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Sponsor/company:	sanofi-aventis	**ClinialTrials.gov Identifier:**	NCT00268710
		Study Code:	XRP6976J_2503
Generic drug name:	Docetaxel	**Date:**	27/Mar/2008

Title of the study:	Canadian Uro-Oncology (CUOG) Multicenter Phase II Study with Taxotere (Docetaxel) Administered Weekly or Every Three Weeks in Combination with Prednisone as second Line Chemotherapy in Patients with Hormone refractory Prostate Cancer (HRPC) Study number: XRP6976J_2503
Investigator(s):	Dr. Fred Saad (Coordinating investigator) CHUM Hôpital Notre-Dame, Pavillon L.C Simard (local Z6910) 1560 rue Sherbrooke est Montréal (Qc) H2L 4M1 Dr Scott Ernst & Eric Winquist London Regional Cancer Center 790 Commissioners Road East London (On) N6A 4L6 Dr Scott North Cross Cancer Institute 11560 University Avenue Edmonton (AB) T6G 1Z2 Dean Ruether Tom Baker Cancer Center 1331-29th Street NW Calgary (AB) T2N 4N2
Study center(s):	4 Canadian centers
Publications (reference):	British Journal of Urology

Study period: Date first **patient** enrolled: 05-Feb-2004 Date last **patient** completed: 02-Mar-2006	**Phase of development:** II

Objectives:	Primary Objectives: To determine the response rate, both measurable and non measurable, to docetaxel in the second line setting. Secondary Objectives: The secondary objectives of this study was: - To evaluate the overall safety and toxicity of

	docetaxel//prednisone combination as second line therapy in HRPC. - To evaluate PSA response. - To evaluate symptomatic response. - To evaluate quality of life. - To evaluate patient safety weekly vs.q3 weekly regimens of docetaxel - To determine survival
Methodology:	Prospective, non-randomized, open label trial. Thirty subjects from 4 centers were enrolled in the study. All had prior MP for symptomatic, metastatic HRPC. Baseline prostate-specific antigen (PSA), pain score, analgesic score, bone scan and CT of the abdomen and chest were obtained in all patients. All had castrate levels of testosterone and were maintained on LHRH therapy.
Number of patients:	Planned: 30 — Treated: 30
Diagnosis and criteria for inclusion:	Subjects with histologically / cytologically proven prostate adenocarcinoma refractory to hormone therapy and progression or non-response on previous chemotherapy which was either mitoxantrone/prednisone or other chemotherapy regimen including estramustine +/- vinblastine. In addition, subjects must have testosterone levels <50 ng/dL, life expectancy of at least 12 weeks and ECOG status from 0 to 2, inclusive
Investigational product: Dose: Administration:	Docetaxel and prednisone Regimen A: Docetaxel 75 mg/m² Prednisone 10 mg Regimen B: Docetaxel 30 mg/m² Prednisone 10 mg. Regimen A: Docetaxel 75 mg/m^2: Intravenous infusion every three weeks Prednisone 5 mg: orally given twice daily Regimen B: Docetaxel 30 mg/m^2: Intravenous infusion weekly on days 1, 8, 15, 22, 29, every 6 weeks Prednisone 5 mg: orally given twice daily
Duration of treatment: Regimen A: 10 cycles (30 weeks) Regimen B: 5 cycles (15 weeks)	**Duration of observation:** Regimen A: Follow-up: until progression on tumor lesions or further anti-tumor therapy Regimen B: Follow-up: until progression on tumor lesions or further anti-tumor therapy
Reference therapy:	None
Criteria for evaluation: Efficacy:	- Pain (pain progression evaluated with the Present Pain Intensity scale form McGill-Melzack questionnaire) - Analgesics (assessed by Pain Medication Log) - PSA (PSA response and PSA progression) - Tumor lesion assessment - Overall survival

	- Progression-free survival
Safety:	Treatment emergent adverse events recorded by the investigator where intensity was according to NCI-CTC criteria. Standard hematology, blood chemistry and clinical exams.
Statistical methods:	**Statistical methods** Categorical data were reported in number of subjects and percentages. Continuous data were summarized with means, standard deviations, median, range and interquartile ranges. Time to event variables was analyzed using the Kaplan-Meier method to account for censored duration. Treatment group comparison was to be based upon the results of the stratified logrank test. The variables of adjustment were the variables of stratification, i.e., the logrank test was adjusted for pain level and for Karnofsky performance status. Quality of life data based on the FACT-P was analyzed using analysis of covariance on the change from baseline with the baseline value as the covariate. **Primary Analysis Variable** 1. <u>Measurable and non measurable response to Docetaxel</u> Response rate in subjects with measurable and non measurable disease were compared between the two Docetaxel groups using the chi-square test. 2. <u>Pain Response and PSA Response Analyses</u> Pain response and PSA response were to be compared between the two Docetaxel groups using the chi-square test in the corresponding evaluable subjects' population. Duration of pain improvement and duration of PSA response were analyzed in the same patient populations. 3. <u>Duration of response</u> Duration of responses was analyzed using the Kaplan-Meier method. The comparison of duration of response was done based upon the adjusted logrank test. 4. <u>Quality of Life evaluation</u> Quality of life evaluation was performed using the FACT-P questionnaire. Changes in total FACT-P score from baseline were the primary endpoint in the QoL assessment, for this study. Changes of other domain scores of the FACT-G and the PCS (Prostate Cancer-Specific module) were described from baseline. The FACT-P scale comprises 5 subscales which were: - Physical well-being : 7 items - Social/Family well-being : 7 items - Emotional well-being : 6 items - Functional well-being : 7 items - Additional concerns (= Prostate Cancer Specific): 12 items Quality of life evaluation was performed on an exploratory basis on the overall population of enrolled subjects for whom at least one QoL questionnaire has been considered evaluable for the analysis. Rules for evaluability were the following: • A baseline QoL questionnaire is considered as evaluable if it was filled in within 14 days prior to enrollment, and no later than the day of enrollment. • An on-treatment questionnaire was considered as evaluable if it was

filled in after 6 days following the current infusion and no later than next infusion ;

- An end-of-study questionnaire was considered as evaluable if it was filled in after 6 days following the last infusion.
- All other follow-up questionnaires were considered as evaluable for the analysis provided that there was sufficient information to derive the score according to the FACT manual.

Analysis of safety variables:

Adverse events

The number (percent) of subjects with treatment emergent adverse events (TEAE), overall and by body system, was tabulated for each treatment group. In addition, the number (percent) of subjects with possibly related TEAE, serious adverse events, and adverse events leading to discontinuation of study drug were tabulated. Serious adverse event hypoglycemia will be handled in the same way as all other serious adverse events. TEAEs were defined as new or worsening adverse event that occurred between the start of study drug until 30 days after the last dose of study drug.

Laboratory variables

- Hematology and clinical chemistry
  - Values at and changes from baseline at each visit (cycle) have been summarized by treatment group using descriptive statistics
  - The number (percent) of subjects at baseline and at each visit below, within and above the normal range have been summarized by 3 x 3 tables for each analyte
  - The number (percent) of subjects at each visit with pre-defined change abnormal (PCA) and last pre-defined change abnormal (LPCA) have been summarized by treatment group.
  - The number (percent) of subjects with clinically noteworthy abnormal values has been summarized by treatment group.
- Vital Signs
  - Values at and changes from baseline at each visit (cycle) have been summarized by treatment group using descriptive statistics
  - The number (percent) of subjects at baseline and at each visit below, within and above the normal range have been summarized by 3 x 3 tables for each analyte
  - The number (percent) of subjects at each visit with pre-defined change abnormal (PCA) and last pre-defined change abnormal (LPCA) have been summarized by treatment group.
  - The number (percent) of subjects at each with clinical noteworthy abnormal values (CNALV)

INTERIM ANALYSIS

No interim efficacy analysis was performed.

Sample size justification

This study was an exploratory trial to compare the efficacy and safety of two non-randomized treatment regimens. All statistical tests were for descriptive purposes only. As a consequence, no sample justification had been proposed.

Summary:

Study conduct:

Thirty (30) subjects were enrolled to the docetaxel 75 mg/m^2 once every 3 weeks with prednisone 5 mg twice daily. No subject was enrolled in the docetaxel 30 mg/m^2 once a week arm with prednisone 5 mg twice daily.

The 30 male subjects all completed one cycle of treatment. The median number of cycles was 10 with an interquartile range of 6 to 11. Sixteen (53.3%) subjects did not complete their planned number of cycles because of adverse events (31.3%), death (12.5%), and progressive disease (18.8%) and did not wish to continue (37.5%). The mean age was 72.5 years and all but one subject was caucasian.

Efficacy results:

At the end of treatment there were 2 subjects with partial response, 21 subjects with stable disease, 1 subject with progressive disease and the remaining 6 subjects were not evaluable. The median progression-free survival was 245 days and death-free survival was 455 days.

The median of the change from baseline for PSA at the end of treatment was 17.9 ng/mL and at the end of follow-up was 17.9 ng/mL. For the 29 subjects with an on-treatment PSA value, 12 (41.4%) had a confirmed 50% decrease from baseline last a median of 105 days.

The median change in Patient Pain Index (PPI) was 0 at the end of treatment and 0 at the end of follow-up. Seventeen (63.0%) of the 30 enrolled patients were responders. Results for the analgesic score were similar.

The median change from baseline for the total score of FACT-P was -2.0 at the end of treatment and -2.0 at the end of follow-up indicating an improvement in quality of life. This decrease was likely driven by the emotional well-being and prostate specific symptoms.

Safety results:

There were 4 cases of febrile neutropenia and 2 treatment-related deaths (1 Pneumonia respiratory failure and 1 Septic shock). With 20 months of follow-up, median overall survival is 15 months.

Treatment Emergent Adverse Event	N (%)
Blood and Lymphatic System Disorders	11 (36.7)
Anemia	5 (16.7)
Febrile neutropenia	4 (13.3)
Neutropenia	3 (10.0)
Eye Disorders	10 (33.3)
Lacrimation increased	3 (10.0)
Conjunctivitis	3 (10.0)
Gastrointestinal Disorders	28 (93.3)
Nausea	19 (63.3)
Constipation	17 (56.7)
Diarrhea	10 (33.3)
Stomatitis	7 (23.3)
Vomiting	5 (16.7)
Mouth ulceration	3 (10.0)
General Disorders	27 (90.0)
Fatigue	26 (86.7)
Edema peripheral	11 (36.7)
Asthenia	7 (23.3)
Pyrexia	5 (16.7)
Edema	3 (10.0)

Infections and Infestations	7 (23.3)
Nasopharyngitis	3 (10.0)
Injury, Poisoning, and Procedural Complications	11 (36.7)
Contusion	7 (21.3)
Investigations	15 (50.0%)
Weight decreased	6 (20.0%)
Metabolism and Nutrition Disorders	13 (43.3)
Anorexia	9 (30.0)
Decreased appetite	4 (13.3)
Musculoskeletal and Connective Tissue Disorders	27 (90.0)
	17 (56.7)
Bone pain	11 (36.7)
Myalgia	8 (26.7)
Back pain	4 (13.3)
Muscular weakness	4 (13.3)
Muscle spasms	3 (10.0)
Arthralgia	
Nervous System Disorders	19 (63.3)
Headache	7 (23.3)
Dysgeusia	6 (20.0)
Dizziness	6 (20.0)
Hypoaesthesia	5 (16.7)
Peripheral sensory disorder	3 (10.0)
Paraesthesia	3 (10.0)
Psychiatric Disorders	11 (36.7)
Insomnia	6 (20.0)
Depression	3 (10.0)
Renal and Urinary Disorders	19 (63.3)
Nocturia	15 (50.0)
Urinary Retention	3 (10.0)
Respiratory, Thoracic and Mediastinal Disorders	19 (63.3)
	6 (20.0)
Dyspnea	5 (16.7)
Cough	4 (13.3)
Dyspnea exertional	4 (13.3)
Epistaxis	
Skin and Subcutaneous Skin Disorders	22 (73.3)
Alopecia	17 (56.7)
Nail disorder	7 (23.3)
Dry skin	6 (20.0)
Vascular Disorders	17 (56.7)
Hot flush	10 (33.3)
Pallor	7 (23.3)
Flushing	3 (10.0)

	The most frequently report TEAEs were: fatigue, nausea, alopecia, constipation, bone pain, nocturia, edema peripheral, myalgia, diarrhea, hot flush, anorexia, back pain, nail disorder, stomatitis, pallor, headache contusion, asthenia, dysgeusia, dizziness, dry skin, dyspnea, weight decreased and weight decrease. Serious adverse events were reported for 10 subjects including 4 subjects with febrile neutropenia. Seven (7) subjects discontinued study medication because of adverse events. The most frequent of these events was fatigue (3 subjects). Grade 3 and/or 4 toxicities were reported by 19 subjects with febrile neutropenia (4 subjects), neutropenia (3 subjects) and bone pain (3 subjects) being the most frequent. <u>Laboratory Data</u> Values and changes from baseline of hematological and biochemical laboratory data were screened using descriptive statistics, displaying out of range changes from baseline at cycle 1 and end of chemotherapy, and percent of patients with PCAs, LPCAs and CNALVs. While, ouut of range values and PCAs were not uncommon among the patients, CNALVs were rarely seen except for alkaline phosphatase which was 1.5 x ULN for 11 (37.9%) of the subjects. CNALVs for AST and ALT were absent. <u>Vital signs</u> Values and changes from baseline vital signs were screened using descriptive statistics, displaying out of range changes from baseline at cycle 1 and end of chemotherapy, and percent of patients with PCAs, and LPCAs. Out of range and PCAs occurred rarely and were of no clinical relevance
Date of report:	26-Mar-2008