

## Protocol summary

<b>Title of the Study</b>	Phase IIIb randomized trial comparing irradiation plus long term adjuvant androgen deprivation with GnRH antagonist versus GnRH agonist plus flare protection in patients with very high risk localized or locally advanced prostate cancer. A joint study of the EORTC ROG and EORTC GUCG.
<b>Objective(s)</b>	<p>The primary objective of the trial is to assess if GnRH antagonists in combination with external beam radiation therapy improve progression free survival (progression that can be biological, clinical, or death) compared to GnRH agonists in combination with external beam radiation therapy.</p> <p>Secondary objectives include:</p> <ul style="list-style-type: none"> <li>◆ documentation of effect of GnRH antagonists on clinically significant cardiovascular events in the subgroup of patients at high risk of such events at baseline;</li> <li>◆ documentation of side effects and quality of life, I-PSS and urinary tract infections;</li> <li>◆ assessment of relative treatment effect on secondary efficacy endpoints (clinical progression, time to next line of systemic therapy, time on therapy, overall and cancer specific survival) and on PSA at 6 months after end of RT.</li> </ul>
<b>Methodology</b>	Phase IIIb randomized stratified open-label comparative 2-arm superiority study with a pre-set non-inferiority boundary.
<b>Number of patients</b> Number planned (Statistical design)	<p>The trial is primarily intended to show superiority but it is also powered to enable a second primary conclusion of non-inferiority using pre-specified hypotheses on the acceptable non-inferiority margin.</p> <p>The sample size calculation uses the following assumptions:</p> <ul style="list-style-type: none"> <li>◆ The patient accrual rate reaches a steady state of 300 patients per year from year 2 of recruitment onwards. During the first year, the yearly accrual rate is assumed to gradually increase quarterly from 76 patients/year (months 1-3), to 124 pts/year (months 4-6), to 174 patients / year (months 7-9), to 227 patients / year (months 10-12).</li> <li>◆ The cumulative rate of patients loss to follow-up is 5% at year 5</li> <li>◆ The trial-level type I error rate is 0.025 1-sided</li> <li>◆ Based on an (unpublished) reanalysis of the data from the 3-year hormone-deprivation therapy arm of EORTC trial 22961, restricted to the subset of patients that had a baseline PSA&gt;10 ng/ml and at least 2 risk factors as specified in the eligibility criteria of the present study, the 5-year progression-free survival rate was 68.7% (95% CI: 62.9%-73.7%). The sample size is thus based on the assumption that the 5-year progression-free survival rate in the comparator arm of this study is 68.5%</li> </ul> <p>The <b>hypothesis test of superiority</b> of the experimental treatment arm for the primary endpoint progression-free survival is</p>

	<p><math>H_{0\text{superiority}} : HR \geq 1</math> versus <math>H_{1\text{superiority}} : HR &lt; 1</math></p> <p>The study is sized to have 80% power to reject <math>H_{0\text{superiority}}</math> under the alternative that the true benefit amounts <math>HR=0.708</math> (i.e. +8% at 5 years from anticipated 68.5% at 5 years in the reference arm).</p> <p>The <b>non-inferiority</b> boundary is set at <math>HR=1.159</math> and corresponds to the non-inferiority test</p> <p><math>H_{0\text{non-inferiority}} : HR \geq 1.159</math> versus <math>H_{1\text{non-inferiority}} : HR &lt; 1.159</math> (i.e. -4% at 5 years)</p> <p>We note that <math>H_{1\text{non-inferiority}}</math> is included in <math>H_{1\text{superiority}}</math>. This justified the closed-testing argument below.</p> <p>With the above specifications, the superiority test requires observing a total of 264 events for the primary endpoint. It is also estimated that <b>with 885 patients entering the study in 3.45 years</b> will provide this number of events, <b>if the total study duration is 7.7 years (i.e. with 4.2 years of follow-up after the entry of the last patient)</b>.</p> <p>With this number of events, the study will also have 80% power of rejecting the null hypothesis of inferiority (<math>H_{0\text{non-inferiority}} : HR \geq 1.159</math>) under the alternative assumption of a marginal treatment benefit in favor of the experimental arm amounting <math>HR=0.821</math> (+4.8% at 5 years), using the 1-sided type I error rate of 0.025. By the closed-testing principle, this strategy guarantees strict control of the trial type I error.</p>
Number analyzed	885
<p><b>Diagnosis and main criteria for Inclusion</b></p>	<p><b>Inclusion criteria</b></p> <ul style="list-style-type: none"> <li>◆ Histologically confirmed diagnosis of prostate adenocarcinoma</li> <li>◆ PSA <math>\geq 10</math> ng/ml and two of the following 4 criteria: <ul style="list-style-type: none"> <li>◆ PSA <math>\geq 20</math> ng/ml,</li> <li>◆ Gleason sum <math>\geq 8</math>,</li> <li>◆ cN1 (regional LN with a short axis length <math>&gt;10</math>mm by CT scan or MRI) or pathologically confirmed lymph nodes (pN1) (see Appendix H),</li> <li>◆ cT3-T4 (by MRI or core biopsy)</li> </ul> </li> </ul> <p>(i.e. If PSA <math>\geq 20</math> ng/ml then only one of the other 3 risk factors is needed)</p> <ul style="list-style-type: none"> <li>◆ M0 by standard imaging work-up (see chapter 6.1.1.1)</li> <li>◆ Testosterone <math>\geq 200</math> ng/dl</li> <li>◆ Adequate renal function: calculated creatinine clearance <math>\geq 50</math> mL/min (Appendix D) Magnesium and potassium within normal limits of the institution or corrected to within normal limits prior to the first dose of treatment.</li> <li>◆ Patients with prolonged QT-intervals due to prescribed Class IA (quinidine, procainamide) or Class III (amiodarone, sotalol) antiarrhythmic medication must be carefully evaluated for GnRH-</li> </ul>

<p><b>Exclusion</b></p>	<p>agonist or GnRH antagonist use, because these drugs may prolong the QT-interval.</p> <ul style="list-style-type: none"> <li>◆ WHO Performance status 0-1 (see Appendix C)</li> <li>◆ Age <math>\geq 18</math> and <math>\leq 80</math> years</li> <li>◆ Participants who have partners of childbearing potential must use adequate birth control measures, as defined by the investigator, during the study treatment period and for at least 3 months after last dose of study treatment. A highly effective method of birth control is defined as those which result in low failure rate (i.e. less than 1% per year) when used consistently and correctly</li> <li>◆ Before patient registration/randomization, written informed consent must be given according to ICH/GCP, and national/local regulations.</li> </ul> <p><b>Exclusion criteria</b></p> <ul style="list-style-type: none"> <li>◆ Previous use of androgen deprivation therapy (ADT), antiandrogens. 5-alpha reductase inhibitors are allowed if interrupted for more than 6 months prior to entering the study</li> <li>◆ History of severe untreated asthma, anaphylactic reactions or severe urticaria and/or angiodema.</li> <li>◆ Hypersensitivity towards the investigational drug</li> <li>◆ The following biological parameters :AST, ALT, total bilirubin, prothrombin time, serum albumin above upper level of normal range No severe hepatic impairment (Child Pugh C)</li> <li>◆ History of gastro-intestinal disorders (medical disorder or extensive surgery) that may interfere with the absorption of the protocol treatment.</li> <li>◆ History of pituitary or adrenal dysfunction</li> <li>◆ Uncontrolled diabetes mellitus</li> <li>◆ History of ulcerative colitis, Crohn's Disease, ataxia, telangiectasia, systemic lupus erythematosus, or Fanconi anemia.</li> <li>◆ Clinically significant heart disease as evidence myocardial infarction, or arterial thrombotic events in the past 6 months, severe or unstable angina, or New York Heart Association (NYHA) class III or IV heart disease or cardiac ejection fraction measurement of <math>&lt; 50\%</math> at baseline</li> <li>◆ Coronary revascularization (PCI or multivessel CABG), carotid artery or iliofemoral artery revascularization (percutaneous or surgical procedure) within the last 30 days prior to entering the trial</li> <li>◆ Certain risk factors for abnormal heart rhythms/QT prolongation: torsade de pointes ventricular arrhythmias (e.g, heart failure, hypokalemia, or a family history of a long QT syndrome), a QT or corrected QT (QTc) interval <math>&gt;450</math> ms at baseline, or intake of medications that prolong the QT/QTc interval</li> <li>◆ Uncontrolled hypertension (systolic BP <math>\geq 160</math> mmHg or diastolic BP <math>\geq 95</math> mmHg); patients with a history of hypertension are allowed provided</li> </ul>
-------------------------	--

	<p>blood pressure is controlled by anti-hypertensive treatment.</p> <ul style="list-style-type: none"> <li>◆ Prior history of malignancies other than prostate adenocarcinoma (except patients with basal cell, squamous cell carcinoma of the skin), or the patient has been free of malignancy for a period of 3 years prior to first dose of study drug(s). Prior history of bladder cancer excludes the patient.</li> <li>◆ Prior radical prostatectomy (TURP or suprapubic adenectomy for benign prostatic hyperplasia is allowed)</li> <li>◆ Prior brachytherapy or other radiotherapy that would result in an overlap of radiotherapy fields</li> <li>◆ Any contraindication to external beam radiotherapy</li> <li>◆ Patients with significantly altered mental status prohibiting the understanding of the study or with psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule or any condition which, in the opinion of the investigator, would preclude participation in this trial.</li> </ul>
<p><b>Treatment</b></p> <p>Test product, dose and mode of administration</p>       <p>Duration of treatment</p>	<p>Registered GnRH antagonists, degarelix, will be given at the dose of 240 mg given as two subcutaneous injections of 120 mg at a concentration of 40 mg/mL on day 1, followed by 80 mg given as one subcutaneous injection at a concentration of 20 mg/mL every 28 days (<math>\pm 2</math> days).</p> <p>External beam radiotherapy (EBRT), delivered as one daily fraction, five days a week, started between day 1 and month 6 of the androgen deprivation therapy as per institution policy. The irradiation is the same as in the reference therapy arm. The institution may choose if patient is treated with conventional fractionation or hypofractionation scheme.</p> <p>The minimum duration of androgen deprivation with GnRH agonist or antagonist therapy is 18 months.</p> <p>For each patient, the duration of therapy must be elected upfront by the treating physician among three possible options: 18, 24 or 36 months. The institution shall also declare upfront the duration of the neoadjuvant treatment they intend to deliver to each patient (between 0 and 6 months).</p>
<p>Reference therapy, dose and mode of administration</p>	<p>Registered GnRH agonists, such as goserelin, triptorelin, leuprorelin, will be administered as 3 or 6 months depot formulation.</p> <p>The minimum duration of androgen deprivation therapy with GnRH agonist or antagonist is 18 months.</p> <p>For each patient, the duration of therapy must be elected upfront by the treating physician among three possible options: 18, 24 or 36 months. They shall also declare upfront the duration of the neoadjuvant treatment they intend to deliver to each patient (between 0 and 6 months).</p> <p>A non-steroidal anti-androgen (e. g. flutamide, bicalutamide) will be given orally one week before the first injection of the GnRH agonist and will be continued for no longer than 8 weeks to protect against flare.</p>

	<p>External beam radiotherapy to a dose of 78-80 Gy, delivered as one daily fraction, five days a week, started between d1 and month 6 of the androgen deprivation therapy as per institution policy. The irradiation is the same in both arms.</p> <p>Day 1 (d1) of treatment in this study is the day of first injection of GnRH-agonist or GnRH-antagonist (depending on allocated treatment group) and corresponds to the start of treatment. Day 1 of treatment should start within 2 weeks after randomization.</p>
<p><b>Criteria for evaluation</b></p> <p>Efficacy</p> <p>Safety</p>	<p>The primary endpoint is progression-free survival defined as the time in days from randomization to death, clinical or biochemical progression, whichever comes first.</p> <p>Where</p> <ul style="list-style-type: none"> <li>◆ PSA progression based on Phoenix definition, i.e. a rise by 2 ng/mL or more above the nadir PSA (Ref. 17) confirmed by a second value measured minimum 3 months later</li> <li>◆ Clinical progression is defined as onset of obstructive symptoms requiring local treatment and demonstrated to be caused by cancer progression or evidence of metastases detected by clinical symptoms and confirmed by imaging</li> <li>◆ Start of another line of systemic therapy in absence of progression</li> <li>◆ Death due to any cause</li> </ul> <p>Secondary endpoints:</p> <ul style="list-style-type: none"> <li>◆ Clinical progression-free survival</li> <li>◆ Time to next systemic anticancer therapy (including secondary hormonal manipulation)</li> <li>◆ Proportion of patients switching from GnRH antagonists to GnRH agonists and total effective duration of treatment with the originally allocated drug.</li> <li>◆ Overall survival</li> <li>◆ Cancer specific survival</li> <li>◆ PSA at six months after completion of RT</li> </ul> <p>Safety will be scored by the CTCAE version 4.0. The major safety endpoints in this study are</p> <ul style="list-style-type: none"> <li>◆ the incidence of clinical cardiovascular events – CCE (i.e. arterial embolic or thrombotic events, hemorrhagic or ischemic cerebrovascular conditions, myocardial infarction, and other ischemic heart disease) in patients who had cardiovascular events before entering the trial and in those without such events.</li> <li>◆ Incidence of urinary tract infection</li> </ul>

<b>Patient reported outcomes</b>	<ul style="list-style-type: none"> <li>◆ Quality of Life (HRQoL) will be measured with the established EORTC tools the EORTC QLQ-C30 and EORTC-PR25 instruments. The primary scale is the overall health related quality of life scale of the EORTC-QLQ-C30.</li> <li>◆ The EQ-5D-5L is also collected in order to enable a future health economics analysis. The EQ--5D-5L includes 5 mobility, self-care, usual activities, pain/discomfort, anxiety/depression. And each dimension now has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems.</li> <li>◆ Urinary symptoms will be assessed using the International Prostate Symptoms Score (I-PSS)</li> </ul>
<b>Statistical methods</b>	<ul style="list-style-type: none"> <li>◆ Treatment allocation method: No blinding is applied in this study. Before the start of the hormonal therapy, the patients are allocated between the two treatment groups in a 1:1 ratio, by means of stratified blocked randomization with variable block sizes. Stratification factors will be the presence of previous clinical cardiovascular event (no vs yes), the country where the patient is treated, and the number of high risk factors that the patient presents (2 vs &gt;2 high risk factors of relapse)</li> <li>◆ Analysis populations <ul style="list-style-type: none"> <li>◆ Intention-to-treat population: All randomized patients will be analyzed in the arm they were allocated by randomization.</li> <li>◆ Per protocol population 1: All patients who are eligible and have received at least 6 months of the allocated treatment</li> <li>◆ Safety population: All patients who have started their allocated treatment (at least one injection of the allocated treatment)</li> <li>◆ Per protocol population 2 (adjusted for switch): All patients who are eligible and have started treatment censoring observations at the time of switching treatment (from GnRH-antagonist to GnRH-agonist) or stopping treatment in absence of progression.</li> </ul> </li> </ul> <p>Analysis methods:</p> <ul style="list-style-type: none"> <li>◆ The primary analysis of the primary endpoint will be performed in the intent-to-treat population for the superiority test. Two sensitivity analyses will be conducted, repeating the test in the per protocol population 1 and in the per protocol population 2.</li> <li>◆ If the superiority test fails to reject the null hypothesis of no difference a non-inferiority test will be conducted. To protect against the risk of false positive conclusions, the primary test for the non-inferiority question will be conducted in the in the per protocol population 2. The test in the intention-to-treat population and in the <i>per-protocol</i> population 1 will be performed as a first sensitivity analysis. A second sensitivity analysis will be conducted in intent-to-treat population.</li> </ul>

	<ul style="list-style-type: none"> <li>◆ All secondary efficacy endpoints will be reported in the intent-to-treat population. A sensitivity analysis of the endpoint PSA at 6 months will also be conducted in the per protocol population</li> <li>◆ Safety will be reported in the per protocol population 2 and in the safety population.</li> <li>◆ Quality-of-life and other patient reported outcomes will be reported in the intent-to-treat population</li> <li>◆ Testing strategy for the primary endpoint:  <p>The 2-sided 95% confidence interval for the hazard ratio for the treatment effect on the primary trial endpoint will be calculated based on a Cox regression model stratified for the stratification factors of the randomization.</p> <p>The test for superiority is conducted first. If it does reject the null hypothesis of no difference (one-sided <math>P &lt; 0.025</math>) then one concludes to superiority of the GnRH-antagonist.</p> <p>If one does not, then the primary test for the non-inferiority question is conducted. If the upper bound of the 2-sided 95% confidence interval around the HR (agonist/antagonist) is <math>&lt; 1.159</math> then one concludes to non-inferiority.</p> <p>Otherwise, one concludes that neither non-inferiority nor superiority of the experimental treatment can be demonstrated compared to the standard treatment.</p> <p>This strategy guarantees full control over the type I error rate of the trial.</p> </li> <li>◆ Analysis of secondary endpoints  <p>The secondary endpoint clinical progression-free survival is also assessed by means of cox regression stratified by the stratification factors of the randomization.</p> <p>The secondary endpoints time to time to next systemic anticancer therapy (including secondary hormonal manipulation) and cancer specific survival are analyzed by means of a Fine-and-Gray model stratified by the stratification factors of the randomization.</p> <p>Quality of life endpoints are analyzed by means of mixed effects regression models adjusted for the stratified by the stratification factors of the randomization. I-PSS scores over time will be reported as change scores from baseline. Health Economic analysis will be done using the scores from the EQ-5D-5L tool (Ref. 39)</p> <p>The other secondary endpoints as well as the main safety endpoints are compared by means of logistic regression models stratified by the stratification factors of the randomization.</p> <p>Other safety parameters are described as frequency tables.</p> </li> <li>◆ Interim monitoring</li> <li>◆ No formal interim stopping rule based on efficacy is planned in this study. The central IDMC for the EORTC studies will review the trial at</li> </ul>
--	---

	<p>regular intervals (q2 years) to review the safety data of the study, and to monitor the assumptions driving the choice of the total number of patients needed to achieve the specified statistical power during the specified time frame; and to advise on an increase of the sample size if the event rate on the control group would appear lower than anticipated by design. The IDMC will also be asked to authorize any release of other data than efficacy during the course of the study, if such intention emerges. The first IDMC review will take place at year 2 or as soon as 10 Clinical Cardiovascular Events will have been recorded in the database</p>
<p><b>Translational research</b></p>	<p>This research project is optional.</p> <p>All patients enrolled in the main study will be offered to participate in this translational research project. For the patients that will have consented, saliva will be collected and stored. Gene profiling of all samples will be performed in the future.</p> <p>Saliva will be collected at the time of inclusion in the main study.</p>