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Biomarkers for Programmed Death-1 Inhibition in Prostate Cancer

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Abstract

Prostate cancer is the second leading cause of cancer death in American men. Despite the common nature of this disease, there is a poor understanding of biomarkers that predict responsiveness to immunotherapeutic agents such as the programmed death-1 (PD-1) and programmed death-ligand 1 (PD-L1) inhibitors. Herein we describe a case of complete remission with pembrolizumab therapy in a metastatic castrate-resistant prostate cancer patient with a complex germline *MSH2* alteration (Boland inversion) in association with a tumor demonstrating high microsatellite instability. Potential utility of high mutational burden assessed by an experimental circulating tumor DNA assay is also shown. The literature concerning biomarkers for PD-1 inhibition is reviewed, including data for various mismatch repair gene deficiencies, microsatellite instability, tumor mutational burden, PD-L1 3' untranslated region mutations, selected *POLE* mutations, and biallelic *CDK12* mutations. Taken together, although prostate cancer is generally believed to be a tumor unresponsive to PD-1 inhibition, careful dissection of tumor biology is able to provide an approach toward predictive biomarkers that has the potential for expanded clinical utility. ***The Oncologist*** 2019;24:444–448

Key Points

- Biomarkers for anti-PD1 and anti-PDL1 therapy are poorly defined in prostate cancer.
- Recent advances are defining new important classes of responsive patients.

Patient Case

A 64-year-old man was diagnosed in December 2015 with Gleason 4 + 5 = 9 prostate cancer. Past medical history was notable only for a colon cancer diagnosed and successfully treated at age 49. The prostate-specific antigen (PSA) was 25 ng/dL; staging revealed pelvic/abdominal nodal metastases only, and androgen deprivation therapy (ADT) was started. The PSA nadir post-ADT was 0.05 ng/dL. By August 2016, the PSA was 16.2 ng/dL despite castrate testosterone. Staging demonstrated new pelvic/abdominal nodal metastases. Thus, metastatic castrate-resistant prostate cancer (CRPC) was evident 7 months after initial ADT. Abiraterone/prednisone began September 2016 with PSA of 21.5 ng/dL. The PSA nadir was 0.01 ng/dL, but progression (both PSA and computed tomography [CT] scan) occurred in April 2017. After progression on abiraterone/prednisone, docetaxel 50 mg/m^2 was administered every 2 weeks for nine cycles. Despite PSA declines, docetaxel was stopped because of poor tolerability. During the midst of his prostate cancer treatments, the patient had a low-grade bladder cancer resected.

The patient's family history included a father with colon cancer diagnosed at age 67 and melanoma at age 90. The mother had an upper gastrointestinal (GI) cancer of unclear origin at age 56, colon cancer at age 66, breast cancer at age 70, and malignant nasal cancer at age 82. No other cancer was known in the family.

Germline genomic testing in March 2017 using the InVitae (San Francisco, CA) 80 gene panel was unremarkable [1]. However, an updated report was issued in November 2017 after InVitae became aware that probes for the Boland inversion in *MSH2* were omitted [2]. The Boland inversion is accompanied by two breakpoints with a resultant inversion of exons 1–7 in the *MSH2* gene. The etiology

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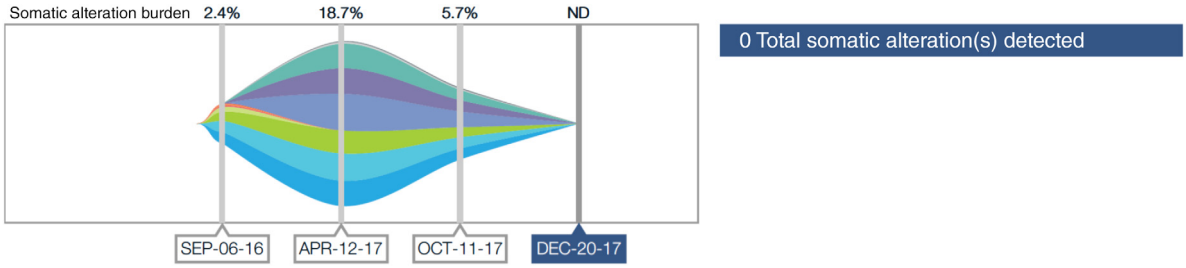

Figure 1. Circulating tumor DNA changes over time in the case described herein.
Abbreviation: ND, not detected.

of this genetic inversion is unknown, but the alteration is associated with Lynch syndrome and loss of expression of the *MSH2* protein [3]. The Boland inversion is detected in 1/1250 Lynch syndrome-spectrum cancers [2] and is present in about 1/14,000 of patients undergoing genetic testing [2]. The testing laboratory retested approximately 50,000 samples after becoming aware of the error.

Prostate cancer biopsies (from diagnosis) were assessed for somatic mutations by Personal Genome Diagnostic (Baltimore, MD). Assays were conducted on 117 cancer-associated gene exons and 29 cancer gene rearrangements. *MSH2* was assessed for mutations but not rearrangements. In the prostate tumor biopsy, microsatellite instability (MSI) was high (2/5 microsatellites assessed by polymerase chain reaction [PCR] were unstable). In addition, 19 mutations (14 missense mutations and 5 frameshift mutations) were detected. Pathogenic frameshift was present in one mismatch repair (MMR)-related gene (*MLH3* E586Nfs*43, mutant fraction 16%). Other genes with pathogenic frameshifts included *MEN1*, *KMT2A*, and *JAK1* (two frameshifts noted). Pathogenic missense mutations were noted in *KMT2A* (inactivating), GNA11 (activating), *MEN1* (inactivating), and *PIK3CA* (H1047R; activating). Although his bladder tumor had numerous somatic mutations, no mismatch repair deficiency (dMMR) and no MSI high was detected. Colon cancer tissue was not available. Immunohistochemistry (IHC) stains were performed on the prostate biopsies and both *MSH2* and *MSH6* proteins were absent, compatible with complete *MSH2* protein loss. This is likely commensurate with a biallelic *MSH2* loss.

Pembrolizumab, a programmed death-1 (PD-1) inhibitor, was U.S. Food and Drug Administration (FDA) approved in May 2017 for MSI-high patients, regardless of tumor site. Pembrolizumab 200 mg every 3 weeks was begun November 8, 2017, at which time the PSA was 15.5 ng/dL and rapidly rising. After one pembrolizumab dose, PSA declined to 0.47 ng/mL. After the second dose, PSA was <0.01 ng/mL, where it remains after 12 cycles (36 weeks). Follow-up CT scanning showed complete response (CR). Pembrolizumab was stopped after 12 doses and CR persists (October 2018).

Guardant (Redwood City, CA) circulating tumor DNA (ctDNA) assay was obtained (Guardant 360) before and after immunotherapy. Before immunotherapy, the ctDNA had a mutant allelic fraction of 5.7% and two known pathogenic mutations: androgen receptor (*AR*; T878A) and *PIK3CA* (H1047R). After pembrolizumab treatment, the mutant allelic fraction was undetectable, confirming remission (Fig. 1). Independently, a research assay designed specifically for prostate cancer ctDNA was assessed using a pre-pembrolizumab sample [3]. By that method, pembrolizumab, *AR* T878A, and *PIK3CA* H1047R mutations were confirmed. Also detected were two additional *PIK3CA* mutations, and frameshift mutations in ATR, *KMT2C*, and *ZFHX3*. The ctDNA total tumor mutation burden (TMB; including silent and subclonal mutations) was exceptionally high for prostate cancer, 40.9 per Mb by ctDNA analyses. A monoallelic deletion of *MSH2* was detected in ctDNA by this research assay [3].

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The relationship between the *MSH2* inversion and prostate cancer carcinogenesis in this case cannot be established, but is strongly suspected. Some studies indicate that germline *MSH2* alterations, but not germline *MLH1* or germline *MSH2* alterations, associate with increased prostate cancer risk [4–6]. Although prostate cancer risk in Lynch syndrome is debated, germline *MSH2* pathogenic alterations appear distinct from other Lynch-associated genes. In a large metastatic series (n = 692), pathogenic germline alterations were found in *MLH1*, *MSH2*, *MSH6*, and *PMS2* in 0.0%, 0.14%, 0.14%, and 0.28% of cases (0.56% total) [7]. In a large series of unstaged patients tested for germline mutations (n = 1,158), germline *MLH1*, *MSH2*, *MSH6*, and *PMS2* mutations were detected in 0.0%, 0.6% 0.7%, and 0.4% of cases, respectively (1.8% total) [8].

In 150 CRPC patients, using metastatic tissues, 4 patients were MSI high (2.7%) and 2 patients (1.3%) had biallelic pathologic somatic *MSH2* mutations [9]. All MSI-high samples had high TMB, approximately 50/Mb. In a separate analysis of 60 very advanced patients (50 autopsy and 10 additional patient-derived xenografts), 12% had MSI-high and hypermutated tumors [10]. Genomic studies using extensive targeted sequencing (that captures intronic and flanking DNA sequences) determined that all MMR pathogenic changes were somatic only, emphasizing that germline mutants are less frequent than somatic changes in prostate cancer patients. Three MSI-high cases involved biallelic *MSH2* change, one had *MLH1* homozygous loss, one had biallelic *MSH6* loss, and one had biallelic loss of both *MSH2* and *MSH6*. These data suggest that complex somatic *MSH2* mutations are the most common reason for dMMR in prostate cancer and that dMMR may be more frequent in advanced CRPC than generally appreciated. The 12% incidence of MSI high was notable in this series (majority autopsy). Four of seven hypermutated cases had complex structural rearrangements in *MSH2* and *MSH6* not detectable by standard exome sequencing. Ductal prostate

Table 1. Potential biomarkers of prostate tumor responsiveness to PD-1 or PD-L1 antagonism

Biomarker	Documented anti-PD-1 responses	Advanced prostate cancer incidence	Other cancers
Tumor PD-L1 expression	Ineffective [19]	66% [19]	Some cancers
MSI high	5/10 clear responses in largest study [20]	2.7%–11.6% [9, 10]	Yes
POLE driver mutation	One case [15]	0.3% [14]	Yes
PD-L1 3' UTR mutation	One case [19]	Unclear	Case report
Biallelic *CDK12* mutation	2/4 cases [21]	6.9% [21]	Unexplored
High TMB (>10/Mb)	At least three cases	2.7%–11.6% [9, 10, 14, 20]	Yes
Biallelic *MSH2* deficiency	One case [20][a]	2.0%–6.7% [9, 10, 20]	Yes
Biallelic *MSH6* deficiency	One case [20][a]	0.6%–3.3% [9, 10, 20]	Yes
Biallelic *MLH1* deficiency	No cases	0.67%–1.7% [9, 10]	Yes
dMMR by IHC	Two cases [20]	2%–3% [20]	Yes

[a]Biallelic *MSH2* and *MSH6* loss occurred in the same patient with response to pembrolizumab
Abbreviations: dMMR, mismatch repair deficiency; IHC, immunohistochemistry; MSI, microsatellite instability; PD-1, programmed death-1; PD-L1, programmed death-ligand 1; TMB, tumor mutational burden; UTR, untranslated region.

carcinomas may harbor dMMR more commonly than typical adenocarcinomas [11]. This is important as ductal carcinomas noted on histology should trigger clinicians to consider additional testing to assess for MMR alterations.

In a large series (n = 1,176), predominantly from radical prostatectomy specimens, 1.2% (14/1,176) of specimens contained *MSH2* protein loss by IHC assays [12]. Of those with *MSH2* loss, 10/14 were high-grade (Gleason ≥9) or had neuroendocrine features. In this series, of cases with primary Gleason 5 (5 + 4 or 5 + 5), 7% harbored *MSH2* loss by IHC, highlighting the association between primary Gleason 5 cancers and dMMR, a fact important for clinicians to recognize. Genomic analysis of these samples indicated biallelic loss in most (10/12) samples. Only 3/12 samples contained germline mutations in this series, emphasizing the somatic nature of most biallelic MSH losses. A total of 61% of cases were MSI high, and 83% had a high TMB (median 26 mutations/Mb) [12].

The genomic assays did not clearly involve documented biallelic change in *MSH2*; however, our IHC demonstrated loss of *MSH2* and *MSH6* protein, as is typical for dMMR tumors. It is possible that the genomic assays missed additional complex genomic rearrangements. An MMR-related gene (*MLH3*) in this case had a frameshift mutation, but allelic fraction was low, and this change is not related to dMMR. *MLH3* forms a heterodimer with *MLH1* to form the MutLγ protein, but this heterodimer has unclear function in humans and is not considered a canonical MMR protein. cBioportal lists *MLH3* truncating mutations in 4/4,365 prostate tumors [13]; none were high TMB. There is no evidence that *MLH3* truncation predisposes to anti-PD-1 responsiveness.

Selected *POLE* exonuclease mutations can generate ultramutated tumors with a very high TMB [14] without high MSI. In a large series [14], ultramutating *POLE* mutations were found in 0.3% (4/1,325) of prostate cancers (all *POLE* V411 L) [14]. A total of 87/1325 (6.6%) of prostate tumors in this large series had high TMB (>10 mutations/Mb), but details on these cases are lacking. *POLE* exonuclease mutations are clearly a small minority of high-TMB prostate tumors. One exceptional responder to pembrolizumab had a documented *POLE* V411 L mutated metastatic CRPC (and high TMB) [15]. POLD1 exonuclease mutations can theoretically induce high TMB, but only one prostate cancer case has been reported (mutation D402N), and that patient also had *MSH2* loss [12].

Pembrolizumab has been tested in several prospective clinical trials in prostate cancer patients with PSA response rates of 0%–18% [16–19]. The largest trial (KEYNOTE-199) had a PSA response rate (>50% decline) of 11% and a radiographic 30% decrease in target lesions of 10% [19]. KEYNOTE-199 indicated that programmed death-ligand 1 (PD-L1) as measured by IHC is not an optimal predictive marker. There were no differences in survival/responses for those with/without PD-L1 expression [19].

Despite the FDA approval for pembrolizumab in MSI-high tumors, agnostic of tissue origin, response rates of MSI-high prostate cancer patients to PD-1 inhibitors are poorly documented. In the largest series of MSI-high pembrolizumab-treated tumors, 3/13 with MSI-high tumors had germline MMR mutations (type unspecified); thus, germline alterations do not explain MSI high in most prostate cancer patients. Ten patients with MSI-high tumors were treated with anti-PD-1/PD-L1, 5/10 had >50% PSA declines, 3/10 had no response, 1/10 was stable, and 1/10 was nonevaluable [20]. Of note, in patients with serial tumor assessments for MSI, 3 of 5 patients acquired their MSI in a second or subsequent sample [20]. In a separate series [18], 1/1 patient with MSI-high tumors responded to pembrolizumab, but two responders occurred in MSI-low tumors. In that series, no patient had a TMB >10/Mb.

Somatic *CDK12* biallelic mutations have recently been implicated in 6.9% of metastatic CRPC patients [21], and preliminary data suggest that biallelic inactivating mutations in this gene may associate with PD-1 inhibitor responsiveness; 2/4 patients with biallelic *CDK12* mutations had PSA responses to pembrolizumab, and one had a radiographic response. All biallelic *CDK12* mutations were somatic, perhaps suggesting that biallelic *CDK12* loss in germlines may be embryonic lethal. *CDK12* biallelic losses may be associated with increased immune infiltrates and higher expression of checkpoint proteins [22]. Furthermore, it is clear that

CDK12 biallelic loss associates with increased focal tandem duplications and increased mutational burden. Taken together, although more work is needed, biallelic *CDK12* loss likely is an important predictive biomarker for anti-PD1 responsiveness.

Analysis of responders to pembrolizumab in the KEYNOTE-199 trial, the largest pembrolizumab experience in prostate cancer, indicated that one patient had loss of the 3'-untranslated region (UTR) of PD-L1 [19]. This UTR disruption results in overexpression of PD-L1 transcripts and is postulated as a genetic marker identifying tumors capable of evading immune detection [23]. Incidence in prostate cancer is unclear. Another KEYNOTE-199 responder was dMMR by IHC (both *MSH2* and *MSH2*). This patient also had multiple mutations in DNA repair genes (*ATM*, *BRCA2*, *FANCA*, and *FANCD2*) plus a monoallelic CDK1212 truncating mutation. The KEYNOTE-199 authors have postulated that those harboring DNA repair mutations in *BRCA1/2* or *ATM* may predispose to higher rates of anti-PD-1 responsiveness. PSA responses were 10% in those with mutated DNA repair genes compared with 3% without [19]. Further data to support the possibility of DNA repair gene mutations in immune-responsiveness are derived from a recent manuscript describing responsiveness to ipilimumab/nivolumab in prostate cancers deficient in *BRCA2* and *ATM* [24].

The typical 5-satellite MSI panel assessed by PCR has inferior sensitivity in prostate cancer specimens, and other methodologies assessing MSI status, including genomic sequencing with expanded panels of markers, likely perform better [25].

Who to test for MSI-high and MMR mutations (both germline and somatic) is debatable for prostate cancer patients. This patient, with a colon cancer diagnosis at a young age, and a mother with multiple GI tumors, would have been tested earlier given current knowledge, but many cases of dMMR are somatic only and cannot be suspected by history alone. Noting that primary Gleason 5 tumors, or those with ductal histology, are at particularly high risk for MMR mutations is important for clinicians to recognize given the potential therapeutic importance of these findings.

Conclusion

Taken together, predictive biomarkers for responsiveness to PD-1 inhibitors in prostate cancer are rapidly evolving in prostate cancer (Table 1). MSI high can potentially serve as a predictive biomarker, and pembrolizumab is FDA approved for any patient with MSI-high or dMMR tumors (using any assay to assess for MMR deficiency). Note, however, that MSI results are imperfectly predictive of anti-PD1 responses. MSI-high patients may not respond, and patients may respond without being MSI high. Deciding which patients should be tested for MSI and dMMR is debatable, but primary Gleason 5 tumors and tumors with ductal histology are more likely to harbor dMMR lesions [12]. Testing tumors for MSI and MMR status in patients with germline MMR mutations is advisable, but most dMMR tumors have acquired somatic mutations, many of which are complex genomic rearrangements (and only some of these are detectable by sequencing exomes). PD-L1 expression does not have significant predictive value in prostate cancer [19]. Selected *POLE* exonuclease pathologic mutants, or those with a high TMB, appear promising as predictive biomarkers for PD-1 antagonists, and such alterations (although rare) are important. Deletions in the 3' UTR of PD-L1 are described but are of unclear frequency. *CDK12* biallelic inactivation has been implicated as a predictive biomarker and these alterations are quite prevalent (6.9% of CRPC cases). Patients with DNA repair mutations may have a higher percentage of response than those without, but response rate is only in the 10% range. Taken together, predictive biomarkers for PD-1/PD-L1 antagonism are both diverse and rapidly evolving in the prostate cancer space.

Author Contributions

Conception/design: Charlotte Manogue, Oliver Sartor
Provision of study material or patients: Charlotte Manogue, Brian Lewis, Oliver Sartor
Collection and/or assembly of data: Charlotte Manogue, Elisa Ledet, Alexander W. Wyatt, Oliver Sartor
Data analysis and interpretation: Alexander W. Wyatt, Oliver Sartor
Manuscript writing: Charlotte Manogue, Oliver Sartor
Final approval of manuscript: Charlotte Manogue, Patrick Cotogno, Elisa Ledet, Brian Lewis, Alexander W. Wyatt, Oliver Sartor

Disclosures

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Editor's Note:
See the related commentary, "A New Molecular Taxonomy to Predict Immune Checkpoint Inhibitor Sensitivity in Prostate Cancer," by Emmanuel S. Antonarakis on page 430 of this issue.