Protocol summary

Title of the Study	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.
Objective(s)	The primary objective of the trial is to assess if GnRH antagonists improve progression free survival (progression that can be biological, clinical, or death) compared to GnRH agonists in combination with external beam radiation therapy in patients with high-risk localized or locally-advanced cancer, who receive this treatment after initial radical prostatectomy or as primary therapy. Secondary objectives include: ♦ documentation of effect of GnRH antagonists on clinically significant cardiovascular events in the subgroup of patients at high risk of such events at baseline; ♦ documentation of side effects and quality of life, I-PSS and urinary tract infections; ♦ assessment of relative treatment effect on secondary efficacy endpoints (clinical progression, time to next systemic therapy, time on therapy, overall and cancer specific survival) and on PSA at 6 months after end of radiation therapy (RT).
Methodology	Phase IIIb randomized stratified open-label comparative 2-arm superiority study with a pre-set non-inferiority boundary.
Number of patients Number planed (Statistical design)	The trial is primarily intended to show superiority of the GnRH agonist treatment arm over the GnRH antagonist arm on average over the patients treated with primary radiotherapy or who received irradiation after primary prostatectomy. The following assumptions support the sample size calculation: ♦ Accrual rate: We assumed that 885 patients would be recruited in a period of 36 months, (681 RT patients from month 1 to month 36 and 204 radical prostatectomy (RP) patients month 8 to month 36) (23% RP patients). Endpoints ♦ Baseline effects: ♦ Based on an (unpublished) reanalysis of the data from the 3-year hormone-deprivation therapy arm of EORTC trial 22961, restricted to the subset of patients that had a baseline PSA > 10 ng/mL and at least 2 risk factors as specified in the eligibility criteria of the present study, we assumed that the 5-year progression free survival rate in the comparator arm of this study is 68.5%

	♦ Patients in the post prostatectomy cohorts are expected to be generally of worse prognosis with an anticipated 5-year PFS rate that we assume at 55% The 5-year PFS rate expected under H0 for the case mix is expected to be 65.4%. ♦ We also assumed that a similar relative effect size of HR=0.708 is expected for all patients, irrespective of primary treatment and disease extension ♦ This test needs **264 events** for 1-sided test against H0: HR=1 with alpha=0.025 and 80% power. Under the above assumption, it is estimated that if a total of **885 patients are recruited over 36 months**, the analysis of the primary endpoint may be conducted at month 82 (**6.8 years total study time**) from first patient (36 months of accrual + 46 additional months of follow up).
Number analyzed	885
Diagnosis and main criteria for Inclusion	**Inclusion criteria** Patients may enter the trial once in either of two clinical settings where a combination therapy involving irradiation combined with androgen deprivation therapy is envisaged: a) patients who are scheduled for primary treatment by irradiation combined with minimum 18 months of androgen deprivation therapy or b) patients who were operated within the EORTC SPECTA 1553 study and who are scheduled to receive adjuvant or early salvage irradiation. **Entry criteria for patients planned for primary radiotherapy:** ♦ Histologically confirmed diagnosis of prostate adenocarcinoma diagnosed on a systematic ultrasound guided biopsy of the prostate containing at least 8 cores or a MRI/MRI-TRUS fusion biopsy of a suspect lesion. A TURP specimen pathology is allowed. Two of the following 4 risk factors for relapse: ♦ PSA ≥ 20 ng/mL, ♦ Gleason sum ≥ 8, ♦ cN1 (regional LN with a short axis length > 10mm by CT scan or MRI) or pathologically confirmed lymph nodes (pN1), ♦ cT3-T4 (by MRI or core biopsy) (*i.e.* If PSA≥ 20 ng/ml then only one of the other 3 risk factors is needed) **Entry criteria for patients previously enrolled in EORTC SPECTA 1553, treated by radical prostatectomy:** ♦ Radical prostatectomy in EORTC SPECTA 1553 performed within 1 year ♦ Scheduled to receive irradiation combined with 6 months of androgen deprivation therapy in the following cases:

	♦ In the adjuvant setting with PSA ≥ 0.1 ng/mL at 12 weeks post-surgery and/or ≥ 2 pathologically confirmed positive nodes after radical prostatectomy ♦ For a biochemical recurrence (BCR) ≤ 1 year after radical prostatectomy (defined as per guidelines as two consecutive rising serum PSA values greater than or equal to 0.2 ng/mL) **Entry criteria for all patients** Either of ♦ M0 M0 according to standard imaging methods (i.e. bone scan and conventional CT/MR image) or M0 according to modern imaging methods (i.e. whole-body MRI, PET/CT) ♦ M0 according to bone scan and conventional CT/MR image and M1a and M1b only with ≤ 3 lesions detected by modern imaging methods are also allowed, called "**Oligometastatic disease**". Patients with oligometastatic disease will undergo metastasis targeted therapy ♦ Testosterone ≥ 200 ng/dL ♦ Adequate bone marrow function (absolute neutrophil count (ANC) ≥ 1.5 10^9/L; hemoglobin ≥ 10.0 g/dl; platelets ≥ 100 10^9/L) ♦ Adequate hepatic function: ♦ Bilirubin: total bilirubin ≤ 1.5 × upper limit of normal (ULN). ♦ AST and/or ALT ≤ 2.5 × ULN. ♦ Adequate renal function: calculated creatinine clearance ≥ 50 mL/min ♦ Magnesium and potassium within normal limits at the institution ♦ WHO Performance status 0-1 ♦ Age ≥ 18 and ≤ 80 years ♦ 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 ♦ Before patient registration/randomization, written informed consent must be given according to ICH/GCP, and national/local regulations.
Exclusion	**Exclusion criteria** ♦ M1c, confirmed by any imaging method or biopsy ♦ Previous use of androgen deprivation therapy, antiandrogens if not interrupted for more than 6 months prior to entering the study ♦ History of severe untreated asthma, anaphylactic reactions or severe urticaria and/or angiodema.

	♦ Hypersensitivity towards any of the active substances, the excipients used and synthetic GnRH or GnRH derivatives ♦ No severe hepatic impairment (Child Pugh C) ♦ Uncontrolled diabetes mellitus ♦ Coronary revascularization (PCI or multivessel CABG), carotid artery or iliofemoral artery revascularizaton (percutaneous or surgical procedure) within the last 30 days prior to entering the trial ♦ 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 >450 ms ♦ 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 (except appropriately treated Tis or T1a) excludes the patient. ♦ Any contraindication to external beam radiotherapy ♦ 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.
Treatment	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 (±2 days). OR Registered GnRH agonists, such as goserelin, triptorelin, leuprorelin, will be administered as 3 or 6 months depot formulation. 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. For patients undergoing primary therapy, external beam radiotherapy (EBRT), delivered as one daily fraction, five days a week, started between D1 and months 6 of the androgen deprivation therapy as per institution policy The institution may choose if patient is treated with conventional fractionation (78-80 Gy in 39-40 fractions) or hypofractionation (60 Gy in 20 fractions) scheme. For patients having undergone a radical prostatectomy, EBRT is given at a dose of 66 Gy (if a boost to the local bed is added, 72 Gy) in 33 (36) fractions. For oligometastatic lesions, a total dose of 30 Gy will be delivered in 3 fractions of 10 Gy separated by 48h to 96h.

Duration of ADT treatment	The duration of treatment androgen deprivation therapy will be 18, 24, or 36 months for patients who receive primary local radiotherapy and 6 months for the patients who had a primary radical prostatectomy. The decision regarding the intended duration of treatment for each patient will be left to the discretion of the investigator who will decide on the basis of the best available current knowledge. For patients treated by primary radiation combined with androgen deprivation therapy, The institution shall declare upfront the duration of the neoadjuvant treatment they intend to deliver to each patient (between 0 and 6 months). 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.
Criteria for evaluation Efficacy	The primary endpoint is progression free survival defined as the time in days from randomization to death, clinical or biochemical progression, whichever comes first. Where ♦ PSA progression based on Phoenix definition, i.e. a rise by 2 ng/mL or more above the nadir PSA confirmed by a second value measured minimum 3 months later ♦ 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 ♦ Start of another line of systemic therapy in absence of progression ♦ Death due to any cause Secondary endpoints: ♦ Clinical progression free survival ♦ Time to next systemic anticancer therapy ♦ Time to next systemic anticancer therapy other than ADT ♦ Proportion of patients switching from GnRH antagonists to GnRH agonists and total effective duration of treatment with the originally allocated drug. ♦ Overall survival ♦ Cancer specific survival ♦ PSA at six months after completion of RT

Safety	Safety will be scored by the CTCAE version 4.0. The major safety endpoints in this study are ♦ 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. ♦ Incidence of urinary tract infection
Patient reported outcomes	♦ 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. ♦ 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. ♦ Urinary symptoms will be assessed using the International Prostate Symptoms Score (I-PSS)
Statistical methods	♦ 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 >2 high risk factors of relapse) ♦ Analysis populations ♦ Intention-to-treat population: All randomized patients will be analyzed in the arm they were allocated by randomization. ♦ Per protocol population 1: All patients who are eligible and have received at least 6 months of the allocated treatment ♦ Safety population: All patients who have started their allocated treatment (at least one injection of the allocated treatment) ♦ 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. ♦ Analysis methods: ♦ 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.

	♦ 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 *per-protocol* population 1 will be performed as a first sensitivity analysis. A second sensitivity analysis will be conducted in intent-to-treat population. ♦ 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 ♦ Safety will be reported in the per protocol population 2 and in the safety population. ♦ Quality-of-life and other patient reported outcomes will be reported in the intent-to-treat population ♦ Testing strategy for the primary endpoint: 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. The test for superiority is conducted first. If it does reject the null hypothesis of no difference (one-sided P<0.025) then one concludes to superiority of the GnRH-antagonist. 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 < 1.159 then one concludes to non-inferiority. Otherwise, one concludes that neither non-inferiority nor superiority of the experimental treatment can be demonstrated compared to the standard treatment. This strategy guarantees full control over the type I error rate of the trial. ♦ Analysis of secondary endpoints The secondary endpoint clinical progression free survival is also assessed by means of cox regression stratified by the stratification factors of the randomization. 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. 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

	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. Other safety parameters are described as frequency tables. ♦ Interim monitoring ♦ 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 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
Translational research	This research project is optional. 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. Saliva will be collected at the time of inclusion in the main study.