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Baseline circulating tumor cell count as a prognostic marker of PSA response and disease progression in metastatic castrate sensitive prostate cancer (SWOG S1216)

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Abstract

PURPOSE: In metastatic castrate sensitive prostate cancer (mCSPC), combined androgen axis inhibition is a standard of care. Noninvasive biomarkers that guide initial therapy decisions are needed. We hypothesized that CellSearch CTC count, an FDA-cleared assay in metastatic castrate resistant PC (mCRPC), is a relevant biomarker in mCSPC.

METHODS: SWOG S1216 is a phase 3 prospective randomized trial of androgen deprivation therapy (ADT) combined with orteronel or bicalutamide for mCSPC. CellSearch CTC count was measured at registration (baseline). Prespecified CTC cutpoints of 0, 1–4 and 5 were correlated with baseline patient characteristics and, in a stratified subsample, were also correlated with two prespecified trial secondary endpoints: 7-month PSA 0.2 ng/ml vs. 0.2–4.0 vs. >4.0 (intermediate endpoint for overall survival); and progression-free survival (PFS) vs. >2 years.

RESULTS: 523 patients submitted baseline samples, and CTCs were detected (median 3) in 33%. Adjusting for two trial stratification factors (disease burden and timing of ADT initiation), men with undetectable CTCs had nearly 9-times the odds of attaining 7-month PSA 0.2 vs. >4.0 (odds ratio [OR] 8.8, 95%CI 2.7–28.6, $p < 0.001$, $N=264$) and 4-times the odds of achieving >2 years PFS (OR 4.0, 95%CI 1.9–8.5, $p < 0.001$, $N=336$) compared to men with baseline CTCs 5.

CONCLUSION: Baseline CTC count in mCSPC is highly prognostic of 7-month PSA and 2-year PFS after adjusting for disease burden and discriminates men who are likely to experience poor survival outcomes.

Keywords

circulating tumor cells; liquid biopsy; metastatic castrate sensitive prostate cancer; biomarker; clinical trials

Introduction

Prostate cancer is the most common malignancy and the second leading cause of cancer mortality in U.S. men, with an estimated 31,620 deaths in 2019.¹ Of particular concern, the incidence of disseminated disease has increased significantly over the past decade.² For metastatic castrate sensitive prostate cancer (mCSPC), androgen deprivation therapy (ADT) constitutes the foundation of systemic therapy, and combining ADT with chemotherapy or with newer androgen receptor signaling inhibitors (ARSIs) further extends survival.^{3–9} Despite these advances, a subset of patients with mCSPC will experience disease progression within a year, and identifying these men upfront is the key to further improving overall survival outcomes.¹⁰ The degree of PSA reduction at month seven after initiation of ADT (7-month PSA) has previously been shown to constitute an intermediate endpoint for overall survival (OS).^{11,12} In particular, men whose PSA was above 4.0 ng/ml at 7 months have a strikingly poor median OS of just 18 months. Yet, by the time the 7-month PSA becomes available to identify men in this poor prognosis category, the window of opportunity to treat these patients “upfront” with further intensification or with novel agents through ongoing trials may have been lost. There are currently no biomarkers in clinical use to identify these poorest responders at the start of systemic therapy.

Circulating tumor cells (CTCs) are shed from tumor sites throughout the body and can be captured and analyzed from a minimally invasive peripheral blood draw.^{13,14} In more advanced metastatic castrate resistant prostate cancer (mCRPC), CTC count using the FDA-cleared CellSearch assay has been extensively evaluated as a biomarker by our group and others and shown to correlate with treatment response and overall survival.^{15–20} In mCSPC, CTC count has been correlated with response to ADT and progression free survival (PFS) in a few small studies conducted before the era of intensified combination therapy.^{21–24}

Based on these data, we tested whether baseline CTC count using the CellSearch platform is independently associated with 7-month PSA response and disease progression in men with mCSPC initiating hormonal therapy in S1216, a phase 3 prospective randomized trial of ADT combined with either orteronel or bicalutamide coordinated by SWOG on behalf of the NCI-sponsored National Clinical Trials Network in collaboration with Alliance, ECOG-ACRIN and NRG.

Materials and Methods

Clinical Cohort:

The clinical trial and correlative studies were approved by the Cancer Therapy Evaluation Program (CTEP) and by the Central Institutional Review Board (CIRB), as well as by the IRBs of all participating centers. Written informed consent was obtained from all subjects, and the studies were conducted in accordance with the ethical guidelines set forth in the U.S. Common Rule.²⁵ S1216 is a phase 3 randomized trial for men with newly diagnosed mCSPC initiating therapy. Trial subjects were randomized from 3/1/2013 to 7/15/2017 in a 1:1 ratio to treatment with ADT plus either orteronel (CYP17 inhibitor) or bicalutamide. ADT and bicalutamide were administered per standard of care: ADT in the form of an LHRH agonist, and bicalutamide 50 mg orally once a day. Orteronel was administered at 300 mg orally twice daily. Treatment allocation was balanced by three stratification factors: disease severity limited to vertebrae and/or pelvic bones and/or lymph nodes (minimal) vs. extending to other areas (extensive), ADT initiated within the month prior to enrollment or after enrollment, and Zubrod performance status (0–1 vs. 2–3). As worse performance status was strongly correlated with extensive disease, it was not included as an adjustment factor in these analyses because it was redundant. Subjects whose baseline CTCs were drawn >30 days after randomization (n=10) were excluded from these analyses. The trial accrual goal was 1186 eligible subjects, with a primary endpoint of overall survival (OS). Secondary endpoints included progression-free survival (PFS) and 7-month PSA (28 weeks post-randomization), specifically dropping to 0.2 ng/ml, 0.2–4.0 ng/ml, or >4.0 ng/ml, previously shown to be an intermediate endpoint for OS.^{11,12} The trial's primary endpoint of randomized treatment outcome comparisons will be reported when the OS data mature in approximately 12 months. The current baseline CTC analysis with comparison to baseline patient characteristics, 7-month PSA, and 2-year PFS were approved by the DSMC in October 2019. The analysis of associations between baseline CTCs and patient characteristics was permitted for the entire cohort, whereas the analysis of 7-month PSA and 2-year PFS was approved with the provision that these clinical outcomes be analyzed across treatment arms using randomly selected, equal-sized patient subsets. This was stipulated in order to preserve equipoise and avoid hinting at treatment effects (e.g. more CTCs or longer PFS in a given treatment arm) before the primary OS endpoint matures.

Sample collection and processing:

Liquid biopsy translational studies were integrated in S1216 as a CTEP/CIRB approved amendment to the protocol and informed consent. At study entry ("baseline") and again at progression to mCRPC, a CellSave preservative tube of blood (7.5ml) was drawn by standard peripheral venipuncture. Immediately after blood draw, the tube was packed into a pre-labeled mailing kit provided in advance by the investigators and mailed by overnight FedEx at room temperature to the Goldkorn Laboratory at the USC Norris Comprehensive Cancer Center Liquid Biopsy Core. Upon receipt, blood samples were processed on the CellSearch platform by certified technicians according to manufacturer instructions as done previously.²⁰ Briefly, CellSearch employs immunomagnetic beads to enrich CTCs by targeting cell surface epithelial cell adhesion molecule (EpCAM), followed by identification via immunofluorescent staining of cytokeratins (CK), CD45 (leukocyte antigen), and nuclear

4',6-diamidino-2-phenylindole (DAPI). Candidate CTCs (CK+CD45-DAPI+) are enumerated in a semi-automated manner by an integrated imaging algorithm, followed by operator verification.

Data analysis:

Baseline CellSearch CTC counts were collected and processed without access to the clinical data, and then CTC count data were submitted to the SWOG Statistical Center for univariate correlation with baseline disease and patient characteristics and two clinical outcomes. Correlations of CTC counts with baseline factors were evaluated using the Kruskal-Wallis test.

As the primary OS analysis has not yet been reported, this analysis was focused on 7-month PSA and 2-year PFS endpoints. A dichotomous cutoff for PFS was required by the DSMC to conceal the full distribution, and 2 years was chosen as the approximate median in the standard arm. Sampling by treatment arm and clinical outcome can be seen in Figure 1. To preserve clinical equipoise and ensure equal representation and sufficient sample sizes from each treatment arm and outcome category of interest, a random sample equal to the number in the smallest cell was taken from each of the larger cells. CTC cutpoints used were 0 vs. 1–4 vs. 5, based on prior associations identified in mCSPC in SWOG S0925.²³

Outcomes were defined as follows: 7-month PSA response was defined as complete response (CR) for PSA ≤ 0.2 ng/ml, partial response (PR) for 0.2 < PSA ≤ 4.0 ng/ml, and no response (NR) for PSA > 4.0 ng/ml. Patients who did not have PSA submitted for this timepoint were considered non-responders. PFS was defined as time from randomization to date of first occurrence of progression, symptomatic deterioration, or death from disease, where progression was defined as 25% relative and 2 ng/ml absolute increase in PSA from nadir, or 20% increase in sum of diameters of soft tissue lesions on CT or MR (per RECIST 1.1), or two or more new bone lesions on bone scan. 7-month PSA was evaluated across pooled treatment arms and adjusted for two pre-specified S1216 stratification factors: disease severity (extensive vs. minimal) and ADT status prior to enrollment (already initiated or not). These factors were prespecified in the clinical protocol, and treatment allocation was dynamically balanced for them. Hence, the CTC vs. 7-month PSA model was also adjusted for these factors in order to closely reflect the underlying study design of the trial.

For 2-year PFS, if a subject progressed or died within 730 days after registration, they were counted as having a 2-year PFS event. Subjects without progression or death within 730 days were counted as having no event. All subjects censored prior to 730 days were excluded from both analyses (n=15). For association with 7-month PSA response, multinomial logistic regression (generalized logit model) was used to assess CTC count (categories: 0, 1–4, 5) as a potential prognostic factor of 7-month PSA complete response (CR) and partial response (PR). As with 7-month PSA, 2-year PFS was evaluated across pooled treatment arms and adjusted for two pre-specified S1216 stratification factors: disease severity (extensive vs. minimal) and ADT status prior to enrollment (already initiated or not). This method models two response functions (outcomes) at once instead of one binary outcome. For association with 2-year PFS, CTC counts (categories: 0, 1–4, 5)

were evaluated using logistic regression across pooled treatment arms as a potential prognostic factor of PFS event within the first 2 years on study, adjusting for the two pre-specified stratification factors. To evaluate other CTC cutpoints that had been previously reported,^{15–20} we also conducted supportive analyses examining CTC 0 vs. 1 (undetectable/detectable) and CTC < 5 vs. 5 and CTC 0 vs. 1–4 vs. 5–9 vs. 10. All reported p-values are two-sided. A significance level of 0.05 is considered statistically significant in this report.

Results

Study cohort:

S1216 opened on 3/1/13 and closed to accrual on 7/15/17 with a total of 1313 subjects enrolled. CTC collection through a protocol amendment was initiated on 8/1/14 and implemented at participating sites by 10/30/14, by which time 518 subjects had already enrolled, leaving an additional 795 to be accrued. A total of 523 baseline CTC samples (489 candidates for analysis) were collected from these remaining accruals (66% submission rate) and analyzed by CellSearch, of whom the analysis subsets for 7-month PSA response and 2-year PFS included 264 and 336 patient samples, respectively (Figure 1). Baseline patient characteristics for the full CTC patient cohort and correlation with baseline CTC category are presented in Table 1. Notably, the men included in this cohort were characterized by a favorable clinical presentation: A majority (78%) denied bone pain, did not have visceral metastases (88%), and had Zubrod performance status of 0–1 (96%). CTCs were detected at baseline in 33% of men in this cohort. Roughly 64% of these CTC+ subjects had 1–4 CTCs / 7.5ml and 36% had 5 or more CTCs. Among men with detectable CTCs, the median CTC count was 3. Higher baseline CTC counts were statistically significantly positively correlated with higher PSA, higher alkaline phosphatase, and lower hemoglobin levels at study entry. Higher baseline CTC counts were also statistically significantly correlated with presence of bone metastases, presence of bone pain, presence of extensive disease, and worse performance status at study entry (all $p < 0.01$).

Association of baseline CTC count with PSA response (n=264):

Association of baseline CTC count with 7-month PSA was analyzed using the categories of 0, 1–4, or 5 CTCs / 7.5 ml and adjusting for trial stratification factors of disease severity (extensive vs. minimal) and ADT status prior to enrollment (already initiated or not) (Figure 2). Compared to men having 5 CTCs, men with 0 CTCs had an odds ratio (OR) of 8.8 ($p < 0.001$) for complete PSA response (< 0.2 ng/ml), and an OR of 2.5 ($p = 0.03$) for partial PSA response (0.2–4.0 ng/ml) relative to no PSA response (> 4.0 ng/ml) 28 weeks after randomization on protocol. Compared to men with 1–4 CTCs, men with 0 CTCs had a trend towards greater odds of a complete (OR 1.3, $p = 0.45$) and partial (OR 1.1, $p = 0.74$) PSA responses that did not reach statistical significance. A univariate regression model of baseline CTC count with 7-month PSA not adjusting for the stratification covariates showed very similar associations: In men with 0 CTCs vs. men with 5 CTCs, OR 9.3 ($p < 0.001$) for complete PSA response and OR 2.6 ($p = 0.02$) for partial response, and non-significant trends toward greater response in men with 0 CTCs vs. men with 1–4 CTCs.

Association of baseline CTC count with 7-month PSA was also analyzed using other relevant cutpoints (Figure 3). Using the traditional CellSearch cutpoint of <5 vs. ≥ 5 CTCs previously validated in mCRPC,^{15–20} men with <5 CTCs had an odds ratio (OR) of 8.1 ($p<0.001$) for complete PSA response and an OR of 2.4 ($p=0.03$) for partial PSA response (Figure 3A). Using a cutpoint of 0 vs. ≥ 1 CTCs recently proposed in mCRPC,¹⁸ men with 0 CTCs had an odds ratio (OR) of 2.5 ($p=0.007$) for complete PSA response and an OR of 1.6 (not statistically significant) for partial PSA response (Figure 3B).

Association of baseline CTC count with 2-year PFS (n=336):

Association of baseline CTC count with 2-year PFS was analyzed using the categories of 0, 1–4, or ≥ 5 CTCs / 7.5 ml and adjusting for trial stratification factors of disease severity (extensive vs. minimal) and ADT status prior to enrollment (already initiated or not) (Figure 4). Of men with ≥ 5 baseline CTCs, 74% experienced a PFS event by 2 years, vs. 64% of men with 1–4 CTCs and only 40% of men with 0 CTCs, associated with ORs for progression of 4.0 ($p<0.001$) for ≥ 5 vs. 0 and of 2.5 ($p=0.001$) for 1–4 vs. 0 baseline CTCs. This trend continued at higher CTC numbers, for example OR 4.7 ($p<0.001$) for ≥ 10 vs. 0 baseline CTCs (not shown). A univariate regression model of baseline CTC count with 2-year PFS not adjusting for the stratification covariates showed very similar associations: Progression OR of 4.3 ($p<0.001$) for ≥ 5 vs. 0 and progression OR of 2.7 ($p<0.001$) for 1–4 vs. 0 CTCs.

As with 7-month PSA, associations with 2-year PFS were also evaluated using additional cutpoints: <5 vs. ≥ 5 CTCs, and 0 vs. ≥ 1 CTCs. Of men with ≥ 5 baseline CTCs, 74% experienced disease progression by 2 years, vs. 46% of men with <5 CTCs (Figure 5A), associated with ORs for progression of 3.1 ($p=0.003$). Of men with ≥ 1 baseline CTCs, 67% experienced disease progression by 2 years, vs. 40% of men with 0 CTCs (Figure 5B), associated with ORs for progression of 2.9 ($p<0.001$).

Discussion

The CellSearch platform has been extensively validated in mCRPC: CTC count <5 vs. ≥ 5 or 0 vs. ≥ 1 at baseline or after start of therapy, alone or in combination with other markers was shown in multiple studies to correlate with disease outcome and response to therapy.^{15–20} However, clinical validation has not translated to significant clinical use in mCRPC, because most approved therapies offer tangible but transient clinical benefit. Clinicians are not presented with a choice between two or three long-term combination therapies but rather between serial single agents, each offering a median benefit counted in months. In that setting, an upfront biomarker has afforded modest clinical utility, as most patients simply advance through serial therapies until their options are exhausted.

The clinical scenario is quite different in men initiating therapy for mCSPC. As demonstrated in this S1216 cohort, an overwhelming majority of these men have excellent clinical status marked by absence of pain or visceral metastases and good performance status. Accordingly, most of these men have a life expectancy counted in years, and recently approved regimens combining ADT with chemotherapy or ARSIs have further extended their overall survival. In this disease setting, a noninvasive biomarker that clearly predicts

likelihood of response and duration of response may offer greater clinical impact by helping to set each man on a long-term therapeutic course that is most likely to maximize survival and minimize toxicity. Based on this rationale and the existing preliminary data in mCSPC, we endeavored to test the biomarker potential of baseline CellSearch counts in S1216.

In the cohort analyzed for this study, one third of men had detectable CTCs at baseline despite their favorable clinical profiles, a detection prevalence that qualifies this assay as a potentially informative biomarker in a large proportion of patients. Median CTC count among patients with detectable cells was 3, consistent with prior studies.^{21–24} Baseline CTCs were highly prognostic of PSA response and disease progression. After adjusting for the prespecified stratification factors of ADT initiation and disease extent, men with 0 baseline CTCs had an OR of 8.8 for complete PSA response (<0.2 ng/ml) to hormonal therapy compared with men with ≥ 5 baseline CTCs. Conversely, men with ≥ 5 CTCs had an OR 4.0 for progressing to castration resistance within two years on hormonal therapy. When the categories were collapsed into the standard binary cutpoint of <5 vs. ≥ 5 previously validated in mCRPC, they yielded very similar discrimination in outcome: OR 8.1 for complete PSA response in men with <5 CTCs, and OR 3.1 for progression in men with ≥ 5 CTCs. As importantly, the recently proposed cutpoint of 0 vs. ≥ 1 also significantly discriminated outcomes, with an OR of 2.5 for complete PSA response with no CTCs and an OR of 2.9 for progression with any detectable CTCs. As discussed in the mCRPC setting,¹⁸ a cutpoint of undetectable vs. any detectable may maximize biomarker utility by applying to a maximal number of patients (33% with any detectable CTCs in this analysis).

Even with our restricted design to protect outcomes from an ongoing trial, the resulting analysis subsets for 7-month PSA and 2-year PFS (N=264 and N=336, respectively) constitute the largest prospective mCSPC dataset to our knowledge. Additional insights will be gained when the full 489 baseline sample cohort will be analyzed at the time of OS reporting, such as analysis of CTC counts as a continuous variable, CTC count at progression to mCRPC, change in CTC count from baseline to progression, and inclusion of additional clinical covariates (e.g. prostate specific antigen and alkaline phosphatase) in the prognostic models. CTC count also will be correlated with OS and assessed for interactions with treatment arm to assess its potential value not only as a prognostic factor but also as a predictive factor of response to specific treatments.

The current results demonstrate that baseline CTC count is strongly prognostic of PSA response and disease progression in men with mCSPC initiating treatment with combination hormonal therapy. The CellSearch assay used is FDA cleared, widely available, and has undergone extensive analytical and clinical validation in mCRPC and other malignancies. Because it is already established at scale among large commercial laboratory test providers, it can foreseeably be accessed at a relatively modest incremental cost by a majority of patients and caregivers. Hence, if newly validated in mCSPC, this assay may readily serve as a minimally invasive prognostic biomarker to immediately identify men likely to have favorable outcomes with hormonal therapy vs. men likely to progress rapidly to castration resistance. Upon further confirmation, such prognostic information may conceivably help with upfront treatment decisions: For example, frail patients with contraindications to chemotherapy or ARSI but no baseline CTCs may be confidently treated with more

conservative ADT, whereas men with detectable or high numbers of baseline CTCs may be treated with intensification therapy based on the expectation of more aggressive disease course. As importantly, by enabling identification of poor risk patients upfront, baseline CTC count will motivate new therapeutic trials aimed at improving clinical outcomes for these men.

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Conflict of Interest

AG reports grants from NIH, during the conduct of the study; personal fees from Albany Capital, outside the submitted work; In addition, Dr. Goldkorn has a patent US Patent # 8,551,425 B2, 2013 licensed to Corestone Biosciences, Circulogix. JKP reports grants from NCI, during the conduct of the study. DAV reports grants from Alliance for Clinical Trials in Oncology, during the conduct of the study; personal fees from Bayer, personal fees from Natera, personal fees from Exelixis, personal fees from Seattle Genetics, personal fees from Genomic Health, personal fees from Bristol Myers, personal fees from Astra Zeneca, non-financial support from Caris, outside the submitted work. DJM reports grants from Astra-Zeneca, personal fees from Janssen, grants and personal fees from Rainier Pharmaceuticals, personal fees from H3 Biomedicine, outside the submitted work; In addition, Dr. McConkey has a patent PCT/US19/17300 pending. MHAH reports other from Pfizer, other from AstraZeneca, other from Bayer, other from Genentech, other from Genentech, other from Pfizer, other from Bayer, other from Astellas Pharma, other from Genentech/Roche, other from PER, other from Projects in Knowledge, other from Astellas Pharma, other from Genentech, other from Sanofi/Genzyme, other from Research to Practice, grants from Genentech, grants from Pfizer, grants from AstraZeneca, grants from Bayer, other from BMS, other from Daiichi Sankyo, outside the submitted work; In addition, Dr. Hussain has a patent SYSTEMS AND METHODS FOR TISSUE IMAGING licensed to Serial Number: UM-14437/US-1/PRO 60/923,385 UM-14437/US-2/ORD 12/101,753, a patent METHOD OF TREATING CANCER licensed to Serial Number: 224990/10-016P2/311733 61/481/671, and a patent Dual Inhibition of MET and VEGF for the treatment of castration resistant prostate cancer and osteoblastic bone metastases licensed to Application No/Patent No. 11764665.4- 1464. DIQ reports personal fees from JANNSEN, personal fees from ASTELLAS, personal fees from PFIZER, personal fees from GENZYME/SANOFI, personal fees from BAYER, personal fees from ASTRAZENECA, personal fees from MERCK, personal fees from ROCHE, outside the submitted work. NJV reports personal fees from Bayer, personal fees from Janssen, personal fees from Pfizer, personal fees from astra zeneca, from null, outside the submitted work. NA reports consultancy to Astellas, Astra Zeneca, Bayer, Bristol Myers Squibb, Clovis, Eisai, Eli Lilly, EMD Serono, Exelixis, Foundation Medicine, Genentech, Janssen, Merck, Nektar, Novartis, Pfizer, Pharmacyclics, and Seattle Genetics; and Research funding to his institution from Astra Zeneca, Bavarian Nordic, Bayer, Bristol Myers Squibb, Calithera, Celldex, Clovis, Eisai, Eli Lilly, EMD Serono, Exelixis, Genentech, Glaxo Smith Kline, Immunomedics, Janssen, Medivation, Merck, Nektar, New Link Genetics, Novartis, Pfizer, Prometheus, Rexahn, Roche, Sanofi, Seattle Genetics, Takeda, and Tracoon.

CT, MP, GJM, AC, TX, SAI, ALH, MK, GRM, AWC, PL, TT and IMT declare no competing interests.

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25. Section 16, Federal Regulatory Guidelines (Ref. Federal Register Vol. 46, No. 17, January 27, 1981, part 56) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46).

Translational Relevance

Combined androgen axis inhibition therapy extends overall survival (OS) in metastatic castrate sensitive prostate cancer (mCSPC), but a significant number of men experience early disease progression and death. Effective biomarkers are needed to identify these poor risk patients, who may benefit from more aggressive therapy earlier or enrollment in clinical trials. In a phase 3 randomized trial for men with mCSPC (SWOG S1216), baseline CTC count was highly prognostic of disease progression at two years and of PSA response at month 7 of systemic therapy (an intermediate endpoint for OS). These results were generated with a well-validated commercial assay (CellSearch), using predetermined categorical cutpoints for CTC and outcome measures. With further validation of these results in the setting of other traditional risk factors, CTC count may be implemented as a noninvasive prognostic biomarker to identify poor risk patients when they first present, which may enhance personalization of treatment and influence design of future clinical trials for newly diagnosed mCSPC.

Figure 1.
Consort diagram for baseline CTC analysis in S1216.

Figure 2.

Association of primary, prespecified baseline CTC count categories with 7-month PSA response. Odds ratios (ORs) for achieving partial response (PR, left) or complete response (CR, right) comparing men with 5 CTCs to 0 CTCs and men with 1–4 CTCs to 0 CTCs. [Sample size for analysis: N=264; 61% CTC 0, 24% CTC 1–4, and 15% CTC 5+].

Figure 3.

Association of secondary baseline CTC count categories with 7-month PSA response using cutpoints previously validated in mCRPC. Odds ratios (ORs) comparing men with ≥ 5 CTCs to <5 CTCs (A) or men with ≥ 1 CTCs to 0 CTCs (B) for achieving partial response (PR) or complete response (CR). [Sample size for analysis: N=264; A. 85% CTC 0–4, 15% CTC 5+; B. 61% CTC 0, 39% CTC 1+].

Figure 4.

Association of primary, prespecified baseline CTC count categories with 2-year PFS. Percent of patients who progressed or died at 2 years among men with 5, 1–4, or 0 CTCs at baseline, with associated ORs. [Sample size for analysis: N=336; 62% undetectable CTC, 24% CTC=1–4, 14% CTC 5+].

Figure 5.

Association of secondary baseline CTC count categories with 2-year PFS using cutpoints previously validated in mCRPC. Percent of patients who progressed or died at 2 years among men with 5 vs. < 5 (A) or 1 vs. 0 (B) CTCs at baseline, with associated ORs. [Sample size for analysis: N=336; A. 86% CTC 0–4, 14% CTC 5+; B. 63% CTC 0, 37% CTC 1+].

Table 1.

Baseline characteristics in patients with and without CTC sampling (left) and associations with primary CTC count categories (right) (* association of risk factor with CTC category; **includes patients ineligible for S1216).

	Total Pts without CTC sample** (N=824)	Total Pts with CTC sample (N=489)	CTC = 0 (N=329, 67%)	CTC 1-4 (N=103, 21%)	CTC 5+ (N=57, 12%)	p-value*
	Columns add to 100%		Rows add to 100%			
Age (median)						0.37
69	58%	52%	69%	19%	12%	
> 69	42%	48%	65%	24%	11%	
Race						0.24
White	83%	86%	68%	20%	12%	
Black	12%	9%	56%	32%	12%	
Other	5%	5%	71%	17%	12%	
Baseline PSA						< 0.001
Low (12)	30%	33%	77%	17%	6%	
Medium	31%	34%	70%	22%	8%	
High (>56)	39%	33%	55%	25%	20%	
Alkaline Phosphatase median (range)	90 (0, 297000)	83 (14, 4800)	79 (14, 3079)	88 (41, 1648)	122 (43, 4800)	< 0.001
Hemoglobin median (range)	14.2 (7.3, 127.0)	14.2 (9.0, 44.6)	14.3 (9.0, 44.6)	14.0 (9.1, 17.2)	13.8 (10.0, 15.7)	0.002
Gleason Score						0.97
6	11%	6%	72%	19%	9%	
7	25%	28%	66%	22%	12%	
8	59%	59%	70%	20%	10%	
Missing	6%	7%	45%	28%	27%	
Bone Pain						< 0.001
Yes	24%	22%	56%	21%	23%	
No/Unknown	76%	78%	71%	21%	8%	
Bone Mets						< 0.001
Yes	76%	73%	62%	23%	15%	
No	24%	27%	81%	15%	4%	
Visceral Mets						0.91
Yes	15%	12%	68%	22%	10%	
No	85%	88%	67%	21%	12%	
Disease Severity						<0.001
Minimal	49%	54%	77%	17%	6%	
Extensive	51%	46%	56%	25%	19%	
Performance Status						0.008

	Total Pts without CTC sample** (N=824)	Total Pts with CTC sample (N=489)	CTC = 0 (N=329, 67%)	CTC 1–4 (N=103, 21%)	CTC 5+ (N=57, 12%)	p-value*
	Columns add to 100%		Rows add to 100%			
0–1	96%	96%	69%	20%	11%	0.16
2–3	4%	4%	38%	33%	29%	
Pre-reg LHRH Suppression						
Yes	54%	50%	70%	21%	9%	
No	46%	50%	65%	21%	14%	