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 **Drug substance(s):** docetaxel	**Study Identifier:** NCT00291005 **Study code:** ARD6562 (XRP6976J/2101)
Title of the study: A multicenter phase II open label non-comparative trial of RP56976 administered every three weeks in combination with daily prednisolone for metastatic hormone refractory prostate cancer	
Study center(s): 28 centers in Japan	
Study period: Date first patient enrolled: 26 August 2004 Date last patient completed: 13 October 2006	
Phase of development: Phase II	
Objectives: Primary: - To evaluate the overall tumor response rate by using Response Evaluation Criteria in Solid Tumor (RECIST) in subjects with metastatic hormone refractory prostate cancer (HRPC) with measurable disease. Secondary: - To evaluate the overall tumor response rate by using Japanese Urological Association (JUA) Response Criteria (defined in General Rule for Clinical and Pathological Studies on Prostate Cancer, 3rd Edition, Japanese Urological Association, The Japanese Society of Pathology) in subjects with metastatic HRPC. - To evaluate the prostate specific antigen (PSA) response rates as a measure of antitumor response in subjects with metastatic HRPC. - To evaluate safety.	
Methodology: A multicenter, open label, non-comparative study, with dosing every three weeks in combination with daily prednisolone in subjects with metastatic HRPC.	
Number of patients: Planned: 42 Enrolled: 44 Treated: 43	
Diagnosis and criteria for inclusion: Subjects with metastatic prostate adenocarcinoma that was unresponsive or refractory to hormone therapy and were 20 to 74 years of age, were included in the study after giving written informed consent. Subjects had to have documented progression detected by PSA increase, physical examination and/or imaging; and had to have measurable lesion. Prior treatment with corticosteroids, prior radiation therapy (to ≤ 25% of the bone marrow only), and prior surgery were allowed. Subjects had to have Performance Status (P.S.) of 0 - 2 and adequate organ function.	

Investigational product: RP56976 (docetaxel)

Dose: 70 mg/m^2

Administration: Intravenous infusion over 60 minutes or longer, repeated every 3 weeks in combination with prednisolone (5 mg twice daily) administered orally, starting on Day 1 (throughout the study).

Duration of treatment: 10 cycles

Duration of observation: The earliest day among followings:
- Six weeks (Day 43) from last infusion of RP56976,
- Start of other anti-cancer therapy for HRPC except corticosteroids,
- The first dose of RP56976 in the extension study,
- Documented date of lost to follow-up.

Reference therapy: Not applicable

Criteria for evaluation:

Efficacy:

Primary: Overall tumor response rate based on RECIST

Secondary: Overall tumor response rate based on JUA Response Criteria, PSA response rate

Safety:

Incidence rate of treatment-emergent adverse events (TEAEs), by grade, as evaluated by National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 2.0

Statistical methods:

Primary efficacy analyses:

For the primary efficacy analysis, tumor response rate by RECIST was calculated [the number of subjects in the full analysis set (FAS) with the best overall tumor response of complete response (CR) or partial response (PR) divided by the number of subjects in the FAS].

The primary efficacy analysis was then based on the 90% exact binominal confidence interval (CI) for this summary statistic with a threshold response rate of 5%.

Safety analyses:

Frequency of TEAEs by worst grade was calculated for the Safety evaluable set (SES), which is all subjects treated with study medication at least once. Toxicity grading was evaluated by NCI-CTC version 2.0. For neutrophil counts, the number of days to nadir from infusion and from nadir to grade 0 was calculated.

Summary:

Efficacy results:

Response in RECIST and JUA Response Criteria were confirmed by the Extramural Review Committee.

In the FAS, PR according to RECIST was seen in 19 of 43 subjects and overall tumor response rate was 44.2% (90% CI [31.20 - 57.80]). The lower limit of 90% CI was 31.20% and much higher than the threshold response rate of 5% specified in the clinical study protocol. Thus, the efficacy of RP56976 in combination with prednisolone on HRPC was confirmed.

The median period to the initial PR judgement (PR in) was 2.0 cycles and the median duration of response was 135.0 days, with a maximum of 178 days (Duration of response was censored at the end of Cycle 10). In the FAS, disease progression was seen in 16 of 43 subjects, and the median time to disease progression was 173.0 days.

The dose of RP56976 was reduced in 13 of 19 subjects with response. Five responders had PR in after a reduction to 60 mg/m^2, and 2 of responders had PR in after a dose reduction to 50 mg/m^2, suggesting that the dose reduction did not interfere with the response.

The influence of background factors on overall tumor response (by RECIST) was examined. Subgroup analyses of overall tumor response were performed for age, P.S., Gleason score, Jewett Staging System, period from initial diagnosis to registration, baseline PSA, number of sites involved, and prior therapy. Overall tumor response was observed irrespective of backgrounds or prior therapies.

In the Per Protocol Set, PR according to RECIST was seen in 17 of 41 subjects giving an overall tumor response rate of 41.5% (90% CI [28.41 – 56.48]).

According to JUA Response Criteria, PR was seen in 17 of 43 subjects, giving an overall tumor response rate of 39.5% (95% CI [24.98 - 55.59]) in the FAS. PSA response was seen in 16 of 36 subjects included in FAS_PSA, giving a PSA response rate of 44.4% (95% CI [27.94 - 61.90]).

Safety results:

Among the TEAEs possibly related to RP56976, the subjective/objective symptoms seen with a high incidence were alopecia (88.4%, 38/43), anorexia (65.1%, 28/43), and fatigue (53.5%, 23/43). The incidence of higher than 5% for grade ≥3 was reported for febrile neutropenia (16.3%, 7/43), infection without neutropenia (14.0%, 6/43) and infection with grade 3 or 4 neutropenia (9.3%, 4/43).

The major laboratory abnormalities were leukocytes (97.7%, 42/43), neutrophils/granulocytes (95.3%, 41/43), lymphopenia (79.1%, 34/43), CRP increased (48.8%, 21/43), LDH increased (46.5%, 20/43), SGPT (ALT) (34.9%, 15/43), hemoglobin (32.6%, 14/43), hypoalbuminemia (32.6%, 14/43), platelets (30.2%, 13/43), and SGOT (AST) (30.2%, 13/43). The incidence of episodes of grade ≥3 exceeded 5% only for hematological toxicities including neutrophils/granulocytes (93.0%, 40/43), leukocytes (81.4%, 35/43) and lymphopenia (30.2%, 13/43).

Edema and nail changes were dependent on the cumulative dose of RP56976, and neuropathy-sensory seemed to be related to the cumulative dose of RP56976. However, nothing greater than a grade 3 toxicity was observed in those 3 TEAEs.

Neither treatment-related deaths nor early deaths were observed.

Serious adverse events (SAEs) were reported in 14 subjects (22 episodes). SAEs for which a causal relationship with the study treatment could not be ruled out were reported in 10 subjects (12 episodes; 3 episodes of infection with grade 3 or 4 neutropenia, 3 episodes of febrile neutropenia, 2 episodes of pneumonitis/pulmonary infiltrates, 1 episode of influenza, 1 episode of infection without neutropenia, 1 episode of neutrophils/granulocytes, and 1 episode of hypotension). All were expected events. Unexpected SAEs were reported in 2 subjects (3 episodes; spinal compression fracture, bladder disorder and anorectal disorder). The causal relationship with RP56976 was ruled out for all these episodes.

Issue date: 23-Oct-2007