Circulating Tumor Cell Number as an Early Response Endpoint foMetastatic Prostate Cancer

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ABSTRACT

PURPOSE: Short-term response endpoints that predict survíval are a critical unmet need in metastatic castration-resistant prostate cancer (mCRPC). Using data from five randomized mCRPC trials, we studied baseline and week 13 prostate-specific antigen (PSA) levels and circulating tumor cell (CTC) counts as response endpoints that predict overall survival as indicators of clinical benefit for an individual patient and phase 2 trials.

METHODS: Three 13-week response endpoints were studied: (i) PSA50 (≥50% PSA decline from baseline), (ii) CTC0 (≥1 CTC/7.5 ml of blood at baseline and 0 CTCs at week 13, (iii) PSA50 *or* CTC0. The relative effectiveness of the response endpoints as predictors of overall survival was evaluated at the patient level (discrimination) and trial level (explained variation).

RESULTS: Evaluable patients totaled 3080. Patient level and trial level analyses were performed in the range 6-18 months of patient follow-up time. At the patient level, a CTC0 response resulted in an 18-month estimated survival probability equal to 0.78, which was greater than either PSA50 (0.66) and CTC0 *or* PSA50 (0.68). At the trial level, the information contained in the 18-month survival probability was best explained by either the proportion of CTC0 responders (R-squared = 0.51) or the proportion of CTC0 *or* PSA50 responders (R-squared = 0.53) relative to the proportion of PSA50 responders (R-squared = 0.46).

CONCLUSION: For the 3-month response endpoints considered, CTC0 alone or in combination with PSA50 (CTC0 *or* PSA50) provides stronger discrimination of survival times at the patient level and greater predictive accuracy at the trial level relative to the commonly applied PSA50 response endpoint. The results suggest that use of CTC0 as a treatment outcome in routine practice or clinical trials provides a measure of clinical benefit to guide management of an individual and further drug development.

INTRODUCTION

Metastatic castration-resistant prostate cancer (mCRPC), the lethal phenotype of the disease, is typically manifest by a rising prostate-specific antigen (PSA) and metastases to bone for which the traditional measures of response do not apply. The result is that prostate cancer drug approvals have been largely based on longer-term time to event endpoints. No drugs have been approved based on changes in PSA, the most widely used endpoint in phase 2 prostate cancer trials, or tumor regression although a RECIST partial response in a defined proportion of patients measurable soft tissue disease has led to a breakthrough designation by the United States Food and Drug Administration (FDA) for three PARP inhibitors. Urgently needed to assess response in bone, the most common site of spread, are analytically- and clinically-validated response biomarkers that can be assessed early and which reflect clinical benefit. Such biomarkers could improve management of an individual patients while shortening drug development times, reducing trial costs significantly, and increasing the number of agents that can be evaluated.

One potential response measure is a favorable change in the number of circulating tumor cells (CTCs) in blood enumerated with the U.S. FDA (FDA)-cleared CellSearch® platform (Menarini Silicon Biosystems, Huntington Valley, PA, USA). Well established in patients with prostate,[1] breast,[2] colorectal[3] and other cancers is that the pre-treatment detection of ≥5 CTCs/7.5 ml of blood (≥3 for colorectal), portends a poor prognosis, and that a post-treatment change to 4 or fewer CTCs/7.5 ml (≤2 for colorectal), an improved survival relative to cases in which this change is not observed. This endpoint, termed CTC conversion, is an FDA-cleared response indicator[4] to be used as an aid to monitoring disease that was studied in two phase 2 post-chemotherapy mCRPC trials of abiraterone acetate and prednisone and the phase 1/2 mCRPC trial of enzalutamide with similar eligibility criteria.[4,5] All three trials showed comparable rates of CTC detection and conversion in the post-chemotherapy setting, which led to a collaboration between the FDA, industry, and academia to address whether a post-treatment biomarker that included CTC number could be qualified as a surrogate for overall survival in mCRPC trials. Accordingly, the CTC biomarker question was embedded in a series of five randomized phase 3 registration trials, providing the data for this analysis.

In an analysis of first completed trial (COU-AA-301), we showed that a composite biomarker of CTC and lactate dehydrogenase, measured at 13 weeks, satisfied the four Prentice Criteria[6] for surrogacy at the individual patient level.[7] More recently, we showed across five

randomized phase 3 trials that a change from the pre-treatment detection of ≥1 (any) CTCs to zero (none) at 13 weeks post-treatment (termed "CTC0") provided the same discrimination in survival as the conversion from unfavorable (≥5) to favorable (≤4).[8] Both the CTC conversion and CTC0 response measures had a stronger discrimination of overall survival than did any proportional change in CTC count or PSA level from baseline. Use of a pre-treatment threshold of ≥1 CTC increased the percent of patients that could be evaluated for response to 75%, versus 51% using the FDA-cleared "conversion" measure with its pre-treatment threshold of ≥5 CTCs. Our attempts to show CTC0 as a surrogate of overall survival at the trial level were limited by the fact that CTC data had been recorded in only five randomized mCRPC trials. It is also unliklely that response measure that is assessed at 13 weeks would serve as a surrogate for overall survival in a phase 3 trial. Other reasons for the reduced expectation of showing surrogacy for overall survival with an early endpoint include trial designs that allowed patient cross-over upon progression, and the fact that as the number of approved and effective life-prolonging treatments increases, the likelihood that a patient would receive secondary treatments that influence the response-survival pathway would also increase.

Historically, phase 2 mCRPC trials use a defined PSA change from baseline, regression in measurable disease defined by RECIST when presen or intermediate-term time-to-event endpoints such as k-year radiographic progression–free survival or overall survival as the measures of clinical benefit. Here we explored whether any of three 3-month response endpoints defined by changes in PSA levels or CTC counts from baseline could predict survival 6 to 18 months after the start of therapy. To do so, we considered each arm of the aforementioned five randomized phase 3 studies as a separate phase 2 trial.

Our resulting analyses were performed at the patient level using discrimination (the separation between responder and non-responder survival curves) and at the trial level using explained variation (the accuracy in predicting k-month survival probability in a trial with the response proportion observed). The results support the use of the CTC0 response measure to guide management of the individual patient as well an indicator of treatment efficacy in the phase 2 setting to inform the decision to continue or discontinue the development of a drug.

METHODS

Patients and Response Measures

For this evaluation, we used individual patient data from five independent randomized phase 3 clinical trials for mCRPC (COU-AA-301 [ClinicalTrials.gov identifier NCT00638690], AFFIRM [NCT00974311], ELM-PC5 [NCT01193257], ELM-PC4 [NCT01193244], and COMET-1 [NCT01605227]).[9-13] The three response endpoints (PSA50, CTC0, PSA50 *or* CTC0) reflected favorable changes in CTC count and PSA levels from baseline (week 1) to 12 weeks later, at week 13. The evaluable study cohorts from each trial were patients who survived to at least week 13 and had a recorded baseline CTC and PSA value. The CTC0 response endpoint was defined as a change from a CTC count ≥1 at baseline to 0 at week 13; the PSA50 response endpoint by a ≥50% decline in PSA from baseline to week 13 among patients with PSA ≥5 ng/ml at the start of therapy. Patients who survived past week 13 but did not have their week 13 biomarkers recorded were defined as non-responders. Overall survival was measured from the start of week 13 to death or last follow-up. Also considered was a 30% (PSA30) and 70% (PSA70) decline in PSA, and CTC conversion.

Patient-Level Response Analysis

Patient-level analyses were undertaken to assess the clinical benefit of the CTC and PSA response endpoints, either individually or jointly, as a determinant of survival time in the ten independent cohorts represented by the individual arms of the five randomized trials. The evaluation was assessed by calculating the estimated probability of survival for responders (positive predictive value [PPV]) and the estimated probability of dying among non-responders (negative predictive value [NPV]). A clinically useful short-term response endpoint would produce good survival rates for responders and poor death rates for non-responders.

Trial-Level Response Analysis

A trial level analysis was constrained due to the availability of only10 treatment cohorts from the 5 randomized clinical trials. To expand this cohort set, the within treatment patient data were randomly divided into subgroups of size approximately 100. This approach increased the number of cohorts from 10 to 29 (pseudo trials) for the trial level analysis. For each of the 29 pseudo trials, the response proportion (CTC0, PSA50, CTC0 *or* PSA50) and the k-month Kaplan-Meier survival estimate were calculated and an R-squared for these 29 response/survival pairs was computed. This R-squared value provides a metric for the amount of survival information that is

contained in the response endpoint. A random resampling to create these 29 pseudo trials was repeated 1000 times and the average R-squared was used to summarize the response information content. In addition, to computing the average R-squared value for each of the three biomarker response endpoints, a 95% bootstrap confidence interval was is computed to compare the difference in the average R-squared values between the response endpoints.

RESULTS

A total of 6081 patients were treated in the five randomized trials, of whom 5660 (93%) survived until week 13 or more and 3080 (51%) met the requirement for inclusion in the analysis of a baseline CTC ≥1 and baseline PSA ≥5 ng/ml (Fig. 1). This common dataset was used to provide an equitable comparison between the response endpoints.

Table 1 shows the percentage of CTC0 and PSA50 responses, summarized by trial and treatment arm. Notable across the trials was that the CTC0 and PSA50 rates were greater for patients in the experimental arms relative to the control arms some of which included a placebo with or without prednisone, neither of which have been shown to prolong life. In the control arm cohorts, PSA50 rates in trials that included prednisone were comparable to CTC0 rates, but in four of the five experimental arm cohorts, PSA50 rates were higher.

PSA50 and CTC0 Based Response Endpoints

The attainment of a CTC or PSA response, based on order of increasing prevalence (%), averaged over the ten cohorts with 3080 patients, was: PSA70 (15%); CTC0 (19%); PSA50 (21%); PSA30 (29%); and PSA50 *or* CTC0 (30%). The prevalence of a CTC conversion response was 23%, based on a smaller cohort of 2113 evaluable patients with ≥5 CTC at baseline. The individual and trial level results for PSA30, PSA70, CTC conversion were comparable to or weaker than the results for CTC0 and PSA50. As a result, our focus is on comparing the CTC0 and PSA50 response endpoints. The results for all other endpoints are included in the Supplemental Section.

Patient-Level Response Analysis

The patient-level endpoint analyses was evaluated utilizing the probability of surviving among responders (PPV) and the probability of dying among the nonresponder (NPV). Table 2 and

Figure 2a provides the positive predictive value and the negative predictive value for the three response endpoints over 6 to 18 months of follow-up. At 18 months the PPV was 0.78 for a CTC0 response, 0.66 for a PSA50 response, and 0.68 for a CTC0 or PSA50 response. As such, the 3-month CTC0 response endpoint was the best at identifying patients with the greatest survival benefit. The most pronounced difference in PPV occured between CTC0 and PSA50, where the difference at 18 months was 0.12 (95% confidence interval for this difference was [0.06, 0.16]). Among non-responders, the response endpoint CTC0 *or* PSA50 improved the negative predictive value [NPV] when compared to CTC0 alone or PSA50 alone (Table 2, Figure 2b) where the 18 month probabilities of dying were 0.70 (PSA50 *or* CTC0), 0.67 (CTC0), and 0.62 (PSA50). The 95% confidence interval for the difference in the probability of dying within 18 months between patients that did not respond by CTC0 and PSA50 was (0.03, 0.07). The magnitude of this difference was even greater when comparing CTC0 *or* PSA50 to PSA50 alone (0.06,0.10). The data indicates that at the patient level, a favorable response provided greater discrimination in the survival probabilities in contrast to a nonresponse and the use of either CTC0 alone or in combination with PSA50 (CTC0 *or* PSA50) improved our understanding of patient survival in comparison to the response endpoint PSA50 alone.

Trial-Level Response Analysis

The trial-level response analysis examines the effect of replacing the survival probability endpoint with a response endpoint when designing a phase 2 clinical trial. The average R-squared value for each response endpoint for the probability of survival from 6 to 18 months is listed in Table 3 and Figure 3. Overall, the information in survival time is best explained by the CTC0 *or* PSA50 response endpoint, with a PSA50 response providing the least survival information. At 18 months, the average R-squared value for CTC0 *or* PSA50 was 0.53. For CTC0 alone and PSA50 alone, the R-squared values were 0.51 and 0.46, respectively. To evaluate the added value of CTC0 to the PSA50 response endpoint, a 95% bootstrap confidence interval for the difference in R-squared values between CTC0 *or* PSA50 versus PSA50 was computed. At 18 months, this difference was 0.07 (95% CI: 0.05-0.10), indicating that augmenting PSA50 with CTC0 improves the trial endpoint. The estimates and 95% confidence intervals for the difference in R-squared values for all pairwise comparisons are included in Figure S2.

DISCUSSION

Defined response measures that represent a pre-specified change in a disease manifestation from baseline that can be measured reliably and reported consistently are biomarkers that can be associated with clinical outcomes. Many of those used in trials or to guide patient management in practice have not been shown independently to reflect patient benefit as defined in regulatory terms as an improvement in how a patient feels, functions or how long he survives. For the mCRPC population and others, survival time is the most meaningful benefit, and post-treatment response measures that accurately predict and maximally distinguish between high vs. low survival rates over time are a critical unmet need. Here we showed that the utilization of CTC0 advances our understanding of survival at the patient level and at the trial level.

Patient level analyses evaluate whether a favorable response translates into longer-term survival and a non-response into an early death. Trial level analyses examine whether the percentage of responders for a patient cohort is predictive of the cohort's k-month survival probability. Our results showed that at the patient level, the use of CTC0 either alone or in combination with PSA50 (CTC0 *or* PSA50) as a response endpoint measured at 13 weeks provided higher survival rates among responders and a higher estimated probability of dying among nonresponders over a 6 to 18 month period relative to PSA50 alone, the most commonly used outcome in prostate cancer clinical trials. At the trial level, the response endpoint CTC0 *or* PSA50 was also more accurate than PSA50 in predicting the survival probabilities during this same time interval.

Traditional analyses of clinical trial endpoints as surrogates for survival are derived from phase 3 studies and require that the treatment effect shown by the comparison of two treatments on survival is almost fully explained by the surrogate. The analyses are carried out at the patient level and the trial level, with measures of discrimination and explained variation producing R-squared values typically above 0.75, an extraordinarily high bar to attain. A limitation in determining trial level surrogacy here was that there were only 5 randomized trials available for study.

The approach applied here does not require the discrimination and explained variation metrics to surpass an idealized threshold, rather the assessments of PSA and CTC response endpoints are compared to each other and the relative survival benefit of the response endpoints defined are determined by which provides a better reflection of the intermediate-term k-month

survival probability endpoint in the single-arm phase 2 setting. The degree of rigor used to validate the relative benefit of the response endpoints based on their survival prediction establishes CTC0 either alone or in combination with PSA50 as a meaningful response endpoint for the management of an individual and in phase 2 trials as a measure of clinical benefit and to determine whether a drug should be considered for further development in large scale definitive trials. It also provides an early measure of clinical benefit for patients with disease limited to bone, the most frequent site of metastatic spread, increasing the number of patients who can be evaluated in the phase 2 setting.

Recently, radiographic progression–free survival (rPFS) was accepted as a clinical trial endpoint to support regulatory approvals for drugs on the basis of its strong association with survival at the patient level.[14,15] Missing in the rPFS endpoint analyses is the determination of whether the strong association is maintained at the trial level, as has been demonstrated here with CTC0 *or* PSA50, and separately for metastasis free survival.(REF) Anticipated is that future studies will fill in this gap and by including the monitoring of CTC counts longitudinally over time to enable the creation of a time to CTC progression endpoint that can also be evaluated in relation to survival, both of which would provide valuable information on how best to use each of these biomarkers in practice. Establishing trial-level surrogacy will require more phase 3 trials evaluating a larger range of drug classes.

The availability of seven life-prolonging drugs, an eighth with a tissue-agnostic accelerated approval for progressing microsatellite instability high (MSI-H) or mismatch repair deficient (dMMR) tumors that are infrequent in prostate cancer,[16,17] and two more with a breakthrough designation[18,19] has changed the outlook for men with the disease. At the same time, it is now more difficult to show a survival benefit for future drugs because of the availability and use of these life-prolonging therapies after discontinuation of protocol therapies, increasing the need for short-term response measures that can be assessed early and which reflect clinical benefit.

Here we have defined a reliable, reproducibly measured and biologically plausible short-term response endpoint, CTC0 alone or in combination with PSA50, determined with an analytically valid FDA-cleared CTC assay that provides consistent prediction of survival across 10 independent patient cohorts. Use of the endpoint would increase the percentage of patients with mCRPC who can be evaluated for response in the phase 2 setting and shorten the time

needed to identify drugs worthy of evaluation in a definitive phase 3 registration trial and the discontinuation of those that are inactive. At the same time, these earlier endpoints of efficacy can also better inform the decision to continue or discontinue a therapy when managing the individual patient, allowing alternative approaches to be started sooner while sparing the toxicity of treatments that are not providing benefit. The result is that the pace of clinical research in the mCRPC space would be accelerated, needed drugs would be made available sooner and the costs of a clinical trial significantly reduced so that more treatments to be evaluated.

Table 1. Patients in each of the 10 cohorts evaluable* for week 13 response with CTC0 and PSA50 response measures (n=3080), and prevalence of response to all combinations of each measure (19% overall for CTC0, 21% overall for PSA50)

Trial	Evaluable patients in both arms	Experimental arm			Control arm		
		No. evaluable patients	CTC0 responders, n (%)	PSA50 responders, n (%)	No. evaluable patients	CTC0 responders, n (%)	PSA50 responders, n (%)
COU-AA-301	647	428	116 (27)	146 (34)	219	22 (10)	13 (6)
AFFIRM	326	219	59 (27)	99 (45)	107	3 (3)	2 (2)
ELM-PC5	645	432	82 (19)	104 (24)	213	15 (7)	17 (8)
ELM-PC4	824	414	120 (29)	161 (39)	410	98 (24)	86 (21)
COMET-1	638	431	52 (12)	30 (7)	207	6 (3)	1 (0.4)
Total	3080	1924	429 (22)	540 (28)	1156	144 (12)	119 (10)

*Baseline PSA ≥5 ng/ml, baseline CTC ≥1, and survival till at least week 13.

Abbreviations: CTC, circulating tumor cell; CTC0, CTC count ≥1 at baseline and 0 at week 13; PSA, prostate-specific antigen; PSA50, PSA level ≥5 ng/ml at baseline and ≥50% decline from baseline to week 13.

Table 2. Survival probabilities for responders (PPV) and probability of dying for nonresponders (NPV). 19% were responders for CTC0, 21% were responders for PSA50, and 30% were responders for CTC0 *or* PSA50. There were a total of 3080 evaluable patients.

	CTC0		**PSA50**		**CTC0 *or* PSA50**	
Month	**Responders (PPV)**	**Non-responders (NPV)**	**Responders (PPV)**	**Non-responders (NPV)**	**Responders (PPV)**	**Non-responders (NPV)**
6	0.99	0.11	0.99	0.11	0.99	0.13
7	0.98	0.17	0.96	0.16	0.97	0.19
8	0.97	0.22	0.95	0.21	0.96	0.25
9	0.96	0.28	0.92	0.26	0.93	0.30
10	0.94	0.33	0.89	0.31	0.90	0.36
11	0.91	0.39	0.86	0.37	0.86	0.42
12	0.89	0.45	0.83	0.42	0.84	0.48
13	0.87	0.49	0.81	0.46	0.81	0.52
14	0.86	0.53	0.79	0.50	0.79	0.57
15	0.83	0.56	0.75	0.53	0.76	0.60
16	0.80	0.61	0.71	0.57	0.73	0.64
17	0.79	0.65	0.68	0.60	0.70	0.68
18	0.78	0.67	0.66	0.62	0.68	0.70

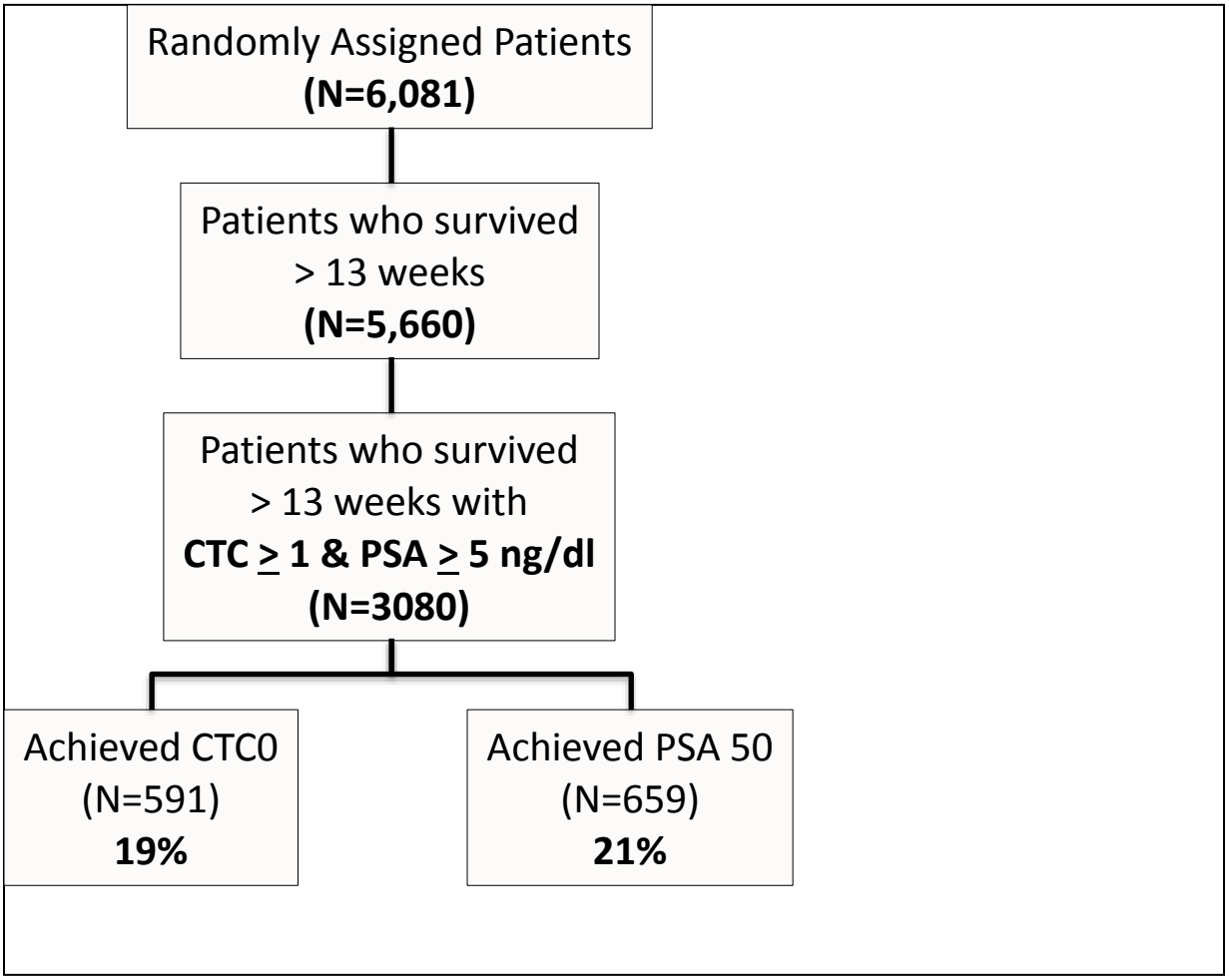
Abbreviations: CTC, circulating tumor cell; CTC0, CTC count ≥1 at baseline and 0 at week 13; PSA, prostate-specific antigen; PSA50, PSA level ≥5 ng/ml at baseline and a ≥50% decline from baseline to week 13; NPV, negative predictive value; PPV, positive predictive value.

Table 3. Trial-level R-squared value for CTC0, PSA50, CTC0 *or* PSA50

Month	CTC0	PSA50	CTC0 *or* PSA50
6	0.55	0.48	0.56
7	0.62	0.53	0.63
8	0.60	0.54	0.62
9	0.59	0.54	0.62
10	0.63	0.55	0.64
11	0.62	0.55	0.63
12	0.60	0.54	0.61
13	0.59	0.52	0.60
14	0.60	0.55	0.62
15	0.55	0.51	0.57
16	0.56	0.52	0.59
17	0.54	0.49	0.57
18	0.51	0.46	0.53

Abbreviations: CTC, circulating tumor cell; CTC0, CTC count ≥1 at baseline and 0 at week 13; PSA, prostate-specific antigen; PSA50, PSA level ≥5 ng/ml at baseline and a ≥50% decline from baseline to week 13.

Figure S1: CONSORT Diagram



Supplemental Table S1: CTC conversion. Survival probabilities for responders and non-responders (23% of 2113 patients were responders with response defined as CTC count ≥5 at baseline and ≤4 at week 13); trial-level R-squared value for CTC conversion

	Individual Level		**Trial Level**
Month	PPV	NPV	R-Squared
6	0.98	0.16	0.27
7	0.97	0.23	0.35
8	0.96	0.30	0.39
9	0.93	0.37	0.38
10	0.89	0.43	0.41
11	0.86	0.51	0.37
12	0.80	0.57	0.35
13	0.78	0.61	0.35
14	0.76	0.65	0.35
15	0.72	0.69	0.32
16	0.67	0.73	0.34
17	0.63	0.77	0.26
18	0.61	0.79	0.22

Abbreviations: CTC, circulating tumor cell; CTC conversion, CTC count ≥5 at baseline and ≤4 at week 13; NPV, negative predictive value; PPV, positive predictive value.

Supplemental Table S2: PSA30. Survival probabilities for responders and non-responders (29% of 3080 patients were responders with response defined as ≥30% decrease in PSA from baseline to week 13); trial-level R-squared value for PSA30

	Individual Level		**Trial Level**
Month	PPV	NPV	R-Squared
6	0.97	0.12	0.47
7	0.95	0.17	0.53
8	0.93	0.23	0.53
9	0.90	0.28	0.53
10	0.88	0.34	0.54
11	0.84	0.39	0.53
12	0.81	0.45	0.52
13	0.79	0.49	0.51
14	0.75	0.52	0.54
15	0.72	0.55	0.49
16	0.69	0.60	0.51
17	0.66	0.63	0.48
18	0.63	0.65	0.45

Abbreviations: NPV, negative predictive value; PPV, positive predictive value; PSA, prostate-specific antigen; PSA30, PSA level ≥5 ng/ml at baseline and a ≥30% decline from baseline to week 13.

Supplemental Table S3: PSA70. Survival probabilities for responders and non-responders (15% of 3080 patients were responders with response defined as ≥70% decrease in PSA from baseline to week 13); trial-level R-squared value for PSA70

	Individual Level		**Trial Level**
Month	PPV	NPV	R-Squared
6	0.99	0.10	0.42
7	0.97	0.15	0.47
8	0.96	0.20	0.48
9	0.94	0.25	0.48
10	0.92	0.30	0.49
11	0.89	0.35	0.49
12	0.86	0.40	0.48
13	0.84	0.44	0.46
14	0.81	0.48	0.49
15	0.78	0.51	0.44
16	0.77	0.55	0.46
17	0.75	0.58	0.44
18	0.72	0.60	0.41

Abbreviations: NPV, negative predictive value; PPV, positive predictive value; PSA, prostate-specific antigen; PSA70, PSA level ≥5 ng/ml at baseline and a ≥70% decline from baseline to week 13.

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Figure 2. Survival probability estimates over months 6 to 18. Survival probabilities are averaged over the 10 trial/treatment Kaplan-Meier estimates. **(a)** The black line indicates survival probability for patients with CTC0 response, the red line indicates survival probability for patients with PSA50 response, and the green line indicates survival probability for patients with either a CTC0 or PSA50 response. These survival probabilities represent the positive predictive value of the response measures. **(b)** The black line indicates the probability of dying for patients without a CTC0 response, the red line indicates the probability of dying for patients without a PSA50 response, and the green line indicates the probability of dying for patients without either a CTC0 or PSA50 response. The probabilities of dying represent the negative predictive value of the response measures.

Figure 3. Variation in k-month survival probability estimate explained by response proportion. Each trial/treatment was divided randomly into cohorts of approximately 100 patients. This random division was repeated 1000 times and the lines indicate the average R-squared value per month, black for the CTC0 response measure, red for PSA50 and green for CTC0 or PSA50.

Figure S1. (a) The differences in the positive predictive values for each pair of response measures and their attendant 95% confidence intervals. **(b)** The differences in the negative predictive values for each pair of response measures and the 95% confidence intervals for these differences.

Figure S2. The differences in the R-squared values for each pair of response measures and the 95% confidence intervals for these differences.