Phase I/II Study of a 3 Weekly Oral Taxane (DJ-927) in Patients with Recurrent, Advanced Non-small Cell Lung Cancer

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Introduction: A phase I/II study was performed to assess the efficacy and toxicity of a new oral taxane in patients with recurrent, advanced Non-small Cell Lung Cancer.

Patients and Methods: Patients who were treated with one prior, taxane free chemotherapy regimen, were eligible for this study. A single oral dose of DJ-927 (27 mg/m^2) was given every 3 weeks. In case of good tolerance, one dose escalation to 35 mg/m^2 was allowed. Response and toxicity were measured and plasma pharmacokinetic analysis was performed during the first course.

Results: From October 2004 to September 2005, 36 patients gave informed consent and 34 received medication. The mean age was 58 years (range, 33–75 years). The majority of patients were pretreated with a combination of cisplatin and gemcitabine. Median interval between end of first treatment and the registration of this study was 7 months (range, 0.8–22 months). Twelve patients died on study of which eight due to disease progression. In four patients with preexisting cardiac disease, toxicity led to cardiac worsening and subsequent death. Grade 3 and 4 toxicities according to the National Cancer Institute Common Toxicity Criteria were neutropenia in 18 patients (53%), anemia in six patients (18%), nausea and fatigue in two patients (6%), febrile neutropenia and neurotoxicity in one patient (3%). The overall response rate for all patients was 5.6% (Confidence Interval [CI] 0.7–18.7%). The percentage of patients with stabilization for >6 weeks was 47%. The median time to progression was 97 days (CI: 47–167 days) and the median survival time was 120 days (CI: 68–222 days) for the ITT group. Since only a minority of patients (3) tolerated the higher drug dose we omitted this dose level because of hematological toxicity. Pharmacokinetic analysis showed that the median area under the curve (t = 0–168 hours) was 1752 ± 1355 ngr/ml/h and the half-life was 167 ± 77 hours.

Conclusion: When administered once every 3 weeks, this oral taxane formulation of DJ-927 was well-absorbed with a long terminal half-life of 167 ± 77 hour. DJ-927 has antitumor activity against Non-small Cell Lung Cancer when given as second-line monotherapy (overall response rate in 5.6%; CI 0.7–18.7%). Ten patients experienced SD for more than 8 weeks. Different types of dose administration (metronomic dosing) or combination with other cytotoxic agents should be considered in future studies.

Key Words: Non-small cell lung cancer, Oral drug, Second line treatment.

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Nearly all patients with advanced Non-small Cell Lung Cancer (NSCLC) experience tumor recurrences after initial chemo (radiation) therapy. At the time of second line treatment, many patients have a diminished performance and are less fit for chemotherapy. Many studies have already focused on oral formulations, as these seem less demanding for patients than I.V. regimes. Medication can be taken outside of the hospital and chronic treatment schedules can be developed. For taxanes it has been shown that long lasting plasma levels, which are considered to be in the active range, can be obtained using oral formulations.[1] One of the major draw backs of oral taxanes is the limited bio-availability due to the presence of a membrane-bound drug efflux pump in intestinal cells (P-glycoprotein; P-gp) which pumps most of the absorbed taxane back into the intestinal lumen. To overcome this problem, P-gp inhibitors like cyclosporin-A are coadministered to improve uptake and increase plasma levels. However, timing, possible interactions and side effects of the comedication make this approach less attractive.

In Europe, popular standard first line treatments of NSCLC are platinum doublets with gemcitabine or vinorelbine, which makes second line treatment with a taxane interesting from the point of view of noncross resistance. Accepted standard second line therapy in NSCLC consists of single agent docetaxel or pemetrexed. Each with comparable activity but a different toxicity or cost profile.

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DJ-927 is a new semisynthetic molecular entity developed as an oral taxane anticancer agent. Its mode of action is comparable to other taxanes (docetaxel, paclitaxel). DJ-927 binds to tubulin and stabilizes microtubules by inhibiting their disassembly.[2] The drug is manufactured as gelatin capsules and the intestinal uptake seems to be independent of P-gp pump.

After oral intake by humans, DJ-927 is protein bound for 92 to 96% of which 38 to 51% is bound to serum albumin.[3] The drug has its peak concentration after 2 hours and a slow bi-phasic elimination. It is metabolized in the liver by the cytochrome phosphate 3A (CYP3A) subfamily of the cytochrome P450 in the liver.[3] The less cytotoxic metabolites are primarily excreted in the bile and faeces and to a lesser extent in the urine.[3,4] The calculated half-life is 180 hours with a reproducible and linear PK.

Phase I studies in man have shown dose limiting toxicity (DLT) at a concentration of 35 mg/m^2 and 40 mg/m^2 given every 3 weeks. But in pretreated patients, a dose of 35 mg/m^2 or less was considered the maximum-tolerated dose. The dose limiting toxicology profile was primarily hematological and gastro-intestinal. Therefore, the recommended dose for further phase II studies was 27 mg/m^2 or 35 mg/m^2. The phase II dose was to be confirmed in the first 12 subjects with NSCLC treated in this study. Based on the noncross resistance with pretreatment drugs and acceptable toxicity profile in Phase I, we decided to examine the efficacy of DJ-927 in an open label phase I/II multicenter setting in patients with previously treated non-small cell lung cancer.[2]

PATIENTS AND METHODS

Eligibility Criteria

Patients with histologic or cytologic confirmed locally advanced or metastatic non-small cell lung cancer were eligible. Patients must have been treated with one prior treatment containing a platinum derivative, had documented progression of the tumor, and measurable disease according to the response evaluation criteria in solid tumors (RECIST). They had to have adequate hematologic, renal, and hepatic function (absolute neutrophil count $\geq 1.5\times 10^9$/liter, platelets $\geq 100\times 10^9$/liter, bilirubin $\leq 1.5\times$ upper limit of normal, Aspartate Serum Amino Transferase and/or Alanine Serum Amino Transferase $<2.5\times$ upper limit of normal, unless liver metastases were present, when values $\leq 5\times$ upper of limit normal, and serum creatinine $\leq 1.5\times$ upper limit of normal were allowed). Eastern Cooperative Oncology Group performance score (ECOG) of 0 to 2 was requested. The exclusion criteria were prior taxane therapy; continuing toxicity related to the previous antitumor therapy; history of known or suspected brain metastases; prior wide field radiation therapy to >25% of the bone marrow within the last 4 weeks; history of other malignancies except for resected nonmelanoma skin cancer or resected carcinoma in situ of the cervix, unless in complete remission for at least 2 years; the use of medication that interact with the CYP3A pathway (e.g., cordarone, carbamazepine); concurrent infectious diseases or uncontrolled underlying medical disorders; a history of severe hypersensitivity reaction; neurotoxicity or diarrhea ≥grade 2. All toxicities were graded according to the NCI CTC scoring system version 3.0.

The study protocol was approved by the medical ethical committees of all institutes and all patients gave written informed consent.

Treatment Plan

The first six patients received DJ-927 (Daiichi Sankyo Co., Ltd.) at a dose of 27 mg/m^2 on day one of subsequent 3 weekly periods. When less than two DLTs were observed during the first course, the next six patients were to receive 35 mg/m^2 at during the first course. When less than two DLTs are observed at 35 mg/m^2, the study was to continue at that dose level. Otherwise, the dosage for all subsequent patients was to be de-escalated to 27 mg/m^2. DLT's were defined as febrile neutropenia, neutropenia grade 4 lasting >5 days; thrombocytopenia ($<25\times 10^9$/liter); grade 3 or 4 vomiting or neurotoxicity; or a dose delay of >1 week after the first course. If patients fulfill the dose reduction or dose escalation criteria, DJ-927 dose could be reduced or escalated one dose level, respectively.

Since the capsules were only available in a fixed dose of 10 mg, the calculated body surface area (BSA) was grouped (BSA <1.57: 40 mg; BSA 1.58–1.85: 50 mg; 1.86–2.03: 50 mg; and BSA >2.04: 60 mg). The capsules were taken orally with 180 cc of water early in the morning on an empty stomach in an outpatient setting. No antiallergic medications (dexamethasone, clemastin, and ranitidine) were taken. To prevent nausea and vomiting, the use of granisetron or ondansetron was allowed. Retreatment was allowed when the following conditions were met: absolute neutrophil count $\geq 1.5\times 10^9$/liter; platelet count $\geq 100\times 10^9$/liter; all associated nonhematological toxicities (excluding alopecia) recovered to either grade 0, grade 1 or baseline value. When patients did not recover within 2 weeks after the planned start of the next course, the study treatment was discontinued. A dose reduction was planned when patients presented with the above mentioned toxicities but recovered within 2 weeks. The prophylactic use of G(M)-CSF was allowed after one dose reduction.

Pharmacokinetic Sampling and Analysis

Sampling for pharmacokinetic (PK) was performed in every patient during the first course on day 1, 3, 8, and 22. On day 1 blood samples of 5 cc each were collected in unheparinized tubes before dosing, after 15 and 30 minutes and 2, 6, 8, 48, 168, and 504 hours (presecond dose) after ingestion of DJ-927. Plasma was separated from whole blood immediate after collection, centrifuged at 3000 rpm for 15 minutes and kept at −20°C until processing. The plasma concentration of DJ-927 was measured using LC/MS/MS. The primary PK end point was evaluation of PK of DJ-927 in plasma by calculating the area under the plasma concentration time curve (AUC), clearance, maximal plasma concentration (C_{max}), time to Cmax (T_{max}), and terminal half-life ($T_{1/2}$). The AUC was calculated from $t = 0$ to $t = 168$ hours. The volume of distribution of the steady state/ bio-availability (Vdss/F) was also calculated.

PK parameters were obtained by employing noncompartimental methods using Winnonlin.

Statistical Analysis

All subjects who were registered in the study were considered eligible for the Intention to Treat (ITT) population ($n = 36$) and were summarized for demographic, and primary and secondary efficacy variables. Any subject who received study medication was considered eligible for the safety and toxicity analysis ($n = 34$). Subjects, who received at least one course of DJ-927 (21 days) and had measurable disease, were considered eligible for response evaluation ($n = 28$).

The primary end point (best overall response) was analyzed for both the ITT and the efficacy populations and 95% exact confidence intervals (CI) were calculated using the Binomial distribution. Tumor response was evaluated using RECIST. All secondary endpoints were analyzed for the efficacy population. Key secondary endpoints (time to progression TTP, time to treatment failure TTF, and median survival time MST) were analyzed for the ITT and efficacy populations and Kaplan-Meier survival plots were constructed. All safety variables were summarized for the safety population.

The sample size was determined based on the following: Null H_0: response rate $\leq$3% versus alternative Ha: response rate was $\geq$15%. For this three-outcome, one-stage-design and $\alpha = 0.05$, a sample size of 28 subjects was to yield type II error $\beta \leq 0.2$, and power $\geq$80%.

RESULTS

Patients Characteristics

A total of 36 patients were included in seven European centers between October 2004 and September 2005. The mean age was 58 years (range, 33–75 years) and 75% were males. Two patients were not included in the analysis because of refusal (1) or early progression (1) and had not received any study medication. The patient characteristics are presented in Table 1. Most patients were in good clinical condition at entry. Six patients did not complete one course of DJ-927 (3 subjects died due to disease progression and three patients died due to drug-unrelated adverse events) and were therefore excluded from the efficacy population.

All patients had received DJ-927 as second-line chemotherapy for their NSCLC. Thirty-one first line regimen were cisplatin- and three carboplatin-based doublets. The most common combination was with gemcitabine (18 of 36 patients), followed by vinorelbine (10), etoposide (7) and vinblastine (2). Response to first line treatment was CR or PR in 23 of 36 patients, stable disease in 7 and progressive disease in five patients.

Response Analysis and Survival

The antitumor activity of DJ-927 was determined by assessing the subject's best overall response using RECIST. A complete response occurred in one patient and in one patient a partial response was observed, giving an ORR of 5.6% in the ITT group, (Table 2).

TABLE 1. Patient Characteristics

	ITT Population $N = 36$
Age (yr)	
Mean (range)	58.2 (33–75)
Gender	
Male	27 (75%)
Female	9 (25%)
No. of metastatic sites*	
1	12
2	6
>3	9
Unknown	1
Response to first line treatment (CR/PR/SD/PD)	1/22/7/5
Interval between first line and study (median wk)	30
Histology	
Squamous	15 (42%)
Adenocarcinoma	5 (14%)
Large cell	3 (8%)
Undifferentiated	4 (11%)
Other (BAC/planocellular)	9 (25%)
ECOG performance status	
0	7 (19%)
1	21 (58%)
2	8 (22%)

*Remaining patients had local recurrences.
CR, complete response; PR, partial response; SD, stable disease; PD, partial disease.

TABLE 2. Best Overall Response

	ITT Population ($N = 36$)		
Tumor Response	**No.**	**(%)**	**95% CI**
Complete response	1	3	0.1–14.5
Partial response	1	3	0.1–14.5
CR + PR	2	6	0.7–18.7
Stable disease	17	47	30.4–64.5
Progressive disease	7	20	8.2–36.0
Not evaluable	10	28	14.2–45.2

Tumor response classified according to RECIST by the investigator.
The best overall response is presented in this table. CI, Exact binomial confidence interval.

Of the 36 patients, 28 (61%) had follow-up scans for at least 42 days. In this group one patient had a complete response; one patient a partial response; seven patients had progressive disease and 17 patients had stable disease. In two patients the responses could not be evaluated. Of the 17 patients with stable disease, six patients were free of tumors for more than 150 days.

In this population, the median TTP was 125 days (CI: 57–196 days) and the median TTF was 78 days (CI: 47–118 days). The estimated median survival time was 160 days (CI: 118–353 days).

Toxicity

Thirty-four patients had received at least one cycle of DJ-927 and were included into the toxicity analysis. Hema-

TABLE 3. Nonhematological Toxicity Reported in 5 or more Patients (Any Grade)

	Safety Population ($N = 34$)		
Adverse Events	**No. of Subjects**	**Patients With Grade 3–4 Toxicity**	**No. of Events**
Gastrointestinal disorders			
Nausea	13 (38%)	2	21
Diarrhea	8 (24%)	0	10
Constipation	6 (18%)	0	6
Vomiting	5 (15%)	1	7
Fatigue	15 (44%)	3	20
Weight loss	9 (27%)	1	9
Dyspnea	5 (15%)	2 (grade 4)	8
Anorexia	7 (21%)	3	15
Alopecia	5 (15%)	–	5
Liver enzyme (ASAT and ALAT) elevations	7 (20%)	3	8

tological toxicity was observed in almost all patients. Thirteen patients received a dose escalation which was associated with an increase in hematological toxicity. The grade 3 to 4 hematological toxicities included neutropenia in 18 patients (53%), leucopenia in 14 patients (41%) and anemia in six patients (18%). One patient had a febrile neutropenic episode. The most frequent nonhematologic toxicities are listed in Table 3.

Twenty-five of the 34 study patients died during the study. Twelve patients died on study of which eight due to disease progression and four due to toxicity. Three of them died because of cardiac related problems. The first patient had no previous cardiac history but died of heart failure after six courses of therapy. The second patient had a history of hypertension and coronary vascular disease and died at home with a suspected cardiac arrest. The third patient was diagnosed 2 years earlier with heart failure and paroxysmal atrial fibrillation. He experienced atrial fibrillation for 10 days after the first course and died of asystoly. No signs of changes in QT time were observed before or during the treatment. The deaths were not reported as definitely related to the drug because of previous cardiac disease. The remaining 13 patients died during the follow-up phase. Of these patients one developed a fatal pneumonia 35 days after he went off study. This event however, was considered to be possibly related because of a just resolved neutropenia. In total, there were 191 drug-related AEs, of which 52 of 191 AEs were grade 3 to 5.

The most common reason for going off-study was progression of the disease in 9 of 34 patients (27%). Six patients (18%) discontinued due to an AE or unacceptable toxicity and eight patients (24%) requested to withdraw. One patient was taken off-study due to noncompliance and one patient because of clinical deterioration (ECOG performance status of 4).

Dose Adjustments

All patients received an initial dose level of 27 mg/m^2 Subjects received a total of 101 courses during the study (median number of cycles with range was 2.5[1–8]). At the dose levels of 18 mg/m^2 three courses were given, at a dose level of 27 mg/m^2 71 courses and the dose could be escalated to the level of 35 mg/m^2 for 27 courses. A higher proportion of treatment courses were associated with grade 3 or 4 neutropenia and leucopenia in patients receiving the 35 mg/m^2 dose level. Thirteen patients received one course at the dose level of 35 mg/kg; 8 received two courses and only three patients received three or more courses at this level.

Pharmacokinetic Analysis

The PK were evaluated during the first cycle of chemotherapy after administration of 27 mg/m^2 of DJ-927. Following oral administration, DJ-927 was rapidly absorbed with a median T_{max} value of 2 hours (range, 1–8 hours). The terminal elimination half-life of DJ-927 was 167 ± 77 hours. At the 27 mg/m^2 dose level, PK analysis showed a C_{max} of 42.72 ± 34.3 ng/mL; AUC_{0-168} of 1752 ± 1355 ng/mL hr; Vdss/F of 2710 ± 1751 L/m^2 and a clearance/F of 12.6 ± 7.3 L/h/m^2. The exposure of DJ-927 in subjects with CR and PR were slightly higher than those who did not respond to therapy.

DISCUSSION

The standard 2nd line treatment in NSCLC is monotherapy with docetaxel.[5] Recently, single agent pemetrexed proved to be as effective and less toxic.[6] These regimen showed a response rate of 5.5 to 8.8% and 9.1% respectively. Despite these modest response rates, a survival benefit was obtained and quality of life was generally not compromised. To improve the benefit of 2nd line therapy for the patient, changes in the therapeutic index are required. This can be achieved by a reduction in toxicity, a higher response rate or by improving the ease of administration. This explains the growing interest in oral formulations for the treatment of (lung) cancer. For paclitaxel, the possibility to avoid the coadministration of Cremophor and its concomitant risk of anaphylactic reactions is very important. The use of other oral formulations of paclitaxel have been reported[7,8] with acceptable toxicity and signs of activity. However, the requirement of cyclosporin to improve the uptake of the oral paclitaxel and the timing were considered a disadvantage. DJ-927 however bypasses the P450 pump mechanism in the intestinal mucosal cells due to its special chemical structure, leading to a better controlled PK profile.

The recommended dose of DJ-927 in this group of patients with NSCLC was confirmed at 27 mg/m^2 with primarily hematological toxicity, gastro-intestinal toxicity, and fatigue. The oral formulation resulted in an acceptable pharmacological profile and initially the ease of administration was well conceived. The types and incidence rates of adverse events observed in this study were comparable to known safety profiles of docetaxel. The most frequent DJ-927-associated grade 3 or higher toxicities were hematologic events, with neutropenia as the most common. These hematologic events appeared to be dose-related. Caution must also be taken with regard to the relative high number of cardiac deaths in this study whereas none of the investigators considered the events likely to be related to the investigational

TABLE 4. Single Agent Phase 2 and 3 Studies with iv. Taxanes or Oral Formulations

	Treatment	No. of Patients	ORR %	MST mo
Shepherd[4]*	Docetaxel 75 mr/m^2 q3 vs. BSC	55	5.5	7.5
		100	0	4.6
Vazques-Estevez[9]	Docetaxel 50 mg/m^2 iv. d1, 14 q28	37	24	4
Buccheri[10]	Paclitaxel 100 mg/m^2 iv. q1	38	15.8	14.5
Juan[11]	Paclitaxel 80 mg/m^2 iv. q1	38	34	10
Berghmans[12]	Paclitaxel 225 mg/m^2 iv. q3	69	11.6	7.1
Schuette[13]*	Docetaxel 35 mg/m^2 iv. q1 vs. docetaxel 75 mg/m^2 iv. q3	105	10.5	9.2
		103	12.6	6.3
Hanna[5]*	Pemetrexed 500 mg/m^2 iv. q3 vs. docetaxel 75 mg/m^2 q3	264	9.1	8.3
		276	8.8	7.9
Kruijtzer[1]	Paclitaxel + cyclosporine 90 mg/m^2 BID oral q3	26	23	6
Thatcher[14]*	Gefitinib 250 mg daily vs. BSC	1129	8	5.6
		563	1	5.1
Shepherd[15]	Erlotinib 150 mg daily vs. BSC	488	8.9	6.7
		243	<1	4.7
Rossi[16]	Vinorelbine 60 mg/m^2 oral q1	20	0	4
Current study	DJ-927 27 mg/m^2 oral q3	36	5.6	4

*Phase III studies.
Second and third line treatment; BSC, Best Supportive care; ORR, Overall Response Rate; MST, Median Survival Time.

agent. We therefore advice that for future studies close follow-up with regular ECGs are performed.

In our study population only two patients showed a radiologic response to DJ-927 (ORR = 5,6% in the ITT). In this phase II study, the response rate of DJ-927 appeared lower than those reported in other second line studies (Table 4). Many studies with oral agents in the second line setting have been performed. Of these, some addressed the use of taxanes. To position this drug in the second line, we have compared our results with another oral taxane study, oral vinorelbine, TKIs, and the accepted standard: iv. docetaxel. Kruijtzer et al. tested the efficacy of an oral taxane and observed a response rate of 23% and a MST that was somewhat better with 6 months.[1] Other toxicity reported in our study was primarily hematologic and grade 2 of 3 neurotoxicity. The study by Rossi tested a weekly oral dose of vinorelbine (60 mg/m^2) and observed no responses in 20 patients.[15] Since this study did not include any PK analysis, insufficient blood concentrations might explain this variation. In addition, differences in patient selection and statistical variation might attribute to the large variation between these studies. A large body of data is available for the TKIs like gefitinib and erlotinib.[13,14] From these studies, it has become clear that the TKIs are potent drugs when proper selection of the patients is performed (such as EGFR status, EGFR FISH and mutation, sex, nonsmoking, race etc). For the taxanes, no such markers have yet been identified.

In comparison to the two phase, 3 randomized studies with iv. docetaxel, the MST in our study was shorter than expected. At the dosing schedule used in this trial, we observed modest anticancer activity with DJ-927 monotherapy when given as second line therapy to non-small cell lung cancer patients, whereas toxicity was more pronounced. However, the dosing regimen may deserve further exploration. Based on available clinical and PK data, one may prefer a weekly-three-times schedule, given the relatively long T½ of the compound. "Metronomic dosing" (i.e., protracted daily administration of low doses) has been proposed for this class of compounds, potentially yielding an antiangiogenic effect. More schedules could be examined to determine a more favorable therapeutic index.

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