PROSTATE CANCER IN 2018

Immunotherapy for lethal prostate cancer.

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Standfirst

Immunotherapy and modulation of the tumour microenvironment are potential new therapeutic approaches that may impact outcome from metastatic prostate cancer. Patient selection may be key to deliver benefit from these agents. Studies reported in 2018 suggest that alterations in the mismatch repair system and aberrations in CDK12 may represent possible biomarkers of response to immunotherapy.

Programmed cell death 1 (PD-1) blocking agents have become crucial components of the treatment of deadly diseases such as metastatic lung cancer and melanoma, but have also changed the treatment paradigm in urologic malignancies such as renal cell carcinoma and bladder cancer[1]. Immune checkpoint inhibitors (ICIs) such as the anti-PD-1 antibody pembrolizumab have received FDA approval for the treatment of patients with advanced microsatellite instability-high (MSI-H) or DNA mismatch repair-deficient (dMMR) solid tumours[2], but their role in the treatment of prostate cancer remains unproven. Here we discuss 4 studies published over the past year that have provided additional insight into the role of immunotherapy in prostate cancer in attempts to elucidate whether ICIs can have a meaningful impact in the treatment of metastatic castration resistant prostate cancer (mCRPC). The relevance of ICIs in mCRPC has been controversial since the cytotoxic T-lymphocyte antigen 4 (CTL-4) targeting antibody (ipilimumab) did not show a survival benefit in a phase III randomized trial in molecularly unselected patients.[4]

Preliminary results from the KEYNOTE-199 phase II trial evaluating the efficacy of pembrolizumab in metastatic castration-resistant prostate cancer (mCRPC) were presented by de Bono et al.[4] at the 2018 American Society of Clinical Oncology (ASCO) Annual Meeting. Within this trial, 258 patients with mCRPC were treated with single-agent pembrolizumab at progression on standard treatment (including docetaxel). Patients were stratified according to programmed cell death 1 ligand 1 (PD-L1) positivity and the presence of measurable or bone-only disease; groups included patients with PD-L1^{+} measurable disease (cohort 1, *n*=131), PD-L1^{-} measurable disease (cohort 2, *n*=67), and bone-only disease with any PD-L1 status (cohort 3, *n*=60). Overall, the results of KEYNOTE-199 indicated limited anticancer activity of pembrolizumab in molecularly unselected patients with mCRPC — only 3.5% had radiological responses among patients with measurable disease (*n*=198; cohorts 1 and 2) with no differences between the PD-L1^{+} and PD-L1^{-} cohorts (4% versus 3%, respectively), with 11% of all patients (*n* = 258) having a PSA decline of >50% and ~10% of patients still on trial at the time of the data cut-off. Interestingly, there was limited evidence that responding patients had tumours with DNA damage repair pathway aberrations, [4] suggesting that such defects may represent putative biomarkers of response to pembrolizumab .

The preliminary KEYNOTE-199 data are extremely relevant in view of new immunogenomic insights into dMMR mCRPC tumours reported by Nava Rodrigues and colleagues[5]. The authors report that up to 8% of mCRPCs had some evidence of dMMR (with either loss of MMR proteins (MSH2, MSH6, MLH1, PMS2) by immunohistochemistry and/or high MSI by other assays) and that dMMR was

associated with poor OS compared with MMR proficient tumours (3.8 versus 7.0 years from the start of luteinizing-hormone-releasing hormone (LHRH) antagonist therapy; *P*=0.005). MSI by targeted panel next-generation sequencing (MSINGS) as well as immunohistochemistry and PCR-based assays detected dMMR prostate cancers with increased T-cell infiltration and elevated PD-L1 protein expression (FIG. 1). MSINGS of mCRPC biopsy samples from the Stand Up To Cancer/Prostate Cancer Foundation (PCF/SU2C) cohort (*n*=254, with 168 having matching transcriptomes) using whole-exome sequencing (WES) confirmed a strong correlation between WES–MSINGS and targeted panel MSINGS scores (*r*=0.73, *P*<0.0001). Four dominant mutation signatures matching previously described Catalogue of Somatic Mutations in Cancer (COSMIC) mutational signatures were also identified — two dMMR-associated signatures, a homologous recombination deficiency (HRD)-associated signature, and an aging-associated signature. High MSINGS scores were associated with dMMR mutational signatures and MMR gene mutations[4]. The mutational signatures of dMMR CRPCs were characterised by increased immune cell, immune checkpoint, and T-cell-associated transcripts, including *CD200R1*, *BTLA*, *PDL1*, *PDL2*, *ADORA2A*, *PIK3CG*, and *TIGIT*[5]. Together, these findings indicate that patients with dMMR prostate cancer are an important subset that merit further evaluation of immunotherapy treatment strategies.

The importance of molecular stratification and predictive biomarkers for response to ICIs was further demonstrated by Wu and coworkers[6], who reported that dMMR and HRD tumours had a markedly higher neoantigen burden than other mCRPC molecular subtypes. However, Wu et al.[6] reported that the mutational burden in HRD tumours is predominantly caused by translocations, whereas fusions caused by focal tandem duplications contributed to most of the neoantigen burden in mCRPCs with biallelic *CDK12* inactivating mutations. Neoantigens have strong binding affinities for major histocompatibility complex (MHC) class I molecules and therefore are highly immunogenic. Moreover, *CDK12* mutant tumours had decreased or low expression of chemokines involved in the recruitment of regulatory T cells (T_{regs}), such as C-C motif chemokine 17 (CCL17), CCL20, and CCL22, and increased levels of chemokines that support dendritic cell migration into the tumour microenvironment, such as CCL21 and CCL25. Consequently, *CDK12*-mutant tumours with evidence of biallelic *CDK12* loss had higher overall T cell infiltration (FIG. 1) and greater numbers of expanded T cell clones[6] compared to tumours without CDK12 or MMR aberrations. In the study by Wu and colleagues[6], four patients with mCRPC who had biallelic deleterious aberrations in *CDK12* were treated with an anti-PD-1 agent; two patients had a marked PSA decline but one patient died owing to a possible immune-related adverse event. Overall these data support the use of next-generation sequencing (NGS)-based patient selection for immunotherapy trials in mCRPC[6].

An alternative approach to increase response rates in immunotherapy trials could be through modulation of the immunosuppressive tumour microenvironment. Calcinotto and colleagues[7] have described how interleukin-23 (IL-23) secreted by polymorphonuclear myeloid-derived suppressor cells (PMN-MDSCs) in mCRPC tumours can drive resistance to androgen deprivation therapy (ADT). MDSCs are known to suppress antitumour immune responses and promote senescence evasion and angiogenesis to support tumorigenesis in prostate cancer [8]. Calcinotto et al.[7] report that mCRPC biopsy specimens have higher MDSC counts ($CD11b^{+}CD33^{+}CD15^{+}$) than castration-sensitive samples from the same patient prior to the emergence of ADT resistance. These data were supported in mouse models, in which the number of PMN-MDSCs was found to increase over time with the emergence of CRPC, and in cell line experiments, whereby MDSC-derived conditioned medium sustained cell survival despite androgen deprivation, suggesting that MDSCs regulate androgen-deprivation sensitivity in a paracrine manner. IL-23 was identified as the major MDSC-derived factor driving CRPC, with the frequency of IL-23-producing tumour-infiltrating PMN-MDSCs increasing at the emergence of ADT resistance. Intriguingly, C-X-C motif chemokine 5 (CXCL5), which is responsible for MDSC chemotaxis via activation of C-X-C chemokine receptor type 2 (CXCR2), was also upregulated in CRPC mouse models. These findings were supported in humans, whereby *IL23A* and *IL23R* mRNA levels were higher in mCRPC biopsy samples than in hormone-naive samples. Interestingly, IL-23 was found to regulate the signal transducer and activator of transcription 3 (STAT3)–retinoid-related orphan receptor γ (RORγ) pathway, which has been reported to drive *AR* and *AR* splice variant transcription and androgen receptor (AR)-driven signalling in prostate cell lines and tumor [9]. Overall, these findings could have a meaningful clinical impact given that anti-IL-23 antibodies are under clinical investigation (for the treatment of psoriasis) and that the CXCR2 antagonist AZD5069 is being tested in combination with enzalutamide in patients with mCRPC who progressed on abiraterone and/or enzalutamide (NCT03177187).

In conclusion, immunotherapies are having a major influence on cancer care for many cancers and could represent a 'real hope' for the treatment of a subset of mCRPC (but not all) as suggested by the publications discussed here. However, optimal biomarkers of response to ICIs need still to be prospectively validated in clinical trials for mCRPC. Finally, modulation of the tumour microenvironment is a new therapeutic approach that could influence patient outcomes, with emerging evidence indicating that chronic inflammation promotes prostate carcinogenesis by increasing AR signaling[10].

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Acknowledgments

[Au: Would you like to add any?]

Competing interests

J.S.dB. has served as a consultant and advisory member for Astellas Pharma, AstraZeneca, Bayer, Genmab, Genentech, GlaxoSmithKline, Janssen, Medivation, Orion Pharma, Pfizer and Sanofi. P.R. declares no competing interests.

Pullquotes

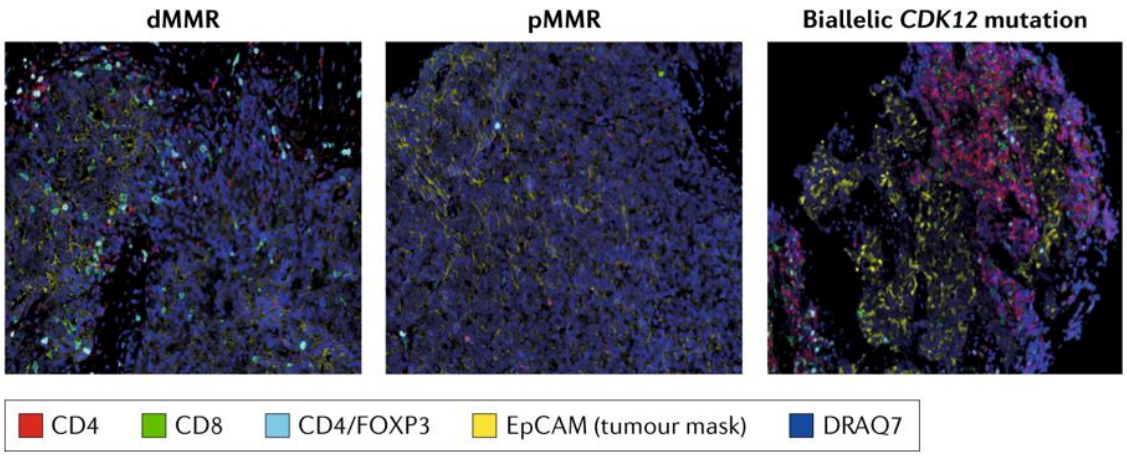
Patients with dMMR prostate cancer and CDK12 mutations are an important subset tha may benefit from immunotherapy.

Key Advances

1. de Bono et al at ASCO 2018 showed that pembrolizumab might be more effective in DDR tumors than in unselected patients.
2. Nava Rodrigues and colleagues reported that a proportion of mCRPC have mismatch repair defects associated with altered immune landscapes potentially actionable in immunotherapeutic strategies.
3. Wu et al showed that CDK12 bi-allelic loss defines a molecular subtype of mCRPC characterized by increased gene fusions, neoantigen burden, and T cell infiltration representing a putative target of immunotherapies.
4. Calcinotto and colleagues identified IL-23 produced by myeloid-derived suppressor cells as driver of castration resistance in prostate cancer.

Figure 1 | **T cell infiltration in mCRPC.**

Multi-spectral, multi-colour immunofluorescence images depicting T cell infiltration in lymph node biopsy samples from three patients with metastatic castration-resistance prostate cancer (mCRPC). Tumours were DNA mismatch repair-deficient (dMMR), DNA mismatch repair-proficient (pMMR), or had biallelic *CDK12* mutations . dMMR and CDK12 mutant tumors present a considerable higher T-cell infiltrate. Image courtesy of M. Crespo, The Institute of Cancer Research, London, UK.


dMMR
pMMR
Biallelic *CDK12* mutation
CD4
CD8
CD4/FOXP3
EpCAM (tumour mask)
DRAQ7