

<p><i>These results are supplied for informational purposes only.</i></p> <p><i>Prescribing decisions should be made based on the approved package insert in the country of prescription</i></p>			
Sponsor/company:	sanofi-aventis	ClinialTrials.gov Identifier:	NCT00432315
Generic drug name:	Docetaxel	Study Code:	TAX_AT1_203
		Date:	13 September 2010

Title of the study:	<p>MULTICENTER PHASE II STUDY EVALUATING DOCETAXEL AND CDDP AS INDUCTION REGIMEN PRIOR TO SURGERY OR RADIOCHEMOTHERAPY WITH DOCETAXEL, FOLLOWED BY ADJUVANT DOCETAXEL THERAPY IN CHEMONAIVE PATIENTS WITH NSCLC STAGE II, IIIa AND IIIb</p> <p>TAX-AT1-203</p>		
Investigator(s):	<p>Univ. Prof. Dr. Richard Greil, M.D. Co-ordinating Investigator Univ.Klinik für Interne Medizin Innsbruck, Klinische Abteilung für Hämatologie und Onkologie Anichstraße 35 6020 Innsbruck Austria</p>		
Study center(s):	5 active centers in Austria		
Publications (reference):	Not applicable		
Study period:	<p>Date first patient/subject enrolled: 9-May-2001</p> <p>Date last patient/subject completed: 20-Oct-2009</p>		Phase of development: Phase II
Objectives:	<p>Induction chemotherapy prior to surgery or radiotherapy clearly improves response rates and prognosis of NSCLC. One aim of neoadjuvant therapy is the early eradication of distant micro-metastases. By administering cytotoxic drugs there is also the possibility of decreasing the size of tumours, making them more suitable for surgery in certain patients, enhancing local tumour control by radiotherapy in others and decreasing the extent of radiation therapy required for this disease. Docetaxel is one of the most active drugs in advanced NSCLC.</p> <p>In patients in whom the tumour could not be resected radiotherapy supported by concomitant chemotherapy can improve survival. Docetaxel as radio-sensitising agent was already investigated in several studies. Radio-chemotherapy with docetaxel after induction chemotherapy with docetaxel / CDDP should be investigated.</p> <p>Though adjuvant chemotherapy in Non Small Cell Lung Cancer (NSCLC) in general was found to be controversial using older compounds and cisplatin-based regimens, this regimen should be investigated again to find out if improvement of outcome can be achieved with new more effective agents like the taxanes. Therefore, the study design included additional adjuvant chemotherapy after induction therapy and surgery or induction therapy and radio-chemotherapy.</p>		

Methodology:	<p>Open label, multi-centre, non-randomised phase II trials with two parallel treatment groups. Patients received an induction chemotherapy regimen of Docetaxel (Taxotere®) + cisplatin, over 3 weeks repeated over 3 cycles. In case of Complete Response (CR), Partial Response (PR), or Stable Disease (SD) patients were evaluated again for respectability according to national guidelines.</p> <p>Resectable patients underwent surgery, unresectable patients received radio-chemotherapy with Docetaxel (Taxotere®) over 5 to 6 consecutive weeks (total dose of radiation: 50 to 50.4 Gy).</p> <p>After surgery or radio-chemotherapy all patients received additionally 3 cycles adjuvant chemotherapy with Docetaxel (Taxotere®) every 3 weeks.</p> <p>Patients who received the total study treatment entered the follow-up period. The status of the patients was assessed every 3 months until tumour progression and, thereafter, every 6 months until death</p>		
Number of patients/subjects:	Planned: 80 patients	Randomized: 80 patients	Treated: 78 patients
Evaluated:		Safety: 78 patients	
Diagnosis and criteria for inclusion:	<p>Five centres included 80 patients, 68 (85%) of whom were selected for the ITT population and 30 (38%) for the per protocol (PP) population. Thirty-eight patients (48%) were selected for the subgroup "drop out after induction" (drop_ind) and 30 (38%) for the group "all scheduled therapies", which was identical to the PP population. Seventy-eight (98%) patients were included in the safety population.</p> <p>Patients with NSCLC.</p> <ul style="list-style-type: none"> • Histologically or cytologically confirmed NSCLC; histology may include: large cell, squamous cell or adenocarcinoma but no Small Cell Lung Cancer (SCLC). • Resectable or unresectable NSCLC stage II (T1-2 N1, T3 N0) or stage IIIa (T1-2 N2 or T3 N1-2) or stage IIIb (T1-3 N3 or T4 N0.3). • Measurable disease (bidimensionally or unidimensionally according to WHO criteria). • 19-75 years. • Karnofsky Status \geq 70; if age > 70 years \rightarrow PS > 70; life expectancy of more than 3 months. • Adequate haematological function (Hb \geq 10 g/dl, ANC \geq 2.0 x 10⁹/l, platelets \geq 100 x 10⁹/l). • Adequate renal and hepatic functions: total bilirubin \leq 1x upper normal limit (UNL), serum creatinine \leq 1x UNL, in case of limit value the creatinine clearance should be \geq 60 ml/min, ASAT and ALAT \leq 2.5 UNL, alkaline phosphatase \leq 5 UNL. • Complete initial work-up within three weeks prior to first infusion for imaging (chest CT scan, abdominal CT scan (if abdominal, additional abdominal ultrasound), brain CT scan, bone scan if indicated, PET scan if indicated), bronchoscopy and mediastinoscopy (mandatory for patients which are primary resectable according to tumour stage and cardiopulmonary function and for patients with T1-3 N3 M0-status. If CT scan does not show any suspected lymph-nodes, mediastinoscopy is optional.), and within 7 days prior to inclusion for clinical evaluation and biological work-up. • Able to comply with scheduled follow-up and with management of toxicity • Signed informed consent prior to protocol specific procedures. 		

<p>Investigational product:</p> <p>Dose:</p> <p>Administration:</p>	<p>Docetaxel (Taxotere®).</p> <p>Induction therapy Day 1: Docetaxel: 75 mg/m², cisplatin (CDDP) 40 mg/m² Day 2: cisplatin (CDDP) 40 mg/m²</p> <p>Radio-chemotherapy Docetaxel: 20 mg/m² combined with radiotherapy 1.8 to 2 Gy per day, five days per week for 5 to 6 consecutive weeks (total dose: 50 to 50.4 Gy).</p> <p>Adjuvant chemotherapy Docetaxel 75 mg/m²</p> <p>Intravenous administration</p>
<p>Duration of treatment:</p> <p>Induction therapy: 3 cycles over 3 weeks</p> <p>Radio-chemotherapy: Docetaxel 30 min infusion weekly for 5 to 6 weeks combined with radiotherapy 1.8 to 2 Gy per day, five days per week for 5 to 6 consecutive weeks</p> <p>Adjuvant chemotherapy: 1 hour infusion on day 1 and then every 21 days over 3 cycles. (3 cycles over 3 weeks)</p>	<p>Duration of observation:</p> <p>Follow up: The status of the patients was assessed every 3 months until tumour progression and, thereafter, every 6 months until death</p>
<p>Reference therapy:</p>	<p>Not applicable</p>
<p>Criteria for evaluation:</p>	
<p>Efficacy:</p>	<p>The primary efficacy variable was the Overall Response Rate (ORR; complete plus partial response) to docetaxel in combination with cisplatin. The secondary efficacy variables were Resectability after induction therapy, Median Time to Progression (TTP), Overall Survival (OS).</p>
<p>Safety:</p>	<p>All adverse events (AEs), toxicities, and laboratory abnormalities were evaluated for the assessment of safety. All clinical signs and symptoms as well laboratory toxicities were assessed at baseline, after each cycle of induction chemotherapy, at end of surgery, postoperative radiation or radio-chemotherapy, and after each cycle of adjuvant chemotherapy. Patients were asked to fill in a quality of life questionnaire.</p>

<p>Statistical methods:</p>	<p>Statistical evaluation:</p> <p>All patients that fulfilled the inclusion and exclusion criteria were defined as eligible. All patients included in the study (eligible and ineligible patients) receiving at least one dose of study medication and having at least one post baseline safety evaluation were evaluated for safety / tolerability of study medication. Efficacy analysis for the primary efficacy variable – Intent-to-treat (ITT) population: All patients included in the study receiving at least 2 cycles of induction chemotherapy at baseline and at least one post baseline evaluation measurement of the primary efficacy variable. Per-protocol (PP) population: All eligible patients available for ITT analysis who completed the planned duration of treatment with induction chemotherapy, who were compliant to the treatment regimen, who had a valid final efficacy evaluation, and who did not violate the protocol in any way liable to influence efficacy outcome were valid for PP evaluation of the primary efficacy variable.</p> <p>Demographic and background information was summarised and displayed using descriptive statistical techniques. For categorical variables frequency tables were presented. For continuous variables descriptive statistics such as mean, median, standard deviation, minimum, maximum etc were tabulated.</p> <p>Safety assessments were performed at baseline, after each cycle of induction chemotherapy, at end of surgery or radio-chemotherapy, and after each cycle of adjuvant chemotherapy. Safety was evaluated in terms of physical examination findings, vital signs, clinical laboratory analysis, and AE findings.</p> <p>Sample size estimation: Assuming a 10% drop-out rate 80 patients should be enrolled into this study.</p>
<p>Summary:</p>	
<p>Efficacy results:</p>	<p>Demographic data and medical history were as expected for the present patient population.</p> <p>After induction therapy the ORR was 66.1% for the ITT population and 78.6% for the PP population. At the end of treatment the ORR was 63.9%. Nearly two thirds (66,1%) of the patients in the ITT population and more than three quarters (78,6%) in the PP population show partial response or overall response after induction therapy. Prior adjuvant chemotherapy 48.5% of the patients showed complete response and 21.2% showed partial response. At the end of therapy 52.8% had complete response and 11.1% had partial response, however, at this time-period 33% of the patients suffered from progressive disease.</p> <p>At baseline there were 21 patients (30.9%) with resectable tumour and 47 patients (69.1%) with unresectable tumours. After induction therapy the number of resectable tumours increased to 35 patients and 32 patients had unresectable tumours</p> <p>Median time to progression was 11.2 months in the ITT population. The overall survival time was 21 months in the ITT population.</p> <p>Docetaxel induction therapy resulted in a promising ORR and an increase of secondary resectable tumours.</p>

<p>Safety results:</p>	<p>In this clinical study safety was assessed by evaluating AEs, toxicities, laboratory abnormalities, physical examination findings, and vital signs.</p> <p>Treatment-emergent AEs, signs and symptoms were experienced by 42 patients (61.8%) during cycle 1 of the induction therapy, 43 patients (63.2%) during cycle 2, 30 patients (45.5%) during cycle 3 and 11 patients (16.4%) at the end of induction therapy. During surgery 22 patients (64.7%) and during radio-chemotherapy 19 patients (79.2%) experienced signs, symptoms, and AEs. During cycle 1 of the adjuvant chemotherapy 15 patients (48.4%) experienced signs, symptoms, and AEs, during cycle 2 8 patients (27.6%), and during 3rd cycle 11 patients experiencing AEs (47.8%) were documented.</p> <p>The severity of most AEs – 380 AEs (53.6%) was rated as '1' according to WHO Grades and 222 AEs (31.3%) were rated as '2' and 83 AEs (11.7%) were rated as '3'. Most AEs, 572 (80.7%) were resolved, 137 AEs (19.3%) were not resolved at the end of the study. Most AEs were probable or possible related to the study medication. 664 AEs (93.4%) did not lead to any action concerning study medication.</p> <p>Fifty-seven AEs (8.1%) were considered as Serious Adverse Events (SAEs). For 44 (65%) patients of the ITT population a death report form existed. Cause of death was mainly 'malignant disease' – 40 patients (93.0%).</p> <p>At baseline 7 patients (10.3%) showed abnormal haematology data and 3 patients (4.4%) showed abnormal biochemistry data. The number of patients with pathologic haematology and biochemistry laboratory data increased slightly during the 3 cycles of induction therapy. During surgery / radio-chemotherapy the number of patients with pathologic haematology and biochemistry laboratory data decreased and showed a slight increase during adjuvant chemotherapy. The number of patients with pathologic data remained stable until end of treatment (9 patients (23.7%) for haematology and 6 patients (15.8%) for biochemistry).</p> <p>Vital signs, physical examinations, pulmonary functions, ECG findings were within ranges expected in patients eligible for this study.</p>
<p>Date of report:</p>	<p>02-Sep-2010</p>