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Sponsor/Company:	sanofi-aventis	**Study identifier:**	NCT00401323
Drug substance(s):	docetaxel	**Study Code:**	EFC6051 (XRP6976G-322)
		Date:	19 October 2006

Title of the study:	A randomized phase II-III multicenter trial of docetaxel (Taxotere®) plus cisplatin and docetaxel plus 5-fluorouracil (5-FU) versus cisplatin plus 5-fluorouracil to improve time to progression and overall survival in the first line treatment of patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck
Investigator(s):	Coordinating investigator (Europe): JP Armand MD (Villejuif CEDEX, France) Coordinating investigator (US): S Urba MD (Michigan, USA)
Study center(s):	Multinational /18 centers
Publications:	No
Study period: Date first patient/subject enrolled: 16 January 1998 Date last patient/subject completed: 30 June 2003	**Phase of development:** Phase II-III
Objectives:	Primary: To compare time to progression (TTP) after treatment with Taxotere plus cisplatin (TP treatment group) versus cisplatin plus 5-FU (PF treatment group). Secondary: To compare overall survival (OS), the main secondary endpoint, after treatment with Taxotere plus cisplatin (TP treatment group) versus cisplatin plus 5-FU (PF treatment group). The following endpoints were also compared between the 2 treatment groups: overall response rate (ORR), duration of response, time to treatment failure (TTF), and toxicity.
Methodology:	This was a multicenter, non-blinded, randomized, stratified phase II-III study. The phase II part of the study was planned to estimate overall response rate and to evaluate toxicity in 3 treatment groups—Taxotere plus cisplatin (TP), Taxotere plus 5-FU (TF), and cisplatin plus 5-FU (PF)—administered as first-line treatment for patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck (SCCHN). Additionally, the phase II part of the study was to determine which regimen(s) to continue in the phase III part of the study. The phase III part of the study compared 2 chemotherapy regimens as first-line treatment for patients with recurrent and/or metastatic SCCHN. Patients were randomized (1:1) to receive either TP or PF. Patients were stratified at inclusion according to country and extent of disease. Patients were to receive 6 cycles of chemotherapy at 3-week intervals unless progression of disease (PD) or unacceptable toxicity occurred, or the patient refused treatment. Further treatment was indicated for patients with objective response or stable disease. All patients were to be followed until death.
Number of patients/subjects evaluated:	568 patients randomized, 286 in the TP treatment group and 282 in the PF treatment group.

Diagnosis and criteria for inclusion:	Patients, 18 to 75 years of age, with histologically or cytologically documented SCCHN (eligible primary sites: oral cavity, oropharynx, hypopharyx, or larynx) presenting with locally recurrent and/or metastatic disease, with at least 1 unidimensionally or bidimensionally measurable lesion.
Investigational product: Dose: Administration:	TP treatment group: Taxotere 75 mg/m^2, one-hour IV infusion on Day 1 of each 3-week cycle followed by cisplatin 75 mg/m^2 administered as a 30-minute to 3-hour infusion on Day 1;
Reference therapy: Dose: Administration:	PF treatment group: Cisplatin 100 mg/m^2, 30-minute to 3-hour infusion on Day 1 of each 3-week cycle followed by the continuous infusion of 5-FU 1000 mg/m^2/day from Day 1 to Day 5.
Criteria for evaluation:	
Efficacy:	Primary efficacy data: TTP Secondary efficacy data: OS, ORR (complete response CR + partial response PR), duration of response, and TTF All lesions (measurable, evaluable, non-evaluable) were described and assessed prestudy; after cycles 2, 4, and 6; at follow-up; and at any time if disease progression was suspected.
Safety:	The investigator observed patients for adverse events (local or systemic) and instructed patients to report any events that occurred during the study. Adverse events (AEs) were recorded according to the National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) expanded toxicity scale. All adverse events, regardless of severity, were to be followed-up by the investigator until satisfactory resolution.
Pharmacokinetics:	Pharmacokinetic parameters were estimated by Bayesian estimation using concentration-time data for each patient and a previously defined population model as prior information. A three-compartment structural model with first-order elimination was used.
Statistical methods:	Time-to-event variables were described using Kaplan-Meier curves and life tables. A non-parametric confidence interval was calculated for the median survival time. Time-to-event intervals between groups were compared with the Wilcoxon linear rank and log-rank tests. Chi-square tests were used to compare groups on categorical variables unless the expected cell frequency was <5, in which case Fisher's exact test was used. Exact confidence intervals were calculated for binary event rates. The primary analysis was a comparison of the TTP in the intent-to-treat (ITT) population using an unadjusted Wilcoxon linear rank test. Kaplan-Meier curves and life tables were calculated in the ITT population.

Statistical methods: (cont'd)	OS was compared in the ITT population with unadjusted Wilcoxon linear or logrank tests. Kaplan-Meier curves and life tables were calculated in the ITT population. ORR and CR rates were compared in the ITT population with an unadjusted Chi-square (X^2) test. Kaplan-Meier curves and life tables were calculated for duration of response (CR + PR) and TTF for the ITT population. In all safety analyses, patients were analyzed in the treatment group they received. All treatment-emergent adverse events (TEAEs) were tabulated according to the NCIC CTG expanded toxicity scale. Occurrence of worst-grade TEAEs are presented, regardless of relationship and possibly related to study treatment for patients evaluable for safety. Special attention was paid to fluid retention, febrile neutropenia, neutropenic infection, neurotoxicity, and renal toxicity. Toxic deaths were also compared using Fisher's exact test.
Summary:	An Independent Data Monitoring Committee (IDMC) reviewed data from 45 patients per arm (response rates and safety profiles) in the three-arm phase II part of the study. The IDMC recommended that the Taxotere 85 mg/ m^2 + 5-FU 750 mg/ m^2/day for 5 days (TF) treatment group be discontinued and that the study continue to phase III with the remaining 2 treatment groups (TP and PF). There were 568 patients randomized, 286 in the TP treatment group and 282 in the PF treatment group. Patients were predominantly male (87.7%) and Caucasion (91.5%); median age was 56, and most patients had performance status scores of 0 (32.2%) or 1 (66.9%). The most common sites of disease were oral cavity (31.2%), oropharynx (29.4%), larynx (24.8%), and hypopharynx (14.3%). More than 98% of randomized patients in both treatment groups received study treatment. A total of 62 patients (21.7%) in the TP treatment group and 39 patients (13.8%) in the PF treatment group completed treatment. The most common reasons for treatment discontinuation were progressive disease (TP: 46.2%; PF: 32.6%), adverse events (TP: 10.1%; PF: 21.6%), death (TP: 9.4%; PF: 13.1%), and consent withdrawn (TP: 5.9%; PF: 10.3%). Of patients who discontinued for adverse events (TP: 29, 10.1%; PF: 61, 21.6%), 11 patients (3.8%) in the TP treatment group and 41 (14.5%) in the PF treatment group discontinued for toxicity (related adverse events). Median duration of study treatment was 13.1 weeks in the TP treatment group and 11.0 weeks in the PF treatment group. Relative dose intensity was high in both treatment groups. In the TP treatment group, relative dose intensity for both Taxotere and cisplatin was 98%; in the PF treatment group, relative dose intensity was 90% for cisplatin and 87% for 5-FU. The median number of TP cycles received was 4, and the median number of PF cycles was 3. A total of 15.0% of TP cycles and 26.6% of PF cycles were delivered at a reduced dose. Treatment groups were similar for demographic characteristics, signs and symptoms, hematological characteristics, tumor characteristics, and prior anticancer therapies at baseline.

Summary:
(cont'd)

Efficacy results:

The primary endpoint (TTP) was not significantly different between the two treatment groups, with a hazard ratio of 1.1 (95% CI: 0.89-1.30; Wilcoxon test, p=0.25). Median TTP was 2.8 months (95% CI: 2.6 –3.7 months) in the TP treatment group and 3.2 months (95% CI: 2.9-3.9 months) in the PF treatment group. The main secondary endpoint, OS, was not statistically different in the TP treatment group compared to the PF treatment group (HR: 1.0, 95% CI: 0.85-1.21; Wilcoxon test, p=0.36). Median OS was 8.0 months (95% CI: 7.1–9.4 months) in the TP treatment group and 7.4 months (95% CI: 6.3-8.4 months) in the PF treatment group. Overall response rates (CR + PR) were similar across treatment groups: 21.0% (95% CI: 16.4%-26.2%) in the TP treatment group and 19.5% (95% CI: 15.0%-24.6%) in the PF treatment group (p=0.66).
Overall the study did not demonstrate any significant differences in efficacy parameters (TTP, OS and RR) between TP and PF treatment arms.

Safety results:

The percentages of patients who experienced at least 1 treatment-emergent adverse event (TEAE) possibly or probably related to study treatment were similar for the treatment groups (TP: 91.5%; PF: 91.7%).
TEAEs considered to be related to study treatment were similar for most NCIC CTG categories with only the system "skin" having a >10% difference in any grade TEAE between the 2 treatment groups (TP: 63.1%; PF: 35.4%). The TEAE category "GI" (gastrointestinal) had grade 3/4 TEAEs with a frequency of >10% in both treatment groups (TP: 18.4%; PF: 33.6%). There were 4 categories with grade 3/4 TEAEs with >3% difference between the 2 treatment groups: gastrointestinal (TP: 18.4% PF: 33.6%), skin (TP: 6.7%; PF: 1.8%), neurologic (TP: 4.6%; PF: 7.9%), and cardiovascular (TP: 2.8% PF: 6.5%).
The 2 treatment groups were similar for most NCIC CTG terms for serious TEAEs during chemotherapy by patient (all grades, regardless of relationship to study medication, TP: 41.8%; PF: 56.3%). The most frequent (>5% in either group) terms were: infection (TP: 14.9%; PF: 15.5%), fever in absence of infection (TP: 5.3%; PF: 6.9%), vomiting (TP: 3.9%; PF: 5.4%), lethargy (TP: 3.2%; PF: 6.5%), hemoglobin (TP: 2.1%; PF: 5.1%), and stomatitis (TP: 2.1%; PF: 9.4%).
Differences ≥3% between groups were noted for lethargy (TP: 3.2%; PF: 6.5%), hemoglobin (TP: 2.1%; PF: 5.1%), stomatitis (TP: 2.1%; PF: 9.4%), granulocytes (TP: 1.4%; PF: 4.7%), hypokalemia (TP: 1.1%; PF: 4.3%), and white blood count (TP: 0.4%; PF: 4.0%). The percentages for all of these were higher for the PF treatment group than the TP treatment group.
Overall, 497 (88.9%) treated patients died during the study: 257 (91.1%) TP-treated patients and 240 (86.6%) PF-treated patients. Of these, 32 (11.3%) TP-treated patients and 40 (14.4%) PF-treated patients died within 60 days of first administration of study treatment. There were 32 deaths (11.3%) in the TP-treatment group, and 47 deaths (17.0%) in the PF-treatment group within 30 days of last administration of study treatment. The percentages of deaths occurring within 30 days of last study medication and due to toxicity were 15.6% (5/32) in the TP treatment group and 29.8% (14/47) in the PF treatment group. The majority of deaths (TP: 79.8%; PF: 69.7%) occurred more than 30 days after last study treatment and were due to disease progression (TP: 74.1%; PF: 64.6%).

Summary: **(cont'd)**	Discontinuation of study treatment due to AEs, regardless of relationship to study treatment, occurred in 10.1% of TP-treated patients and 21.6% of PF-treated patients. The most frequent NCIC CTG terms associated with treatment discontinuations regardless of relationship were infection (TP: 3.8%; PF: 3.2%), GI (TP: 1.0%; PF: 6.7%), flu-like symptoms (TP: 1.4%; PF: 3.2%), and blood bone marrow (TP: 1.0%; PF: 3.9%). For the TP treatment group, 14 of 29 (48.3%) of AEs leading to discontinuation of study treatment were considered related to the study treatment; for the PF treatment group, 44 of 61 (72.1%). Analyzed by patient, anemia of any grade occurred frequently, and the incidence was comparable for both treatment groups (TP: 94.9%; PF: 93.2%). Grade 3/4 anemia occurred in 15.1% of patients in the TP treatment group compared to 20.8% in the PF treatment group. Leukopenia of any grade occurred in the vast majority of patients in both the TP treatment group (89.3% patients) and the PF treatment group (84.9% patients), regardless of the use of prophylactic granulocyte colony-stimulating factor (G-CSF). Grade 3/4 leukopenia was more frequent in the TP treatment group (59.9%) than in the PF treatment group (38.1%), regardless of the use of G-CSF, with the majority of these being grade 3 leukopenia. The percentage of patients with any grade thrombocytopenia was higher in the PF treatment group (42.6%) than in the TP treatment group (16.6%). Grade 3/4 thrombocytopenia was also more frequent in the PF treatment group (15.1%) than in the TP treatment group (4.8%). Neutropenia of any grade occurred in the vast majority of patients in both the TP treatment group (85.6% patients) and the PF treatment group (80.1% patients), regardless of the use of G-CSF. Grade 3/4 neutropenia was more frequent in the TP treatment group (70.1%) than in the PF treatment group (51.7%), regardless of the use of G-CSF. The majority of these were grade 4, particularly in the TP treatment group (TP: 127 of 185; PF: 75 of 135). The percentage of patients with neutropenic infection, any relationship, and regardless of prophylactic G-CSF (TP: 11.7%; PF: 11.5%) was similar in both treatment groups, but for febrile neutropenia (TP: 2.7%; PF: 5.8%), the percentage was higher for the PF treatment group. There were 4 deaths in each group from neutropenic infection. During the study, the percentages of patients with 1 or more renal toxicities were similar (TP: 33.3%; PF: 32.5%). There were no renal failures or renal insufficiency TEAEs and there were no grade 3/4 renal TEAEs. Overall, TP demonstrated a safety profile that was manageable and generally tolerable, and consistent with the expected safety profile of Taxotere and cisplatin.
Pharmacokinetic results:	The median docetaxel clearance estimated for 9 patients treated at the dose of 75 mg/m², for a total of 13 cycles, was 27.8 L/h/m^2.
Date of full report:	27-Sep-2006