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

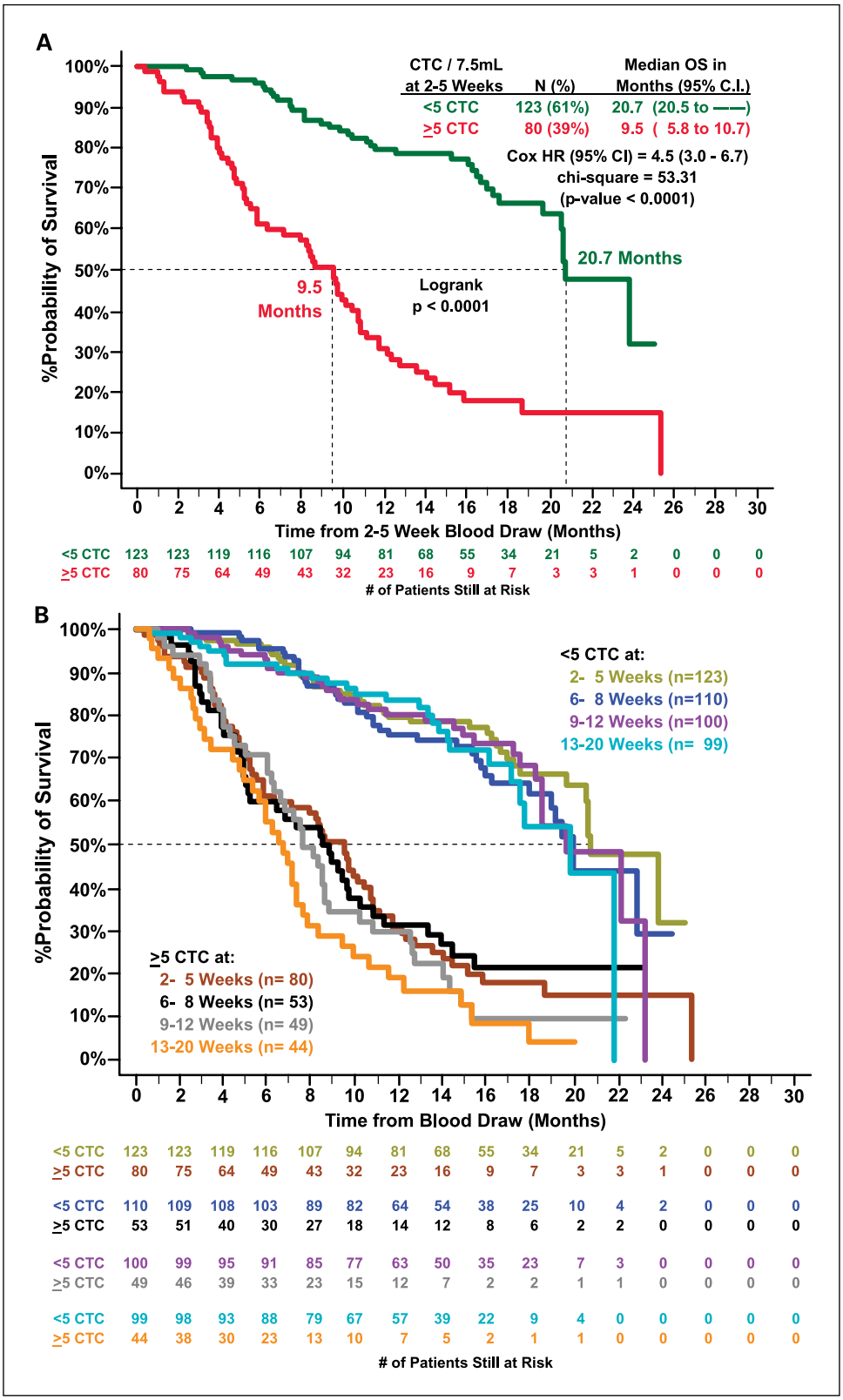

Fig. 2. Kaplan-Meier estimates of probabilities of OS of CRPC patients with Favorable (<5) and Unfavorable (≥5) CTC: *A,* 2 to 5 wk after initiation of therapy; *B,* 2 to 5, 6 to 8, 9 to 12, and 13 to 20 wk after initiation of therapy.

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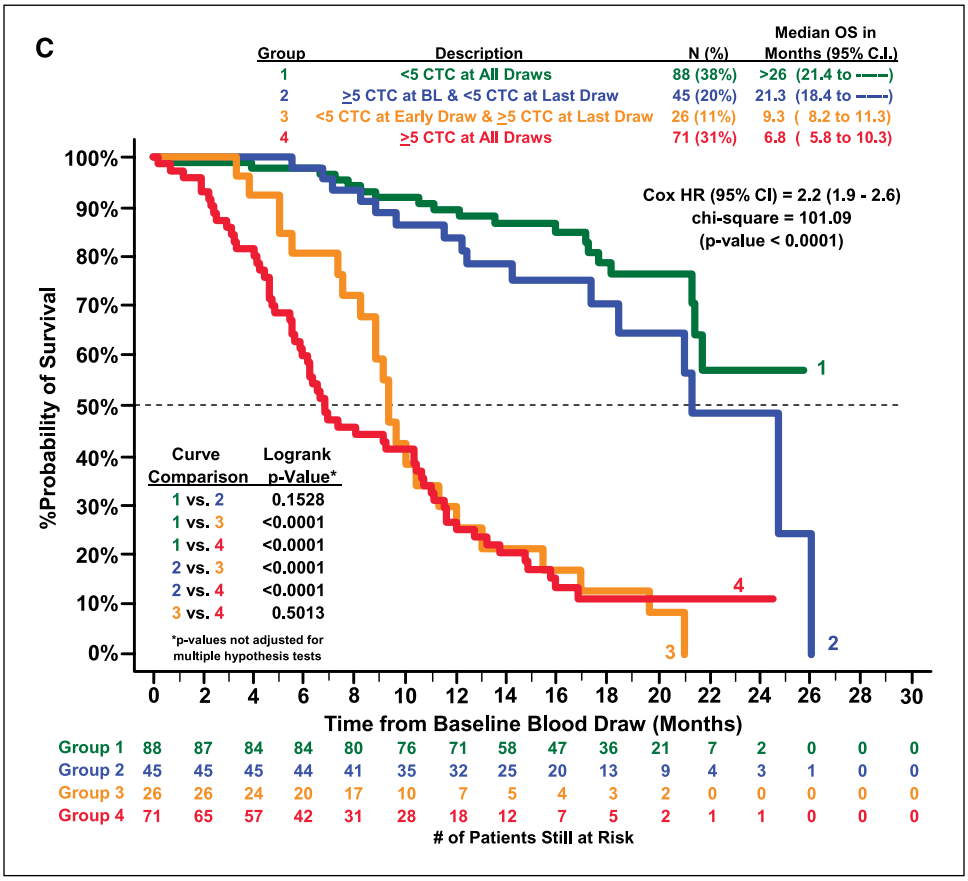

Fig. 2 *Continued.* *C,* patients whose CTC did or did not convert from the favorable or unfavorable groups after therapy.

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.

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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*	HR	N	<30 (%)	Median OS		Log-rank *P*	HR	*n*	<50 (%)	Median OS		Log-rank *P*	HR
			<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

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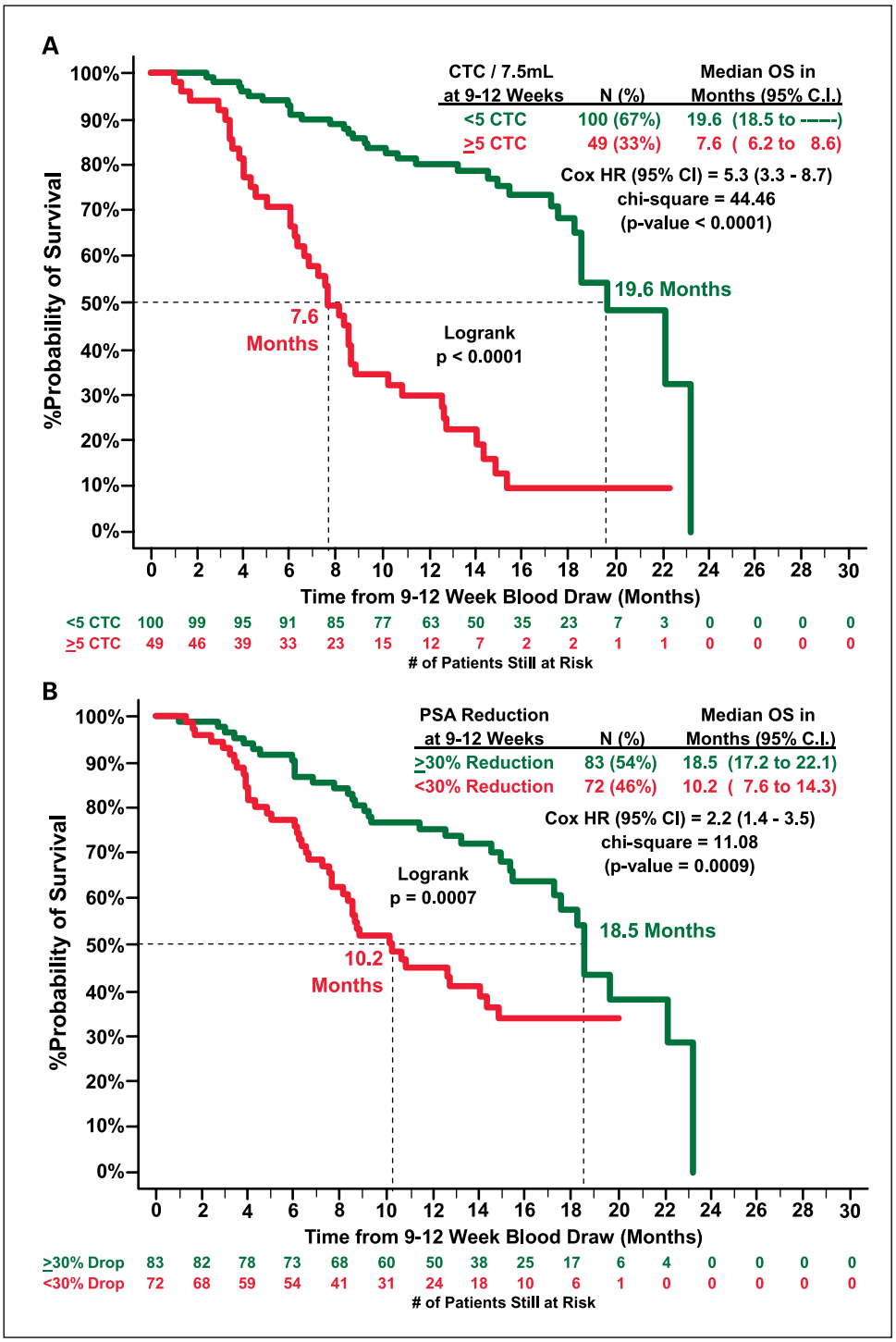

Fig. 3. *A,* Kaplan-Meier estimates of probabilities of OS of CRPC patients with Favorable (<5) and Unfavorable (≥5) CTC after 9 to 12 wk of therapy. *B,* Kaplan-Meier estimates of probabilities of OS of CRPC patients with Favorable, (≥30%) and Unfavorable (<30%), PSA decrements after 9 to 12 wk of therapy.

(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

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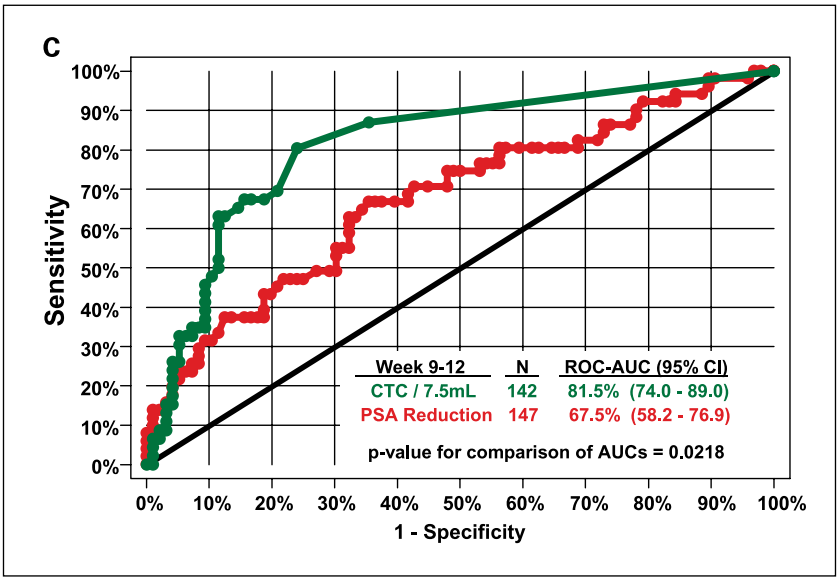

Fig. 3 *Continued. C,* receiver operator characteristic curves for the ability of CTC and 30% PSA reduction to predict death within 12 mo of the baseline draw 9 to 12 wk (*C*) after the initiation of therapy.

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

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