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Sponsor/company:	sanofi-aventis	ClinialTrials.gov Identifier:	NCT00357149
		Study Code:	XRP6976F_2501
Generic drug name:	DOCETAXEL	Date:	06 October 2008

Title of the study:	Randomised phase II trial of neoadjuvant docetaxel (RP56976, Taxotere®) plus cisplatin and 5-fluorouracil (TPF) followed by concomitant chemoradiotherapy and chemoradiotherapy alone in patients with locally advanced squamous cell carcinoma of the head and neck (SCCHN).
Investigator(s):	Dr. Adriano Paccagnella Dipartimento di Oncologia Medica Ospedale Civile San Giovanni e Paolo Campo San Giovanni e Paolo Venezia ITALY
Study center(s):	18 active centers, Italy
Publications (reference):	Abstract and oral presentations were presented at the 44th Annual Meeting of the American Society of Clinical Oncology, 2008. A Poster was presented at the 33rd Congress of the European Society for Medical Oncology, 2008

Study period: Date first patient enrolled: 20-Jan-2003 Date last patient completed: 21-Feb-2008	Phase of development: Phase II

Objectives:	Primary: to evaluate the rate of clinical complete response after treatment with TPF followed by chemoradiotherapy and after chemoradiotherapy alone in patients with locally advanced SCCHN. Secondary: to evaluate the duration of response, the progression free survival, the rate of organ preservation, the overall survival and the 2 years survival, the time to treatment failure, the tolerability, and quality of life of each arm.
Methodology:	This is an open label multicenter phase II randomised study. The primary objective of the trial is to rank the two treatment arms (Arm A concomitant chemoradiotherapy and Arm B induction chemotherapy (TPF) followed by chemoradiotherapy). The main endpoint has been the response rate (complete response) in patients evaluable for response.

Number of patients:	Planned: 96	Randomized: 101	Treated: 100
Evaluated:	Efficacy: 93 Pts (arm A:47 Pts, arm B:46 Pts) Overall Survival: ITT population	Safety: 93 (arm A:49 Pts, arm B:44 Pts)	
Diagnosis and criteria for inclusion:	Histologically or cytologically proven SCCHN; primary tumor sites eligible: oral cavity, oropharynx, hypopharynx; stage III or IV disease without evidence of distant metastases; at least one measurable lesion; no previous chemotherapy, radiotherapy or immunotherapy for any reason and no previous surgery for SCCHN (other than biopsy). KPS $\geq$ 70; adequate bone marrow, hepatic and renal functions; patients aged ≥18 years.		
Investigational product: Dose: Administration:	Docetaxel (Docetaxel, Cisplatin, 5-FU followed by concomitant chemoradiotherapy) 75 mg/m² Arm B: Docetaxel 75 mg/m², 1 hour IV infusion on day 1, followed by cisplatin 80 mg/m² (30-minute IV infusion, day 1) and continuous IV infusion of 5-FU 800 mg/m²/day from day 1 to day 4 starting after the end of cisplatin infusion. The cycle was repeated every 3 weeks up to a total of 3 cycles. After 3-6 weeks from the end of neoadjuvant chemotherapy, patients will receive with the same modality of arm A (reference arm).		
Duration of treatment: Arm A: Chemoradiotherapy 7 weeks Arm B: Induction and chemoradiotherapy 15-16 weeks		Duration of observation: Until death, at least 8 weeks for primary endpoint.	

Reference therapy:	Concomitant Chemoradiotherapy
Dose:	**Chemotherapy** Cisplatin: 20 mg/m^2/day 5-FU: 800 mg/m^2/day **Radiotherapy** Tumor: 70 Gray (Gy) using once daily fractionation (2 Gy/day, 5 days per week for 7 weeks). Lymph-nodes: at least 50 Gy using once daily fractionation (2 Gy/day, 5 days per week for 5 weeks) in patients N0 and/or candidate to neck dissection; at least 60 Gy in patients N+ not candidate to surgery. Prophylactic neck dissection was planned for stage N2–N3 patients who achieved a pathologically confirmed CR at the primary site and a radiologic CR at the neck.
Administration:	Arm A: Cisplatin was given as a 30 minutes IV infusion from day 1 to day 4 and 5-FU as continuous IV infusion for 4 days starting immediately after the end of cisplatin infusion on day 1. Both drugs were administered during week 1 and 6 of irradiation, starting from day 1 of weekly radiotherapy.
Criteria for evaluation:	
Efficacy:	Clinical examinations with appropriate CT scans, MRI, physical examination were performed as follows: Arm A: 6-8 weeks after completion of chemoradiotherapy. Arm B: after completion of neoadiuvant chemotherapy (day 21 to 28 of cycle 3) and 6-8 weeks after completion of chemoradiotherapy. Pathological complete response at the primary site was evaluated by performing a biopsy of the primary tumor in patients willing and able to allow pathological confirmation of response. Biopsies were performed after 8-12 weeks from completion of chemoradiotherapy for both arms. Responses were assessed by CT scans or MRI according to RECIST criteria and reviewed by an internal committee (consisting of a radiologist, a radiotherapist, and a medical oncologist) who were blinded to treatment assignment. Salvage surgery was considered for recurrence at the primary site and/or residual disease after CT/RT at one or both sites.

Safety:	Toxicity during neoadjuvant TPF and CT/RT was assessed using National Cancer Institute of Canada–Clinical Trials Group (NCIC–CTG) expanded common toxicity criteria. Late reactions to radiotherapy (for both of arms) were graded by the Radiation Therapy Oncology Group (RTOG)/ European Organisation for Research and Treatment of Cancer (EORTC) late radiation morbidity criteria.
Pharmacokinetics:	Not Applicable
Pharmacokinetic sampling times and bioanalytical methods:	Not Applicable
Statistical methods:	The primary objective of the trial was to rank the two treatment arms The main endpoint has been the response rate (complete response) in patients evaluable for response. Assuming a CR rate of 30% in the control arm and 45% in the experimental arm, with 90% power and a 0.05 type–I error, two-sided, 43 evaluable patients per arm were required. Estimating that 10% of patients would be non-evaluable, a total of 96 patients was planned (48 patients per arm). Selection was based on the method of statistical ranking and selection theory described by Simon (1985). The population evaluable for response consisted of all eligible patients receiving treatment assigned at randomization, with all baseline lesions assessed at least once by the same method used at baseline. Analyses of PFS and OS were performed on the intent-to-treat population. A Chi-square test was used to compare variables; if the frequency was <5, Fisher's exact test was used. Statistical testing was two-sided at a .05 significance level. Time-to-event data were described using Kaplan-Meier curves and life tables. Confidence intervals (95% CI) for median times were calculated using nonparametric methods. All patients receiving $\geq$ 2 cycles were considered evaluable for response, patients developing progressive disease after receiving < 2 cycles were considered as early progression. Duration of response was calculated in each arm as interval between the date of first response to the date of documented PD. Progression free survival was calculated from the date of randomisation until progression of disease or local relapse. Time to treatment failure was calculated from the date of treatment start to the date of diagnosis of progression, withdrawal from study treatment for any reason, administration of other antitumor treatment, or death for any cause, whichever is the earliest event. Survival was measured from the randomisation date to the date of death.

Summary:	Squamous cell carcinoma of the head and neck (SCCHN) represents 5% of newly diagnosed cancers in adult patients and more than 500.000 new cases are predicted annually worldwide. More than 50% of patients with SCCHN present with locoregionally advanced disease and surgery is not feasible. Several phase III studies and data from the Meta-Analysis of Chemotherapy in Head and Neck Cancer (MACH-NC) have shown that concomitant chemoradiotherapy (CT/RT) is the optimal treatment for patients with unresectable disease. Although induction chemotherapy is frequently used in clinical practice and has a proven role in organ preservation and in reducing the incidence of distant metastases, its ability to prolong survival has not yet been demonstrated. Results of three phase III studies comparing two different induction chemotherapy regimens (cisplatin/fluorouracil [PF] with or without a taxane) followed by either radiotherapy alone or radiotherapy plus chemotherapy, have recently reported that adding a taxane (docetaxel or paclitaxel) to PF improves response rate, time to progression (TTP) and overall survival (OS) compared with PF alone. A previous phase I–II study has been performed in order to evaluate the feasibility of 3 cycles of induction docetaxel plus PF (TPF) followed by PF combination concomitant to RT). During the study, the number of planned chemotherapy cycles during CT/RT was reduced from 3 to 2 because of toxicity that required interruption of planned radiotherapy. Based on these results, has been designed the current phase II randomized trial to compare the radiologic complete response (CR) at the end of treatment in patients receiving either CT/RT alone, or 3 cycles of neoadjuvant TPF followed by the same CT/RT regimen. Secondary objective was to determine the feasibility, based on acceptable toxicity and efficacy of neoadjuvant TPF.

Efficacy results:	After induction TPF, in the 46 evaluable patients the radiologic ORR was 69.5% (95%CI: 49.2%–77.1%) and the CR was 6.5% (3 patients). Five patients (10.8%) progressed during TPF and were treated according to the corresponding center's practice. Following CT/RT, the radiologic CR rate was 21.3% (95%CI: 10.7%–35.7%) in arm A and 50% (95%CI: 34.9%–65.1%) in arm B (*P*= .004) (Table 2). A PR was observed in 29 of 47 evaluable patients in arm A (61.7%) and in 14 of 46 evaluable patients in arm B (30.4%) (*P*= .003); ORRs were 83% (95%CI: 69.2%–92.3%) and 80.4% (95%CI: 66.1%–90.6%), respectively. Prophylactic neck dissections were performed in 3 and 8 patients in arms A and B, respectively, who had a pathologic CR at the primary site and a radiological CR at the neck. Salvage surgery for residual disease was performed in twice the number of patients in arm A *v* arm B (18/47 [38.3%] *v* 9/46 [19.6%]; *P*= .047). The majority of salvage was due to residual on the neck: 34.0% of patients in arm A (16/47) *v* 10.9% in arm B (5/46) (*P*= .012). Radiological CR rates evaluated at 8 months after treatment for non-operated patients (including prophylactic or salvage surgery) were 40% (10/25) in arm A and 57.1% (16/28) in arm B. In arm A, 5 patients maintained a CR and 5 patients shifted from PR to CR; 2 patients had progressed after an initial CR. In arm B, 13 patients maintained CR and 3 shifted from PR to CR; 1 patient had progressed after an initial CR. Median duration of overall response (CR or PR) was 29.7 months in arm A and 30.4 months in arm B. After a median follow-up of 42 months, 32 patients (62.7%) in arm A and 26 patients (52.0%) in arm B progressed or died, resulting in a median PFS of 19.7 and 30.4 months respectively (Figure 2A), with 44.7% and 55.6% of patients remaining progression-free at 2 years. Median OS was 33.3 months in arm A and 39.6 months in arm B (Figure 2B), with 1- and 2-year survival rates of 77.6% and 57.1% in arm A and 86.0% and 61.0% in arm B, respectively.

Safety results:	The rate of early death (occurring within 30 days following CT/RT) in arm A was 9.8% (5 patients). The 5 causes of death were: cardiac disease, bilateral pulmonitis, hematologic toxicity, gastric perforation, and unknown. There were no early deaths in arm B. During induction TPF (arm B), the most common grade 3–4 hematologic toxicity was neutropenia (52%; 26 of 44 evaluable patients), with 8% of patients (n=4) experiencing febrile neutropenia. Both grade 3–4 anemia and thrombocytopenia occurred at a rate of 2.0% (one patient each). Grade 3–4 nonhematologic toxicities occurring >2% of patients were alopecia (18%), stomatitis/mucositis (6.0%) and nausea (4.3%). Rates of grade 3–4 hematologic adverse events occurring during concomitant treatment were not clinically relevant, however more leukopenia and neutropenia were observed in CT/RT arm. With respect to the most clinically relevant nonhematologic toxicities (mucositis/stomatitis, skin toxicity, dysphagia), they were not increased in the induction TPF arm.
Pharmacokinetic results:	Not Applicable
Date of report:	**15-Sep-2008**