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Can dutasteride delay or prevent the progression of prostate cancer in patients with biochemical failure after radical therapy? Rationale and design of the Avodart after Radical Therapy for Prostate Cancer Study

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OBJECTIVE

To describe the Avodart after Radical Therapy for prostate cancer Study (ARTS), investigating the use of dutasteride (a dual 5α-reductase inhibitor that suppresses intraprostatic dihydrotestosterone, reduces tumour volume and improves other markers of tumour regression in prostate cancer) to prevent or delay disease progression in patients with biochemical recurrence after therapy with curative intent.

PATIENTS AND METHODS

An increasing serum prostate-specific antigen (PSA) level after radical prostatectomy (RP) or radiotherapy (RT) is indicative of recurrent prostate cancer and typically pre-dates clinically detectable metastatic disease by several years. ARTS is an ongoing European multicentre trial in which patients are stratified by previous therapy (RP with or without salvage RT vs primary RT) and randomized to double-blind treatment with dutasteride 0.5 mg or placebo once daily for 2 years. Eligible patients will have a PSA doubling time (DT) of 3–24 months. Biochemical recurrence is defined as three increases in PSA level from the nadir, with each increase ≥4 weeks apart and each PSA level ≥0.2 ng/mL, and a final PSA level of ≥0.4 ng/mL (after RP) or ≥2 ng/mL (after primary RT). Study endpoints include time to PSA doubling, time to disease progression, treatment response (PSA decrease or an increase of ≤15% from baseline), changes in PSA and PSADT, and changes in anxiety (Memorial Anxiety Scale for Prostate Cancer).

CONCLUSIONS

ARTS will be the first study to evaluate the effects of dutasteride on PSADT, disease progression and treatment response in patients with biochemical failure after RP or RT, and should help to elucidate the potential role of dual 5α-reductase inhibition in prostate cancer.

KEYWORDS

5α-reductase inhibitor, dutasteride, prostate cancer, radical therapy

INTRODUCTION

Prostate cancer is highly prevalent and represents a significant disease burden among ageing men. In Europe, prostate cancer is the most frequently diagnosed male cancer (excluding nonmelanoma skin cancers), with an estimated 345 900 cases in 2006 (20% of all male cancers) [1]. In the same year, over 87 000 deaths were attributed to prostate cancer, making it the third most common cause of cancer death in men, after lung and colorectal cancers. This mortality rate represents an increase of 16% since 1995, which can be largely attributed to greater life-expectancy, as well as other as yet unknown factors. Given its high prevalence and increasing mortality rate in Europe, strategies to help reduce the risk of prostate cancer (primary prevention) and treatments that slow or prevent disease progression (secondary prevention) or delay progression in patients for whom curative therapy has failed (tertiary prevention) are required.

Prostate cancer screening programmes increase the number of patients diagnosed with clinically localized prostate cancers, with up to 85% detected at clinical stage T1–T2 [2–4]. Most patients with early-stage prostate cancer undergo radical prostatectomy (RP) or radiotherapy (RT). However, disease can recur after surgery or RT in 27–53% of all patients

within 10 years of initial therapy, and 16–35% of patients will receive second-line therapy within 5 years [5].

An elevated or increasing serum PSA level after RP or RT is indicative of recurrent prostate cancer. This biochemical recurrence typically pre-dates clinically detectable metastatic disease by several years. In a review of almost 2000 men who had RP, the median time from a PSA increase (≥0.2 ng/mL) to metastases was 8 years, while the median time from metastases to death was 5 years [5]. Factors that predicted distant metastases on multivariate analysis included time to biochemical recurrence, Gleason score and PSA doubling time (PSADT).

A median PSADT of 11.7 months after RP has been shown to predict local failure, whereas a median PSADT of ≤4.3 months is associated with distant metastases [6]. In the study by Pound *et al.* [7], a PSADT of <10 months was predictive of subsequent metastatic disease. Similarly, other studies have shown that patients with a PSADT of <3 months are at higher risk of prostate cancer-specific mortality [8,9]. However, patients with such a short PSADT represent only a small proportion of the population in these studies (≈6%). More recently, a retrospective analysis of 379 patients treated with RP reported that most deaths from prostate cancer 15 years after biochemical recurrence were in patients with an intermediate PSADT of 3.0–8.9 months [10]. Prostate cancer accounted for 90% of all deaths in patients with a PSADT of <15 months and only patients with a PSADT of ≥15 months were more likely to die from causes unrelated to prostate cancer. Although patients with a PSADT of <3 months were at the greatest risk of prostate cancer-specific mortality, the few patients in this group meant that they accounted for only 13% of deaths from prostate cancer.

Patients with increasing PSA values after RP and/or RT constitute a significant proportion of those with prostate cancer, and their management is a complex and controversial issue. While watchful waiting might be appropriate for some patients, other therapeutic options include adjuvant and salvage treatment, such as local irradiation, salvage surgery and androgen-deprivation therapy (ADT). However, good evidence to support these options is limited, as there is a lack of prospective, randomized trials in this population. Recent European Association of Urology (EAU) guidelines recommend either watchful waiting with possible delayed ADT (grade B recommendation) or salvage RT (grade C recommendation) in patients with presumed local failure after RP [5]. Watchful waiting with possible ADT is also recommended for patients with presumed local failure after RT. Selected patients might be candidates for salvage RP, although this has previously been associated with a high risk of complications.

ADT might provide significant local control, although evidence to support a survival benefit is less clear. In a retrospective observational study of patients with PSA recurrence after RP, early ADT resulted in a significant reduction in the development of metastases compared with delayed ADT, although there was no significant effect on long-term survival [11]. By contrast, prospective studies have suggested a survival benefit with immediate ADT in patients with minimal metastatic disease, suggesting that patients with PSA-only recurrence might also have improved survival with ADT [12,13]. A recent update of American Society of Clinical Oncology practice guidelines concluded that, although early ADT results in a 17% decrease in relative risk of prostate cancer-specific mortality, it had no effect on overall survival and therefore could not be recommended [14]. Also, ADT is well known to be associated with significant side-effects, including loss of libido, impotence, hot flushes, gynaecomastia and breast pain [5]. In addition, studies have also shown ADT to be associated with an increased risk of metabolic syndrome, diabetes, cardiovascular disease and osteoporosis [15–17]. The risk of these serious adverse effects is likely to increase with a longer duration of ADT.

Salvage RT might potentially cure patients with disease recurrence after RP. A review of patients with increasing PSA levels after RP showed that those with high-grade disease and/or a rapid PSADT had a durable response to salvage RT [18]. More recently, 48% of patients with PSA levels of ≤0.50 ng/mL treated with salvage RT were disease-free at 6 years, including 41% who also had a PSADT of <10 months or poorly differentiated cancer (Gleason grade 8–10) [19].

Therapeutic decision-making for patients with prostate cancer and biochemical recurrence needs to consider several factors. The potential long duration of the disease, the likelihood of death from other causes and the potential side-effects of treatment have to be balanced against the risk of metastatic progression and prostate cancer-related mortality, and the need to assuage anxiety often associated with rising PSA levels.

Adjuvant pharmacological treatment with minimal side-effects that potentially delays disease progression without compromising the response to any subsequent ADT would be a useful therapeutic option for many patients after potentially curative therapy, and could also help to reduce the anxiety associated with a rising PSA level.

The rationale for the Avodart after Radical Therapy for prostate cancer Study (ARTS) is as follows. The disease state, natural history and desire to avoid the adverse effects of second-line ADT and/or delay more aggressive treatment (e.g. salvage surgery or RT) mean that patients with isolated PSA recurrence after local RP or RT are an ideal population for evaluating novel therapies to delay or prevent cancer progression. Previous tertiary prevention trials in prostate cancer have investigated the effects of finasteride [20], exisulind [21], rosiglitazone [22], celecoxib [23], and dietary supplements [24] (Table 1). In the study by Andriole *et al.* [20], which is the only previous randomized trial of 5α-reductase inhibitor (5ARI) use in patients after RP, treatment with finasteride 10 mg for 1 year delayed the increase in serum PSA level by ≈9 months, compared with placebo, in 120 men with serum PSA levels of 0.6–10.0 ng/mL, no evidence of skeletal metastasis on bone scan, and with no previous ADT. There were fewer recurrences in the finasteride group, although differences were not statistically significant from placebo. However, the reduction in local and distant recurrences in the finasteride group suggests that the effect on PSA reflects a direct effect on tumour growth without affecting the initial response to subsequent hormonal therapy.

Unlike finasteride, which only inhibits type 2 5AR, dutasteride is a dual 5ARI that inhibits both type 1 and type 2 5AR isoenzymes (5AR1 and 5AR2). Dual inhibition of both 5AR1 and 5AR2 provides greater and more consistent inhibition of the conversion of testosterone to dihydrotestosterone (DHT) than selective inhibition of 5AR2 alone [25]. As a result of this dual inhibition, it is possible that dutasteride might have greater activity against prostate cancer than has finasteride.

TABLE 1 Previous clinical trials for the tertiary prevention of prostate cancer in patients with biochemical recurrence after radical therapy

Ref	Study design and patients (*n*)	Treatment arms	Endpoints	Key results
[20]	DB, R, PC trial in men with detectable PSA levels (0.6–10 ng/mL) after RP (120) Men had no evidence of skeletal metastases and no previous ADT	Finasteride 10 mg/day vs placebo for 1 year All patients treated with finasteride in year 2	Serum PSA levels Recurrence rates (defined as positive bone scan or positive biopsy)	Finasteride resulted in a delayed increase in PSA of ≈9 months vs placebo after 1 year. There were fewer recurrences in the finasteride group (NS)
[21]	R, PC trial in men with increasing PSA after RP (96)	Exisulind 250 mg × 2 daily vs placebo for 1 year	Change in PSA and PSADT	Exisulind inhibited the increase in PSA vs placebo ($P = 0.017$). Median PSADT increased in high-risk patients on exisulind vs placebo ($P = 0.048$)
[22]	R, PC trial in men with increasing PSA after RP and/or RT (106) No radiographic evidence of metastases and no recent ADT	Rosiglitazone 4 mg × 2 daily vs placebo. Treatment continued until disease progression or adverse event (median duration 338 days for rosiglitazone and 315 for placebo)	Change in PSADT Positive outcome defined as PSADT >150% baseline with no new metastases	38% of men in rosiglitazone group and 40% in placebo had a positive outcome ($P = 1.0$). Time to disease progression similar in both groups
[23]	R, PC trial in men with increasin PSA after RP and/or RT (78). No radiographic evidence of metastases	Celecoxib 400 mg × 2 daily vs placebo	A positive outcome defined as PSADT >200% baseline with no new metastases	Eight (20%) of 40 men in placebo group and 15 (40%) of 38 in celecoxib group had a positive outcome ($P = 0.08$) Mean PSA velocity increased by 3% for the placebo group and decreased by 3.4% for the celecoxib group ($P = 0.02$)
[24]	R, DB, PC crossover trial in men with increasing PSA after RP (34) or RT (15)	Soy-based dietary supplement (including isoflavones, lycopene, silymarin and antioxidants) vs placebo Two 10-week treatment periods separated by 4-week washout period	PSA slope Change in PSADT	Significant decrease in PSA slope ($P = 0.03$) and 2.6 fold increase in PSADT (from 445 to 1150 days) with dietary supplement vs placebo

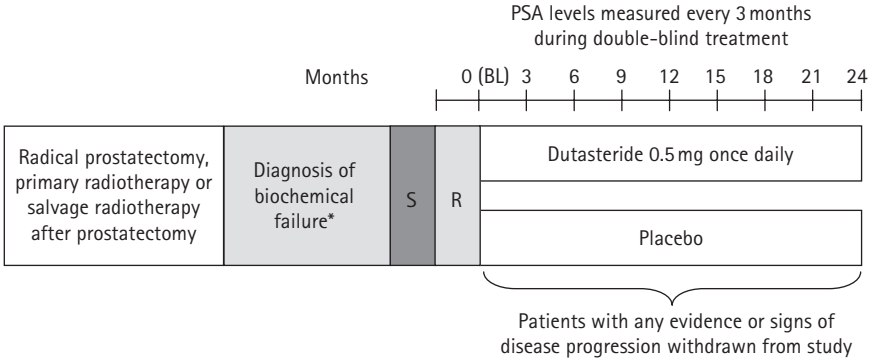
DB, double-blind; R, randomized; PC, placebo-controlled; NS, not significant.

In a rat prostate cancer model, finasteride reduced the host prostate weight and DHT content but did not inhibit growth or reduce the DHT content of the R-3327H xenograft in intact (uncastrated) rats. By contrast, dutasteride reduced both host prostate and tumour DHT content and weight [26]. Similarly, dutasteride was more effective than finasteride at inhibiting the growth of LNCaP human prostate cancer xenografts in intact male nude mice [26].

Dutasteride has also been shown to improve phenotypic markers of tumour regression in men with prostate cancer. Patients with clinically staged T1 or T2 prostate cancer who received dutasteride 5 mg/day for 6–10 weeks before RP had a 97% decrease in intraprostatic DHT, increased apoptosis, a decrease in mean benign epithelial cell width and a trend toward a lower microvessel density in prostate cancer tissue than with placebo [27]. Moreover, Iczkowski *et al.* [28] reported that short-term dutasteride treatment before RP was associated with the involution and decrease in height of benign epithelium, while prostate cancer tissue showed a significant decrease in tumour volume as well as a decrease in epithelium relative to stroma. In another study of 81 men with clinically localized prostate cancer, 4 months of treatment with dutasteride before RP was associated with ≥90% lower serum and intraprostatic DHT levels, an increase in serum testosterone, and smaller prostate and tumour volumes, than in the control group [29]. Treatment with dutasteride has also been shown to induce changes in gene expression consistent with androgen deprivation in benign prostatic epithelia from men with prostate cancer [30].

Immunostaining with specific antibodies for 5AR1 and 5AR2 to evaluate gene expression has shown that 5AR1 expression increases and 5AR2 expression decreases in prostatic intraepithelial neoplasia and prostate cancer cells compared with normal prostate or BPH tissue [31]. Higher nuclear expression of 5AR1 than 5AR2 was reported in recurrent prostate cancer and androgen-stimulated prostate cancer [32]. Luo *et al.* [33] showed lower expression of 5AR2 in 25 prostate cancer samples than in normal and BPH samples. It was also recently reported that both 5AR1 and 5AR2 isoenzymes are at higher levels in localized high-grade than in low-grade prostate cancers [34]. This increase in 5AR1 might offer a possible explanation for the reduced efficacy of finasteride against high-grade prostate cancers reported in the Prostate Cancer Prevention Trial [35].

FIG. 1. The ARTS design.



*Biochemical failure defined as three rises in PSA level from nadir (lowest value recorded after therapy) with each rise at least 4 weeks apart. Patients treated with radical prostatectomy are eligible providing each PSA level is ≥0.2 ng/ml and final PSA level is 0.4–10 ng/ml, whereas patients treated with primary radiotherapy are eligible if final PSA level is 2–20 ng/ml.

BL = baseline, S = screening, R = randomisation (stratified by radical prostatectomy vs primary radiotherapy)

These findings suggest that dual inhibition of 5AR1 and 5AR2, and the subsequent more complete suppression of DHT provided by dutasteride than by finasteride, might translate into improved clinical outcomes in men with prostate cancer. This, combined with the lack of serious side-effects during long-term 5ARI treatment, provides a scientific rationale for further investigation of the potential role of dutasteride as a therapeutic option for patients with PSA recurrence after RP and/or RT.

ARTS is an ongoing pan-European (Spain, Germany, Sweden, UK, the Netherlands, Finland, Estonia, France and Russia), 2-year, multicentre, randomized, double-blind, placebo-controlled trial that will assess the efficacy and safety of dutasteride in extending the PSADT in men who have an asymptomatic biochemical failure after radical therapy with curative intent (RP, primary RT or salvage RT after RP) for clinically localized prostate cancer.

In patients treated with RP (with or without salvage RT), biochemical failure is defined as three increases in PSA level from nadir (lowest value recorded after therapy) with each increase ≥4 weeks apart, each PSA level ≥0.2 ng/mL and a final PSA level of 0.4–10 ng/mL. In patients treated with primary RT, biochemical failure is defined as three increases in PSA level from the nadir, with each rise ≥4 weeks apart and a final PSA level of 2–20 ng/mL. Also, because PSA levels decline more slowly after RT than RP, there should be at least a year from the end of RT to the observed increase in PSA level.

Men with a fast PSADT (≤3 months) will be excluded, because these patients could benefit from more aggressive treatment. Similarly, men with a PSADT of >24 months will also be excluded, as watchful waiting could be considered adequate for this group. The study inclusion and exclusion criteria are listed in Appendix 1.

Eligibility criteria and other study protocol characteristics were decided upon by an expert group (consisting of most of the authors of the present report) which considered available evidence, guideline recommendations from the EAU and Radiotherapy Oncology Group-American Society for Therapeutic Radiology and Oncology, and an expert panel consensus statement [36]. The placebo-controlled design was chosen because there is no existing standard treatment in this patient group, with watchful waiting being recommended in selected cases. A no-treatment period is also usual strategy with intermittent androgen blockade (IAB), patients having to reach a certain PSA threshold before active therapy is initiated. In a study comparing IAB with continuous androgen blockade, IAB started when PSA levels were >10 ng/mL had no detrimental effect on progression-free survival or overall survival, but was associated with a potential benefit in quality of life [37]. Moreover, because of concerns over possible side-effects [15–17], the start of hormonal therapy is often delayed for as long as possible in clinical practice. As such, the use of placebo in this study is consistent with usual clinical care and so unlikely to have a negative effect on outcomes. Finally, previous trials in similar patient populations also used placebo as comparison [20–24].

The primary study objective of ARTS is to assess the PSADT with dutasteride 0.5 mg once daily compared with placebo. The PSADT is defined as the time from the start of double-blind treatment to the when the PSA level has doubled from baseline (last PSA measurement before start of treatment), as observed for the first time in an actual assessment during the treatment period.

Secondary endpoints are time to disease progression, treatment response, changes in PSA and changes in PSADT (Appendix 2). In addition, given the known anxiety and concern experienced by patients with biochemical recurrence after potentially curative therapy, changes in anxiety will be evaluated using the Memorial Anxiety Scale for Prostate Cancer (MAX-PC). This is an 18-item self-reported questionnaire that assesses general anxiety related to prostate cancer and treatment, fear of recurrence and anxiety specifically related to PSA testing. The safety of dutasteride will also be evaluated by adverse events, physical examination, vital signs and clinical laboratory tests.

An estimated 276 patients are expected to be randomized to either dutasteride 0.5 mg or placebo once daily (Fig. 1). Patients will be stratified by previous therapy (RP with or without salvage RT vs primary RT) as these two groups could be expected to respond differently to treatment. Patients will be treated for 2 years and will be monitored with PSA levels measured every 3 months. Any patients with evidence or signs of disease progression will be identified and more aggressive treatment strategies considered.

The planned sample size of 276 patients is based on the primary endpoint of PSADT. Assuming a median PSADT of 10–11 months in the placebo group, and that 31.8% of dutasteride-treated patients have a DT at this time-point (hazard ratio 0.605) then 110 evaluable patients per arm are required to provide 80% power using a two-sided log-rank test at $\alpha = 0.05$. Assuming a 20% withdrawal rate, ≈138 patients per arm need to be randomized. The primary population for analysis will be the intent-to-treat population, which consists of all randomized patients, and the primary endpoint will be analysed using a log-rank test stratified by previous therapy and investigative-site

cluster. A two-sided log-rank test will be conducted at a 0.05 level of significance to compare dutasteride treatment with placebo for the primary study endpoint.

CONCLUSIONS

The management of patients with biochemical recurrence after RP or RT represents a significant clinical challenge for physicians. ARTS will be the first study to evaluate the effects of dutasteride on PSADT, disease progression, treatment response and changes in PSA and PSADT in this population. Previous studies have indicated that the dual 5ARI, dutasteride, suppresses intraprostatic DHT, increases apoptosis in malignant tissue, reduces tumour volume and improves other phenotypic markers of tumour regression in men with prostate cancer. Dual inhibition of both 5AR1 and 5AR2 provides more complete suppression of DHT and so might offer an additional benefit over 5AR2 inhibition alone.

The use of dutasteride in these patients might delay the time to disease progression and reduce the need for more aggressive treatment, without compromising the response to subsequent hormonal therapy. Together with ongoing studies of dutasteride for primary and secondary prevention of prostate cancer (REDUCE and REDEEM) [38,39], the ARTS tertiary prevention trial should help to elucidate the potential role of dual 5AR inhibition in prostate cancer.

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CONFLICT OF INTEREST

Fritz H. Schröder is a Paid Consultant to and Study Investigator funded by Sponsor. Francesco Montorsi is a Paid Consultant to GSK. Tom A. McNicholas is a Paid Consultant to GSK and an Investigator for GSK funded trials. Ramiro S. Castro and Indrani M. Nandy are Employees of Sponsor. Antonio Alcaraz is an Advisor to GSK. Source of Funding: Glaxo SmithKline.

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Abbreviations: **RP**, radical prostatectomy; **RT**, radiotherapy; **ARTS**, Avodart after Radical Therapy for prostate cancer Study; **DT**, doubling time; **ADT**, androgen-deprivation therapy; **EAU**, European Association of Urology; **5-AR(I)**, 5α-reductase (inhibitor); **DHT**, dihydrotestosterone; **IAB**, intermittent androgen blockade; **MAX-PC**, Memorial Anxiety Scale for Prostate Cancer.

APPENDIX 1

Key inclusion and exclusion criteria

Inclusion criteria

Men aged <85 years
Patients with asymptomatic PSA failure after radical therapy with curative intent for clinically localized prostate cancer. PSA failure is defined as:

1 After RP with or without salvage RT, three increase in PSA level from nadir PSA, with each determination ≥4 weeks apart and each PSA level ≥0.2 ng/mL and a final PSA level ≥0.4 ng/mL (nadir PSA is defined as the lowest PSA value achieved after therapy)
2 After primary RT, three increases in PSA levels from nadir PSA, with each determination ≥4 weeks apart and a final PSA level of ≥2 ng/mL above nadir PSA. Time from RT should be ≥1 year from termination of RT.

Serum PSA levels:

1 ≥0.4 ng/mL and ≤10 ng/mL for RP with or without salvage RT
2 ≥2 ng/mL and ≤20 ng/mL for primary RT
PSADT >3 months and ≤24 months

Clinical stage T1-T3a N0M0

Non-metastatic prostate cancer, as confirmed on a negative bone scan taken within 6 months before randomization.

No evidence of local recurrence in patients after RP or salvage RT

Expected survival ≥2 years

Eastern Cooperative Oncology Group performance status 0–2

Exclusion criteria

Any unstable serious coexisting medical condition(s) or disease history that, in the opinion of the investigator, might confound the results or pose an additional risk to the patient

Abnormal liver function tests

Serum creatinine >1.5 × upper limit of normal

History of another malignancy within 5 years that could affect the diagnosis of prostate cancer

History or current evidence of drug or alcohol abuse within 12 months before Visit 1

Known hypersensitivity to any 5ARI or to any drug chemically related to dutasteride

Biochemical failures in patients after brachytherapy

Previous treatment for prostate cancer with chemotherapy, oestrogens, anti-androgenic agents (except when adjuvant or neoadjuvant in the context of a primary radical treatment in which case their use should have been for ≤6 months and should have completed ≥1 year before Visit 1), GnRH analogues (except when adjuvant or neoadjuvant in the context of a primary radical treatment (in this case use should have been for ≤6 months and should have finalized ≥1 year before Visit 1) or orchidectomy

Treatment with glucocorticoids (except inhaled or topical) within 3 months before visit 1, finasteride or dutasteride within 6 months before visit 1, or anabolic steroids within 6 months before Visit 1

APPENDIX 2

Secondary endpoints in ARTS

1. Time to disease progression and percentage of patients with disease progression, defined as:

PSADT ≤3 months and confirmed in a subsequent PSA assessment within 2 weeks.

2. PSA level >10 ng/mL (RP) or >20 ng/mL (primary RT) associated with a ≥50% increase in PSA level from baseline and confirmed in a subsequent PSA assessment within 2 weeks.

3. Need for any prostate cancer rescue therapy (e.g. GnRH agonists, antiandrogens) during the 2-year study period. Any confirmed local clinical tumour progression in clinical stage during the 2-year study period. Metastatic disease: any radiographic evidence of metastatic disease during the 2-year study period.

4. Percentage of patients with treatment response, defined as:

PSA response; PSA decrease or increase of ≤15% from baseline to up to 2 years of treatment confirmed in all PSA measurements.

Changes in PSA; Time to PSA increase from baseline and percentage of patients with a PSA increase from baseline, defined as first PSA value showing a >15% increase from baseline confirmed in all subsequent measurements (baseline PSA is defined as the last PSA measurement before randomization).

Time to PSA progression and percentage of patients with PSA progression based on the definition of a patient having a PSADT of ≥3 months or a PSA level of >20 ng/mL (primary RT) or a PSA level of >10 ng/mL (RP, with or without salvage RT) associated with a ≥50% increase from the baseline PSA measurement and confirmed in a subsequent PSA determination (within 2 weeks).

Absolute and percentage PSA change from baseline PSA and from nadir PSA.

4. Changes in PSADT

PSADT during treatment – PSADT before treatment

5. Change from baseline in disease-related patient anxiety (measured by the MAX-PC)

6. Safety of dutasteride

Assessed by changes in physical examination, adverse events, vital signs and laboratory tests.