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Association of *SPOP* Mutations with Outcomes in Men with De Novo Metastatic Castration-sensitive Prostate Cancer

Umang Swami[a], **Pedro Isaacsson Velho**[b], **Roberto Nussenzveig**[a], **Jonathan Chipman**[c,d], **Victor Sacristan Santos**[e], **Stephanie Erickson**[f], **Divya Dharmaraj**[g], **Ajjai Shivaram Alva**[f], **Ulka N. Vaishampayan**[g], **John Esther**[a], **Andrew W. Hahn**[h], **Benjamin Louis Maughan**[a], **Emmanuel S. Antonarakis**[b,*], **Neeraj Agarwal**[a,*]

[a]Department of Internal Medicine, Huntsman Cancer Institute, University of Utah, Salt Lake City, UT, USA

[b]Sidney Kimmel Comprehensive Cancer Center, John Hopkins University, Baltimore, MD, USA

[c]Division of Biostatistics, Department of Population Health Sciences, University of Utah, Salt Lake City, UT, USA

[d]Cancer Biostatistics Shared Resource, Huntsman Cancer Institute, University of Utah, Salt Lake City, UT, USA

[e]Complejo Hospitalario Universitario de Pontevedra, Pontevedra, Spain

[f]University of Michigan Comprehensive Cancer Center, Ann Arbor, MI, USA

[g]Karmanos Cancer Center, Wayne State University, Detroit, MI, USA

[h]Division of Cancer Medicine, MD Anderson Cancer Center, Houston, TX, USA

Abstract

[*]Corresponding authors. Huntsman Cancer Institute, University of Utah (NCI-CCC), 2000 Circle of Hope Drive Suite 5726, Salt Lake City, UT 84112, USA. Tel. +1801-213-5658; Fax: +18015850124 (N. Agarwal). Departments of Oncology and Urology, Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University, School of Medicine, 201 N Broadway, Baltimore, MD, USA. Tel. +1-410-502-8341 (E.S. Antonarakis). neeraj.agarwal@hci.utah.edu (N. Agarwal); eantona1@jhmi.edu (E.S. Antonarakis).

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Study concept and design: Agarwal, Antonarakis.

Acquisition of data: Swami, Velho, Nussenzveig, Chipman, Santos, Erickson, Dharmaraj, Alva, Vaishampayan, Esther, Hahn, Maughan, Antonarakis, Agarwal.

Analysis and interpretation of data: Swami, Velho, Nussenzveig, Chipman, Santos, Erickson, Dharmaraj, Alva, Vaishampayan, Esther, Hahn, Maughan, Antonarakis, Agarwal.

Drafting of the manuscript: Swami, Velho, Nussenzveig, Chipman, Santos, Erickson, Dharmaraj, Alva, Vaishampayan, Esther, Hahn, Maughan, Antonarakis, Agarwal.

Critical revision of the manuscript for important intellectual content: Swami, Velho, Nussenzveig, Chipman, Santos, Erickson, Dharmaraj, Alva, Vaishampayan, Esther, Hahn, Maughan, Antonarakis, Agarwal.

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Recently, mutations in speckle-type pox virus and zinc finger protein (*SPOP*) gene (mutant *SPOP* [*mtSPOP*]) have been associated with improved outcomes to abiraterone in the castration-resistant setting. We hypothesized that *mtSPOP* would be associated with improved outcomes to systemic therapy in men with de novo metastatic castration-sensitive prostate cancer (d-mCSPC). Retrospective data of newly diagnosed d-mCSPC patients were collected from four institutions. Eligibility criteria included standard androgen deprivation therapy without intensification, and *SPOP* mutational status (*mtSPOP* or wild-type *SPOP* [*wtSPOP*]) determination by targeted next-generation sequencing from tumor biopsies. A total of 121 men (25 *mtSPOP* [21%] and 96 *wtSPOP* [79%]) were included. After adjusting for covariates, *mtSPOP* was significantly associated with better median progression-free survival (35 vs 13 mo; adjusted hazard ratio [HR] 0.47; $p = 0.016$) and overall survival (97 vs 69 mo; adjusted HR 0.32; $p = 0.027$), with similar HR and p value on the univariate analysis. These findings, upon external validation, may assist with counseling and prognostication in the clinic, and inform the design of future clinical trials in this setting.

Patient summary:

Presence of tumor mutation in speckle-type pox virus and zinc finger protein (*SPOP*) gene was associated with improved survival outcomes in men with de novo metastatic castration-sensitive prostate cancer receiving standard androgen deprivation therapy.

Keywords

SPOP; Androgen deprivation therapy; Progression-free survival; Overall survival; Metastatic hormone-sensitive prostate cancer

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Genomic markers associated with outcomes to systemic therapy are not currently used in the clinic in men with metastatic prostate cancer. These markers have the potential to assist with prognostication and shared decision making with patient, and inform the design of future clinical trials in this setting.

Recurrent missense mutations in the gene encoding speckle-type pox virus and zinc finger (POZ) protein (*SPOP*) are the most common point mutations in primary prostate cancer, with an estimated incidence of 10% in clinically localized prostate cancer and a slightly lower prevalence in metastatic castration-resistant prostate cancer (mCRPC) [2,3]. Recently, Boysen et al [4] reported, in a single-center study involving 89 men diagnosed with mCRPC, that men harboring mutant *SPOP* (*mtSPOP*) treated with abiraterone ($n = 17$) had an improved prostate-specific antigen (PSA) 50% response rate (odds ratio 14.5, $p = 0.001$) and a longer time on abiraterone (hazard ratio [HR] 0.37; $p = 0.002$) as compared with men with wild-type *SPOP* (*wtSPOP*).

Based on these data, we hypothesized that *mtSPOP* would be associated with improved outcomes to systemic therapy in men with de novo metastatic castration-sensitive prostate cancer (d-mCSPC). Herein, we report the results of a retrospective multicenter investigation on the impact of *mtSPOP* on outcomes in men diagnosed with d-mCSPC.

Patient data were retrospectively collected from four academic institutions. Eligibility criteria included the receipt of standard androgen deprivation therapy (sADT) without treatment intensification, diagnosis of d-mCSPC (defined as metastatic prostate cancer with no prior history of treatment for prostate cancer), and established *SPOP* mutational analysis (*mtSPOP* or *wtSPOP*) as determined by targeted next-generation sequencing (NGS) of a tumor tissue biopsy by a Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory (Foundation Medicine, Caris Life Sciences, Myriad Genetics, and previously published platforms [5]; Supplementary Table 1). The primary outcomes of interest included progression-free survival (PFS) and overall survival (OS). The study was performed with the approval of the Institutional Review Boards of each respective institution.

The primary analysis compared the hazard of having *mtSPOP* on PFS and OS (vs *wtSPOP*), as estimated using the Mantel-Haenszel test. PFS was determined as PSA or radiographic or clinical progression as per the modified Prostate Cancer Working Group 2 (PCWG2) criteria [6], from the time of starting sADT. OS was defined as the time from starting sADT to death from any cause or loss to follow-up (the last date of evaluation by the treating physician).

Baseline patient characteristics were compared between men with *mtSPOP* and *wtSPOP* (Table 1). Differences in age and baseline PSA were evaluated by Kruskal-Wallis test, while race and Gleason score were compared using chi-square test. A Cox proportional hazards model was fit to estimate the covariate-adjusted hazard. The adjusted model accounted for age, baseline PSA, and Gleason score. Missing data were imputed from 100 chained equations and conditioning on *mtSPOP* exposure and the adjusting covariates. Wald test was used to determine statistical significance of the HR comparing *mtSPOP* versus *wtSPOP* with respect to PFS and OS. Interactions between *mtSPOP* and each covariate were tested to assess effect modifications.

Of 937 patients with metastatic prostate cancer, who received treatment between May 21, 2007 to May 28, 2019 and had targeted NGS testing, 121 men met all the eligibility criteria and were included in the analysis (flow diagram in Supplementary Fig. 1). In this cohort, 82 patients did not experience death and were followed for a median of 33.9 mo, and 36 patients did not progress on disease and were followed for a median of 13.3 mo. Twenty-five men (21%) harbored an *mtSPOP* and 96 (79%) had *wtSPOP*. Baseline characteristics including age, Gleason score, and PSA were similar between the *mtSPOP* and *wtSPOP* cohorts (Supplementary Table 2). The patterns of metastasis at initial presentation are presented in Supplementary Table 3.

Men harboring *mtSPOP* had significantly improved median PFS compared with those with *wtSPOP* after adjusting for clinical covariates (35 vs 13 mo, adjusted HR [aHR] 0.47, 95% confidence interval [CI] 0.25–0.87; $p = 0.016$; Table 1 and Fig. 1A). Similarly, the median OS was significantly higher in men with mCSPC with *mtSPOP* than in those with *wtSPOP* (97 vs 69 mo, aHR 0.32, 95% CI 0.12–0.88; $p = 0.027$; Fig. 1B). The HR and p value for PFS and OS on univariate analysis were similar to aHR.

There was no observed effect modification of baseline age or total Gleason score; however, lower baseline PSA was associated with a stronger *mtSPOP* protective effect. An increase in

PSA of 50 ng/ml further increased the PFS HR by 1.10 (95% CI 1.01–1.20; $p = 0.033$) and the OS HR by 1.14 (95% CI 1.02–1.27; $p = 0.019$) in patients with mtSPOP. Supplementary Figure 2 demonstrates PFS and OS of individual patients (in the same chronological order as Supplementary Table 1). In a post hoc multivariable analysis, after adjusting for BRCA2, PTEN, RB1, and TMPRSS2-ERG mutations, mtSPOP was still significant for PFS (aHR 0.48, 95% CI 0.24–0.95; $p = 0.034$), and although we saw some evidence of improved OS, it did not meet conventional levels of statistical significance (aHR 0.32, 95% CI 0.12–1.02; $p = 0.054$).

We show significantly improved survival outcomes in men with d-mCSPC harboring *mtSPOP* and undergoing sADT. Recently, longer time on treatment with first-line abiraterone and/or enzalutamide has been reported in men with mCRPC [4,7]. SPOP mutations often occur in MATH domain and are determined to be an early event in prostate cancer tumorigenesis (Supplemental Fig. 3) [8]. SPOP protein acts as a substrate adaptor for the CUL3-based E3 ubiquitin-protein ligase complex for ubiquitinating target proteins, which thereafter undergo proteasomal degradation [9,10]. Androgen receptor (AR) is a target for ubiquitination in prostate cancer. Hence, SPOP mutations may lead to increased tumor AR protein levels [9,11–13]. Additionally, evidence suggests that *SPOP* functions as a tumor suppressor gene by enhancing degradation of multiple oncogenic substrates, such as AR, SRC3, ERG, TRIM24, c-Myc, DEK, SENP7, EglN2, ATF2, Cdc20, BRD4, PD-L1, and cyclin E1, and mtSPOP leads to tumor genomic instability [8,14,15]. Furthermore, results from The Cancer Genome Atlas shows that mtSPOP (along with FOXA1) has the highest AR transcriptional activity of all genotypically distinct prostate cancer subsets [16]. Based on these data, we hypothesized that mtSPOP prostate cancer may primarily be driven by AR signaling and thus in turn will be more responsive to androgen/AR targeted therapy.

The strength of our study is its multi-institutional cohort design and homogeneity in the study population. We included men with d-mCSPC only, as prior ADT (with or without other systemic therapies) in the localized prostate cancer setting can attenuate the response to ADT in the subsequent metastatic setting. Moreover, inclusion of patients who received ADT with intensified treatment (docetaxel or novel androgen-axis inhibitors) would have resulted in treatment and outcome heterogeneity. Many of these biases, confounders, and effect modifiers were reduced by the inclusion of only de novo mCSPC patients treated with ADT alone. A limitation of our study is the inability to analyze the impact of CHD1 loss due to limitations of testing platforms. CHD1 deletions have been reported to coexist with SPOP mutations [4]. It is possible that sensitivity to hormonal therapies is driven by CHD1 loss and not by SPOP mutation. Finally, our study still remains prone to the most common limitations associated with a retrospective design.

Men with *d*-mCSPC and *mtSPOP* have improved PFS and OS on standard first-line ADT compared with men with *d*-mCSPC and *wtSPOP*. These findings warrant prospective validation in larger datasets. If confirmed, these novel results could aid in the design of future trials involving men with *d*-mCSPC.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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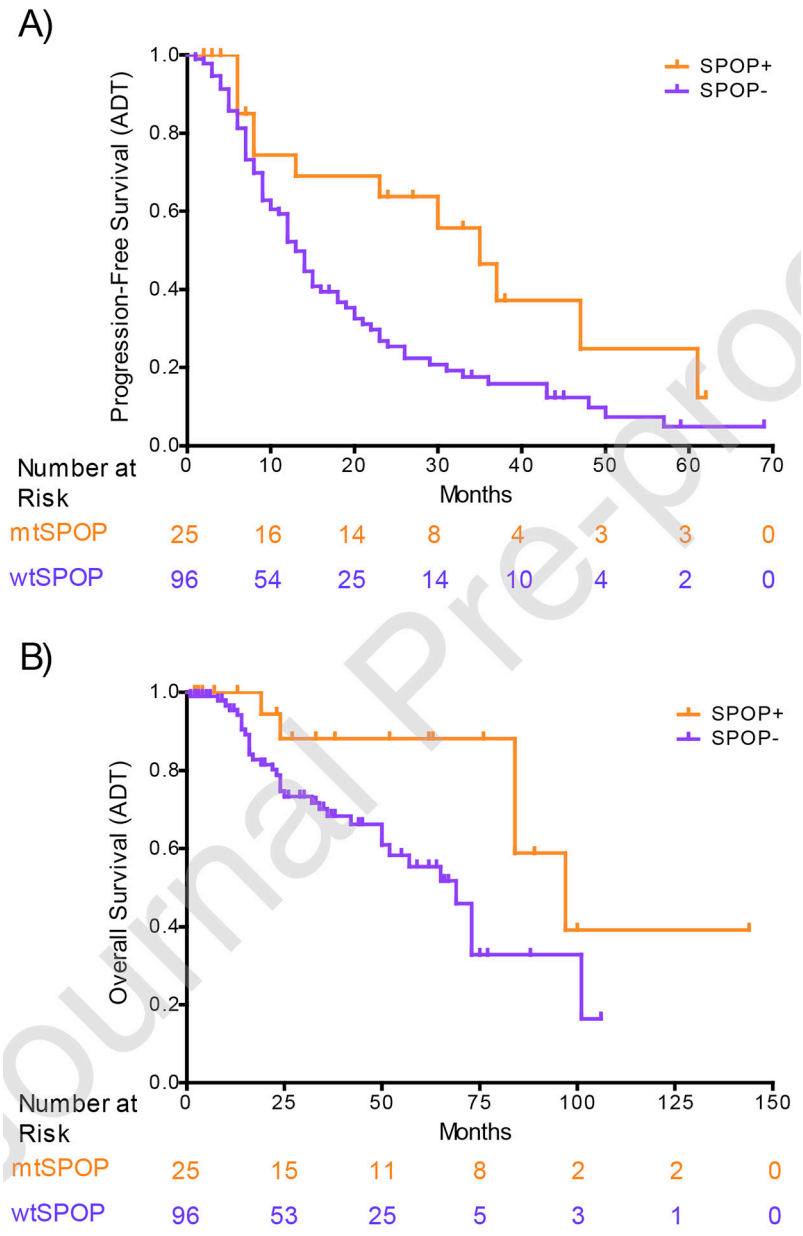

Fig. 1 –.

Kaplan-Meier (A) progression-free survival and (B) overall survival curves of men with de novo metastatic castration-sensitive prostate cancer with mutant SPOP (*mtSPOP*) and wild-type SPOP (*wtSPOP*). ADT = androgen deprivation therapy; SPOP = speckle-type pox virus and zinc finger protein.

Table 1 –

Multivariable Cox proportional hazards model

Variable	Progression-free survival			Overall survival		
	Hazard ratio	95% CI	*p* value	Hazard ratio	95% CI	*p* value
Mutant SPOP	0.47	0.25–0.87	0.016	0.32	0.12–0.88	0.027
Age	0.93	0.68–1.28	0.7	1.00	0.62–1.62	>0.9
Baseline PSA	1.04	1.00–1.10	0.044	0.97	0.85–1.11	0.7
Gleason Sum	1.40	1.01–1.93	0.040	1.36	0.84–2.2C	0.21

CI = confidence interval; PSA = prostate-specific antigen; SPOP = Speckle-type pox virus and zinc finger protein.