The Bicalutamide 150 Mg Early Prostate Cancer Program: Findings of the North American Trial at 7.7-Year Median Followup

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Purpose: We describe the results of North American Trial 23 of the bicalutamide (Casodex™) early prostate cancer program in the context of the overall early prostate cancer program findings.

Materials and Methods: In Trial 23, 3,292 men with T1b–4, N0–Nx (N+ not allowed) M0 prostate cancer who had undergone radical prostatectomy or radiotherapy at 96 specialist referral centers in the United States (2,974) and Canada (318) were randomized 1:1 to 150 mg bicalutamide daily or placebo in addition to standard care for 2 years.

Results: In Trial 23 at a 7.7-year median followup there were few clinical events in the bicalutamide or standard care groups and the rates of objective progression were 15.4% and 15.3%, respectively. Mortality rates were 12.9% in the treatment group and 12.3% in the standard care group, including 11.2% and 11.0% for nonprostate cancer deaths in the absence of objective progression and 1.6% and 0.9%, respectively, for mortality due to prostate cancer. No differences in the primary end points (objective progression-free and overall survival) were seen between patients treated with bicalutamide and those treated with standard care alone. Bicalutamide (150 mg) significantly improved time to PSA progression (HR 0.80, 95% CI 0.72 to 0.90, $p < 0.001$). The tolerability profile of bicalutamide was similar to that previously described.

Conclusions: In Trial 23 the current data suggest that early or adjuvant therapy may not benefit patients at low risk for recurrence, such as those with localized disease. The findings of Trial 23 contrast with the results in the overall early prostate cancer program and in other published literature, in which bicalutamide has been shown to provide significant clinical benefit for locally advanced disease.

Key Words: prostate, androgen antagonists, prostatic neoplasms, clinical trials, bicalutamide

The introduction of PSA screening in the United States in the late 1980s transformed management practices for prostate cancer with a significant increase in radical therapies, particularly radical prostatectomy.[1–3] While radical therapy is given with curative intent, not all patients with localized or locally advanced disease experience long-term disease-free survival.[4] Studies in North American patients have assessed the benefits of adding hormonal therapy (castration) adjuvant to radiotherapy and surgery for locally advanced disease.[5–7] In these studies castration prolonged PFS and in some cases OS, although quality of life implications of castration in some men have prompted interest in evaluating other therapy options.

The bicalutamide (Casodex™) EPC program is assessing the nonsteroidal antiandrogen bicalutamide (150 mg) given in addition to standard care, including radical prostatectomy, radiotherapy and watchful waiting, for localized and locally advanced prostate cancer. The EPC program comprises 3 studies being performed in different regions that were designed and powered for combined analysis, including Trial 23 in North America, Trial 24 in Europe, South Africa, Mexico, Israel and Australia, and Trial 25 in Scandinavia.[8] In addition to their shared characteristics, the trial populations have unique features. For example, in the North American trial patients with poor prognostic features in whom the investigators considered radiotherapy or prostatectomy alone to be inappropriate were not recruited. This reflects the tendency in North America in the mid 1990s to actively treat early disease.[1] Hence, patients enrolled in Trial 23 have a lower overall risk profile and tumor burden than those in Trials 24 and 25. These factors also influenced treatment duration, with patients enrolled in Trial 23 receiving a shorter period of randomized therapy (2 years) than in Trials 24 and 25 (at least 5 years).[9]

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Study received Independent Ethics Committee approval at each center.

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This article is the first full, separate publication of Trial 23. It describes the third analysis of the trial done at a median followup of 7.7 years. Overall results of the third combined analysis of the EPC program have been reported previously.[10]

MATERIALS AND METHODS

Trial 23 Design

Trial 23 is 1 of 3 studies forming the bicalutamide EPC program, which involves 8,113 patients worldwide. The trial is an ongoing, randomized, double-blind, placebo controlled, parallel group study involving 82 centers in the United States and 14 in Canada.

Men 18 years or older with clinically or pathologically confirmed, localized or locally advanced prostate cancer and with no distant metastases (T1b–4, N0–Nx) who had undergone radical prostatectomy or radiotherapy were recruited. Patients with known lymph node metastases were excluded. Patients could have received neoadjuvant therapy of the investigator's choice but other prior therapy for prostate cancer was not permitted. All patients provided written informed consent.

Enrolled patients were randomized 1:1 to receive 150 mg bicalutamide daily or placebo in addition to standard care (referred to as standard care alone throughout the rest of this article), commencing within 16 weeks of radical prostatectomy or radiotherapy and continued a maximum of 2 years or until objective progression. In the event of progression randomized therapy was stopped and second line therapy was initiated according to investigator choice.

The trial was done in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines with Independent Ethics Committee approval at each center. A Data and Safety Monitoring Committee regularly reviewed efficacy and safety data. The study blind was broken at the database level following the first analysis of the EPC program at a minimum followup of 2 years (median 3) due to the significant differences in objective PFS seen between the treatment groups.[11] Investigators and patients were informed of these results and patients had the option of breaking the blind. Although all patients in Trial 23 had completed randomized therapy at the time of the first analysis, 769 (23.3%) chose to break the blind. However, they continue to be followed for progression and survival according to the trial protocol.

Assessments and End Points for Trial 23

Patients were assessed for disease status and PSA at trial entry and then every 12 weeks until objective progression or death. Primary end points were objective PFS and OS. Objective PFS was defined as the time from randomization to the earliest objective progression, as confirmed by bone scan, computerized tomography/ultrasound/magnetic resonance imaging or histological evidence of distant metastases, or death from any cause without progression. Secondary end points were time to PSA progression and tolerability. PSA progression was defined as the earliest of 1) PSA attaining 0.4 ng/ml if undetectable after surgery (less than 0.2 ng/ml), 2) detectable PSA after radiotherapy or surgery that had doubled from baseline, 3) objective progression or 4) death from any cause. Thus, this end point represents biochemical disease recurrence in patients treated with radical prostatectomy. Histopathological specimens were initially assessed at individual centers. However, a central review of the pathology reports has since been done in 2,116 patients (79.9%) who underwent radical prostatectomy.

Statistical Analyses for Trial 23

This third analysis was performed at a minimum followup of 7.5 years. Time to event data were analyzed on an intent to treat basis using a Cox proportional hazards regression model. As part of the statistical analysis plan, a statistical interaction test was performed that examined whether the relative effect of bicalutamide on PFS and OS depended on certain prespecified baseline prognostic factors, including disease stage, Gleason score and PSA.

RESULTS

Patients

Approximately 80% of the 3,292 men recruited into Trial 23 underwent radical prostatectomy and 20% received radiotherapy (table 1). The 2 randomized treatment groups were well balanced in terms of demographics and baseline disease characteristics (table 1).

Median followup at this analysis of Trial 23 was 7.7 years. The median duration of randomized therapy was 1.83 years for bicalutamide and 1.84 years for standard care alone. A similar number of patients in each group received systemic therapy for prostate cancer, in addition to randomized therapy (14.9% vs 19.1%). Overall 618 (37.5%) and 329 patients (20.2%) withdrew prematurely from bicalutamide and standard care alone, including 8 (0.5%) and 57 (3.5%), respectively, due to increasing PSA.

Efficacy

There was no difference in the risk of objective progression between patients treated with bicalutamide vs standard care alone (HR 1.00, 95% CI 0.84, 1.19, p = 0.991, table 2 and fig. 1). Likewise OS did not differ between the 2 groups (HR 1.04, 95% CI 0.85, 1.26, p = 0.723, table 2). The proportion of objective progression events and deaths due to

TABLE 1. *Patient demographics and baseline disease characteristics*

	Bicalutamide	Standard Care Alone
No. pts	1,647	1,645
Mean age (range)	64.5 (42–85)	64.4 (38–83)
% Tumor stage:		
T1	9.6	9.7
T2	62.7	63.2
T3	27.4	26.9
T4	0.2	0.2
% Nodal status:		
N−	72.0	71.2
Nx	27.9	28.8
N+	0.1	0
% Tumor grade (Gleason score):		
Well differentiated (2–4)	4.2	4.8
Moderately differentiated (5–6)	47.9	48.5
Poorly differentiated (7–10)	47.9	46.7
% Standard care:		
Radical prostatectomy	80.3	80.5
Radiotherapy	19.7	19.5
Radical prostatectomy plus radiotherapy	0	0.1
Median ng/ml prerandomization PSA (range)	NQ (NQ–34.0)	NQ (NQ–50.0)