Cancer Chemother Pharmacol (2010) 65:227–234
DOI 10.1007/s00280-009-1026-5

ORIGINAL ARTICLE

A phase I study of larotaxel (XRP9881) administered in combination with carboplatin in chemotherapy-naïve patients with stage IIIB or stage IV non-small cell lung cancer

Francisco Robert · Karen Harper · Judie Ackerman · Sunil Gupta

Received: 19 January 2009 / Accepted: 3 May 2009 / Published online: 29 May 2009

Abstract
Purpose This primary objective of this phase I dose-escalation study was to define the maximum tolerated dose (MTD) and dose limiting toxicity (DLT) of larotaxel administered in combination with carboplatin in chemotherapy-naïve patients with advanced/metastatic non-small cell lung cancer (NSCLC).
Methods Eighteen patients with stage IIIB or IV NSCLC, in cohorts of three to six evaluable patients, were to receive every 3 weeks: larotaxel beginning at 45 mg/m^2 administered as a 1-h infusion, followed after 30 min by carboplatin (area under the concentration–time curve (AUC) = 6 mg/mL × min, later AUC = 5) as a 1-h infusion. Dose escalation of larotaxel up to 90 mg/m^2 was permitted according to DLT occurrence. Patients received ondansetron as prophylactic anti-emetic premedication.
Results In view of the toxicity encountered, the carboplatin dose was decreased for the later part of the study to AUC = 5 mg/mL × min. Eight of 18 treated patients experienced DLTs in the first cycle, including neutropenia and associated complications, diarrhea and fatigue. The MTD of the combination was defined as larotaxel 60 mg/m^2 with a carboplatin AUC of 6 mg/mL × min. Neutropenia, reported at grade 3/4 in 15/18 patients (83%), was the most common severe adverse event, reaching grade 4 in 14 patients (78%). Eleven patients (61%) experienced grade 3/4 non-hematological toxicity, predominantly dehydration, fatigue, infection, nausea and vomiting. One patient (6%) achieved a partial response and 11 (61%) had stable disease.
Conclusions The combination of larotaxel and carboplatin is feasible and shows modest activity in chemotherapy-naïve patients with advanced/metastatic NSCLC. The principal toxicity was grade 3/4 neutropenia.

Keywords Metastatic NSCLC · Locally advanced NSCLC · Larotaxel · XRP9881 · Taxane · Taxoid · First-line · Chemotherapy · Carboplatin

F. Robert (✉) · K. Harper
UAB Comprehensive Cancer Center, University of Alabama at Birmingham, CC-2555 (North Pavilion), 1802, 6th Avenue South, Birmingham, AL 35294-3300, USA
e-mail: pacorobertuab@cs.com

F. Robert
Birmingham Veteran's Administration (VA) Medical Center, Birmingham, USA

J. Ackerman
sanofi-aventis U.S., Bridgewater, USA

S. Gupta
sanofi-aventis U.S., Malvern, USA

Introduction

The mainstay of palliative treatment for patients of good performance status with non-resectable advanced non-small cell lung cancer (NSCLC) remains a platinum-based therapy (cisplatin or carboplatin) coupled with a third generation cytotoxic agent such as gemcitabine, vinorelbine or a taxane (docetaxel or paclitaxel) [1–3]. In large randomized studies, such doublets have been associated with response rates of 20–40% and median overall survival times of 7–11 months [4–8]. While there seems to be little difference in the efficacy delivered by different first-line doublets, there is also a lack of clear evidence to suggest that the addition of a third cytotoxic agent to existing regimens adds anything more than extra cost and increased toxicity [2]. The general acknowledgment of this efficacy plateau with existing cytotoxic combinations has provided the impetus to investigate rationally

designed targeted agents as components of first-line NSCLC regimens [9–14]. This approach led to the approval of bevacizumab plus carboplatin and paclitaxel for the treatment of non-squamous NSCLC [15]. A complimentary strategy to the development of specifically targeted biological agents may lie in the development of new cytotoxic compounds with improved clinical profiles.

Larotaxel is a novel semi-synthetic taxoid derivative, selected for development on the basis of its spectrum of in vitro and in vivo activity against taxane-resistant and multidrug-resistant tumors. Promoting tubulin assembly in vitro and stabilizing microtubules against cold-induced depolymerization, larotaxel shares a common and unique mode of action with the approved taxanes. Interestingly, larotaxel was also found to effectively cross the blood brain barrier, showing marked antitumor activity in nude mice bearing early-stage intracranial glioblastomas [16, 17]. In previous phase I clinical studies of this agent, partial responses were observed in several tumor types at the recommended doses, including NSCLC, with neutropenia and diarrhea identified as the principal dose-limiting toxicities (DLTs) [18–23]. Of particular interest, given the preclinical data, Sessa et al. [21] noted a response of 14 weeks duration in both the primary tumor and also in the brain metastasis of a previously untreated NSCLC patient. Taken together, these data suggested that larotaxel may have an expanded spectrum of clinical activity compared with currently approved taxanes.

The rationale for this study in chemotherapy-naïve patients was based upon the larotaxel activity and tolerability in phase I studies in patients who were refractory to conventional treatment or for which no curative therapy existed and that docetaxel or paclitaxel plus carboplatin doublets were known to be active in the treatment of advanced NSCLC [4, 6]. The primary aim of the current phase I study was to determine the DLT and the maximum tolerated dose (MTD) of larotaxel in combination with carboplatin when given to chemotherapy-naïve patients with metastatic or locally advanced (stage IIIB or IV) NSCLC. The data obtained were intended to complement a parallel study defining these parameters in a similar patient population receiving larotaxel in combination with cisplatin, gemcitabine or vinorelbine (manuscript in preparation) with a view to comparing the efficacy and safety of the recommended doses of combinations of larotaxel and carboplatin versus larotaxel and cisplatin.

Patients and methods

Main eligibility criteria

Chemotherapy-naïve patients between 18 and 75 years of age with histologically or cytologically proven non-irradiable stage IIIB or stage IV NSCLC with a life expectancy of at least 12 weeks and an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2 were eligible. Adequate organ function was necessary, including: neutrophils $\geq 2.0 \times 10^9$/L; platelets $\geq 100 \times 10^9$/L; creatinine within upper normal limits (if borderline, creatinine clearance of $\geq$60 mL/min was needed); total bilirubin within normal limits and alanine aminotransferase/aspartate aminotransferase (ALT/AST) and alkaline phosphatase (AP) $\leq$2.5 times the upper limit of the institutional norms or ALT/AST $\leq$1.5 times and AP $\leq$5 times the upper limit of the institutional norms. The presence of at least one measurable lesion, according to RECIST guidelines, was recommended, but not required; patients with non-measurable disease were eligible [24]. Principal exclusion criteria were: hypercalcemia (>2.8 mM/L); prior chemotherapy, radiotherapy (to a major bone marrow area within 4 weeks prior to study entry or to >10% of bone marrow area) or surgery for NSCLC; symptomatic brain or leptomeningeal metastases; peripheral neuropathy >grade 1; another serious comorbid condition; a prior history of cancer (excluding basal cell skin or in situ disease); concomitant treatment with other experimental drugs, other anticancer therapy or corticosteroids (with the exception of chronic treatment); or pregnancy.

Study design and treatment

This was a two-center, open-label phase I dose finding study of larotaxel combined with carboplatin; however, the majority of patients (18 out of 19) were enrolled at one site. The protocol was reviewed and approved by the local Institutional Review Boards for the sites involved and all patients provided signed informed consent prior to the initiation of study-related procedures.

Larotaxel (in polysorbate 80 and ethyl alcohol) was administered as a 1-h infusion, every 3 weeks, followed after 30 minutes by carboplatin (AUC = 6 or 5 mg/mL × min) given as a 1-h infusion. The dose of carboplatin was calculated according to the Calvert formula [25]. All patients received prophylactic anti-emetic premedication from cycle 1, consisting of ondansetron 8 mg intravenous (IV) before the administration of carboplatin on day 1, and then 8 mg PO every 12 hours during the following 2 days. For subsequent cycles, in the case of nausea/vomiting, patients could receive preventive anti-emetic treatment in compliance with the conventional anti-emetic protocol of the treating center. Corticosteroids were not permitted as anti-emetic treatment for nausea and/or vomiting. No prophylaxis of diarrhea was allowed, however, patients could be treated with loperamide following the onset of diarrhea. Oral hydration including electrolytes and large volumes of water were also prescribed. Hospitalization was

recommended for diarrhea with concomitant neutropenia ≥grade 3, as well as treatment with an appropriate antibiotic, i.e. ciprofloxacin. Dexamethasone was given as prophylaxis against hypersensitivity reactions: on day −1; 16 mg split into two doses (8 mg PO at −25 and −13 h before larotaxel administration) and on day 1; 8 mg IV 30 min before larotaxel administration. Dexchlorpheniramine (5 mg) or diphenhydramine (25 mg) or equivalent doses of other antihistamine drugs were also given IV on day 1, 30 min before infusion of larotaxel.

The starting dose of larotaxel was chosen based on DLTs observed in a phase I study of the 1-h infusion every 3 weeks schedule. As the recommended dose for the intermittent schedule was defined in previous phase I trials as 90 mg/m^2 IV administered every 3 weeks, [20, 21] it was decided to treat the first patient in the current study at a starting dose of 45 mg/m^2. Dose-escalation was carried out according to the scheme defined in Table 1. A minimum of three evaluable patients were to be recruited at each dose level, with a 1-week gap between the inclusion of the first patient and the next two for observation of DLTs. The dose was escalated if none of the first three patients experienced a DLT (defined in Table 2) during the first 3-week cycle of treatment. If one out of the first three patients at a given dose-level developed a DLT at the first cycle, three additional patients were entered at the same dose-level in order to reach a minimum of six evaluable patients. Dose-escalation was permitted if no further patients experienced a DLT. The MTD was reached when two or more patients at a dose level developed a DLT at the first cycle of treatment, with the recommended dose for phase II studies generally corresponding to one dose level below the MTD. If the MTD was reached at dose level 3, then three additional patients were to be entered at the carboplatin-reduced dose level 3B with no escalation to dose level 4. If the MTD was reached at dose level 4, then three additional patients were to be entered at the carboplatin-reduced dose level, 4B. Treatment was continued until the occurrence of disease progression, unacceptable toxicity or patient refusal.

Table 1 Dose escalation scheme

Dose level	Larotaxel mg/m^2	Carboplatin
1	45	AUC = 6 mg/ml × min
2	60	AUC = 6 mg/ml × min
3	75	AUC = 6 mg/ml × min
3B	75	AUC = 5 mg/ml × min
4	90	AUC = 6 mg/ml × min
4B	90	AUC = 5 mg/ml × min

Table 2 Definition of dose-limiting related toxicities

Toxicity	Grade	Value
Hematological		
Neutrophils	Grade 4 > 5 days	<0.5 × 10^9/L
Platelets	Grade 4	<10× 10^9/L
Febrile neutropenia		
Neutrophils/fever	Grade 4 neutropenia with a single elevation of fever ≥38.5°C (rectal) or ≥38.0°C (oral/axillary/aural)	
Non-hematological (excluding nausea, vomiting and hypersensitivity)	Grade 3 or 4	

Patient assessments

The planned duration of enrollment was 18 months and the overall planned study duration was 24 months. During the course of the study, a medical history was taken and physical examination carried out every 3 weeks. Hematological parameters were measured twice weekly (or every other day in the case of grade 4 neutropenia until the absolute neutrophil count was >500), with biochemistry and toxicity assessed weekly. Adverse events (AEs) were graded by investigators according to the National Cancer Institute Common Toxicity Criteria (Version 2.0). Patients who started at least one larotaxel infusion were evaluable for safety. Radiological examination was carried out every two cycles (6 weeks). Tumor responses were assessed according to RECIST guidelines [24]. Recruitment of approximately 20 patients was envisaged.

Results

Patient demographics

Nineteen patients were initially enrolled into the study between April 2002 and October 2005 (following a pause in study enrollment). One patient withdrew consent and was not treated; therefore, a total of eighteen patients were treated. The first patient treated was later found not to have NSCLC and was replaced. Three of 18 patients withdrew due to AEs (grade 3 asthenia in one patient; and grade 4 infection in two patients). Demographic and baseline characteristics are summarized in Table 3. Following study completion, 12 patients (67%) received additional antitumor post-study therapies, including chemotherapy alone in nine patients, combined chemotherapy and radiotherapy in two patients, and radiotherapy alone in one patient.

Table 3 Demographic and baseline characteristics

Characteristic	Larotaxel + Carboplatin $N = 18$
Sex, *N* (%)	
Male	13 (72)
Female	5 (28)
Age, years	
Median	62
Range	[46–73]
Race, *N* (%)	
Caucasian	17 (94)
Black	1 (6)
ECOG PS, *N* (%)	
0	3 (17)
1	12 (67)
2	3 (17)
Histology, *N* (%)	
Adenocarcinoma	8 (44)
Squamous cell carcinoma	4 (22)
Bronchioalveolar carcinoma	1 (6)
NSCLC undetermined	2 (11)
Others	3 (17)
Clinical stage, *N* (%)	
IIIB	4(22)
IV	14(78)

ECOG PS Eastern Cooperative Oncology Group performance status

Dose-limiting toxicity

As planned, patients were treated in cohorts of three, beginning with dose level 1 (larotaxel 45 mg/m^2 followed by carboplatin AUC 6 mg/mL × min) through to dose level 3 (larotaxel 75 mg/m^2 followed by carboplatin AUC 6 mg/mL × min). Initially, no DLT was reported at dose level 1, one DLT was reported at dose level 2 and one DLT at dose level 3.

In view of the level of toxicity encountered, the study was amended to reduce the dose of carboplatin administered from AUC = 6 to 5 mg/mL × min. This lower carboplatin dose was to be explored in combination with larotaxel at 75 and 90 mg/m^2 (dose levels 3B and 4B). Following this amendment, two patients were enrolled at dose level 3B. Both experienced DLTs of infection and neutropenia. Given the occurrence of four DLTs in the first 11 patients treated, the study was subsequently put on hold for further review of the DLTs and overall safety data. During this review, DLTs not previously reported at dose levels 1 (one patient) and 3 (one patient) were discovered. Upon completion of the interim evaluation, a decision was taken to restart the study with the enrollment of three additional patients at dose level 1 and dose level 2 (a minimum of six evaluable patients at each). The last patient was enrolled in January 2006.

The total number of patients treated at each dose level and the DLTs ultimately reported are detailed in Table 4. The DLTs observed were predominantly febrile neutropenia, fever, diarrhea, dehydration, fatigue, and infection. Overall, only one out of seven patients enrolled at dose level 1 had experienced a DLT and, as per protocol, dose escalation to level 2 was justified. Three out of six patients enrolled at dose level 2 experienced DLTs (although in one patient, grade 3 fatigue and anorexia were not initially recognized as non-hematological DLTs). In addition, two out of three and two out of two patients treated at dose levels 3 and 3B, respectively, also experienced DLTs. The MTD of the combination was therefore defined as larotaxel 60 mg/m^2 with a carboplatin AUC of 6 mg/mL × min.

Safety

Eighteen patients received a total of 60 cycles of treatment and were evaluable for safety. The median number of cycles administered was 4 (range 1–6). Three cycles were

Table 4 Treated patients per dose level and DLTs observed at the first cycle

Dose level	Treated	Patients with DLT	DLT term description
1	7	1	Febrile neutropenia
2	6	3[a]	Anorexia, Fatigue (lethargy/malaise/asthenia)
			Infection (documented clinically or microbiologically) with grade 3 or 4 neutropenia
			Neutropenia
3	3	2	Abdominal pain NOS, Dehydration, Febrile neutropenia
			Diarrhea, Fatigue (lethargy/malaise/asthenia)
3B	2	2	Dehydration, Muscle weakness (not due to neuropathy, Infection (documented clinically or microbiologically) with grade 3 or 4 neutropenia
			Diarrhea, Infection (documented clinically or microbiologically) with grade 3 or 4 neutropenia

DLT dose-limiting toxicity, *NOS* not otherwise specified

[a] Grade 3 fatigue and anorexia occurring in one patient were not initially recognized as non-hematological DLTs

administered with dose reductions of larotaxel and carboplatin; two cycles due to hematological toxicity and one cycle due to non-hematological toxicity. Three cycles were delayed for a maximum of 14 days: one due to hematological toxicity and two for other reasons (holidays, herpes zoster). All patients experienced at least one non-hematological AE, with 11 patients (61%) experiencing grade 3/4 events (Table 5). The most common non-hematological grade 3/4 AE's were dehydration, fatigue, infection with grade 3/4 neutropenia, nausea and vomiting (17% each). In relation to hematological toxicity, one patient experienced grade 3 neutropenia and 14 patients (78%) experienced grade 4 neutropenia (two further patients had grade 1/2 neutropenia). Ten patients had grade 3/4 leucopenia (five patients, grade 1/2) and while only a single patient had grade 3 thrombocytopenia, a further five (28%) developed this at grade 1 or 2. Nail discoloration was not reported in this study, and mild edema was noted in only one patient (grade 1). Sensory neuropathy was seen in four patients (22%) but was invariably, mild (grade 1).

Three deaths (including one due to cardiac arrest unrelated to study medication and two due to progressive disease) occurred within 30 days of the last dose of study drug.

Efficacy

Four patients were not evaluable for response (one patient did not have NSCLC and three patients did not receive more than 1 cycle of treatment). Of the remainder, one patient achieved a partial response, giving a response rate of 6%. Stable disease was reported in 11 patients (61%) providing an overall disease control rate of 67%. Two patients (11%) had progressive disease.

Discussion

The development of cytotoxic agents with improved clinical profiles is one strategy that may improve beyond the current efficacy plateau of first-line treatment regimens for patients with advanced/metastatic NSCLC. The taxanes, docetaxel and paclitaxel, are key components of platinum-based doublets currently used in this setting [26] with single-agent docetaxel also shown to be an appropriate treatment for elderly or frail patients [27, 28]. In general, toxicity aside, chemotherapy for advanced disease will initially or ultimately fail either as a result of the resistance of a significant fraction of the tumor cell population to the treatment agent(s) or, due to the failure of those agents to reach secondary tumor sites (for example, the brain). Larotaxel is a novel taxoid which has been selected for further development based on the demonstration of preclinical activity in drug-resistant tumor models and its ability to cross the blood/brain barrier [17, 21]. Such properties are consistent with minimal recognition of this new taxoid by the drug efflux pump P-glycoprotein 1, the product of the *ABCB1* gene, high level expression of which has been linked to a multidrug resistance phenotype in tumors [29, 30]. The aim of the current study was to define an effective dose of larotaxel combined with carboplatin, one of the two platinum analogs commonly used in doublets for the first-line treatment of advanced NSCLC.

Previous phase I dose-escalation studies of single-agent larotaxel have identified neutropenia (and its complications) and diarrhea as the most common DLTs, with dose-related neutropenia as the most common severe AE reported for the every 3 weeks schedule [19–21]. In particular, in two linked studies of larotaxel monotherapy including 63 patients with advanced solid tumors, grade 3/4 neutropenia was reported to have occurred in 5/6 patients treated at 60 mg/m^2, 3/3 patients treated at 75 mg/m^2 and 15/17 patients (grade 4 in 14/17) treated at 90 mg/m^2. In the second study, grade 3/4 neutropenia was reported for 22/29 patients (76%; grade 4 18/29, 62%) treated at the selected doses of 75 or 90 mg/m^2 [21]. In contrast, non-hematological toxicity tended to be mild, with the most common grade 3/4 AEs reported in the monotherapy studies being diarrhea or nausea [19–21]. 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 (manuscript in preparation).

Subsequently, a phase II study was conducted to investigate the activity and tolerability of larotaxel combined with either cisplatin or gemcitabine in the first-line treatment of NSCLC [31]. Response rates in the per protocol population (PPP) and intent to treat (ITT) population for the larotaxel and cisplatin combination were 27 and 28%, respectively; there were no complete responses. In addition, 40% (PPP) and 41% (ITT) of patients had stable disease. Median progression-free survival time was 4.7 months and median overall survival time was 8.6 months in the ITT population. The most common non-hematological grade 3/4 adverse events were infection (9.4%) and vomiting (6.3%). The incidence of peripheral neurotoxicity was 18.8%. Neutropenia, 47%, was the most common grade 3/4 hematological toxicity with two (6.3%) patients experiencing febrile neutropenia. The adverse events were largely predictable and manageable.

The current study is therefore largely consistent with these earlier studies, with the main DLTs reported being neutropenia and related complications, diarrhea and fatigue. Given that grade 3/4 neutropenia has also been frequently reported in between 50 and 74% of patients receiving carboplatin (AUC = 6 mg/mL × min) plus docetaxel or paclitaxel in phase III NSCLC studies, [4–7, 32, 33] it is not surprising

Table 5 Grade 2–4 adverse events by NCI-CTC preferred term, $N = 18$ (%)

Preferred term, *N* (%)	Grade 2	Grade 3	Grade 4
Non-hematological			
Abdominal pain NOS		1 (6)	
Abdominal pain or cramping	1 (6)	1 (6)	
Allergic reaction/hypersensitivity	2 (11)		
Alopecia	3 (17)		
Anorexia		1 (6)	
Arthralgia (joint pain)	2 (11)		
Cardiac arrest			1 (6)
Chest pain (non-cardiac and non-pleuritic)	1 (6)		
Cough	1 (6)		
Dehydration		2 (11)	1 (6)
Diarrhea	5 (28)	2 (11)	
Dyspnea[a]	11 (61)	2 (11)	
Fatigue (lethargy/malaise/asthenia)[a]	9 (50)	3 (17)	
Febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection)		1 (6)	
Fever			1 (6)
Hallucinations		1 (6)	
Hypoglycemia[a]		1 (6)	
Hypotension		1 (6)	
Hypoxia[a]		1 (6)	
Infection (documented clinically or microbiologically) with grade 3/4 neutropenia			3 (17)
Infection with unknown ANC	1 (6)		
Infection without neutropenia	1 (6)		
Muscle weakness (not due to neuropathy)	3 (17)	1 (6)	
Myalgia (muscle pain)	1 (6)		
Nausea	5 (28)	3 (17)	
Neutrophils/granulocytes			1 (6)[b]
Pneumonia NOS[a]		1 (6)	
Renal failure acute	1 (6)		
Restless leg syndrome	1 (6)		
Stomatitis/pharyngitis	1 (6)		
Supraventricular arrhythmia			1 (6)
Thrombosis/embolism	1 (6)		
Vision blurred	1 (6)		
Vomiting	3 (17)	3 (17)	
Weight gain	1 (6)		
Not defined		1 (6)	
Hematological[c]			
Hemoglobin	7 (39)	1 (6)	
Neutrophils	2 (11)	1 (6)	14 (78)
Platelets	5 (28)	1 (6)	
WBC	5 (28)	6 (33)	4 (22)

NCI-CTC National Cancer Institute-Common Toxicity Criteria, *ANC* absolute neutrophil count, *NOS* not otherwise specified, *WBC* white blood cell count

[a] Three of seven patients at dose level 1 (the recommended phase II dose: larotaxel 45 mg/m^2 and carboplatin AUC of 6 mg/mL × min) experienced grade 3/4 adverse events (one patient, grade 3 hypoglycemia and fatigue; one patient, grade 3 dyspnea; and one patient, grade 3 dyspnea, hypoxia and pneumonia NOS)

[b] This patient is also reported under grade 4 neutropenia in the neutrophils category of hematological adverse events

[c] Grade 2 events shown are a combination of grade 1 and 2 events

that 15/18 (83%) patients in the current study reported grade 3/4 neutropenia, with a high incidence of grade 4 events (78%). This observation is consistent with the existence of an additive effect of these two agents in relation to hematological toxicity. In view of the level of toxicity encountered and the apparently modest levels of activity, further

exploration of this combination with de-escalated carboplatin doses was not deemed to be appropriate.

A partial response was seen in one patient (6%) and disease was stabilized in a further 11 patients (61%). Reported first-line response rates for carboplatin combined with either docetaxel or paclitaxel in phase III NSCLC studies range from 17 to 32% [4–7, 32, 33]. Although definitive conclusions cannot be drawn from the small series of patients in the current study, one possible explanation for the low response rate observed is the existence of an additive effect of the two agents in relation to hematological toxicity, in particular neutropenia, which may have restricted the tolerable dose of the larotaxel/carboplatin combination to a level which resulted in only limited activity.

In summary, although dose level 1 (larotaxel 45 mg/m^2 with a carboplatin AUC of 6 mg/mL × min) was clearly feasible with only one DLT reported in seven patients, early data do not encourage further clinical development of this particular combination in this setting.

Acknowledgments We would like to thank the patients for enrolling on this study and the medical and clinical research staff in each center who contributed to their care as well as Jim Heighway for his assistance in submitting this manuscript. This study was supported by a research grant from sanofi-aventis.

Conflict of interest statement JA and SG are salaried employees of sanofi-aventis and both hold stock in this organization.

References

1. D Addario G, Pintilie M, Leighl NB, Feld R, Cerny T, Shepherd FA (2005) Platinum-based versus non-platinum-based chemotherapy in advanced non-small-cell lung cancer: a meta-analysis of the published literature. J Clin Oncol 23:2926–2936
2. Bunn PA Jr (2002) Chemotherapy for advanced non-small-cell lung cancer: who, what, when, why? J Clin Oncol 20:23S–33S
3. Blackhall F, Thatcher N (2004) Chemotherapy for advanced lung cancer. Eur J Cancer 40:2345–2348
4. Schiller JH, Harrington D, Belani CP, Langer C, Sandler A, Krook J, Zhu J, Johnson DH (2002) Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. N Engl J Med 346:92–98
5. Kelly K, Crowley J, Bunn PA Jr, Presant CA, Grevstad PK, Moinpour CM, Ramsey SD, Wozniak AJ, Weiss GR, Moore DF, Israel VK, Livingston RB, Gandara DR (2001) Randomized phase III trial of paclitaxel plus carboplatin versus vinorelbine plus cisplatin in the treatment of patients with advanced non-small-cell lung cancer: a Southwest Oncology Group trial. J Clin Oncol 19:3210–3218
6. Fossella F, Pereira JR, von Pawel J, Pluzanska A, Gorbounova V, Kaukel E, Mattson KV, Ramlau R, Szczesna A, Fidias P, Millward M, Belani CP (2003) Randomized, multinational, phase III study of docetaxel plus platinum combinations versus vinorelbine plus cisplatin for advanced non-small-cell lung cancer: the TAX 326 study group. J Clin Oncol 21:3016–3024
7. Scagliotti GV, De Marinis F, Rinaldi M, Crino L, Gridelli C, Ricci S, Matano E, Boni C, Marangolo M, Failla G, Altavilla G, Adamo V, Ceribelli A, Clerici M, Di Costanzo F, Frontini L, Tonato M (2002) Phase III randomized trial comparing three platinum-based doublets in advanced non-small-cell lung cancer. J Clin Oncol 20:4285–4291
8. Kubota K, Watanabe K, Kunitoh H, Noda K, Ichinose Y, Katakami N, Sugiura T, Kawahara M, Yokoyama A, Yokota S, Yoneda S, Matsui K, Kudo S, Shibuya M, Isobe T, Segawa Y, Nishiwaki Y, Ohashi Y, Niitani H (2004) Phase III randomized trial of docetaxel plus cisplatin versus vindesine plus cisplatin in patients with stage IV non-small-cell lung cancer: the Japanese Taxotere Lung Cancer Study Group. J Clin Oncol 22:254–261
9. Giaccone G, Herbst RS, Manegold C, Scagliotti G, Rosell R, Miller V, Natale RB, Schiller JH, Von Pawel J, Pluzanska A, Gatzemeier U, Grous J, Ochs JS, Averbuch SD, Wolf MK, Rennie P, Fandi A, Johnson DH (2004) Gefitinib in combination with gemcitabine and cisplatin in advanced non-small-cell lung cancer: a phase III trial-INTACT 1. J Clin Oncol 22:777–784
10. Herbst RS, Giaccone G, Schiller JH, Natale RB, Miller V, Manegold C, Scagliotti G, Rosell R, Oliff I, Reeves JA, Wolf MK, Krebs AD, Averbuch SD, Ochs JS, Grous J, Fandi A, Johnson DH (2004) Gefitinib in combination with paclitaxel and carboplatin in advanced non-small-cell lung cancer: a phase III trial-INTACT 2. J Clin Oncol 22:785–794
11. Herbst RS, Prager D, Hermann R, Fehrenbacher L, Johnson BE, Sandler A, Kris MG, Tran HT, Klein P, Li X, Ramies D, Johnson DH, Miller VA (2005) TRIBUTE: a phase III trial of erlotinib hydrochloride (OSI-774) combined with carboplatin and paclitaxel chemotherapy in advanced non-small-cell lung cancer. J Clin Oncol 23:5892–5899
12. Gatzemeier U, Pluzanska A, Szczesna A, Kaukel E, Roubec J, De Rosa F, Milanowski J, Karnicka-Mlodkowski H, Pesek M, Serwatowski P, Ramlau R, Janaskova T, Vansteenkiste J, Strausz J, Manikhas GM, Von Pawel J (2007) Phase III study of erlotinib in combination with cisplatin and gemcitabine in advanced non-small-cell lung cancer: the Tarceva Lung Cancer Investigation Trial. J Clin Oncol 25:1545–1552
13. Sandler A, Gray R, Perry MC, Brahmer J, Schiller JH, Dowlati A, Lilenbaum R, Johnson DH (2006) Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. N Engl J Med 355:2542–2550
14. Pirker R, Szczesna A, von Pawel J, Krzakowski M, Ramlau R, Park K, Gatzemeier U, Bajeta E, Emig M, Pereira JR (2008) FLEX: a randomized, multicenter, phase III study of cetuximab in combination with cisplatin/vinorelbine (CV) versus CV alone in the first-line treatment of patients with advanced non-small cell lung cancer (NSCLC). J Clin Oncol 26:(suppl; abstr 3)
15. Cohen MH, Gootenberg J, Keegan P, Pazdur R (2007) FDA drug approval summary: bevacizumab (Avastin) plus Carboplatin and Paclitaxel as first-line treatment of advanced/metastatic recurrent nonsquamous non-small cell lung cancer. Oncologist 12:713–718
16. Bissery MC (2001) Preclinical evaluation of new taxoids. Curr Pharm Des 7:1251–1257
17. Bissery M-C, Vrignaud P, Combeau C, Riou J-F, Bouchard H, Commerçon A, Lavelle F (2004) Preclinical evaluation of XRP9881A, a new taxoid. Proceedings of the 95th annual meeting of the American association for cancer research, vol 45, Abstract #5430
18. Barthier S, Dieras V, Kalla S, Boaziz C, Beuzeboc P, Perard D, SL. M, Guerin M, Semiond D, Besenval M, Pouillart P (1998) A phase I and pharmacokinetics (PK) study of RPR 109881A given as 6-hour iv infusion in patients (pts) with advanced solid tumors. Proc Am Soc Clin Oncol 16:Abstract 747
19. Gelmon KA, Latreille J, Tolcher A, Genier L, Fisher B, Forand D, D'Aloisio S, Vernillet L, Daigneault L, Lebecq A, Besenval M, Eisenhauer E (2000) Phase I dose-finding study of a new taxane, RPR 109881A, administered as a one-hour intravenous infusion days 1 and 8 to patients with advanced solid tumors. J Clin Oncol 18:4098–4108

20. Kurata T, Shimada Y, Tamura T, Yamamoto N, Hyodo I, Saeki T, Takashima S, Fujiwara K, Wakasugi H, Kashimura M (2000) Phase I and pharmacokinetic study of a new taxoid, RPR 109881A, given as a 1-hour intravenous infusion in patients with advanced solid tumors. J Clin Oncol 18:3164–3171
21. Sessa C, Cuvier C, Caldiera S, Bauer J, Van Den Bosch S, Monnerat C, Semiond D, Perard D, Lebecq A, Besenval M, Marty M (2002) Phase I clinical and pharmacokinetic studies of the taxoid derivative RPR 109881A administered as a 1-hour or a 3-hour infusion in patients with advanced solid tumors. Ann Oncol 13:1140–1150
22. Slaughter M, Dumas P, Hoff P et al. (1998) Clinical and pharmacokinetic study of XRP9881 (RPR): a phase I trial of a novel taxoid derivative administered as a 24-hour continuous infusion. NCI-EORTC 1998, Amsterdam, Abstract 381 and poster
23. Vernillet L, Semiond D, Vergniol JC, Pasquier O, Dieras V, Marty M, Sessa C, Gelmon K, Latreille J, Pazdur R, Besenval M (1998) Pharmacokinetics of a new taxoid (RPR 109881A): comparison of five different administration schedules. Proc Am Soc Clin Oncol 16:Abstract 749
24. Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, Verweij J, Van Glabbeke M, van Oosterom AT, Christian MC, Gwyther SG (2000) New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 92:205–216
25. Calvert AH, Newell DR, Gumbrell LA, O'Reilly S, Burnell M, Boxall FE, Siddik ZH, Judson IR, Gore ME, Wiltshaw E (1989) Carboplatin dosage: prospective evaluation of a simple formula based on renal function. J Clin Oncol 7:1748–1756
26. Rigas JR (2004) Taxane-platinum combinations in advanced non-small cell lung cancer: a review. Oncologist 9(Suppl 2):16–23
27. Hesketh PJ, Lilenbaum RC, Chansky K, Dowlati A, Graham P, Chapman RA, Crowley JJ, Gandara DR (2007) Chemotherapy in patients > or =80 with advanced non-small cell lung cancer: combined results from SWOG 0027 and LUN 6. J Thorac Oncol 2:494–498
28. Kudoh S, Takeda K, Nakagawa K, Takada M, Katakami N, Matsui K, Shinkai T, Sawa T, Goto I, Semba H, Seto T, Ando M, Satoh T, Yoshimura N, Negoro S, Fukuoka M (2006) Phase III study of docetaxel compared with vinorelbine in elderly patients with advanced non-small-cell lung cancer: results of the West Japan Thoracic Oncology Group Trial (WJTOG 9904). J Clin Oncol 24:3657–3663
29. Fojo AT, Menefee M (2005) Microtubule targeting agents: basic mechanisms of multidrug resistance (MDR). Semin Oncol 32:S3–S8
30. Bendayan R, Lee G, Bendayan M (2002) Functional expression and localization of P-glycoprotein at the blood brain barrier. Microsc Res Tech 57:365–380
31. Zatloukal P, Gervais R, Vansteenkiste J, Bosquee L, Sessa C, Brain E, Dansin E, Urban T, Dohollou N, Besenval M, Quoix E (2008) 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. J Thorac Oncol 3:894–901
32. Rosell R, Gatzemeier U, Betticher DC, Keppler U, Macha HN, Pirker R, Berthet P, Breau JL, Lianes P, Nicholson M, Ardizzoni A, Chemaissani A, Bogaerts J, Gallant G (2002) Phase III randomised trial comparing paclitaxel/carboplatin with paclitaxel/cisplatin in patients with advanced non-small-cell lung cancer: a cooperative multinational trial. Ann Oncol 13:1539–1549
33. Booton R, Lorigan P, Anderson H, Baka S, Ashcroft L, Nicolson M, O'Brien M, Dunlop D, O'Byrne K, Laurence V, Snee M, Dark G, Thatcher N (2006) A phase III trial of docetaxel/carboplatin versus mitomycin C/ifosfamide/cisplatin (MIC) or mitomycin C/vinblastine/cisplatin (MVP) in patients with advanced non-small-cell lung cancer: a randomised multicentre trial of the British Thoracic Oncology Group (BTOG1). Ann Oncol 17:1111–1119