Dutasteride and bicalutamide in patients with hormone-refractory prostate cancer: The Therapy Assessed by Rising PSA (TARP) study rationale and design

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Introduction: *Bicalutamide blocks androgen action in men with prostate cancer but has low affinity for the androgen receptor compared to dihydrotestosterone (DHT). Dutasteride, a dual 5α-reductase inhibitor (5ARI), blocks the conversion of testosterone to DHT, reduces tumor volume and improves PSA in prostate cancer. Bicalutamide should be a more effective antiandrogen if it competes against intraprostatic testosterone, rather than DHT, for the androgen receptor. The Therapy Assessed by Rising PSA (TARP) study investigates dutasteride in combination with bicalutamide to prevent or delay disease progression in patients with castrate-refractory prostate cancer (CRPC) after initial androgen deprivation therapy.*

Patients and methods: *This ongoing US and Canada multicenter trial with patients with rising PSAs while on a GnRH analogue are randomized to double-blind treatment with dutasteride 3.5 mg and bicalutamide 50 mg or placebo and bicalutamide 50 mg once daily. Inclusion criteria include three rising PSA levels despite a GnRH analogue or surgical castration, and no radiographic evidence of metastases. The entry PSA values must be 2.0 ng/ml-20.0 ng/ml and serum testosterone level < 50 ng/dl. The primary endpoint is time to disease progression determined by PSA, or radiographic progression.*

Conclusions: *TARP will be the first study to evaluate the effects of dutasteride and an antiandrogen in patients failing GnRH analogue and help elucidate the potential role of a dual 5ARI in reducing the rate of progression in non-metastatic CRPC.*

Key Words: prostate cancer, dutasteride, bicalutamide, clinical trial

Introduction

Prostate cancer is the most frequently diagnosed non-cutaneous malignancy in the US with an estimated 192,280 new cases and 27,360 deaths in 2009 based on the American Cancer Society projections.[1] Androgen deprivation therapy (ADT) with either medical or surgical castration is the preferred initial medical treatment for advanced prostate cancer.[2] ADT typically results in improvement in 80%-90% of patients with advanced prostate cancer.[3] While circulating testosterone is significantly reduced after ADT, intraprostate cancer dihydrotestosterone (DHT), testosterone (T) and adrenal androgens are still present.[2,4] Typically, the first sign of recurrence post-ADT is a rising PSA. Though optimal therapy in this situation is controversial, antiandrogens,

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such as bicalutamide, are often added as an initial therapeutic maneuver.

The rationale for the antiandrogen is to prevent any remaining intraprostatic androgens from stimulating androgen receptor (AR)-mediated prostate cancer cell growth.[5] Several studies have confirmed the advantage of combining a luteinizing hormone-releasing hormone (LHRH) analogue plus an antiandrogen over LHRH therapy alone in lengthening the time to treatment failure or time to disease progression,[6-8] however other studies have not confirmed these observations.[9]

Bicalutamides' affinity to the AR compared with DHT is 50-100 times less in wild-type rat prostate[10,11] and about 60 times less in a normal human cytosol preparation.[12] These data suggest available antiandrogens are not optimal at blocking ligand-dependent activation of AR by T or DHT. Dutasteride inhibits both Type 1 and 2 5α-reductase enzymes (5AR), significantly decreases intraprostatic DHT in men with localized prostate cancer, and causes apoptosis and regression of some prostate cancers.[13,14]

At the mRNA and protein level Type 1 5AR is elevated in prostate cancer while Type 2 5AR is either decreased or unchanged.[15] At the enzyme level, the Type 1 has been shown to be active.[16] At the protein level, both 5AR1 and 5AR2 isoenzymes are increased in localized high-grade cancers compared with low-grade prostate cancers.[17] By blocking the conversion of testosterone to DHT, dutasteride could allow bicalutamide to be a more effective antiandrogen (thus prolonging bicalutamide's efficacy).

Tay and colleagues investigated the use of finasteride in combination with a LHRH agonist and antiandrogen at the first PSA nadir[18] and showed a potential benefit of CAB and blocking the conversion of T to DHT. Scher[19] and Fujii[8] evaluated bicalutamide in patients with rising PSA's while receiving ADT GnRH monotherapy and found CAB with bicalutamide to be of benefit in some patients by prolonging their PSA progression-free survival time. Accordingly, the Therapy Assessed by Rising PSA (TARP) trial was planned to assess DHT suppression with dutasteride plus androgen blockade with bicalutamide in men with failure after GnRH agonist therapy as demonstrated by a rising PSA.

Material and methods

Study management

TARP is a GlaxoSmithKline (GSK) sponsored and monitored, double-blind, placebo-controlled clinical trial. The study was designed in consultation with a panel of external experts. Ongoing study management and medical oversight, including compliance with study-related procedures, subject safety monitoring, data management and statistical support is provided by GSK. Each study site has its own local principal investigator and study coordinator.

Study population

Enrollment was initiated in May 2007 and is currently recruiting. A total of 66 sites are anticipated to recruit patients. No advertising is done and no financial incentives are provided to patients other than reimbursement for travel and other related expenses. Randomization was stratified by site. Eligible patients are to be between ≥ 40 and ≤ 90 years of age with asymptomatic, prostate cancer, no radiographic evidence of metastases, and PSA progression despite GnRH agonist therapy or surgical castration. PSA progression is defined as three rises in PSA each measured at least 4 weeks apart within the previous year. The entry serum PSA must be 2 ng/ml-20 ng/ml and serum testosterone < 50 ng/dl from a central laboratory. To help ensure "non-metastatic" disease, a bone scan is performed within 8 weeks of screening. It is recognized that the majority of patients in this setting will have non-radiographic detectable metastases.

Patients cannot have had additional hormonal therapy, excluding the current use of a GnRH analogue, or drugs with antiandrogenic properties within the past 6 months. The use of an antiandrogen during GnRH analogue induction for < 6 weeks is acceptable, but none within the 3 months prior to study entry. In addition, treatment with oral glucocorticoids during the 3 months prior to randomization or prior chemotherapy for prostate cancer is excluded. A prior prostatectomy or radiotherapy to the prostate is allowed. Use of dietary and herbal supplements (e.g., saw palmetto), excluding daily vitamins, during the study is discouraged, but not prohibited. Subjects who have had prostate surgery (e.g. TUNA, TURP, TUIP, laser treatment, thermotherapy, balloon dilatation, prosthesis, cryosurgical ablation) within 2 months prior to enrollment are excluded. Patients are also excluded if they are currently taking or within 6 months of study participation, finasteride, dutasteride or anabolic steroids.

Study design

Subjects who meet the inclusion and exclusion criteria, Table 1, and signed informed consent are randomized to receive dutasteride 3.5 mg/day, as a single capsule, and bicalutamide 50 mg/day or placebo and bicalutamide 50 mg/day for up to 18 months. Subjects who complete the 18 month treatment phase with either stabilization or a positive response to their prostate cancer will be

TABLE 1. **Key inclusion and exclusion criteria**

Inclusion criteria
Men ≥ 40 and ≤ 90 years of age.
Asymptomatic prostate cancer that has progressed during androgen deprivation therapy (rising PSA). PSA progression must have occurred after first-line treatment with GnRH analogues (e.g. leuprolide, goserelin) or orchiectomy. PSA progression is defined by three rises in PSA each measured at least 4 weeks apart within the previous year.
Serum PSA ≥ 2 ng/ml and ≤ 20 ng/ml at entry.
Serum testosterone < 50 ng/dl from central laboratory.
Non-metastatic prostate cancer as confirmed on prior bone scan performed within 8 weeks of screening.
Expected survival ≥ 2 years.
Eastern Cooperative Oncology Group (ECOG) performance status 0, 1, or 2.
Exclusion criteria
Additional hormonal therapy* within the past 6 months of: estrogens (e.g. megestrol, medroxyprogesterone, cyproterone, DES), drugs with antiandrogenic properties such as spironolactone if > 50 mg/day, ketoconazole**, or progestational agents.
Prior use of antiandrogenics such as flutamide and bicalutamide is prohibited, except if the medications were used during GnRH analogue induction used for < 6 weeks and not used with 3 months prior to study entry.
Use of dietary and herbal supplements (e.g., saw palmetto), or vitamins, during the study is discouraged, but not prohibited.
Treatment with oral glucocorticoids during the 3 months prior to randomization or expectation of their use during the study.
Prior chemotherapy for prostate cancer, (prior prostatectomy or radiotherapy to the prostate are allowed).
Prostate surgery including TUNA, TURP, TUIP, laser treatment, thermotherapy, balloon dilatation, prosthesis, and cryosurgical ablation within 2 months prior to enrollment.
Current and/or previous use of the following medications: Finasteride or dutasteride exposure within 6 months prior to study entry Anabolic steroids (within 6 months prior to study entry)
Participation in any investigational or marketed drug trial within the 30 days prior to the first dose of study drug or anytime during the study period.
Any unstable serious coexisting medical condition(s) that in the opinion of the investigator might interfere with the study or pose an additional risk to the patient.
Abnormal liver function tests > 1.5 or serum creatinine > 2.0 times the upper limit of normal.
History of another malignancy within 5 years that could affect the treatment of prostate cancer or survival of the subject.
History or current evidence of drug or alcohol abuse within the last 12 months.
History of any illness (including psychiatric) that, in the opinion of the investigator, might confound the results of the study or pose additional risk to the subject.
Known hypersensitivity to any 5α-reductase inhibitor or to any drug chemically related to dutasteride.

*Current use of GnRH analogue (i.e., Lupron) is acceptable.

**The use of topical ketoconazole is permitted prior to and during the study.

offered participation in a 2 year extension phase for up to 42 months. The extension phase of the study allows subjects to remain on their currently assigned medication for an additional 2 years. Follow up visits are monthly in the 18 month treatment phase and every 3 months in the extension phase, Figure 1.

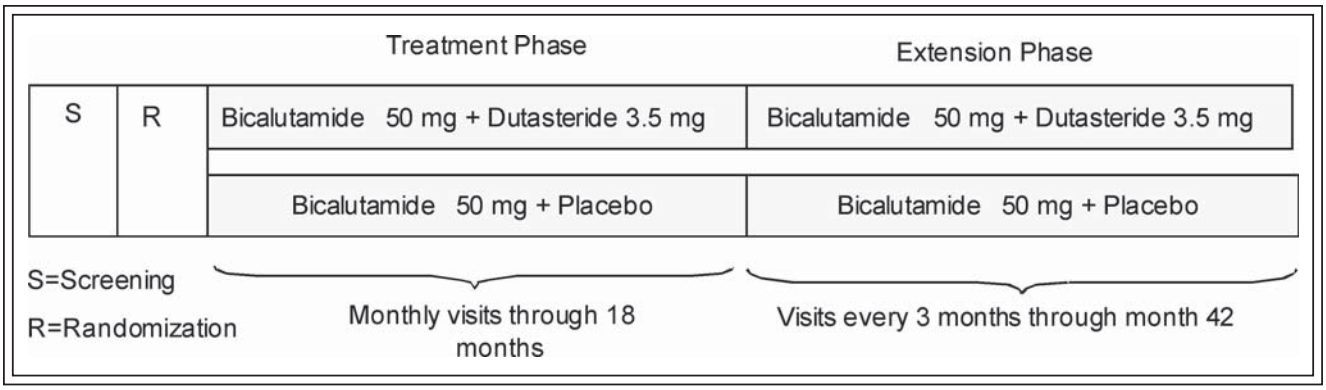

Figure 1. The Therapy Assessed by Rising PSA (TARP) design.

Assessments

Because total PSA is the primary monitoring tool in this study it will be assessed every month during the treatment phase and every 3 months in the extension phase. Actual PSA values will be reported to the investigator for both phases of the study. No adjustments to PSA values will be performed since study subjects are already diagnosed with prostate cancer and clinicians use PSA as part of subject management. Treatment decisions are often made from these PSA values, and it is not appropriate to adjust these values to attempt to account for an effect dutasteride might have on PSA levels. All site staff and study participants will remain blinded to study treatment. Clinical chemistry and hematology will be assessed monthly for the first 4 months then every 6 months thereafter. T will be drawn at screening then every 6 months and DHT at screening then at month 6 or early withdrawal during the treatment phase.

Study endpoints

The primary endpoint of the study is time to disease progression as defined in Table 2. The subject may remain in the study until the secondary endpoint of treatment failure is reached, even if the primary endpoint of disease progression has been met. The secondary endpoints of the study include the following:

- Time to treatment failure as defined in Table 2. Subjects will be discontinued from the study when treatment failure is reached.

TABLE 2. **Primary and secondary endpoints**

Criteria	Definition of progression	Time	Disease progression (primary)	Treatment failure (secondary)
PSA progression from baseline	PSA value is 25% and at least 2 ng/ml above baseline, *confirmed by a second PSA value	Date of 1st PSA value that meets criteria	Yes	Yes
PSA progression from nadir, without a 50% decrease from baseline	PSA value is 25% and at least 2 ng/ml above nadir, *confirmed by a second PSA value	Date of 1st PSA value that meets criteria	Yes	No
PSA progression from nadir, with a ≥ 50% decrease from baseline	PSA value is > 50% and 2 ng/ml above nadir, *confirmed by a second PSA value	Date of 1st PSA value that meets criteria	Yes	No
Metastatic disease	Radiographic evidence of metastatic disease	Date of scan	Yes	Yes

*Confirmation PSA value must occur within two PSA measurements of the first occurrence.

- Percentage of subjects having PSA response defined as a 50% decrease in PSA from baseline, confirmed by a second PSA measurement. The time of this response is the date of the first PSA measurement which shows a 50% decrease from the baseline PSA measurement.
- Change in PSA value from baseline.
- Percentage of subjects having radiographic evidence of metastatic disease as evidenced by a radiographic assessment.

Interim analysis

This study will include an interim analysis and a final analysis on unblinded data, analyzed by the study statistician. The interim analysis will be performed after all subjects have reached the month 30 visit or withdrawn from the study prior to reaching the month 30 visit. In addition, a final analysis will be performed after all subjects have completed the study or withdrawn from the study after up to 42 months of treatment.

Adjustments to the significance level used for testing the primary endpoint of time to disease progression will be made to account for multiple testing of this endpoint at the interim analysis and final analysis using the Pocock alpha-spending method, which specifies a two sided significance level of 0.029 for testing the primary endpoint at the interim analysis and at the final analysis in order to maintain an overall Type 1 error rate of 0.05 for the study.

The original analysis was to be performed after up to 18 months of treatment. However, based on blinded data during the ongoing study, it was observed that the overall number of patients having disease progression was lower than anticipated. The protocol was amended such that an interim analysis is to be performed after 30 months of treatment and a final analysis after 42 months of treatment to provide a longer time period for observing events, and therefore higher power to detect a treatment difference.

Statistical analysis

The sample size is based on the primary endpoint of time to disease progression. Assuming a median time to disease progression of 6 months for the bicalutamide/placebo group[8] and 11 months for the bicalutamide/dutasteride 3.5 mg group, then approximately 74 subjects per treatment arm are required to provide at least 80% power for both the interim analysis (after up to 30 months of treatment) and the final analysis (after up to 42 months of treatment) using a two sided log rank test at $\alpha = 0.029$ and assuming 20% withdrawal during the study. To obtain approximately 150 total randomized subjects, approximately 190 subjects will be screened. Randomization to treatment groups will be performed in blocks, stratified by center.

The baseline PSA value is defined as the latest PSA assessment prior to randomization. The nadir PSA value is defined as the lowest PSA value (below the baseline PSA value) after randomization.

The primary analysis of the primary endpoint will be performed using the log rank test stratified by investigative site cluster. As a supportive analysis of the primary endpoint, a Cox Proportional Hazards model stratified by investigative site cluster will be used with treatment as the only covariate. Effects of baseline covariates on the relationship between treatment group and the primary endpoint will be investigated via a Cox Proportional Hazards. Subgroup analyses of the primary endpoint will be conducted to assess the effects of baseline characteristics (such as age, race, and baseline PSA) on the percentage of subjects experiencing disease progression.

Discussion

Patients with PSA recurrence after initial ADT desire to avoid the adverse effects of chemotherapy. Typically, in this disease state, a variety of secondary hormonal manipulations are used in the hopes that cancer progression can be delayed. TARP is an ongoing North American (US and Canada), multicenter, randomized, double-blind, placebo-controlled trial that will assess the efficacy and safety of dutasteride in extending the time to PSA progression (PSA progression free survival) in men who experience an asymptomatic biochemical failure after initial ADT therapy for prostate cancer.

Rationale for 3.5 mg dose

Type 1 5α-reductase isozyme is over expressed in malignant tissue compared to benign tissue and the dual inhibition of the Type 1 and Type 2 5AR makes dutasteride a logical choice. The dose of dutasteride in this study is 3.5 mg once daily. The dose FDA approved for benign prostatic hyperplasia and being tested for prostate cancer risk reduction is 0.5 mg once daily. In a 4 month preradical prostatectomy study comparing 0.5 mg and 3.5 mg dutasteride with a control group, mean reduction of intraprostatic DHT was 94% in the 0.5 mg dutasteride arm and 99% in the 3.5 mg arm with a safety and tolerability profile similar to the 0.5 mg dose. The median tumor volume was 40% lower in both dutasteride groups compared to the control group;[20] however, total PSA and its various isoforms were reduced to a greater extent with the 3.5 mg

group. Daily doses of 5.0 mg dutasteride have also been administered for 6 months in a study of men with BPH, with a safety and tolerability profile similar to the 0.5 mg dose.[21] The 3.5 mg dose has been chosen as giving the "best chance" for efficacy in this population of subjects.

Rationale for primary measure of efficacy

In 1999, the Prostate-Specific Antigen Working Group (PCWG1) proposed a set of criteria for clinical trial development in patients whose prostate cancer was progressing despite castrate levels of testosterone.[22] The Prostate Cancer Clinical Trials Working Group (PCWG2) recently provided updated recommendations.[23] Consistent with the framework of PCWG2, the TARP study is evaluating patients who have asymptomatic, non-metastatic disease in a trial designed to delay progression using rising PSA as the primary measure of efficacy. PSA was chosen at the primary endpoint based on the mechanism of action of the non-cytotoxic properties of dutasteride and bicalutamide. Discontinuation rules for patients with a rising PSA is a reflection that the treatment is ineffective. The PSA inclusion criteria of $\geq$ 2 ng/ml is consistent with the PCWG2 recommendations. The inclusion criteria of an upper limit of 20 ng/ml was based on the increased risk of disease progression at higher PSA values. Consistent with PCWG2, (1) pre-therapy PSA values are being collected for evaluation of doubling time and (2) PSA values are being measured every 4 weeks.

TARP incorporates the concepts of progression from both PCWG1 and PCWG2. Namely, TARP retains (1) the distinction of the percent decrease from baseline and (2) in patients with > 50% decrease in PSA from baseline, a 50% increase from nadir compared with a 25% increase recommended by PCWG2. TARP incorporates the lower threshold of a PSA absolute increase of 2 ng/ml from PCWG2 compared with the 5 ng/ml from PCWG1. It incorporates a confirmatory PSA value 4 weeks later using the first PSA value that meets the definition of progression (not the date of the confirmatory value) for reporting purposes. In patients who do not have a decline in their PSA from baseline, the protocol incorporates the PCWG2 updated recommendations as a 25% increase from the baseline value and an increase in the absolute value of $\geq$ 2 ng/ml (rather than 5 ng/ml in PCGW1). In this group of patients, the PCWG2 recommends waiting for 12 weeks of treatment before making a decision about treatment effectiveness. However, in TARP patients are seen every 4 weeks, and requiring a confirmatory PSA value would mean that patients will be in the study for at least 8 weeks, slightly less than the recommended 12 weeks. In addition to disease progression, patients are considered treatment failures if they develop radiographic evidence of metastatic disease.

Conclusion

The management of patients with rising PSA after initial ADT often includes addition of a non-steroidal antiandrogen. However, over time even patients who are receiving both a GnRH agonist and antiandrogen often demonstrate biochemical failure and eventually these patients are expected to develop radiographic progression as well. TARP will be the first study to evaluate the effects of the combination of dutasteride and an antiandrogen (in this case bicalutamide) on time to PSA progression in patients failing ADT as demonstrated by a rising PSA. Previous studies have indicated that the dual 5ARI, dutasteride, suppresses intraprostatic DHT, increases apoptosis in malignant tissue, and improves other phenotypic markers of tumor regression in men with prostate cancer. Dual inhibition of both 5AR1 and 5AR2 should reduce the androgen burden at the AR and thus allow bicalutamide to be a more effective AR antagonist.

It is our hypothesis that the use of dutasteride and bicalutamide may delay the time to disease progression and reduce the need for more aggressive treatment for those with non-metastatic CRPC. The TARP trial, along with other studies of dutasteride for primary prevention of prostate cancer (REDUCE trial) and in the continuum of prostate cancer treatment (REDEEM trials),[24,25] should help further elucidate the potential role of 5ARIs in prostate cancer. The addition of dutasteride to ketoconazole failures in CRPC has resulted in PSA declines, suggesting the CRPC remains partially sensitive to 5ARI inhibition.[26]

Disclosure

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Paul Gagnier, Rebekkah Dann and Karen Melich are employees of GlaxoSmithKline. □

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