

Circulating Tumor Cells Predict Survival Benefit from Treatment in Metastatic Castration-Resistant Prostate Cancer

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Abstract Purpose: A method for enumerating circulating tumor cells (CTC) has received regulatory clearance. The primary objective of this prospective study was to establish the relationship between posttreatment CTC count and overall survival (OS) in castration-resistant prostate cancer (CRPC). Secondary objectives included determining the prognostic utility of CTC measurement before initiating therapy, and the relationship of CTC to prostate-specific antigen (PSA) changes and OS at these and other time points.

Experimental Design: Blood was drawn from CRPC patients with progressive disease starting a new line of chemotherapy before treatment and monthly thereafter. Patients were stratified into predetermined Favorable or Unfavorable groups (<5 and ≥ 5 CTC/7.5mL).

Results: Two hundred thirty-one of 276 enrolled patients (84%) were evaluable. Patients with Unfavorable pretreatment CTC (57%) had shorter OS (median OS, 11.5 versus 21.7 months; Cox hazard ratio, 3.3; $P < 0.0001$). Unfavorable posttreatment CTC counts also predicted shorter OS at 2 to 5, 6 to 8, 9 to 12, and 13 to 20 weeks (median OS, 6.7-9.5 versus 19.6-20.7 months; Cox hazard ratio, 3.6-6.5; $P < 0.0001$). CTC counts predicted OS better than PSA decrement algorithms at all time points; area under the receiver operator curve for CTC was 81% to 87% and 58% to 68% for 30% PSA reduction ($P = 0.0218$). Prognosis for patients with (a) Unfavorable baseline CTC who converted to Favorable CTC improved (6.8 to 21.3 months); (b) Favorable baseline CTC who converted to Unfavorable worsened (>26 to 9.3 months).

Conclusions: CTC are the most accurate and independent predictor of OS in CRPC. These data led to Food and Drug Administration clearance of this assay for the evaluation of CRPC.

Prostate cancer is the second leading cause of cancer death in men in Western societies. The majority succumb to progressing disease despite hormone treatments, which has been termed hormone-refractory prostate cancer. Castration-resistant prostate cancer (CRPC) may be a more accurate description for this disease because it can remain hormone-driven despite androgen deprivation (1, 2). In spite of intense efforts, development of new therapies remains problematic due to the lack of qualified surrogate measures of clinical benefit (3-7). It was hoped that posttherapy changes in prostate-

specific antigen (PSA) could fulfill this role. Analysis of two recent phase 3 trials demonstrating a survival benefit for docetaxel also showed that posttherapy changes in PSA are unlikely to become a Food and Drug Administration-accepted surrogate end point for drug registration studies because of the proportion of patients for whom PSA response does not predict long-term benefit (3, 5, 6). In the current climate of Food and Drug Administration and other regulatory authorities, the demonstration of overall survival (OS) benefit, compared with established treatments, remains the main route to drug approval. Although this is very reasonable, it does potentially lead to significant delays in the introduction of new therapies, especially when survival data are confounded by second- and third-line regimens. In the clinical setting, discordant symptoms, PSA, and bone scan results after treatment frequently lead to therapeutic dilemmas for both the clinician and the patient where it is not clear whether to continue or abandon therapy when the various indicators are not in synchrony.

Assessment of circulating tumor cells (CTC) using CellSearch has been cleared by the Food and Drug Administration as a prognostic indicator for patients with metastatic breast, prostate, and colorectal cancers (8-15). Several groups have shown that CTC are detected at high frequency in CRPC and are correlated with clinical outcomes (13, 14, 16, 17). As a result, we designed a prospective study to assess whether CTC enumeration preinitiation and postinitiation of a new cytotoxic treatment could predict OS. The primary objective was to

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Translational Relevance

This method for enumerating circulating tumor cells (CTC) may have utility in predicting prognosis and monitoring the antitumor effects of treatment in castration resistant prostate cancer. It may serve as an intermediate end point for drug approval in this disease. These studies have led to the Food and Drug Administration clearance of this technology for CTC evaluation for this disease.

establish that CTC levels 2 to 5 weeks after initiating a new treatment were predictive of OS. Additional objectives were to establish the relationships between OS, CTC levels, and PSA decrements before and after treatment.

Materials and Methods

Study design. Patients with histologically confirmed prostate cancer that was metastatic and progressing despite castrate levels of testosterone (<50 ng/mL) and who were commencing a new cytotoxic therapy were eligible. Progression required any or all of the following: a rising PSA as defined by PSA Working Group criteria (7), new osseous lesions, or new or enlarging soft tissue metastases. Other eligibility criteria included a PSA level of >5 ng/mL; Eastern Cooperative Oncology Group performance status of 0 to 2; a 4-wk (6-wk for nilutamide, bicalutamide) washout after discontinuation of an antiandrogen, and no radiation or radionuclide therapy within 30 d of entry. A bone scan within 60 d of the first blood draw was also required. Patient with brain metastases or a history of other malignancies within the last 5 years were excluded. A total of 65 clinical centers throughout the United States and Europe participated after formal institutional review board approval. All patients were required to provide written informed consent.

Baseline laboratory studies included blood sample collection for CTC, PSA, alkaline phosphatase, and lactate dehydrogenase levels before treatment. Assessment of CTC and PSA were repeated before each course of therapy until disease progression or for up to 18 mo.

Patients were categorized prospectively as having either Unfavorable (>5 CTC/7.5 mL) or Favorable (<5 CTC/7.5 mL) CTC counts. This dichotomous cutoff has been previously defined in studies of breast cancer, and from our own preliminary modeling data (8, 9). An independent clinical research organization collected and monitored all of the clinical and laboratory data. Patients were followed up with regular chart review for up to 36 mo from the time of the baseline blood draw for the survival analysis. OS was measured as the time from the date of the CTC blood draw being evaluated to the date of death or last follow-up; thus, analyses were done either on the initial (pretreatment) blood draw or on posttreatment draws, where survival was calculated from the time of the sample. In the case of posttreatment samples, the measurement was taken from the time of the sample to avoid lead time bias. Locked and validated databases containing the combined clinical and laboratory data were analyzed separately by the principal investigators, the clinical research organization, and the sponsor.

Isolation and enumeration of CTCs. CTC enumeration was done as described previously (8–13). Blood samples were drawn into 10-mL evacuated blood draw tubes (CellSave; Immunicon), maintained at room temperature, and processed within 96 h of collection. The evaluations were done in a blinded fashion in one of four central laboratories (Immunicon, Huntingdon Valley, PA; Immunicon, Enschede, the Netherlands; IMPATH Predictive Oncology; and Cleveland Clinic). The CellSearch System (Veridex LLC) consists of the CellTracks Autoprep (an automated sample preparation system) and

the CellSearch Epithelial Cell kit, to immunomagnetically enrich cells expressing the epithelial cell adhesion molecule and fluorescently label all nuclei with 4',2-diamidino-2-phenylindole, dihydrochloride, leukocytes with monoclonal antibodies specific for leukocytes (CD45-Allophycocyan), and epithelial cells (cytokeratin 8,18,19-Phycoerythrin). Identification and enumeration of CTC was done using the CellSpotter Analyzer or CellTracks Analyzer II, semiautomated fluorescence-based microscopy systems that permit computer-generated reconstruction of cellular images. CTC were defined as nucleated cells lacking CD45 and expressing cytokeratin. Technical details of the CellSearch and CellTracks systems, including accuracy, precision, linearity, and reproducibility, have been described elsewhere (8).

Statistical design. The primary objective was to show that the median OS for patients with Unfavorable CTC counts (>5 CTC/7.5 mL blood) 2 to 5 wk after the initiation of a new line of chemotherapy was half the median OS of patients with Favorable CTC (<5 CTC/7.5 mL blood) at this same time point. The cutoff of 5 CTC per 7.5 mL of

Table 1. Patient demographics

Variable	Categories	Evaluable patients (N = 231)
Age at Baseline (n = 231)	Average ± SD Median (range)	70 ± 9 70 (45-92)
Race:	White Black Hispanic Asian	209 (90%) 17 (7%) 3 (1%) 2 (1%)
Baseline ECOG	0 1 2 Unknown	101 (44%) 100 (43%) 21 (9%) 9 (4%)
Gleason score	≤5 6 7 8 ≥9 Unknown	18 (8%) 28 (12%) 63 (27%) 45 (20%) 54 (23%) 23 (10%)
Line of cytotoxic therapy	1st 2nd ≥3rd	154 (67%) 38 (16%) 39 (17%)
Taxotere used in current therapy line	No Yes Unknown	67 (29%) 162 (70%) 2 (1%)
Bone metastasis	Negative Positive Unknown	20 (8%) 207 (90%) 4 (2%)
Visceral metastasis	No Yes Unknown	141 (61%) 89 (39%) 1 (0%)
Baseline PSA (ng/mL)	Average ± SD	546.9 ± 1,615.9
Centrally determined (n = 231)	Median (range)	144 (1.9-17,800)
Baseline hemoglobin (g/dL)	Average ± SD	12.3 ± 1.6
Site determined (n = 221)	Median (range)	12.4 (8.2-15.7)
Baseline alkaline phosphatase (IU/mL)	Average ± SD	235 ± 271
Centrally determined (n = 223)	Median (range)	144 (39-2,215)
Baseline LDH (IU/mL)	Average ± SD	293 ± 228
Centrally determined (n = 219)	Median (range)	224 (103-2,092)
Baseline albumin (g/dL)	Average ± SD	3.9 ± 2.6
Site determined (n = 214)	Median (range)	3.8 (2.1-41.0)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase.

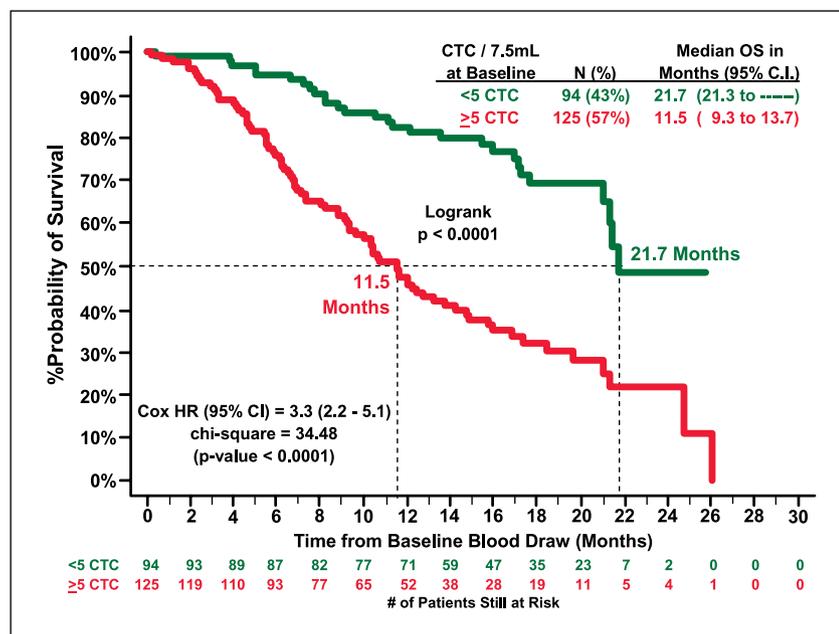


Fig. 1. Kaplan-Meier estimates of probabilities of OS of CRPC patients with Favorable (<5) and Unfavorable (≥5) CTC before initiation of therapy in 7.5 mL of blood.

blood was based on the results of breast cancer studies showing that this cutoff robustly predicted OS (9 – 12). Secondary objectives included the prognostic utility of CTC enumeration before and at other time points after the initiation of therapy. The ability of posttreatment PSA changes to predict OS was also explored alone and in relation to the acquired CTC data.

The statistical design was based on a sample size of 200 evaluable patients enrolled over a 12-mo period with the assumption that 50% of the evaluable patients would have Unfavorable CTC counts 3 to 4 wk after the initiation of therapy. It was assumed prospectively that 20% of patients would be nonevaluable. Evaluable patients with Favorable (*n* = 80) and Unfavorable (*n* = 80) CTC counts were projected to have median OS of 28 and 14 mo, respectively. Under these assumptions, a log-rank test for the equality of survival curves with a one-sided type I error (α) of 0.05 would have 80% power to detect a difference between the survival curves of the Favorable and Unfavorable patient cohorts equating to a hazard ratio (HR) of 2.0 after a minimum of 52 death had been observed. Accrual was to be continued until data on at least 80 evaluable patients with Unfavorable CTC counts and 80 evaluable patients with Favorable CTC counts ~3 to 4 wk after the initiation of therapy had been enrolled and followed for a minimum of 12 mo or until a minimum of 52 deaths had been observed.

For the survival analysis, Kaplan-Meier plots were generated based on CTC at baseline and follow-up blood collections. For all survival analyses, the elapsed time between the date of the blood collection and death or the last follow-up was used. Survival curves were compared using log-rank testing. Cox proportional hazards regression was used to determine univariate and multivariate hazards ratios for OS. Receiver operating characteristic curves were used to examine the global performance characteristics of the outcome tests being evaluated. The area under the receiver operating characteristic curves were compared using a nonparametric method, which accounts for the correlation induced through measurement of the two independent variables on the same set of patients.

Results

Patient demographics. A total of 276 patients with progressing CRPC were enrolled between October 2004 and February

2006, of whom 45 (16%) did not meet the required eligibility criteria: 13 commenced radiotherapy or a new hormonal therapy within 30 days of the baseline blood draw; 10 did not have evaluable baseline blood draws or scans; 8 had insufficient washout from antiandrogens; 7 lacked progressive disease at accrual; 3 had a history of other cancers within the previous 5 years; 2 withdrew consent; 1 had a PSA of <5 ng/mL; 1 was not castration resistant. Of the 231 evaluable patients, 219, 203, 163, 149, and 143 had evaluable CTC at baseline, 2 to 5, 6 to 8, 9 to 12, and 13 to 20 weeks after the initiation of therapy, respectively. Patient demographics are presented in Table 1. At the time of analysis, 119 (52%) of the 231 evaluable patients had died (111 of the 219 with evaluable baseline CTC), resulting in a median OS of 17.2 months [95% confidence interval (95% CI), 14.2-21.0 months]. The average length of follow-up time for the 112 patients still alive was 16.1 + 4.9 months (range, 1.9-25.7 months).

Baseline CTC number and prognosis. At the time of analysis 30% (28 of 94) of the Favorable (<5 CTC at baseline) and 66% (83 of 125) of the Unfavorable (≥5 CTC at baseline) group patients were alive (Fig. 1), with a median OS of 21.7 (95% CI, 21.3 months to Not Reached) and 11.5 months (95% CI, 9.3-13.7 months), respectively, (Log-rank *P* < 0.0001; Cox HR, 3.3; $\chi^2 = 34.48$; *P* < 0.0001).

CTC number 2 to 5 weeks after treatment and OS. Two to 5 weeks after treatment, the median OS of patients with Favorable CTC was 20.7 months (95% CI, 20.5 months to Not Reached), compared with 9.5 months (95% CI, 5.8-10.7 months) for the Unfavorable group (Log-rank *P* < 0.0001; Cox HR, 4.5; $\chi^2 = 53.31$; *P* < 0.0001; Fig. 2A). The median OS differences between patients with Favorable and Unfavorable CTC at 6 to 8, 9 to 12, and 13 to 20 weeks after the initiation of therapy were similar to differences in OS at 2 to 5 weeks (Fig. 2B).

Univariate and multivariate Cox proportional hazards regression analyses. Univariate and multivariate Cox proportional hazards regression analyses were done, evaluating a number

of factors including CTC count, age, Eastern Cooperative Oncology Group performance status, PSA doubling time, PSA velocity, hemoglobin, albumin, baseline testosterone, lactate dehydrogenase, alkaline phosphatase, line of cytotoxic therapy,

and presence of visceral metastases. These studies revealed that baseline and posttreatment CTC counts were highly prognostic and independent of the number of lines of cytotoxic chemotherapy and established prognostic markers including

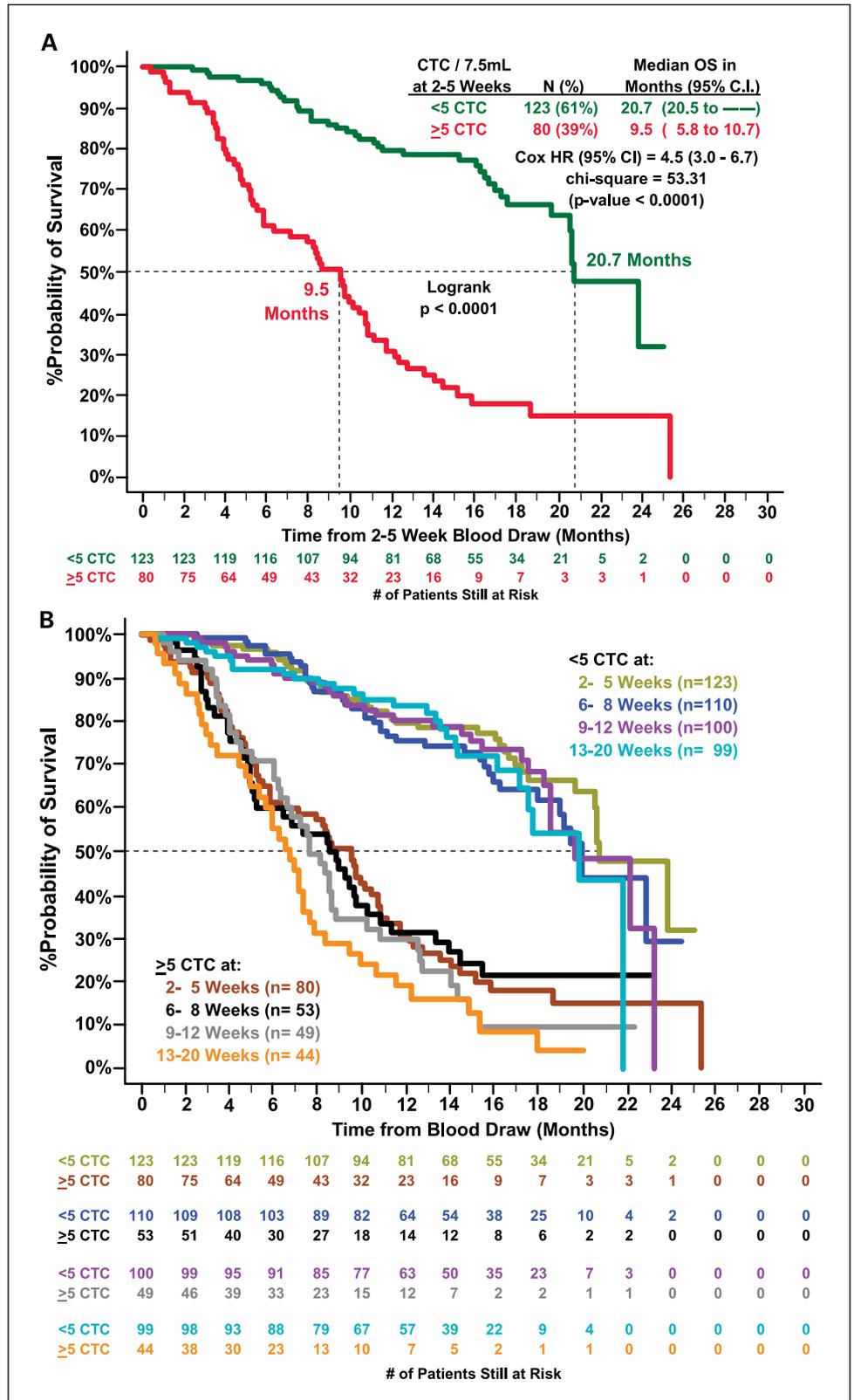


Fig. 2. Kaplan-Meier estimates of probabilities of OS of CRPC patients with Favorable (<5) and Unfavorable (≥5) CTC: A, 2 to 5 wk after initiation of therapy; B, 2 to 5, 6 to 8, 9 to 12, and 13 to 20 wk after initiation of therapy.

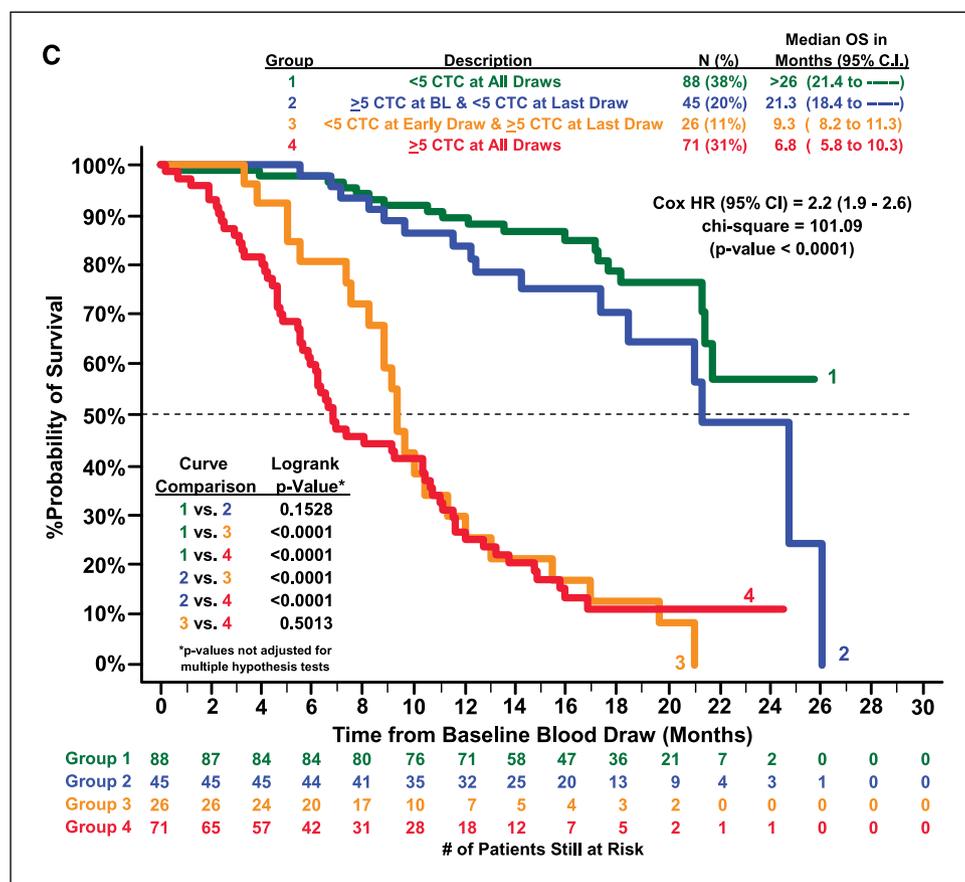


Fig. 2 Continued. C, patients whose CTC did or did not convert from the favorable or unfavorable groups after therapy.

hemoglobin, lactate dehydrogenase, Alkaline phosphatase, albumin and performance status (Table 2; Supplementary Table).

Conversion between Unfavorable and Favorable groups after treatment. Additional exploratory analyses showed the effect on OS of converting from Unfavorable to Favorable CTC or from Favorable to Unfavorable CTC (Fig. 2C). Patients with Unfavorable CTC at all time points (group 4, 71 patients) had the shortest median OS (6.8 months; 95% CI, 5.8-10.3), which was significantly different from those who converted from Unfavorable to Favorable CTC after treatment (group 2, 45 patients; median OS, 21.3 months; 95% CI, 18.4 to not reached; log-rank $P < 0.0001$) and those who had Favorable CTC throughout (group 1, 88 patients; median OS, >26 months; 95% CI, 21.4 months to not reached; log-rank $P < 0.0001$). A change from Favorable to Unfavorable CTC after treatment (group 3) was associated with a poor prognosis (median OS, 9.3 months; 95% CI, 8.2-11.3 months), although the number of patients in this group was small ($n = 26$).

Posttreatment CTC count is superior to PSA decrements at predicting OS. A reduction in PSA after initiating therapy by either 30% or 50% has been proposed as a potential predictor of OS (5-7). The predictive ability of Favorable and Unfavorable CTC after treatment were therefore compared with both. The differences in median OS between the Favorable (>30% or >50% PSA reduction from baseline) and Unfavorable (<30% or <50% PSA reduction from baseline) PSA reduction groups were statistically significant after 6 to

8 weeks (HR, 2.2 for 30% PSA decrement; HR, 2.1 for 50% PSA decrement), becoming most significant at 13 to 20 weeks (HR, 2.9 for 30% PSA decrement; 2.6 for 50% PSA decrement). The separation between the Favorable (<5 CTC) and Unfavorable (>5 CTC) CTC cohorts was greater than for either of these PSA decrement algorithms at all time points after the initiation of therapy (HR, 5.3 at 9-12 weeks and 6.5 at 13-20 weeks; Table 3). This is illustrated further in Fig. 3, which shows the survival distributions for patients with Favorable and Unfavorable CTC (19.6 versus 7.6 months; Cox HR, 5.3; log-rank $P < 0.0001$) at 9 to 12 weeks (A) compared with patients who achieved a >30% decline in PSA and those who did not (18.5 versus 10.2 months; Cox HR, 2.2; $P = 0.0007$; B). The predictive superiority of CTC over PSA reduction algorithms is even more striking at 2 to 5 and 6 to 8 weeks. Similar data were observed for both 30% and 50% PSA decrements after therapy (Table 3).

To evaluate this further, we then compared the ability of CTC counts and PSA reduction to predict death within 12 months of the baseline blood draw using receiver operator characteristic curve analyses. The area under the receiver operating characteristic curve for survival at 12 months was 81.5% (95% CI, 74-89%) for CTC enumeration and 67.5% (95% CI, 58-77%) for 30% PSA decrements (C), and the P value for the comparison of these curves was 0.0218. These results show that CTC enumeration 9 to 12 weeks after treatment had superior predictive power compared with posttreatment PSA changes to predict death within 12 months of the baseline blood draw.

Table 2. Multivariate Cox regression OS analysis

A. Prognostic factors prior to the initiation of therapy in androgen-independent prostate cancer patients				
Variable	Categories		OS risk from baseline	
	Positive	Negative	HR (95% CI)	P*
Baseline CTC number	>5	<5	1.81 (1.10-2.97)	0.019
ECOG status at study entry	2 vs 1 vs 0		1.48 (1.05-2.08)	0.025
Baseline hemoglobin (g/dL)	Continuous		0.83 (0.71-0.96)	0.013
Baseline LDH (IU/mL) [†]	Continuous		1.00 (1.00-1.00)	<0.001
Baseline alkaline phosphatase (IU/mL) [†]	Continuous		1.00 (1.00-1.00)	0.449
Line of therapy	Continuous (1-6)		1.09 (0.87-1.36)	0.439
Type of therapy (taxotere: yes/no)	Yes	No	0.72 (0.45-1.17)	0.185
Bone metastasis?	Yes	No	1.60 (0.56-4.54)	0.376
B. Prognostic factors 9-12 weeks after initiation of therapy in androgen-independent prostate cancer patients				
9-12 wk CTC number	>5	<5	4.40 (2.43-7.97)	<0.001
ECOG status at study entry	2 vs 1 vs 0		2.50 (1.70-3.67)	<0.001
Line of therapy	Continuous (1-6)		1.16 (0.89-1.53)	0.277
Type of therapy (taxotere: yes/no)	Yes	No	1.22 (0.67-2.25)	0.515
9-12 wk PSA reduction from baseline (%) [†]	<30%	>30%	1.38 (0.77-2.47)	0.281

NOTE: See supplementary table for univariate analysis.

*P value from Wald test of Z statistic.

[†] Determined from serum drawn on the same date as the blood drawn for CTC.

Discussion

The present study adds to the growing body of evidence that CTC counts are prognostic and predict OS in multiple metastatic carcinomas (9–12, 15). This multicenter prospective study specifically showed that CTC number at different time points after treatment was the strongest independent predictor of OS in CRPC. These data clinically qualify the prognostic significance of baseline CTC and for the first time, show that posttreatment CTC number predicts survival after treatment. CTC number was more predictive than posttherapy changes in PSA, raising the likelihood that CTC number may be an intermediate end point of efficacy. Statistical confirmation of the ability of CTC counts to be an intermediate end point for drug approval, robustly predicting OS benefit, now requires further evaluation.

If CTC counts prove to be a surrogate of outcome, these could also potentially assist in guiding earlier discontinuation of ineffective treatment. This would be a significant advance because making therapeutic decisions in CRPC is frequently a major challenge for both patient and physician due to frequent

inconsistent changes in PSA, symptoms, and radiographic findings. A decision to discontinue treatment with inactive agents at an earlier time point could decrease morbidity from toxicity, reduce treatment costs, and allow patients to receive alternative management. Importantly, this earlier cessation of ineffective treatment could also potentially increase the pool of fit patients available for clinical trials investigating novel agents.

A large number of these molecularly targeted therapies—and their combinations—are now available for evaluation in clinical trials in patients with CRPC (1, 2). Currently, the development of such novel agents depends in large part on phase II trials with PSA reduction algorithm end points followed by the conduct, successful completion, and positive outcome of large randomized phase III studies with OS as the primary end point. These phase III trials require large patient numbers, high fiscal costs, and many years of follow-up. It is the continued need to measure OS as a primary end point in these trials and the lack of informative intermediate end points that reflect accurately whether a treatment is efficacious that has hindered the drug development process (3–7). Replacing this primary end point (the “true” end point) with another

Table 3. Median OS of Favorable and Unfavorable CTC and 30% and 50% PSA decrement groups in CRPC patients

Time Point	CTC/7.5 mL				30% PSA Reduction from baseline (%)				50% PSA Reduction from baseline (%)									
	n	≥5 (%)	Median OS	Log-rank P	N	<30 (%)	Median OS	Log-rank P	n	<50 (%)	Median OS	Log-rank P						
		<5	≥5	≥30%		<30%	≥50%	<50%										
2-5 wk	203	39	20.7	9.5	<0.0001	4.5	207	71	17.2	15.2	0.3653	1.2	207	83	17.5	16.2	0.56	1.2
6-8 wk	163	33	19.9	8.5	<0.0001	3.6	167	60	22.8	11.5	0.0011	2.2	167	75	22.8	14.4	0.01	2.1
9-12 wk	149	33	19.6	7.6	<0.0001	5.3	155	46	18.5	10.2	0.0007	2.2	155	59	19.6	10.8	0.0006	2.3
13-20 wk	143	31	19.8	6.7	<0.0001	6.5	142	41	17.7	8.7	<0.0001	2.9	142	46	17.7	9.9	0.0001	2.6

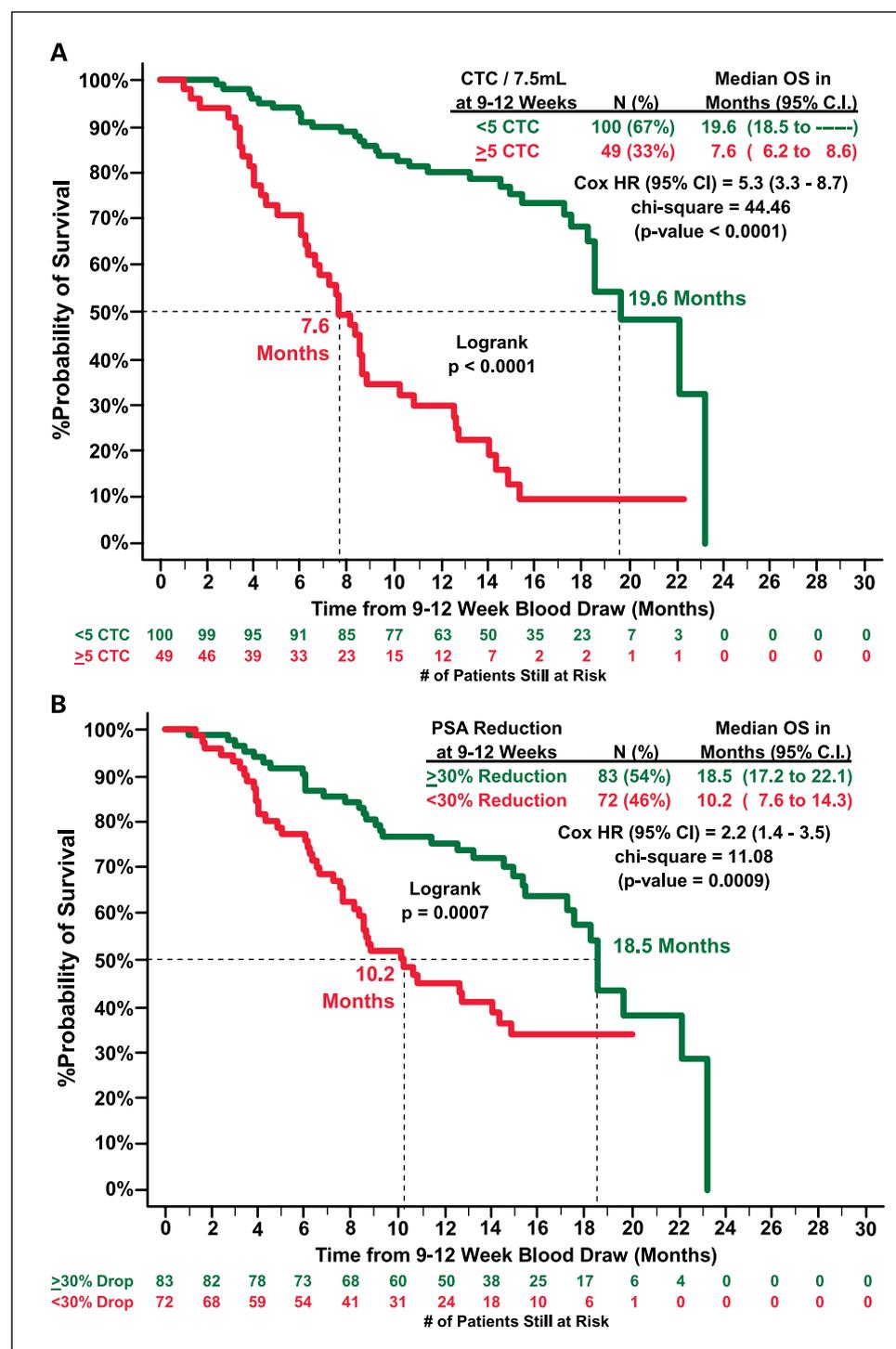


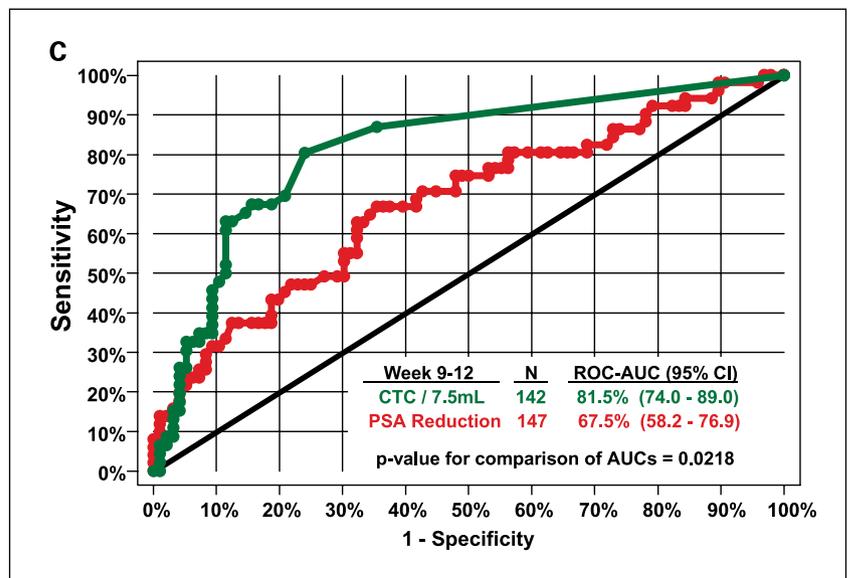
Fig. 3. A, Kaplan-Meier estimates of probabilities of OS of CRPC patients with Favorable (<5) and Unfavorable (≥5) CTC after 9 to 12 wk of therapy. B, Kaplan-Meier estimates of probabilities of OS of CRPC patients with Favorable, (≥30%) and Unfavorable (<30%), PSA decrements after 9 to 12 wk of therapy.

(a “surrogate” end point), which could be measured earlier, more conveniently or more frequently, and that would adequately reflect the clinical benefit of new treatments on the true end point has the potential to accelerate the determination of which treatments might be effective. The development of such biomarkers that accurately predict outcome remains, however, controversial and complex. The U.S. Food and Drug Administration have attempted to address this issue through a series of meetings on end points in advanced prostate cancer. No general consensus has yet been

reached at these meetings, although it has been agreed that surrogate markers allowing an earlier assessment of the utility of novel therapies expediting drug approval are urgently needed. The Oncology Biomarker Qualification Initiative provides the roadmap for these investigations.

Based on these data, we have now started using CTC as an exploratory end point in several trials of novel agents in patients with CRPC. The first clinical studies to do this were trials of abiraterone acetate, an inhibitor of the enzyme CYP17 and androgen synthesis and of a human monoclonal antibody to the

Fig. 3 Continued. C, receiver operator characteristic curves for the ability of CTC and 30% PSA reduction to predict death within 12 mo of the baseline draw 9 to 12 wk (C) after the initiation of therapy.



insulin-like growth factor-1 receptor (18, 19). It is envisioned that CTC will become a vital component of the evaluation of the antitumor activity of novel agents in phase II trials in this disease to optimize the selection of agents to be taken forward into phase III trials. Overall, although these data do not establish CTC as a true surrogate of outcome, they do support this claim (20, 21). Demonstrating true surrogacy remains complex and controversial with evolving statistical methodology. Establishing that CTC can be used as a surrogate for survival benefit will now require evaluation in multiple prospective, randomized phase 3 therapeutic trials, powered on survival end points and CTC as a biomarker, with meta-analytic analyses (22).

In summary, the measurement of CTC provides a useful prognostic determinant for CRPC patients. In addition, the comparison of CTC before and after treatment constitutes a predictor of outcome. It is envisioned that CTC will provide the surrogate end point that has been sought by the regulatory authorities for use in the efficacy assessment and expedited approval of novel anticancer therapies for the treatment of CRPC.

Disclosure of Potential Conflicts of Interest

L. Terstappen, C. Miller, and G. Doyle are employed by Immunicon, Inc., which funded this trial.

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