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Sponsor/company:	sanofi-aventis	**ClinialTrials.gov Identifier:**	NCT00425191
		Study Code:	XRP6976B_2501
Generic drug name:	Docetaxel	**Date:**	13/Mar/2008

Title of the study:	A multicenter randomized phase II study evaluating the feasibility and activity of two different combinations of Docetaxel (RP56976, Taxotere®) and Gemcitabine and of Cisplatin/Gemcitabine followed by Docetaxel as first line therapy for locally advanced unresectable or metastatic non small cell lung cancer. XRP6976B_2501		
Investigator(s):	Prof. Giorgio Vittorio SCAGLIOTTI M.D, University of Turin, Department of Clinical & Biological Sciences, Azienda Ospedaliera S. Luigi Regione Gonzole 10, 10043 ORBASSANO (Turin) Italy; Dr. Massimo RINALDI M.D. Regina Elena Institute for Cancer Research, Department of Medical Oncology B, Via Chianesi 52, Rome –Italy		
Study center(s):	Giuseppe ALTAVILLA; Messina; Franco BUZZI, Terni; Luigi SACCA', Napoli; Antonio CONTU, Sassari; Lucio CRINO', Bologna; Filippo DE MARINIS, Roma; Alfredo FALCONE, Livorno; Felice GOZZELLINO,Biella; Cesare GRIDELLI, Avellino; Alfredo LAMBERTI, Napoli; Bruno MASSIDDA, Cagliari; Silvio MONFARDINI, Padova; Mario NARDI, Reggio Calabria; Luigi PORTALONE, Roma; Paolo PRONZATO, Genova; Alberto ROSA BIAN, Tiene; Maurizio TONATO, Perugia.		
Publications (reference):	-		
Study period: Date first patient enrolled: 03 July 2002 Date last patient completed: 06 April 2005		**Phase of development:** II	
Objectives:	To assess the antitumor activity as measured by response rate in patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) of two different combinations of docetaxel and Gemcitabine and of a sequential treatment of cisplatin/Gemcitabine followed by docetaxel as first line chemotherapy		
Methodology:	Multicenter, open-label, randomized phase II study of two different combinations of docetaxel and Gemcitabine and of a sequential treatment of Gemcitabine/cisplatin followed by docetaxel as first line chemotherapy in out-patients with unresectable locally advanced (stage IIIB with N3 supraclavicular or T4 for pleural effusion) or metastatic (stage IV) NSCLC. Using a central randomization process, patients were stratified according to disease stage (stage IIIb versus stage IV)		
Number of patients/subjects:	**Planned**: 162 eligible patients, (54 patients in each arm)	**Randomized**: 54 in Arm A, 57 in Arm B, 54 in Arm C	**Treated**: 54 in Arm A, 57 in Arm B, 54 in Arm C
Evaluated:	**Efficacy/Pharmacodynamics**: 27 (50%) in Arm A, 17 (30%) in Arm B, 37 (69%) in Arm C	**Safety:** 54 in Arm A, 57 in Arm B, 54 in Arm C	

Diagnosis and criteria for inclusion:	Patients with histologically or cytologically confirmed diagnosis of NSCLC (squamous cell, large cell, adenocarcinoma or undifferentiated NSCLC), stage IIIB (only N3 supraclavicular or T4 for pleural effusion) or stage IV. To be eligible, patients were required to have at least one measurable lesion (according to RECIST definition). Other inclusion criteria were: age 18-70 years, World Heath Organization (WHO) performance status (PS) $\leq$2, an adequate bone marrow and renal function. Previous radiotherapy was allowed if completed 4 weeks before study entry. Previous radical surgery was permitted if performed more than 30 days from randomization and pathological proof of neoplastic residual disease was documented. Patients with asymptomatic brain metastasis or asymptomatic under corticosteroids were also admitted. Main exclusion criteria were: peripheral neuropathy $\geq$2 NCI CTC grading, prior chemotherapy or biological therapy for metastatic disease, other concomitant illness which occurred less than 1 year from study entry, unstable diabetes or other contraindication to corticosteroids treatment.
Investigational product:	Docetaxel (Taxotere®) 80 mg concentrate for solution for infusion in combination with Gemcitabine, also to be also administered by infusion
Dose:	**Arm A**: Docetaxel 40 mg/m², Gemcitabine 1200 mg/m^2 **Arm B**: Docetaxel 50 mg/m², Gemcitabine: 1600 mg/m^2, **Arm C**: Gemcitabine 1200 mg/m^2, Cisplatin 75 mg/m^2, then Docetaxel 75 mg/m^2
Administration:	**Arm A**: Docetaxel 40 mg/m², administered intravenously over 60 minutes given on day 1 and 8 immediately followed by Gemcitabine 1200 mg/m^2, administered intravenously over 30 minutes on day 1 and 8 **Arm B**: Docetaxel 50 mg/m², administered intravenously over 60 minutes on day 1 and 15 immediately followed by Gemcitabine: 1600 mg/m^2, administered intravenously over 30 minutes on day 1 and 15. **Arm C**: Gemcitabine 1200 mg/m^2, administered intravenously over 30 minutes on day 1 and 8 followed by Cisplatin 75 mg/m^2, administered intravenously over 30-60 minutes on day 2. The cycle was repeated every 3 weeks for 3 cycles; the treatment was continued with Docetaxel 75 mg/m^2, administered intravenously over 60 every 3 weeks for 3 cycles.

Duration of treatment: 18 weeks (6 cycles of chemotherapy) for Arm A and C, 24 weeks (6 cycles of chemotherapy) for Arm B ▪ Arm A Frequency: every 3 weeks ▪ Arm B Frequency: every 4 weeks ▪ Arm C Frequency: every 3 weeks	**Duration of observation:** 25 months

Reference therapy: Dose: Administration:	Not Applicable NA NA
Criteria for evaluation:	
Safety:	▪ Toxicity was assessed on the basis of adverse events classified according to NCIC-CTG criteria. ▪ Adverse events (worst NCI-CTC grade by patient and type of event) ▪ Hematology laboratory assessment (worst NCI-CTC grade by patient and type of hematological parameter)
Efficacy:	**Primary end-point:** Activity: ▪ Overall response rate defined as complete plus partial response as defined by RECIST Criteria Secondary: ▪ Overall survival ▪ Progression free survival ▪ Health Outcomes: Lung Cancer Symptom Scale (LCSS)
Pharmacokinetic sampling times and bioanalytical methods:	N.A.
Statistical methods:	Statistical: Baseline characteristics were analyzed on all randomized patients, by means of count and percentage for categorical variable and means, standard deviation, median and range for continuous variable. No statistical tests were performed to test homogeneity across the three treatment arms. All the analyses for efficacy, safety and health outcomes were performed on all treated patients. Overall response rate was estimated and 95% confidence intervals were calculated using a method based on binomial distribution. Overall survival and progression free survival analysis were performed using the Kaplan-Meier method and compared with Log-rank test. Treatment emergent adverse events, defined as any new event occurred during the study or present at the time of the enrolment and worsened during the study within 30 days from last drug administration, were described with frequency, and rate. Serious drug-related events were defined as all the events with drug relationship judged as probable or possible or remote; for Arm C, adverse events that occurred in cycle 4, 5 or 6 were considered treatment emergent for the Docetaxel, if they were not present before or if present before worsening during cycle 4 or cycle 5 or cycle 6. No statistical tests were performed to test homogeneity across the three treatment arms. Health Outcomes were described using specific symptoms affecting quality of life, such as: loss of appetite, fatigue, cough, dyspnoea, and haemoptysis. Data were described using mean, standard deviation, range and effect size, and compared at baseline and selected time points using ANOVA approach. Sample size determination The primary objective of the study was to rank the response rate (complete or partial) of the three treatment arms (docetaxel and gemcitabine day 1 & 8 every 3 weeks or docetaxel and gemcitabine day 1 & 15 every 4 weeks or sequential treatment of gemcitabine and cisplatin followed by docetaxel alone) in order to select the treatment having the more promising activity in chemo-naive locally advanced or metastatic NSCLC patients. The selection was based on "the method of statistical ranking and selection theory" described by Simon. The smallest response rate was assumed to be 30%: with this assumption, with 52 evaluable patients for response per test arm, there would be 90% probability of selecting the treatment that would be superior to all the others by an absolute difference of 15% in response rate (i.e. the treatment that would have a true response rate of 45 %.). Taking into account a rate of 5% of non evaluable patients, 162 patients in total had to be enrolled.

Summary:	No combination chemotherapy is widely accepted as a standard therapy for advanced NSCLC. Platinum-based combination therapy is now commonly administered as first-line chemotherapy for patients with advanced NSCLC. Phase III studies comparing platinum based combination with "old" cytotoxic agents such as vinka alkaloid or etoposide with those including "new" compounds such as taxanes and gemcitabine showed increased response rates with new drugs; however no significant advantage in survival were observed. There is a clear need for an alternative to existing cisplatin-based chemotherapy for NSCLC and for regimens that improve on its efficacy. Among new chemotherapeutic agents, docetaxel and gemcitabine have shown promising results. Both of these new agents have proven activity as first-line single agents; with docetaxel, response rate of 21% to 33% and a median survival of 9.2 months have been reported and with gemcitabine, response rate of 20% to 22.5% and a median survival of 6 to 8 months can be expected. Based on these promising results the combination of gemcitabine and docetaxel was tested in several dose finding studies; however no definite data are available concerning the optimal doses of both drugs to be used, and the best scheduling of administration. The present study evaluated the activity of two different schedules of a combination including docetaxel and gemcitabine as first line therapy for locally advanced unresectable or metastatic disease. In addition, considering that combination therapy can results in unacceptably high level of toxicity, a new approach has been introduced which used multiple chemotherapy agents given sequentially rather than in combination. Based on this finding, the present study evaluated a sequential treatment consisting in gemcitabine cisplatin combination followed by docetaxel in order to assess the feasibility and activity of this approach in poor prognosis stage IIIB and in metastatic disease.
Safety results:	Safety was assessed at every cycle in all patients who received at least 1 cycle of treatment. The percentage of patients who experience at least one treatment related grade 3-4 event was: 33.3%, 33.9% and 16.7% in Arm A and B and C, respectively. Serious drug related adverse events occurred in 5 patients in Arm A, in 6 patients in Arm B and in 3 patients in Arm C (Table 7). Ten patients died during treatment. In 3 cases, the death was considered related to the treatment assigned and was due to cardiac failure (Arm B). The incidence of NCI-CTC grade 3-4 neutropenia was higher in Arm C during Docetaxel administration. Febrile neutropenia occurred in 3 patients and none experienced infection with NCI-CTC grade 4 neutropenia. The most frequent NCI-CTC grade 3-4 hematological side effect during treatment with cisplatin/gemcitabine was thrombocytopenia (Table 5), which occurred in 20.4% of patients; however no platelet support was requested. Use of granulocyte colony-stimulating factor occurred in 8.2% of the cycles. Growth factor was administered more frequently in Arm C during the 3 cycles of docetaxel (12.3%). The incidence of non-haematological toxicities was similar in the 3 treatment arms (Table 6), except for diarrhoea which was higher in Arm A and NCI-CTC grade 1 and 2 alopecia which was more frequent in Arm C. Grade 1 and 2 nail disorders occurred more frequently in patients who received 6 cycles of combination with docetaxel with respect those who were given only 3 cycles of the drug. Two patients in Arm B experienced a NCI-CTC grade 3-4 event. The incidence of NCI-CTC grade 3 and 4 adverse events was higher in Arm A and B compared with Arm C. The most frequent adverse event in all the treatment arms was asthenia. In Arm B there were more NCI-CTC grade 3 and 4.

Study results:

Main and secondary parameters

Primary Endpoint:

Response rate was assessed after 3 cycles and after 6 cycles in all the patients who received at least one cycle of treatment (intent to treat population). The percentage of objective (Complete plus Partial) response was 22.2%, 23.2% and 33.3% after 3 cycles whereas after 6 cycles, it was 24%, 12.5% and 27.8% in Arm A, B, and C, respectively. Only 1 patient in Arm C achieved a Complete Response after 6 cycles of treatment.

	Arm A (N=54)		Arm B (N=56)		Arm C (N=54)	
	N	**%**	**N**	**%**	**N**	**%**
Tumor Response after 3 cycles						
Partial Response	12	22.2	13	23.2	18	33.3
Stable Disease	17	31.5	14	25	16	29.6
Progressive Disease	14	25.9	15	26.8	10	18.5
Not Valuable	4	7.4	4	7.1	7	13
Objective Response Rate % (95% Confidence Interval)	22.2 (12-35.6)		23.2 (13-36.4)		33.3 (21.1-47.5)	
Tumor Response after 6 cycles						
	N	%	N	%	N	%
Complete Response					1	1.9
Partial Response	13	24.1	7	12.5	14	25.9
Stable Disease	8	14.8	6	10.7	12	22.2
Progressive Disease	20	37	25	44.6	17	31.5
Not Valuable	2	3.7	-		5	9.3
Objective Response Rate % (% Confidence Interval)	24 (13.5- 37.6)		12.5 (5.2-24.1)		27.8 (16.5-41.6)	

Secondary Endpoint:

The median time to progression was similar in all the 3 arms. The median survival for all the patients randomized seems longer in Arm A and C when compared with Arm B, with the highest rate of survival at 1-year and 2-year occurring in Arm C (53.8% and 34.4%)

	Arm A (N=54)	Arm B (N=56)	Arm C (N=54)
Duration of response Median (months) Range	8.2 (4.7-13.6)	7.8 (5.7-8.8)	5.9 (4.7-9.8)
Time to Progression (TTP) Median TTP (months) Range: TTP 1 year (%) TTP 2 years (%)	10.2 (9.7-11.9) 29.9 -	10.4 (8.3-11.7) 19.9 -	9.7 (6.7-12.6) 33.7 11.2
Survival Median survival (months) Range: 1 year Survival (%) 2 years Survival (%)	10.7 (6.8-15.6) 46.3 19.8	8.9 (7.4-14.0) 39.4 7.5	14.6 (8.0-22.4) 53.8 34.4

Date of report: 12 March 2008