Original Article

Landscape and prognostic significance of oncogene drivers in metastatic castration sensitive prostate cancer

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Background: Tumor suppressors are well known drivers of cancer invasion and metastasis in metastatic castration sensitive prostate cancer (mCSPC). However, oncogenes are also known to be altered in this state, however the frequency and prognosis of these alterations are unclear. Thus, we aimed to study the spectrum of oncogene mutations in mCSPC and study the significance of these alteration on outcomes.

Methods: Four hundred and seventy-seven patients with mCSPC were included who underwent next generation sequencing. Oncogene alterations were defined as mutations in *ALK*, *AKT1-3*, *BRAF*, *CCND1-3*, *CTNNB1*, *EGFR*, *ERBB2*, *FGFR1*, *FGFR2*, *HRAS*, *KRAS*, *MDM2*, *MET*, *MITF*, *MYC*, *NOTCH1-3*, *NRAS*, *PIK3CA*, *PI3KCB*, *PIK3R1*, *RET*. Endpoints of interests were radiographic progression-free survival (rPFS), time to development of CRPC (tdCRPC), and overall survival (OS). Kaplan Meier analysis was performed and Cox regression hazard ratios (HR) calculated.

Results: A total of 477 patients were included with baseline characteristics with 117 patients (24.5%) harbored a mutation within an oncogene. A total of 172 oncogene mutations were found within the population with the most common being *MYC* (n=29; 16.9%), *PIK3CA* (n=24; 14%), *CTNNB1* (n=22, 12.8%), *BRAF* (n=10, 5.8%), and *CCND1* (n=10, 5.8%). Oncogene mutations were associated with inferior rPFS (19.2 *vs.* 32.2 months, P=0.03), tdCRPC (15.7 *vs.* 32.4 months, P<0.001), and OS (5-year OS 75.3% *vs.* 55.4%, P=0.01). On multivariable analysis oncogene mutations were strongly associated with tdCRPC (HR 1.42, P=0.03).

Conclusions: Oncogenes are frequency mutated in mCSPC and associated with aggressive features and inferior outcomes. Future work will need to validate these results to better assess its significance in allowing for personalization of care.

Keywords: Prostate cancer; oncogene; metastatic castration sensitive

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Introduction

Prostate cancer represents one of the most frequently diagnosed malignancies in the United States, and when locally advanced or metastatic, represents a substantial cause of morbidity and mortality for patients (1). Significant improvements in treatment options are now available for patients with metastatic prostate cancer (2-6), and often times have been developed by taking advantage of precision medicine approaches (7-9). These advancements have been facilitated by an increasing understanding of prostate cancer genomics. Within metastatic castration resistant prostate cancer (mCRPC) alterations in pathways related to DNA damage repair and androgen receptor (AR) signaling are drivers of cancer invasion and metastasis and prognosis for patients (10-12). In localized non metastatic prostate cancer, similar pathways are altered in addition to *SPOP* and *FOXA1* (13).

Despite our increasing knowledge of localized and mCRPC genomics, relatively less is reported on the genetic landscape of metastatic castration sensitive prostate cancer (mCSPC) (10-13). Recent work reported by Deek *et al.*, Sutera *et al.*, and Stopsack *et al.* suggests alterations in pathways and genes including *TP53*, the Wnt pathway, and DNA damage repair are important causes of disease progression and provides information regarding response to therapy in mCSPC (14-16). Within mCSPC, the prognostic significance of tumor suppressors is best elucidated. Work by Hamid *et al.* suggests mutations, especially compound alterations, in *TP53*, *PTEN*, and *Rb1* are associated with poor prognosis in mCSPC (17). On the other hand, the impact of alterations in oncogenes is less understood. These mutations are much less frequent in incidence likely contributing to this. Therefore, this study aimed to profile the spectrum of oncogene mutations in mCSPC and assess their prognostic significance on outcomes. We present this article in accordance with the REMARK reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-123/rc).

Highlight box

Key findings

- Oncogene alterations are commonly seen in metastatic castration sensitive prostate cancer.
- These alterations appear to be associated with poor prognosis.

What is known and what is new?

- It is well known tumor suppressor genes are commonly altered in metastatic castration sensitive prostate cancer.
- We report here that oncogenes are also commonly altered in metastatic castration sensitive prostate cancer and are associated with poor prognosis.

What is the implication, and what should change now?

- An understanding of the significance of oncogene alterations in metastatic castration sensitive prostate cancer can allow for more personalized therapy and targeting of these mutations to improve treatment outcomes.

Methods

Patients with mCSPC were retrospectively included in the analysis. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Rutgers University institutional review board (Pro2021002438) and individual consent for this retrospective analysis was waived. Patients underwent standard of care next generation sequencing (NGS) using College of American Pathologists-Clinical Laboratory Improvement Amendments certification approved panels including Foundation One CDx (324-gene panel), Personal Genome Diagnostics CancerSELECT 125 (125-gene panel) and Tempus xT (648 genes) assays on the primary tumor or castration sensitive metastatic site. Alterations were defined as pathogenic alterations in known oncogenes according to the commercial tests or publicly available COSMIC tumor variant database as previously described. Oncogenes of interest included *ALK*, *AKT1-3*, *BRAF*, *CCND1-3*, *CTNNB1*, *EGFR*, *ERBB2*, *FGFR1*, *FGFR2*, *HRAS*, *KRAS*, *MDM2*, *MET*, *MITF*, *MYC*, *NOTCH1-3*, *NRAS*, *PIK3CA*, *PI3KCB*, *PIK3R1*, *RET*. Variants of unknown significance (VUS) or alterations not listed in COSMIC were not considered pathogenic.

Statistical analysis

Endpoints of interest were time to radiographic progression-free survival (rPFS; defined as development of new metastasis, growth of existing metastasis, or death), time to development of CRPC (tdCRPC) [according to Prostate Cancer Working Group 3 criteria (18)], and overall survival (OS), each measured from the time of development of metastatic disease. Baseline characteristics were compared using a Pearson's χ^2 test or Fisher's exact test for categorical variables, and Wilcoxon rank-sum test or *t*-test for continuous variables. Kaplan-Meier survival analysis was performed to calculate median time to rPFS, tdCRPC,

Table 1 Baseline characteristics

Characteristic	Oncogene mutation	No oncogene mutation	P value
Grade group			<0.001
1	4 (3.4)	10 (2.8)	
2	5 (4.3)	29 (8.1)	
3	9 (7.7)	62 (17.2)	
4	13 (11.1)	52 (14.4)	
5	71 (60.7)	195 (54.2)	
NA	15 (12.8)	12 (3.3)	
N stage			<0.001
N0	49 (41.9)	204 (56.7)	
N1	53 (45.3)	119 (33.1)	
Nx	14 (12.0)	15 (4.2)	
NA	1 (0.9)	22 (6.1)	
M stage			0.001
M0	45 (38.5)	205 (56.9)	
M1	72 (61.5)	155 (43.1)	
Met location			<0.001
Bone	65 (55.6)	215 (59.7)	
Node	22 (18.8)	108 (30.0)	
Visceral	30 (25.6)	33 (9.2)	
NA	0 (0)	4 (1.1)	
Met volume			<0.001
Low	60 (51.3)	263 (73.1)	
High	57 (48.7)	97 (26.9)	
Age, years	64.4 (43.1–89.5)	63.1 (24.7–87.2)	0.07

Data are presented as n (%) or median (interquartile range).

and OS, which were stratified by variables of interest and compared using the log-rank test. Univariable Cox regression was performed to calculate hazard ratios (HR) and 95% confidence intervals (CI) for variables to assess their association with endpoints described above. Multivariable Cox regression was performed and adjusted for variables *a priori* felt to be associated with outcomes as described previously (14). All analyses were conducted using R.

Results

A total of 477 patients were included with baseline characteristics are shown in *Table 1*. One hundred and seventeen patients (24.5%) harbored a mutation within an oncogene. A total of 172 oncogene mutations were found within the population with the most common being *MYC* (n=29; 16.9%), *PIK3CA* (n=24; 14%), *CTNNB1* (n=22, 12.8%), *BRAF* (n=10, 5.8%), and *CCND1* (n=10, 5.8%, Table S1).

Mutations within oncogenes were associated with more aggressive disease features including higher rates of *de novo* metastatic disease (61.5% *vs.* 43.1%, P=0.001), high volume disease (48.7% *vs.* 26.9%), and higher prostate-specific antigen (PSA) (33.4 *vs.* 14.6 ng/mL).

Oncogene mutations were associated with inferior rPFS (19.2 *vs.* 32.2 months, P=0.03, *Figure 1A*), tdCRPC (15.7 *vs.* 32.4 months, P<0.001, *Figure 1B*), and OS (5-year OS 75.3% *vs.* 55.4%, P=0.01, *Figure 1C*). Compound mutations were also associated with worse median OS (none: 94.2 months, one: 96.1 months, two: 62.8 months, P=0.02, Figure S1). When looking at specific mutations, *MYC* alterations were associated with poorer rPFS (median 19.8 *vs.* 28.8 months, P=0.27), tdCRPC (median 15.7 *vs.* 32.4 months, P<0.001), and OS (median 42.9 *vs.* 101.5 months, P=0.01, *Figure 2A-2C*). *CTNNB1* mutations were associated with inferior tdCRPC (median 14.7 *vs.* 29.8 months, P=0.01), but not rPFS (median 28.8 *vs.* 27.6 months, P=0.86) nor OS [median not reached (NR) *vs.* 96.1 months, P=0.12, *Figure 3A-3C*]. *PIK3CA* mutations were not associated with rPFS (27.1 *vs.* 28.2 months, P=0.59), tdCRPC (16.9 *vs.* 29.1 months, P=0.26), or OS (NR *vs.* 96.1 months, P=0.44, Figure S2A-S2C).

On univariate analysis, oncogene mutations were associated with poorer rPFS (HR 1.35, 95% CI: 1.03–1.77, P=0.03), tdCRPC (HR 1.81, 95% CI: 1.37–2.40, P<0.001), and OS (HR 1.78, 95% 1.16–2.73, P=0.01, Table S2). Several other factors were associated with outcomes of interest on univariate analysis including *de novo* metastasis and low volume disease. On multivariable analysis, oncogene mutations were strongly associated with tdCRPC (HR 1.42, 95% CI: 1.03–1.95, P=0.03) and mildly associated with rPFS (HR 1.30, 95% CI: 0.96–1.77, P=0.09, *Table 2*). Other factors associated with outcomes were low volume disease (rPFS HR 0.73, P=0.09; tdCRPC HR 0.47, P<0.001; OS HR 0.54, P=0.03) and Gleason grade group (tdCRPC HR 1.28, P=0.002; OS HR 1.43, P=0.02).

Tumor suppressor alterations in relation to oncogene mutation status is shown in *Figure 4*. *TP53* (38% *vs.* 30%, P=0.09) and *PTEN* (33% *vs.* 24%, P=0.05) mutations were more common in oncogene mutated tumors.

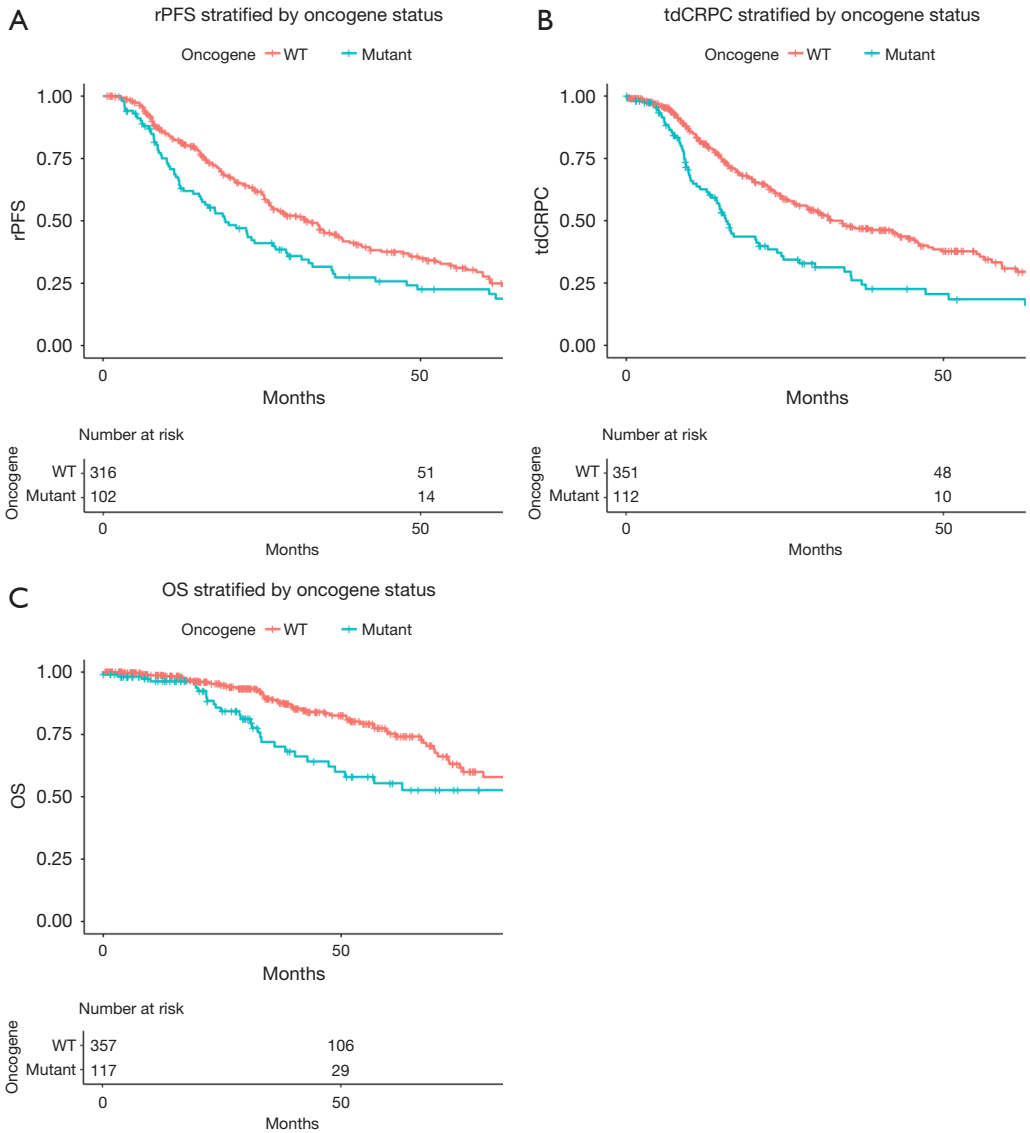

Figure 1 rPFS (A), tdCRPC (B), and OS (C) stratified by oncogene. mutational status. Oncogene alterations were associated with inferior rPFS (19.2 *vs.* 32.2 months, P=0.03), tdCRPC (15.7 *vs.* 32.4 months, P<0.001), and OS (5-year OS 75.3% *vs.* 55.4%, P=0.01). WT, wild type; rPFS, radiographic progression-free survival; tdCRPC, time to development of castration resistant prostate cancer; OS, overall survival.

Discussion

Our understanding of the genomic landscape of prostate cancer, especially mCSPC, is rapidly expanding. Much is known regarding the significance of tumor suppressor genes (14,17,19), however the role of oncogene mutations is less studied. As such, the goal of this investigation was to better understand the landscape of oncogenes in mCSPC as well as understand their prognostic significance within this state. This study identified *MYC*, *PIK3CA*, and *CTNNB1* mutations were frequently seen in mCSPC. We note alterations in oncogenes were associated with more aggressive features such as higher Gleason score and rates of *de novo* metastasis, and was associated with poor prognosis such as tdCRPC and rPFS. These alterations were also noted to be more common in patients who were *PTEN* and *TP53* mutated.

The most commonly mutated oncogene in our population was *MYC*, which was associated with poorer rPFS (median 19.8 *vs.* 28.8 months, P=0.27), tdCRPC

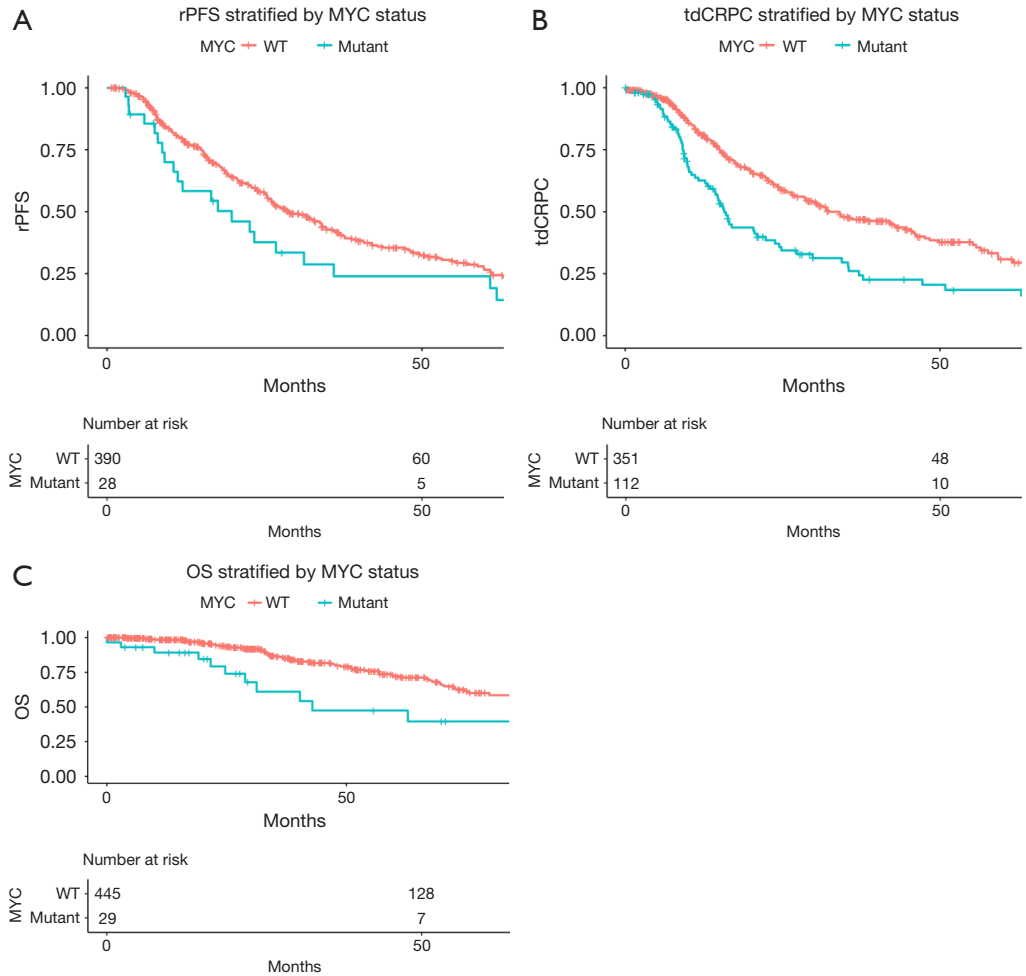

Figure 2 rPFS (A), tdCRPC (B), and OS (C) stratified by *MYC* mutational status. *MYC* alterations were associated with poorer rPFS (median 19.8 *vs.* 28.8 months, P=0.27), tdCRPC (median 15.7 *vs.* 32.4 months, P<0.001), and OS (median 42.9 *vs.* 101.5 months, P=0.01). WT, wild type; rPFS, radiographic progression-free survival; tdCRPC, time to development of castration resistant prostate cancer; OS, overall survival.

(median 15.7 *vs.* 32.4 months, P<0.001), and OS (median 42.9 *vs.* 101.5 months, P=0.01) within the population. The prognostic significance of *MYC* within prostate cancer is unclear with conflicting results regarding the significance of overexpression as it relates to biochemical recurrence following radical prostatectomy (20,21), but some studies suggest it is associated with tdCRPC (19). However, *MYC* is well known to be important in driving progression within pre-clinical models suggesting its importance in cancer invasion and metastasis in prostate cancer (22). Our results seem to be more in line with suggestions that *MYC* is a poor prognostic feature within mCSPC given its negative association with rPFS, tdCRPC, and OS.

Expression of *MYC* is highly dependent on BRD4, a member of the bromodomain and extra-terminal (BET) family. BRD4 recognizes acetylated lysine residues of histone 4 and recruits transcription factors for expression of multiple genes, most notably *MYC* (23). This is the rationale for the development of BET inhibitors (BETi), which have been found to attenuate growth via G1 cell cycle arrest and subsequent apoptosis in ovarian cancer. Furthermore, *MYC* overexpressing ovarian cancers were found to be sensitive to BETi treatment, thereby building the case for BRD4's role in *MYC* expression and uncontrolled cell proliferation (24). In prostate cancer, *MYC* has been demonstrated to be a downstream mediator of AR signaling and can drive cell growth in the absence of androgen, which suggests a role for *MYC* in progression of mCRPC (25-27). However, it is

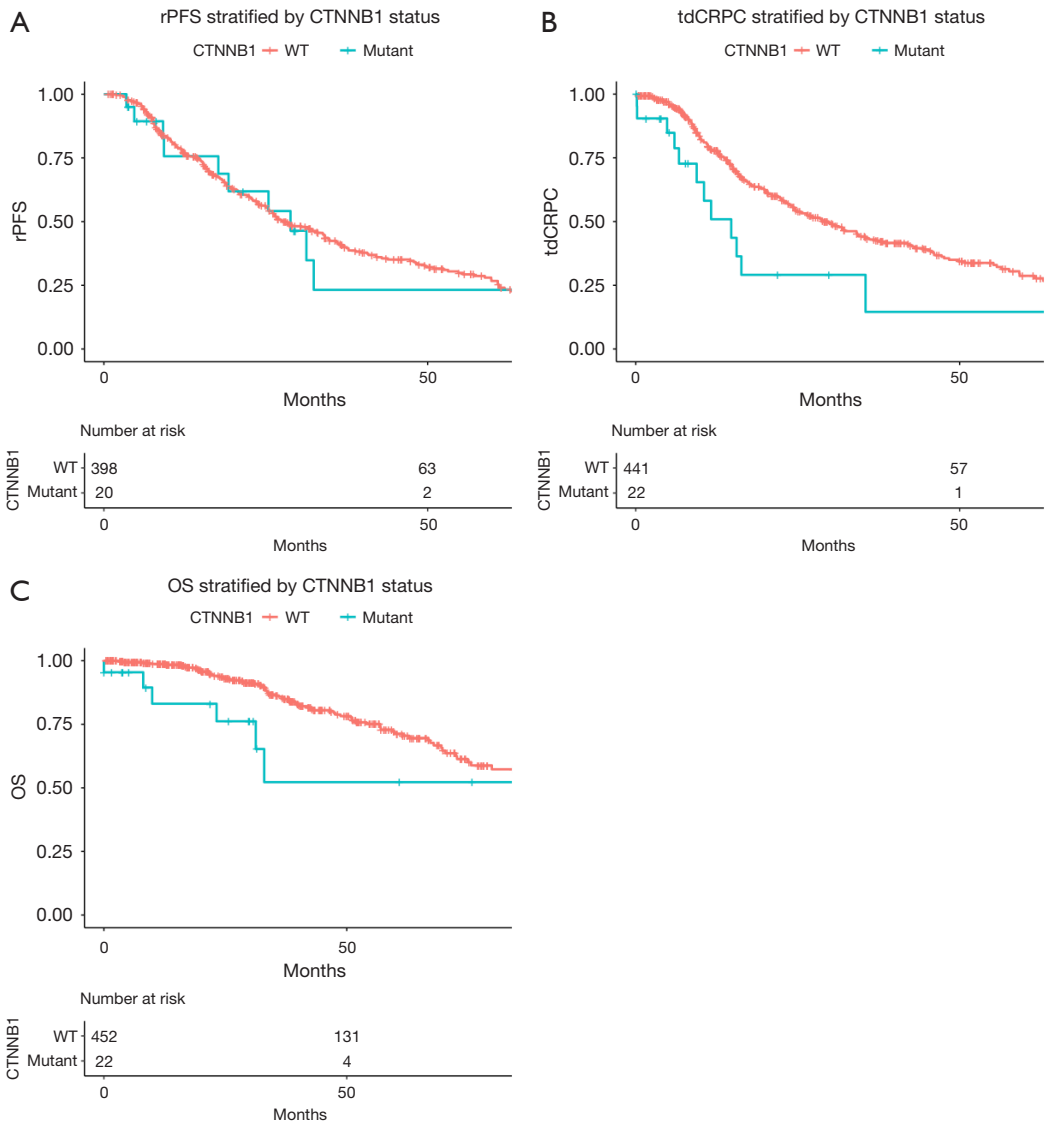

Figure 3 rPFS (A), tdCRPC (B), and OS (C) stratified by *CTNNB1* mutational status. *CTNNB1* mutations were associated with inferior tdCRPC (median 14.7 *vs.* 29.8 months, P=0.01), but not rPFS (median 28.8 *vs.* 27.6 months, P=0.86) nor OS (median NR *vs.* 96.1 months, P=0.12). WT, wild type; rPFS, radiographic progression free survival; tdCRPC, time to development of castration resistant prostate cancer; OS, overall survival; NR, not reached.

significance in mCSPC is less well understood. Additionally, BET family proteins facilitate AR expression via interaction with the N-terminal which is preserved in AR-V7, a key splice variant of AR that is constitutively active and thought to be a mechanism of resistance to ADT and progression of mCSPC (27). These molecular functions of *MYC* underpin the rationale for BETi use in prostate cancer harboring *MYC* amplifications. Early phase clinical trials are underway to determine the safety and efficacy of BETi in prostate cancer. Some proposed combinations for prostate cancer include BETi plus AR-targeted therapies, AKT/PI3K inhibitors, Wnt signaling inhibitors, and PARP inhibitors (27). BETi is therefore a promising avenue to treat specific patients found to have *MYC* amplifications in the setting of mCSPC. As genomic profiling of different prostate cancers develops, a better understanding of patients' specific prognoses may inform decisions to pursue more aggressive therapy.

Table 2 Multivariable analysis for factors associated with rPFS, tdCRPC, and OS

Characteristic	HR (95% CI)	P value
rPFS		
Oncogene mutation	1.30 (0.96–1.77)	0.09
Gleason group	1.01 (0.89–1.15)	0.83
Met location (*vs.* bone)		
Node	1.14 (0.81–1.58)	0.46
Visceral	0.92 (0.57–1.48)	0.73
De novo metastasis	1.12 (0.83–1.53)	0.46
Low volume (*vs.* high)	0.73 (0.51–1.05)	0.09
Age	1.03 (1.01–1.04)	0.002
tdCRPC		
Oncogene mutation	1.42 (1.03–1.95)	0.03
Gleason group	1.28 (1.09–1.49)	0.002
Met location (*vs.* bone)		
Node	0.77 (0.52–1.14)	0.19
Visceral	0.94 (0.59–1.49)	0.78
De novo metastasis	1.30 (0.94–1.81)	0.12
Low volume (*vs.* high)	0.47 (0.33–0.67)	<0.001
Age	1.02 (1.01–1.04)	0.01
OS		
Oncogene mutation	1.28 (0.77–2.14)	0.33
Gleason group	1.43 (1.07–1.90)	0.02
Met location (*vs.* bone)		
Node	0.68 (0.34–1.32)	0.25
Visceral	1.39 (0.68–2.84)	0.36
De novo metastasis	1.46 (0.85–2.52)	0.17
Low volume (*vs.* high)	0.54 (0.31–0.94)	0.03
Age	1.02 (0.99–1.05)	0.20

rPFS, radiographic progression-free survival; tdCRPC, time to development of castration resistant prostate cancer; OS, overall survival; HR, hazard ratio; CI, confidence interval.

The *PIK3/Akt/mTOR* family genes are commonly altered in prostate cancer, specifically *PIK3CA*, *PIK3CB*, and *PIK3R1* in this study. *PIK3/Akt/mTOR* family genes are commonly overactive in cancer and lead to reduced apoptosis subsequent proliferation, epithelial-to-mesenchymal transition (EMT), and metastasis and in pre-clinical studies, use of PIK3/Akt/mTOR can impair growth and metastasis of prostate tumor cells (28-30) and use of PIK3/Akt/mTOR inhibitors in prostate cancer is well studied and found to impair growth and promote apoptosis of prostate tumor cells (31,32). Within the *PIK3/Akt/mTOR* pathway, *PTEN* is commonly altered within prostate cancer and is a well-known poor prognostic factor associated with adverse pathologic findings such as higher Gleason grade at time of radical prostatectomy and is also known to be associated with more aggressive disease in mCSPC (17,33-36). Within mCSPC, the role of oncogene alteration in the *PIK3/Akt/mTOR* family is less understood. *PIK3/Akt/mTOR* oncogenes are commonly altered within mCSPC as seen in our study, though it is not clear if they are associated with poorer prognosis. We did not note differences in outcomes in our cohort based on *PIK3/Akt/mTOR* status, though sample size was still small and further larger studies are needed. Alterations within the *PIK3/Akt/mTOR* pathway will become more significant given our ability to better target these mutations with systemic agents. Ipatasertib is a small molecule inhibitor of *Akt* and recent evidence demonstrated its combination with Abiraterone in mCRPC resulted in significantly prolonged rPFS (37). Future work will likely continue to integrate molecular knowledge into treatment paradigms of prostate cancer to allow for better treatment personalization and outcomes.

The third most commonly mutated oncogene in our population was *CTNNB1* (13% of oncogene mutations), which was associated with inferior tdCRPC (median 14.7 *vs.* 29.8 months, P=0.01), but not rPFS (median 28.8 *vs.* 27.6 months, P=0.86) nor OS (median NR *vs.* 96.1 months, P=0.12, *Figure 3A-3C*). *CTNNB1* is involved in activation of the Wnt/β-catenin pathway that promotes cell division, proliferation, and EMT and is overexpressed across multiple different cancer types including prostate adenocarcinoma. Wang *et al.* found that mutations of genes in the Wnt/β-catenin pathway were associated with resistance to abiraterone acetate-prednisone treatment in a prospective study of patients with mCRPC (38). Patel *et al.* found that patients with mCRPC who have elevated β-catenin expression have earlier relapse and reduced survival; murine models with β-catenin activation demonstrated refractory response to ADT, thereby suggesting *CTNNB1* mutation's role in driving mCRPC (39). These findings altogether suggest that *CTNNB1* mutation may arise during the mCSPC disease stage and become clinically relevant upon mCRPC progression, in which β-catenin overactivation lends resistance to AR-targeted therapies.

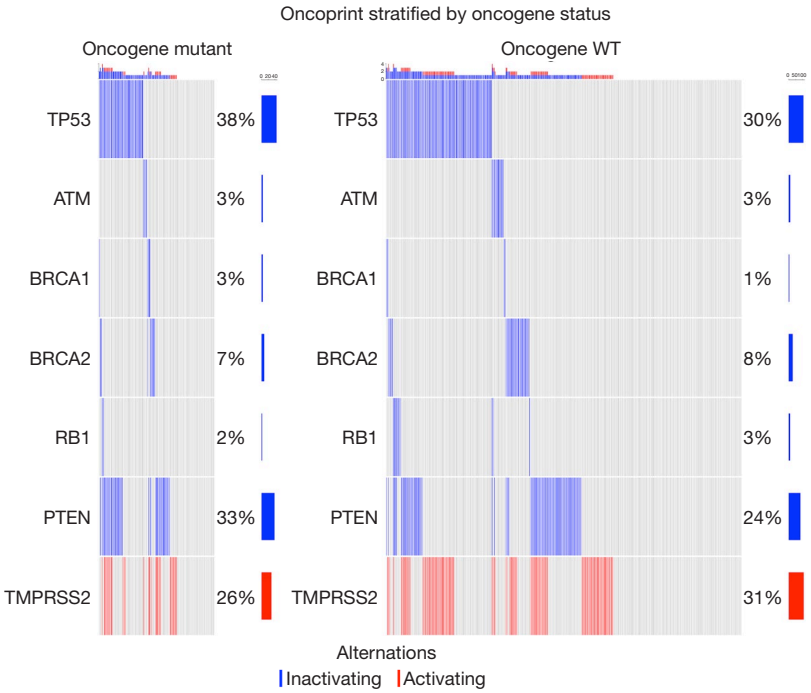

Figure 4 Oncoprint of other mutations of interests split by oncogene mutation status. *TP53* (38% *vs.* 30%, P=0.09) and *PTEN* (33% *vs.* 24%, P=0.05) mutations were more common in oncogene mutated tumors. WT, wild type.

Several other oncogene mutations which are frequently seen in other malignancies, such as *EGFR*, *ALK*, and *BRAF*, are also seen in mCSPC, but with low incidence (5% or less). Kinase inhibitors have been successful in targeting many of these alterations in other malignancies, for example, *EGFR*- and *ALK*-mutant patients with non-small cell lung cancer (NSCLC) or *MEK* inhibitors are used in combination with *BRAF* inhibitors in patients with melanoma, where very high response rate and prolonged progression-free survival (PFS) times are seen (40). Within mCSPC, studying the efficacy of such agents has been challenging given the low incidence of these alterations. In some early phase small studies, tyrosine kinase inhibitors targeting *EGFR* in mCRPC did not show strong efficacy signal. BRAF-MEK inhibitors have typically been used in *BRAF* V600E mutated melanoma, though these *BRAF* alterations mutations are exceedingly rare in prostate cancer with more alterations comprising class II alterations (rearrangements K601E, G469A) (41). However, use of trametinib (*MEK* inhibitor) administration in a patient with a rare prostate cancer harboring SND1-BRAF fusion who was refractory to standard therapies demonstrated dramatic response (42). More research will ultimately be necessary to study these commonly targetable alterations that are seen with less frequency in mCSPC.

This study has several key limitations. First off, it represents a retrospective cohort and data collection and endpoints were not prospectively defined. Thus, this study is susceptible to the caveats of a retrospective study. Multivariable analysis was performed to attempt to mitigate possible confounders but prospective validation will still be necessary. Additionally, genes were limited to those on the panel, which are common mutated with malignant processes, however other oncogenes are known. Finally, biopsies were mostly taken from the primary site, and metastatic lesions may harbor additional oncogenic drivers as the disease progresses, however some evidence suggests driver mutations have high concordance between primary tumor and metastatic sites (43).

Conclusions

In conclusion, oncogene alterations are common within mCSPC. These appeared to be associated with more aggressive disease features and poorer prognosis. Further work will be necessary to study the significance of these

findings and better personalize treatment.

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Footnote

Reporting Checklist: The authors have completed the REMARK reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-123/rc

Data Sharing Statement: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-123/dss

Peer Review File: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-123/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-123/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Rutgers University institutional review board (Pro2021002438) and individual consent for this retrospective analysis was waived.

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