate was 38.1% (95% CI: 20.0%–56.4%). Twenty-one patients received additional therapy after removal from the study. Systemic therapy was received by 17 patients (range of one to four regimens), with gefitinib being most frequent ($n = H1100510$). Seven patients received radiation therapy after removal from the study.

**Study Drug Administration and Toxicity**

Patients received a median of two cycles of docetaxel and two cycles of exisulind. Three patients completed six cycles of docetaxel, and two patients completed eight cycles of docetaxel at the discretion of the principal investigator. Overall, 90 cycles of therapy (combined or single agent) were delivered.

Dose reductions were common. Dose adjustments for docetaxel included five (15%) attributable to adverse events/toxicity (hyperlacerimation [1], rash [1], nausea and/or vomiting [2], and diarrhea [1]) and four (12%) attributable to laboratory abnormalities (neutropenia [2], elevated transaminases [1], and elevated bilirubin [1]). Dose reductions for exisulind included five (15%) attributable to toxicities, which included diarrhea (1), digital erythema (1), rash (1), elevated bilirubin (1), and elevated AST (1). Nine (27%) patients discontinued study therapy (exisulind and/or docetaxel) because of adverse events/toxicities, including severe nausea and vomiting (1); mental status changes (1); arthralgia, asthenia, ataxia, chest pain, dizziness, elevated liver-function tests, and lower-extremity pain (1); cholecystitis (1); onychomycosis (1); radiation pneumonitis (1); fatigue (1); abdominal pain, fatigue, and elevated liver-function tests (1); and neuropathy (1). Only two patients continued on docetaxel when exisulind was discontinued.

Laboratory hematologic and nonhematologic toxicity was moderate (Table 2). Grade 3/4 lymphopenia, neutropenia, anemia, and thrombocytopenia occurred in 48.5%, 12.1%, 9.1%, and 3.0% of patients, respectively. No cases of febrile neutropenia occurred. Grade 3/4 abnormalities in serum chemistry were seen in ALT (9.1%), total bilirubin (6.1%), and creatinine (6.1%). Severe toxicity was seen in 12.1%, 6.1%, 3%, and 3% of patients for nausea/vomiting, dyspnea, abdominal pain, and increased lacrimation, respectively (Table 3). Nail disorders or increased lacrimation were reported in six patients each (Table 3). There were no toxic deaths.

**DISCUSSION**

This phase II trial of weekly docetaxel plus exisulind as second-line therapy was tolerable, but it failed to produce objective responses. One possible explanation for the lack of response is the use of the weekly docetaxel schedule. Two randomized trials comparing weekly versus docetaxel every 3 weeks in advanced NSCLC did not show a significant differences in survival or response rates.23,24 Camps et al.23 studied 259 advanced NSCLC patients previously treated with platinum-based chemotherapy comparing docetaxel (75 mg/m²) every 3 weeks versus docetaxel (36 mg/m²) weekly for six consecutive weeks every 8 weeks. The response rates were 9.3% and 4.8%, and median overall survival was 6.6 and 5.4 months ($p = H110050.076$), in the every-3-weeks versus weekly arm, respectively. The second study24 involved 220 advanced NSCLC patients in two dosing schemes in the second-line setting (docetaxel [75 mg/m²] every 3 weeks for six cycles versus docetaxel [33.3 mg/m²] weekly for six consecutive weeks every 8 weeks for two cycles). The response rates were


2.7% and 5.5%, and median overall survival was 7.3 versus 6.3 months (p = not significant) in the every-3-weeks versus weekly arm, respectively.

Another possible reason for the lack of response was that the study only included patients who had failed a platinum-based regimen in the past 6 months. In fact, the majority of patients enrolled (73%) failed systemic therapy with a platinum-based regimen in the past 6 months. In fact, the study only included patients who had failed a prior platinum-based therapy.

Most likely is the lack of antitumor activity of exisulind when combined with chemotherapy. The Eastern Cooperative Group conducted a phase II trial of carboplatin and gemcitabine with exisulind in untreated, advanced NSCLC patients in 58 patients using gemcitabine (1000 mg/m²) on days 1 and 8 and carboplatin (AUC = 5) on day 1, every 21 days, along with exisulind (250 mg, orally) twice daily.25 Grade 3 and 4 hematologic toxicities were neutropenia (35% and 21%) and thrombocytopenia (23% and 7%). Grade 3/4 nonhematologic toxicity was nausea and fatigue, seen in 14% and 18% of patients, respectively. The overall response rate was 17%, and median survival was 7.1 months. The authors conclude that the addition of exisulind did not benefit overall chemotherapy. CPI-028, a randomized phase III trial of docetaxel with or without exisulind, completed accrual, with its primary endpoint.

The CALGB has reported on a phase II study of carboplatin, etoposide, and exisulind in 43 patients with advanced NSCLC.26 Toxicity was evaluable in all 43 patients, with grade 4 toxicities of neutropenia (43%), anemia (2%), and hypokalemia (2%), and grade 3 toxicities of thrombocytopenia (38%), neutropenia (24%), febrile neutropenia (17%), anemia (14%), hyperglycemia (12%), and fatigue (10%). There was one treatment-related death (stroke). Thirty-eight patients were assessable for response, with 15% complete and 66% partial. The median overall survival was 10.5 months, and the study did not meet its primary endpoint.

Numerous targeted agents have failed after first-line therapy, including studies of epidermal growth factor receptor tyrosine kinase inhibitors in combination with standard chemotherapy (concurrent administration),27–30 a metalloproteinase inhibitor,31 a retinoid X-receptor–specific ligand,32 and an antisense protein kinase C-alpha inhibitor.33 Nevertheless, there are also examples where single agents that produce stable disease in the advanced setting show enhanced activity with chemotherapy, such as bevacizumab in combination with carboplatin and paclitaxel.34

Overall, the exisulind and docetaxel combination had moderate toxicity, mainly with an increase in hepatotoxicity, nausea, and vomiting. The high incidence of lymphopenia observed is typical for docetaxel. The lack of a response in the 26 evaluable patients fulfilled stage 1 of the Fleming design to halt the study. According to these results, this combination of docetaxel and exisulind given in these doses and schedule should not be pursued in advanced NSCLC patients who have failed a prior platinum-based therapy.

### REFERENCES


### TABLE 2. Laboratory Toxicity by Patient (n = 33)

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Grade</th>
<th>Toxicity</th>
<th>Grade</th>
<th>Toxicity</th>
<th>Grade</th>
<th>Toxicity</th>
<th>Grade</th>
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<tbody>
<tr>
<td>Neutropenia</td>
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<td>2</td>
<td>12.1</td>
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<tr>
<td>Lymphopenia</td>
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<td>16</td>
<td>0</td>
<td>48.5</td>
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<tr>
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<td>3</td>
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<tr>
<td>Thrombocytopenia</td>
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<tr>
<td>Alanine transferase</td>
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<td>Total bilirubin</td>
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### TABLE 3. Nonhematologic Toxicity by Patient (n = 33)

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Mild (no.)</th>
<th>Moderate (no.)</th>
<th>Severe (no.)</th>
<th>Severe (%)</th>
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</thead>
<tbody>
<tr>
<td>Nausea/vomiting</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>12.1</td>
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<tr>
<td>Abdominal pain</td>
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<td>1</td>
<td>3.0</td>
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<tr>
<td>Dyspepsia</td>
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<td>1</td>
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<td>Nail disorder</td>
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<td>0</td>
<td></td>
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<td>Increased lacrimation</td>
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<td>1</td>
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