The PD-1/PD-L1 pathway in advanced prostate cancer—have we milked this cow?

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We would like to thank Dr. Fay and Dr. Antonarakis for their insightful comments on immunotherapy (IO) in advanced prostate cancer and specifically their commentary on the recently published KEYNOTE-028 study on the use of pembrolizumab in programmed cell death protein-1 ligand (PD-L1) positive metastatic castrate resistant prostate cancer (mCRPC) (1). As described by the authors, monotherapy with checkpoint inhibitors has not demonstrated the dramatic response rates in mCRPC that were shown in other cancer types such as melanoma and non-small cell lung cancer (NSCLC). In particular, our study demonstrated no complete responses (CR) while only 2 (1.5%) PD-L1 positive patients in KEYNOTE-199 had a CR, compared with rates of 5–6% in melanoma treated with pembrolizumab, and higher CR rates with combination IO (2-5). Interestingly, in NSCLC with tumour positive score (TPS) >50%, pembrolizumab monotherapy demonstrated impressive response rates of 39–44%, but the CR rates are low, reported as <1% (6,7). The use of objective response rates in mCRPC to evaluate clinical benefit from experimental therapy (including IO) may not be the most discriminating endpoint to estimate activity in early phase clinical trials (8).

Identification of the subset of patients who respond to checkpoint inhibitors with either tumor-based or circulating biomarkers has long been a goal of researchers in both the pre-clinical and clinical settings. In prostate cancer, responses to IO have been seen in patients with DNA mismatch-repair deficiency, although the frequency of this deficiency is low and estimated to be 3–8% including an acquired microsatellite-unstable phenotype (9,10). Other potential biomarkers for response include mutations in CDK12 or POLE/POLD1 and homologous repair deficiency (11-13). While there has been some success with biomarkers in IO e.g., head and neck squamous cell carcinoma (HNSCC) [combined positive score (CPS) >1%], cisplatin-ineligible bladder cancer (CPS >10%), NSCLC (TPS >50%) and microsatellite instability (MSI)-high disease, identification of biomarkers that sensitize to IO has been limited to very immune-responsive tumors. Markers such as PD-L1 positivity, tumor mutational burden, immune infiltrate or gut microbiome composition present many challenges regarding testing platforms and standardization, with wide variability between different IO agents and patients.

For CRPC, a mainly non-immunoreactive tumor, these efforts to identify a biomarker to IO, while laudable and needed, face many challenges. Therefore, the future of IO in prostate cancer will need to broaden efforts beyond the identification of predictive biomarkers, to explore IO resistance mechanisms and combination strategies to enhance antitumor immunity. Combining IO with non-IO agents has already proven successful in cancers such as small cell lung cancer, renal cell carcinoma and breast cancer (14-16). In prostate cancer, studies are underway examining combinations of IO with non-IO agents to potentiate anti-tumor T cell responses including chemotherapy, hormonal agents and PARP inhibitors (*Table 1*).

Numerous agents are in clinical trials to enhance the effects of IO by targeting the innate and adaptive immune

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Table 1 Ongoing studies in CRPC examining combinations of IO with non-IO agents

Study title	Treatment arms	Estimated completion date	Early results	Ref/NCT
KEYNOTE-365 (NCT02861573)	Pembrolizumab + olaparib, docetaxel, enzalutamide or abiraterone	May 2022	Safety and efficacy of combinations, response rates 7–20%	NCT02861573 (17,18)
PROSTRATEGY	Docetaxel + nivolumab +/– ipilimumab	December 2023		NCT03879122
Checkmate 9KD	Nivolumab + rucaparib, docetaxel, or enzalutamide	November 2020		NCT03338790
KEYNOTE-199	Multiple cohorts-pembrolizumab/ enzalutamide cohorts pending	December 2020	Antitumor activity and disease control with acceptable safety regardless of PD-L1 status, in both RECIST-measurable and non-measurable disease	NCT02787005 (5)
IMbassador-250	Enzalutamide +/– atezolizumab	July 2022		NCT03016312
	Rucaparib + nivolumab	November 2022		NCT03572478
KEYLYNK-010	Pembrolizumab + olaparib *vs.* abiraterone or enzalutamide	September 2022		NCT03834519
	Olaparib + durvalumab	February 2021		NCT03810105
	Durvalumab + olaparib +/– cediranib	December 2020	Acceptable toxicity, evidence of efficacy particularly in men with DDR abnormalities	NCT02484404 (19)

CRPC, castrate resistant prostate cancer; IO, immunotherapy; PD-L1, programmed cell death protein-1 ligand.

systems. Blockade of T-cell receptors such as LAG-3 may upregulate PD-1 and CTLA-4 expression, while combination therapy with IO and anti-LAG-3 antibodies demonstrated activity in mouse models and is currently in phase I/II clinical trials (20,21). Other potential targets include TIM-3, an immune-inhibitory molecule found on T-cells which may be involved in IO resistance (22) and VISTA, an immunomodulatory protein increased on macrophages in IO-treated prostate cancer (23), antibodies to both of which are in early-phase trials in humans. Agonists to molecules such as TLR4, ICOS and CD27 have shown promise in pre-clinical work and phase I/II trials are ongoing (24-26).

Studies are currently examining IO in combination with radiation, with the rationale that radiation may increase antigen release, leading to antigen presentation and immune activation to augment IO response, and also may facilitate the elusive abscopal effect. Pembrolizumab in combination with stereotactic body radiation therapy (SBRT) with or without a TLR9 agonist, which promotes T cell activation and homing, is being studied in patients with castrate-sensitive oligometastatic prostate cancer (NCT03007732). Stereotactic ablative radiotherapy to multiple disease sites in combination with Sipuleucel T in mCRPC is currently in a phase II trial, with results expected early next year (NCT01818986). Numerous oncolytic viruses are in pre-clinical and clinical testing in prostate cancer, using vectors such as adenoviruses or herpes simplex viruses that are modified to preferentially target cancer cells and elicit anti-tumor immunity (27). Therefore these viruses could potentially be combined with IO to further enhance efficacy of both treatments through further immune activation. PROSTVAC is a poxviral-based vaccine which targets PSA as its tumor antigen, and is currently in early-phase trials in combination with nivolumab (NCT02933255), nivolumab/ipilimumab (NCT03532217) and other IO agents (NCT03315871), although PROSTVAC as a single agent has not proven effective in mCRPC (28).

In conclusion, IO remains a therapy with much potential in advanced prostate cancer, but trials to define its clinical benefit are ongoing. Given the tolerable toxicity profile of checkpoint inhibitor monotherapy, combination treatment

is a rationale option to improve survival outcomes. While biomarkers for IO response are an attractive prospect in terms of patient selection and personalization of IO treatment, they have proven elusive in many cancers. Combination therapy with IO agents and chemotherapy, hormonal therapy, targeted treatment or even oncolytic virus-based therapy may provide improvements in efficacy by enhancing adaptive immunity, altering the tumor immune microenvironment to promote anti-cancer immune responses through T cell activation and tumor-antigen generation. Beyond identifying a small subset of patients whose tumors are inherently IO-sensitive, manipulating the immune system to turn cold or non-immunogenic tumors such as CRPC into immunoresponsive cancers could prove to be an alternative strategy. This could enable the promise of IO to produce long term durable responses and extend overall survival in mCRPC to be realized.

Acknowledgments

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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