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Immediate Treatment with Bicalutamide 150 mg as Adjuvant Therapy Significantly Reduces the Risk of PSA Progression in Early Prostate Cancer

W. See[a,*], P. Iversen[b], M. Wirth[c], D. McLeod[d], L. Garside[e], T. Morris[e]

[a]*Division of Urology, Medical College of Wisconsin, Froedtert Memorial Lutheran Hospital, 9200 W. Wisconsin Avenue, Milwaukee, WI, USA*
[b]*Department of Urology, Rigshospitalet, Copenhagen, Denmark*
[c]*Department of Urology, Technical University of Dresden, Germany*
[d]*Walter Reed Army Medical Center, Washington, DC, USA*
[e]*AstraZeneca, Mereside, Alderley Park, Macclesfield, Cheshire, UK*

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Abstract

Objective: To evaluate the effect of bicalutamide ('Casodex'[1]) 150 mg (in addition to standard care), on the risk of prostate-specific antigen (PSA) progression, in patients with early prostate cancer.

Methods: The bicalutamide 150 mg Early Prostate Cancer (EPC) programme is the largest clinical trial programme in the treatment of prostate cancer to date. This paper reports the PSA progression data from the EPC programme at a median of 3 years' follow-up, for the overall study population, and across the radical prostatectomy and radiotherapy primary therapy strategies. PSA progression was predefined as the earliest occurrence of PSA doubling from baseline, objective progression, or death from any cause.

Result: Overall, bicalutamide 150 mg in addition to standard care significantly reduced the risk of PSA progression by 59% compared with standard care alone (HR 0.41; 95% CI 0.38, 0.45; $p \ll 0.0001$). Significant reductions were observed following radical prostatectomy (51%; HR 0.49; 95% CI 0.43, 0.56; $p \ll 0.0001$) and radiotherapy (58%; HR 0.42; 95% CI 0.33, 0.53; $p \ll 0.0001$). Further exploration of the data by disease stage, nodal status, Gleason score and pre-treatment PSA level revealed significant reductions in the risk of PSA progression across most prognostic risk factor subgroups.

Conclusions: Bicalutamide 150 mg significantly reduces the risk of PSA progression, irrespective of whether patients received radical prostatectomy or radiotherapy as standard care. The EPC programme is ongoing and further progression and survival data are awaited.

Keywords: Bicalutamide; Hormone therapy; Prostate-specific antigen progression; Localised; Locally advanced; Prostate cancer

1. Introduction

The introduction of prostate-specific antigen (PSA) screening means that prostate cancer is now being detected in younger men and at earlier disease stages than was previously possible [1]. Management options for these early stage patients include radical prostatectomy, radiotherapy, hormonal therapy, and watchful waiting.

Many men who undergo early treatment for prostate cancer have an excellent outcome, however a significant proportion experience disease recurrence. PSA progression is generally considered to be the earliest evidence of persistent or recurrent disease after primary therapy of curative intent [2,3]. Approximately one-third of men with clinically localised disease develop PSA progression following radical prostatectomy [2,4,5] or radiotherapy [3,6]. Recently, data suggest that patients

* Corresponding author. Tel. +1-414-456-6949; Fax: +1-414-456-6217.
E-mail address: wsee@mcw.edu (W. See).

[1] 'Casodex' is a trademark of the AstraZeneca group of companies.

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receiving radiotherapy rather than radical prostatectomy [7] and those with more advanced disease stage (e.g. T3–T4, pre-treatment PSA level >10 ng/ml, Gleason score >7) [8,9], are at higher risk of developing both disease and PSA progression.

Predicting outcome after PSA progression remains a challenging issue. PSA progression often precedes clinical progression and may signal the onset of this process [10]. However, the prognosis is widely variable and not all patients with PSA progression proceed to clinical progression. Nonetheless, a rising PSA level is a cause of anxiety in many prostate cancer patients, despite being the expected outcome in those managed by watchful waiting.

Results of the bicalutamide 150 mg Early Prostate Cancer (EPC) programme, which is the largest clinical trial programme in the treatment of prostate cancer to date, are expected to provide valuable information on the use of PSA changes in predicting clinical progression and survival. The EPC programme is evaluating the efficacy and safety of bicalutamide 150 mg once daily as immediate therapy, in patients with localised or locally advanced prostate cancer, when given either alone or as adjuvant to therapy of curative intent (radical prostatectomy or radiotherapy) [11]. In the first analysis of this programme, at a median follow-up of 3 years, bicalutamide 150 mg was found to significantly reduce the risk of objective disease progression by 42% compared with standard care alone (hazard ratio [HR] 0.58; 95% confidence interval [CI] 0.51, 0.66; $p \ll 0.0001$) [12]. Of 922 patients with objective progression, 363 progressed in the bicalutamide 150 mg group compared with 559 in the standard care alone group. The tolerability profile of bicalutamide 150 mg was generally in line with its pharmacological profile; the most common adverse events were mild-to-moderate gynaecomastia and/or breast pain. The EPC programme is ongoing and patients continue to be followed-up for progression and survival.

This article reports the PSA progression data from the EPC programme, for the overall study population, and across the radical prostatectomy and radiotherapy primary therapy strategies. PSA progression was predefined as the earliest occurrence of PSA doubling from baseline, objective progression, or death from any cause.

2. Methods

2.1. Patients

The continuing EPC programme consists of three randomised, double-blind, placebo-controlled trials (Trials 23, 24 and 25) that were designed and powered for combined analysis. The methodology for these three trials has been published elsewhere [11]. A total of 8113 patients with localised or locally advanced prostate cancer were randomised to receive bicalutamide 150 mg or placebo once daily in addition to standard care. Across the programme, the two treatment groups were well matched in terms of demographic and baseline characteristics. However, there are some variations between the three studies, which relate to differences in entry criteria. For example, in Trial 23 only patients who had undergone either radical prostatectomy or radiotherapy were eligible for inclusion, whereas Trials 24 and 25 also included patients who were considered suitable candidates for watchful waiting. Moreover, patients with lymph node involvement were excluded from Trial 23, but not from the other two trials. Treatment duration also differs between the studies: 2 years in Trial 23 and at least 5 years in Trials 24 and 25. Thus, the entire programme reflects the whole spectrum of patients with early stage prostate cancer, with a higher proportion of better prognosis patients in Trial 23 than in the other two trials.

2.2. PSA progression

Primary endpoints of the EPC programme are time to objective progression and overall survival. Secondary endpoints include time to PSA progression, time to treatment failure and tolerability. Time to PSA progression measures the PSA progression-free survival interval. The median follow-up time in the present analysis was 3 years (minimum 2 years) and the mean duration of allocated treatment was 2 years.

Time to PSA progression, relative to the PSA level immediately before the start of randomised treatment, was defined as the time from randomisation to the earliest occurrence of PSA doubling from baseline, objective progression, or death from any cause. Serum PSA levels were measured every 12 weeks using the Hybritech assay (Hybritech Inc., San Diego). The limits of quantification were set at 0.2 ng/ml in Trial 23 and 1.0 ng/ml in Trials 24 and 25. Patients with pre-randomisation PSA levels below the limit of quantification were considered to have reached PSA doubling if their PSA level increased to $\geq$2 times the limit of quantification.

In view of the lack of a standardised definition of PSA progression, it was also examined using a second definition, the second consecutive increase in PSA level from the PSA nadir value. PSA nadir was defined as the lowest PSA level measured after trial entry. The findings using this definition of PSA progression were entirely consistent with analyses based on time to PSA doubling; therefore the data are not shown.

2.3. Statistical analyses

Time to PSA doubling was analysed using a Cox proportional hazards regression model with covariates for trial, randomised treatment, initial therapy, pre-therapy PSA level, tumour grade and stage. Time to PSA doubling data were further explored by: the initial therapy of curative-intent given (radical prostatectomy or radiotherapy); and by prognostic factors: disease stage (localised or locally advanced); nodal status (N−, Nx, N+); Gleason score (2–4, 5–6 or 7–10); pre-therapy PSA level ($\leq$4 ng/ml, >4–10 ng/ml, >10 ng/ml); and the post-therapy PSA level in the radical prostatectomy (quantifiable [Q] or non-quantifiable [NQ]) and radiotherapy ($\leq$4 ng/ml, >4 ng/ml) groups.

In addition to conventional Cox regression analysis, which estimates the reduction in the risk of an event, a new analysis that estimates the event–time ratio (ETR) was applied [13]. ETR analysis calculates the relative increase in the time to an event and can be used to estimate treatment differences in progression-free survival, irrespective of the maturity of the data. For example, if the HR = 0.80 and the ETR = 1.30, then the risk of an event is reduced by 20% while, simultaneously, the progression-free survival time is increased

by 30%. An ETR >1 indicates a benefit for bicalutamide 150 mg and a 95% CI excluding 1 indicates that the benefit is statistically significant. The time taken for 10% of patients to experience PSA progression was estimated from the ETR model. Estimation of percentiles greater than the observed proportion of progressions (approximately 10% at the time of this analysis) involves extrapolation of the model beyond the observed data. Estimates are considered to be increasingly less reliable with further extrapolation.

3. Results

3.1. Patients

The mean age of the 8113 men included in the EPC programme was 66.9 years (range 38–93 years) and 91% were Caucasian. Most patients (67%) had T1/T2 disease and the majority of the remainder had locally advanced T3 disease (31%); 2% had T4 disease [11]. Less than 2% of patients had known N+ disease. Overall, 55% of patients received radical prostatectomy and 17% received radiotherapy, as standard care. The median PSA levels prior to standard therapy differed between the three trials, with a gradation in prognosis evident—being best in Trial 23 (Trial 23: 7.1 ng/ml; Trial 24: 11.7 ng/ml; Trial 25: 16.1 ng/ml) [12]. The bicalutamide 150 mg and placebo groups were well matched demographically [11].

3.2. PSA progression in the overall EPC population

The overall population included 3292 patients from Trial 23, 3603 patients from Trial 24 and 1218 patients from Trial 25. In the overall EPC population, bicalutamide 150 mg significantly reduced the risk of PSA progression by 59% relative to standard care alone (HR 0.41; 95% CI 0.38, 0.45; $p \ll 0.0001$). At a median 3 years' follow-up, 17% of the bicalutamide 150 mg group had experienced PSA progression (i.e. PSA doubling, objective progression or death) compared with 33% of the placebo group. ETR analysis showed a significant 106% increase in the PSA progression-free survival interval (ETR 2.06; 95% CI 1.90, 2.23). With current follow-up of 3 years, this translates into a delay in PSA progression of 0.95 years.

Treatment differences in PSA progression also reached statistical significance across the individual trials (Trial 23 [HR 0.62; 95% CI 0.53, 0.72; $p \ll 0.0001$]; Trial 24 [HR 0.37; 95% CI 0.32, 0.43; $p \ll 0.0001$]; and Trial 25 [HR 0.24; 95% CI 0.20, 0.30; $p \ll 0.0001$]).

3.3. Radical prostatectomy subgroup

The radical prostatectomy subgroup included 2647 patients from Trial 23, 1648 patients from Trial 24 and 159 patients from Trial 25. Bicalutamide 150 mg as adjuvant to radical prostatectomy significantly reduced the risk of PSA progression by 51% (HR 0.49; 95% CI 0.43, 0.56; $p \ll 0.0001$) (Fig. 1). ETR analysis showed a significant 94% increase in the PSA progression-free survival interval (ETR 1.94; 95% CI 1.71, 2.21). With current follow-up of 3 years, this translated into a delay in PSA progression of 0.9 years.

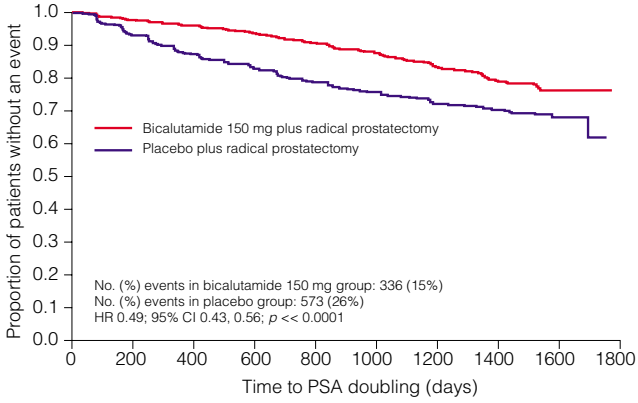

Fig. 1. Kaplan-Meier analysis of time to PSA doubling in the radical prostatectomy subgroup.

Among the radical prostatectomy subgroup, 15% of patients on bicalutamide 150 mg met the criteria for PSA progression (PSA doubling, 262 patients; objective progression, 20 patients; and death, 54 patients) compared with 26% of patients on placebo (PSA doubling, 496 patients; objective progression, 30 patients; and death, 47 patients).

Exploratory analyses of the radical prostatectomy subgroup by risk factor revealed significant reductions in the risk of PSA progression with bicalutamide 150 mg compared with placebo, irrespective of disease stage, nodal status, Gleason score, pre-prostatectomy PSA levels (>4 ng/ml), and all post-prostatectomy PSA levels, with the greatest reductions in those at highest risk of progression (Table 1). Relatively few events occurred in the PSA $\leq$4 ng/ml group and this was the only risk factor group in which no significant reduction in risk was observed.

3.4. Radiotherapy subgroup

The radiotherapy subgroup included 645 patients from Trial 23, 660 patients from Trial 24 and 65 patients from Trial 25. Bicalutamide 150 mg as adjuvant to radiotherapy significantly reduced the risk of PSA progression by 58% relative to placebo (HR 0.42; 95% CI 0.33, 0.53; $p \ll 0.0001$) (Fig. 2) and significantly increased the PSA progression-free survival interval by 99% (ETR 1.99; 95% CI 1.65, 2.40). With current follow-up of 3 years, this translates into a delay in PSA progression of 0.9 years.

Table 1
PSA progression by risk factor in the radical prostatectomy subgroup

Risk group	No. patients	HR (95% CI)	ETR (95% CI)	Time taken for first 10% of patients to progress (years)	
				Bicalutamide 150 mg/day	Placebo
Overall population	4454	0.49 (0.43, 0.56)	1.94 (1.71, 2.21)	2.0	1.1
Disease stage					
Localised disease	2734	0.59 (0.48, 0.72)	1.65 (1.36, 2.00)	2.6	1.7
Locally advanced disease	1719	0.42 (0.35, 0.50)	2.22 (1.87, 2.65)	1.5	0.7
Nodal status					
N0	3970	0.50 (0.43, 0.58)	1.90 (1.66, 2.19)	2.1	1.2
Nx	410	0.57 (0.37, 0.87)	1.65 (1.11, 2.44)	1.9	1.1
N+	74	0.11 (0.04, 0.30)	6.00 (2.64, 13.60)	1.6	0.3
Gleason score					
2–4	456	0.57 (0.34, 0.96)	1.56 (1.02, 2.38)	2.7	1.7
5–6	2020	0.50 (0.40, 0.62)	1.94 (1.56, 2.41)	2.5	1.4
7–10	1959	0.48 (0.40, 0.58)	1.98 (1.66, 2.35)	1.6	0.9
Pre-therapy PSA level					
≤4 ng/ml	451	0.97 (0.57, 1.65)	1.03 (0.60, 1.76)	2.5	2.6
>4–10 ng/ml	2229	0.53 (0.43, 0.66)	1.79 (1.46, 2.19)	2.4	1.4
>10 ng/ml	1636	0.40 (0.33, 0.49)	2.31 (1.92, 2.79)	1.6	0.7
Post-prostatectomy PSA level					
Non-quantifiable	3792	0.52 (0.45, 0.61)	1.78 (1.54, 2.05)	2.3	1.4
Quantifiable	587	0.38 (0.28, 0.51)	2.75 (2.02, 3.74)	2.0	0.4

CI, confidence intervals; ETR, event–time ratio; HR, hazard ratio; PSA, prostate-specific antigen.

Among the radiotherapy subgroup, 17% of patients receiving bicalutamide 150 mg met the criteria for PSA progression (PSA doubling, 62 patients; objective progression, 22 patients; and death, 35 patients) compared with 32% of patients on placebo (PSA doubling, 153 patients; objective progression, 24 patients; and death, 36 patients).

Exploratory risk factor analyses revealed significant reductions in the risk of PSA progression in favour of bicalutamide 150 mg compared with placebo as adjuvant to radiotherapy across all of the prognostic subgroups, except N+ disease and pre-radiotherapy PSA level ≤4 ng/ml, where there were too few events to calculate the HR (Table 2).

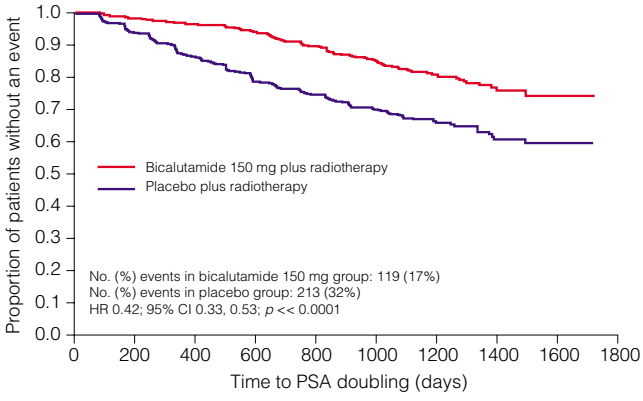

Fig. 2. Kaplan-Meier analysis of time to PSA doubling in the radiotherapy subgroup.

4. Discussion

A rising PSA level often triggers treatment intervention in patients with prostate cancer depending upon the type of primary therapy received (watchful waiting, surgery, radiotherapy or androgen deprivation). Given that PSA progression is widely believed to represent a failure of initial therapy, treatments that delay PSA progression may be predicted to reduce the risk of clinical progression and subsequently may increase overall or symptom-free survival. These treatments may additionally reduce patient anxiety associated with a rising PSA level and may also minimise patient desire to use unproven therapies to treat a rising PSA level.

The first analysis of the overall EPC population [12] showed a significant benefit, in terms of risk of objective progression and PSA progression, for bicalutamide 150 mg as immediate therapy either alone or as adjuvant to therapy of curative intent, in patients with localised or locally advanced prostate cancer. The analyses presented here at a median follow-up of 3 years show that, compared with standard care plus placebo, bicalutamide 150 mg significantly reduced the risk of PSA progression and increased the PSA

Table 2
PSA progression by risk factor in the radiotherapy subgroup

Risk group	No. patients	HR (95% CI)	ETR (95% CI)	Time taken for first 10% of patients to progress (years)	
				Bicalutamide 150 mg/day	Placebo
Overall population	1370	0.42 (0.33, 0.53)	1.99 (1.65, 2.40)	1.9	1.0
Disease stage					
Localised disease	1065	0.51 (0.38, 0.67)	1.72 (1.37, 2.15)	2.2	1.3
Locally advanced disease	305	0.29 (0.19, 0.43)	2.62 (1.89, 3.65)	1.4	0.5
Nodal status					
N0	437	0.33 (0.22, 0.51)	2.33 (1.65, 3.27)	1.9	1.0
Nx	919	0.46 (0.35, 0.60)	1.89 (1.50, 2.37)	1.9	1.0
N+	14	–[a]	–[a]	–[a]	–[a]
Gleason score					
2–4	314	0.47 (0.28, 0.79)	1.66 (1.17, 2.35)	2.0	1.4
5–6	697	0.42 (0.31, 0.58)	1.92 (1.49, 2.49)	2.0	1.1
7–10	348	0.43 (0.28, 0.65)	2.16 (1.47, 3.18)	1.5	0.7
Pre-radiotherapy PSA level					
≤4 ng/ml	105	–[a]	–[a]	–[a]	–[a]
>4–10 ng/ml	491	0.44 (0.29, 0.67)	2.07 (1.39, 3.08)	2.5	1.2
>10 ng/ml	726	0.40 (0.29, 0.53)	2.04 (1.61, 2.58)	1.6	0.9
Post-radiotherapy PSA level					
≤4 ng/ml	766	0.48 (0.36, 0.65)	1.81 (1.41, 2.33)	1.8	1.0
>4 ng/ml	578	0.35 (0.24, 0.51)	2.06 (1.58, 2.70)	2.1	1.2
Trial					
23	645	0.59 (0.42, 0.83)	1.59 (1.17, 2.17)	2.1	1.3
24	660	0.38 (0.27, 0.53)	2.06 (1.59, 2.68)	2.0	0.9
25	65	0.21 (0.10, 0.42)	2.95 (1.86, 4.68)	1.2	0.4

[a] Too few events to calculate hazard ratio (HR) and event–time ratio (ETR); CI, confidence intervals; PSA, prostate-specific antigen.

progression-free survival by approximately 1 year in patients with early prostate cancer. Analysis by the type of primary therapy of curative intent received gave similar results.

In the radical prostatectomy and radiotherapy subgroups, the decreased risk of PSA progression with bicalutamide 150 mg was seen regardless of disease stage but, as expected, was greater in patients with locally advanced disease. In addition, patients with higher pre-therapy PSA levels were generally more likely to experience PSA progression than those with lower pre-therapy PSA levels. Bicalutamide 150 mg significantly reduced the risk of PSA progression regardless of initial therapy of curative intent when pre-therapy PSA levels were >4 ng/ml. In patients with pre-therapy PSA levels ≤4 ng/ml, there were often too few events to reliably calculate HRs. However, the absence of a significant treatment effect for any particular prognostic risk factor subgroup in the current analyses may be due to the data being immature: benefits may become apparent with longer-term follow-up. The time to PSA doubling findings are supported by analyses based on the second consecutive increase in PSA level, suggesting that these findings are reliable.

The significant reduction in the risk of PSA progression with bicalutamide 150 mg compared with placebo in the overall EPC population was not unexpected, given the well known effect of hormone therapy on serum PSA levels [14–16]. A rising PSA level is known to precede objective disease progression [17] and can be a concern for many patients. In the overall EPC population at a median of 3 years' follow-up, the 59% reduction in the risk of PSA progression with bicalutamide 150 mg was accompanied by a 42% reduction in the risk of objective progression [12]. In one of the trials included in the overall EPC population (Trial 23), no differences in the risk of objective progression were observed between the bicalutamide 150 mg and placebo groups. However, the patients in Trial 23 had organ-confined disease (no lymph node involvement) and therefore were at an earlier disease stage than those included in the other trials. Nonetheless in this trial, bicalutamide 150 mg significantly reduced the risk of PSA progression, which may suggest that with longer follow-up, significant differences in objective progression may also be observed.

A recent study has shown that significantly better sexual and hormonal health-related quality-of-life

scores were observed among PSA progression-free patients compared with those with a rising PSA level, irrespective of primary therapy [18]. These findings suggest that PSA progression-free survival after prostate cancer therapy may have health-related quality-of-life benefits relative to disease progression [18]. However, adjuvant hormonal therapy, as used in the EPC programme, may also impact on health-related quality of life. In fact, data from one of the trials included in the overall EPC analyses (Trials 25) showed that although differences were relatively small, the proportion of patients retaining or maintaining sexual frequency and function was lower in the bicalutamide 150 mg group than in those receiving standard care plus placebo [19].

In summary, this primary therapy subgroup analysis of PSA progression data from the EPC programme demonstrates that at a median of 3 years' follow-up, bicalutamide 150 mg significantly reduces the risk of PSA progression and significantly increases the PSA progression-free survival interval when given as adjuvant to radical prostatectomy or radiotherapy. Reductions in the risk of PSA progression with bicalutamide 150 mg are maintained across most prognostic risk factors. The EPC programme is ongoing and additional progression and survival data are awaited to enable further conclusions to be drawn regarding the benefit of bicalutamide as adjuvant therapy in early prostate cancer.

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Editorial Comment

Peter G. Hammerer, *Braunschweig*, *Germany*
p.hammerer@klinikum-braunschweig.de

This large prospective randomised study may answer the important question if early hormonal therapy improves survival in men with prostate cancer. Hormonal therapy for prostate cancer has traditionally been reserved for advanced disease, but there is current evidence that earlier use can confer a survival advantage. Survival benefit has been observed for patients

with nodal metastases who received immediate hormonal treatment after radical prostatectomy and pelvic lymphadenectomy.

In 2002 See et al. published their first results of the three ongoing, randomized, double-blind, placebo controlled trials (Trials 23, 24, and 25) with 8113 patients and a median follow-up of 3 years [1]. They demonstrated a highly significant reduction in the risk of disease progression and concluded that a longer follow-up will determine whether this reduced risk in disease progression will translate into a survival benefit for these patients.

In this updated version with a follow-up of 3 years See et al. could show that, with bicalutamide 150 mg in addition to standard care, the risk of PSA progression is reduced by 59% compared to placebo alone. Does this reduced risk of PSA progression translate in an improved survival or improved quality of life aspects? The only survival data given in this manuscript for the radical prostatectomy group showed 54 deaths in the bicalutamide group versus 47 deaths in the placebo group. With longer follow-up valid and statistical significant data will be available and answer the ongoing debate on early versus late hormonal therapy.

Reference

[1] See WA, Wirth MP, McLeod DG, Iversen P, Klimberg I, Gleason D, et al., on behalf of the Casodex Early Prostate Cancer Trialist Group. Bicalutamide as immediate therapy either alone or as adjuvant to standard care of patients with localized or locally advanced prostate cancer: first analysis of the Early Prostate Cancer Program. J Urol 2002;168(2):429–35.