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Sponsor/company:	sanofi-aventis	ClinialTrials.gov Identifier:	NCT00174772
		Study Code:	XRP6976B_2505
Generic drug name:	Docetaxel	Date:	08 Feb 2010

Title of the study:	A two arm phase II study comparing docetaxel/cisplatin induction therapy followed by concurrent chemoradiotherapy versus concurrent chemoradiotherapy followed by consolidation docetaxel/cisplatin in patients with locally advanced unresectable NSCLC (stage IIIA-multiple cN2 or IIIB); XRP6976B/2505
Coordinating Investigators:	Prof. G. Scagliotti, University of Torino, Azienda Ospedaliera San Luigi, 10043 Orbassano (Torino) – Italy; Prof.U. Ricardi, Department of Radiation Therapy, University of Torino, Azienda Ospedaliera San Giovanni Battista, Via Genova 3, 10126 Torino – Italy; Prof. S. Senan, VU Medical Center, Department of Radiation Oncology, P.O. Box 7057, 1007 MB Amsterdam, The Netherlands
Study center(s):	The study was conducted in 15 centers in Belgium, Finland, France, Italy, the Netherlands, Spain, Turkey and the United Kingdom.
Publications (reference):	o Sörnsen De Koste JR van, Senan S, Underberg RWM, Oei SS, Elshove D, Slotman BJ, Lagerwaard FJ. Use Of CD-ROM–Based Tool For Analyzing Contouring Variations In Involved-Field Radiotherapy For Stage III NSCLC. Int J Radiation Oncology Biol Phys 2005;63:334–9. o Meerbeeck JP van, et al. Activity and Toxicity in PulmonArt: Involved-field 3D radiotherapy (RT) and docetaxel/cisplatin chemotherapy (CT) in a randomised phase 2 study comparing concurrent CT-RT followed by consolidation CT, with induction CT followed by concurrent CT-RT in patients (pts) with stage III non-small cell lung cancer (NSCLC). Ann Oncol 2006;17(Suppl 9):ix213, Abs:711O. 31st Congr Eur Soc Med Oncol (ESMO), Istanbul (Sep-Oct 2006). o Senan S, et al. Treatment Compliance and Early Toxicity of 3D Involved-field Radiotherapy (RT) And Chemotherapy (CT) in A Randomized Study Comparing Induction CT Followed By Concurrent CT-RT with Concurrent CT-RT Followed By Consolidation CT, in Non-Small Cell Lung Cancer (NSCLC). Int J Radiat Oncol Biol Phys 2006;66:S89-S90, Abs:159. 48th Annu Meet Am Soc Ther Radiol Oncol (ASTRO), Philadelphia PA (Nov 2006). o Meerbeeck JP van, et al. Mature results of PulmonArt: Involved-field 3D radiotherapy (RT) and docetaxel/cisplatin chemotherapy (CT) in a randomised phase 2 study comparing concurrent CT-RT followed by consolidation CT, with induction CT followed by concurrent CT-RT in patients (pts) with stage III non-small cell lung cancer (NSCLC). J Thorac Oncol 2007;2:S349-S350, Abs:B5-06. 12th World Conf Lung Cancer - Int Assoc Study Lung Cancer (IASLC), Seoul (Sep 2007).

Study period: Date first patient enrolled: 10 March 2004 Date last patient completed: 25 February 2009			Phase of development: Phase II
Objectives:	The primary objective was to evaluate the toxicity/safety profile of docetaxel/cisplatin induction therapy followed by concurrent chemoradiotherapy versus concurrent chemoradiotherapy followed by consolidation docetaxel/cisplatin in patients with locally advanced unresectable NSCLC (stage IIIA-multiple cN2 or IIIB). The secondary objective was to estimate efficacy parameters in overall response rate (ORR), progression-free survival (PFS) and 1-year survival for each of the two above-mentioned arms.		
Methodology:	This was a multicenter, multinational, open label, randomized phase II trial. Patients with locally advanced unresectable NSCLC were randomized to one of two treatment arms.		
Number of patients:	Planned: 70 patients (35 in each arm)	Randomized: 72 patients (36 to Arm A and 36 to Arm B)	Treated: 70 patients (41 in Arm A and 29 in Arm B)
Evaluated:	ITT: 70 patients (36 in Arm A and 34 in Arm B)	PP: 59 patients (29 in Arm A and 30 in Arm B)	Safety: 70 patients (41 in Arm A and 29 in Arm B)
Diagnosis and criteria for inclusion:	Male or non-pregnant and non-breast feeding female patients, 18-75 years of age, with not-pretreated (unless surgery > 5 years ago) locally advanced unresectable NSCLC (stage IIIA-multiple cN2 or IIIB) without distant metastases, having a WHO performance status (PS) of 0-1, lung function tests of > 50% of normal, weight loss of ≤ 10% within the last 3 months, a life expectancy of > 12 weeks and no concomitant serious illnesses or medical conditions.		
Investigational product: Dose: Administration:	Docetaxel (XRP6976), vials of 80 mg/2 ml, manufactured by sanofi-aventis. Patients in Arm A were to receive two 3-weeks cycles of docetaxel 75 mg/m^2 on Day 1 and cisplatin 40 mg/m^2 on Days 1 and 2 of every cycle as induction chemotherapy, followed by 6 weeks of once weekly docetaxel 20 mg/m^2 and cisplatin 20 mg/m^2 (on Day 1 of every week), concurrent with radiotherapy at a dose of 2 Gy/day, for 5 days per week for 6.5 consecutive weeks to a total dose of 66 Gy. Patients in Arm B were to receive 6 weeks of once weekly docetaxel 20 mg/m^2 and cisplatin 20 mg/m^2 (on Day 1 of every week), concurrent with radiotherapy at a dose of 2 Gy/day, for 5 days per week for 6.5 consecutive weeks to a total dose of 66 Gy, followed by two 3-weeks cycles of docetaxel 75 mg/m^2 on Day 1 and cisplatin 40 mg/m^2 on Days 1 and 2 of every cycle as consolidation chemotherapy. If a planning CT revealed a V_{20} > 35%, patients randomized to Arm B were instead to be treated according to Arm A. Docetaxel: Induction or consolidation: 75 mg/m² was to be administered as a 60-minute intravenous (IV) infusion. Concurrent with radiotherapy: 20 mg/m² was to be administered as a 30-minute IV infusion. Cisplatin: Induction or consolidation: 40 mg/m^2 administered IV over 30 – 60 minutes (on Day 1 immediately after docetaxel infusion). Concurrent with radiotherapy: 20 mg/m^2 administered IV over 30 – 60 minutes, immediately after docetaxel infusion. The radiotherapy was to be started 2-4 hours after the end of cisplatin infusion.		

Duration of treatment: Until progressive disease (PD) or unacceptable toxicity with a maximum of 12.5 weeks (6 weeks chemotherapy and 6.5 weeks concurrent chemoradiotherapy).	Duration of observation: Maximum 13.5-19.5 weeks (including pre-study screening and post-study periods), followed by 1-3 years post-study follow-up.
Reference therapy:	In both study arms the same study drugs were administered, but in a reverse order, see above under 'investigational product'. No (other) reference therapy was administered.
Criteria for evaluation:	The current report is an abbreviated report, and as such, the efficacy results are reported briefly and only the safety results are being presented in full. The following safety parameters were evaluated, and analyzed using descriptive statistics: • at baseline and end-of-treatment: hematology (hemoglobin, WBC, neutrophil and platelet count), biochemistry (total bilirubin, alkaline phosphatase, ASAT, ALAT, creatinine, creatinine clearance (as indicated), and total protein), physical examination, weight, vital signs and 12-lead ECG (the latter not at end-of-treatment); • weekly during treatment: adverse events (AEs) and hematology; • 3-weekly during treatment: biochemistry, physical examination, weight, vital signs and 12-lead ECG. The following efficacy parameters were evaluated, and analyzed using descriptive statistics: • ORR: complete response (CR) plus partial response (PR) according to the RECIST criteria; • PFS, calculated from the date of first infusion to the first date of documented disease progression or date of death due to any cause, whichever occurred first; • 1-year survival rate, calculated on the number of patients alive 1 year after the date of first infusion; • overall survival (OS) time, calculated from the date of first infusion to the date of death due to any cause.
Statistical methods:	Quantitative data were described by number of patients, mean, standard deviation (SD), median and range; categorical variables are presented with frequency and percentage. The primary analysis was the safety analysis including the rate of toxicity (defined by the incidence of grade 3-4 oesophagitis), occurrences of hematological and non-hematological AEs, serious adverse events (SAEs) and deaths for each treatment group. This analysis was performed on the safety population, defined as those patients who had received at least one dose of study medication. If patients had received treatments that differed from those assigned according to the randomization schedule, the safety analysis was to be conducted according to the treatment received rather than according to the treatment randomized to. The secondary analysis was the efficacy analysis including ORRs, PFS, 1 year survival rate and OS time. This analysis was performed on: 1) the intention-to-treat (ITT) population, including all patients who were randomized into the study and who had measurable/evaluable disease at baseline and had at least one post baseline evaluation; the ITT analysis was performed according to the treatment group patients were randomized to; 2) the per-protocol (PP) population, consisting of all eligible patients with no major protocol deviations and who had received 6 weeks of concurrent chemoradiotherapy and 2 cycles of induction/consolidation chemotherapy; the PP analysis was performed according to the treatment patients had actually received;

	The results of the PP analysis are not presented in the core report. For a description of the results of the PP analysis, one is referred to the statistical report in Appendix 13.1.9, Section 8.1 'Methods' and Section 8.4 'Analysis of efficacy', and to Appendix 13.2 for the summary tables. 3) an exploratory efficacy analysis was performed on a subpopulation of patients with V20 ≤ 35% according to the treatment patients had received.
Summary:	In total 72 patients were randomized, 36 to each Arm. Two patients in Arm B were randomized incorrectly and not treated. Five patients were switched from Arm B to Arm A treatment because the planning CT revealed a V_{20} > 35% in these patients. Therefore, the ITT population consisted of 36 patients in Arm A and 34 in Arm B, and the Safety population consisted of 41 patients in Arm A and 29 in Arm B. Mean (median) age was 60 (60) years in Arm A and 63 (63) years in Arm B; the overall range was 39-76 years. Male to female ratio was 0.2 to 0.8; all patients had a PS of 0-1. The percentage females was larger in Arm A (22%) than in Arm B (10%). Mean DL_{co} was 70% of normal in Arm A and 88% in Arm B; mean FEV_1 was 80% and 83% of normal in Arms A and B, respectively. WHO performance status was equally distributed among both groups. Exposure: One patient in Arm A received only 1 cycle; all other patients in both Arms received the planned 8 cycles of treatment. The mean (median) docetaxel dose administered was 231 (259) mg/m^2 in Arm A and 218 (243) mg/m^2 in Arm B. The mean (median) cisplatin dose administered was 241 (266) mg/m^2 in Arm A and 228 (265) mg/m^2 in Arm B. The minority of the patients had received the planned cumulative chemotherapy dose, 34% and 41% for docetaxel and cisplatin, respectively, and only 53% received the planned cumulative radiotherapy dose of 66 Gy; the mean cumulative radiotherapy dose was 62 Gy in Arm A and 64 Gy in Arm B. About 12% more patients in Arm A received the planned cumulative chemotherapy dose and about 2% more patients in Arm B received the planned cumulative radiotherapy dose. In total 18 patients were discontinued prematurely, 20% of the patient treated according to Arm A and 35% of the patients treated according to Arm B. the most frequent reason for discontinuation was an AE, i.e. in 17% of the patients in both treatment arms. Safety: All patients experienced one or more treatment-emergent AEs (TEAEs) and in all patients one or more of these events were considered study treatment-related. AEs that occurred in ≥ 20% of the patients were in decreasing order of frequency oesophagitis (67% all; 67% related), fatigue (64% all; 57% related), nausea (60% all; 56% related), anorexia (53% all; 50% related), dysphagia (47% all; 47% related), alopecia (46% all; 44% related), diarrhea (40% all; 34% related), constipation (37% all; 20% related), vomiting (37% all; 34% related), cough (37% all; 20% related), neutropenia (36% all; 34% related), anemia (31% all; 31% related), dyspnea (31% all; 16% related), pneumonitis (30% all; 26% related), dyspepsia (26% all; 23% related), pyrexia (24% all; 18% related), chest pain (23% all; 4% related), epistaxis (23% all; 11% related), respiratory tract hemorrhage (23% all; 6% related) and peripheral sensory neuropathy (21% all; 19% related). Other study treatment-related AEs that occurred in ≥ 10% of the patients were in decreasing order of frequency stomatitis (14%), pharyngolaryngeal pain (13%), exfoliative rash (13%), abdominal pain (11%), epistaxis (11%), febrile neutropenia (10%), leukopenia (10%), edema peripheral (10%) and weight decrease (10%). In general, AEs seemed to have occurred more frequently in Arm B than in Arm A, especially blood and lymphatic system disorders, constipation, pyrexia, weight decrease, anorexia, radiation skin injury and exfoliative rash, arthralgia, epistaxis, dyspepsia and possibly dysphagia, and respiratory disorders like dyspnea, pneumonitis, respiratory tract hemorrhage and pharyngolaryngeal pain. Diarrhea and alopecia on the other hand, seemed to have occurred more frequently in Arm A.

	Most AEs were of grade 1-2 severity; grade 3 AEs that were considered study treatment-related were reported for 25 patients (61%) in Arm A and for 21 patients (72%) in Arm B; study treatment-related grade 4 AEs were reported for 5 (12%) and 9 (31%) patients in Arm A and Arm B, respectively. The most frequently reported grade 3 AE was oesophagitis (32% in Arm A and 21% in Arm B, all related), followed by neutropenia (12% in Arm A and 28% in Arm B, all but one related) and pneumonitis (12% in Arm A and 10% in Arm B, all but one related). The most frequently reported grade 4 AE was neutropenia (10% in Arm A and 28% in Arm B, all related). The other grade 4 events occurred in one patient each. Grade 3-4 oesophagitis was the safety end-point the sample size of the study was based upon. The proportion of patients with this rate limiting toxicity was tested in each arm against a null hypothesis of at least a 25% toxicity level at a significance level of 0.20. In Arm A, 32% of the patients had a rate limiting toxicity at end of treatment and at end of follow-up, which was statistically different from the null hypothesis according to a one-sided Chi2 test (p=0.1606 [significance level of 0.20]) and thus supports the alternative hypothesis that the incidence of grade 3-4 oesophagitis was larger than 25%. In Arm B, 24% of the patients had a rate limiting toxicity at end of treatment and at end of follow-up; this was not statistically different from the null hypothesis according to a one-sided Chi2 test (p=0.4573). Twenty-one patients in Arm A (51%) and 23 patients in Arm B (79%) experienced one or more SAEs; in 16 (39%) and 18 patients (62%), respectively, one or more of these SAEs were considered study treatment-related. The most frequently reported study treatment-related SAEs were oesophagitis (20%), neutropenia (13%), pneumonitis (11%) and febrile neutropenia (7%). The other SAEs were considered study treatment-related in ≤ 3 patients each (≤ 4%). Most SAEs were of grade 3 severity; grade 3-5 AEs were reported for 18 patients (44%) in Arm A and for 22 patients (76%) in Arm B; study treatment-related grade 3-5 AEs were reported for 34% and 62% of the patients in Arm A and Arm B respectively. The most frequently reported grade 3 SAEs were oesophagitis (17%, all related), pneumonitis (9%, 5/6 related), febrile neutropenia (7%, all related) and neutropenia (7% 4/5 related). There were 32 other grade 3 SAEs which occurred in 1-2 patients each. The most frequently reported grade 4 SAE was neutropenia (9%, all related). There were 5 other grade 4 SAEs which occurred in 1 patient each. The grade 5 events were death (n=1, unrelated), disease progression (n=1, unrelated) and pneumonitis (n=2, both considered study treatment-related). Two patients in Arm B (7%) died within 30 days after last dose. The cause of death was malignant disease in both patients. Efficacy: In the Safety and ITT analyses, 3 patients (4.3%) achieved a CR and 47 patients (67%) a PR, resulting in an ORR of 71%. In the exploratory analysis, 3 patients (5.1%) achieved a CR and 39 patients (66%) a PR, also resulting in an ORR of 71%. In all three analyses, the ORR was 15-20% higher (absolute difference) in Arm B than in Arm A. The differences were, however, not statistically significant. WHO PS was a statistically significant prognostic factor in the ITT, Safety and PP analyses at end of follow-up (p=0.03490, 0.04474 and 0.04352, respectively) but not in the exploratory analysis. For all three analyses, the median PFS time was slightly longer in Arm B than in Arm A, 13 versus 9 months in the Safety and ITT analyses and 13 versus 8 months in the exploratory analysis; the differences were not statistically significant. Statistically significant prognostic factors for PFS were stage of disease (p=0.00382 in the ITT analysis, p=0.00051 in the exploratory analysis and p=0.00011 in the Safety analysis), treatment (p=0.02540 in the exploratory analysis and p=0.00563 in the Safety analysis) and age (p=0.01429 in the Safety analysis. Median OS time in Arm A was 20.4 months in the Safety and ITT analyses and 17.5 months in the exploratory analysis. In Arm B, OS time was 41.1 months in the ITT analysis and was not yet reached in the Safety and exploratory analyses. The 1-year

	survival rate was similar in both treatment arms whatever the population: 61-63% in Arm A and 64-68% in Arm B for the Safety, ITT and exploratory populations. The overall survival rate in the ITT analysis was 36% and 47% for Arm A and Arm B, respectively, and 41% and 53%, in the exploratory analysis. In the Safety analysis, the overall survival rate was 0% in Arm A and 55% in Arm B. Stage of disease was a statistically significant prognostic factor for OS (p=0.00382 in the ITT analysis, p=0.00307 in the exploratory analysis and p=0.00248 in the Safety analysis.
Date of report:	03 December 2009