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Changes in PSA Kinetics Predict Metastasis-Free Survival in Men with PSA-Recurrent Prostate Cancer Treated with Non-Hormonal Agents: Combined Analysis of 4 Phase II Trials

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Abstract

Background—Several phase II trials in men with non-castrate PSA-recurrent prostate cancer have assessed the impact of novel non-hormonal agents on PSA kinetics. However, it is unknown whether changes in PSA kinetics influence metastasis-free survival (MFS).

Methods—We performed a retrospective *post hoc* analysis of 146 men treated in four phase II trials examining the investigational agents marimastat (a matrix metalloproteinase inhibitor; n=39), imatinib (a tyrosine kinase inhibitor; n=25), ATN-224 (a copper/zinc-superoxide dismutase inhibitor; n=22), and lenalidomide (an antiangiogenic/immunomodulatory drug; n=60). We investigated factors influencing MFS, including within-subject changes in PSA kinetics (PSA slope, doubling time, and velocity) before and after treatment initiation.

Results—After a median follow-up of 16.8 months, 70 patients (47.9%) developed metastases. In multivariable Cox regression models, factors that were independently predictive of MFS after adjusting for age and other clinical prognostic variables were baseline PSA doubling time (PSADT) (*P*=.05), baseline PSA slope (*P*=.01), on-study change in PSADT (*P*=.02), and on-study change in PSA slope (*P*=.03). In a landmark Kaplan-Meier analysis, median MFS was 63.5 months (95% CI 34.6–not reached) and 28.9 months (95% CI 13.5–68.0) for men with or without any decrease in PSA slope by 6 months after treatment, respectively.

Conclusions—This hypothesis-generating analysis suggests that within-subject changes in PSADT and PSA slope after initiation of experimental therapy may correlate with MFS in men with biochemically-recurrent prostate cancer. If validated in prospective trials, changes in PSA kinetics may represent a reasonable intermediate endpoint for screening new agents in these patients.

INTRODUCTION

In men with non-metastatic prostate-specific antigen (PSA)-recurrent prostate cancer following definitive local therapy, there is currently no consensus on optimal management.[1,2] Treatment options include observation,[3,4] continuous androgen deprivation therapy (ADT) initiated upon PSA recurrence,[5,6] deferred ADT administered after the development of metastases or upon symptomatic progression,[7,8] intermittent ADT,[9,10] or enrollment in clinical trials.[11] In addition, a subset of patients with PSA recurrence may benefit from salvage pelvic irradiation.[12] In practice, early ADT is often employed in this

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patient population but this approach is associated with long-term cardiovascular and metabolic risks.[13–15] Furthermore, a recent meta-analysis has shown that compared to deferred ADT, early ADT decreases prostate cancer-specific mortality but increases non-prostate cancer-specific mortality, and has no significant effect on overall survival.[8] However, since no prospective randomized trial has specifically been conducted in men with non-metastatic PSA-recurrent disease to evaluate hormonal therapy initiated immediately or at the time of metastatic progression, there is still significant controversy surrounding the optimal timing of androgen suppression in these patients.[16]

In recent years, interest has emerged in identifying hormone-sparing therapies for the initial management of men with PSA-recurrent disease without detectable metastases. To date, a large number of biological and immunological agents have been evaluated in phase II clinical trials in these patients.[17–25] However, progress in this area has been hampered by the use of suboptimal study endpoints, the absence of placebo-controlled trials, and the short duration of follow-up. Because of the inability to follow radiographic or clinical parameters in this setting, the majority of such studies have utilized changes in PSA kinetics (PSA doubling time, PSA slope, and PSA velocity) as their primary endpoint. Importantly, it is not known whether such PSA alterations are related to clinically meaningful outcomes such as metastasis-free survival (MFS) and overall survival.

We have previously conducted four phase II trials investigating experimental non-hormonal agents in men with non-metastatic PSA-recurrent prostate cancer after local therapy.[19–22] All of these studies examined changes in PSA kinetics before and after study drug initiation as their primary endpoint, and none specifically evaluated MFS. The present study is a combined retrospective analysis of these four trials (n = 146), aiming to investigate the potential relationship between intra-subject changes in PSA kinetics and MFS. We hypothesized that improvements in PSA kinetics after initiation of such non-hormonal treatments would correlate with prolonged MFS in these patients.

PATIENTS AND METHODS

Patients

The designs of the four phase II studies included in this combined analysis have been described in detail previously.[19–22] The first study[19] was a randomized phase I/II trial evaluating 3 doses of an oral matrix metalloproteinase inhibitor, marimastat (5 mg, 20 mg, or 40 mg daily). A total of 39 patients were enrolled, and the primary efficacy endpoint was change in median PSA slope after 6 months of the study drug. The second trial[20] was a single-arm phase II study of the oral tyrosine kinase inhibitor, imatinib (800 mg daily). A total of 25 men participated, and the primary endpoint was PSA response rate defined as a 50% decrease in PSA from baseline. The third study[21] was a randomized phase II trial of 2 doses of an oral copper/zinc-superoxide dismutase inhibitor, ATN-224 (30 mg or 300 mg daily). A total of 47 patients were accrued, and the primary endpoint was change in mean PSA slope and mean PSA doubling time on study. The fourth trial[22] was a randomized phase I/II study evaluating the oral antiangiogenic and immunomodulatory drug, lenalidomide (5 mg or 25 mg daily). A total of 60 men were enrolled, and the primary endpoint was change in median PSA slope after 6 months. None of these trials were designed *a priori* to capture data on MFS or overall survival.

All four studies were conducted at the Johns Hopkins Kimmel Cancer Center, Baltimore, MD. Three trials were single-center experiences while the ATN-224 study was performed through the Department of Defense/Prostate Cancer Foundation-sponsored consortium that also included 5 other centers. In all studies, eligible patients were required to have PSA-recurrent prostate cancer after local therapy (prostatectomy or radiotherapy), non-castrate

levels of serum testosterone, non-metastatic disease as determined by CT and/or bone scan, and rising PSA levels. All trials used experimental agents that were not expected to mediate their effects through the endocrine axis. While on study, patients were required to have PSA assessments either every month (marimastat, ATN-224) or every 2 months (imatinib, lenalidomide). Patients were treated with study drug for either 6 months (marimastat, ATN-224, lenalidomide) or 12 months (imatinib), or less if unmanageable drug-related toxicities developed. In all trials, patients came off study upon PSA progression, clinical progression, metastatic progression, or death (whichever occurred first).

Study Design

The present study was a *post hoc* analysis of MFS using combined data from the four phase II studies outlined above. We retrospectively examined patient charts and/or electronic medical records for information on first metastatic occurrence and death. Metastatic disease was defined as the presence of osseous metastases visualized on bone scan (or MRI scan); and/or visceral (liver, lung, brain) or extra-pelvic nodal metastases visualized on CT scan. In the four studies, radiographic evaluations were performed either every 3 months (ATN-224) or every 6 months (marimastat, imatinib, lenalidomide), or sooner if clinically indicated. After trial completion, imaging studies were ordered at the discretion of the treating physicians (and scanning intervals ranged from 2 to 12 months). Radiologists were blinded to PSA results. Metastasis-free survival was defined as the time interval from study entry until initial metastasis or death. Patients were captured at the time of their first positive scan or censored at the time of their last confirmed negative scan. The data cut-off date was set as March 1st, 2010. This study was approved by the Johns Hopkins University institutional review board.

We used all available PSA values in the 12 months preceding study enrollment to calculate the baseline PSA kinetics parameters, and all available PSAs in the first 6 months after treatment initiation to calculate the on-study PSA kinetics. PSA slope was defined as the linear regression line of the natural log of PSA (in ng/mL) against time (in months).[26] PSA doubling time (PSADT) was defined as the natural log of 2 divided by the slope of the linear regression line of the natural log of PSA against time (in months).[26] PSA velocity was defined as the linear regression line of PSA (in the natural scale) against time (in months).[27] Within-subject changes in PSA kinetics parameters before and after study enrollment were determined by comparing baseline values to on-study values. The aim of this study was to investigate the correlation between intra-subject changes in PSA kinetics and MFS, after adjusting for other clinical factors known to influence MFS.

The number of pre-treatment or on-study PSA values measured on any given patient ranged from a minimum of 3 to a maximum of 7. When calculating the ($\log_e$) PSA slope with a linear regression of the natural log of PSA against time, our assumption was that the PSA values on a logarithmic scale over time approximated a straight line, that the variance of residuals calculated from these regressions was constant over time, and that residuals were normally distributed. Given the small number of PSA values (3–7) per regression, assumptions of homoscedasticity and normality of the residuals from these regressions could not be evaluated for each individual patient. However, while not an assumption of the linear regressions, a test of normality of the distribution of the log of the PSA values was not significant (Kolmogorov-Smirnov test, P=.14).

Statistical Analysis

The primary objective of this study was to determine the independent contribution of changes in PSA kinetics on MFS. Time to metastasis was calculated from study entry to the date of metastasis or death. Event time distributions for this endpoint were estimated using

the Kaplan-Meier method[28] and 95% confidence intervals (CIs) were calculated by the method of Brookmeyer and Crowley.[29] Landmark stratified Cox proportional hazards regressions were used to assess the effects of PSA kinetics on MFS. Models were stratified by study, and the landmark time was set at 6 months. This time point was chosen because all PSA values during the first 6 months after study entry were used to calculate on-study PSA kinetics. Such a landmark analysis prevents metastatic events that might occur during the first 6 months on study to be included in the analysis.

In the univariate analysis, factors that entered the model included age at study initiation (continuous variable), Gleason score (<7 vs. ≥7), tumor stage at diagnosis (T1/2 vs. T3/4), lymph node involvement at diagnosis (N0 vs. N1), use of ADT after PSA recurrence but before metastasis (yes vs. no), baseline PSADT (≥6 mo vs. <6 mo), baseline PSA velocity (below median vs. above median), baseline PSA slope (below median vs. above median), change in PSADT before and after study initiation (increase in PSADT vs. no increase), change in PSA velocity (decrease in velocity vs. no decrease), and change in PSA slope (decrease in slope vs. no decrease). In the multivariable analysis, only those variables with *P*-values from the univariate model of ≤0.10 were included. Notably, because all three PSA kinetic measures are a function of changes in PSA against time and are all strongly interrelated, three separate multivariable models each evaluating one kinetic measure at a time were created.

To account for the fact that on-study determinations of PSA kinetics are dependent upon the time point at which they are calculated, time-dependent covariate analyses of the relationship between log PSA or changes in log PSA and MFS were also conducted. This was performed using 3, 4 and 6 months of PSA data, respectively.

All *P*-values reported are two-sided, and the significance level was set at ≤0.05 for all analyses. Statistical analyses were performed using SAS version 9.2 (SAS Institute Inc, Cary, North Carolina) and R version 2.1 (National Cancer Institute, Bethesda, Maryland).

RESULTS

Patient Characteristics

Table 1 describes the clinical characteristics of men in each of the four trials. Twenty-five of 47 patients in the ATN-224 study (those enrolled at the other sites), did not have available data on metastasis and were excluded from the analysis. All 39 patients in the marimastat study, all 25 patients in the imatinib study, and all 60 patients in the lenalidomide study had full information available to determine metastasis-free survival (MFS). There were no statistically significant differences in any of the clinical variables listed in Table 1 between patients with (n=146) and without (n=25) metastasis information (data not shown). With a median follow-up in the combined evaluable cohort of 16.8 months, 70 patients (47.9%) developed metastases. The median MFS in the whole cohort was 38.1 months (95% CI, 22.9 to 61.7 months).

Overall (n=146), median age at study entry was 63 years; 58 men (40%) had primary prostatectomy, 27 (18%) had primary radiotherapy, and 61 (42%) had prostatectomy and salvage radiotherapy; 26 men (18%) had Gleason score ≤6, 74 (51%) had Gleason score 7, and 46 (31%) had Gleason score ≥8; 12 men (8%) had T1 disease, 47 (32%) had T2 disease, and 87 (60%) had T3 disease; 130 men (89%) had node-negative disease, and 16 (11%) had node-positive disease; 110 men (75%) did not receive androgen deprivation therapy between developing PSA recurrence and metastatic disease, and 36 (25%) did receive ADT between PSA recurrence and metastasis (no patient received chemotherapy before metastasis); median PSA at baseline was 7.1 ng/mL; median PSA doubling time at baseline was 5.0

months; median PSA slope at baseline was 0.14; and median PSA velocity at baseline was 0.7 ng/mL/month.

Correlation of Changes in PSA Kinetics with Metastasis-Free Survival

In time-dependent covariate analysis, there was a statistically significant relationship between (log) PSA as well as changes in (log) PSA and MFS, using 3 months, 4 months, and 6 months of on-study PSA data (Table 2).

In univariate proportional hazards regression analyses (stratified by study), significant associations with MFS were observed for age, Gleason score, use of ADT before metastasis, baseline PSA doubling time (PSADT), baseline PSA velocity, baseline (log) PSA slope, change in PSADT, change in PSA velocity, and change in (log) PSA slope (Table 3). In these analyses, changes in the three measures of PSA kinetics were treated as dichotomous variables in an effort to facilitate clinical interpretation of the results. However, when treated as continuous variables, changes in the PSA kinetics parameters retained their association with MFS (change in PSADT: HR 0.99, 95% CI 0.98–1.00, P=.06; change in PSA velocity: HR 0.83, 95% CI 0.75–0.92, P=.01; change in PSA slope: HR 0.99, 95% CI 0.98–1.00, P=.06).

Figure 1 demonstrates the effect of changes in PSADT (increase in PSADT after study entry vs. no increase), changes in PSA velocity (decrease in PSA velocity vs. no decrease), and changes in (log) PSA slope (decrease in PSA slope vs. no decrease) on MFS using Kaplan-Meier analysis.

In landmark multivariable analyses (Table 4), change in PSADT and change in (log) PSA slope emerged as significant independent predictors of MFS, while change in PSA velocity did not retain statistical significance. Our multivariable models were stratified by study to avoid assuming proportional hazards across the 4 different protocols. To test the discriminatory ability of the multivariable models, we calculated the concordance index (C) for Cox regressions. The c-statistics for the multivariable models using PSADT, velocity, and slope were 0.76, 0.76, and 0.78 respectively. These are within the range of acceptable discrimination ($0.7 \leq$ c-statistic < 0.8). The univariate kinetics models in Table 3 and the multivariable models in Table 4 were tested for proportional hazards by including time-by-covariate interaction terms in the models. To this end, none of these terms were significant (if a term had been significant, we would have adjusted the model by retaining the interaction term). In addition, plots of Schoenfeld residuals (with restricted cubic splines showing the smoothed relationship of the residuals with time) for each predictor in all models did not show any consistent trends with time. Global correlation with time tests of these Schoenfeld residuals for each multivariable model in Table 4 was not significant. This suggested that the proportional hazards assumption was satisfied by our data.

Figure 2A considers on-study changes in (log) PSA slope as falling into one of 3 distinct clinical subgroups: those cases in which PSA slope decreases and becomes negative after study drug initiation (*i.e.* absolute PSA levels decline), those cases in which PSA slope decreases but remains positive (*i.e.* absolute PSA levels continue to increase but at a slower rate), and those cases in which PSA slope increases (*i.e.* absolute PSA levels rise at an accelerated rate). Figure 2B shows the stratification of MFS according to these 3 subgroups, demonstrating that post-landmark median MFS is 77.5 months (95% CI, 31.6 to not reached), 55.7 months (95% CI, 23.3 to not reached), and 28.9 months (95% CI, 13.5 to 68.0 months), respectively.

DISCUSSION

In men with non-castrate biochemically-recurrent prostate cancer after local therapy, the use of changes in PSA kinetics as an intermediate endpoint for evaluating the efficacy of non-hormonal experimental agents is attractive but unfounded. Exploring a potential association between changes in PSA kinetic measures and clinical outcomes would be important, as these PSA kinetics changes could serve as intermediate endpoints in therapeutic trials of such agents. This could offer the potential to derive reasonable conclusions about treatment efficacy while shortening the duration of follow-up required, overcoming a significant obstacle in testing novel non-hormonal agents in this patient population.

To our knowledge, this study is the first to document a correlation between changes in PSA kinetics and metastasis-free survival (MFS). Specifically, we have demonstrated that men whose PSADT increased after study entry (compared to pre-study PSADT) or whose PSA slope decreased (compared to pre-study PSA slope) had improved MFS. Importantly, the ability of changes in PSADT and PSA slope to predict MFS persisted after accounting for relevant clinical factors (*e.g.* age, Gleason score, and use of hormonal therapy before metastasis) as well as pre-treatment PSADT and PSA slope. Therefore, in addition to baseline PSA kinetic factors derived at study entry, post-treatment changes in these PSA kinetic measures were independently predictive of MFS.

For ease of clinical interpretation and applicability, we subdivided PSA kinetics changes into two clinical subgroups for use in the univariate and multivariable models. Interestingly, when patients were partitioned into 3 categories of PSA slope change, discreet MFS curves emerged in Kaplan-Meier analysis. To this end, MFS was longest for men whose PSA slopes decreased and became negative after study drug initiation, while MFS was shortest for men whose PSA slopes failed to decrease after study entry.

The results of this analysis can be compared to those of two related studies evaluating the correlation between PSA parameters and overall survival. In the first study involving patients with metastatic non-castrate prostate cancer receiving ADT, a PSA of ≤4 ng/mL after 7 months of ADT was a strong predictor of survival.[30] In that same study, PSA progression (according to the Prostate Cancer Working Group 2 [PCWG2] definition[31] within 7 months of ADT initiation also predicted for inferior survival.[32] In the second study involving patients with castration-resistant prostate cancer receiving chemotherapy, a PSA decline of ≥30% was predictive of overall survival.[33] In that same study, PSA progression (using the PCWG2 definition[31]) within 3 months of beginning chemotherapy also portended a worse survival.[32] Although the present study was unable to evaluate overall survival due to an insufficient number of observed deaths at last follow-up, it adds to the body of literature suggesting that PSA parameters may correlate with meaningful clinical outcomes in men with prostate cancer.

This study has several limitations. First, this was a retrospective study and none of the four trials included in the combined analysis were designed to capture data on metastasis. In addition, because the majority of metastatic events occurred after patients had been taken off study, the frequency of subsequent bone scan and CT scan evaluations was dependent upon investigator practices and was not regulated. Second, there was no control over additional therapies (including hormonal therapy) administered to patients after they came off study in each of the four trials. Therefore, it was essential to adjust for the use of hormone therapy before metastasis in the multivariable models. Third, a minority of patients (14.6%) were excluded from analysis because of lack of available metastasis data. This may have introduced bias, although these patients did not differ statistically from those who did have available metastasis information with respect to any of the clinical variables. Fourth, the

causal relationship between the study drugs and PSA kinetics changes cannot be proven in the absence of placebo control arms. A change in PSA kinetics after study entry, for example, may have been caused by more frequent PSA assessments on-study compared to pre-study PSA evaluations (which would not have been regulated). To this end, in a placebo-controlled trial evaluating the effect of celecoxib on PSADT in a similar patient population, 20% of 40 men in the placebo group had a post-treatment PSADT that was ≥200% of baseline.[18] Finally, this study suffers from the known limitations of the landmark method,[34] although this method was appropriately used here. For instance, this approach may result in loss of statistical power if a significant number of events (*i.e.* metastases, in this case) occur before the landmark time. In addition, it is generally difficult to determine whether the variable of interest (*i.e.* change in PSA kinetics, in this case) actually influences survival or if it simply acts as a marker of a more favorable prognosis.

In addition, because the studies included in this analysis used agents that are not particularly effective at altering PSA (with the exception of lenalidomide), this may have diminished our ability to detect a stronger association between PSA kinetics changes and MFS. Furthermore, the use of marginal drugs may potentially render the results of this analysis uninterpretable, because there is no direct evidence that on-study PSA kinetics changes were induced by the study drugs. Ultimately, the findings of this study will require confirmation in prospective trials using more effective agents as well as longer and more regimented follow-up.

In conclusion, this hypothesis-generating analysis suggests that within-subject changes in PSA kinetics (PSA doubling time, PSA slope) after initiation of non-hormonal experimental therapies may correlate with MFS in men with non-castrate PSA-recurrent prostate cancer. If these findings are validated in prospective trials using MFS as the primary endpoint, changes in PSA kinetics may represent a reasonable intermediate endpoint for screening new agents in this patient population. A prospective randomized trial aiming to validate these retrospective data is currently being designed.

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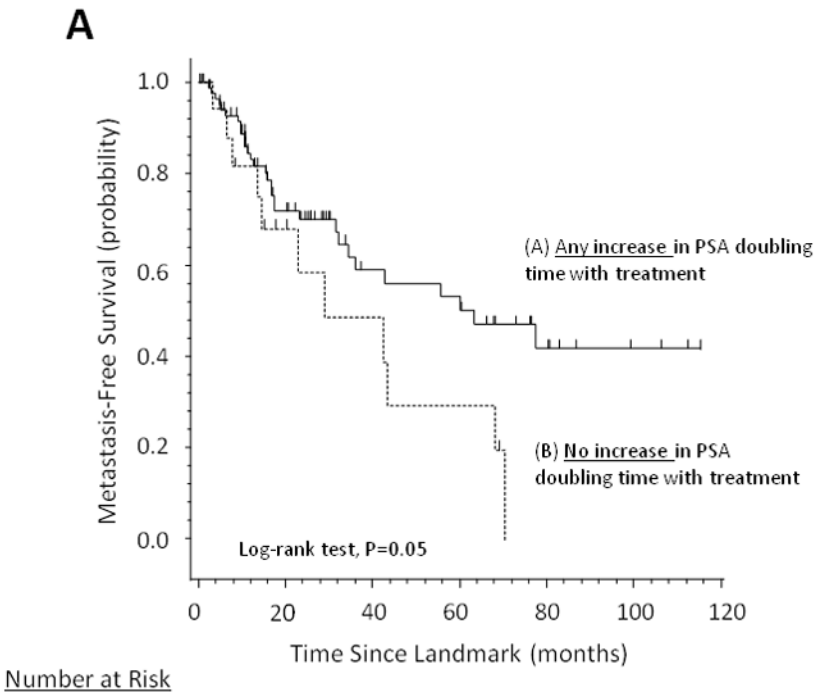
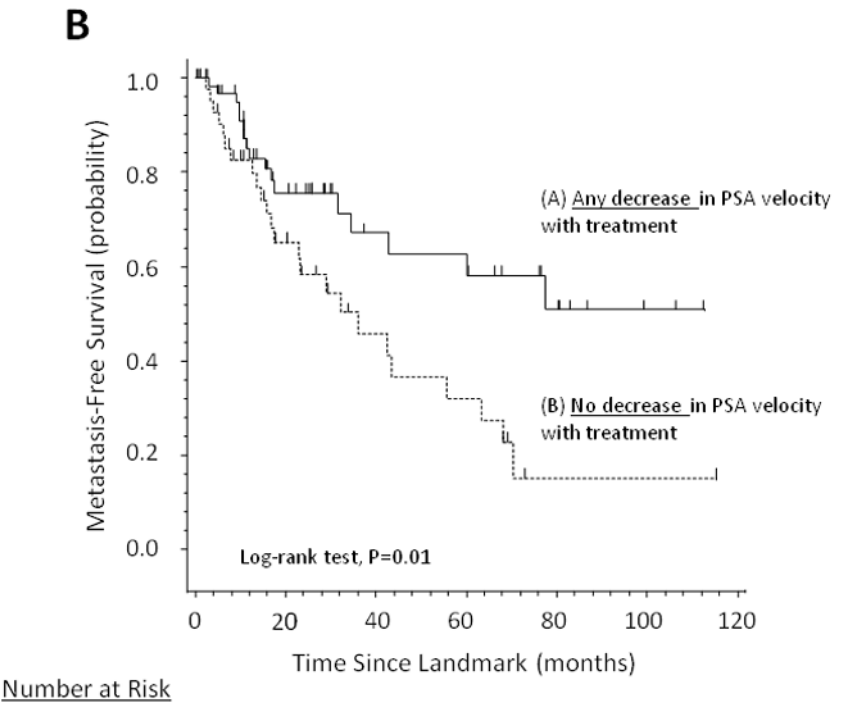


Number at Risk

Group A:	88	42	20	18	8	3	0
Group B:	17	8	5	3	0	0	0



Number at Risk

Group A:	62	29	15	14	7	2	0
Group B:	43	21	10	7	1	1	0

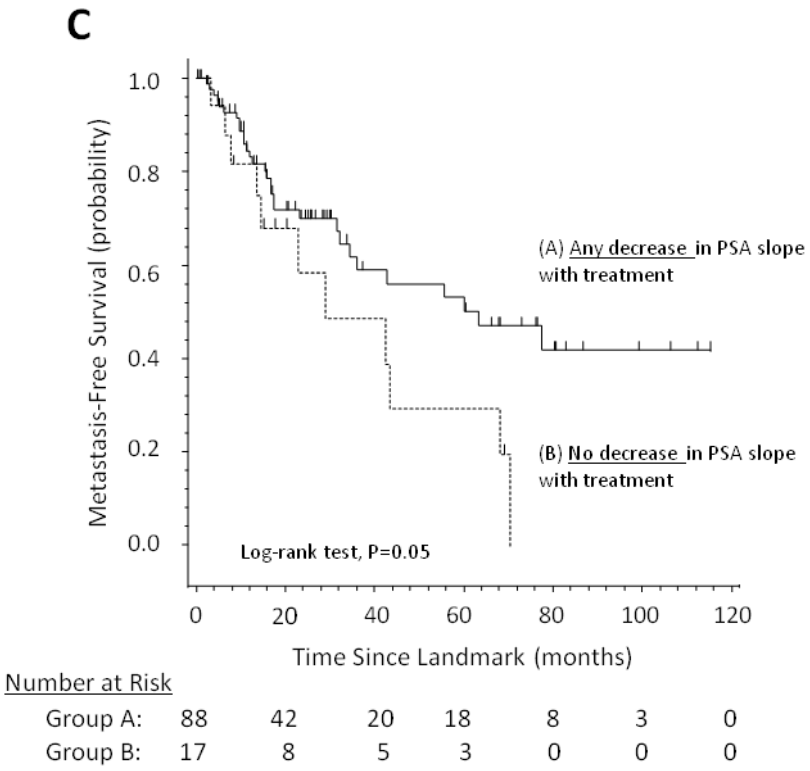


Fig 1.

Metastasis-free survival stratified by (A) changes in PSA doubling time, (B) changes in PSA velocity, and (C) changes in log PSA slope.

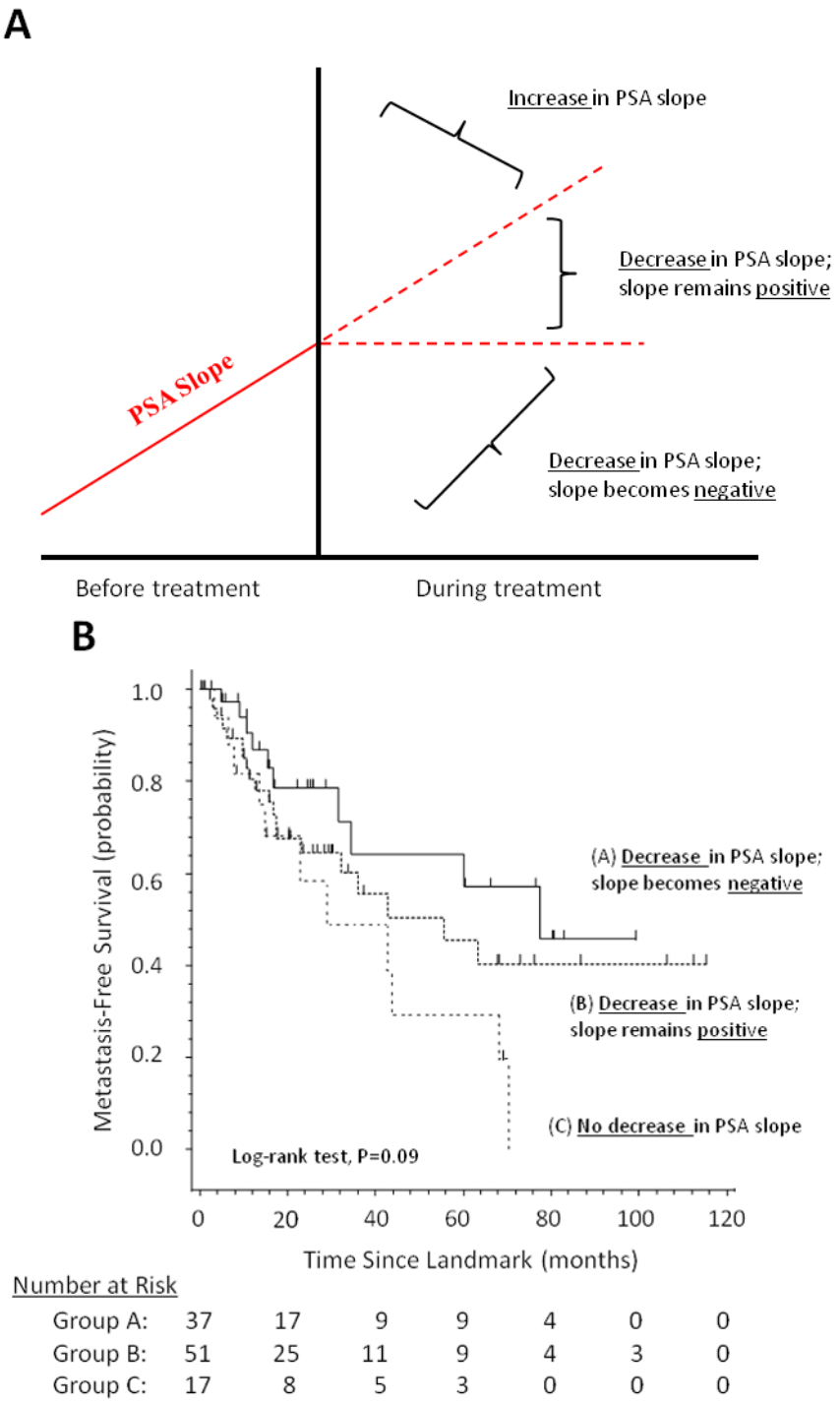


Fig 2.

(A) Model showing theoretical changes in PSA slope after initiation of a non-hormonal experimental therapy. (B) Metastasis-free survival stratified by these three categories of PSA slope change

Table 1

Patient Characteristics

	Trial			
Characteristic	**Marimastat (n=39)**	**Imatinib (n=25)**	**ATN-224 (n=22)**	**Lenalidomide (n=60)**
Minimum PSA requirement for trial entry	PSA ≥1.0 ng/mL	PSA ≥1.0 ng/mL	PSA ≥2.0 ng/mL	PSA ≥1.0 ng/mL
PSADT requirement for trial entry	Any PSADT	Any PSADT	PSADT ≤12 months	Any PSADT
Age, years				
Mean (Range)	61 (48 to 77)	65 (50 to 77)	62 (53 to 75)	63 (50 to 81)
Median	58	67	63	64
Local therapy				
Prostatectomy only	19 (49%)	5 (20%)	10 (45%)	24 (40%)
Radiotherapyonly	4 (10%)	9 (36%)	3 (14%)	11 (18%)
Both	16 (41%)	11 (44%)	9 (41%)	25 (42%)
Gleason score				
≤ 6	0 (0%)	8 (32%)	5 (23%)	13 (22%)
7	24 (62%)	12 (48%)	7 (32%)	31 (51%)
≥ 8	15 (38%)	5 (20%)	10 (45%)	16 (27%)
T stage				
T1	0 (0%)	5 (20%)	0 (0%)	7 (12%)
T2	7 (18%)	10 (40%)	12 (55%)	18 (30%)
T3	32 (82%)	10 (40%)	10 (45%)	35 (58%)
N stage				
N0	34 (87%)	25 (100%)	18 (82%)	53 (88%)
N1	5 (13%)	0 (0%)	4 (18%)	7 (12%)
Use of ADT before metastases				
No	27 (69%)	13 (52%)	17 (77%)	53 (88%)
Yes	12 (31%)	12 (48%)	5 (23%)	7 (12%)
Baseline PSA, ng/mL				
Mean (Range)	6.8 (0.7 to 36.5)	15.0 (1.3 to 53.3)	16.8 (2.1 to 89.3)	13.3 (1.0 to 92.8)
Median	3.9	11.0	7.1	7.0
Baseline PSA doubling time, mo				
Mean (Range)	4.9 (1.4 to 12.8)	9.4 (1.9 to 26.2)	4.7 (1.2 to 13.3)	7.1 (0.8 to 32.2)

Characteristic	Trial			
	Marimastat (n=39)	**Imatinib (n=25)**	**ATN-224 (n=22)**	**Lenalidomide (n=60)**
Median	4.8	8.6	4.4	4.7
Baseline PSA slope				
Mean (Range)	0.18 (0.05 to 0.50)	0.12 (0.03 to 0.37)	0.22 (0.05 to 0.57)	0.19 (0.02 to 0.88)
Median	0.15	0.08	0.16	0.15
Baseline PSA velocity, ng/mL/mo				
Mean (Range)	0.6 (0.1 to 3.9)	0.9 (0.1 to 3.2)	2.6 (0.2 to 23.8)	1.5 (0.1 to 16.6)
Median	0.4	0.7	0.9	0.7
Follow-up, mo				
Mean (Range)	38.4 (4.7 to 121.4)	43.5 (3.1 to 88.8)	16.9 (1.2 to 34.3)	15.7 (0.9 to 40.6)
Median	21.8	39.7	18.1	15.3

Abbreviations: ADT, androgen deprivation therapy; PSA, prostate specific antigen; PSADT, prostate specific antigen doubling time.

Table 2

Stratified Time-Dependent Covariate Analysis of the Relationship Between (log) PSA or Changes in (log) PSA and Metastasis-Free Survival

	(log) PSA			Change in (log) PSA		
Analysis Type	**HR**	**95% CI**	**P-value**	**HR**	**95% CI**	**P-value**
3 Mo of on-study data	1.47	(1.16 – 1.88)	0.0017	4.30	(2.48 – 7.46)	<0.0001
4 Mo of on-study data	1.62	(1.26 – 2.07)	0.0001	2.64	(1.79 – 3.90)	<0.0001
6 Mo of on-study data	1.84	(1.44 – 2.36)	<0.0001	3.23	(2.24 – 4.66)	<0.0001

Abbreviations: PSA, prostate-specific antigen; HR, hazard ratio; CI, confidence interval.

Table 3

Stratified Univariate Cox Regression Analyses for Predicting Metastasis-Free Survival in Men with PSA-Recurrent Prostate Cancer Enrolled in All 4 Trials

Variable	Hazard Ratio	95% CI	P-value
Age, years (Continuous)	0.92	(0.89 – 0.96)	0.0001
Local therapy			
Surgery (± salvage radiotherapy)	0.55	(0.25 – 1.23)	0.150
Radiotherapy only	1 [reference]		
Gleason score			
< 7	0.17	(0.05 – 0.56)	0.003
≥ 7	1 [reference]		
T stage			
T1–2	0.63	(0.36 – 1.10)	0.110
T3	1 [reference]		
N stage			
N0	0.60	(0.30 – 1.16)	0.130
N1	1 [reference]		
Use of ADT before metastases			
Yes	0.08	(0.03 – 0.21)	<0.0001
No	1 [reference]		
Baseline PSA doubling time, mo			
≥ 6 mo	0.26	(0.13 – 0.49)	<0.0001
< 6 mo	1 [reference]		
Baseline PSA velocity, ng/mL/mo			
Below median (=0.7 ng/mL/mo)	0.57	(0.35 – 0.92)	0.020
Above median	1 [reference]		
Baseline (log) PSA slope			
Below median (=0.14)	0.23	(0.13 – 0.42)	<0.0001
Above median	1 [reference]		
Change in PSA doubling time*, mo			
Increase	0.30	(0.14 – 0.65)	0.002
No increase	1 [reference]		
Change in PSA velocity*, ng/mL/mo			
Decrease	0.32	(0.16 – 0.64)	0.001
No decrease	1 [reference]		
Change in (log) PSA slope*			
Decrease	0.30	(0.14 – 0.65)	0.002
No decrease	1 [reference]		

*Because these variables are time-dependent covariates, a landmark univariate regression analysis was performed in these cases (with the landmark time set at 6 months).

Abbreviations: PSA, prostate-specific antigen; ADT, androgen deprivation therapy; CI, confidence interval.

Table 4

Stratified Landmark Multivariable Cox Regression Analyses for Predicting Metastasis-Free Survival, Considering Separately the Effect of **(A)** PSA Doubling Time Changes, **(B)** PSA Velocity Changes, and **(C)** PSA Slope Changes

Variable	Hazard Ratio	95% CI	P-value
(A) Effect of PSA doubling time changes on metastasis-free survival			
Age, years (Continuous)	0.97	(0.91 – 1.03)	0.290
Gleason score			
< 7	0.23	(0.05 – 1.16)	0.080
≥ 7	1 [reference]		
Use of ADT before metastases			
Yes	0.15	(0.05 – 0.40)	0.0002
No	1 [reference]		
Baseline PSA doubling time, mo			
≥ 6 mo	0.38	(0.15 – 1.00)	0.050
< 6 mo	1 [reference]		
Change in PSA doubling time, mo			
Increase	0.35	(0.15 – 0.83)	0.020
No increase	1 [reference]		
(B) Effect of PSA velocity changes on metastasis-free survival			
Age, years (Continuous)	0.95	(0.90 – 1.01)	0.080
Gleason score			
< 7	0.14	(0.03 – 0.65)	0.010
≥ 7	1 [reference]		
Use of ADT before metastases			
Yes	0.12	(0.04 – 0.37)	0.0002
No	1 [reference]		
Baseline PSA velocity, ng/mL/mo			
Below median (=0.7 ng/mL/mo)	0.49	(0.22 – 1.10)	0.080
Above median	1 [reference]		
Change in PSA velocity, ng/mL/mo			
Decrease	0.60	(0.27 – 1.30)	0.190
No decrease	1 [reference]		
(C) Effect of PSA slope changes on metastasis-free survival			
Age, years (Continuous)	0.98	(0.92 – 1.04)	0.430
Gleason score			
< 7	0.19	(0.04 – 1.00)	0.050
≥ 7	1 [reference]		
Use of ADT before metastases			
Yes	0.12	(0.04 – 0.35)	0.0001
No	1 [reference]		

(C) Effect of PSA slope changes on metastasis-free survival

Baseline (log) PSA slope			
Below median (=0.14)	0.35	(0.15 – 0.80)	0.010
Above median	1 [reference]		
Change in (log) PSA slope			
Decrease	0.40	(0.18 – 0.93)	0.030
No decrease	1 [reference]		

Abbreviations: PSA, prostate-specific antigen; ADT, androgen deprivation therapy; CI, confidence interval.