These results are supplied for informational purposes only. Prescribing decisions should be made based on the approved package insert in the country of prescription			
Sponsor/company:	sanofi-aventis	ClinialTrials.gov Identifier:	NCT00258739
		Study Code:	TAX_ES1_209
Generic drug name:	DOCETAXEL	Date:	06 October 2008

Title of the study:	"Randomized phase II study of concomitant treatment (radiotherapy and carboplatin-docetaxel) followed by docetaxel-gemcitabine versus docetaxel-gemcitabine followed by concomitant treatment (radiotherapy and carboplatin-docetaxel), for stage IIIB or IIIA non-small cell lung cancer"
Investigator(s):	Coordinating Investigators: Dr Garrido. Servicio de Oncología Médica (GECP) Hospital Ramón y Cajal Carretera de Colmenar Viejo Km 9.100. Madrid. Dr Ramos. Servicio de Oncología Radioterápica (GICOR) Hospital Ramón y Cajal. Carretera de Colmenar Viejo Km. 9100. Madrid Dr Rosell. Servicio de Oncología Médica (GECP) Hospital Germans Trias i Pujol. Carretera del Canyet s/n. Badalona (Barcelona) Dr Arellano. Servicio de Oncología Radioterápica Hospital Germans Trias i Pujol. Carretera del Canyet s/n. Badalona (Barcelona).

Study center(s):	1. Hospital Germans Trias I Pujol - SPAIN 2. Hospital Virgen de los Lirios - SPAIN 3. Hospital General de Alicante - SPAIN 4. Hospital Marqués de Valdecilla - SPAIN 5. Institut Català d'Oncología - SPAIN 6. Hospital Ramón y Cajal - SPAIN 7. Hospital General de Albacete - SPAIN 8. Hospital Gregorio Marañón - SPAIN 9. Hospital Arnau de Vilanova de Valencia - SPAIN 10. Hospital Fundación Alcorcón - SPAIN 11. Hospital Fundación Jiménez Díaz - SPAIN 12. Hospital General de Mataró - SPAIN 13. Hospital Lozano Blesa - SPAIN 14. Hospital Carlos Haya - SPAIN 15. Hospital del Mar - SPAIN		
Publications (reference):	N/A		
Study period: Date first patient enrolled: 19-Oct-2001 Date last patient completed: 05-Sep-2007		Phase of development: Phase II	
Objectives:	Primary : To classify the two test arms according to the tumor response rate. Secondary : To evaluate the local control rate at 1 year. To calculate the progression free survival (PFS). To calculate the overall survival (OS). To evaluate the safety profile.		
Methodology:	After having checked all eligibility criteria, patients will be randomly assigned to receive either concomitant treatment (radiotherapy and docetaxel-carboplatin: RDC) followed by docetaxel-gemcitabine (DG) or DG followed by RDC.		
Number of patients	Planned: 140 patients	Randomized: 139 (70 on arm B and 69 on arm C)	Treated: 135 (67 on arm B and 68 on arm C)
Evaluated:	Efficacy: 135 (67 on arm B and 68 on arm C)	Safety: 135 (67 on arm B and 68 on arm C)	

Diagnosis and criteria for inclusion:	1. Histologically or cytologically confirmed NSCLC. 2. Histology types may include: large cell, squamous cell, or adenocarcinoma. 3. IIIB or IIIA stage: patients with pleural effusion, growth vessels invasion or supraclavicular disease were excluded. 4. No prior therapy for NSCLC was allowed (no prior chemotherapy, radiation therapy or surgery). 5. Patients must have bidimensionally measurable disease. 6. Males or females aged between 18 and 75 years. 7. Life expectancy of at least 12 weeks. 8. WHO performance status 0 or 1. 9. Weight loss < 5% within the last 3 months 10. Adequate laboratory requirements
Investigational product: Dose: Administration:	Docetaxel / Carboplatin / Gemcitabine <u>Arm B:</u> ▪ Docetaxel 20 mg/m² followed immediately by carboplatin AUC 2, weekly + concomitant radiotherapy (60 Gy), followed by ▪ Docetaxel 40 mg/m² followed immediately by gemcitabine 1200 mg/m²/d (same schedule than arm A). <u>Arm C:</u> ▪ Docetaxel 40 mg/m² followed immediately by gemcitabine 1200 mg/m²/d (same schedule than arm A)), followed by ▪ Docetaxel 20 mg/m² followed immediately by carboplatin AUC 2, weekly + concomitant radiotherapy (60 Gy). Intravenous. In arm B patients will receive RDC and will be evaluated; unless progression, unacceptable toxicity or patient refusal, patients will receive 2 cycles of DG. In arm C patients will receive 2 cycles of DG and will be evaluated; unless progression, unacceptable toxicity or patient refusal, patients will be treated with RDC, starting 3-5 weeks after chemotherapy.
Duration of treatment: The planned duration of treatment was 91 days.	Duration of observation: Every 3 months until death.
Reference therapy:	N/A (2 active experimental arms)
Criteria for evaluation:	
Efficacy:	Measurements of disease were performed at baseline, after RDC (arm B) or after DG (arm C), and at the end of the overall treatment (both arms). RECIST criteria were applied. Local control rate was defined as the proportion of patients without dissemination at distance of the disease. PFS was defined as the time from randomization until objective tumor progression or death. OS was defined as the time from randomization until death from any cause.
Safety:	CALGB/Expanded CTC and RTOG toxicity criteria were applicable.
Statistical methods:	The main objective of this trial was to assess the response rate of two combined therapeutic modalities as first line therapy for Non Small Cell Lung Cancer. This study was intended to permit further investigations if the results are sufficiently relevant.

	Regarding these considerations, and following the Fleming's single stage method, a sample size of 70 eligible patients per treatment arm was planned to detect an improvement in the response rate from 66 to 85%, with a power of 80% at a significance level for two-sided test with alpha of 0.05 Randomization was centralized, without patients' stratification. Chi-square tests were used to compare categorical variables between treatment groups. For continuous variables, Student's t tests were used. The Kaplan-Meier method was used to estimate survival curves, and the log-rank test to compare the curves. Cox proportional hazards modeling was used to calculate hazard ratios and 95% confidence intervals (CI). All randomized patients were included in an intention-to-treat analysis; patients who canceled before the initiation of therapy were excluded from the toxicity analyses. The safety of the treatments will be assessed by analyzing the frequency and type of adverse events, including serious ones, and the overall management of adverse events, e.g., dose reductions/delays and supportive measures. The SAS statistical pack was used to make all analyses.

Summary:	
Efficacy results:	*Response to treatment* Four patients were non-evaluable for efficacy, three on B arm and one on C arm, because they do not receive any dose of study treatment. The best response observed during the complete treatment in each group is summarized in table 1. In the intent-to-treat analysis, where all treated patients were included (135 patients), the overall response rates on B and C arms were 56.7% (95% CI, 44.0 to 68.8%) and 57.4% (95% CI, 44.8 to 69.3%), respectively: no statistically significant differences were detected (p = 0.94). A locoregional control was reached in 25 patients (37.3%) included in arm B and in 36 (52.9%) included in arm C.

Table 1. Best treatment response

	Arm B		Arm C	
	No. of Patients	%	No. of Patients	%
CR	3	4.48	5	7.35
PR	35	52.24	34	50.00
SD	10	14.93	16	23.53
PD	12	17.91	9	13.24
NE	7	10.45	4	5.88
Total	67	100.00	68	100.00

CR: complete response; PR: partial response; SD: stable disease;
PD: progressive disease, NE: non evaluable

Survival analysis
After a median follow-up of 12.2 months on B arm and 12.8 months on C arm, 49 patients (73%) had progressed or died on B arm and 46 (68%) on C arm. A 55% and 60% of patients remained alive 1 year after the inclusion on B and C arms, respectively (p = 0.6). The median progression free survival in B arm was 7.4 months (95% CI, 5.1 to 9.6 months) versus 9.0 months (95% CI, 7.5 to 18.1 months) in C arm (p = 0.12). The median overall survival was 13.2 months (95% CI, 8.8 to 16.5 months) in patients treated on B arm compared with 14.7 months (95% CI, 11.8 to 29.0 months) in C arm (p = 0.17).

Safety results:

Four patients (3 on B arm and 1 on C arm) did not receive any treatment infusion, all of them due to incompliance with the inclusion criteria "stage IIIB or IIIA", detected after the randomization. Fifty-one patients (76.1%) in the B arm and fifty-five (80.9%) in the C arm, completed the proposed sequential treatment:

- B arm: RDC (67 pts) → DG (51 pts).
- C arm: DG (68 pts) → RDC (54 pts).

Grade 3 and 4 toxic effects occurring at a frequency of 5% or more are shown in table 2. Noteworthy, grade 3-4 hematological toxicity was significantly more frequent in the B arm (p = 0.0047).

Table 2. Maximum grade 3-4 toxicity occurring at a frequency ≥ 5%, after treatment ending

Hematological	Arm B (N = 67)		Arm C (N = 68)	p
Neutropenia	13 (19.40 %)		7 (10.29 %)	0.1363
Leucopenia	8 (11.94 %)		4 (5.88 %)	0.2162
Thrombopenia	6 (8.96 %)		2 (2.94 %)	0.1649*
Anemia	4 (5.97 %)		0 (0.0 %)	0.0579*
Subtotal	24 (35.82 %)		10 (14.71 %)	0.0047
Nonhematological				
Esophagitis	12 (17.91 %)		8 (11.76 %)	0.3149
Disnea	7 (10.45 %)		10 (14.71 %)	0.4559
No neutropenic infection	11 (16.42 %)		5 (7.35 %)	0.1033
Fatigue	6 (8.96 %)		7 (10.29 %)	0.7920
Mucositis	6 (8.96 %)		4 (5.88 %)	0.5313*
Pain	3 (4.48 %)		5 (7.35 %)	0.7182*
Subtotal	41 (61.19 %)		38 (55.88 %)	0.5311
Total	47 (70.15 %)		41 (60.29 %)	0.2294

*Fisher's test

Date of report: 22-Sep-2008