Circulating Tumor Cell Number as a Response Measure of Prolonged Survival for Metastatic Castration-Resistant Prostate Cancer: A Comparison With PSA Across Five Randomized Phase 3 Clinical Trials

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ABSTRACT

PURPOSE: Measures of response that are clinically meaningful and occur early are an unmet need in metastatic castration-resistant prostate cancer (mCRPC) clinical research and practice. We explored, using individual patient data, week 13 circulating tumor cell (CTC) and prostate-specific antigen (PSA) response endpoints in five prospective randomized phase 3 trials that enrolled a total of 6081 patients (COU-AA-301, AFFIRM, ELM-PC-5, ELM-PC-4, and COMET-1).

PATIENTS AND METHODS: Eight response endpoints were explored: CTC non-zero at baseline and 0 at 13 weeks (CTC0), CTC conversion (≥5 CTC at baseline, ≤4 at 13 weeks – the FDA cleared response measure), 30%, 50%, and 70% decrease in CTC, and 30%, 50%, and 70% decrease in PSA. Patients missing week 13 values were considered non-responders. The discriminatory strength of each endpoint with respect to overall survival in each trial was assessed using the weighted c-index.

RESULTS: Of the 8 response endpoints, CTC0 and CTC conversion had the highest weighted c-indices with smaller standard deviations. For CTC0 the mean (standard deviation) was 0.81 (0.04); CTC conversion 0.79 (0.03); CTC30 0.72 (0.06); CTC50 0.72 (0.06); CTC70 0.73 (0.05); PSA30 0.71 (0.03); PSA50 0.72 (0.06); PSA70 0.74 (0.05). Seventy-five percent of eligible patients could be evaluated with the CTC0 endpoint, compared to 51% with the CTC conversion endpoint.

CONCLUSIONS: The CTC0 and CTC conversion endpoints had the highest discriminatory power for overall survival. Both are robust and meaningful response endpoints for early-phase mCRPC clinical trials. CTC0 is applicable to a significantly higher percentage of patients than CTC conversion.

INTRODUCTION

The therapeutic landscape for men with metastatic castration-resistant prostate cancer (mCRPC) has changed substantially. Since 2010, six new treatments with diverse mechanisms of action have been approved by the FDA. All were based on the demonstration of a survival benefit in large-scale phase 3 trials. In parallel, new and ongoing molecular profiling studies have led to a more biologically based disease taxonomy identifying subsets of patients likely to respond or not to specific classes of drug.[1] Historically, clinical research in the mCRPC population has relied on prostate-specific antigen (PSA) changes such as the maximal percent or percent at a fixed time point as indicators of treatment efficacy, though neither are strong indicators of overall survival.[2,3] Other response endpoints such as radiographic measures for bone metastases are problematic because of the difficulty distinguishing whether early unfavorable changes represent worsening or improving disease status. Changes in measurable disease, assessed by RECIST, are also used although they occur infrequently. With these limitations, along with the increasing number of possible treatment combinations, the unmet need for response indicators that reliably reflect survival and that occur early so trials can be completed in a shorter time frame, has become more urgent.

Most metastasizing cancers spread through the blood as single cells or in clusters. At present, there are a range of devices and assays that enable the detection, enumeration, and biologic characterization of circulating tumor cells (CTCs).[4,5] Only one, CellSearch®, has achieved the level of an FDA clearance for the context of use as an "aid in the monitoring of patients with metastatic breast, colorectal, and prostate cancer … in conjunction with other clinical methods."[6] Studies in mCRPC patients have shown that the number of CTCs detected is higher in patients with bone disease relative to lymph node disease, and that association with disease burden is modest,[7-9] which shows that the ability of a cancer cell to detach, circulate, survive, and colonize a distant site is an intrinsic property of the tumor. It follows that inhibiting the spread of cells through the circulation would represent a therapeutic objective that is clinically meaningful.[8,10-14]

Following the demonstration of CTC conversion rates between 35-40% in 3 phase 2 studies of abiraterone and enzalutamide,[15-17] a collaboration was initiated with the Center for Diseases and Radiologic Health (CDRH) of the United States Food and Drug Administration to study post-treatment CTC-containing endpoints as potential surrogates for survival. To do so, the CTC biomarker question was embedded in a series of phase 3 registration trials with a primary endpoint of overall survival. In this study, we compared the ability of CTC number and PSA as short-term (week 13) response endpoints to reflect survival in patients with mCRPC treated with systemic therapies. The analyses were performed using data from five independent randomized clinical trials, all completed within the past six years, that enrolled diverse mCRPC patient populations ranging from chemotherapy-naïve to failure on one or two approved life-prolonging therapies. Our objective was to generate evidence that an early post-treatment decrease in CTC number is a meaningful indicator of prolonged survival for use in early-phase

clinical trials. Finding a robust short-term indicator of prolonged survival would suggest that utilization of a CTC endpoint in an early-phase clinical trial could accelerate drug development and aid clinical decision making in clinical practice for the mCRPC population.

METHODS

Patients

The individual patient data from five independent randomized phase 3 clinical trials for mCRPC were used for this evaluation; see Table 1, Figure 1, and Appendix Figures S1-S5 (online only).[10-14] A description of the studies can be found on Appendix page S1 (online only). In each trial, the primary endpoint was overall survival.

Response Measures

CTC counts and PSA levels at baseline and week 13 were used to define a series of response endpoints. The evaluable study cohorts from each trial were patients who survived at least 13 weeks and had a recorded baseline CTC or PSA value. The eight CTC and PSA response measures considered were CTC0: patients with CTC count ≥1 at baseline and 0 at week 13; CTC conversion (CTC conv): CTC count ≥5 at baseline and ≤4 at week 13; percent change in CTC (CTC30, CTC50, CTC70): CTC count ≥5 at baseline and a 30%, 50%, or 70% decline from baseline to week 13; and percent change in PSA (PSA30, PSA50, PSA70): PSA level ≥5 ng/ml at baseline and a 30%, 50%, or 70% decline from baseline to week 13. Patients who achieved these biomarker thresholds were recorded as responders. All other patients were recorded as non-responders, including those with recorded baseline data who survived more than 13 weeks but dropped out of the biomarker component of the study prior to week 13.

Missing data: in all five trials, baseline CTC data were missing for some patients who survived longer than 13 weeks. Reasons included geographic restrictions such as the unavailability of the CTC assay in a particular region or country, and patient- and disease-related factors. To ascertain whether the missing data had a significant effect on the analyses, a logrank test for survival was performed for each study to assess whether the patient populations with missing baseline CTC data differed from the analyzed populations.

Discriminatory value of the response endpoints: to evaluate the discriminatory power of the response endpoints on survival time, the weighted c-index for each of the eight endpoints was calculated separately for each trial.[18] The weighted c-index ranges from 0.5 to 1.0 and represents the likelihood that responders survive longer than non-responders, with an increasing index indicating a greater probability of longer survival for responders. A weighted c-index near 1.0 would indicate that nearly all patients classified as non-responders would have died prior to the shortest survival time among the responding patients. A weighted c-index near 0.5 would signify very little discriminatory power, that patients classified as responders and non-responders would have virtually

superimposed survival curves. Because the weighted c-index scale is difficult to discern, Kaplan-Meier estimates of survival for responders versus non-responders were used to show the magnitude of the gap between the responder and non-responder survival curves. All survival analyses were landmarked at week 13 to coincide with the response evaluation. To account for the individual effects of the experimental and control arms on discrimination, a supplemental analysis was undertaken based on a stratified by treatment arm weighted c-index analysis.

RESULTS

Patient Populations

A total of 6081 patients were randomized across the five trials; see Table 1 for a synopsis of trials. Table 2 provides summarized baseline and week 13 CTC and PSA data for each trial. These summaries show significant heterogeneity with a range of prognoses across the studies, consistent with the range of mCRPC states they represent. Noteworthy is that the highest median baseline CTC and PSA values were seen in COMET-1, which enrolled patients whose disease had progressed on at least two approved life-prolonging therapies (a taxane-based chemotherapy and either abiraterone or enzalutamide), and the lowest baseline CTC and PSA values occurred in ELM-PC-4, which enrolled patients who had not received any prior proven life-prolonging therapy for mCRPC. The other three trials, with baseline values falling in the middle, enrolled patients who had previously received only one life-prolonging therapy, docetaxel.

The flow of evaluable patients for each study is shown in Table 1, Figure 1, and Figures S1-S5. The percentage of patients with qualifying CTC data varied widely (see Table 1). For example, in the ELM-PC-4 clinical trial (Fig. S4), 1288 of the 1560 randomized patients (83%) had baseline CTC data and survived at least 13 weeks. Among the 1288 patients, 848 (66%) had a baseline CTC value >0 and were evaluable for the CTC0 response endpoint. Evaluability for the CTC conversion and percent change in CTC response endpoints required a baseline CTC value ≥5, which only 497 of the 1288 patients (39%) in the ELM-PC-4 study had. Evaluability of the PSA response endpoints required a baseline PSA value ≥5, which rendered 1412 of the 1474 patients (96%) evaluable.

CTC and PSA Response Rate Survival Discrimination

Table 3 and Figure 2 show the strength of the CTC and PSA response endpoints to discriminate overall survival using the weighted c-index. In Figure 2, the horizontal axis lists the eight endpoints studied and the vertical axis indicates the weighted c-index. Each trial is represented by a letter (A through E); the size of the letter is inversely proportional to the standard error of the weighted c-index on the study it represents. Using this size distinction, larger letters represent more accurate estimates of discrimination.

As shown, the ability to differentiate the survival outcomes for week 13 responders and non-responders was greatest using the CTC0 and CTC conversion endpoints. Finding no CTCs after treatment, or finding that the value had converted from above to below the threshold of 5 CTCs, provided greater discrimination for patient survival than the percent change in CTC or PSA response endpoints. The average weighted c-index for the CTC0 and CTC conversion response endpoints was 0.81 and 0.79, respectively, whereas the average weighted c-indices for the percent change CTC and PSA endpoints ranged from 0.71 to 0 .74 (Table 3). Among the PSA endpoints, the average weighted c-index for PSA70 was slightly higher than that for PSA50 and PSA30. A test to compare the weighted (by the number of patients) average difference across studies between the CTC0 and PSA70 endpoints produced a p-value = 0.026, which demonstrates improved discriminatory power for the CTC0 endpoint compared with the PSA70 endpoint and, by extension, to each of the PSA response endpoints examined.

In addition to greater discrimination, the CTC0 and CTC conversion response endpoints were more robust, producing consistent weighted c-indices across the five trials as shown by the smaller standard deviations in Table 3 and the tighter clustering of letters in Figure 2. A supplemental analysis, based on the stratified (by treatment) weighted c-index, produced comparable results (Table 3).

Evaluability Rates for the CTC0 and CTC Conversion Endpoints

Although the discriminatory strength of the CTC0 and CTC conversion endpoints was similar, an important distinction between the two is the percentage of patients for whom these response measures could be utilized. Overall, 75% of eligible patients were evaluable for the CTC0 endpoint (CTC $\geq$1 at baseline) but only 51% were eligible for the CTC conversion endpoint (CTC $\geq$5 at baseline) (see Table 1). In these five studies, the relative increase in the percentage of patients evaluable for the CTC0 endpoint compared with CTC conversion ranged from 29% to 71%, with the greatest proportional increase (71%, 848 vs 497) occurring among patients who were chemotherapy-naïve (ELM-PC-4) and the least difference (29%, 660 vs 510) occurring among patients who had been exposed to at least two prior treatments (COMET-1) (Table 1).

Graphical Interpretation of the Weighted C-indices

To illustrate how the magnitude of the weighted c-index represents the relationship between the response endpoint and the survival endpoint, Kaplan-Meier estimates of survival for responders and non-responders were generated for each study, along with the associated weighted c-index. Those for CTC0 and PSA50 response are shown in Figures 3a-3e. For example, an examination of the ELM-PC-5 Kaplan-Meier estimates (Fig. 3c) clearly depicts an improved survival profile for CTC0 responders relative to CTC0 nonresponders, which is reflected in the large weighted c-index (weighted c-index = 0.83). In contrast, the moderate survival benefit conferred upon the PSA50 responders is summarized by a weighted c-index equal to 0.74. In comparison, in the COU-AA-301 Kaplan-Meier

estimate (Fig. 3a), the difference in discrimination between CTC0 and PSA50 is small, appropriately since the weighted c-indexes are 0.78 and 0.76, respectively.

Recognizing that the response analyses could be performed only on eligible patients who survived at least 13 weeks and had baseline marker data, a logrank test was performed to determine whether the survival rates for each trial differed for the analyzed patient population versus patients who survived more than 13 weeks but were missing baseline CTC or PSA data and were not included in the analysis. The results shown in Table S1 (Appendix, online only) indicate that no difference in survival rates was observed in any of the five studies.

DISCUSSION

Treatment effects in therapeutic trials are typically assessed using predefined criteria which represent an early-occurring change in a disease manifestation that was present at the start of a new therapy, or time-to-event measures that represent the delay or prevention of later-occurring potential disease manifestations which indicate or predict for a deterioration in quality of life or death. For the development of drugs, no single post-treatment early response measure has been established as a true indicator of clinical benefit, with the exception of the palliation or control of pain, for which specific therapies are approved (mitoxantrone) or indicated for use when symptoms of osseous disease are present (radium-223 dichloride). The results presented in this analysis establish that the defined CTC0 endpoint, a change in the number of CTCs from detectable (present) to undetectable (absent), using the FDA-cleared CellSearch assay, is a response indicator biomarker that is strongly associated with longer survival, an unambiguous clinical benefit to patients. The strength of the CTC0 response endpoint to reflect a survival improvement was established using individual patient data from more than 3000 men who were evaluable for a CTC response assessment, and was consistent across five phase 3 randomized registration trials powered on survival in which the CTC biomarker question was embedded prospectively. Each of the response measures considered in the individual trials was evaluated independent of the specific intervention under evaluation in the trial and the treatment arm on which a patient was enrolled. The interventions included placebo, prednisone monotherapy, three next-generation androgen receptor signaling inhibitors given alone or in combination with prednisone, and a signaling inhibitor. The trials were conducted in three distinct mCRPC patient populations: patients at the first, second and third decision point in disease management, who had been previously exposed to either no, one (docetaxel), or two (docetaxel and an approved androgen receptor signaling inhibitor) life-prolonging therapies, respectively. Taken together, the consistency of the outcomes across treatments and disease states shows the generalizability of the results and further supports the CTC0 endpoint as a measure of clinical benefit for use in clinical trials.

To our knowledge, this is the first reported exploration of CTC0 as a response endpoint. Of particular note was that the CTC0 endpoint was superior to the more widely used percent change in PSA endpoints, which did not

discriminate survival to the same degree. Four of the trials included hormonal agents that can in themselves modulate PSA levels independent of an effect on cell kill, thereby limiting post-therapy PSA change measures as a reliable indicator of efficacy. This was one of the reasons CTC number, a measure that is not affected by modulations in androgen receptor signaling, was included in the early phases of development of these agents. Reaching a post-therapy PSA less than 1 ng/ml occurred too infrequently in these cohorts to be useful as an outcome (Table 1).

The discriminatory power of CTC0 for survival was matched by the CTC conversion measure.[6] The benefit of the CTC0 endpoint is the increased patient eligibility. The CTC0 endpoint requires ≥1 CTCs at baseline, whereas the CTC conversion endpoint requires ≥5 CTCs at baseline for eligibility. In these five studies, use of the CTC0 endpoint improved the ability to evaluate response (increases ranging from 29% to 71%), compared with the need to detect ≥5 CTCs at baseline. This increase in the percent of evaluable patients, 71% in the first-line, 46% in the second-line, and 29% in the third-line setting, significantly enlarges the patient population, enabling more rapid trial accrual and shorter drug evaluation times in trials while providing greater reliability in studies of treatment efficacy.

A limitation of the study was the number of patients who did not have baseline CTC counts and were therefore not assessable using the CTC response measures proposed here. Excluding the AFFIRM trial, the number of patients lacking baseline CTC counts ranged from 14% to 18% of the patients surviving 13 weeks, which raises the possibility of bias in interpreting the outcome. Sixty-three percent of patients in the AFFIRM trial did not have baseline CTC values, with the majority of CTC samples being obtained in North America. This lack of baseline CTC data most commonly resulted from the unavailability of the assay in the country in which the trial was being conducted, or from limitations in access to the reference laboratory performing the assay. To address this, sensitivity analyses were conducted in which we were unable to discern a survival difference for patients with missing baseline counts in any of the five studies. Further questions to be addressed include the reproducibility of the CTC count measured at baseline; specifically, if two samples are drawn, will the results be the same? A second issue is the need for confirmation of the CTC endpoint measurement, which is traditionally required for blood-based biomarkers such as PSA, and responses by imaging.

To develop new therapeutic agents requires the ability to determine whether a systemic therapy has clinical benefit, e.g., improving how a patient feels and functions, and how long he survives. This seemingly simple need has been one of the most challenging aspects of drug development for patients with mCRPC because reliable and informative early-occurring indicators of clinical benefit are lacking. Post-therapy PSA changes fall short in prognostic reliability, while pre-treatment measurable disease which can be objectively assessed post-treatment is not only infrequent, but has not been shown prospectively to associate with an improvement in survival. The

CTC0 endpoint is an indicator that cancer cells that were circulating in the blood are no longer detectable, an easily recognized outcome that is clinically meaningful to patients. It is an outcome that occurs shortly after treatment initiation, providing researchers and practitioners with objective and reliable evidence that the therapy being given has altered the patient's prognosis in a favorable way. Taken together, the results of this study support the use of CTC0 as a response endpoint in early-phase clinical trials.

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TABLES

Table 1. mCRPC phase 3 studies contributing data to this analysis

	COU-AA-301 [10]	AFFIRM [13]	ELM-PC-5 [11]	ELM-PC-4 [12]	COMET-1 [14]	Total
Clinicaltrials.gov	NCT00638690	NCT00974311	NCT01193257	NCT01193244	NCT01605227	
Comparators	Abiraterone acetate + prednisone vs placebo + prednisone	Enzalutamide vs placebo	Orteronel + prednisone vs placebo + prednisone	Orteronel + prednisone vs placebo + prednisone	Cabozantinib vs prednisone	
Patient population	Failed docetaxel-based therapy	Progressed during or after docetaxel-based therapy	Progressed during or after docetaxel-based therapy	Chemotherapy-naive	Prior docetaxel and either abiraterone or enzalutamide	
Randomized patients, n	1195	1199	1099	1560	1028	6081
Patients surviving ≥13 weeks, n (% of randomized patients)	1091 (91)	1151 (96)	1001 (91)	1495 (96)	922 (90)	5660 (93)
Qualifying patients: surviving ≥13 weeks with qualifying* baseline CTC and/or PSA data, n (% of patients surviving ≥13 weeks)						
CTC data	890 (82)	430 (37)	831 (83)	1288 (86)	757 (82)	4196 (74)
PSA data	1085 (99)	1151 (100)	985 (98)	1474 (99)	909 (99)	5604 (99)
Evaluable patients: eligible for 13-week response evaluation (13-week CTC and/or PSA data as well as qualifying* baseline values), n (% qualifying patients)						
CTC0 data	660 (74)	332 (77)	658 (79)	848 (66)	660 (87)	3158 (75)
CTC conversion data	441 (50)	217 (50)	487 (59)	497 (39)	510 (67)	2152 (51)
CTC % change data	441 (50)	217 (50)	487 (59)	497 (39)	510 (67)	2152 (51)
PSA % change data	1057 (97)	1124 (98)	953 (97)	1412 (96)	882 (97)	5428 (97)
Responders: patients who met criteria for a given response endpoint at 13 weeks, n (% evaluable patients)						
CTC0[†]	141 (22)	63(19)	102 (16)	228 (27)	57 (9)	591 (19)
CTC conversion[‡]	124 (29)	52 (24)	96 (20)	153 (31)	77 (15)	502 (23)
≥30% CTC decrease from baseline	184 (44)	78 (36)	182 (37)	247 (50)	167 (33)	858 (40)
≥50% CTC decrease from baseline	168 (40)	75 (35)	162 (33)	215 (43)	147 (29)	767 (36)
≥70% CTC decrease from baseline	136 (32)	63 (29)	126 (26)	186 (37)	119 (23)	630 (29)
≥30% PSA decrease from baseline	386 (37)	473 (42)	274 (29)	618 (44)	77 (9)	1828 (34)
≥50% PSA decrease from baseline	288 (27)	388 (35)	200 (21)	486 (34)	39 (4)	1401 (26)
≥70% PSA decrease from baseline	207 (20)	305 (27)	118 (12)	336 (24)	20 (2)	986 (18)
PSA < 1 ng/ml	26 (2)	44 (4)	15 (2)	59 (4)	0 (0)	144 (3)

All trials were randomized, multicenter, and double-blind.

*Patients were eligible for PSA30, PSA50, and PSA70 evaluation if baseline PSA ≥5 ng/ml. Patients were eligible for CTC30, CTC50, CTC70, and CTC conversion evaluation if baseline CTC count ≥ 5, and eligible for CTC0 evaluation if baseline CTC count ≥ 1.

[†]Criteria met if CTC count ≥1 at baseline and 0 at 13 weeks.

[‡]Criteria met if CTC count ≥5 (unfavorable) at baseline and ≤4 (favorable) at 13 weeks.

Table 2. Median (range) of PSA and CTC measures

	Baseline PSA, ng/ml	Week 13 PSA, ng/ml	Baseline CTC, cells per 5 ml blood	Week 13 CTC, cells per 5 ml blood
COU-AA-301	131 (0.4–10110)	98 (0.1–8985)	6 (0–100)	1 (0–100)
AFFIRM	111 (0–19000)	67 (0–12910)	5 (0–145)	2 (0–163)
ELM-PC-5	125 (0.2–19010)	95 (0.1–19750)	10 (0–3851)	2 (0–5273)
ELM-PC-4	55 (0.06–15530)	31 (0–15600)	2 (0–9537)	0 (0–1635)
COMET-1	192 (0–10960)	308 (0.1–18080)	20 (0–30250)	7 (0–5133)

Table 3. Weighted c-index by study and response indicator endpoint

	Absolute Measures		**Relative Measures**					
	CTC0	**CTC conversion**	**CTC30**	**CTC50**	**CTC70**	**PSA30**	**PSA50**	**PSA70**
Unstratified analysis								
COU-AA-301	0.78	0.80	0.77	0.77	0.78	0.74	0.76	0.76
AFFIRM	0.86	0.84	0.80	0.80	0.79	0.75	0.77	0.80
ELM-PC-5	0.83	0.78	0.65	0.67	0.70	0.71	0.74	0.76
ELM-PC-4	0.77	0.77	0.67	0.69	0.71	0.69	0.68	0.69
COMET-1	0.79	0.77	0.71	0.69	0.67	0.67	0.64	0.70
Mean	**0.81**	**0.79**	**0.72**	**0.72**	**0.73**	**0.71**	**0.72**	**0.74**
Standard deviation	**0.04**	**0.03**	**0.06**	**0.06**	**0.05**	**0.03**	**0.06**	**0.05**
Stratified by treatment (experimental arm vs control arm)								
COU-AA-301	0.77	0.79	0.76	0.76	0.77	0.73	0.76	0.75
AFFIRM	0.85	0.82	0.80	0.80	0.80	0.77	0.77	0.81
ELM-PC-5	0.83	0.76	0.66	0.68	0.69	0.72	0.74	0.77
ELM-PC-4	0.77	0.78	0.68	0.70	0.72	0.70	0.69	0.70
COMET-1	0.80	0.78	0.72	0.71	0.68	0.66	0.62	0.66
Mean	**0.80**	**0.79**	**0.72**	**0.73**	**0.73**	**0.71**	**0.71**	**0.73**
Standard deviation	**0.04**	**0.02**	**0.06**	**0.05**	**0.05**	**0.04**	**0.06**	**0.06**

FIGURES

Figure 1. CONSORT diagram for the five randomized clinical trials combined.

Figure 2. Discriminatory power of post-therapy CTC and PSA response measures for survival in mCRPC registration trials.

Figures 3a-3e. Kaplan-Meier estimates of responders versus non-responders along with 95% confidence intervals for the CTC0 and PSA50 response endpoints at 13 weeks, for the five mCRPC registration trials.

Fig. 3a: COU-AA-301
Fig. 3b: AFFIRM
Fig. 3c: ELM-PC-5
Fig. 3d: ELM-PC-4
Fig. 3e: COMET-1

ONLINE-ONLY:

Table S1: Sensitivity analysis for missing baseline PSA or CTC values: median survival time (sample size) for patients who survived ≥13 weeks. The p-value is generated from the logrank test comparing the survival rates between the groups with and without missing baseline PSA or CTC data. The hazard ratio and 95% confidence intervals are computed from Cox proportional hazards models. In each study, the proportional hazards assumption was evaluated and could not be rejected.

	Median survival, months (no. patients)		**p-value**	**Hazard ratio (95% CI)**
	Not missing	Missing		
COU-AA-301	15.8 (846)	16.0 (245)	0.74	1.03 (0.86−1.23)
AFFIRM	19.5 (430)	18.1 (721)	0.71	0.96 (0.80−1.16)
ELM-PC-5	18.0 (831)	16.6 (170)	0.56	1.07 (0.84−1.37)
ELM-PC-4	31.4 (1288)	29.9 (207)	0.56	0.93 (0.73−1.19)
COMET-1	11.4 (757)	11.9 (165)	0.33	0.89 (0.71−1.12)

Figures S1-S5: CONSORT diagrams for the COU-AA-301, AFFIRM, ELM-PC-5, ELM-PC-4, and COMET-1 studies.