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Antiandrogen Withdrawal in Castrate-refractory Prostate Cancer:

A Southwest Oncology Group Trial (SWOG 9426)

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Abstract

BACKGROUND—Antiandrogen withdrawal is a potential therapeutic maneuver for patients with progressive prostate cancer. This study was designed to examine antiandrogen withdrawal effects within the context of a large multi-institutional prospective trial.

METHODS—Eligibility criteria included progressive prostate adenocarcinoma despite combined androgen blockade. Eligible patients received prior initial treatment with an antiandrogen plus orchiectomy or luteinizing hormone-releasing hormone (LHRH) agonist. Patients were stratified according to type of antiandrogen, type of progression (prostate-specific antigen [PSA] or radiographic), presence or absence of metastatic disease, and prior LHRH agonist versus surgical castration.

RESULTS—A total of 210 eligible and evaluable patients had a median follow-up of 5.0 years; 64% of patients previously received flutamide, 32% bicalutamide, and 3% nilutamide. Of the 210 patients, 21% of patients had confirmed PSA decreases of ≥50% (95% CI, 16% to 27%). No radiographic responses were recorded. Median progression-free survival (PFS) was 3 months (95% CI, 2 months to 4 months); however, 19% had 12-month or greater progression-free intervals. Median overall survival (OS) after antiandrogen withdrawal was 22 months (20 and 40 months for those with and without radiographic evidence of metastatic disease, respectively). Multivariate analyses indicated that longer duration of antiandrogen use, lower PSA at baseline, and PSA-only progression at study entry were associated with both longer PFS and OS. Longer antiandrogen use was the only significant predictor of PSA response.

CONCLUSIONS—These data indicate a relatively modest rate of PSA response in patients who were undergoing antiandrogen withdrawal; however, PFS can be relatively prolonged (≥1 year) in approximately 19% of patients.

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Keywords

antiandrogen withdrawal; prostate cancer; PSA; prognosis; survival; secondary hormonal therapy; hormone-refractory prostate cancer

Responses to withdrawal of various hormonal therapies have long been documented in oncologic literature. For instance, descriptions of withdrawal responses have been described after estrogenic therapy withdrawals in breast cancer patients 2 decades ago.[1] Additional observations in breast cancer patients who were withdrawing from antiestrogenic therapy underscored the potential of steroid-receptor antagonists as well as steroid-receptor agonists to elicit withdrawal responses in certain patients.[1,2]

Withdrawal responses in prostate cancer patients were initially documented after treatment with flutamide (a nonsteroidal antiandrogen).[3,4] Several case series of flutamide withdrawal responses, some occurring in those who were receiving a combination with other agents, were subsequently described from single-institution cohorts.[5–10] Withdrawal responses in prostate cancer patients have been described in patients treated with other antiandrogens, including bicalutamide,[11–13] nilutamide,[14,15] and chlormadinone.[16] Although improvements in cancer-related anemia, pain palliation, and radiographic regression of measurable disease have been documented, PSA declines have been most commonly detected. In addition to antiandrogens, withdrawal responses in prostate cancer patients have been documented after their cessation of megestrol acetate,[17,18] diethylstilbestrol,[19] 13-cis-retinoic acid,[20] and estramustine.[21] In general, withdrawal responses occur several weeks after drug withdrawal; however, bicalutamide, which has a relatively long serum half-life, may not have evident withdrawal responses until 6 to 8 weeks after ceasing administration of this medication.[13] All of these agents are known to interact with intracellular ligand-regulated receptors that modulate gene transcription.

With the exception of 2 trials,[13,22] the antiandrogen withdrawal studies published to date have used single-institution experiences. We designed a prospective multi-institutional clinical trial that used the cooperative group mechanism, which examines antiandrogen withdrawal effects in patients with progressive prostate cancer. Although initial inclusion criteria allowed only patients pretreated with flutamide with radiographic evidence of metastatic disease, the protocol was subsequently amended to include patients who were withdrawing from other nonsteroidal antiandrogens (bicalutamide and nilutamide) as well as patients without radiographic evidence of metastases at the time of initial disease progression. The results reported herein represent the largest single prospective trial reported with antiandrogen withdrawal.

MATERIALS AND METHODS

Eligibility Criteria

Patient enrollment took place from March 15, 1995 to June 1, 2001. Patients were required to sign informed consent forms and to have histologically proven prostate adenocarcinoma and progressive disease at the time of study entry. Eligible patients must have either 1) been previously enrolled in SWOG 8894[22] and randomized to the flutamide arm, 2) have received continuous antiandrogen therapy as part of their initial hormonal therapy for radiographic demonstrated metastatic (stage D2) prostate cancer, or 3) have received continuous antiandrogen therapy as part of their initial hormonal therapy but not have been diagnosed with metastatic prostate cancer. Patients entering this study after failing SWOG protocol 8894 had to have progressed by the radiographic criteria set forth in that protocol.[23] SWOG 8894 was a protocol that examined orchidectomy plus or minus flutamide administration as

initial treatment for patients with metastatic prostate cancer. Criteria for PSA progression before enrollment on this protocol included a confirmed 50% increase in PSA compared with the PSA nadir after initial androgen deprivation. PSA progression required a minimal increase of ≥4 ng/mL. Patients must have had prior treatment with either surgical orchiectomy or an luteinizing hormone-releasing hormone (LHRH) analog and be receiving an antiandrogen (bicalutamide, flutamide, or nilutamide) on a regular basis at the time that they were enrolled into the protocol. No other concomitant therapy was allowed (except LHRH analogs) during the therapeutic period of antiandrogen withdrawal. Within 30 days of registration, patients could not be receiving therapy other than androgen deprivation and an antiandrogen. All patients had a PSA level ≥4 ng/mL at study entry.

Requested baselines studies included a medical history and physical examination; tests included PSA level, complete blood count (CBC), alkaline phosphatase level, lactate dehydrogenase (LDH) level, and a bone scan. A computed tomography (CT) scan at baseline was required only when “clinically indicated.” Follow-up studies defined by the protocol included PSAs every 2 weeks during the initial 12 weeks postantiandrogen withdrawal. The remaining laboratory and clinical studies were scheduled on a monthly basis. Initial positive imaging studies were to be re-evaluated at 3-month intervals. LHRH analogs were continued postwithdrawal of antiandrogens.

Response and Progression Criteria

Responses and progression were monitored by bone scans and CT scans as previously described.[23] PSA response was defined as a 50% decline in PSA from baseline, with a confirmed decrease 4 or more weeks later. We note that the protocol was written before consensus criteria were developed.[24] Criteria for PSA progression included a 50% increase in PSA compared with either baseline PSA or the PSA nadir postantiandrogen withdrawal (whichever value was lower). The increased PSA was confirmed before removing the patient from study for progressive disease; however, the date of the first >50% increase was noted as the date of progression. PSA progression required an increase of ≥4 ng/mL.

Descriptive Factors

Patients were prospectively described according to several variables (at the time of trial entry) including the following: 1) PSA-only progression: yes versus no; 2) patient type: SWOG 8894 versus prior stage D2 diagnosis versus no prior D2 diagnosis; 3) method of castration: orchiectomy versus LHRH agonist; and 4) type of antiandrogen: flutamide versus bicalutamide versus nilutamide.

Statistical Analysis

Univariate and multivariate logistic regression models were used to assess factors associated with confirmed PSA declines of ≥50%. Univariate and multivariate proportional hazard models were used to assess factors associated with both progression-free survival (PFS) and overall survival (OS). The methods of Kaplan-Meier were used to estimate PFS curves. PFS was defined as time from registration to the date of progression or death, whichever came first. OS was defined as time from registration to death from any cause. Patients without an event documented were censored at their last contact date.

RESULTS

The study closed to new accrual after 259 patients had registered. Eight patients were deemed ineligible for various reasons, ie, 4 did not have prestudy laboratory tests within the specified time frame, 1 had incomplete initial forms, 2 had no histologically proven diagnosis of prostate adenocarcinoma, and 1 had therapy for renal cell carcinoma before

antiandrogen withdrawal. An additional 41 patients were not eligible as a consequence of not starting an antiandrogen at the time of initiation of androgen deprivation therapy (a clear condition of eligibility for the protocol). Consequently, a total of 210 eligible patients were both evaluable and analyzed. Median follow-up was 5.0 years. Demographics and baseline characteristics of these patients are shown in Table 1. The average baseline PSA was 128 ng/mL, and the average duration of prior antiandrogen use was 25 months. The majority (58%) of patients had PSA-only progression before entry on the trial; 17% of patients were enrolled after completing SWOG 8894 (which required radiographic progression). Flutamide was withdrawn in 64% of cases, bicalutamide in 32% of cases, and nilutamide in 3%. Bone-scan positive metastases were present in 75% of patients; no radiographic evidence of metastases was noted in 22% of cases.

A total of 9 patients were not assessable for response because of lack of adequate data after antiandrogen withdrawal. These patients were assumed to be nonresponders in subsequent analyses. Of 210 patients, there were 44 (21%; 95% CI, 16–27%) confirmed (≥4 weeks later) PSA responses. All but 2 of these patients had a response duration that exceeded 8 weeks. PSA responses were noted in 24% (95% CI, 17–33%) of patients pretreated with flutamide, 13% (95% CI, 6–24%) of patients pretreated with bicalutamide, and 25% (95% CI, 4–71%) of patients pretreated with nilutamide. No radiographic responses were noted after antiandrogen withdrawal.

Factors associated with confirmed PSA response rates were examined first in a univariate analysis (see Table 2). Race, method of androgen deprivation (surgical vs medical), Gleason score, and PSA-only progression were not statistically significant predictors of PSA responses. Patients with confirmed stage D2 disease (radiographically detected metastases) were less likely to have a PSA response. Patients with a baseline serum PSA in the lowest quartile (≤10 ng/mL) were more likely to have a PSA response postwithdrawal compared with those in the highest quartile (≥83.1 ng/mL). Longer duration of antiandrogen therapy (>32 months before withdrawal) was associated with a higher probability of PSA response. In the multivariate analysis evaluating all factors, as noted in Table 2, only duration of prior antiandrogen exposure was a significant predictor of PSA response postwithdrawal.

Of the 210 eligible and evaluable patients, 203 showed progression of disease; thus, these data are mature. Overall median PFS was 3 months (Fig. 1A). Of note, several patients had a significantly prolonged time to progression with 19% of patients having no evidence of progression 1 year after antiandrogen withdrawal. Occasionally, patients had no evidence of progression even 2 or more years after antiandrogen withdrawal, thus indicating that duration of response is surprisingly durable in a subset of patients. Stratifying patients into those with and without radiographic evidence of metastatic disease provided median progression-free survival estimates of 2 and 7 months, respectively (Fig. 1B).

As shown in Figure 2A, median OS after antiandrogen withdrawal was 22 months (95% CI, 19 months to 28 months). Stratification of patients into those with and those without radiographically detectable metastatic disease revealed median survivals of 20 and 40 months, respectively (Fig. 2B). The mean baseline PSA at study entry for all patients was 128 ng/mL (median, 20.8). For patients without radiographically demonstrable metastatic disease, PSA mean ± SD was 24 ± 42, and the median was 10.7 ng/mL. For patients with radiographically demonstrable disease, the mean PSA ± SD was 160 ± 434, and the median was 28.4 ng/mL.

As shown in Table 3A, African-American race, Gleason score, type of antiandrogen, age, or method of androgen deprivation therapy (medical vs surgical) had no bearing on PFS in the univariate analysis. Univariate factors associated with longer time to progression after

antiandrogen withdrawal included lower PSA value, longer duration of prior antiandrogen treatment, and no radiographic evidence of metastases. In the multivariate analysis (Table 3B), evaluating all factors in Table 3A, longer durations of antiandrogen use, lower baseline PSA values, and PSA-only progression before trial entry were predictive of longer PFS.

OS was examined as shown in Table 4. In univariate analyses (Table 4A), PSA-only progression, lower PSAs at time of protocol entry, no radiographic evidence of metastases, and longer preprotocol antiandrogen therapy duration were associated with prolonged OS, whereas type of antiandrogen, age, type of androgen suppression (orchiectomy vs LHRH), and Gleason score were not. In the multivariate analysis (Table 4B), longer duration of antiandrogen use, PSA-only progression, and lower PSAs at protocol entry were associated with significantly longer overall survival.

DISCUSSION

Taken together, these data from a large multi-institutional prospective trial indicate that the confirmed PSA response rate after antiandrogen withdrawal is 21% when taken in aggregate. This study, although larger than previously published studies, has PSA response rates (considering confidence intervals) similar to those previously published.[6–8,13,22] No radiographic responses were observed, although the vast majority of men had bone-only metastatic disease assessed by bone scans. It is well known that improvement in bone scans is rare in this setting.

There are several limitations to this study. Although study entry criteria required regular use of antiandrogens before study entry and specified that antiandrogens should be used as part of the initial androgen deprivation treatments, no methods to directly assess compliance with these measures were incorporated into the study. Given that antiandrogens have traditionally been an “out of pocket” cost,[25] compliance assessment is a potentially important issue; withdrawal responses would only be anticipated in patients who were regularly taking the prescribed antiandrogen. We also note that there is no control group in this study. This trial is simply a phase II trial, and potential deleterious effects of continuing antiandrogens were not examined. Thus, we cannot determine whether antiandrogen withdrawal altered survival. Furthermore, no quality-of-life measurements were obtained.

It is important to recognize that only data derived from patients who initiated antiandrogen therapy at the same time as androgen deprivation therapy (LHRH or orchiectomy) were analyzed for this study. In clinical practice, many patients currently receive antiandrogens as a secondary hormonal manipulation (after disease progression postandrogen-deprivation therapies). One cannot extrapolate these findings to distinct patient populations. In this protocol, treatments subsequently administered after antiandrogen withdrawal were not assessed; these treatments could have influenced the overall survival of patients.

Variations in the response rate to flutamide, nilutamide, and bicalutamide withdrawal occurred in this study; however, the type of antiandrogen was excluded as a candidate predictor for the multivariate model because it was confounded with stage D2 status and type of progression. Consequently, a direct analysis of the type of prior antiandrogen on response rate, progression-free survival, and overall survival was statistically invalid. There were only 7 patients in the nilutamide group, so stable estimates for that group could not be ascertained. Little data on nilutamide withdrawal exist in the literature.[12,13] Two of the nilutamide patients had >50% PSA declines, and each of these patients had a relatively prolonged period without progression (14 months and 22 months).

Duration of antiandrogen pretreatment was linked in this study to time to disease progression and overall survival after antiandrogen withdrawal in the multivariate analysis.

We hypothesized that at least 2 issues played a role in this process. Duration of initial antiandrogen therapy, as defined in this study, is a surrogate for duration of response to initial endocrine therapy; thus, a longer PFS may be anticipated simply on the basis of disease kinetics, ie, patients with longer PFS intervals after initial hormonal therapy also had longer PFS intervals after antiandrogen withdrawal. Alternatively, longer antiandrogen usage may be associated with particular molecular changes that help to govern disease progression. For instance, studies of flutamide pretreated patients have indicated that flutamide usage can be associated with androgen receptor mutations in metastatic prostate cancer cells.[26]

Baseline PSA and PSA-only progression were linked in this study to both PFS and OS. Those individuals with lower PSAs and those individuals with PSA-only progression before antiandrogen withdrawal had a better prognosis compared with those with higher PSAs or radiographic progression at time of trial entry. We note that this study did not measure variables reported by others to have prognostic importance in castrate-refractory prostate cancer (such as hemoglobin, LDH, and alkaline phosphatase).[27,28] Regardless, these data provide excellent estimates of overall survival in a broad population of patients in the United States with castrate-refractory disease.

Radiographic responses have been previously recorded after antiandrogen withdrawal[6] but were not documented in this trial. These data indicate that clinical trials that are measuring radiographic responses may enroll patients postantiandrogen withdrawal without significant concern that these types of responses will be routinely attributed to antiandrogen withdrawal.

Antiandrogen withdrawal should be the first therapeutic maneuver to take place in a patient whose disease is progressing after combined androgen blockade. Although confirmed PSA declines of >50% are seen in a minority of cases, the time to progression for patients after antiandrogen withdrawal may be prolonged in selected patients. Caution in follow-up is warranted when following patients with PSA alone under these circumstances, as evidence of objective progression without PSA increases has been documented.[29]

Taken together, these data are both mature and include multivariate analyses of important endpoints such as time to PFS and OS. Our studies indicate that duration of prior antiandrogen therapy, PSA-only progression, and lower PSA levels at the time of antiandrogen withdrawal are significantly associated with both longer PFS and OS in patients with castrate-refractory prostate cancer.

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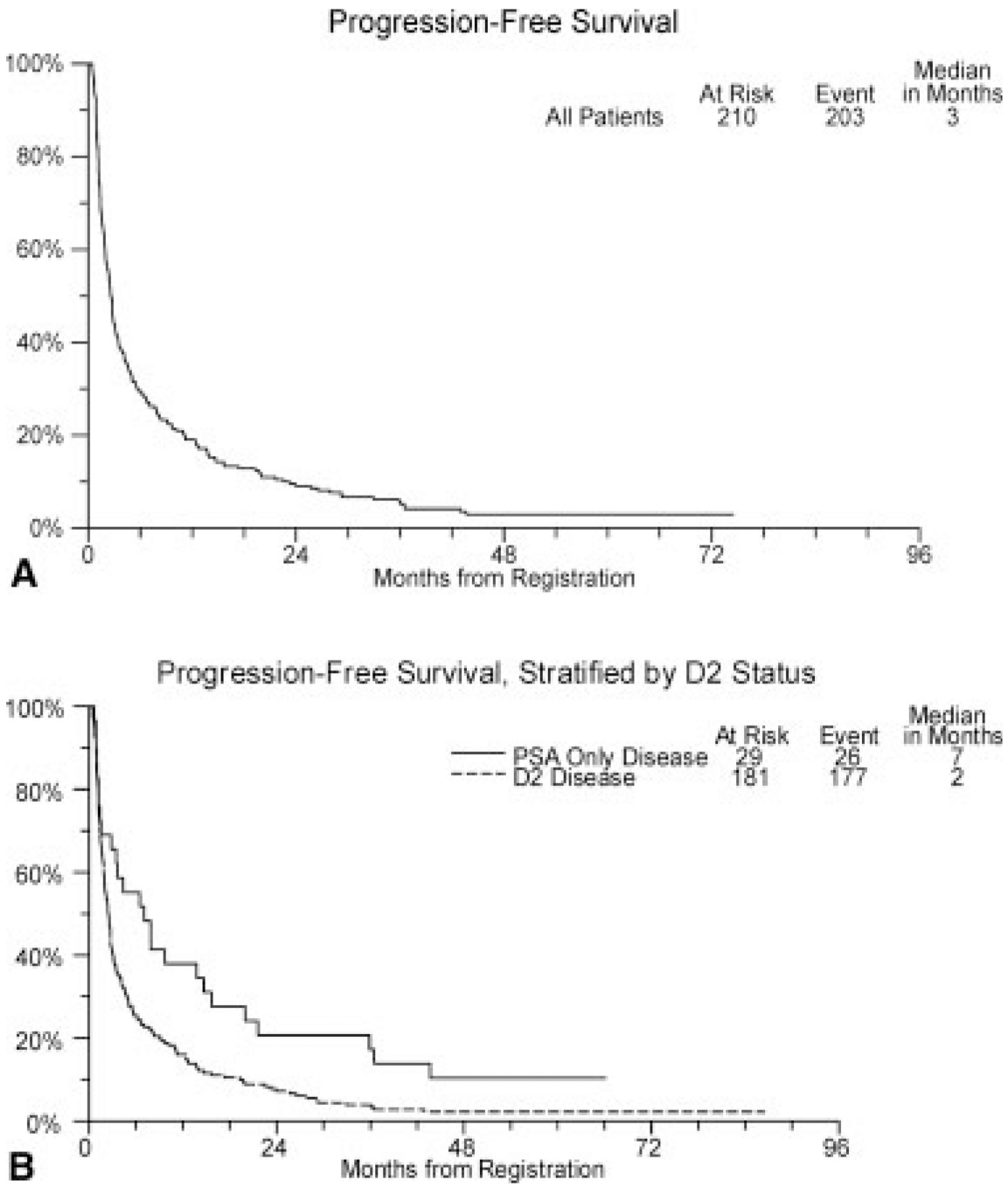

FIGURE 1.

A) Progression-free survival (PFS) is shown as a function of time after antiandrogen withdrawal for all patients. B) PFS is stratified by the presence or absence of radiographic metastases at baseline.

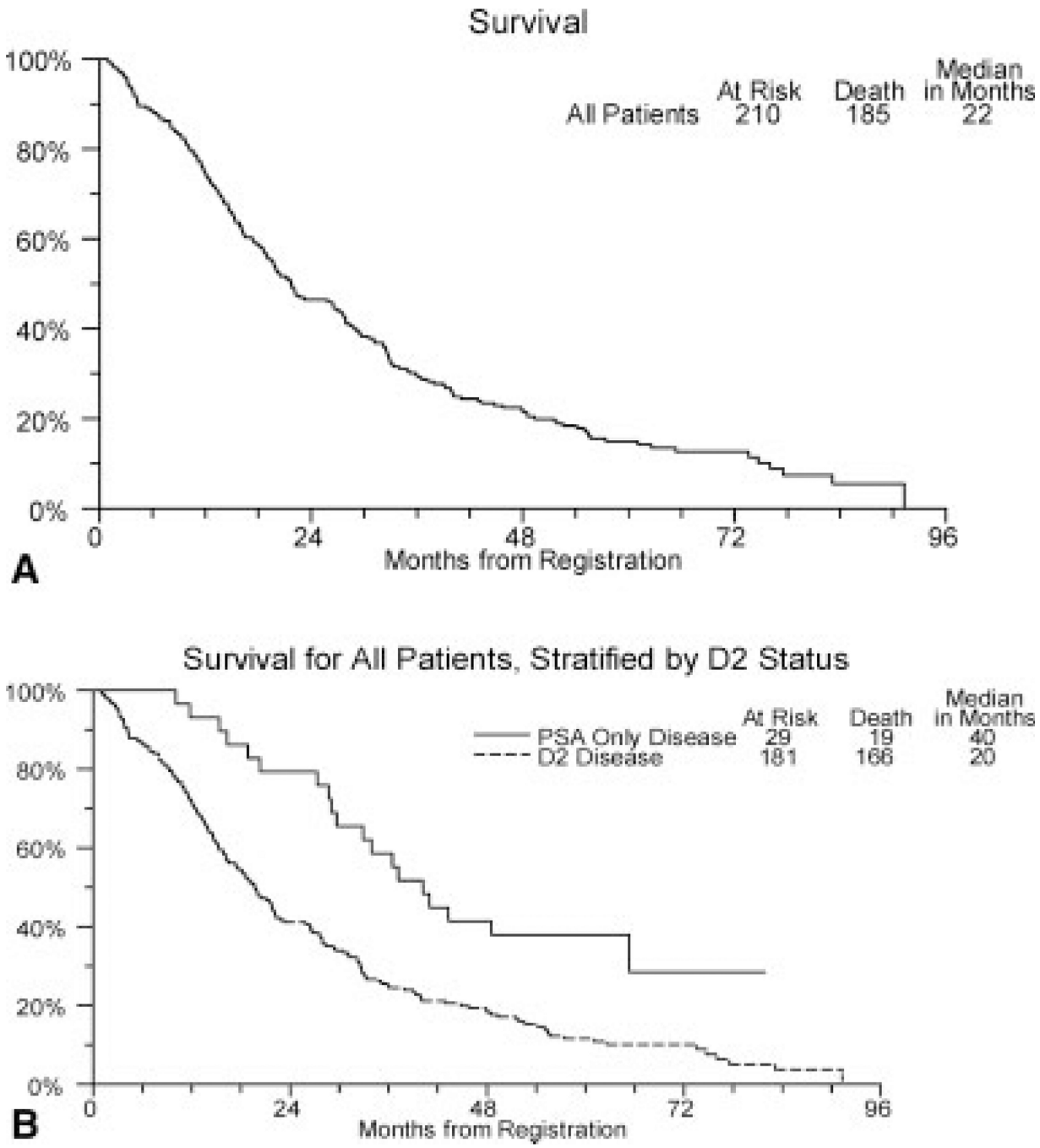

FIGURE 2.

A) Overall survival (OS) is shown as a function of time after antiandrogen withdrawal for all patients. B) OS is stratified by the presence or absence of radiographic metastases at baseline.

TABLE 1

Demographics and Baseline Data for SWOG 9426 for 210 Eligible and Evaluable Patients

Demographics	Baseline data
Median age, y (range)	69 (47–87)
Ethnic group	
White	70%
African American	29%
Other	<1%
Baseline PSA, mean ± SD	
All patients	128 ± 385 ng/mL
PSA-only disease	24 ± 42
D2 disease	160 ± 434
Antiandrogen duration, mean ± SD	25 ± 22 m
PSA only progression pre-enrollment	
Yes	58%
No	42%
Androgen deprivation method	
Surgical orchiectomy	21%
LHRH agonist	79%
Antiandrogen type	
Flutamide	64%
Bicalutamide	32%
Nilutamide	3%
Performance status	
0	57%
1	36%
≥2	7%
Gleason Sum category	
<7	18%
7	27%
>7	55%
Missing value for n = 40 of 210	—
Type of metastatic disease	
Bone only	68%
Tissue only	3%
Both	7%
None	22%

SWOG indicates Southwest Oncology Group; PSA, prostate-specific antigen; SD, standard deviation from the mean; D2, stage D2; LHRH, luteinizing hormone-releasing hormone.

TABLE 2

Predicting Confirmed PSA Response Using Logistic Regression, Results of Univariate Modeling

Univariate predictor	Odds ratio (95% CI)	*P*
PSA-only progression	1.93 (0.94–3.95)	.074
D2 disease vs not D2	0.42 (0.18–1.00)	.049
Type of antiandrogen		
Nilutamide	Excluded; too few	—
Bicalutimide	1.00 (reference)	—
Flutamide	2.04 (0.91–4.56)	.084
African American vs Other	0.57 (0.26–1.27)	.17
Baseline PSA quartiles, ng/mL		
≤10	1.00 (reference)	—
10.1–25	0.46 (0.18–1.16)	.099
25.1–83	0.61 (0.25–1.50)	.28
≥83.1	0.26 (0.09–0.78)	.016
Global 3 df test	—	.051
Age group		
≤65	1.00 (reference)	—
66–70	1.53 (0.58–4.02)	.39
71–76	2.65 (1.08–6.49)	.033
>76	1.13 (0.39–3.23)	.82
Global 3 df test	—	.19
Orchiectomy vs LHRH	0.71 (0.29–1.72)	.45
Duration of antiandrogen, m		
≤9	1.00 (reference)	—
10–17	1.51 (0.32–7.17)	.61
18–32	3.87 (0.99–15.14)	.052
>32	5.51 (1.48–20.50)	.011
Global 3 df test	—	.041
Disease involvement		
Neither	1.00 (reference)	—
Bone only	0.43 (0.20–0.90)	.024
Tissue only	.40 (0.04–3.72)	.42
Both tissue and bone	0.15 (0.02–1.28)	.084
Global 3 df test	—	.13
Gleason Score		
<7	1.00 (reference)	—
7	0.83 (0.27, 2.54)	.75
>7	0.94 (0.35, 2.49)	.90
Global 2 df tes	—	.99

PSA indicates prostate-specific antigen; D2, stage D2; PSA, prostate-specific antigen; df, degrees of freedom; LHRH, luteinizing hormone-releasing hormone.

TABLE 3

Results of Univariate (3A) and Multivariate (3B) Regression Modeling Predicting Progression-free Survival

A. Univariate predictor	**Hazard ratio (95% CI)**	***P***
PSA-only progression	0.57 (0.43–0.76)	<.001
D2 disease vs not D2	1.76 (1.16–2.67)	.008
Type of antiandrogen		
Nilutamide	Excluded; too few	—
Bicalutimide	1.00 (reference)	—
Flutamide	0.75 (0.56–1.02)	.063
African American vs Other	1.13 (0.84–1.53)	.42
Baseline PSA, ng/mL		
≤10	1.00 (reference)	—
10.1–25	1.20 (0.80–1.79)	.38
25.1–83	1.05 (0.70–1.59)	.81
≥ 83.1	2.17 (1.44–3.28)	<.001
Global 3 df test	—	001
Age group, y		
≤65	1.00 (reference)	—
66–70	0.85 (0.59–1.24)	.40
71–76	0.68 (0.47–0.98)	.04
>76	0.70 (0.48–1.04)	.08
Global 3 df test	—	.15
Orchiectomy vs LHRH	0.88 (0.63–1.24)	.47
Duration of antiandrogen, m		
≤9	1.00 (reference)	—
10–17	1.00 (0.66–1.52)	.99
18–32	0.64 (0.43–0.97)	.035
>32	0.45 (0.30–0.67)	<.001
Global 3 df test	—	.0001
Metastatic disease involvement		
Neither	1.00 (reference)	—
Bone only	1.84 (1.31–2.60)	<.001
Tissue only	0.95 (0.38–2.41)	.92
Both tissue and bone	2.71 (1.47–4.99)	.001
Global 3 df test	—	.0008
Gleason score		
<7	1.00 (reference)	—
7	0.93 (0.58–1.48)	.75
>7	1.20 (0.79–1.81)	.39
Global 2 df test	—	.35

B. Multivariate predictors	**Hazard ratio (95% CI)**	***P***
Duration of antiandrogen, m		

B. Multivariate predictors	Hazard ratio (95% CI)	*P*
≤9	1.00 (reference)	—
10–17	0.91 (0.57–1.46)	.69
18–32	0.62 (0.39–0.96)	.032
>32	0.48 (0.30–0.76)	.002
Baseline PSA, ng/mL		
≤10	1.00 (reference)	—
10.1–25	1.56 (1.00–2.44)	.048
25.1–83	1.12 (0.70–1.79)	.64
83.1	1.79 (1.13–2.83)	.013
Global 3 df test	—	.001
PSA-only progression	0.65 (0.46–0.92)	.014

PSA indicates prostate-specific antigen; D2, stage D2; df, degrees of freedom; LHRH, luteinizing hormone-releasing hormone.

TABLE 4

Results of Univariate (A) or Multivariate (B) Proportional Hazards Regression Modeling Predicting All-Cause Mortality

A. Univariate predictor	**Hazard ratio (95% CI)**	***P***
PSA-only progression	0.57 (0.43–0.77)	<.001
D2 disease vs not D2	2.30 (1.43–3.71)	<.001
Type of antiandrogen		
Nilutamide	Excluded; too few	—
Bicalutimide	1.00 (reference)	—
Flutamide	0.95 (0.69–1.30)	.73
African American vs Other	1.02 (0.74–1.40)	.90
Baseline PSA, ng/mL		
≤10	1.00 (reference)	—
10.1–25	1.26 (0.83–1.93)	.28
25.1–83	1.35 (0.87–2.09)	.18
>83.1	4.47 (2.85–7.00)	<.001
Global 3 df test	—	.001
Age group, y		
≤65	1.0 (reference)	—
66–70	0.81 (0.54–1.20)	.29
71–76	1.10 (0.75–1.61)	.64
>76	0.76 (0.50–1.16)	.20
Global 3 df test	—	.28
Orchiectomy vs LHRH	0.90 (0.63–1.29)	.56
Duration of antiandrogen, m		
≤9	1.00 (reference)	—
10–17	0.56 (0.36–0.86)	.006
18–32	0.31 (0.20–0.48)	<.001
>32	0.24 (0.16–0.38)	<.001
Global 3 df test	—	.001
Metastatic disease involvement		
Neither	1.00 (reference)	—
Bone only	1.99 (1.38–2.86)	<.001
Tissue only	0.52 (0.16–1.69)	.28
Both tissue and bone	3.48 (1.87–6.50)	<.001
Global 3 df test	—	.001
Gleason score		
<7	1.00 (reference)	—
7	1.48 (0.88–2.48)	.14
>7	1.50 (0.95–2.38)	.08
Global 2 df test	—	.21

B. Multivariate predictors	Hazard ratio (95% CI)	*P*
Duration of antiandrogen, m		
≤9	1.00 (reference)	—
10–17	0.54 (0.35–0.85)	.007
18–32	0.31 (0.20–0.48)	<.001
>32	0.29 (0.18–0.45)	<.001
Baseline PSA, ng/mL		
≤10	1.00 (reference)	—
10.1–25	1.16 (0.76–1.77)	.48
25.1–83	1.21 (0.78–1.89)	.39
≥83.1	2.80 (1.79–4.39)	.00
PSA-only progression	0.61 (0.44–0.84)	.002

PSA indicates prostate-specific antigen; D2, stage D2; df, degrees of freedom; LHRH, luteinizing hormone-releasing hormone.