EORTC
European Organisation for Research and Treatment of Cancer
AISBL International Non-Profit Association under Belgian law IVZW

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Short Study Report to Authorities

Name of Sponsor/Company: **EORTC**	Individual study Table Referring to Part of the Dossier	*(For National Authority Use Only)*
Name of the finished product	Volume:	
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Title of the Study	Randomized Phase II trial of Docetaxel (Taxotere) and Oblimersen (antisense oligonucleotide directed to bcl-2) vs. Taxotere alone in patients with hormone-refractory prostate cancer	
Investigators & Study Centers		

	N (%)
Institution Name (Physician's name)	
U.Z. Leuven (Pr. Allan T. Van Oosterom) Herestraat 49 BE 3000 Leuven Belgium	20 (17.4)
MARIA SKLODOWSKA-CURIE CANCER CENTER-INSTITUTE OF ONCOLOGY (Dr. Iwona Skoneczna) Ulica Wawelska 15 PL 02 034 Warsaw 22 Poland	19 (16.5)
SAN CAMILLO AND FORLANINI HOSPITALS (Dr. Cora Sternberg) Circonvallazione Gianicolense, 87 IT 00152 Roma Italy	14 (12.2)
ASSAF HAROFEH MEDICAL CENTER (Dr. Avishay Sella) IL 70300 Zerifin Israel	10 (8.7)
RIGSHOSPITALET (Dr. Gedske Daugaard) Blegdamsvej 9 DK 2100 Copenhagen Denmark	9 (7.8)
INSTITUT JULES BORDET (Dr. Thierry Gil) Rue Heger-Bordet, 1 BE 1000 Brussels Belgium	7 (6.1)
ONZE LIEVE VROUW ZIEKENHUIS (Dr. Paul Carpentier) Moorselbaan BE 9300 Aalst Belgium	7 (6.1)
WESTERN INFIRMARY (Dr. John Graham) Dumbarton Road GB Glasgow G11 6NT United Kingdom	7 (6.1)
ACADEMISCH MEDISCH CENTRUM (Pr. Dirk J. Richel) Meibergdreef 9 NL 1105 AZ Amsterdam The Netherlands	6 (5.2)
KAISER FRANZ JOSEF SPITAL (Dr. Maria De Santis) Kundratstr. 3 AT 1100 Vienna Austria	6 (5.2)
UNIVERSITEIT GENT (Pr. A. Verbaeys) De Pintelaan 185 BE 9000 Gent Belgium	3 (2.6)
CHR DE GRENOBLE - LA TRONCHE (Dr. François. Ringeisen) BP 217 X FR 38043 Grenoble CEDEX France	2 (1.7)
HOSPITAL GENERAL VALL D'HEBRON (Dr. Joaquim Bellmunt) Pg. Vall d'Hebron, 119-129 ES 08035 Barcelona Spain	2 (1.7)
KLINIKUM KASSEL GMBH (Pr. Peter Albers) Moenchenbergstrasse 41-43 DE 34125 Kassel Germany	2 (1.7)
HOSPITAL DO DESTERRO (Dr. Fernando Calais Da Silva) Rua Nova do Desterro 1169 PT 1000 Lisboa Portugal	1 (0.9)
TOTAL	115 (100.0)

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Publication (reference)	The overall study data have not been published yet, however, publications about part of the data have been presented at the 2007 ASCO prostate cancer symposium: C. N. STERNBERG, H. DUMEZ, H. VAN POPPEL, I. SKONECZNA, A. SELLA, G. DAUGAARD, T. GIL, J. GRAHAM, P. CARPENTIER, L. COLLETTE for the EORTC Genitourinary Group, Brussels, Belgium. Multicenter randomized EORTC trial 30021 of Docetaxel + Oblimersen and Docetaxel in patients (pts) with hormone refractory prostate cancer (HRPC). ASCO Prostate Cancer Symposium, Orlando, Florida, 22-24 February 2007 (Oral).	
Objective(s)	**The primary objective of the trial** is to evaluate the toxicity and activity (in terms of PSA response) of the combination of docetaxel and oblimersen in hormone refractory prostate cancer. The group treated with docetaxel alone will serve as a reference group to further validate the sample used in the trial. The trial is based on a Bryant and Day design and therefore two primary endpoints are considered : • PSA response • Major toxic event *Success criterion required lower bound of 80%CI for PSA response (Bubley) rate > 30% and upper bound of 80%CI for major toxic event rate <45%. RECIST was used for measurable lesions* **The secondary objectives of the trial** are to assess time to progression, progression-free survival, toxicity and overall survival in the two treatment groups.	
Methodology	Randomized Phase II trial	
Number of patients Number planed (Statistical design) Number analyzed	115 entered Planned sample size 102 patients in the "per protocol population". **Number of Patients analyzed :** 115	

Analysis Population	(N=115) N (%)
Intent-to-treat Population (ITT)	115 (100.0)
Per Protocol Population (PP)	111 (96.5)
PP with measurable disease	49 (44.1)
Safety Population	111 (96.5)

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Diagnosis and main criteria for inclusion	• Prostate cancer patients with PSA progression under prior hormonal treatment (Bubley criteria) – PSA ≥ 5 ng/ml. • No evidence of painful and / or destructive bone metastases for which RT, bisphosphonates or bone-seeking radionucleotides are considered necessary. No brain metastases • Castrate level of testosterone (≤ 50 ng/ml). Patients on medical castration (LHRH) must continue treatment. • No pre-treatment with chemotherapy (prior Estramustine allowed). No prior use of bone-seeking radionucleides nor RT involving > 25 % of marrow producing area. Prior biosphophonates allowed. • WHO performance status 0-2	
Treatment Test product, dose and mode of administration (batch number if applicable) Duration of treatment	Oblimersen 7 mg/kg/day d1- 7 of each cycle Docetaxel 75 mg/m² is given with dexamethasone premedication over 60 minutes on d5 of each cycle. Cycle duration is 3 weeks 12 cycles of treatment	
Reference therapy, dose and mode of administration (batch number if applicable)	Docetaxel 75 mg/m² is given with dexamethasone premedication over 60 minutes on d1 of each cycle. Cycle duration is 3 weeks	
Criteria for evaluation Efficacy	**Primary endpoint:** *PSA response* **Secondary endpoints:** *Time to progression, Overall survival, Progression-free survival.* • **PSA response** defined as a 50% decline from baseline value confirmed by a second value obtained at least 4 weeks apart according to Bubley (Bubley GJ, Carducci M, Dawson N, Daliani D, Eisenberger M, Figg WD et al. Eligibility and response	

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guidelines for phase II clinical trials in androgen-independent prostate cancer: recommendations from the Prostate-Specific Antigen Working Group. *J Clin Oncol* 1999;17(11):3461-7; with erratum in *J Clin Oncol* 2000; 18(13): 2644)

- **PSA progression is defined as follows:**

1. For patients without PSA decrease since entry on study, progression is an increase of 25% over baseline value, by at least 5 ng/ml (HYBRITECH equivalent).

2. For patients whose PSA has decreased but has not reached the response criteria, progressive disease is defined as an increase of 25% in PSA value taking as reference the nadir provided that this increase in the absolute value exceeds 5 ng/ml (HYBRITECH equivalent).

3. For patients who had a PSA response, progressive disease is defined as a 50% increase over the nadir if it is more than 5ng/ml (HYBRITECH equivalent).

The date of PSA progression is the date of the first PSA increase defined according to the definition of PSA progression as defined above.

To be assigned a status of PSA progression, changes in the PSA level should be confirmed by repeated measures that should be performed not less than 4 weeks after the first 25% or 50% increase (progression, see above).

- **Objective response and progression criteria** are essentially based on a set of measurable lesions identified at baseline as target lesions, and followed until disease progression. In this trial, only few patients are expected to present with measurable disease at entry on study.

The complete criteria are included in the published RECIST document (P. Therasse, S.G. Arbuck, E. Eisenhauer et al. New Guidelines to Evaluate the Response to Treatment in Solid Tumors. JNCI 92:3, 2000) also available at http://ww3.oup.co.uk/jnci/extra/920205.pdf.

The date of first objective progression is the first date when one or more of the above criteria are met.

- **Time to progression** is counted from the date of randomization to the date of the first event of PSA progression (as defined above) or objective clinical progression or death due to the disease. Patients who start another treatment in absence of disease progression will be considered as failures at the time they started the new treatment. Patients without the event of interest will be censored at the date of most recent follow-up visit.
- **Overall survival** is counted from the date of randomization. Patients who die are reported as events, irrespective of the cause of death. Patients without the event of interest are censored at the time of most recent follow-up visit. Overall survival duration therefore is the number of days elapsed between the day of randomization and the day of death or most recent follow-up visit.

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	• **Progression-free survival** is counted from the date of randomization until the date of first progression as defined above or the date of death, whichever occurs first. Patients who start another treatment in absence of disease progression will be considered as failures at the time they started the new treatment. Patients without the event of interest are censored at the time of most recent follow-up visit. Progression-free survival duration is therefore the number of days elapsed between the day or randomization and the minimum of the date of PSA progression, the date of objective clinical progression, the date of death or most recent follow-up visit
Safety	**Primary endpoint:** *Major toxic event* **Secondary endpoints:** *Adverse events (CTCAE, version 3.0)* ***Major toxic event:*** **Severe toxic events** are defined as any events of • Any grade 4 haematological and non hematological toxicity except asymptomatic grade 4 neutropenia (ANC<500/mm^3) lasting less than 7 days • Febrile neutropenia grade 3 for > 5 days or any Grade 4 febrile neutropenia • Sepsis (=grade 3 or 4) • Severe (grade 3 or 4) hemorrhage-bleeding associated with grade>2 thrombocytopenia (<50.000/mm^3) • Renal toxicity grade 3 or 4 (serum creatinine > 3xULN or need of dialysis) • Stop of treatment due to unacceptable toxicity • Death at least possibly due to toxicity
Statistical methods	This trial is a randomized phase II design. A 1-stage Bryant and Day decision rule will be applied separately to the two treatment arms. The two primary endpoints of the trial are PSA response and Major toxic events The parameters of the design are: ♦ Type I error rate (α) for the endpoint major toxic event: 10% ♦ Type I error rate (α) for the endpoint PSA response: 10% ♦ Type II error rate (β) for both endpoints: 10% ♦ P0 (maximum insufficient response rate): 30% ♦ P1 (minimum acceptable response rate): 50% ♦ T0 (maximum unacceptable rate without severe toxic event: 55% (i.e.: minimum unacceptable severe toxic event rate 45%) ♦ T1 (minimum acceptable rate without severe toxic event): 75% (i.e.: maximum acceptable severe toxic event rate 25%) According to this design, **the study requires 51 patients** in each treatment group. The main analysis of the primary trial endpoints is carried out in the "per protocol

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	population" (all eligible patients having started their allocated treatment), the protocol thus requires a total of 102 patients in the "per protocol population". A treatment arm is considered to be ***sufficiently active and safe*** if ≥ 20 of the 51 patients have a PSA response (≥ 39.2%) and if ≤18 of the 51 patients (≤35.3%) experience a major toxic event. The treatment that fulfills both conditions is considered worth evaluating in a phase III trial. If ≤ 19 of the 51 patients have a PSA response, the treatment is not considered sufficiently active to warrant evaluation in the phase III setting. If ≥ 19 of the 51 patients experience a major toxic event, the treatment is judged too toxic to warrant further evaluation in this patient population.
Summary of Results Efficacy Results	The trial recruited 115 patients between 16 April, 2004 and 17 January, 2006. Patients with metastatic hormone-refractory prostate cancer were randomized between **Docetaxel (Arm A) and Oblimersen with Docetaxel (ARM B).** 4 patients were not evaluable on B (2 ineligibles and 2 untreated due to immediate progression). Median age was 68.9 years on A and 64.4 years on B. Of 111 evaluable patients, 7 entered with PSA progression only, 43 with PSA+bone progression and 61 with visceral mets, 49 had measurable disease. PSA response rate was 45.6% on A (80%CI: 36.5-54.9%) and 37.0% on B (80%CI: 28.2-46.6%). Partial responses (RECIST) were observed in 5/28 and 5/21, respectively. 1-year survival rate was 85.4% on A vs 81.2% on B. Median PFS was 6.2 m on A vs 4.4 on B.
Safety Results	Grade 3/4 toxicities on A vs B: fatigue 1.8% vs 13.0%; febrile neutropenia 14.0% vs 13.0%; infection 15.8% vs 16.8%; diarrhea 5.3% vs 9.3%; mucositis 1.8% vs 9.3%; neutropenia was 84.2% vs 79.7%. Growth factors was given to 9 (15.8%) and 14 (25.9%). Toxic deaths occurred in 1 pt in each arm. Major toxic event rate was 24.6% on A (80%CI: 17.2-33.4) and 42.6% on B (80%CI: 33.4-52.2%).
Conclusions	This is the first evaluation of the concept of lowering Bcl-2 prior to Docetaxel chemotherapy in HRPC. Addition of Oblimersen to Docetaxel did not increase PSA response nor survival and was associated with increased side effects.
Date of Report	Final analysis report : 05-02-2008