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Sponsor/company:	sanofi-aventis	ClinialTrials.gov Identifier:	NCT00271323
		Study Code:	XRP6976B_2507
Generic drug name:	Docetaxel	Date:	29-Oct-2008

Study title	A two-arm phase II study assessing docetaxel/cisplatin induction therapy followed by concurrent chemoradiotherapy *or* concurrent chemoradiotherapy followed by consolidation docetaxel/cisplatin in patients with locally advanced unresectable NSCLC (stage IIIA-multiple cN2 or IIIB)
Sponsor	Sanofi-aventis France
Research Coordinator/Country	Professeur CALAIS
Centers	15 centers
Country	France
Phase	Phase II randomized with direct individual benefit
Study period	Date first patient enrolled: 31/05/2005 Date last patient enrolled: 20/06/2006 Last patient out : 28/02/2007
Study objectives	Primary: To determine the safety profile of each treatment group. Secondary: To determine efficacy in term of overall response, disease free survival and survival at 1 and 2 years.
Methodology	Open-label, randomized phase II study
Number of patients	86 patients (43 per arm) were expected

	From May 2005 to June 2006, 14 patients were included and treated in this Phase II study. On June 15, 2006, the study was stopped prematurely because of difficulty in recruitment related to the advent of PET showed disseminated tumours (exclusion criteria).
Inclusion criteria	1. Informed consent form obtained, signed and dated before specific protocol procedures. 2. Histologically or cytologically confirmed NSCLC (adenocarcinoma, squamous cell carcinoma, large cell carcinoma or a combination of these) 3. Patients must have a loco regionally advanced unresectable NSCLC; • Stage IIIA with clinical multiple N2 nodes (preferably with histological or cytological confirmation). ▪ Patients with peripheral tumours of the lower lobe with contralateral upper mediastinal nodes at station N2 are excluded • Stage IIIB T4 or N3. ▪ In the T4 category, patients with pleural or pericardial effusion and multiple nodules in the same lobe are excluded. ▪ Patients with T4 disease secondary to extensive and massive involvement of the great vessels are excluded. Patients should be excluded when the expected risk of pulmonary toxicity is likely to be high, e.g. V20 in excess of 35%. 4. Males or females aged between 18 and 75 years. 5. Life expectancy of at least 12 weeks. 6. WHO performance status 0 or 1. 7. Weight loss $\leq$ 10% within the last 3 months. 8. Laboratory requirements at entry (within 7 days before randomization): • Blood cell counts: ▫ Absolute neutrophils $\geq$ 2.0 x 10^9/L ▫ Platelets $\geq$ 100 x 10^9/L ▫ Hemoglobin $\geq$ 10 g/dl • Renal function: ▫ Serum creatinine $\leq$ 1 x the upper limit of normal (UNL). In case of borderline value of serum creatinine, the 24h creatinine clearance should be $\geq$ 60 mL/min. • Hepatic function: ▫ Serum bilirubin $\leq$ 1 x UNL ▫ ASAT and ALAT $\leq$ 2.5 x UNL ▫ Alkaline phosphatase $\leq$ 5 x UNL Patients with ASAT and/or ALAT > 1.5 x UNL associated with alkaline phosphatase> 2.5 x UNL are **not eligible** for the study. 9. Lung function tests at entry: • FEV_1: $\geq$ 50 % x Normal value • DL_{CO}: $\geq$ 50 % x Normal value 10. Adequate cardiac function. 11. Patient with either measurable and/or non-measurable lesion (according to RECIST criteria).

Exclusion criteria	1. Diagnosis of small cell lung cancer. 2. Pregnant or lactating women. 3. Patients (male or female) with reproductive potential not implementing adequate contraceptive measures. 4. Prior systemic chemotherapy, immunotherapy, or biological therapy including neoadjuvant or adjuvant treatment for NSCLC. 5. Prior surgery for NSCLC, if less than 5 years from study. 6. Prior radiotherapy for NSCLC. 7. History of prior malignancies, except for cured non-melanoma skin cancer, curatively treated in-situ carcinoma of the cervix or other cancer curatively treated and with no evidence of disease for at least five years. 8. Symptomatic peripheral neuropathy Grade $\geq$ 2 except if due to trauma. 9. Other serious concomitant illness or medical conditions: • Congestive heart failure or angina pectoris except if it is medically controlled. Previous history of myocardial infarction within 1 year from study entry, uncontrolled hypertension or arrhythmias. • History of significant neurological or psychiatric disorders including dementia or seizures. • Active infection requiring IV antibiotics. • Active ulcer, unstable diabetes mellitus or other contra-indication to corticosteroid therapy. • Superior vena cava syndrome contra-indicating hydration. • Preexisting pericardial effusion. • Preexisting symptomatic pleural effusion. 10. Significant gastrointestinal abnormalities, including requirement for intravenous nutrition, active peptic ulcer disease, prior surgical procedures affecting absorption. 11. Distant metastasis. 12. Concurrent treatment with any other experimental anti-cancer drugs. 13. Concomitant or within 4-week period administration of any other experimental drug under investigation. 14. Significant ophthalmologic abnormalities. 15. Moderate to severe dermatitis. 16. Hypersensitivity to docetaxel, cisplatin, or any of its excipients. 17. Concomitant use of phenytoin, carbamazepin, barbiturates, or rifampicin. 18. Mental condition rendering the patient unable to understand the nature, scope, and possible consequences of the study. 19. Patient unlikely to comply with protocol, i.e., uncooperative attitude, inability to return for follow-up visits, and not likely to complete the study.

Exposure to treatment	<u>Arm A: Induction chemotherapy followed by concurrent chemoradiotherapy</u> Docetaxel (75 mg/m^2, IV, Day 1) and cisplatin (40 mg/m^2, IV, Day 1, 2) every 3 weeks for 2 cycles, followed by concurrent chemo-radiotherapy with docetaxel (20 mg/m^2, IV) and cisplatin (20 mg/m^2) weekly for 6 weeks + radiotherapy 2 Gy/day, 5 days per week to a total dose of 66 Gy. <u>Arm B: Concurrent chemo-radiotherapy followed by consolidation chemotherapy</u> Docetaxel (20 mg/m^2, IV) and cisplatin (20 mg/m^2) weekly for 6 weeks + radiotherapy 2 Gy/day, 5 days per week to a total dose of 66 Gy followed by docetaxel (75 mg/m^2, IV, Day 1) and cisplatin (40 mg/m^2, IV, Day 1, 2) every 3 weeks for 2 cycles.
Efficacy Data (Incl. Time and Method of Collection)	Efficacy will be estimated by the overall response rate (complete plus partial responses) in population of patients eligible and evaluable for response (RECIST). Time to progression will be calculated from the date of start treatment until progression. Duration of response will be calculated in the same manner, but only on responders. All patients will be evaluated for Survival. Survival will be measured from the randomization date to the date of death.
Safety Data (Incl. Time and Method of Collection)	Clinical and laboratory toxicities will be graded according to NCIC-CTG Expanded Common Toxicity Criteria. The adverse events which are not reported in NCIC-CTG Expanded Common Toxicity Criteria will be graded as mild, moderate, severe, life threatening.
Statistical Procedures (Primary Analysis Variable and Most Important Secondary Analysis, Primary Study Population, Statistical Methods)	Safety (primary) : The grade 3-4 esophagitis is considered as limiting toxicity, the sample size is calculated in order to have enough power to detect the expected proportion of rate limiting toxicity of grade 3-4 esophagitis, estimated at about 12.5%. Historically the incidence of grade 3-4 esophagitis has typically been in the range of 10–15 %, with 25 % regarded as the maximum clinically allowable rate. Assuming a maximum allowable rate of 25%, the null hypothesis of the statistical test is that the toxicity level is too high (25%) to be tolerable. The 2 arms will be tested separately. If we allow a type I error rate (significance level) of 0.10, with at least 39 eligible patients in each arm, we will have about 80% power. Hematological and non-hematological adverse events will be displayed in term of worst grade (NCI-CTC) by subject, by cycle and by each of the concurrent chemo-radiotherapy and induction/consolidation phase of the study. The percentage of patients with rate limiting toxicity level will be tested against a null hypothesis of at least a 25% toxicity level at a significance level of 0.20. This test will be performed separately for each treatment group. The 80% bilateral Confidence Interval of the percentage will be given. Other statistical analyses will be mainly descriptive. Quantitative data will be described by number of patients, median and range, if relevant, mean and standard deviation will be added. Efficacy (secondary) : The response rate will be analyzed descriptively and the confidence interval will be calculated based on binomial distribution or normal approximation. The response rate will also be analyzed with a logistic regression modeling approach. Time to event data (overall survival, progression free survival and time to progression) will be estimated with Kaplan-Meier survival curves. Cox proportional hazard model will be used to analyze the major prognostic factors. Efficacy analyses will be performed for both ITT and evaluable populations, and separately for each arm.
Adverse Events	On these 14 patients included and treated in this Phase II study, some of these patients had presented more one SAE : 7 serious adverse events related and 2 not related in 6 patients One patient with: Death (not related: autolysis)

	One patient with: Digestive disorder, nausea, vomiting, dehydration, asthenia, cardiac arrest fatal (death seems likely related to hypovolemic shock as a result of massive hemorrhage. Related to the treatment) One patient with: Death (mild hematemesis and death not related to the treatment) One patient with: Fatal cardiorespiratory disorder (related to the treatment) One patient with: Grade 4 neutropenia (related to the treatment) General physical health deterioration (related to the treatment) Cholecystitis without lithiasis (related to the treatment One patient with: Fatal cerebrovascular accident and pulmonary embolism (related to the treatment)
Date of report:	29 September 2008