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	**clinicaltrials.gov Identifier:**	NCT00772681
		Study Code:	XRP6976F_6007
Generic drug name:	docetaxel	**Date:**	15 May 2009

Title of the study:	The evaluation of the efficacy of chemoradiotherapy following neo-adjuvant treatment with docetaxel-cisplatin, in undifferentiated and nonkeratinized squamous cell carcinoma of the nasopharynx - Phase IV Clinical Trial		
Co-Investigator:	Omer Uzel, Prof. MD Istanbul University, Cerrahpasa Faculty of Medicine Department of Radiation Oncology Istanbul		
Study center(s):	13 centers in Turkey were planned to be enrolled in the study, however two centers could not enroll any patients, so the number of active centers was 11.		
Publications (reference):	NA		
Study period: Date first patient enrolled: 08-10-2004 Date last patient completed: 24-03-2008		**Phase of development:** IV	
Objectives:	<u>Primary objective:</u> To evaluate the efficacy of chemoradiotherapy following neo-adjuvant docetaxel-cisplatin chemotherapy, in undifferentiated and non-keratinized squamous cell carcinoma of the nasopharynx. <u>Secondary objectives:</u> To evaluate the safety of chemoradiotherapy following neo-adjuvant docetaxel-cisplatin chemotherapy, in undifferentiated and non-keratinized squamous cell carcinoma of the nasopharynx. To evaluate the loco-regional control, the disease-free survival, the distant metastasis-free survival and the overall survival of the study population.		
Methodology:	A prospective, national, open label, multi-center, non-comparative, phase IV clinical study.		
Number of patients:	Planned: 49	Randomized: NA	Enrolled: 57
Evaluated:	51 patients.	Safety: 57 patients.	Treated: 54

Diagnosis and criteria for inclusion:	Patients aged over 18 years with a histologically confirmed diagnosis of WHO II-III squamous cell carcinoma of the nasopharynx, in stages TN2-3M0 or T2b-T4N1M0 tumor, with an ECOG performance score of 0-1,with an acceptable hematological profile and adequate renal and hepatic function, were enrolled in the study.
Investigational product: Dose: Administration:	Docetaxel and cisplatin 75mg/m² /day docetaxel and cisplatin Docetaxel 75 mg/m², in 250 ml 5% dextrose was infused over 1 hour (slow infusion for the first 5 minutes) in the 1st day of chemotherapy. Cisplatin 75 mg/m² was infused immediately after docetaxel infusion in 500 ml isotonic solution over 1 hour, in the 1st day of chemotherapy. Pre-medication: Dexamethasone 2x8 mg daily or its equivalent oral methylprednisone administered for total 3 days initiated 1 day before chemotherapy. In addition, adequate hydration (according to the clinical standard of each centre, preferably 1.5 liter prior to cisplatin, 0.5 liter with cisplatin and 1 liter after cisplatin infusion) and appropriate antiemetic treatment were given for cisplatin therapy.
Duration of treatment: 17weeks	**Duration of observation:** 43.1 months
Reference therapy: Dose: Administration: **Criteria for evaluation:**	Cisplatin + Radiotherapy (concurrent chemoradiotherapy)+ Cisplatin: 75 mg/m² Radiotherapy: 70 Gy **Concurrent Chemotherapy** Radiotherapy and concurrent chemotherapy was initiated 3 to 4 weeks after the completion of neo-adjuvant chemotherapy. Cisplatin 75 mg/m² was administered on days 1, 22 and 43, 2 hours before the radiotherapy. In addition, adequate hydration (according to the clinical standard of each centre, preferably 1.5 liters prior to cisplatin, 0.5 liters with cisplatin and 1 liter after cisplatin infusion) and appropriate antiemetic treatment was administered. **Radiotherapy** With the conventional dose of 2 Gy per fraction, 70 Gy was administered to nasopharynx and involved cervical lymph nodes and 50 Gy was administered to bilateral cervical and supraclavicular lymph nodes for total 7 weeks and 5 fractions per week.
Efficacy:	Primary: Complete response rate after neo-adjuvant chemotherapy. Secondary: • Loco-regional control rate: Defined as the proportion of patients with loco-regional control. • Disease-free survival: Defined as the time between the date of complete response and recurrence of loco-regional disease. • Distant metastasis-free survival: Defined as the time between the date of enrollment and development of distant metastasis. • Overall survival: Defined as the time between the date of enrollment and the date of death or the last contact.

Safety:	Before each chemotherapy cycle, the patients were questioned on toxicities developed since the previous cycle. Clinical and laboratory toxicities were evaluated according to NCI-CTC criteria. The adverse events irrelevant with these criteria were evaluated as mild, moderate and severe. Serious adverse events and deaths were reported according to relevant regulations. Toxicity related to radiotherapy was assessed by RTOG-EORTC criteria.
Statistical methods:	Descriptive analysis was performed for the efficacy and safety evaluations. Categorical variables were given as numbers and percentages; numerical variables were given as mean, standard deviation, minimum, maximum and median. Repeated measures ANOVA test and Cochran Q test was used in the evaluation of the changes in follow-up. Kaplan-Meier Survival analysis was used to calculate the survival rates. The factors effecting survival was evaluated using Cox regression analysis. First interim analysis was performed on Jan. 19, 2006
Summary:	Totally, 57 patients with undifferentiated and nonkeratinized squamous cell carcinoma of the nasopharynx were enrolled in the study. Among the patients, 70.1% was male (n=40) and 29.9% was female (n=17) and mean age was 45.0±11.7. All patients were planned to receive a total of 3 cycles of neo-adjuvant chemotherapy, administered in every 3 week intervals. Radiotherapy and concurrent chemotherapy was initiated 3 to 4 weeks after the completion of neo-adjuvant chemotherapy. The dose of radiotherapy was 70Gy for the involved field (nasopharyngeal and nodal). Totally 6 patients could not be evaluated, as 4 of them withdrew their consents and TNM staging of the remaining 2 patients were T2AN0M0 and T3N0M0. Minimum follow up time was 2 years and the median follow up duration was 43.1 months (27.6-49.9 month).
Efficacy/ results:	Primary variable for evaluation of efficacy was the rate of complete response after neo-adjuvant chemotherapy. In the analysis performed on the entire study population; Complete response rate was 14% (n=8) and partial response rate was 56% (n=32). Stable disease was observed in 22.8% of patients (n=13). The rates of patients who showed complete and partial response after chemoradiotherapy were 47.4% (n=27) and 33.3% (n=19), respectively. In the analysis performed among the evaluable patients; The response rates after neoadjuvant treatment were evaluated among 51 patients. Among the evaluable 51 patients, complete response rate was 15.7% (n=8) and partial response rate was 58.8% (n=30). Stable disease was observed in 21.6% (n=11). The rates of complete response and partial response after chemoradiotherapy were 49.0% (n=25) and 37.3% (n=19), respectively. Secondary variables for the evaluation of efficacy were the rate of overall survival, disease free survival, distant metastasis free survival and loco-regional control. Three-year overall survival rate was 84.1% among all patients participated in the study. Overall survival rate was assessed according to patient baseline characteristics (gender, age), TNM/AJCC stage and decrease in chemotherapy dosage. Overall survival rate was significantly longer in patients with TNM/AJCC stages I-IIB-III, than the patients in stages IVA-IVB (p=0.026). However, there was no significant difference in overall survival according to baseline characteristics of patients (gender, age) and decrease in chemotherapy dosages. Three-year disease free survival rate was 73.2%. Disease free survival was significantly longer in patients with stage I-IIB-III, than the patients in stages IVA-IVB (p=0.044).

	Totally, 88% of the patients survived without distant metastasis at three years. Loco-regional control rate was 83%. Regarding evaluable patients' analyses, three-year overall survival rate was 84.2%. Overall survival was assessed according to baseline characteristics of patients (gender, age), TNM/AJCC stage and decrease in chemotherapy dosages. Overall survival was significantly longer in patients with TNM/AJCC stages I-IIB-III, than the patients in stages IVA-IVB (p=0.018). However, there was no significant difference in overall survival according to gender, age and decrease in chemotherapy dosages. Three-year disease free survival rate was 72.8%. Disease free survival rate was significantly longer in patients with TNM/AJCC stages I-IIB-III, than the patients in stages IVA-IVB (p=0.033). There was no significant difference in disease free survival according to gender, age and decrease in chemotherapy dosages. Totally, 89.5% of the patients survived without distant metastasis at three years. Loco-regional control rate was 82.3%.
Safety results:	Toxicities related to chemotherapy and radiotherapy, according to systems and NCI-CTC and RTOG/EORTC Acute and Late Radiation Morbidity Scoring, were also noted. In the toxicity evaluations according to NCI-CTC in neo-adjuvant chemotherapy, a total of 19 grade 3 and 2 grade 4 toxicities were observed. Grade 3 toxicities according to systems were, gastrointestinal (15.8%), hematological (14%), allergy and skin related (1.8%) and cardiovascular (1.8%) among entire study population. Grade 4 hematological toxicities were observed in 3.5% of the patients. In the analysis of hematological toxicities; grade 3 toxicities were neutropenia in 8.8% of patients, anemia in 3.5%, leukopenia in 1.8%, lymphopenia in 1.8% and thrombocytopenia in 1.8%. Grade 4 hematological toxicities were neutropenia in 1.8% and lymphopenia in 1.8% of the patients. In acute radiation morbidity evaluation according to RTOG/EORTC; a total of 58 grade 3 and, 4 grade 4 toxicities were observed. Grade 3 toxicites due to radiotherapy were observed in mucous membrane (36.8%), pharyngeal-esophageal (21.1%), hematological (17.5), larynx (8.8%), skin (7%), gastrointestinal (7%) and eye-ear (3.5%) of the patients. The observed Grade 4 toxicities were hematological (7.0%). In the late radiation morbidity evaluation 1.8% of the patients had grade 3 toxicity in the brain. The most common adverse events were nausea-vomiting, dry mouth, anemia, dysphagia, mucositis and neutropenia. Overall, 37 serious adverse events were reported. There were 3 early deaths during the study period and only one of them, febrile neutropenia in one of the patients, was considered to be related to chemotherapy. In the final evaluation, among the patients with adverse events, 52.7% have recovered, 17.2% have been recovering, 19.5% have not recovered, 0.2% has recovered with sequela and 1.8% has resulted in death. The results of 8.6% of the adverse events were not known.
Date of report:	26-Mar-2009