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# Randomized Multicenter Phase II Study of Larotaxel (XRP9881) in Combination with Cisplatin or Gemcitabine as First-Line Chemotherapy in Nonirradiable Stage IIIB or Stage IV Non-small Cell Lung Cancer

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## ABSTRACT

**Introduction:** This randomized phase II study investigated the efficacy and safety of a new taxane, larotaxel (XRP9881), in combination with either cisplatin or gemcitabine in the first-line treatment of patients with nonirradiable stage IIIB or stage IV non-small cell lung cancer to select the combination having the most promising antitumor activity.

**Methods:** Patients received either larotaxel (50 mg/m$^2$) as a 1-hour infusion, followed by a 1-hour infusion of cisplatin (75 mg/m$^2$), every 3 weeks (arm A), or gemcitabine (800 mg/m$^2$) as a 30 minute infusion, on days 1 and 8, and larotaxel (60 mg/m$^2$) as a 1-hour infusion, on day 8 (following gemcitabine), every 3 weeks (arm B). The primary end point was the objective response rate (per-protocol population).

**Results:** Thirty-two patients were randomized to arm A and 30 to arm B. The response rate was higher in arm A compared with arm B in both the per-protocol (26.7% versus 18.2%) and intention-to-treat (28.1% versus 13.3%) populations. In the intention-to-treat population, median progression-free survival for arm A versus arm B was 4.7 versus 3.3 months and median overall survival was 8.6 versus 7.3 months, respectively. Fifty percent of patients in arm A and 66.7% in arm B experienced at least one National Cancer Institute common toxicity criteria grade 3/4 adverse event and grade 3/4 neutropenia was observed in 46.9% and 41.4% of patients, respectively.

**Conclusions:** Both larotaxel combinations were effective and manageable, however all measured efficacy parameters (response rate, progression free survival, and survival) seemed to favor the combination with cisplatin.

**Key Words:** Advanced NSCLC, Combination chemotherapy, First-line, Taxane, Larotaxel.

Globally, lung cancer is the most frequently diagnosed malignancy and the disease remains the most common cause of cancer-related death.[1] The majority of tumors (~80%) are non-small cell lung cancers (NSCLCs).[2] As a consequence of the absence of effective, clinically-validated screening procedures, most NSCLCs are locally advanced or metastatic at presentation (stage IIIB and IV),[3] and therefore nonresectable. Treatment for advanced disease may comprise chemoradiotherapy (stage IIIB) or chemotherapy (stage IV).[4] Such essentially palliative treatment aims at controlling symptoms, improving quality of life, and lengthening survival.

A number of cytotoxic agents have been shown to be effective as first-line treatments for NSCLC. Currently, patients with good performance status will commonly receive a doublet comprising a platinum analogue

(cisplatin or carbo-platin) combined with a third-generation cytotoxic agent (gemcitabine, vinorelbine, or a taxane). Various combinations seem to be essentially equally effective,[5,6] with differences between regimens primarily limited to their side effect profiles.[7,8] Nonplatinum-based doublets, especially gemcitabine plus a taxane have been developed in an attempt to overcome cisplatin-associated toxicities. Results available at time of this study led to the recommendation by American Society of Clinical Oncology in 2003 of their use as an alternative to platinum-based doublets.[4]

The taxanes, paclitaxel and docetaxel, are both effective and approved in combination with platinum in first-line NSCLC therapy.[9] Docetaxel is also approved-as-a-single agent for second-line treatment. There is however a need to increase the effectiveness of such compounds in relation to increasing cytotoxicity in taxane-resistant tumors and decreasing systemic toxicity.[10] Larotaxel (XRP9881) is a novel semi-synthetic taxane compound that seems to be a potent microtubule stabilizer, blocking tubulin disassembly and thereby inhibiting mitosis. The drug efflux pump, P-glycoprotein 1 (encoded by the multidrug resistance gene, *ABCB1*), which is commonly overexpressed in tumors, may play a key role in taxane resistance. Larotaxel has a much lower affinity for P-glycoprotein 1 than docetaxel and was shown to be active in cell lines resistant to doxorubicin, vinblastine, paclitaxel, and docetaxel. In addition, this compound seems to cross the blood-brain barrier.[11]

Several phase I studies have explored different schedules of administration of larotaxel as a single agent and have recommended dose levels for phase II studies of 60 and 90 mg/m$^2$ for the every 3 weeks regimen.[11-15] Hematologic toxicity was the main dose-limiting toxicity in all the tested regimens. Other nonhematologic toxicities characteristically associated with taxanes, such as alopecia, gastrointestinal effects, neurosensory disorders, hypersensitivity reactions, skin disorders, and fluid retention were generally mild or moderate. Objective responses were observed in several tumor types. Of particular interest, Sessa and colleagues noted responses in three NSCLC patients. In one case, a response was seen in both the patient's primary tumor and also associated brain metastases.[11] This study provided a rational basis for the further testing of larotaxel in advanced NSCLC patients.

A preliminary three-arm phase I study investigated larotaxel in combination with cisplatin, gemcitabine, or vinorelbine. The recommended doses for the combination of larotaxel and cisplatin were 50 and 75 mg/m$^2$, respectively and for larotaxel and gemcitabine; 60 and 800 mg/m$^2$, respectively. However, larotaxel combined with vinorelbine showed poor tolerability, even at the lowest doses tested, and so this combination was rejected for phase II development (manuscript in preparation). Using response rate as the primary efficacy measure, the current phase II study was designed to investigate whether cisplatin or gemcitabine was the most appropriate partner for larotaxel in patients with chemotherapy naive advanced NSCLC.

## PATIENTS AND METHODS

### Major Eligibility Criteria

Chemotherapy naive patients were eligible for inclusion if they had histologically or cytologically-confirmed nonirradiable stage IIIB or stage IV NSCLC and were ≥18 and ≤75 years of age, with a life expectancy of at least 12 weeks and an Eastern Cooperative Oncology Group performance status of 0 to 2. They were not to have received surgery for NSCLC within the previous 4 weeks (excluding simple surgery for diagnosis or to implant a venous access device) and required adequate hematologic (neutrophils >2 x $10^9$/l, platelet count >100 x $10^9$/1), renal (creatinine within upper normal limits or if borderline, with a creatinine clearance >60 mL/min), and hepatic (total bilirubin within normal limits, serum aspartate aminotransferase/alanine aminotransferase and alkaline phosphatase ≤2.5 times the upper limits of normal or aspartate aminotransferase/alanine aminotransferase ≤ 1.5 times associated with alkaline phosphatase ≤5 times the upper limits of normal) function. Patients were required to have at least one measurable lesion according to response evaluation criteria in solid tumors criteria.[16] The study was conducted in accordance with the declaration of Helsinki and written informed patient consent was obtained before the implementation of any study-related procedures.

Main exclusion criteria were: a prior history of cancer (excluding basal cell skin or in situ disease); symptomatic brain or leptomeningeal metastases; hypercalcemia (>2.8 mmol/l); peripheral neuropathy > grade 1; another serious comorbid condition; had received prior chemotherapy or radiotherapy (except for bone metastases) or were receiving another anticancer treatment or experimental drug.

**Study Design and Treatments**

This was a multicenter, randomized study conducted in 11 centers in four countries (France, Belgium, Czech Republic and Switzerland). The primary objective was to select the combination having the most promising antitumor activity (response rate). Patients were randomly assigned centrally into two arms. Those in arm A received larotaxel (50 mg/m$^2$) as a 1-hour infusion, followed after 30 minutes by a 1-hour infusion of cisplatin (75 mg/m$^2$), every 3 weeks. Patients in arm B received gemcitabine (800 mg/m$^2$) as a 30 minute infusion, on days 1 and 8, and larotaxel (60 mg/m$^2$) as a 1-hour infusion, on day 8 (following gemcitabine, with no interval), every 3 weeks. Administration of larotaxel on day 8 in this arm was selected to match docetaxel/gemcitabine NSCLC schedules, which have been designed to avoid do-cetaxel-induced neutropenia (which generally occurs 5 to 8 days after administration) causing a delay in the day 8 administration of gemcitabine.[17] All patients in arm A received a setron (ondansetron or alternative) as a prophylactic antiemetic premedication from cycle 1. Patients in this arm were to be adequately hydrated to avoid the nephrotoxicity secondary to cisplatin administration. No prophylactic antiemetic drugs were allowed during the first cycle for patients in arm B. In subsequent cycles, in the case of nausea/ vomiting, patients could receive preventive antiemetic treatment in compliance with the standard protocol of the center. Prophylaxis with dexamethasone was given (16 mg the day before, 24 mg the day of, and 16 mg the day after larotaxel administration).

Adverse events (AEs) were graded according to National Cancer Institute-Common Toxicity Criteria Version 2. In the event of long lasting AEs, the cycle could be extended for 1 week. No dose reduction was permitted for arm A and if such toxicity did not resolve by day 28, the patient was to discontinue the study treatment. For arm B, in the case of severe toxicity related to larotaxel or gemcitabine, a dose reduction to 50 and/or 650 mg/m$^2$, respectively, was allowed.

The interval between day 1 of 2 consecutive cycles could be extended to 5 weeks for nondrug-related AEs, but only once during the study. Treatment was continued until disease progression, unacceptable toxicity, or the withdrawal of patient consent.

**Evaluations Before and During Therapy**

Within 7 days before first study drug administration, medical history (including NSCLC histology/cytology, prior surgery other than for cancer, concurrent illness, prior medications, history of allergy) was recorded and a physical examination (height, weight, Eastern Cooperative Oncology Group performance status, vital signs) carried out. Standard hematologic and biochemical analyses and an evaluation of existing signs and symptoms were also completed. Within 4 weeks before treatment a cardiologic examination and radiologic scanning of the chest (x-ray or computed tomography; CT), abdomen (CT), brain (CT or magnetic resonance imaging) and when indicated, bone (scan or x-ray) were carried out, encompassing all target and nontarget (when indicated) lesions. During the study, a physical examination was carried out immediately before treatment, on day 1 of each cycle. Toxicity was evaluated weekly. Hematologic assessments were carried out every week, or every other day in the case of grade four neutropenia or thrombopenia (arm B) until recovery to grade $\leq$3 or <3, respectively. Radiologic assessment of the chest and abdomen and all target and nontarget lesions was performed every 2 cycles (6 weeks) using the same method as the baseline evaluation.

**Statistical Methods and Considerations**

The intention-to-treat (ITT) population comprised all randomized patients. The per-protocol population (PPP) was defined as a subset of the treated population: patients had to be eligible, evaluable for response, and without any major protocol deviations during the course of the study. The safety population was the treated population, defined as all patients who had been administered at least one (even incomplete) infusion of one study drug.

The primary objective was to rank the activity of the two test regimens using the Simon design.[18] An independent External Response Review Committee reviewed radiologic assessments to evaluate the best tumor response and to establish the date of progression (response evaluation criteria in solid tumors[16]). The primary efficacy variable was the objective response rate for the PPP, as assessed by the External Response Review Committee and as defined by the percentage of patients achieving a confirmed complete (CR) or partial (PR) response (CR + PR). Twenty-one patients/arm were to be included. Taking into account a likely rate of exclusion from the PPP of 10%, 23 patients/arm were to be enrolled. With this sample size, and assuming that the lowest response rate was 10%, there was a probability of 90% that the best treatment would be selected, provided that it was superior to the other by at least 15%.

Secondary efficacy variables included: duration of response (DR; defined as the time interval between meeting the criteria for a CR or PR and the date of the first documented progression or death from any cause), duration of stable disease (SD) (defined as the time from randomization until disease progression or death for patients with SD as best overall response),progression-free survival (PFS; defined as the time from randomization until disease progression or death), and overall survival (OS; defined as the time from randomization until death). For DR and PFS evaluations, progression or death occurring 84 days or more after the last evaluable tumor assessment was censored back to the date of that assessment. OS was censored at the date of last contact or the cutoff date, whichever came first.

Categoric variables were summarized by frequency and percentage. Ninety five percent confidence intervals [95%] were calculated using the Clopper-Pearson exact method,[19] where appropriate. Continuous variables were presented with summary statistics (mean, standard deviation, median, range). Kaplan-Meier curves[20] and estimates[21] (median and its 95% confidence interval) were used to analyze variables of duration and event.

## RESULTS

### Patient Demographics

Sixty-two patients were randomized between 30th July 2002 and 17th June 2003: 32 to arm A (larotaxel/cisplatin) and 30 to arm B (larotaxel/gemcitabine). Patient characteristics at baseline were generally well balanced between the arms, except gender (Table 1). Similarly, baseline tumor characteristics were well balanced with only slight differences in the interarm frequencies of the number and type of organs involved and stage of disease at first diagnosis (Table 1). The majority of patients had stage IV disease, with adenocarcinoma being the most common histologic class. Most patients had three or more organs affected.

### Treatment Administration

Thirty-two patients in arm A received a total of 127 cycles (median 4, range 1-8) and 30 patients in arm B received a total 116 cycles (median 4, range 1-6). Table 2 summarizes drug exposure. Reflecting the absence of protocol-permitted dose reduction in arm A, the relative dose intensity was 0.98 for both larotaxel and cisplatin. In arm B, 28 of 30 patients received larotaxel, with 2 discontinuing treatment immediately after the first gemcitabine infusion (day 1) following, in 1 case, grade 4 supraventricular arrhythmia and in 1 case, pulmonary embolism (neither considered related to study treatment). The relative dose intensity in this arm for larotaxel was 0.94 and for gemcitabine was 0.93, with these intensities demonstrating the feasibility of the combination. Although not allowed, 1 (3.1%) patient (1 cycle, 0.8%) in arm A did have a dose reduction (larotaxel; cycle 3) following anemia. In arm B, 7 (23.3%) patients experienced a dose reduction in 9 cycles (7.8%), due to hematologic toxicity for two patients, nonhematologic toxicity for three patients (diarrhea, nausea, and vomiting); for the two remaining patients no specific reason was given. Among the 9 cycles with dose reduction, larotaxel was reduced in eight and gemcitabine in one. Eleven patients (34.4%) in arm A and 13 patients (43.3%) in arm B had a delay in at least 1 cycle. A total of 16 (12.6%) cycles were delayed in arm A and 22 Arm A, larotaxel + cisplatin; Arn B, larotaxel + gemcitabine; PS, performance status; NSCLC, non-small cell lung cancer. (19.0 %) in arm B. The most common reasons for cycle delays were other reason (administrative reasons) in arm A and hematologic toxicity in arm B. All patients had discontinued treatment by the cutoff date of 15th May 2005, with the most common reason in both arms being progressive disease, followed by no further benefit expected and adverse event.

***TABLE 1.*** *Patient and Disease Characteristics at Baseline*

| Characteristic | **Arm** A (*N* = 32) | **Arm B** (*N* = 30) | **All Patients** (*N*=62) |
|---|---|---|---|
| Gender, *n* (%) | | | |
| Male | 21 (65.6) | 26 (86.7) | 47 (75.8) |
| Female | 11 (34.4) | 4(13.3) | 15 (24.2) |
| Race, *n* (%) | | | |
| Caucasian | 32 (100.0) | 30(100.0) | 62 (100.0) |
| Age, yr | | | |
| Median (range) | 57 (43-75) | 62 (40-72) | 60 (40-75) |
| <65 yr, *n* (%) | 21 (65.6) | 22 (73.3) | 43 (69.4) |
| ≥65 yr, *n* (%) | 11 (34.4) | 8 (26.7) | 19 (30.6) |
| PS before first infusion, *n* (%) | | | |
| Median (range) | 1 (0-2) | 1 (0-2) | 1 (0-2) |
| 0 | 9 (28.1) | 7 (23.3) | 16 (25.8) |
| 1 | 20 (62.5) | 19 (63.3) | 39 (62.9) |
| 2 | 3 (9.4) | 4(13.3) | 7 (11.3) |
| Signs and symptoms at baseline, *n* (%) | 27 (84.4) | 28 (93.3) | 55 (88.7) |
| Histology type, *n* (%) | | | |
| Adenocarcinoma | 17 (53.1) | 15 (50.0) | 32 (51.6) |
| Large cell carcinoma | 2 (6.3) | 4(13.3) | 6 (9.7) |
| NSCLC undetermined | 2 (6.3) | — | 2 (3.2) |
| Squamous cell carcinoma | 11 (34.4) | 11 (36.7) | 22 (35.5) |
| Stage of disease at baseline | | | |
| IIIB | 5 (15.6) | 5 (16.7) | 10 (16.1) |
| IV | 27 (84.4) | 25 (83.3) | 52 (83.9) |
| Measurable disease, *n* (%) | 32 (100.0) | 30 (100.0) | 62 (100.0) |
| Number of organs involved | | | |
| 1 | 1 (3.1) | 4 (13.3) | 5 (8.1) |
| 2 | 12 (37.5) | 6 (20.0) | 18 (29.0) |
| 3 | 13 (40.6) | 15 (50.0) | 28 (45.2) |
| 4 or more | 6 (18.8) | 5 (16.7) | 11 (17.7) |
| Organ involvement, *n* (%) | | | |
| Lung | 30 (93.8) | 24 (80.0) | 54 (87.1) |
| Soft tissue (lymph nodes) | 27 (84.4) | 22 (73.3) | 49 (79.0) |
| Brain | 4(12.5) | 6 (20.0) | 10 (16.1) |
| Bone | 9 (28.1) | 5 (16.7) | 14 (22.6) |
| Adrenal gland | 6 (18.8) | 8 (26.7) | 14 (22.6) |
| Liver | 5 (15.6) | 7 (23.3) | 12 (19.4) |
| Pleura | 5 (15.6) | 6 (20.0) | 11 (17.7) |

**Efficacy**

Primary and secondary efficacy data are detailed in Table 3. There were no CR. Response rates in the PPP for arm A and arm B were 26.7% and 18.2% and for the ITT population 28.1% and 13.3%, respectively. In addition, 40.0% and 36.4% (PPP), 40.6% and 33.3% (ITT) of patients respectively had SD. In brain lesions (10 patients), no objective responses were observed but stabilization was achieved in three of four patients in arm A and one of six in arm B.

As only 13 patients (including six censored in arm A and two in arm B) had an objective response, Kaplan-Meier plots for DR were not constructed. The DR ranged between 1.45 + and 20.63+ months. Median PFS was similar in arm A of the PPP compared with arm B (4.3 versus 4.4 months) but a difference of 1.4 months was observed in the ITT population (4.7 versus 3.3 months, respectively). In arm B, two out of four patients with very short PFS were excluded from the PPP (baseline tumor assessment done more than 31 days before first infusion) and probably explain the difference in PFS between ITT and PPP. In the ITT population, median OS was 8.6 months in arm A and 7.3 months in arm B (Figure 1) and the 1-year survival rate was 40.6% in arm A and 30.0% in arm

B.

**Safety**

Eight (25.0%) patients in arm A and nine (30.0%) patients in arm B experienced grade 3/4 treatment emergent adverse events related to study treatment (Table 4). The highest incidences of such events (nonhematological) were infection (9.4%) and vomiting (6.3%) in arm A, and infection (10.0%), diarrhea and allergic reaction (6.7%) in arm B. Of note, a similar rate of patients experienced grade 3/4 infection related to study treatment. However, more patients experienced grade 3/4 infection regardless of relationship to study treatment (with or without neutropenia) in arm B compared with arm A (12.5% in arm A; 26.7% in arm B). Given that the excess of infection cases in arm B seemed not to be related to treatment, that the patients were randomized to the study arms and that there were no obvious imbalances in patient/ disease characteristics at baseline that might explain this excess, this is most likely a chance finding.

Neutropenia was the most common grade 3/4 hematologic toxicity in both arms (arm A: 46.9%, arm B: 41.4%), with grade 3/4 thrombocytopenia reported for only one patient (3.4%) in arm B. Two (6.3%) patients experienced febrile neutropenia in arm A (no patients in arm B), and three (10.0%) patients experienced neutropenic infection in each arm.

The incidence of peripheral neurotoxicity was similar in both arms (arm A: 18.8%, arm B: 20.0%) with no patients experiencing grade 3. More any grade creatinine increase was noted for arm A compared with arm B (37.5% versus 10%). However, this was grade 1 in all but two (6.3%) patients (grade 2, which subsequently improved to grade 1).

One patient in arm A (3.1%) and four patients in arm B (13.3%) died within 30 days of the last treatment administration (Table 5). Two of the deaths in arm B (6.7%) were considered to be related to study treatment: one patient died of infection (with concomitant grade 3/4 neutropenia) on day 11 of the last infusion at cycle 2, and another died of infection (with concomitant grade 3/4 neutropenia) on day 7 of the last infusion at cycle 1.

***TABLE 2.*** *Exposure to Treatment*

| **Exposure** | **Arm A** | | **Arm B** | |
|---|---|---|---|---|
| | **Larotaxel** | **Cisplatin** | **Larotaxel** | **Gemcitabine** |
| No. of treated patients | 32 | 32 | 28 | 30 |
| Cumulative dose, ($mg/m^2$) | | | | |
| Median (range) | 200.9 (49.3-397.9) | 301.4 (73.9-588.4) | 238.0 (59.5-364.9) | 6373.3 (767.1-9731.8) |
| Actual dose intensity, ($mg/m^2/wk$) | | | | |
| Median (range) | 16.3 (14.3-17.4) | 24.5 (21.3-25.7) | 18.9 (10.9-20.2) | 498.3 (255.7-539.9) |
| Relative dose intensity | | | | |
| Median (range) | 0.98 (0.86-1.04) | 0.98 (0.85-1.03) | 0.94 (0.54-1.01) | 0.93 (0.48-1.01) |

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***TABLE 3.*** *Primary and Secondary Efficacy Data in the Per-Protocol and ITT Populations*

| Parameter | PPP | | ITT | |
|---|---|---|---|---|
| | **Arm A (*N* = 30)** | **Arm B (*N* = 22)** | **Arm A (*N* = 32)** | **Arm B (*N* = 30)** |
| Response, *n* (%) | | | | |
| Complete response (CR) | — | — | — | — |
| Partial response (PR) | 8 (26.7) | 4 (18.2) | 9 (28.1) | 4 (13.3) |
| No change/stable disease | 12 (40.0) | 8 (36.4) | 13 (40.6) | 10 (33.3) |
| Progressive disease | 8 (26.7) | 9 (40.9) | 8 (25.0) | 10 (33.3) |
| Not evaluable | 2 (6.7) | 1 (4.5) | 2 (6.3) | 6 (20) |
| Overall response rate (CR + PR) | 8[a] (26.7) | 4 (18.2) | 9 (28.1) | 4 (13.3) |
| [95% CI] | [12.3, 45.9] | [5.2, 40.3] | [13.7, 46.7] | [3.8, 30.7] |
| Median PFS (mo) | 4.3 | 4.4 | 4.7 | 3.3 |
| [95% CI] | [2.76, 4.96] | [1.54, 6.08] | [2.92, 6.21] | [1.45, 5.42] |
| Median overall survival (mo) | ND | ND | 8.6 | 7.3 |
| [95% CI] | | | [5.39, 16.03] | [4.76, 11.07] |
| 1-yr survival (mo) | | | 40.6% | 30.0% |

[a] One patient achieving a response was ineligible for inclusion in the PPP population as a consequence of major protocol deviations at study entry (baseline tumor assessment more than 31 d prior to first infusion and previous radiotherapy).
PPP, per-protocol population; ITT, intention to treat population; Arm A, larotaxel + cisplatin; Arm B, larotaxel + gemcitabine; PFS, progression-free survival; ND, not determined; CI, confidence interval.

***FIGURE 1.*** *Kaplan-Meier curve for overall survival in the ITT population.*

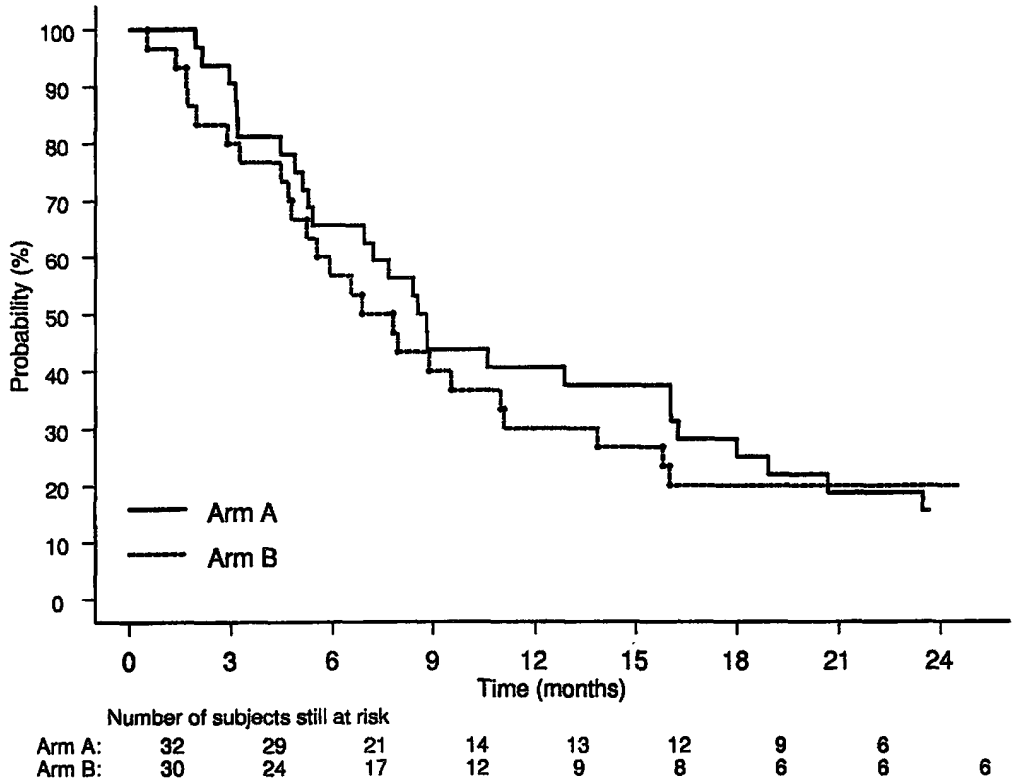

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***TABLE 4.*** *Summary of Adverse Events in Each Study Arm, Treatment Emergent Adverse Events Related to Study Treatment by Category and Terms (Reported for ≥2 Patients at Grade 3/4 or ≥3 Patients at any Grade) and Hematological Toxicity*

| **Adverse Events Summary, *N* (%)** | **Arm A (*N* = 32)** | | **Arm B (*N* = 30)** | |
|---|---|---|---|---|
| At least one TEAE regardless of relationship to study treatment | 30 (93.8) | | 30 (100.0) | |
| At least one TEAE possibly or probably related to study treatment | 26 (81.3) | | 26 (86.7) | |
| At least one grade 3/4 TEAE regardless of relationship to study treatment | 16 (50.0) | | 20 (66.7) | |
| At least one grade 3/4 TEAE possibly or probably related to study treatment | 8 (25.0) | | 9 (30.0) | |
| **Adverse Events: NCI-CTC Category/Term, *N* (%)** | **Grade 3/4** | **Any Grade** | **Grade 3/4** | **Any Grade** |
| Allergy/immunology | — | 4(12.5) | 2 (6.7) | 3 (10.0) |
| Allergic reaction/hypersensitivity | — | 4(12.5) | 2 (6.7) | 3 (10.0) |
| Cardiovascular (general) | — | 2 (6.3) | — | 5 (16.7) |
| Edema | — | 1 (3.1) | — | 3 (10.0) |
| Constitutional symptoms | 2 (6,3) | 14 (43.8) | — | 11 (36.7) |
| Fatigue | 1 (3.1) | 13 (40.6) | — | 9 (30.0) |
| Fever | — | 3 (9.4) | — | 3 (10.0) |
| Dermatology | — | 14 (43.8) | — | 19 (63.3) |
| Alopecia | — | 14 (43.8) | — | 16 (53.3) |
| Rash/desquamation | — | 1 (3.1) | — | 5 (16.7) |
| Gastrointestinal | 3 (9.4) | 22 (68.8) | 3 (10.0) | 19 (63.3) |
| Anorexia | — | 8 (25.0) | — | 7 (23.3) |
| Constipation | — | 4(12.5) | _ | 2 (6.7) |
| Diarrhea | 1 (3.1) | 10(31.3) | 2 (6.7) | 10 (33.3) |
| Nausea | — | 17 (53.1) | 1 (3.3) | 15 (50.0) |
| Stomatitis/pharyngitis | — | 3 (9.4) | — | 4 (13.3) |
| Vomiting | **2 (6.3)** | 12 (37.5) | 1 (3.3) | 10 (33.3) |
| Infection | 3 (9.4) | 3 (9.4) | 3 (10.0) | 4(13.3) |
| Infection[a] | 3 (9.4) | 3 (9.4) | 3 (10.0) | 3 (10.0) |
| Neurology | — | 7 (21.9) | — | 7 (23.3) |
| Neuropathy sensory | — | 6 (18.8) | — | 6 (20.0) |
| Pain | — | 4 (12.5) | 1 (3.3) | 5 (16.7) |
| Abdominal pain cramping | — | 3 (9.4) | — | 1 (3.3) |
| Hematological | | | | |
| Leukopenia | 9 (28.1) | 19 (59.4) | 8 (27.6) | 18 (62.1) |
| Neutropenia | 15 (46.9) | 21 (65.6) | 12 (41.4) | 19 (65.5) |
| Anemia | 3 (9.4) | 29 (90.6) | 1 (3.4) | 26 (89.7) |
| Thrombocytopenia | — | — | 1 (3.4) | 11 (37.9) |
| Neutropenic complications | | | | |
| Febrile neutropenia | 2 (6.3) | | — | |
| Related neutropenic infection Grade 3 | 2 (6.3) | | 1 (3.3) | |
| Related neutropenic infection Grade 4 | 1 (3.1) | | 2 (6.7) | |

[a] Neutropenic infection.
Arm A, larotaxel + cisplatin; Arn B, larotaxel + gemcitabine; NCI-CTC, National Cancer Institute Common Toxicity Criteria; TEAE, treatment emergent adverse event

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## DISCUSSION

Cisplatin is one of the most efficient drugs in NSCLC, but requires hyperhydration and induces some cumulative toxicities that may be difficult to manage such as renal impairment, peripheral neuropathy, and ototoxicity. To decrease toxicity associated with cisplatin-based doublets, a number of studies have investigated whether carboplatin-based and nonplatinum combinations including gemcitabine instead of cisplatin might confer equivalent efficacy but lower toxicity. A first meta-analysis has suggested the superiority of cisplatin over carboplatin in terms of survival.[22] Another recent meta-analysis of 11 phase III studies has indicated that patients treated with a platinum-based regimen benefited from a statistically significant reduction in the risk of death at 1 year ($p = 0.04$) compared with those receiving a nonplati-num regimen. This benefit was associated with a significantly increased but acceptable risk of severe toxicity.[23] Following these two meta-analyses, the standard of care in this setting therefore remains a cisplatin-based doublet.

***TABLE 5.*** *Summary of Deaths*

| | **Arm A (*N* = 32)** | **Arm B (*N* = 30)** | **ALL (*N* = 62)** |
|---|---|---|---|
| Total deaths | 29 (90.6) | 25 (83.3) | 54 (87.1) |
| Within 30 d of last administration of study treatment | 1 (3.1) | 4 (13.3) | 5(8.1) |
| Malignant disease | — | 1 (3.3) | 1 (1.6) |
| Toxicity from study medication | — | 2 (6.7) | 2 (3.2) |
| Other causes[a] | 1 (3.1) | 1 (3.3) | 2 (3.2) |
| More than 30 d after last administration of study treatment | 28 (87.5) | 21 (70.0) | 49 (79.0) |
| Malignant disease | 27 (84.4) | 21 (70.0) | 48 (77.4) |
| Toxicity from study medication | — | — | — |
| Other causes[b] | 1 (3.1) | — | 1 (1.6) |

[a] Other causes, "progression of lung cancer" in arm A and "cerebrovascular event" in arm B.
[b] Other cause, infection considered as not related to study treatment, occurring on day 63 after last study treatment administration.

The objective of the current study was to investigate the activity and tolerability of a new taxane, larotaxel, combined with either cisplatin (arm A) or gemcitabine (arm B) in the first-line treatment of NSCLC. The objective response rates favored arm A over arm B in both the per-protocol (difference of 8.5%) and ITT (difference of 14.8%) populations. In addition, with the caution due to the small sample size in both arms, the observed median OS time was longer in the ITT population for larotaxel combined to cisplatin compared with larotaxel combined to gemcitabine by 8.6 and 7.3 months and the 1-year survival rate was higher (40.6% versus 30.0%, respectively).

Several phase II and large phase III studies have reported efficacy data for docetaxel/cisplatin or paclitaxel/ cisplatin combinations used as first-line treatments for advanced NSCLC. Response rates ranged between 17% and 37%, with median OS lying between 7.4 and 11.3 months and 1-year survival between 31% and 48%.[6,24-26] Efficacy parameters for larotaxel/cisplatin are therefore included within these ranges. However, efficacy parameters for larotaxel/ gemcitabine generally compare less favorably with the taxane/gemcitabine arms of phase II and III first-line NSCLC studies, in which response rates were reported to lie between 20% and 35%, OS between 6.8 and 13 months and 1-year survival between 30% and 56%.[27-31] Efficacy data in the current study therefore favor the combination of larotaxel/ cisplatin, especially given the meta-analysis data indicating that platinum-based doublets may generally be more effective than nonplatinum regimens.[23]

The overall incidence of grade 3/4 toxicities related to study treatment was comparable between arms. However, grade 3/4 infection, with or without neutropenia was more common in arm B including two treatment-related deaths, due to neutropenic infection. Levels of neurotoxicity were comparable between arms and with no grade 3/4 events observed. Severe neurotoxicity seemed to be less common than has previously been reported for taxane/cisplatin combinations.[6,24,26] Renal toxicity, which was more frequent in arm A, was mild (grade 1 or 2) as was edema, which occurred in 3% and 10% of patients in arms A and B, respectively. Nail changes, characteristically associated with taxane therapy,[32] were not reported for any patient. The safety profile of both combinations was considered to be acceptable.

In summary, although there were some differences in the safety profile, with more grade 1/2 renal toxicity with larotaxel/cisplatin, and more infection with larotaxel/gemcit-abine, this study has demonstrated that larotaxel in

combination with either cisplatin or gemcitabine is feasible. As for previous new agents in NCSLC, and noting that the results of this randomized phase II study cannot be generalized to other untested nonplatinum/larotaxel combinations, the combination of larotaxel with cisplatin had a more favorable efficacy (comparable to established taxane/cisplatin combinations) than the combination of larotaxel with a nonplatinum compound. Future phase II studies exploring the efficacy of cisplatin/larotaxel/targeted agent combinations in this setting can be envisaged.

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