

Words of Wisdom.

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Regarding: Antonarakis ES, Piulats JM, Gross-Goupil M, et al. Pembrolizumab for Treatment-Refractory Metastatic Castration-Resistant Prostate Cancer: Multicohort, Open-Label Phase II KEYNOTE-199 Study. *Journal of Clinical Oncology*. 2019; JCO.19.01638 DOI: 10.1200/JCO.19.01638

Experts' summary:

The KEYNOTE-199 study [1] is a phase II clinical trial of immunotherapy using the humanised antibody Pembrolizumab (anti-Programmed cell Death protein 1, anti-PD-1) in men with metastatic castrate-resistant prostate cancer (mCRPC) who previously received endocrine therapies and docetaxel. Men were stratified into three cohorts: cohorts 1 and 2 with Response Evaluation Criteria In Solid Tumours (RECIST)-measurable and Programmed Death-Ligand 1 (PD-L1) positive or negative disease respectively, and cohort 3 with bone disease irrespective of PD-L1 expression. Nine (5%) patients in cohorts 1 and 2 responded to treatment per RECIST, two having a complete response, and five having on-going responses at 16.8 months' follow-up. Overall survival (OS) in the three cohorts was 9.5, 7.9 and 14.1 months respectively. Pembrolizumab response did not correlate with DNA damage response (DDR) gene mutations or PD-L1 positivity.

Experts' opinion:

This study adds to growing evidence suggesting that despite the immunosuppressive tumour immune microenvironment (TIME) of mCRPC, immunotherapy may have a role in extending the survival curve tail in some patients. Whilst the results of this study are encouraging in a subset of patients, it will be important to determine in a randomised control trial whether a RECIST or PSA response translates into increased OS. In addition, 15% of patients suffered grade 3-5 adverse events, and 5% stopped Pembrolizumab early, suggesting some patients suffering adverse effects did not benefit from treatment. It is crucial to identify accurate prognostic and predictive biomarkers of response to Pembrolizumab, to better stratify patients most likely to benefit, thereby minimising risks of harm to likely non-responders. Exploratory biomarker analysis did not identify a clear relationship between Pembrolizumab response and mutations in DDR genes or PD-L1 positivity, demonstrating the limitation of using tumour mutational burden or PD-L1 expression as predictive biomarkers of sensitivity to immune checkpoint blockade. This is particularly relevant to mCRPC, where the TIME has a relatively low somatic mutational burden [2,3] and relatively low neoantigen expression compared to other tumours such as lung cancer, together with infiltration of pro-tumorigenic monocyte populations [4]. Despite this, earlier trials such as those using Sipuleucel-T (Provenge) have demonstrated the tantalising potential for immunotherapy in mCRPC [5]. Enhanced understanding of the heterogenous pre-treatment TIME, together with reliable identification of

responders versus non-responders, and mechanisms to harness response in hitherto poor responders, is crucial to unleash the full exciting potential of future immunotherapy strategies in mCRPC.

Blog title:

Harnessing the potential of immunotherapy in advanced prostate cancer.

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Conflict of Interest Disclosure:

The authors have no relevant conflict of interest to declare.