Editorial Commentary

Biomarkers of response to immune checkpoint inhibitors for metastatic castration resistant prostate cancer: looking for the needle in the haystack

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The only immunotherapy approved for metastatic castration resistant prostate cancer (mCRPC) is the dendritic cell vaccine sipuleucel-T. No immune checkpoint inhibitor (ICI) has demonstrated significant anti-tumor activity in mCRPC as a monotherapy. Pembrolizumab is an ICI that targets programmed cell death protein-1 (PD-1) and has been tested in a variety of different clinical states of mCRPC. In KEYNOTE-028, 23 heavily pretreated mCRPC patients with measurable disease and PD-L1 positive tumors (CPS ≥1%) received pembrolizumab, which produced 0 complete responses (CR), 4 (17%) partial responses (PR) and 8 (35%) stable diseases (SD) (1).

KEYNOTE-199 was a phase II trial that enrolled mCRPC patients into several cohorts: (I) PD-L1 positive (CPS ≥1%) and measurable disease (n=133); (II) PD-L1 negative (CPS <1%) and measurable disease (n=66); and (III) bone only metastases regardless of PD-L1 status (n=59). The primary endpoint was the objective response rate (ORR). Median follow-up was 9.5 months for cohort 1; 7.9 months for cohort 2; and 14.1 months for cohort 3. Results demonstrated ORR of 5%, 3% and 1% for cohort 1, 2 and 3, respectively. Two patients (0.77%) in cohort one achieved a CR, and 5 in cohort 1 and 2 in cohort 2 had a PR (2). Of the 258 patients enrolled, 153 had tumor samples available for whole exome sequencing, and of the 9 responders, 6 had tumor samples for analysis. Aberrations in *BRCA1* or *2* and *ATM* were identified in 19 (12%) patients, and mutations in other homologous recombination repair (HRR) genes were identified in 10 (6.5%) patients. Of the 6 responders, none had microsatellite instability (MSI) as determined centrally by mSINGS assay. However, by local immunohistochemistry testing, 2 of the responders had a mismatch repair defect (dMMR). Two patients with *BRCA1/2* or *ATM* mutations had a PR, and no responses were seen in patients with other HRR defects.

A variety of molecular aberrations that may sensitize mCRPC tumors to different treatments such as immunotherapy or PARP inhibitors have been identified. Immunohistochemical analysis for PD-1/PDL-1 expression in tumor cells of 202 radical prostatectomy cases showed that PD-1 was expressed (CPS ≥1%) in 17 (7.7%) patients and PD-L1 was expressed in 29 (13.2%) with no statistically significant association between PD-1/PD-L1 expression and patient characteristics including pre-operative PSA levels, Gleason score and risk of disease recurrence (3). In another subset of patients who received neoadjuvant androgen deprivation therapy (ADT), abiraterone acetate and prednisone, 3 out of 44 cases (7%) were PDL-1 positive whereas 9 out of 44 (20%) of matched tumor control in patients who did not receive neoadjuvant treatment were PD-L1 positive (4). HRR gene defects are associated with mCRPC and it is estimated that these aberrations may be detected in 23–27% of mCRPC cases and these tumors harbor a worse prognosis (5,6). In a recent analysis, 23% of 150 metastatic lesions revealed HRR gene defects. *BRCA2* was most commonly altered gene occurring in 13%

of samples, while other genomic abnormalities included, *ATM* (7.3%), *MSH2* (2%), and *BRCA1*, *FANCA*, *MLH1*, *RAD51B*, and *RAD51C* (0.3%) (7). A review of 680 primary tumor samples and 333 metastatic lesions, identified HRR defects in 10% of the primary tumors and 27% of the metastatic samples (8). Wu and colleagues reported that cyclin dependent kinase-12 (*CDK-12*) aberrations occurred in 25 (6.9%) of 360 mCRPC patients and concluded that patients with *CDK-12* bi-allelic inactivating mutations constitute a subtype of prostate cancer distinct from MSI-H/dMMR and HRR gene defects, and resulted in more gene fusions, increased tumor antigen burden and higher T-cell infiltration which may cause better responses to ICIs (9).

KEYNOTE-158 was a multi-cohort trial and has reported results for patients with non-colorectal MSI-high (MSI-h) tumors, which included 6 (2.6%) patients with mCRPC. The ORR in these tumors was around 30%. However, the ORR, specifically for mCRPC, was not reported. In a large series of mCRPC patients, the frequency of MSI-high/dMMR was approximately 3%. Of these patients, 11 had received PD-1/PD-L1 ICIs, and 4 (36%) had a PR (10). Given that the frequency of MSI-high/dMMR is not reported for the entire population of KEYNOTE-199, it is not possible to know the impact of this molecular aberration in this trial. However, in an unselected population of mCRPC patients for MSI-high/dMMR, in the KEYNOTE-199 trial, 2 to 3 responses would be expected.

Clearly, given the 9 responders identified in KEYNOTE-199, MSI-h/dMMR aberrations must not be the only factor driving response to pembrolizumab in mCRPC patients. The authors raise the possibility that *BRCA1/2* and *ATM* aberrations may sensitize patients to checkpoint blockade. In CHECKMATE-650, patients with mCRPC who had progressed on a novel antiandrogen therapy were treated with nivolumab and ipilimumab. In the patients with tumor samples available for analysis, 4 out of 10 patients with DNA repair defects (40%) and 3 out of 6 patients (50%) with HRR defects responded to dual checkpoint therapy, which was higher than those without aberrations in these pathways (11). In patients with metastatic melanoma, the presence of *BRCA2* mutations was associated with higher responses to immune checkpoint inhibition, although the number included in this analysis was small (n=38) (12). In a phase I trial of avelumab in 125 women with recurrent platinum-refractory ovarian cancer, *BRCA* mutations were not associated with better ORRs (13). In mCRPC, there is scant data, outside of KEYNOTE-199, to suggest mutations in *BRAC1/2* or *ATM* are associated with improved responses to checkpoint blockade. Apart from the melanoma data, there is minimal information in other tumor types that *BRCA1/2* or *ATM* mutations correlate with improved outcomes with immunotherapy. In fact the majority of the data across multiple tumor types would suggest that *BRCA1/2* or *ATM* mutations are not biomarkers that predict for response to checkpoint inhibitors. Further analysis is needed before mutations in these genes can be used to select patients with mCRPC for treatment with PD-1 inhibition. Based on the data presented in KEYNOTE-199, it is not clear that aberrations in *BRCA1/2* or *ATM* can explain the responses to pembrolizumab.

Although not reported specifically by the KEYNOTE-199 investigators, *CDK-12* loss was observed in 1 patient who had a response. In a multi-institutional retrospective review of both tumor and blood samples from mCRPC patients, biallelic *CDK12* loss was detected in 14.5% of cases. Other studies estimate the frequency of *CDK12* biallelic loss at 3% to 7%. A recent retrospective analysis showed that 2 out of 5 patients with known *CDK12* mutation had a >50% PSA decline to PD-1 inhibitors, and 1 had a PR (14). In 8 *CDK12*-mutated mCRPC patients treated with PD-1 inhibition: 3 (38%) had either a >50% PSA decline or an objective tumor response (15).

The impact of PD-1 inhibition in mCRPC appears to have substantial benefits, albeit in a very small group of patients. What is still not clear is how to identify that small proportion of patients who are likely to respond to checkpoint therapy. PD-L1 expression does not appear to predict for response to ICIs in mCRPC. The KEYNOTE-199 trial has certainly raised the possibility that *BRCA1/2* or *ATM* mutations may be a biomarker to select the patients with the best chances of a response, but more data is required to confirm this hypothesis generating observation.

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Footnote

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