Finnish Uro-Oncological Group Study 1-2003 ("PROSTY"-trial)

A PHASE III TRIAL COMPARING DOCETAXEL EVERY THIRD WEEK TO BIWEEKLY DOCETAXEL MONOTHERAPY IN METASTATIC HORMONE REFRACTORY PROSTATE CANCER PATIENTS

AMENDMENT 6: Irish, Swedish and Finnish version 4 May 2007

Protocol Date: 07 January 2004

AMENDMENT 4: 10 March 2005
Swedish final version
AMENDMENT 5: 16 February 2006
Swedish version
Finnish version 24 February
AMENDMENT 6: Irish, Swedish and Finnish version 4 May 2007

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1 BACKGROUND

Successful initial treatment of advanced prostate cancer involves androgen deprivation either through LHRH analogues, orchiectomy, or estrogen suppression of GnRH. (1) Addition of antiandrogens, such as flutamide or bicalutamide to androgen deprivation as initial therapy for advanced disease (combined androgen blockage, CAB) may improve response duration and survival in a selected group of patients with advanced prostate cancer (2,3). Unfortunately, addition of antiandrogens after progression on androgen deprivation therapy has been less successful (3). Recently, a number of groups have reported objective PSA responses in patients who have had withdrawal of the antiandrogens flutamide and bicalutamide (4). This is presumably based on an agonist effect on the non-steroidal antiandrogens on mutated androgen receptors (5).

Although clinical trials using single agent chemotherapy have yielded objective response rates up to 10% with subjective or stable response rate in another 20 to 40%, no single agent or combination treatment of old cytotoxic agents has demonstrated a survival benefit in Phase III trials (6). The reported survival in these studies has been short, ranging from 5 – 11 months (7). Palliative benefit can be obtained by the administration of mitoxantrone with either prednisone or hydrocortisone (8). There is an obvious need for new therapies based on novel methods on inhibition of cancer growth. In a recent randomized phase II trial (9) also survival benefit was shown with docetaxel estramustine phosphate combination when compared to mitoxantrone plus prednisone.

The use of PSA in monitoring relapse has changed our understanding of the biology of androgen-independent prostate cancer. In the past, the majority of patients entered in clinical trials had serum PSA levels > 100, osseous metastases, and nodal disease. However, frequent monitoring of PSA detects relapse earlier. These patients often will have a period of four to six months without other objective evidence of progression and without symptoms. (10). Although these patients have longer survival compared to patients with measurable disease, progression to symptomatic and ultimately fatal hormone refractory prostate cancer is inevitable. Given the powerful impact of poor performance status on response to chemotherapy in several previous studies, this group of patients may well represent "early" relapse, a subset of patients with hormone refractory disease with low tumor burden that may be optimally approached with more aggressive therapy, especially cytotoxic chemotherapy (11). It is clear that three categories of patients with metastatic disease exist: 1) PSA only response, 2) symptomatic relapse and 3) visceral disease.

Mitoxantrone and Prednisone in HRPC

Based on pilot data from Raghavan suggesting a similar palliative benefit of mitoxantrone in this disease, Tannock then added mitoxantrone 12 mg/m^2 every three weeks to the previously tested prednisone in 27 patients with hormone refractory prostate cancer (HRPC) and observed a reduction in pain score in 36% and further improvements in QOL indices (8, 27, 28). In 25 patients with evaluable disease, one patient had a partial response and 12 had stable disease; in the nine patients with measurable disease, one partial response was observed. The toxicity of this approach was quite acceptable, with the most serious observed toxicity being WHO Grade 3 neutropenia in 65% of treatment cycles and Grade 4 neutropenia in 15% of cycles. Tannock next compared prednisone alone

to the combination of prednisone plus mitoxantrone (8). This study randomized 161 hormone refractory patients to prednisone 10mg/day or the combination of mitoxantrone (12mg/m^2, every three weeks) plus prednisone. Prednisone failures were crossed over to mitoxantrone therapy. Primary endpoint of the trial was palliative response and defined by two-point pain reduction on a six-point scale, with secondary endpoints being reduction in analgesic use, duration of response, and survival. In this important study, palliative response was more common in the chemotherapy arm (29% vs. 12%, p = .01), and was more durable (median 43 weeks vs. 18 weeks, p < .0001). There was no evidence of survival benefit (median approximately 12 months in both arms). PSA response (as defined by at least a 50% reduction in baseline PSA) was observed in 33% of chemotherapy patients and 22% of prednisone only patients (= NS). PSA response correlated with palliative response in both groups (p = .001). Toxicity was comparable to that observed in the Phase II study, though there were nine episodes of neutropenic fever, and five cases of cardiac dysfunction with two episodes of clinical congestive heart failure.

In an effort to validate the role of mitoxantrone palliative chemotherapy in HRPC, the Cancer and Leukemia Group B performed a similar study comparing hydrocortisone to the same hydrocortisone dose plus mitoxantrone 14 mg/m^2 every 21 days (29). Two hundred forty-two patients were enrolled, with a primary endpoint of survival and secondary endpoints being PSA response, objective response, time to treatment failure and quality of life. Survival duration was not improved with chemotherapy (p = .329), though there was a trend toward prolonged time to treatment failure (218 days vs. 122 days, p = .065). PSA response to > 50% reduction was more common with chemotherapy (33% vs. 18%, p = .035). The objective response rate was 8.3% in the mitoxantrone plus cortisone arm versus 1.9% for cortisone alone. Although there was a significant reduction in pain scores with the addition of chemotherapy, there were no improvements in QOL. Taken together, these studies suggest the primary palliative benefit of the addition of mitoxantrone to corticosteroides is the improvement in extent and duration of pain control in these hormone refractory patients. However, there is no evidence of prolongation of life, and this is perhaps explained by the very modest objective response rates, as quantified by reduction in PSA and objective response rates.

Docetaxel in HRPC

Docetaxel Three-Weekly Schedule in HRPC

Docetaxel (Taxotere®) is a chemical entity of the taxoid class. Docetaxel monotherapy is indicated in the treatment of patients with locally advanced or metastatic breast cancer after failure of cytotoxic therapy. It is also indicated in the treatment of non-small cell lung cancer, ovarian cancer in some countries (30). The latest indication is in the treatment of hormone refractory prostate cancer (HRPC).

A phase II trial has shown evidence of docetaxel activity in HRPC, with the incidence of PSA decline >50% on 45% of the patients and >80% on 20% of the patients. An objective response has been reported in 28% of patients with measurable disease. Responses were maintained for a median of 9 months (range:2-24). The safety profile was assessed as tolerable. Grade 4 toxicities requiring discontinuation of treatment included stomatitis, small bowel obstruction, and a gluteal abscess. There were 2 deaths on study due to lung toxicity/pneumonia and pulmonary embolus. Six patients stopped the treatment voluntarily due to fatigue or edema. Other common toxicities were neutropenia, anemia, mild edema and hyperglycemia (steroids), anorexia, myalgia and alopecia. Thus, this study provides

evidence that single agent docetaxel given at the dose of 75 mg/m^2 every 3 weeks is feasible, active and assessed as tolerable for the treatment of HRPC patients (30,31).

A newly published phase III study shows a significant increase in survival for patients treated with Taxotere®. (25) In the TAX327 study 1006 patients with advanced hormone refractory prostate cancer received 5 mg of prednisone twice daily and were randomized to 12 mg/m^2 of mitoxantrone every three weeks, 75 mg/m^2 of docetaxel every three weeks or 30 mg/m^2 of docetaxel weekly for five of every six weeks. The hazard ratio for death was in the three weekly docetaxel group compared to the mitoxantrone group 0.76 (P=0.009) and in the weekly docetaxel group 0.91 (P=0.39). The median survival was 16.5 months in the mitoxantrone group, 18.9 months in the every three weeks docetaxel group and 17.4 months in the weekly docetaxel group. Among these three groups, 32%, 45% and 48% had at least 50% decrease in the serum PSA level (P<0.001). 22%, 35% and 31% had predefined reductions in pain and 13%, 22% (P<0.009) and 23% (P<0.005) had improvements in the quality of life. Adverse events such as grade 3/4 neutropenia, fatigue, nail changes, sensory neuropathy and infection were more frequent in the docetaxel group while the incidence of cardiac events was higher in the mitoxantrone group.

Docetaxel Weekly Schedule in HRPC

Berry et al. (32) have performed a phase II trial of single-agent weekly docetaxel in HRPC. The purpose of the study was to determine the response rate and safety in patients treated with weekly docetaxel for hormone-refractory, symptomatic, metastatic prostate cancer. Sixty-one patients were enrolled in this study and 60 were considered to be evaluable. Docetaxel was administered by weekly infusion of 36 mg/m^2 for 6 weeks followed by 2 weeks of rest, for 3 cycles. ECOG performance status (0/1/2) was 15/35/10 and median age was 72 years (41-86). The median serum PSA at baseline was 91.6ng/ml. Sixteen patients received a prior chemotherapy (27%) and 3 (5%) a prior Strontium therapy. Forty-two patients (70%) received a prior radiation therapy. Disease sites were identified in the majority of patients (bone 77%, bone+nodes 7%, bone+visceral lesions 7%, bone+nodes+visceral lesions 5%, nodes 2%, visceral lesions 2%, nodes+visceral 2%). Eight patients (13%) responded to treatment; one had a complete response and seven had a partial response. The median duration of response was 13 weeks (4-24 weeks), and an additional 24 patients (40%) had stable disease for more than 3 months. Twenty-four patients (41%) had a ≥50% reduction in serum PSA from baseline for at least 2 months. The estimated median time to progression for all patients was 5.1 months (0.9 – 14.8 months). Estimated median survival for all patients from the start of treatment was 9.4 months (1.6-14.8 months).

As far as the safety profile in concerned, grade ≥3 toxicities consisted of diarrhea (10%), stomatitis (3%), asthenia (10%), neuropathy (5%), anemia (7%), and neutropenia (3%). One patient had renal insufficiency, one had a thrombocytopenia, and 2 patients had a grade 3 sepsis. There was no treatment related death. This trial with weekly docetaxel single agent chemotherapy might provide evidence of the favorable risk-benefit ratio of docetaxel in HRPC even in patients at an advanced stage of the disease and who have been heavily pretreated.

In addition to the scope of HRPC, phase I studies have been published in various tumor types with weekly docetaxel (33-36). These studies have used different dose levels ranging from 20 mg/m^2/week to 52 mg/m^2/week. There was evidence of antitumor activity at the various doses tested. Interestingly, Hainsworth et al. (20) conducted a phase I study to determine the MTD of weekly docetaxel

administered as a 30-minute infusion for 6 consecutive weeks followed by 2 weeks without treatment. Premedication consisted of a 3-dose dexamethasone regimen: 8mg PO at 12 hours and 1 hour prior to docetaxel, and then 12 hours after. Dose limiting toxicity of fatigue/asthenia was observed at the 43mg/m^2/week and 52mg/m^2/week dose levels. No grade 4 leucopenia of grade ¾ thrombocytopenia was observed at any of the dose levels tested. There were no arthralgias, myalgias and peripheral neuropathy using this schedule. At the 30mg/m^2/week dose level, there was no grade 3 or 4 toxicities reported. These studies suggest that weekly docetaxel is a suitable alternative, which can result in higher dose intensity without increased toxicity. This improvement of the therapeutic index is particularly important in the elderly such ad HRPC patients.

Docetaxel in combination therapy in HRPC

In vitro studies have demonstrated greater than additive cytotoxicity against the LNCaP, PC3 and Dui145 prostate cell lines. A clinical study was conducted with estramustine administered orally at a dose of 280 mg PO TID and docetaxel at dosages of 40, 60, 70 and 80 mg/m^2. Thirty-four patients were stratified into 2 groups; Minimally Pretreated (MPT) ($\leq$ 2 chemotherapies, $\leq$ 2 sites of radiation, no prior Strontium^{89}) and Extensively Pretreated (EPT) (All other patients). In the MPT patients, dose-limiting myelosuppression was reached at 80 mg/m^2 with 6 patients experiencing Grade ¾ granulocytopenia. In EPT patients, escalation was not attempted above 70 mg/m^2. Of the 20 minimally pretreated patients, 14 (70%) have had a greater than 50% decline in serum PSA on 2 consecutive measurements al least 2 weeks apart, with 45% manifesting a > 75% decline. Overall, 63% manifested a > 50% decline, while 34% demonstrated a > 75% decline. Of the 18 patients with measurable soft tissue metastases, 5 (28%, 95% Cl = 11 – 54%) demonstrated a partial response. Significant reduction of bone pain was noted, in 8 of 15 patients (53%) who were treated, (19 are still alive) with 68% surviving 1 year. Median survival is 24 months. Granulocytopenic fevers occurred in 1 patient (the minimum sepsis) with 53% of patients developing Grade 3 or 4 granulocytopenia (3%) usually of short duration. Two patients developed deep venous thrombosis (5.9%) both of whom had a prior history of this complication. Thus, these preliminary studies indicate that this combination can relieve symptomatic bone pain, result in both objective and PSA responses, and may actually improve survival with acceptable toxicity. (37-39)

The data demonstrate the activity of docetaxel at various dosing regimen in the range of 40 mg/m^2 to 70 mg/m^2 for the three-weekly schedule and at 20 to 40 mg/m^2 for the weekly schedule, in combination with estramustine at the dose of 280 mg tid for 5 days or 420 mg tid for 3-4 days. Estramustine 560 to 840 mg/day as single agent given in two or three divided doses, produced objective responses in 19% to 69% of patients and reduced the PSA level in 14% of patients. Evidence of the activity of the docetaxel-estramustine combination includes PSA decline (>50% decline in the range of 31 to 92% of patients), objective response in bidimensionally measurable lesions (17 to 75%), improved Karnofsky performance score or pain/symptom control from 53% to 88%. The safety of the combination has been assessed as acceptable. In the data published by Petrylak et al. (39), 2 episodes of grade 4 granulocytopenia were observed in patients who received more than 3 cycles of therapy. The incidence of thromboembolic events was 8.8%. No myocardial infarctions or pulmonary emboli were reported on the study. Gastrointestinal toxicity was observed, primarily nausea in 29% and vomiting in 12% patients. Fluid retention, generally of minimal severity, was reported in 65% of patients. In addition in a recent randomized study (9) significant survival benefit was observed with combination of estramustine+docetaxel+prednisone compared to mitoxantorene+prednisone (18.8-18 months vs 11.6 months p=0.002).

A newly published phase III study shows a significant increase in survival for patients treated with Taxotere®. (27) In the SWOG9916 study 770 patients with advanced hormone refractory prostate cancer were randomized to 280 mg of estramustine three times daily on days 1-5 and 60 mg/m^2 of docetaxel on day 2 given every three weeks or to 12 mg/m^2 of mitoxantrone on day 1 and 5 mg of prednisone twice daily given every three weeks. The overall survival was 17.5 months in the docetaxel group compared to 15.6 months in the mitoxantrone group (P=0.02). The corresponding hazard ratio for death was 0.80. PSA declines of at least 50% occurred in 50% and 27% of patients (P<0.001). Grade 3/4 neutropenic fevers (P=0.01), nausea and vomiting (P<0.001) and cardiovascular events (P=0.001) were more common in the docetaxel group than in the mitoxantrone group. Pain relief was similar in both groups.

2 RATIONALE

Promising results have been reported with docetaxel in HRPC in terms of i) objective responses in measurable lesions, ii) palliative response (pain relief, analgesic intake, symptom control, iii) PSA decline of more than 50%.

These results of docetaxel in HRPC, which compare favorably with data from other cytotoxic combinations reported thus far should be confirmed and further prospectively investigated through a multicenter randomized phase trials. Three weekly schedules of docetaxel have been widely used in oncology. In addition weekly dosing has shown to be effective. However it would be more suitable to the patient to be treated every second week especially in Nordic countries where distances from home to hospitals are very long for many patients. In addition biweekly docetaxel has shown to be effective and well tolerated in other tumor types (42,43). That is why biweekly dosing has been chosen to the experimental arm of this phase III randomized study.

Most recent studies in advanced prostate cancer have employed PSA as a marker of the therapeutic benefit. There is clear a correlation between PSA response and objective response in hormone sensitive prostate cancer, and some correlation with response in hormone refractory prostate cancer, though the relationship is imprecise (44,45).

We are aiming to use the simple**Quality of Life** instruments FACT-P (appendix) and VAS pain scale in this trial.

3 DRUG INFORMATION

3.1 Docetaxel (Taxotere®)

3.1.1 Origin

In the late1960's the National Cancer Institute large-scale plant-screening program found that a crude extract of the bark from the Pacific yew, Taxus brevifolia, had activity against the P388 mouse leukemia. In 1971, Wani, Taylor et al. isolated and characterized paclitaxel (Taxol®), the active

principle of the extract. It has become evident that paclitaxel (Taxol®)) has active against several human malignancies including refractory ovarian cancer and breast cancer.
Several years ago, researchers at Rhone-Poulenc Rorer with the cooperation of the French "Centre National de Recherche Scientifique (CNRD)" were able to prepare docetaxel (Taxotere®), a semisynthetic analog of paclitaxel, using a precursor extracted from the needles of the European yew, Taxus baccata, a renewable source.

3.1.2 Name and chemical information

- Chemical name: (2R, 3S)-N-Carboxy-3-phenylisoserine, N-*tert*-butyl ester, 13-ester with 5β-20-epoxy-1, 2α, 4, 7β, 10β, 13α-hexahydroxytax-11-en-9-one4-acetate 2-benzoate, trihydrate

- Empirical formula: $C_{43}H_{53}NO_{14}.3H_2O$
- Molecular weight: 861.9
- Appearance: White to off white powder

3.1.3 Mechanism of action

Docetaxel has a mechanism of action which is similar to (or may be identical to) paclitaxel. Docetaxel enhances microtubule assembly and inhibits the depolymerization of tubulin. As with paclitaxel, this can lead to bundles of microtubules in the cell, which by blocking cells in the M phase of the cell cycle, results in the inability of the cells to divide. This contrasts with the action of other spindle poisons in clinical use such as colchicines or vinca-alkaloids which inhibit tubulin assembly in microtubules.

Comparing docetaxel and paclitaxel using the "tubulin *in vitro* assay", the concentration required to provide 50% inhibition of microtubule disassembly (or IC50) is 0.2 μm for docetaxel and 0.4 μm for paclitaxel.

3.1.4 Toxicology

The major toxic effect of docetaxel which limits dose is neutropenia. Other toxic effects which may be seen include leucopenia, thrombocytopenia, anemia, asthenia, dysgeusia, myalgia, arthralgia, nail changes and conjunctivitis. Severe anaphylactoid reactions, characterized by a flush associated with hypo- or hypertension, with or without dyspnea, may occur. Other toxicities include cutaneous reactions (e.g., skin rash, desquamation following localized pruriginous maculopapular eruption, skin erythema with edema), hypersensitivity reactions (flushing, pruritis, fever, chills, rigor, lower back pain), dyspnea with restrictive pulmonary syndrome, pleural effusions, arrhythmias, pericardial effusions, fluid retention syndrome, ascites, myopathy, digestive tract toxicities (nausea, vomiting, oral mucositis, diarrhea, anorexia), alopecia, extravasation reaction (erythema, swelling, tenderness, pustules), reversible peripheral phlebitis, peripheral edema, reversible increase in liver function tests, hepatic failure and neurotoxicity (reversible dysesthesias or paresthesias, peripheral neuropathy, seizure, headache, lethargy or somnolence). Patients with SGOT> 1.5 times normal and alkaline phosphatase > 2.5 times normal appear to have decreased docetaxel clearance and appear to be more likely to suffer severe toxicity, including drug-related death.

3.1.5 Pharmaceutical particulars

Formulation: Each blister carton of TAXOTERE 80 mg concentrate and solvent for solution for infusion contains: one single-dose TAXOTERE vial and, one single-dose solvent for TAXOTERE vial.

TAXOTERE 80 mg concentrate for solution for infusion vial:
The TAXOTERE 80 mg concentrate for solution for infusion vial is a 15 ml clear glass vial with a red flip-off cap. This vial contains 2 ml of a 40 mg/ml solution of docetaxel in polysorbate 80 (fill volume: 94.4 mg/2.36 ml). This fill volume has been established during the development of TAXOTERE to compensate for liquid loss during preparation of the premix due to foaming, adhesion to the walls of the vial and "dead-volume". This overfill ensures that after dilution with the entire contents of the accompanying solvent for TAXOTERE vial, there is a minimal extractable premix volume of 8 ml containg 10 mg/ml docetaxel which corresponds to the labeled amount of 80 mg per vial.

Solvent vial: The solvent vials is a 15 ml clear glass vial with a transparent colourless flip-off cap. Solvent vial contains 6 ml of a 13% w/w solution of ethanol in water for injections (fill volume: 7.33 ml). The addition of the entire contents of the solvent vial to the contents of the TAXOTERE 80 mg concentrate for solution for infusion vial ensures a premix concentration of 10 mg/ml docetaxel.

Storage: Vials should be stored between 2°C and 25°C and protected from bright light.

Preparation for the intravenous administration:

preparation of the TAXOTERE premix solution (10 mg docetaxel/ml):
If the vials are stored under refrigeration, allow the required number of TAXOTERE boxes to stand at room temperature for 5 minutes. Using a syringe fitted with a needle, aseptically withdraw the entire contents of the solvent for TAXOTERE vial by partially inverting the vial. Inject the entire contents of the syringe into the corresponding TAXOTERE vial. Remove the syringe and needle and mox manually by repeated inversions for at least 45 seconds. Do not shake. Allow the premix vial to stand for 5 minutes at room temperature and then check that the solution is homogenous and clear (foaming is normal even after 5 minutes due to the presence of polysorbate 80 in the formulation). The premix solution contains 10 mg/ml docetaxel and should be used immediately after preparation. However the chemical and physical stability of the premix solution has been demonstrated for 8 hours when stored either between 2°C and 8°C or at room temperature.

Preparation of the infusion solution:
More than one premix vial may be necessary to obtain the required dose for the patient. Based on the required dose for the patient expressed in mg, aseptically withdraw the corresponding premix volume containing 10 mg/ml docetaxel from the appropriate number of premix vials using graduated syringes fitted with a needle. For example, a dose of 140 mg docetaxel would require 14 ml docetaxel premix solution. Inject the required premix volume into a 250 mg infusion bag or bottle containing either 5% glucose solution or 0.9% sodium chloride solution. If a dose greater than 200 mg of docetaxel is required, use a larger volume of the infusion vehicle so that a concentration of 0.74 mg/ml docetaxel is not exceeded. Mix the infusion bag or bottle manually using a rocking motion. The TAXOTERE infusion solution should be used within 4 hours and should be aseptically administered as a 1-hour infusion under room temperature and normal lighting conditions. As with all parenteral products,

TAXOTERE premix solution and infusion solution should be visually inspected prior to use, solutions containing a precipitate should be discarded.

Disposal:
All materials that have been utilized for dilution and administration should be disposed of according to standard procedures.

Supplier: Commercially available Taxotere® will be used in this study. It is produced by sanofi-aventis.

3.2 Prednisone

Prednisone is a glucocorticoid rapidly absorbed from the GI tract.

3.2.1 Toxicology

Human Toxicology: Possible adverse effects associated with the use of prednisone are: fluid and electrolyte disturbances, congestive heart failure in susceptible persons, hypertension, euphoria, personality changes, insomnia, mood swings, depression, exacerbation of infection (e.g., tuberculosis), exacerbation or symptoms of diabetes, psychosis, muscle weakness, osteoporosis, vertebral compression fractures, pancreatitis, esophagitis, peptic ulcer, dermatological disturbances, convulsions, vertigo and headache, endocrine abnormalities, ophthalmic changes, and metabolic changes. Some patients have experienced itching and other allergic, anaphylactic or other hypersensitivity reactions. Withdrawal from prolonged therapy may result in symptoms including fever, myalgia and arthralgia. Phenytoin phenobarbitol and ephedrine enhance metabolic clearance of corticosteroids.

Corticosteroids should be used cautiously in patients with hypothyroidism, cirrhosis, ocular herpes simplex, existing emotional instability or psychotic tendencies, nonspecific ulcerative colitis, diverticulitis, fresh intestinal anastomoses, peptic ulcer, renal insufficiency, hypertension, osteoporosis and myasthenia gravis. Immunization procedures (especially smallpox vaccination) should not be undertaken in patients on corticosteroids.

3.2.2 Pharmacology

Kinetics: Natural and synthetic glucocorticoids are readily and completely absorbed from the GI tract. Prednisone is very slightly soluble in water. Glucocorticoids have salt-retaining properties. The anti-inflammatory property of this drug is its ability to modify the body's immune system. On the other hand, glucocorticoids suppress the body's response to viral as well as bacterial infections. Equivalent doses are ad follows:

Dexamethasone	Methyl-prednisolone and Triamcinolone	Prednisolone and Prednisone	Hydrocortisone	Cortisone
0.75 mg	4 mg	5 mg	20 mg	25 mg

Formulation: Prednisone is available in 2,5 mg, 5 mg, 10 mg, 20 mg and 50 mg tablets.

Storage and Stability: Prednisone should be stored at room temperature.

Administration: Prednisone is administered orally.

Supplier: Prednisone is commercially available and should be purchased by third party.

4 AIMS OF THE STUDY

The study is designed to evaluate the effect of biweekly docetaxel monotherapy compared to the docetaxel monotherapy given every third week in the treatment of metastatic hormone refractory prostate cancer (HRPC). The primary end point is time to treatment failure. Secondary end points include response rate, quality of life, safety and overall survival.

5 PRIMARY OBJECTIVE

To compare time to treatment failure in the two arms.

6 SECONDARY OBJECTIVE

To compare:
- Quality of life
- Response rates
- Safety
- Overall survival

Only in Finland to study the need of epoetin beta in the the different chemotherapy
To study the effect of epoetin beta
- **on hemoglobin**
- **on transfusion rate**
- **on quality of life**

7 TRIAL DESIGN AND STUDY TREATMENT

7.1 Prospective, non-blinded randomized phase III trial

7.1.1 Treatment arms

Arm A: Taxotere® 50 mg /m^2 IV in 1 hour on day 1 and 15, one cycle is 28 days
Prednisone 10 mg PO daily

Dexamethasone 7.5 mg PO
12 hours and 1 hour prior to docetaxel infusion
evening of day 1

In Ireland Dexamethasone 8.0 mg PO
8.0 mg Day before treatment
8.0 mg BD day of treatment
8.0 mg day after treatment

Arm B: Taxotere® 75 mg/m^2 IV on day 1, one cycle is 21 days
Prednisone 10 mg PO daily

Dexamethasone 7.5 mg PO
12 hours and 1 hour prior to docetaxel infusion
evening of day 1, morning and evening of day 2, morning of day 3

For Ireland: Dexamethasone 8 mg PO. **Day before treatment 8 mg BD day of treatment, 8mg day after treatment**.

Only in Finland: In each treatment arm patients who, at any time during chemotherapy experiences anemia (Hb < 110 g/l) will start epoetin beta (NeoRecormon®) as a study drug. The starting dose is 30 000 IU once weekly. In non-responding patients the dose will be escalated to 60 000 IU/week as detailed below.

Randomization will be centralized and stratified for center and WHO performance status (Z 0-1 vs Z2).

7.2 Number of Patients and enrollment period

360 patients altogether; 180 patients in each arm / Enrollment period 12/2003 – 12/2007

7.3 Duration of treatment

In both arms treatment should be continued until treatment failure defined as; disease progression, unacceptable toxicity, patient's refusal to continue or death.

7.4 Concomitant treatment

Local palliative radiotherapy can be administered for pain. If patient have ongoing bisphosphonate treatment or chemical castration treatment with LHRH analogues at start of the study, these treatments can be continued. Starting bisphosphonate treatment or chemical castration treatment during the study is not allowed.

Patients testosterone must be at castration level induced either by orchiectomy or by using LH-RH analogue. If LH-RH analog treatment has been stopped for any reason, it should be re-started. Testosterone (castration level) and PSA levels (rising PSA) should be tested before inclusion of the patient to the study. Patients on continuous treatment with polyestradiol phosphate (Estradurin) as castration therapy (with serum testosterone at castration level) are also eligible for inclusion in study.

8 SELECTION OF PATIENTS

8.1 Inclusion criteria

(1) Histologically/ cytologically proven adenocarcinoma of prostate.

(2) Metastatic disease (confirmed by imaging or clinical examination)

(3) Hormone refractory prostate cancer defined as rising PSA values in 2 sequential measurements **(at least 2 weeks apart)**

(4) Testosterone levels must be within the institutions castration levels.

(5) PSA > 10 µg/l

(6) No previous cytostatic treatment except extramustine phosphate which should be stopped ≥ 3 weeks before starting trial medication

(7) Anti-androgen treatment must be stopped ≥ 3 weeks before starting trial medication.

(8) WHO performance status ≤ 2

(9) Age > 18 years

(10) Laboratory requirements :

(a) Hematology :
- neutrophils ≥ 1.5 x 10^9/ l
- hemoglobin ≥ 110 g/l **, HB ≥ 100 g/l in Sweden and Ireland**
- platelets ≥ 100 x 10^9/l

(b) Hepatic function :
- total bilirubin ≤ 1 x UNL
- ALAT and ASAT ≤ 2.5 x UNL, Alkaline Phosphate ≤ 6 x UNL. In the presence of extensive bone disease, Alkaline. Phosphate is > 6 x UNL, the patient is eligible for ~~in~~ the study.

(c) Renal function :
-Creatinine ≤ 1.5 x UNL (ie NCI grade ≤ 1)

8.2 Exclusion criteria

(1) Less than 4 weeks since the completion of surgery.

(2) Prior radiotherapy > 25% of bone marrow

(3) Less than 3 weeks since estramustine phosphate treatment

(4) Prior therapy with radioisotopes

(5) Other malignant disease/ malignancy (except basalioma) within the past 5 years.

(6) Serious liver disease

(7) Other serious illness or medical condition:
(a) Serious cardiac disease; ischemic or tromboembolic cardiac disease, pulmonary emboli, cardiac infarction within 12 months

(b) Active infection
(c) Active peptic ulcer, uncontrolled diabetes mellitus or other contraindications for the use of corticosteroids.
(d) Auto-immune disease (lupus, scleroderma, rheumatoid polyarthritis)

9 EFFICACY ENDPOINT DEFINITIONS

9.1 Primary endpoint

9.1.1 Time to treatment failure

1) the progression of the disease will be defined as:

1a) progression in PSA (defined by AUA guidelines)

1 b) progression of evaluable or measurable metastases

2) unacceptable toxicity

3) patient's refusal to continue treatment

4) death

9.2 Secondary endpoint:

9.2.1 Quality of life

Quality of life assessment will be performed using the quality of life questionnaire FACT–P. Pain measurement will be analyzed by VAS (Visual Analogue Scale).

9.2.2 Response rates

Will be defined according to the AUA criteria and/or RECIST criteria for measurable disease

9.2.3 Safety

Will be measured by using CTC-AE **Version 2.0** common toxicity criteria

9.2.4 Overall survival

Overall survival is defined as the time between randomization and death

In Finland: 9.2.5 and 9.2.6 as in original protocol 07.01.2004, 9.2.7.as amendment 4 10.03.2005

10 STATISTICAL ANALYSIS

The sample size calculations are based on time to progression. Median time to progression in the every 3 weeks Taxotere® group is, according to findings in earlier reports, approximately five months. It is considered of clinical importance to detect a difference of two months in time to treatment failure (TTF); hence a median TTF on in the biweekly Taxotere® group of seven months would be clinically relevant. Using a two-sided test, a significance level of 5%, a power of 80%, an inclusion rate of 40 patients every five months and a minimum observation time of six months, a total of 348 patients is required (174 patients in each treatment arm). These calculations are based on the assumption that time to progression is approximately exponentially distributed.

11 DETAILED PLAN

INVESTIGATIONS	**TIMING prior to randomization**	**TIMING on-study**	**TIMING end of study & follow-up**
1. Informed consent	per registration		
2. History / physical exam (including clinical tumor assessment)	within 14 days	every 6 weeks (day 1 before infusion)	end of study Clinical tumor assessment: every 12 weeks
3. Hematology*	within 14 days	on day 1 before infusion. Every 2 days in case of febrile neutropenia or infection up to fever $\geq$-38ºC and neutrophils $\geq$-1.0 x 10^9/L	end of study
4. Biochemistry (+)	within 14 days	every 3 or 4 weeks (day 1 before infusion)	end of study
5. PSA**	within 14 days	every 6 weeks (day 1 before infusion)	end of study, every two months until PSA progression or further therapy
6. Adverse events	within 14 days	every 3 or 4 weeks (day 1 before infusion)	30 days after the last study drug infusion***
7. Radiology (#) Tumor assessment (§)	within **6 weeks** 6 weeks	every 12 weeks and to confirm a response	end of study every two months

		within 28 days	until progression
8. **Bone Scan**	**within 6 weeks**	target lesions are followed by x-rays every 12 weeks	
9. ECG	within 21 days	as indicated	end of study
10. Quality of life (++)	within 3 days	every 6 weeks (before infusion)	end of study every two months up to further therapy
11. Other investigations	within 14 days	as indicated	as indicated

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* WBC, neutrophils, platelet, hemoglobin. Hb level must also be determined and recorded immediately prior to any transfusion being given. For the first 20 patients in treatment arm B additional hematology sample is taken on Day 8 and when clinically indicated for safety reasons.

** Confirmatory value of rising PSA at study entry should be obtained within 4 weeks prior to randomization. In addition, a baseline PSA should be obtained within 14 days prior to randomization. To ensure comparability, PSA assessments for one patient must be performed in the same laboratory from baseline up to the end of study.

(+) Alkaline phosphatase, bilirubin, ASAT (SGOT), ALAT (SGPT), serum creatinine, calcium, albumin and other tests if clinically indicated. Testosterone level at baseline. Serum samples stored at - 20°C .

(#) To ensure comparability, the baseline X-rays/ultrasounds/scans and subsequent X-rays/ ultrasounds/scans to assess response must be performed using identical techniques (i.e., scans performed immediately following bolus contrast administration using a standard volume of contrast, the identical contrast agent, and preferably the same scanner).
Each lesion must be followed with the same method throughout the study (from baseline until follow-up) with the exception of baseline bone scan.

(§) To be performed at baseline: chest x-ray/CT scan, abdominal and pelvic CT scan; other procedures as indicated.
If initially positive, repeat after every 12 weeks, then 28 days after the response is observed.
If initially negative, repeat when clinically indicated.

++ Fact-P and VAS

11.1 Blood transfusions

Blood transfusions may be given in case of medical need, for example in case of severe symptoms of anemia (eg angina pectoris, exercise intolerance, dyspnoea at rest). Every reasonable effort should be made to avoid blood transfusions in patients with hemoglobin levels above 80 g/l. A target Hb level for transfusion should not exceed 100 g/l. Transfusions should be recorded in the dedicated log sheet provided in the CRF.

12 TOXICITIES TO BE MONITORED AND DOSAGE MODIFICATIONS

12.1 Dose Modifications

12.1.1 Dose Modifications for Docetaxel

Dose adjustments are to be made according to the system showing the greatest degree of toxicity. Toxicities will be graded using the NCI-CTC (Appendix 4). It toxicity occurs, the appropriate treatment will be used to ameliorate signs and systems including antiemetics for nausea and vomiting, anti-diarrhoeal for diarrhea, and antipyretics and antihistamines for drug fever toxicity grade is determined. Dose adjustments for toxicity should be made according to guidelines, which follow. In general, doses which have been reduced for toxicity should not be re-escalated back to starting level. Treatment may be delayed no more than three weeks to allow recovery from toxicity. If treatment must be delayed longer than three weeks, patient should be removed from protocol treatment.

DOSE MODIFICATION TABLE

DOSE LEVEL	3-WK DOCETAXEL	BIWEEKLY DOCETAXEL
0	**75 mg/m^2**	**50 mg/m^2**
-1	**60 mg/m^2**	**40 mg/m^2**
-2	**45 mg/m^2**	**30 mg/m^2**
-3	**30 mg/m^2**	**20 mg/m^2**

Note: Patients requiring dose reduction below Level –3 should be removed from protocol treatment.

12.1.1.1 Myelosuppression

Grade 1, 2 and 3 myelosuppression (neutropenia, thrombocytopenia) and Grade 4 neutropenia except as defined below, with recovery, does not require dose modification.

In order to maximize dose intensity, patients with a febrile Grade 4 neutropenia $\geq$ 7 days or Grade $\geq$ 3 neutropenia associated with fever (one reading of oral temperature > 38.5°C, or three readings of oral temperature > 38.0°C in a 24-hous period) should be retreated after recovery but with a one level dose reduction.

Grade 4 trombocytopenia (platelet count < 25,000) at any time necessitates a dose reduction by one level.

G-CSF is not in general permitted. **Standard G-CSF administration can be applied in accordance to your hospital guidelines.**

12.1.1.2 Neurotoxicity

If ≥ Grade 3, the patient will be removed from protocol treatment.

If Grade 2, patient should be retreated upon recovery to a ≤ Grade 1 toxicity with a dose reduction of docetaxel by one level.

12.2 Management of acute hypersensitivity reactions

Acute hypersensitivity reaction to docetaxel should be managed as outlined in the following table:

Management of Hypersensitive Reactions

Hypersensitive	**Treatment Guidelines**
Grade 1	● consider decreasing the rate of infusion until recovery from symptoms, stay at beside and monitor patient ● then, complete docetaxel infusion at the initial planned rate
Grade 2 and Grade 3	● interrupt docetaxel infusion ● give diphenhydramine 50 mg IV with or without dexamethasone 10 mg IV, monitor patient until resolution of symptoms ● resume docetaxel infusion after recovery of symptoms; depending on the physician's assessment of the patient, docetaxel infusion should be resumed at a slower rate, then increased incrementally to the initial planned rate, (e.g., infuse ad an 8 hour rate 5 minutes, then at a 4-h rate for 5 minutes, then at a 2-h rate for 5 minutes, then finally, resume at the 1-h infusion rate)
Grade 2 and Grade 3	●depending on the intensity of the reaction observed, additional oral or IV premedication with an antihistamine should also be given for the **next cycle** of treatment, and the rate of infusion should be decreased initially and then increased back to the recommended 1-hour infusion, (e.g., infuse ad an 8 hour rate for 5 minutes, then at a 4-h rate for 5 minutes, then at 1 2-h rate for 5 minutes, and finally, administer at the 1-h infusion rate)
Grade 4	●***REMOVE PATIENT FROM PROTOCOL TREATMENT***

Any hypersensitivity reaction should be recorded as an adverse event.

In case of late-occurring hypersensitivity symptoms (e.g., appearance within 1 week after treatment of a localized or generalized pruritis), symptomatic treatment may be given (e.g., oral antihistamine). Additional oral or parenteral premedication with antihistamine may also be given for the next cycle of

treatment, depending on the intensity of the reaction observed. No dose reductions will be made in any case.

Standard Acute Hypersensitivity Reaction Management can be applied in accordance to your hospital guidelines.

12.2.1 Management of subsequent cycles

Patients with hypersensitivity reactions to docetaxel are at risk for recurrent reactions. These patients must be informed of the potential risk of recurrent allergic reactions and must be carefully monitored.

Fluid Retention (docetaxel)

No dose reduction is planned. Patients developing new onset or symptomatic edema, or other signs of increasing fluid retention, should be treated with oral diuretics. .

Further therapy should be customized depending upon the clinical situation. The clinical tolerance of the patient, the overall tumor response and the medical judgment of the investigator will determine if it is in the patient's best interest to continue or discontinue protocol treatment. It the patient is discontinued due to any toxicity, they must be followed to monitor duration of toxicity, response, and time to progression, until the initiation of any new systemic therapy.

Standard Management of Fluid Retention can be applied in accordance to your hospital guidelines.

12.3 Abnormal Liver Function Tests

Patients, who develop abnormal liver function tests (if alkaline phosphatase increased due to extensive bone metastases don't apply these reductions) while on the study, for any reason, will have the following dose reduction:

DOSE MODIFICATIONS FOR ABNORMAL LIVER FUNCTION

BILIRUBIN	ALKALINE PHOSPHATASE	SGOT	ACTION
> ULN **OR**	> 5 x ULN **OR**	> 5 x ULN	Wait 3 weeks. If recovered *, reduce docetaxel dose by one level
≤ ULN **AND**	≤ 5 x ULN **AND**	1.6 – 5 x ULN	Reduce docetaxel dose by one level

* Bilirubin ≤ 1.5 UNL and alkaline phosphatase ≤ 5 x ULN and SGOT ≤ 5 x ULN.

Note: Patients requiring dose reduction below Level –3 should be removed from protocol treatment.
ULN = upper limit of normal for institution.

12.4 Cutaneous Toxicity

If Grade 1 or 2 cutaneous toxicity occurs, no change in the dose will be made. If occurring at the time of scheduled retreatment, withhold treatment until ≤ Grade 1 for a maximum of two weeks and retreat with a one level dose reduction. It there is no recovery to ≤ Grade 1 within 2 weeks, the patient will be removed from protocol treatment. If Grade 3 or 4 toxicity occurs, proceed ad follows:

If occurring at the time of scheduled retreatment, withhold treatment until ≤ Grade 1 for a maximum of two weeks and retreat with a one level dose reduction. If there is no recovery to ≤ Grade 1 within 2 weeks, the patient will be removed from protocol treatment.

If the toxicity occurs during the cycle, and they have recovered at the time of scheduled retreatment, retreat with a one level dose reduction.

12.5 Diarrhea

In the case of severe diarrhea, octreotide is recommended. It the patient has significant diarrhea (≥ 3 loose stools/24 hr), the patient should be treated prophylactically in the subsequent cycles with 2 tablets of loperamide or dishenoxylate in addition to 1 or 2 tablets after each loose stool. In case of diarrhea ≥ Grade 2 despite the prophylactic treatment, patient must go off protocol treatment. Appropriate symptomatic treatment with loperamide or disphenoxylate hydrochloride with atropine sulfate should be given.

Standard treatment of Diarrhea on can be applied in accordance to your hospital guidelines.

12.6 Thromboembolic Event

If a documented deep venous thrombosis or pulmonary embolism occurs docetaxel may continue, but patient must be anticoagulated according to the current practice of the individual hospital.

12.7 Other Toxic Effects

If toxicities ≤ Grade 2, manage symptomatically, if possible and retreat without dose reduction.

If toxities ≥ Grade 3 (not mentioned above), drug should be withheld (expect for anemia) until resolution to ≤ Grade 1 or baseline if baseline was greater than Grade 1, then reinstituted, if medically appropriate, at a dose reduction of one level.

13 CRITERIA FOR EVALUATION AND ENDPOINT DEFINITIONS

13.1 Definitions

RECIST criteria, Therasse et al. J Natl Cancer Inst 2000; 92:205-16 (50)

Measurable lesion: lesions that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm with conventional techniques or as ≥ 10 mm with spiral CT scan

Non-measurable lesion: all other lesions, including mall lesions (longest diameter < 20 mm with conventional techniques or < 10 mm with spiral CT scan and truly non-measurable lesions. Truly non-measurable lesions include the following: bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, abdominal ~~n~~ masses that are not confirmed and followed by imaging techniques, and cystic lesions.

Target lesions: All measurable lesions up to a maximum of 5 lesions per organ and 10 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size and their suitability for accurate repeated measurements. A sum of the longest diameter will be used as the reference by which to characterize the objective tumor response.

Non-target lesions: all other lesions (or sites of disease) should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

1. **Complete Response (CR):** Complete disappearance of all target and non-target lesions. This should be determined by observations not less than 4 weeks apart. No new lesions. No disease related symptoms. Normalization of markers and other abnormal laboratory values.

2. **Complete Response Non-Measurable (CRNM)**: The term "PSA complete response" will not be used.

3. **Partial Response (PR)**: Applies only to patients with at least one measurable lesion. At least a 30% decrease in the sum of the longest diameters of target lesions, taking reference the baseline sum longest diameter. This observation must be confirmed by a repeat assessment not less than 4 weeks after the criterion is first met. .No progression of non-target lesions. No new lesions.

4. **Partial Response Non-Measurable (PNRNM):** Two or more measures of PSA that indicate a reduction of 50% or greater relative to baseline. Patients achieving a PSA of less than 0.2 ng/ml will be coded as PRNM.

5. **Stable:** Does not quality for CR, PR, PRNM or Progression

6. **Progression:** At least 20% increase in the sum of the longest diameters of target lesions, taking as a reference the smallest sum longest diameter recorded since the treatment started or the appearance of one or more new lesions. Reappearance of a lesion that had disappeared or clear worsening of nontarget lesions will constitute progression.

Exceptions: (1) In cases for which initial tumor flare reaction is possible (hypercalcemia, increased bone pain, erythema of skin lesions), either symptoms must persist beyond four weeks on there must be additional evidence of progression. (2) Lesions which appear to increase in size due to presence of necrotic tissue will not be considered to have progressed.

7. **Rising PSA:** Progressive disease is a 25% increase in PSA over the last pre-registration measure and this must be at least 5 μg/l in absolute value. For patients whose PSA decreased on trial, progressive disease would be considered to have occurred when a 25% increase over the nadir in confirmed (provided that the increasing measure is at least of 5 μg/l).

8. **Unknown:** Progression has not been documented and one or more measurable or evaluable sites have not been assessed.

Time to treatment failure is measured from the time of initiation of chemotherapy until the time to documented progressive disease, permanent cessation of therapy, loss of follow up, or to death whichever came first.

Best Response:

This will be calculated from the sequence of objective statuses.

a. CR: Two or more objective statuses on CR a minimum of three weeks apart documented before progression.
b. PR: Two or more objective statuses of PR or better a minimum of three weeks apart, but not qualifying as CR.
c. PRNM: Two or more objective statuses of PRNM or better a minimum of three weeks apart, but not qualifying as CR.
d. Unconfirmed CR: One objective status of CR documented before progression and at least weeks after registration, but not qualifying as CR.
e. Unconfirmed PR: One objective status of PR documented before progression and at least 3 weeks after registration, not qualifying as CR, PR or unconfirmed CR.
f. Stable/no response: At least one objective status of stable/no response at least 3 weeks after registration, but not qualifying as anything else above.
g. Increasing disease: First objective recorder (other than Unknowns or ones before 3 weeks) is Progression, provided this occurs within 8 weeks of registration.
h. Inadequate assessment, response unknown: Progression greater than 8 weeks after registration and either all objective statuses prior to progression are unknown, or the only known objective statuses occurred less than 3 weeks after registration.

Progression–free Survival: From date of registration to date of first observation of progressive disease, or death due to any cause.

Time to Death: From date of registration to date of death due to any cause.

14 ETHICAL AND REGULATORY CONSIDERATIONS

The study will be performed in accordance with the new EU Directive, Good Clinical Practice, Declaration of Helsinki (52nd WMA General Assembly Edinburgh, Scotland, October 2000) and local regulations.

14.1 Informed Consent

Written informed consent is obtained from every patient before randomization.

14.2 Institutional Review

This study must be approved by an appropriate national and institutional review committee.

14.3 Monitoring

This study will be monitored regularly according to GCP and local regulations. A local monitor in each involved country will be assigned.

15 DRUG ACCOUNTABILITY

For each drug supplied for a study, an accountability ledger containing current and accurate inventory records covering receipt, dispensing, ant the return of study drug supplies must be maintained as standard practice of the hospital. Drug supplies must be kept in a secure, limited access storage area under the recommended storage conditions.

16 PUBLICATION AND INDUSTRY CONTACT

Taxotere®, used in this protocol is produced by sanofi-aventis and is commercially available.

Collaborator(s) data is confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators.

17 ADVERSE EXPERIENCES

An adverse event is any symptom, sign, illness or experience, which develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

Any adverse event shall be reported on the adverse event form of the CRF. The report should include, whenever possible, the investigator's written medical judgment as to relationship of the adverse experience to study medications(s) (i.e., "probable", "possible", or "unrelated").

If the event is considered to be serious, it shall be reported as a serious adverse event.

A serious adverse event is any event that is:

- fatal
- life-threatening
- requires or prolongs hospitalization
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event.

Unexpected serious adverse events during the study should be reported to the local Medical Product Agency according to national regulations and to the study coordinator in its country, if they are considered to be related to study medication and unexpected. The study coordinator in each country is responsible for this report to be forwarded without delay to the local sanofi-aventis Drug Safety Office and to Roche Oy in Finland. If the event is life-threatening or results in death it should be reported as soon as possible or at the latest within 7 days.

Symptoms and death related to proven tumor progression should not be considered as serious adverse events.

An annual report will be produced yearly.

18 DATA MANAGEMENT

There will be a database in Tammerfors for data management. The signed original Case-Report Forms (CRF) shall be sent to the study secretariat in Tammerfors for further working. A copy of the CRF shall remain in the patient's file.

18.1 Safety and Efficacy Analyses

An interim hematological toxicity analysis will occur once 50 patients has been at least 3 months in the trial. The toxicity and tolerability of the two treatment arms may be analyzed based on the calculation of decease in Grade 3-4 side-effects from 40% to 20% using α=0.05 and β=0.20, 79 patients would be required in each arm, total 148 patients. These results of this interim safety analysis may be published separately. The primary efficacy analysis will be done 6 months after the randomization the last patient.

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APPENDIX 1 INSTRUCTIONS FOR USE AND HANDLING OF NEORECORMON® (EPOETIN BETA) PRE-FILLED SYRINGES (30,000 IU/0.6 ML)

Only for Finland as in Amendment 4 10 March 07

APPENDIX 2 QUALITY OF LIFE QUESTIONNAIRE Fact P (Version 4)

Below is a list of statements that other people with your illness have said are important. **By circling one (1) number per line, please indicate how true each statement has been for you <u>during the past 7 days.</u>**

PHYSICAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
I have a lack of energy	0	1	2	3	4
I have nausea (I feel sick)	0	1	2	3	4
Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
I have pain	0	1	2	3	4
I am bothered by side effects of treatment	0	1	2	3	4
I feel ill	0	1	2	3	4
I am forced to spend time in bed	0	1	2	3	4

SOCIAL/FAMILY WELL-BEING	**Not at all**	**A little bit**	**Some what**	**Quite a bit**	**Very much**
I feel close to my friends	0	1	2	3	4
I get emotional support from my family	0	1	2	3	4
I get support from my friends	0	1	2	3	4
My family has accepted my illness	0	1	2	3	4
I am satisfied with family communication about my illness	0	1	2	3	4
I feel close to my partner (or the person who is my main support)	0	1	2	3	4

Regardless of your current level of sexual activity, Please answer the following question. If you prefer not to answer it, please check this box □ and go to the next section.

I am satisfied with my sex life	0	1	2	3	4

By circling one (1) number line, please indicate how true each treatment has been for you during the past 7 days.

EMOTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
I feel sad	0	1	2	3	4
I am satisfied with how I am coping with my illness	0	1	2	3	4
I am losing hope in the fight against my illness	0	1	2	3	4
I feel nervous	0	1	2	3	4
I worry about dying	0	1	2	3	4
I worry that my condition will get worse	0	1	2	3	4

FUNCTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
I am able to work (include work at home)	0	1	2	3	4
My work (include work at home) is fulfilling	0	1	2	3	4
I am able to enjoy life	0	1	2	3	4
I have accepted my illness	0	1	2	3	4
I am sleeping well	0	1	2	3	4
I am enjoying the things I usually do for fun	0	1	2	3	4

I am content with the quality of my life right now	0	1	2	3	4

By circling one (1) number per line, please indicate how true each statement has been for you <u>during the past 7 days.</u>

ADDITIONAL CONCERNS	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
I am loosing weight	0	1	2	3	4
I have a good appetite	0	1	2	3	4
I have aches and pains that bother me	0	1	2	3	4
I have certain area of my body where I experience significant pain	0	1	2	3	4
My pain keeps me from doing things I want to do	0	1	2	3	4
I am satisfied with my current level of physical comfort	0	1	2	3	4
I am able to feel like a man	0	1	2	3	4
I have trouble moving my bowels	0	1	2	3	4
I have difficulty urinating (passing water)	0	1	2	3	4
I urinate more frequently than usual	0	1	2	3	4
My problems with urinating limit my activities	0	1	2	3	4
I am able to have and maintain an erection	0	1	2	3	4

APPENDIX 3 INVESTIGATOR'S AGREEMENT

I have read the preceding protocol, A PHASE III TRIAL COMPARING DOCETAXEL EVERY THIRD WEEK TO BIWEEKLY DOCETAXEL MONOTHERAPY IN METASTATIC HORMONE REFRACTORY PROSTATE CANCER PATIENTS (PROSTY-trial), and agree that it contains all necessary details for conducting this study.

I will conduct the study as outlined therein and will attempt to complete the planned enrolment of patients during the defined enrollment period 12/2003-12/2007. I will provide copies of the protocol and all drug information to all relevant staff members. I will discuss this material with them to assure that they are fully informed regarding the drug and conduct of the study. I agree to keep accurate records on all patient information (Case Report Forms and patient's informed consent statement), and all other information collected during the study for a minimum of 15 years or local law.

All parties agree to ensure direct access to examine, analyze, verify and reproduce source data/documents, and reports from all trial related sites for the purpose of inspection by domestic and foreign regulatory authorities or for the purpose of monitoring by the investigators.

Investigator:	**Principal Investigator:**
_____ name, printed	professor Pirkko Kellokumpu-Lehtinen
_____ signature	_____ signature
_____ / _____ / 20____ date	_____ / _____ / 20____ date

APPENDIX 4 Response Evaluation Criteria in Solid Tumors (RECIST) Quick Reference: http://ctep.cancer.gov/forms/quickrcst.doc

Eligibility

Only patients with measurable disease at baseline should be included in protocols where objective tumor response is the primary endpoint.

Measurable disease **- the presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology**.

Measurable lesions - lesions that can be accurately measured in at least one dimension with longest diameter ≥20 mm using conventional techniques or ≥10 mm with spiral CT scan.

Non-measurable lesions - all other lesions, including small lesions (longest diameter <20 mm with conventional techniques or <10 mm with spiral CT scan), i.e., bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, cystic lesions, and also abdominal masses that are not confirmed and followed by imaging techniques; and. All measurements should be taken and recorded in metric notation, using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

- The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.

- Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

- Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response when all lesions have disappeared.

- Cytology and histology can be used to differentiate between PR and CR in rare cases (e.g., after treatment to differentiate between residual benign lesions and residual malignant lesions in tumor types such as germ cell tumors).

Baseline documentation of "Target" and "Non-Target" lesions

- All measurable lesions up to a maximum of five lesions per organ and 10 lesions in total, representative of all involved organs should be identified as ***target lesions*** and recorded and measured at baseline.

Target lesions should be selected on the basis Methods of Measurement

- CT and MRI are the best currently available and reproducible methods to measure target lesions selected for response assessment. Conventional CT and MRI should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen and pelvis. Head and neck tumors and those of extremities usually require specific protocols.

- Lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

- When the primary endpoint of the study is objective response evaluation, ultrasound (US) should not be used to measure tumor lesions. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.

- The utilization of endoscopy and laparoscopy for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in specialized centers. However, such techniques can be useful in confirming complete pathological response when biopsies are obtained.

- of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically).

- A sum of the longest diameter (LD) for *all target lesions* will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor.

- All other lesions (or sites of disease) should be identified as ***non-target lesions*** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

Response Criteria

Evaluation of target lesions

* Complete Response (CR):	Disappearance of all target lesions
* Partial Response (PR):	At least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum LD
* Progressive Disease (PD):	At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions
* Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started

Evaluation of non-target lesions

* Complete Response (CR):	Disappearance of all non-target lesions and normalization of tumor marker level
* Incomplete Response/ Stable Disease (SD):	Persistence of one or more non-target lesion(s) or/and maintenance of tumor marker level above the normal limits
* Progressive Disease (PD):	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions (1)

(1) Although a clear progression of "non target" lesions only is exceptional, in such circumstances, the opinion of the treating physician should prevail and the progression status should be confirmed later on by the review panel (or study chair).

Evaluation of best overall response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria

Target lesions	Non-Target lesions	New Lesions	Overall response
CR	CR	No	CR
CR	Incomplete response/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration". Every effort should be made to document the objective progression even after discontinuation of treatment.
In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the complete response status.

Confirmation

- The main goal of confirmation of objective response is to avoid overestimating the response rate observed. In cases where confirmation of response is not feasible, it should be made clear when reporting the outcome of such studies that the responses are not confirmed.

- To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met. Longer intervals as determined by the study protocol may also be appropriate.

- In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval (in general, not less than 6-8 weeks) that is defined in the study protocol

Duration of overall response

- The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever status is recorded first) until the first date that recurrence or PD is objectively documented, taking as reference for PD the smallest measurements recorded since the treatment started.

Duration of stable disease

- SD is measured from the start of the treatment until the criteria for disease progression are met, taking as reference the smallest measurements recorded since the treatment started.

- The clinical relevance of the duration of SD varies for different tumor types and grades. Therefore, it is highly recommended that the protocol specify the minimal time interval required between two measurements for determination of SD. This time interval should take into account the expected clinical benefit that such a status may bring to the population under study.

Response review

For trials where the response rate is the primary endpoint it is strongly recommended that all responses be reviewed by an expert(s) independent of the study at the study's completion. Simultaneous review of the patients' files and radiological images is the best approach.

Reporting of results

All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data).
All of the patients who met the eligibility criteria should be included in the main analysis of the response rate. Patients in response categories 4-9 should be considered as failing to respond to treatment (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate. Precise definitions for categories 4-9 will be protocol specific.
All conclusions should be based on all eligible patients.
Subanalyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (e.g., early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.). However, these subanalyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis should be clearly reported.
The 95% confidence intervals should be provided.

APPENDIX 5 COMMON TOXICITY CRITERIA (CTC VERSION 2.0) (delivered earlier to each center)

APPENDIX 6: Abbreviations and Definitions of Terms

ALAT	Alanine Aminotransferase
ALP	Alkaline Phosphatase
ANC	Absolute Neutrophil Count
ASAT	Aspartate Aminotransferase
AUA	American Urological Association
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
FACT-P	Functional Assessment of Cancer Therapy-Prostate
GCP	Good Clinical Practice
HRPC	Hormone Refractory Prostate Cancer
Hb	Haemaglogin
ITT	Intention to Treat
I.V.	Intravenous
LHRH analogue	Luteinizing Hormone Releasing Hormone- analogue
PLT	Platelets =Thrombocytes
PP	Per Protocol
PSA	Prostate Specific Antigen
PSADT	PSA Doubling Time
QOL	Quality of Life
RECIST	Response Evaluation Criteria in Solid Tumour
SWOG	Southwest Oncology Group
SUSAR	Suspected Unexpected Serious Adverse Reaction
TTF	Time to Treatment Failure
TNM	Classification of tumour stage. T=Tumour, N= Nodes, M= Metastasis
ULN	Upper Limit of Normal
WBC	White Blood cell Count
WHO	World Health Organisation
VAS	Visual Analogue Scale