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Sponsor/company:	sanofi-aventis	**ClinialTrials.gov Identifier:**	NCT00271271
		Study Code:	L_8907
Generic drug name:	Oxaliplatin	**Date:**	12 February 2008

Title of Study: An Open Phase II Trial of Gemcitabine, Oxaliplatin and Vinorelbine Combination in Untreated Advanced Non-Small Cell Lung Cancer Patients (Final study report).

Investigators: Prof. Stéphane Culine[1], Prof Jean Tredaniel[2], Dr François Chomy[3], Prof Hubert De Cremoux[4], Dr Jérôme Alexandre[5]

Study Centres: CRLC Val d'Aurelle, Montepellier[1]; Hôpital Saint Louis, Paris[2]; Institut Bergonié, Bordeaux[3]; CH Victor-Dupouy, Argenteuil[4]; Hôpital Cochin, Paris[5]

Publication:
Abstract submitted to ASCO: A multicentric phase II trial of gemcitabine (GEM), oxaliplatin (Oxa) and vinorelbine (VNB) in untreated stage IIIB and IV Non-Small Cell Lung Cancer (NSCLC) patients (pts): Preliminary results of GON triplet regimen J. Tredaniel, C. Becht, M. Bekradda, S. Culine, H. de Cremoux, J. Misset, A. Alexandre, F. Goldwasser, F. Chomy, E. Ecstein-Fraisse, E. Cvitkovic;

Study period:
First enrolment: 4 February, 2004
Last enrolment: 15 November, 2005
Date of cut-off for final analysis: 16 September, 2006

Clinical Phase: II

Objectives:
Primary
To evaluate the activity of the combination of gemcitabine, oxaliplatin and vinorelbine in untreated advanced non-small cell lung cancer patients.
Secondary
To determine the safety profile of the combination.

Methodology: A multicentric, single arm, open label, non-randomised Phase II trial.

Number of patients: A maximum of 39 evaluable patients were to be entered, according to a Simon mini-max two-stage design. Twenty-one evaluable patients were to be accrued during a first step. If = 8 objective responses (PR/CR) were observed in the first step, the trial was to be discontinued; otherwise an additional 18 patients were to be entered. On May 9, 2005, Amendment #2 allowed for the addition of a further 49 patients to the study to give a planned total of 88 patients

Inclusion criteria:

1. Histologically and/or cytologically proven non-small cell lung carcinoma;
2. Advanced (stage III_B or IV) or recurrent disease;
3. At least one measurable uni-dimensional lesion (longest diameter ≥ 20 mm by conventional techniques or ≥ 10 mm by spiral CT) outside an irradiated field;
4. No prior chemotherapy;
5. Prior radiotherapy allowed with = 4 weeks recovery period;
6. Age ≥18 years;
7. ECOG Performance Status (PS) of 0 or 1;
8. Life expectancy > 3 months;
9. Patients must have adequate organ function including the following:
   - Bone marrow: white blood cell count (WBC) = 3.0 x 10^9/L, Absolute Neutrophil count (ANC) = 1.5 x 10^9/L, platelets = 150 x 10^9, and Haemoglobin = 9 g/dL;
   - Hepatic: Total bilirubin within normal range of institutional normal value, aspartate transaminases (AST) or alanine transaminases (ALT) = 2.5 times the upper limit of normal;
   - Renal; Creatinine clearance ≥ 40 mL/min (calculated according to Cockroft and Gault formula)
10. Patients of reproductive age must be using effective contraceptive methods
11. Signed informed consent obtained prior to all study procedures

Exclusion criteria:

1. Pregnant or breast-feeding women;
2. History of other prior or concomitant malignancies (other than excised non melanoma skin cancer or cured in-situ cervical carcinoma);
3. Symptomatic brain or leptomeningeal involvement;
4. Symptomatic peripheral neuropathy > NCI-CTC grade 1;
5. Other serious illness or medical conditions that, in the investigator's opinion, would be a contra-indication or would not permit patient's compliance;
6. Treatment with any other experimental drugs or participation in other clinical trial within 4 weeks prior to study entry;
7. Concomitant treatment with any anticancer therapy;
8. Concomitant treatment with Phenytoin

Test product, dose and mode of administration, batch numbers:

	Vinorelbine	Gemcitabine	Oxaliplatin
Formulation	10 mg vials, solution at 10 mg/mL	Hydrochloride salt, 200 mg and 1000 mg vials	Lyophilised product for parenteral use, 50 mg and 100 mg
Dose	25 mg/m² in 100 mL 5% glucose or normal saline on D1, every 2 weeks	700 mg/m² in 100 mL normal saline on D1, immediately after vinorelbine administration	85 mg/m² in 500 mL 5% glucose solution on D2 every 2 weeks
Administration	1st: 20 minute intravenous infusion	2nd: 70 minute intravenous infusion, 10 mg/m²/minute	3rd: 2 hour intravenous infusion

Duration of treatment (per subject):

Patients were to continue treatment until disease progression, unacceptable toxicity, patient refusal, physician's decision, or treatment delay lasting > 2 weeks. Patients experiencing response or stable disease were to receive at least 10 cycles in the absence of any of the above reasons for discontinuation. Amendment #2 allowed for the accrual of 49 additional patients and for these patients the oxaliplatin dose was to be reduced to 65mg/m² per cycle from the fifth cycle.

After receiving at least 10 cycles, patients with stage III disease could be discontinued to undergo locoregional radiotherapy or chemoradiotherapy, at the discretion of the investigator. Amendment #2 added that radiotherapy or chemoradiotherapy must be started at least 4 weeks after the last gemcitabine infusion. However, this 4-week period could be shortened if required by the patient's condition.

Duration of observation:

After treatment discontinuation, patients were to be observed for one month after the last infusion of study treatment. Thereafter, at intervals of 2 months, tumour measurement by the same methods used during the study, were to be performed for those patients with objective response or no change. Further treatment and survival updates were to be made every 6 months after progression.

Authorised treatment:

Authorized treatment included preventive and/or curative anti-emetic treatment, maintenance and palliative treatments (i.e. nutritional, transfusion support, pain control, etc.), G-CSF treatment, and radiotherapy for pain.

Criteria for evaluation:

Primary endpoint: Evaluation of objective confirmed response rate (CR, PR), according to RECIST and as assessed by an external expert assessment committee.

Secondary endpoints:

Efficacy

- Response duration
- Progression free survival
- Overall survival

Safety

- Incidence and severity of toxicity, according to the NCI-CTC Version 2
- Incidence of Serious Adverse Events
- Incidence of discontinuations due to toxicity

Statistical methods:

A Simon Minimax two-stage design was applied. Twenty-one patients were to be entered in the first stage, with a total of 39 patients to be treated if sufficient responses were observed during the first stage.

Descriptive statistics (mean, median, standard deviation, 95% confidence interval, and range) were to be used for all demographic data in this open non-comparative study. Response rate was to be characterised using descriptive statistics. Time-related efficacy parameters were to be analysed according to the Kaplan-Meïer method. Descriptive statistics were to be employed to characterise the toxicity, toxic deaths, SAEs and toxicity-related treatment discontinuation profiles. Amendment 2 allowed for the accrual of 49 additional patients.

RESULTS

Patient Disposition

Patients	**Total**	
	N	**%**
Included	39	100
Treated (evaluable for safety)	39	100
Eligible	39	100
Eligible and treated (evaluable for time-related parameters)	39	100
Evaluable for efficacy	39	100

Patient Characteristics:

Number of patients	**N (N=39)**	**%**
Sex		
Female	13	33
Male	26	67
Age (years)		
≤ 40	2	5
40 - 65	24	61
65 - 75	12	31
> 75	1	3
Median	58	
Range	36-76	
ECOG Performance Status		
0	17	44
1	22	56

Disease characteristics at inclusion

Number of patients	**N=39**	**%**
Staging at inclusion		
IIIB	6	15
IV	33	85
Histological type		
Adenocarcinoma	20	51
Large-cell carcinoma	9	23
Squamous carcinoma	8	21
Undifferentiated carcinoma	1	3
Other (specify)	1	3
Interval between diagnosis and study entry (weeks)		
median	3.6	
range	[0.86-46.43]	

Patient characteristics at inclusion

Number of patients	**N**	**%**
Number of involved organs (N= 39)		
1	3	8%
2	8	21%
3	14	36%
4	7	18%
5-7	7	18%
Median	3	
Range	1-7	
Sites of disease		
Adrenal glands	9	23%
Bone	18	46%
Brain/CNS	2	5%
Liver	6	15%
Lung	38	97%
Lymph nodes	20	51%
Mediastinum	24	62%
Pleura	7	18%

Skin	2	5%
Other*	3	8%

Efficacy Results:

Response according to expert if patients reviewed otherwise according to investigator

Number of patients	Step				All steps		
	1		2				
	N=21	%	N=18	%	N=39	%	95% CI
CR	-	-	1	6	1	3	[0.1-13.5]
PR	8	38	7	39	15	38	[23.4-55.4]
SD	7	33	6	33	13	33	[19.1-50.2]
PD	6	29	4	22	10	26	[13.0-42.1]

Safety Results:

Extent of exposure

N of patients/cycles	
Gemcitabine	
N infusions	306
Dose intensity (mg/m²/wk)	
Median	327.3
Range	[209.8-364.6]
Relative dose intensity (%)	
Median	93.5
Range	[59.9-104.2]
Cumulative dose (mg/m²)	
Median	5589.5
Range	[1396.4-10126.8]
Oxaliplatin	
N infusions	302
Dose intensity (mg/m²/wk)	
Median	37.8
Range	[25.9-44.6]
Relative dose intensity (%)	
Median	88.8
Range	[60.9-104.8]
Cumulative dose (mg/m²)	
Median	663.2
Range	[168.7-1167.4]
Vinorelbine	
N infusions	306
Dose intensity (mg/m²/wk)	
Median	11.7
Range	[8.2-13.4]
Relative dose intensity (%)	
Median	93.9
Range	[65.3-106.9]
Cumulative dose (mg/m²)	
Median	199.9
Range	[50.4-350.2]

Adverse events

No treatment-related deaths occurred. Two patients had febrile neutropenia in 4 cycles. One additional case (#250304) of grade 4 neutropenia with grade 1 fever occurred. Paraesthesia was a common adverse event occurring in 26 patients

(67%) with only 2 events being grade 3. Similarly dysaesthesia was seen in 13 patients (33%) with no grade 3 events. General disorders included asthenia in 29 patients (74%) with 1 grade 3 and pyrexia in 14 patients (36%). Gastrointestinal disorders included nausea in 24 patients (62%) and vomiting in 20 patients (51%) with one grade 3.
Date of report: 11 January 2007