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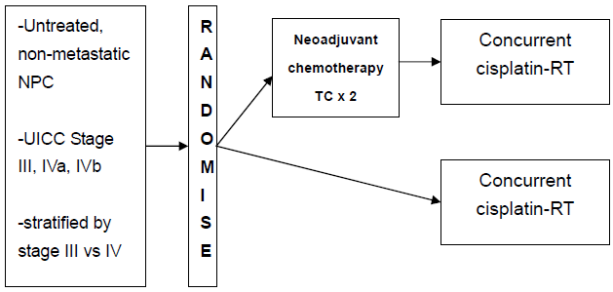
Sponsor/company:	sanofi-aventis	**ClinialTrials.gov Identifier:**	NCT00436293
		Study Code:	XRP6976F_6002
Generic drug name:	Docetaxel	**Date:**	24 October 2008

Title of the study:	A randomized phase II study of concurrent cisplatin-radiotherapy with or without neoadjuvant chemotherapy using Taxotere and Cisplatin in advanced nasopharyngeal carcinoma.	
Investigator(s):	Prof Anthony CHAN (PI)/ Dr. Pun HUI (Co-I) Prince of Wales Hospital Hong Kong	
Study center(s):	1 center	
Publications (reference):	ASCO 2007 Abstract 6037 + Oral presentation Manuscript is accepted by Journal of Clinical Oncology (JCO)	
Study period: Date first patient/subject enrolled: 02-Dec-2002 Date last patient/subject completed: ongoing long-term follow-up for survival		Phase of development: Phase II
Objectives:	Primary: To assess and compare the toxicities of patients with advanced NPC treated with concurrent cisplatin-RT with or without neoadjuvant taxotere and cisplatin.	

Methodology:	Open-labelled, comparative study  		
Number of patients/subjects:	Planned: 60	Randomized: 65	Treated: 60
Evaluated:	Efficacy/Pharmacodynamics: 60	Safety: 60	Pharmacokinetics: N/A
Diagnosis and criteria for inclusion:	Diagnosis: <u>Advanced nasopharyngeal carcinoma (NPC)</u> <u>Inclusion Criteria:</u> 1. Have given written informed consent, prior to pre-study screening, with the understanding that consent may be withdrawn at any time without prejudice. 2. Loco-regional advanced NPC UICC Stages T3 - 4 any N, or any Stage T, N2 - 3. A histological diagnosis of NPC must have been established at some time and the investigator must review and confirm the diagnosis prior to randomization. 3. No evidence of distant metastases in staging work up. 4. Evaluable disease must be present. 5. Performance status of ECOG grade 0 or 1. 6. Adequate bone marrow reserve: white blood cell count and platelet count must be ≥ lower limit of normal. 7. At least 18 years of age, of either sex. 8. If female, must be either (i) post-menopausal or surgically sterilized, or (ii) use a hormonal contraceptive, intra-uterine device, diaphragm with spermicide for the duration of the study and must be neither pregnant nor breast-feeding.		

Investigational product: Dose: Administration:	Docetaxel Neo-adjuvant therapy: Docetaxel 75 mg/m^2 IV infusion over 1 hour on day 1 and cisplatin 75 mg/m^2 IV infusion over 3 hours with hydration on day 1, for 2 cycles. IV Infusion	
Duration of treatment: Every cycles: Q 3 weeks; for 2 cycles		Duration of observation: Till death
Reference therapy: Dose: Administration:	Radical radiotherapy concurrently with cisplatin 40 mg/m^2 IV infusion over 2 hours from week 7-14 will be given. Cisplatin 40mg/m^2 together with radical radiotherapy IV infusion	
Criteria for evaluation:		
Efficacy: Or Pharmacodynamics:	Tumour response Quality of Life Survival	
Safety:	Toxicity (NCI CTC version 2 toxicity)	
Pharmacokinetics:	N/A	
Pharmacokinetic sampling times and bioanalytical methods:	N/A	
Statistical methods:	Incidence of toxicity will be used as primary endpoint. About 30 patients in each of the two arms allow us to exclude a difference of about 20% on one side of a 95% confidence interval. Secondary endpoint includes progression-free survival (PFS). Assumed a two-year PFS of 78% for advanced NPC patient receiving concurrent chemo-radiation, we would recruit 30 patients and observe at least 12 events in one arm so that the upper 95% confidence limit around the 2-year PFS excludes 88%. Similarly, we will recruit 30 patients and observed at least 8 events in the study arm so that the lower limit of the 95% confidence interval around 2-year PFS excludes 78%. A total of 60 patients will be entered in the study.	

Summary:	
Efficacy results: or Pharmacodynamic results:	

	Response Rate				P value*
	Neoadjuvant arm (n=34)		Control arm (n=26)		
After neoadjuvant chemotherapy, n (%)	**NP** (n=34)	**LN**** (n=26)			
CR	8 (23.5)	14 (53.8)			
PR	20 (58.8)	8 (30.8)			
SD	6 (17.6)	4 (15.4)			
PD	0	0			
Combined response	**NP + LN** (n=34)				
CR	6 (17.6)				
ORR (CR + PR)	26 (76.5)				
After cisplatin-radiotherapy, n (%)	**NP** (n=34)	**LN**** (n=26)	**NP** (n=26)	**LN**** (n=24)	
CR	32 (94.1)[a]	21 (80.8)[b]	22 (84.6)[a]	16 (66.7)[b]	0.22 [a] 0.26 [b]
PR	2 (5.9)	4 (15.4)	4 (15.4)	8 (33.3)	
SD	0	1 (3.8)	0	0	
PD	0	0	0	0	
Combined response	**NP + LN** (n=34)		**NP + LN** (n=26)		
CR	28 (82.4)		16 (61.5)		0.07
ORR (CR + PR)	33 (97.1)		26 (100)		0.38

* NP, nasopharynx; LN, regional neck lymph nodes; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, overall response rate.

** Patients with N0 at baseline were excluded for the calculation of LN response.

+ P values, calculated with the use of Chi-squared test, are for the difference in the response rate between the two treatment arms.

[a] difference in the CR rate of NP between the two treatment arms.

[b] difference in the CR rate of LN between the two treatment arms.

The 3-year progression-free survival for neoadjuvant versus control arm was 88.2% and 59.5% (hazard ratio 0.49; 95% C.I.=0.20 to 1.19; p=0.12).

The 3-year overall survival for neoadjuvant versus control arm was 94.1% and 67.7% (hazard ratio 0.24; 95% C.I.=0.078 to 0.73; p=0.012)

No significant difference was observed in the global quality of life scores in the two treatment arms

Safety results:	Summary of Grade 3 and 4 adverse events during treatment.* **Neoadjuvant arm (n=34)** / **Control arm (n=26)** / P value** |	Neoadjuvant arm (n=34)		Control arm (n=26)		P value**
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	Grade 3	Grade 4	Grade 3	Grade 4	
(a) During neoadjuvant chemotherapy, n (%)					
Haematologic:					
Neutropenia	6 (17.7)	27 (79.4)			
Neutropenic fever	4 (11.8)	0			
Non-haematological:					
Fatigue	2 (5.9)	0			
Nausea/Vomiting	3 (8.8)	0			
(b) During cisplatin-radiotherapy, n (%)					
Haematologic:					
Anaemia	3 (8.8)	0	5 (19.2)	0	0.23
Thrombocytopenia	1 (2.9)	2 (5.9)	0	1 (3.8)	0.44
Neutropenia	6 (17.7)	28 (82.4)	3 (11.5)	1 (3.8)	<0.0001
Neutropenic fever	1 (2.9)	0	1 (3.8)	0	0.16
Non-haematologic:					
Anorexia/nausea/vomiting	3 (8.8)	0	2 (7.7)	0	0.87
Dehydration/renal	8 (23.5)	0	6 (23.1)	0	0.96
Fatigue	5 (14.7)	0	2 (7.7)	0	0.40
Electrolytes	10 (29.4)	0	9 (34.9)	0	0.66
Mucositis/odynophagia	8 (23.5)	0	2 (7.7)	0	0.11
Transfusion	5 (14.7)	0	4 (15.4)	0	0.94	 * Adverse events were graded according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC), version 2.0. ** P values, calculated with the use of Fisher's exact test, are for the difference in the incidence of Grade 3 and 4 adverse events between the two treatment arms. The main G3/4 adverse events during neoadjuvant chemotherapy were hematological toxicity. Although G3/4 neutropenia occurred in 97% of patients during neoadjuvant docetaxel-cisplatin chemotherapy, the rate of febrile neutropenia was only 12%, which were all uncomplicated. During the CRT phase, no significant differences were observed in the rates of overall haematological or non-hematologic toxicities between the two study arms (except in neutropenia). The difference in neutropenia in CRT phase is probably related to the previous neutropenia during the neo-adjuvant treatment. Also there is no primary or secondary prevention using GCSF or antibiotics due to the lack of guideline at this time.
Pharmacokinetic results:	N/A
Date of report:	14 Oct 2008