available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Brief Correspondence

# Association Between RECIST Changes and Survival in Patients with Metastatic Castration-resistant Prostate Cancer Receiving Docetaxel

*Guru Sonpavde* [a,†,*], *Gregory R. Pond* [b,†], *Arnoud J. Templeton* [c], *Abderrahim Fandi* [d], *Bertrand Tombal* [e], *Mark Rosenthal* [f], *Andrew J. Armstrong* [g], *Daniel P. Petrylak* [h]

[a] *University of Alabama, Birmingham (UAB) School of Medicine, Birmingham, AL, USA;* [b] *McMaster University, Hamilton, Ontario, Canada;* [c] *Department of Medical Oncology and Hematology, Kantonsspital St. Gallen, St. Gallen, Switzerland;* [d] *Celgene Corporation, Summit, NJ, USA;* [e] *Cliniques universitaires Saint Luc, Brussels, Belgium;* [f] *Royal Melbourne Hospital, Parkville, Australia;* [g] *Duke Cancer Institute, Durham, NC, USA;* [h] *Yale University, New Haven, CT, USA*

**Article info**

***Article history:***
Accepted October 5, 2015

***Associate Editor:***
Giacomo Novara

***Keywords:***
Castration-resistant prostate cancer
Response Evaluation Criteria in Solid Tumors
Response
Overall survival

**Abstract**

We explored the association between Response Evaluation Criteria in Solid Tumors (RECIST) 1.0 and 1.1 changes and overall survival (OS) in patients with metastatic castration-resistant prostate cancer (mCRPC) from the control arms of the VENICE and MAINSAIL phase 3 trials, respectively, receiving docetaxel, prednisone, and placebo. We used Cox proportional hazards regression to evaluate the OS prognostic ability of RECIST changes after adjusting for prognostic factors. In the VENICE trial, the OS hazard ratio (HR) was 0.64 (95% confidence interval [CI] 0.42–0.99; $p = 0.045$) for patients with a partial response (PR) compared to those without PR, and 1.78 (95% CI 1.07–2.95; $p = 0.026$) for those with progressive disease (PD) compared to those without PD. After adjusting for prostate-specific antigen (PSA) changes, PD remained significant (HR 1.85, 95% CI 1.10–3.12; $p = 0.020$). Data from the MAINSAIL trial corroborated the association of PR (HR 0.51, 95% CI 0.22–1.18; $p = 0.12$) and PD (HR 3.51, 95% CI 1.92–6.43; $p < 0.001$) with OS. After adjusting for PSA changes, PD was associated with poor OS (HR 2.36, 95% CI 1.11–5.04; $p = 0.026$). Given the association between RECIST changes and OS, more frequent detection of measurable disease with current imaging techniques, and the poor reliability of bone scan and PSA changes, assessment of RECIST changes on treatment with novel agents in patients with measurable tumors may provide an objective signal of efficacy.

***Patient summary:*** In this study, we found an association between changes in objectively measurable tumors according to Response Evaluation Criteria in Solid Tumors (RECIST) and survival in patients with metastatic prostate cancer receiving docetaxel chemotherapy. Since bone scan and prostate-specific antigen changes are unreliable and measurable tumors are more frequently detected now because of better radiographic technology, a focus on RECIST changes should be considered during drug development to provide an objective signal of efficacy.



† These authors contributed equally to this work.
* Corresponding author. UAB Comprehensive Cancer Center, NP2540B, 1802 6th Avenue South, Birmingham, AL 35294, USA. Tel. +1 205 9752914; Fax: +1 205 9753910.
E-mail address: gsonpavde@uabmc.edu (G. Sonpavde).

http://dx.doi.org/10.1016/j.eururo.2015.10.008
0302-2838/

Phase 2 trials evaluating new agents for most solid tumors have assessed measurable disease changes using Response Evaluation Criteria in Solid Tumors (RECIST) to identify benefit [1,2]. By contrast, phase 2 trials investigating agents in metastatic castration-resistant prostate cancer (mCRPC) have not required measurable disease owing to the historically low incidence of measurable tumors. However, the reliability of bone scan and prostate-specific antigen (PSA) changes in capturing benefit is modest [3]. This practice should be revisited since modern imaging is facilitating more frequent detection of measurable tumors in mCRPC. One study demonstrated an association between measurable disease changes according to World Health Organization (WHO) criteria and overall survival (OS) in men with mCRPC receiving chemotherapy [4]. We evaluated the association between RECIST changes and OS in men with mCRPC receiving docetaxel.

Individual patient data from the control arm of the VENICE and MAINSAIL trials were used [5,6]. Both were phase 3 trials in chemotherapy-naïve men with mCRPC who were administered docetaxel and prednisone (DP) with placebo in the control arms. Tumor response was assessed using RECIST 1.0 (VENICE) or RECIST 1.1 (MAINSAIL). In the VENICE trial, progression was defined as an increase in measurable disease, new lesions on bone scans, or two successive rises in PSA and an absolute increase of ≥2 ng/ml. In the MAINSAIL trial, progression was defined using RECIST 1.1 or progression of bone lesions, but not a PSA rise alone. Cox proportional hazards regression was used to evaluate the association between RECIST outcomes and OS. Outcomes were as follows: partial response (PR), defined as a decrease of ≥30% in the sum of the diameter of all target lesions; stable disease (SD); and progressive disease (PD), defined as an increase in the sum of diameters of target lesions by ≥20% or the appearance of new lesions. The analysis was adjusted for selected baseline clinical prognostic factors. PSA response (unconfirmed PSA decline ≥50%) and PSA progression (unconfirmed PSA increase ≥25%) were also included in the multivariable analysis. A 90-d landmark analysis was conducted for patients who were alive and had follow-up beyond 90 d. All tests were two-sided and $p \leq 0.05$ was considered statistically significant.

A total of 612 and 526 men were recruited to the control arms (DP plus placebo) of the VENICE and MAINSAIL trials, respectively (Supplementary Table 1). In the VENICE trial, measurable tumors according to RECIST 1.0 were present in 363 men (59.3%). Among the 296 patients eligible for landmark analysis of responses, the unconfirmed RECIST result by day 90 was ≥PR, SD, and PD for 71 (24.0%), 202 (68.2%), and 12 (4.1%) men, respectively, while 11 men had no objective response evaluation by day 90; 153 (51.7%) had a PSA response by day 90. In the MAINSAIL trial, measurable tumors according to RECIST 1.1 were evaluable in 464 men (88.2%) for landmark analysis at day 90. By day 90, 64 (13.8%), 296 (63.8%) and 28 (6.0%) had unconfirmed ≥PR, SD, and PD, respectively, while 76 (16.4%) had no measurements by day 90; 210 (45.3%) had a PSA response by day 90.

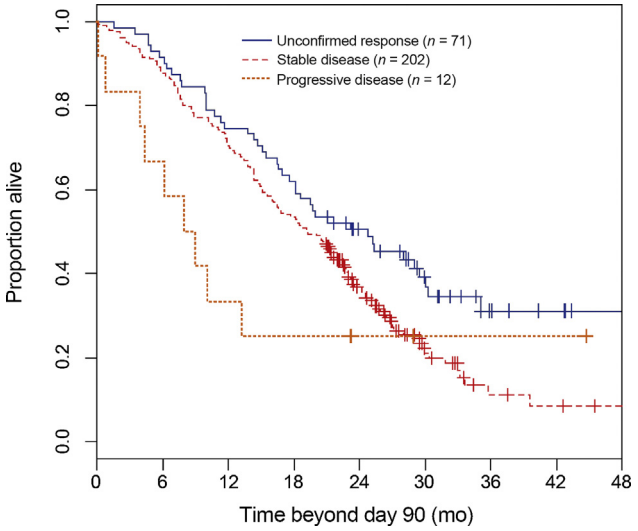


**Fig. 1 – Overall survival based on the RECIST 1.0 response within 90 d for patients in the control arm of the VENICE trial, who received docetaxel, prednisone, and placebo (among 285 evaluable patients with both baseline and day-90 RECIST measurements and subsequent follow-up). RECIST = Response Evaluation Criteria in Solid Tumors.**

The median OS in the VENICE trial was 28.3, 23.3, and 11.4 mo for men with ≥PR, SD, and PD within 90 d, respectively (Fig. 1). For every 10% change in RECIST measurements from baseline, there was an 11.5% (95% CI 6.5–16.8%) change in the hazard of dying. PSA response (HR 0.60, 95% CI 0.49–0.73) and PSA progression (HR 2.17, 95% CI 1.70–2.78) within 90 d were associated with OS. In the MAINSAIL trial, the median OS was not reached and was 15.7 and 7.9 mo for men with unconfirmed RECIST ≥PR, SD, and PD within 90 d, respectively; the corresponding 1-yr OS was 84.8%, 74.2%, and 43.4% (Fig. 2). PSA response (HR 0.42, 95% CI 0.26–0.68) and PSA progression (HR 2.65, 95% CI 1.14–6.15) within 90 d were associated with OS. On multivariable analyses (Supplementary Table 2) of VENICE data including baseline prognostic variables, PSA, and RECIST 1.0 changes within 90 d, there was an independent association between PD by day 90 and OS (HR 1.85; $p = 0.020$). In the MAINSAIL data set including baseline variables, PSA, and RECIST 1.1 changes within 90 d (Supplementary Table 3), PD by day 90 was associated with OS (HR 2.86; $p = 0.007$).

Although radiographic progression according to bone scans and objective progression appears to be associated with OS in specific settings, its applicability across all agent classes is unclear [7,8]. The benefits observed in terms of radiographic progression-free survival and bone scan improvements for treatment with tasquinimod and cabozantinib, respectively, did not translate to increases in OS in phase 3 trials. PSA alterations within 90 d are associated with OS in the setting of chemotherapy, but the relevance of PSA changes on treatment with biologic agents is unclear [9]. The phenomenon of PSA or bone scan flares is also a confounding factor [10].

Our study is limited by the retrospective design, although the remarkably similar association of both RECIST