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Validation of the association of RECIST changes with survival in men with metastatic castration resistant prostate cancer treated on SWOG study S0421

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Abstract

Background—Phase II trials evaluating new agents for metastatic castration-resistant prostate cancer (mCRPC) have relied on bone scan and prostate specific antigen (PSA) changes to assess activity. Given the increasing detection of measurable disease, RECIST changes warrant consideration to evaluate activity. We validated the association of RECIST 1.0 changes with survival in men with mCRPC receiving docetaxel.

Materials and methods—Data for men with measurable disease from the SWOG S0421, a phase III trial in men with mCRPC receiving docetaxel and prednisone plus placebo or atrasentan, were used. Cox proportional hazards regression was used to evaluate the association of RECIST 1.0 outcomes within 120 days, i.e. unconfirmed partial response (uPR), stable disease (uSD) and progressive disease (PD), with OS from day 120, adjusted for prognostic factors.

Results—Overall, 326 men were evaluable for landmark analysis, of whom 23 patients had PD, 230 had SD, and 73 had uPR. OS beyond day 120 was significantly different ($p=0.004$) amongst these subgroups, with median (95% CI) OS of 7.1 (3.5–8.8), 13.4 (11.4–15.6) and 16.3 (10.0–19.6) months for those with PD, SD and uPR, respectively. In a multivariable model, the hazard ratio (95% CI) for patients with PD was 2.47 (1.42 to 4.29) compared to patients with an uPR ($p=0.002$).

Conclusions—The association of RECIST 1.0 changes with OS in men with mCRPC receiving docetaxel was validated. Given limitations of bone scan and PSA alterations, improvements in objective RECIST 1.0 changes should be reported in phase II trials evaluating before launching phase III trials.

Keywords

Prostate; Metastatic; castration-resistant; RECIST 1.0; Survival

Introduction

Objective changes of measurable tumors employing Response Evaluation Criteria in Solid Tumors (RECIST) are commonly used to evaluate new agents for most solid tumors in phase II trials.^{1, 2} However, metastatic castration-resistant prostate cancer (mCRPC) has been historically observed to have a low proportion of patients with measurable disease. Hence, phase II trials evaluating new agents for metastatic castration-resistant prostate cancer (mCRPC) have mostly relied on bone scan changes to assess radiographic progression and prostate specific antigen (PSA) changes to assess biochemical impact. Unfortunately, bone scan and PSA changes do not always accurately represent objective changes in tumor burden.³ Indeed, this limitation may partly explain why agents with promising activity

observed in phase II trials using PSA and/or bone scans as surrogates of activity did not translate into improved survival in subsequent phase III trials.⁴⁻⁸

Objective changes by RECIST may warrant serious consideration even in mCRPC, since body imaging with CT or MRI is required more frequently and hence detecting measurable tumors in mCRPC.⁹ Recent studies have discovered the association of measurable disease changes by World Health Organization (WHO) criteria and RECIST 1.0 and 1.1 changes with overall survival (OS) in men with mCRPC receiving docetaxel-based chemotherapy.^{10, 11} This study was undertaken to validate the association of RECIST 1.0 changes with OS in men with mCRPC receiving docetaxel-based chemotherapy in the Southwest Oncology Group S0421 trial.¹²

Methods

Patient selection

S0421 was a double-blind phase III trial in men with mCRPC men treated with first-line docetaxel 75 mg/m² every 21 days and prednisone plus either placebo or atrasentan in a 1:1 ratio.¹² Patients were stratified by type of progression (PSA vs. radiographic) to prior therapy, baseline pain, extra-skeletal disease and bisphosphonate use. Therapy was administered every 3 weeks for up to 12 cycles or until progressive disease, prohibitive toxicity, patient decision or delays of >3 weeks. Radiographic assessment was performed at baseline and every 12 weeks with computerized tomography (CT) or magnetic resonance imaging (MRI) of the abdomen, and pelvis and technetium bone scan. Imaging of the chest was permitted by either chest x-ray or CT scan. Progression was defined in S0421 by bone scan, RECIST 1.0 soft tissue or pain progression. Bone scan progression required new lesions confirmed by further new lesions 6 weeks later in accordance with Prostate Cancer Working Group (PCWG)-2 guidelines.¹³ Pain progression was defined as a two-point increase in the Brief Pain Inventory Worst Pain score or increased opioid analgesic intake score. PSA increase alone was not used to discontinue trial therapy. Individual patient data from patients with measurable disease from both arms were combined for analysis since no differences in PFS or OS outcomes were observed. The conduct of this retrospective study was covered by protocol X120917005, which was approved by the University of Alabama at Birmingham (UAB) Institutional Review Board (IRB)

Primary Outcome Measures

Two measures of radiographic tumour change were available: 1) the change in the sum of lesion sizes from baseline to the first on-study assessment within 120 days, and 2) the best objective response, based on RECIST 1.0, measured at any time on study. Hence, for landmark analyses, it is possible that the best objective response assessment occurred after the landmark date, although, the best objective response assessment generally occurs at the first on-study assessment, which would occur at around day 84 in this study. The primary analysis was based on change in lesion size, defined as: (sum of the maximum diameter of all lesions (SMDL) at the first on-study measurement – SMDL at baseline)/SMDL at baseline, multiplied by 100%. Patients were categorized based on change in lesion size as: 20% increase (progressive disease, PD), between 20% increase and 30% decrease (stable

disease, SD), decrease of at least 30% (unconfirmed partial response, uPR). A supportive analysis was performed using the best observed RECIST 1.0 response at any time on the trial.

Statistical methods

Descriptive statistics were used to summarize patient baseline information and outcomes. The Kaplan-Meier method was used to estimate OS outcomes. Transformations of laboratory variables (PSA, alkaline phosphatase, platelets) were performed for statistical normalization purposes. A 120 day landmark analysis was performed which included only patients who had first on-study assessment prior to day 120, and survival beyond day 120. The Kaplan-Meier method was used to estimate OS and Cox proportional hazards regression evaluated the association of radiographic tumour dimension change on OS. Regression analyses were adjusted for selected (based on known prognostic importance) major baseline prognostic factors: hemoglobin, alkaline phosphatase, PSA, treatment arm, performance status, visceral disease, progression type, pain and Gleason score. All tests were two-sided and $P \leq 0.05$ was considered statistically significant and statistical analyses were performed in SAS v9.4 (SAS Institute, Cary, NC) or R v3.2.2 (www.r-project.org).

Results

Patient characteristics

Overall, 469 of 994 (47.2%) eligible patients had measurable disease at baseline when combining both arms of the trial. Of these, 365 (36.7% of overall population 994 patients) had radiographic assessed lesion measurements within 120 days of initiating therapy or objective RECIST response assessment at any time and survival beyond day 120. Patient characteristics of these 365 patients were typical for this population (Table 1) and similar to the population of 469 patients with measurable disease (data not shown). Additionally, the 365 evaluable patients for our analysis exhibited a median OS of 17.2 months, which was similar to the median OS of all 994 patients enrolled in the trial (Median OS was 17.8 months in the atrasentan group versus 17.6 months in the placebo group). Patients were obtained almost equally from both arms of the trial, with 186 (51.0%) having received docetaxel plus atrasentan, and median OS was 17.2 (95% confidence interval [CI]=15.5 to 19.2) months.

Association of changes in lesion sizes by day 120 with OS

Three hundred and twenty-six patients (32.8% of overall population of 994 patients) were evaluable for landmark analysis (i.e. measurable radiographic assessments at baseline and within 120 days, and survival beyond day 120), of whom 23 patients had $\geq 20\%$ increase in lesion size (e.g. progressive disease or PD), 230 had between a 20% increase and 30% decrease in lesion size (SD), and 73 had a decrease in lesion size of at least 30% (uPR). OS beyond day 120 was significantly different ($p=0.004$) amongst these subgroups, with median (95% CI) OS of 7.1 (3.5–8.8) for patients with PD, 13.4 (11.4–15.6) months for those with SD and 16.3 (10.0–19.6) months for those with PR (Table 2 and Figure 1). After adjusting for prognostic factors in a multivariable model (Table 3), the hazard ratio (95% CI) for patients with PD was 2.47 (1.42 to 4.29), and was 1.02 (0.75 to 1.39) for SD, compared to

patients with an uPR ($p=0.002$). As a continuous measure, changes in lesion size was significantly associated with OS (Hazard Ratio=1.05 per 10% increase in the change, 95% CI=1.02–1.09, $p=0.002$) beyond 120 days in univariable analysis, and (HR=1.06, 95% CI: 1.02 to 1.10, $p=0.003$) after adjusting for prognostic factors in a multivariable analysis. The c-statistic improved from 0.647 to 0.649 with RECIST change category within 120 days added to the multivariable model. When adding change in lesion size as a continuous variable, the c-statistic increased from 0.647 to 0.655 in the multivariable model.

Association of RECIST 1.0 changes with OS

There were 43 patients who had a best RECIST 1.0 response of PD at any time, 233 had a best response of SD, 60 had a best response of PR and 29 were deemed not assessable. Not assessable patients had a median (95% CI) OS beyond the landmark time of 8.4 (6.2 to 10.0) months, compared with 7.1 (4.4 to 9.2) months for PD patients, 13.3 (11.6–15.6) for SD patients and 23.8 (19.0 to 31.2) months for those with PR (Figure 2). This difference was statistically significant ($p\text{-value}<0.001$) in both univariable (HR=4.74, 95% CI=3.08 to 7.29 for PD and 1.82, 95% CI=1.31 to 2.52 for SD, relative to PR patients; NA patients excluded) and multivariable (HR=3.90, 95% CI=2.45 to 6.19 for PD and 1.62, 95% CI=1.15 to 2.30 for SD) models. The addition of best RECIST response improved the c-statistic in the multivariable model from 0.641 to 0.674.

Discussion

Previously reported recent studies have described an association between measurable disease changes by WHO, RECIST 1.0 and RECIST 1.1 and OS in men with mCRPC receiving docetaxel-based chemotherapy.¹⁰ The post hoc analysis reported in this paper analyzed 365 evaluable patients from the S0421 phase III trial to validate the association between unconfirmed RECIST 1.0 alterations within 120 days or confirmed RECIST 1.0 alterations at any time with OS in men with mCRPC receiving docetaxel-based chemotherapy after controlling for previously validated baseline prognostic factors. The association between RECIST 1.0 response and OS was confirmed. Moreover, for every 10% increase in lesion size, the hazard of dying increased by 6%. These data support the contention that objective measurable disease alterations are prognostic and may indicate a signal of activity of systemic therapy translating to extension of survival. It is intriguing that in addition to RECIST changes, the multivariable analysis demonstrated the independent significance of some (hemoglobin, alkaline phosphatase, pain) but not other historically validated prognostic factors (performance status, visceral metastasis). These findings suggest the independence and potential primacy of RECIST alterations, a dynamic marker, when compared with these baseline static factors.

mCRPC is the sole exception to the practice of utilizing measurable disease changes to evaluate new agents in phase II trials for solid tumors owing to the dominance of bone metastases.^{1, 2} Historically, measurable tumors have been identified in a small minority of approximately 10% to 20% of patients enrolled in phase II trials performing routine baseline CT imaging.^{14, 15} The low historical rate of measurable disease may be attributable partly to the use first generation CT technology and partly to limited CT imaging of the pelvis.

However, more recently, a pooled analysis of phase III trials completed since 2002 identified measurable disease in 47.8% of patients, which appears higher than historical measurable disease rates probably due to better CT technology and more frequent whole body CT imaging.⁹ Similarly, in the S0421 study, 47.2% of patients were identified as having measurable disease at baseline. Indeed, it is provocative to speculate that routine CT scans of the chest in S0421 may have detected additional patients with measurable disease. Hence, the practice of relegating RECIST changes to a frequently neglected secondary endpoint not accounted for in the go-no-go decision process for a phase III trial needs to be revisited. Interestingly, one ongoing phase II trial, the Keynote-199 trial, enrolls patients with mCRPC into separate cohorts with or without measurable disease, with a primary endpoint of RECIST 1.1 response when using pembrolizumab, a programmed death (PD)-1 inhibitor immunotherapeutic. Indeed, the detection of a signal of activity with immunotherapy is particularly challenging in the absence of objective measures of tumor burden.

The updated PCWG-3 guidelines recommend using RECIST 1.1 to evaluate measurable tumors in mCRPC with one difference compared to RECIST 1.1 guidelines: up to 5 lesions per organ site of metastatic spread is suggested (classic RECIST 1.1 suggests measuring up to 2 lesions per organ, while RECIST 1.0 proposes measuring up to 5 lesions per organ) to address heterogeneity of this malignancy and to permit tracking of various patterns of progression. It is noteworthy that RECIST 1.1 defines a measurable lymph node as one with short axis dimension of ≥ 1.5 cm, which is different from RECIST 1.0, which requires a maximum dimension of ≥ 1 cm, and these differences may have some impact on the proportion of patients with measurable disease. PCWG guidelines do not recommend using PSA changes alone to capture benefit from therapy. In the context of docetaxel, PSA decline $\geq 30\%$ within 3 months was demonstrated to be a moderate surrogate for OS.¹⁶ However, PSA declines have not appeared to be robust surrogate endpoints in other settings, e.g. cabazitaxel second-line chemotherapy.¹⁷ Moreover, early PSA flares responses can occur in advanced prostate cancer in multiple scenarios.¹⁸ Preliminary data suggest that early PSA decline $\geq 30\%$ or $\geq 50\%$ within 4 weeks when using novel anti-androgens (e.g. abiraterone acetate, enzalutamide) maybe associated with longer survival, but extensive validation is required.¹⁹ In summary, PSA declines remain a questionable intermediate endpoint with poor reliability across different classes of agents.

PCWG guidelines recommend bone scan as the primary modality for following bone lesions in prostate cancer, with a proviso for repeating bone scans after ≥ 6 weeks to confirm progression, given the phenomenon of early bone scan flares caused by healing of responding osteoblastic lesions.²⁰ The composite radiographic progression endpoint accounting for progression on bone scan by PCWG guidelines and RECIST for measurable disease was associated with OS in the context of docetaxel and abiraterone acetate.^{21, 22} Conversely, trials demonstrating dramatic bone scan improvements by cabozantinib did not translate to extensions of survival in subsequent phase III trials.^{23–25} Novel methods to quantify bone metastases such as bone scan index (BSI), defined as the percentage of bone mass involved by lesions on bone scan compared to a historical bone mass, have been proposed but may also be plagued by the inherent limitations of bone scans.²⁶ Additionally, the extrapolation of PCWG or BSI defined bone scan progression across all classes of novel agents is problematic. It is noteworthy that tasquinimod did not yield an extension of OS in a

phase III trial despite an improvement in BSI and radiographic progression-free survival in preceding phase II trials.^{27–29} Additionally, multiple phase III trials combining docetaxel with biologic agents have not demonstrated increments in survival despite preliminary evidence for benefits mostly in terms of PSA and bone scan changes (and not RECIST changes) in preceding phase II trials.^{4–8, 30} Indeed, the phenomena of early PSA spikes coupled with the probability of early bone scan flares, prompted the PCWG to recommend a minimum of 12 weeks of therapy before making clinical decisions regarding continuation of a regimen. Other tools to potentially better assess tumor burden including magnetic resonance imaging (MRI), circulating tumor cell (CTC) counts and PET imaging using novel tracers such as sodium fluoride, fluorothymidine, choline, acetate, fluciclovine, and prostate-specific membrane antigen, also indirectly measure tumor burden but may be limited in application by cost.^{31–35}

Our study is limited by a somewhat modest sample size and post hoc design. Of 994 eligible patients enrolled in the SWOG S0421 trial, 365 (36.7%) were eligible for our analysis, and 326 (32.8%) were evaluable for the landmark analysis, which required baseline measurable disease and repeat radiographic assessment within 120 days as well as survival data beyond day 120. However, these 365 eligible patients were not significantly different in terms of OS outcomes from the 469 patients with measurable disease or the overall trial population of 994 patients. We did not aim to identify a differential impact of RECIST response based on sites of measurable disease. However, updated prognostic models in the setting of first-line docetaxel chemotherapy suggest that the presence of measurable tumor itself is not independently prognostic, although visceral and especially liver metastasis confers an adverse impact.³⁶ We did not investigate the impact of RECIST changes independent of PSA changes, since our sole objective was the external validation of association of RECIST 1.0 changes with survival. Notably, in previous discovery studies of other trials, measurable tumor changes were associated with survival after accounting for PSA changes.^{10, 11} Our previous study, which discovered the association of RECIST 1.0 changes with survival employed a 90 day landmark analysis, while the current validation study employed a 120 day landmark analysis in order to capture a larger number of patients undergoing radiographic assessment. However, this slight difference in landmark timepoint is unlikely to impact our results. While our analysis included most known clinical prognostic factors, we could not include lactate dehydrogenase and CTCs, which were not performed in all patients on this trial but appear to be major prognostic factors according to other studies.³⁵ Central radiology review was not conducted, although institutions with track records on SWOG advanced prostate cancer trials with more than 20 years of experience participated in this trial, with academic radiologists often interpreting the scans. In addition, RECIST progression was not the sole reason for removing patients from therapy for progressive disease; bone scan and/or pain progression were probably primarily used for defining progression. Our study merely provides validation for RECIST 1.0 changes as a prognostic marker for survival in the setting of docetaxel-based chemotherapy, and generates the hypothesis that it may be a surrogate endpoint. Indeed, surrogacy for survival can only be confirmed by analyzing ‘positive’ phase III trials with a significant difference in OS between the arms. Finally, the level of increment of RECIST 1.0 responses in a phase II trial, which

may translate to extension of OS requires further study and may be evaluated in positive phase III trials.

Conclusions

This retrospective study externally validates the association of RECIST 1.0 changes with OS in men with mCRPC receiving docetaxel-based first-line chemotherapy. Given that body imaging using currently improved CT scan technology is required on clinical trials in contrast to limited imaging using older CT technology historically, measurable disease is being detected more frequently in mCRPC. Hence, objective RECIST changes are more feasible to demonstrate now in phase II trials investigating new regimens. Given that RECIST 1.1 will be used in the future, the external validation of association of RECIST 1.1 alterations with survival is necessary. With further evaluation across other classes of agents including second-generation anti-androgen agents, biologic agents and immunotherapy, RECIST changes may be employed as critical supportive or co-primary endpoints in phase II trials seeking signals of activity before launching phase III trials.

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References

1. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *European journal of cancer*. 2009; 45:228–247. [PubMed: 19097774]
2. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *Journal of the National Cancer Institute*. 2000; 92:205–216. [PubMed: 10655437]
3. Scher HI, Morris MJ, Stadler WM, et al. Trial Design and Objectives for Castration-Resistant Prostate Cancer: Updated Recommendations From the Prostate Cancer Clinical Trials Working Group 3. *Journal of clinical oncology: official journal of the American Society of Clinical Oncology*. 2016; 34:1402–1418. [PubMed: 26903579]
4. Kelly WK, Halabi S, Carducci M, et al. Randomized, Double-Blind, Placebo-Controlled Phase III Trial Comparing Docetaxel and Prednisone With or Without Bevacizumab in Men With Metastatic Castration-Resistant Prostate Cancer: CALGB 90401. *Journal of clinical oncology: official journal of the American Society of Clinical Oncology*. 30:1534–1540.
5. Tannock IF, Fizazi K, Ivanov S, et al. Aflibercept versus placebo in combination with docetaxel and prednisone for treatment of men with metastatic castration-resistant prostate cancer (VENICE): a phase 3, double-blind randomised trial. *The lancet oncology*. 2013; 14:760–768. [PubMed: 23742877]
6. Petrylak DP, Vogelzang NJ, Budnik N, et al. Docetaxel and prednisone with or without lenalidomide in chemotherapy-naïve patients with metastatic castration-resistant prostate cancer (MAINSAIL): a randomised, double-blind, placebo-controlled phase 3 trial. *The lancet oncology*. 2015; 16:417–425. [PubMed: 25743937]
7. Araujo JC, Trudel GC, Saad F, et al. Docetaxel and dasatinib or placebo in men with metastatic castration-resistant prostate cancer (READY): a randomised, double-blind phase 3 trial. *The lancet oncology*. 2013; 14:1307–1316. [PubMed: 24211163]

8. Chi KN, Higano CS, Blumenstein B, et al. Custirsen in combination with docetaxel and prednisone for patients with metastatic castration-resistant prostate cancer (SYNERGY trial): a phase 3, multicentre, open-label, randomised trial. *The lancet oncology*. 2017; 18:473–485. [PubMed: 28283282]
9. Sonpavde G, Madan A, Baker MK, et al. The prevalence of measurable disease in phase III trials of metastatic castration-resistant prostate cancer. *Clin Genitourin Cancer*. In Press.
10. Sonpavde G, Pond GR, Templeton AJ, et al. Association Between RECIST Changes and Survival in Patients with Metastatic Castration-resistant Prostate Cancer Receiving Docetaxel. *European urology*. 2015
11. Sonpavde G, Pond GR, Berry WR, et al. The association between radiographic response and overall survival in men with metastatic castration-resistant prostate cancer receiving chemotherapy. *Cancer*.
12. Quinn DI, Tangen CM, Hussain M, et al. Docetaxel and atrasentan versus docetaxel and placebo for men with advanced castration-resistant prostate cancer (SWOG S0421): a randomised phase 3 trial. *The lancet oncology*. 2013; 14:893–900. [PubMed: 23871417]
13. Scher HI, Halabi S, Tannock I, et al. Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: recommendations of the Prostate Cancer Clinical Trials Working Group. *Journal of clinical oncology: official journal of the American Society of Clinical Oncology*. 2008; 26:1148–1159. [PubMed: 18309951]
14. Hudes GR, Greenberg R, Krigel RL, et al. Phase II study of estramustine and vinblastine, two microtubule inhibitors, in hormone-refractory prostate cancer. *Journal of clinical oncology: official journal of the American Society of Clinical Oncology*. 1992; 10:1754–1761. [PubMed: 1383436]
15. Seidman AD, Scher HI, Petrylak D, Dershaw DD, Curley T. Estramustine and vinblastine: use of prostate specific antigen as a clinical trial end point for hormone refractory prostatic cancer. *J Urol*. 1992; 147:931–934. [PubMed: 1371564]
16. Petrylak DP, Ankerst DP, Jiang CS, et al. Evaluation of prostate-specific antigen declines for surrogacy in patients treated on SWOG 99-16. *Journal of the National Cancer Institute*. 2006; 98:516–521. [PubMed: 16622120]
17. Halabi S, Armstrong AJ, Sartor O, et al. Prostate-specific antigen changes as surrogate for overall survival in men with metastatic castration-resistant prostate cancer treated with second-line chemotherapy. *Journal of clinical oncology: official journal of the American Society of Clinical Oncology*. 2013; 31:3944–3950. [PubMed: 24101043]
18. Angelergues A, Maillet D, Flechon A, et al. Prostate-specific antigen flare induced by cabazitaxel-based chemotherapy in patients with metastatic castration-resistant prostate cancer. *European journal of cancer*. 2014; 50:1602–1609. [PubMed: 24725337]
19. Rescigno P, Lorente D, Bianchini D, et al. Prostate-specific Antigen Decline After 4 Weeks of Treatment with Abiraterone Acetate and Overall Survival in Patients with Metastatic Castration-resistant Prostate Cancer. *European urology*. 2016
20. Ryan CJ, Shah S, Efstathiou E, et al. Phase II study of abiraterone acetate in chemotherapy-naïve metastatic castration-resistant prostate cancer displaying bone flare discordant with serologic response. *Clinical cancer research: an official journal of the American Association for Cancer Research*. 2011; 17:4854–4861. [PubMed: 21632851]
21. Sonpavde G, Pond GR, Armstrong AJ, et al. Radiographic progression by Prostate Cancer Working Group (PCWG)-2 criteria as an intermediate endpoint for drug development in metastatic castration-resistant prostate cancer. *BJU international*. 2013
22. Morris MJ, Molina A, Small EJ, et al. Radiographic progression-free survival as a response biomarker in metastatic castration-resistant prostate cancer: COU-AA-302 results. *Journal of clinical oncology: official journal of the American Society of Clinical Oncology*. 2015; 33:1356–1363. [PubMed: 25624432]
23. Smith DC, Smith MR, Sweeney C, et al. Cabozantinib in patients with advanced prostate cancer: results of a phase II randomized discontinuation trial. *Journal of clinical oncology: official journal of the American Society of Clinical Oncology*. 2013; 31:412–419. [PubMed: 23169517]
24. Smith MR, De Bono JS, Sternberg CN, et al. Final analysis of COMET-1: Cabozantinib versus prednisone in metastatic castration-resistant prostate cancer patients previously treated with

- docetaxel and abiraterone and/or enzalutamide. *Journal of clinical oncology: official journal of the American Society of Clinical Oncology*. 2015; (suppl 7) abstr 139.
25. Basch EM, Scholz MC, De Bono JS, et al. Final analysis of COMET-2: Cabozantinib versus mitoxantrone/prednisone (MP) in metastatic castration-resistant prostate cancer patients with moderate to severe pain who were previously treated with docetaxel and abiraterone and/or enzalutamide. *Journal of clinical oncology: official journal of the American Society of Clinical Oncology*. 2015; (suppl 7) abstr 141.
 26. Dennis ER, Jia X, Mezheritskiy IS, et al. Bone scan index: a quantitative treatment response biomarker for castration-resistant metastatic prostate cancer. *Journal of clinical oncology: official journal of the American Society of Clinical Oncology*. 2012; 30:519–524. [PubMed: 22231045]
 27. Armstrong AJ, Kaboteh R, Carducci MA, et al. Assessment of the bone scan index in a randomized placebo-controlled trial of tasquinimod in men with metastatic castration-resistant prostate cancer (mCRPC). *Urologic oncology*. 2014; 32:1308–1316. [PubMed: 25240761]
 28. Pili R, Haggman M, Stadler WM, et al. Phase II randomized, double-blind, placebo-controlled study of tasquinimod in men with minimally symptomatic metastatic castrate-resistant prostate cancer. *Journal of clinical oncology: official journal of the American Society of Clinical Oncology*. 2011; 29:4022–4028. [PubMed: 21931019]
 29. Ipsen Active Biotech. Apr 16.2015 Press release.
 30. Sonpavde G, Armstrong AJ. Drug development in prostate cancer: time to embrace RECIST? *The lancet oncology*. 2017; 18:419–421. [PubMed: 28283283]
 31. Jagaru A, Young P, Mittra E, Dick DW, Herfkens R, Gambhir SS. Pilot prospective evaluation of 99mTc-MDP scintigraphy, 18F NaF PET/CT, 18F FDG PET/CT and whole-body MRI for detection of skeletal metastases. *Clin Nucl Med*. 2013; 38:e290–296. [PubMed: 23455520]
 32. Even-Sapir E, Metser U, Mishani E, Lievshitz G, Lerman H, Leibovitch I. The detection of bone metastases in patients with high-risk prostate cancer: 99mTc-MDP Planar bone scintigraphy, single- and multi-field-of-view SPECT, 18F-fluoride PET, and 18F-fluoride PET/CT. *J Nucl Med*. 2006; 47:287–297. [PubMed: 16455635]
 33. Lecouvet FE, Geukens D, Stainier A, et al. Magnetic resonance imaging of the axial skeleton for detecting bone metastases in patients with high-risk prostate cancer: diagnostic and cost-effectiveness and comparison with current detection strategies. *Journal of clinical oncology: official journal of the American Society of Clinical Oncology*. 2007; 25:3281–3287. [PubMed: 17664475]
 34. Umbehre MH, Muntener M, Hany T, Sulser T, Bachmann LM. The role of 11C-choline and 18F-fluorocholine positron emission tomography (PET) and PET/CT in prostate cancer: a systematic review and meta-analysis. *European urology*. 2013; 64:106–117. [PubMed: 23628493]
 35. Scher HI, Heller G, Molina A, et al. Circulating tumor cell biomarker panel as an individual-level surrogate for survival in metastatic castration-resistant prostate cancer. *Journal of clinical oncology: official journal of the American Society of Clinical Oncology*. 2015; 33:1348–1355. [PubMed: 25800753]
 36. Halabi S, Lin CY, Kelly WK, et al. Updated prognostic model for predicting overall survival in first-line chemotherapy for patients with metastatic castration-resistant prostate cancer. *Journal of clinical oncology: official journal of the American Society of Clinical Oncology*. 2014; 32:671–677. [PubMed: 24449231]

Clinical practice points

- Objective changes of measurable tumors employing Response Evaluation Criteria in Solid Tumors (RECIST) are commonly used to evaluate the activity of new agents for most solid tumors in phase II trials.
- Since metastatic castration-resistant prostate cancer (mCRPC) has been historically observed to have a low proportion of patients with measurable disease, phase II trials evaluating new agents for metastatic castration-resistant prostate cancer (mCRPC) have mostly relied on consensus but subjective bone scan and prostate specific antigen (PSA) changes to assess activity.
- The association of RECIST 1.0 changes within 120 days with survival in men with mCRPC receiving docetaxel based chemotherapy was validated in this retrospective analysis of 327 evaluable patients from the SWOG S0421 phase III trial.
- Given the increasing detection of measurable disease, improvements in objective RECIST 1.0 changes should be reported in phase II trials evaluating before launching phase III trials.

Figure 1. Survival beyond 120 days based on change in RECIST 1.0 size within 120 days
Median survival (95% CI) beyond day 120 was significantly different ($p=0.004$) based on the sum of the maximum diameter of measurable lesions increase $\geq 20\%$ (7.1 months [3.5–8.8]), change of between an increase $\geq 20\%$ and decrease $\geq 30\%$ (13.4 months [11.4–15.6]) and decrease $\geq 30\%$ (16.3 months [10.0–19.6])

Figure 2. Survival beyond 120 days based on best RECIST 1.0 response at any time

Median survival (95% CI) beyond day 120 was significantly different ($p < 0.001$) based on best RECIST 1.0 change at any time: 8.4 (6.2 to 10.0) months for not assessable patients, 7.1 (4.4 to 9.2) months for progressive disease (PD) patients, 13.3 (11.6–15.6) months for stable disease (SD) patients and 23.8 (19.0 to 31.2) months for those with partial response (PR)

Table 1

Patient characteristics

Characteristic	Statistic	N	Result
Age	Mean (sd)	365	67.8 (9.0)
Hemoglobin	Mean (sd)	363	12.4 (1.4)
Platelets ($\times 10^3$)	Median (range)	362	236 (100, 709)
Alkaline Phosphatase	Median (range)	362	118 (27, 8560)
PSA	Median (range)	365	85 (0.1, 7417)
Treatment	N (%) Atrasentan	365	186 (51.0)
SWOG Performance Status	0	364	160 (44.0)
	1		183 (50.3)
	2		21 (5.8)
Visceral Disease	N (%) Yes	365	168 (46.0)
Gleason Score	N (%) 8	350	211 (60.3)
Type of Progression	N (%) PSA Only	365	49 (13.4)
Worst Level of Pain	N (%) 4 [†]	365	149 (40.8)
Outcomes			
Best RECIST change within 120 days	Overall N 20% Increase <20% Increase to <30% Decrease 30% Decrease	326	23 (7.1%) 230 (70.6%) 73 (22.4%)
Sum, Baseline Lesions	Median (range)	365	5.4 (1.0, 113.2)
Days to First CT Scan Prior to Landmark	Median (range)	326	94 (41, 119)
Sum, Lesions at 1 st CT Prior to Landmark	Median (range)	326	4.7 (0, 120.5)
Change in Lesion Size (cm) at 1 st CT Prior to Landmark	Median (range)	326	-13.7 (-100, 191)
Overall Survival, months, from BASELINE	N (%) Deaths Median (95% CI) 1-year (95% CI) 2-year (95% CI)	365	321 (87.9) 17.2 (15.5, 19.2) 73.1 (68.2, 77.3) 33.1 (28.3, 37.9)

[†] as assessed by Brief Pain Inventory Worst Pain score or increased opioid analgesic intake score

Table 2

Overall Survival from day 120 based on best RECIST change within Day 120

Best RECIST 1.0 change within 120 days	20% Increase	<20% Increase to <30% Decrease	30% Decrease
N	23	230	73
N (%) Deaths	22 (95.6)	201 (87.4)	63 (86.3)
Median (95% CI) OS	7.1 (3.5–8.8)	13.4 (11.4–15.6)	16.3 (10.0–19.6)
1-year (95% CI)	21.7 (7.9–39.9)	53.5 (46.8–59.7)	58.6 (46.4–68.9)
2-year (95% CI)	13.0 (3.3–29.7)	28.7 (23.0–34.7)	30.7 (20.5–41.5)

Log-rank p-value=0.004

Table 3

Multivariable model for association of factors with OS

Factor	Categorization	Hazard Ratio (95%CI)	p-value
LANDMARK TIME=DAY 120 (n=326)			
Hemoglobin	/ unit	0.83 (0.75, 0.91)	<0.001
Alkaline Phosphatase	Log-transformed	1.57 (1.32, 1.86)	<0.001
Baseline PSA	Log-transformed	1.07 (0.99, 1.16)	0.092
Treatment	Artrasentan vs. Placebo	1.00 (0.78, 1.28)	0.99
Performance Status	1 vs 0	0.87 (0.67, 1.13)	0.28
Visceral Disease	Yes vs No	1.11 (0.87, 1.42)	0.42
PSA Progression	Yes vs No	1.03 (0.71, 1.50)	0.88
Worst Pain *	4 vs <4	1.37 (1.05, 1.78)	0.02
Gleason Score	8 vs 7	0.92 (0.71, 1.20)	0.54
RECIST Change in Lesion Size by Day 120	-100% to -30% -29.9% to +19.9% +20%	REFERENCE 1.02 (0.75, 1.39) 2.47 (1.42, 4.29)	0.002

*
as assessed by Brief Pain Inventory Worst Pain score