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Sponsor/company:	sanofi-aventis	**ClinialTrials.gov Identifier:**	NCT00705822
Generic drug name:	Docetaxel	**Study Code:**	XRP6976J_3502
		Date:	22 November 2010

Title of the study:	A phase III, randomised, multicentre, multidisciplinary comparative clinical trial of the docetaxel + estramustine + hydrocortisone combination versus docetaxel + prednisone in patients with advanced prostate cancer who have biochemical relapse during androgen blockade therapy
Investigator(s):	Dr. Antonio Antón and Prof. Luis A. Rioja – Hospital Universitario Miguel Servet; Pº de Isabel la Católica, 1-3; 50009 Zaragoza
Study center(s):	Hospital Central Asturias Clínica Universitaria de Navarra Hospital Clínico Universitario de Salamanca Complejo Hospitalario Ourense Hospital 12 de Octubre Hospital General Universitario Alicante Hospital General Universitario de Guadalajara Hospital de León Hospital del Mar Institut Català Oncologia Instituto Valenciano Oncología Hospital Juan Canalejo Hospital Universitario Marqués de Valdecilla Hospital Universitario Miguel Servet Hospital Ntra. Señora de Valme Hospital Puerto Real Hospital Río Ortega Hospital Universitari Vall Hebrón Hospital Virgen del Rocío Hospital Xeral Calde de Lugo Hospital General universitario Valencia Hospital Reina Sofia Hospital Son Llàtzer Hospital Son Dureta Hospital Basurto
Publications (reference):	--

Study period: Date first **patient** enrolled: 16-Aug-2006 Date last **patient** completed: 18-Jul-2009			**Phase of development:** III
Objectives:	Primary • To compare the efficacy of the two regimens through determination of the PSA response rate, measured by the reduction in the prostate-specific antigen (PSA) according to the criteria of the PSA Working Group (Bubley, 1999), of the reference treatment (docetaxel + prednisone) versus the study treatment (docetaxel + estramustine + hydrocortisone combination) Secondary • To determine the time to treatment failure with both regimens • To compare the time to biochemical and/or clinical progression of the two chemotherapy combinations • To determine the overall survival rate and specific cause with both treatment regimens • To compare the objective clinical response rates in patients with measurable disease according to the Response Evaluation Criteria In Solid Tumors (RECIST) criteria • To assess the safety profile of both treatment regimens • To analyse the patients' quality of life • To identify predictive clinical factors of the response and/or survival • To evaluate the prognostic value of PSA reduction on specific-cause survival		
Methodology:	The assignment of patients to receive treatment was random, with a 1:1 ratio and centralised. The patients were stratified according to functional status (ECOG/Eastern Cooperative Oncology Group 0-1 vs. 2) and prior duration of the disease (only biochemical relapse vs. clinical disease) to receive either the investigational treatment arm or the control arm.		
Number of patients:	Planned: 172	Randomized: 54	Treated: 54
Evaluated:	Efficacy: 53	Safety: 54	
Diagnosis and criteria for inclusion:	Patients with histologically confirmed diagnosis of prostate adenocarcinoma who have shown progression or biochemical relapse (PSA) during or after androgen suppression therapy (orchidectomy or Luteinizing-Hormone-Relasing Hormone/LHRH analogues) associated with peripheral antiandrogen and withdrawal of same.		

<table>
<tr><td>Investigational product:

Dose:</td><td>

Docetaxel
Estramustine
Prednisone
Hydrocortisone

EXPERIMENTAL TREATMENT: Docetaxel every 3 weeks in combination with Estramustine and Hydrocortisone
Estramustine
Dose: 10mg /kg / day
Route: oral; total daily dose divided up three times a day; the total dose will be fitted according to the commercial presentation (1 capsule = 140mg)
Guideline: from 4 to 6 tablets (according to the patient weight), taken every 8 hours on an empty stomach (prior to meals), days 1 to 5 from each cycle.
<table>
<tr><th>WEIGHT (Kg)</th><th>DOSE (mg/kg)</th><th>Nº capsules /day</th></tr>
<tr><td>< 63</td><td>560</td><td>4</td></tr>
<tr><td>63 – 76</td><td>700</td><td>5</td></tr>
<tr><td>≥ 76</td><td>840</td><td>6</td></tr>
</table>
Docetaxel
Dose: 70mg/m^2 day 2
Route: intravenous infusion lasting 1 hour
Guideline: every 3 weeks
Hydrocortisone
Dose: 40 mg daily (30 mg on the morning and 10 mg at noon), starting on day 1
Route: oral
Guideline: daily, continuous till the end of the treatment period.
A treatment cycle is defined by the period of 3 weeks including the administration of 3 drugs. Duration: 8 cycles. Hydrocortisone could be continued after the end of the treatment cycles.
</td></tr>
<tr><td colspan="2">Duration of treatment: Maximum of 24 weeks</td><td>Duration of observation: Minimum of 24 months</td></tr>
</table>

Reference therapy: Dose:	**CONTROL TREATMENT**: Docetaxel every 3 weeks in combination with prednisone Docetaxel Dose: 75mg/m^2 day 1 Route: intravenous infusion lasting 1 hour Guideline: every 3 weeks Prednisone Dose: 5mg twice a day starting on day 1 Route: oral Guideline: daily, continous This is defined as 1 treatment cycle. Duration: 8 cycles. Prednisone could be continued after the end of the treatment cycles.
Criteria for evaluation:	
Efficacy:	PSA evaluation: the PSA value will be determined in the 14 days prior to the first infusion (elevated PSA defined by the protocol), every three weeks the day before the infusion, at the end of the study and subsequently every month until progression of the PSA or administration of further anti-tumour treatment. In order to ensure comparability, it is recommended that the PSA values in a given patient be determined in the same laboratory from baseline until the end of the study.
Safety:	All patients will be regularly assessed for the potential development of adverse events, which will be classed according to their severity. Where possible, the Common Terminology Criteria for Adverse Events (CTCAE) grading system will be used for the classification of adverse events. MedDRA terminology will also be used to analyse all the adverse events, including those classified as "Other" by the CTCAE system. Haematological toxic effects will be assessed through neutrophil, leucocyte, platelet and haemoglobin counts.
Statistical methods:	Definition of populations for the analysis: 1.- Overall population or intention-to-treat population: All randomly assigned patients will be included in the intention-to-treat analysis, and they will be analysed in the treatment group to which they have been assigned. The primary endpoint (time to progression) and overall survival and specific cause will be analysed according to the intention-to-treat principle. 2.- Assessable population for safety: all patients who have received at least one dose of the study drugs will be eligible for the toxicity and safety evaluation. 3.- Assessable population for response: all patients who have received treatment and have at least one PSA response assessment (except in cases of early progression of the disease which will be considered to have no response) will be eligible for the response analysis and the duration of same. No intermediate analyses are planned during the study period.

Summary:	Of the total sample of 172 patients predicted to be included in the study (156 evaluable), only 54 patients were included in the study due to its early termination, communicated on 30 January 2009, a result of the low recruitment rate of the trial, the data published in the literature, the limited use of estramustine and the decision to end the study by the sponsor, together with the Spanish Oncology Genitourinary Group (SOGUG) participating in the study. The distribution of the 54 patients included in the two treatment arms was as follows: 26 patients in the control arm and 28 patients in the investigational arm. The mean age of the patients in both treatment groups was 69 years (71 for the control group and 66 for the study group), a mean weight of 80 kilos and mean height of 1.67 metres. A total of 61% of patients presented a baseline ECOG of 1. A total of 59.3% of patients had stage IV cancer on entering the study.
Efficacy results:	Patient response to treatment, according to PSA indicator, was classified as follows: • Response: if the patient presents a PSA reduction of ≥ 50% (17 patients in the control arm and 20 patients in the investigational arm) • Stable disease: when there is a PSA reduction of < 50% or an increase of < 25% (6 patients in the control arm and 8 patients in the investigational arm) • Biochemical progression: if there is a PSA increase of ≥ 25% with no response or an increase of ≥ 50% in patients with response or non-evaluable patients (2 patients in the control arm and none in the investigational arm) The median time to treatment failure was 8 months in the control arm and 9.5 months in the investigational arm (95% CI)
Safety results:	The 54 patients presented some type of adverse effect at some point in the study and 28 (51.8%) patients suffered a serious adverse event (grade 3-4), 12 (46.1%) in the control group and 16 (57.1%) in the study group. Most frequent toxicities grade 3-4 in the experimental group were: alopecia (14.29%), febrile neutropenia (7.14%), diarrhea (7.14%) and pain (7.14%). It should be mentioned that most frequent toxicities grade 3-4 in the control group were alopecia (19.23 %) and febrile neutropenia (15.38%), being superior in terms of percentage from the ones described at the experimental arm. Nine (16.7%) patients, 4 (15.4%) in the control group and 5 (17.9%) in the study treatment group, died, 7 (77.8%) patients due to tumour progression and 2 (22.2%) due to other causes. The patient who died due to other causes in the study group suffered an episode of syncope with sudden death, possibly related to estramustine.
Date of report:	15-Oct-2010