

## Spotlight

# Anti-PD-L1 plus enzalutamide does not improve overall survival in prostate cancer

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The addition of atezolizumab (anti-PD-L1) to enzalutamide (androgen receptor antagonist) did not prolong survival in metastatic prostate cancer.<sup>1</sup> Efficacy with immunotherapies in prostate cancer will require additional studies to elucidate and target mechanisms of resistance within the prostate tumor microenvironment.

T cell-inflamed cancers, which respond to immune checkpoint therapies (ICTs), are associated with high interferon (IFN)- $\gamma$  and PD-L1 expression levels and high tumor mutational burden (TMB) (Figure 1A). Although ICTs have limited single-agent activity in prostate cancer, we and others have found that intratumoral T cell density correlated with durable responses to ICTs.<sup>2,3</sup> Consistent with this observation, pembrolizumab (anti-PD-1) is FDA-approved for prostate cancers with mismatch repair deficiency (dMMR), high microsatellite instability (MSI-H), or high TMB ( $\geq 10$  mutations/megabase [mut/Mb]), tumor subtypes frequently characterized by significant T cell infiltration. However, in most prostate cancers, the tumor microenvironment (TME) harbors few T cells, and there is an unmet need to develop strategies to increase intratumoral T cell density (Figure 1B).

The backbone of systemic treatment for advanced prostate cancer is hormonal therapy (i.e., androgen deprivation therapy [ADT]), which induced infiltration of IFN- $\gamma$ -expressing T cells into the prostate TME.<sup>4</sup> A different hormonal agent, enzalutamide (an androgen receptor antagonist), increased activation of IFN- $\gamma$  signaling pathways and decreased frequency of immunosuppressive cells in peripheral blood mononuclear cells (PBMCs) from prostate cancer patients.<sup>5</sup> In addition, resistance to enzalutamide was associated with higher expression of the inhibitory immune checkpoints PD-L1 and PD-L2 on dendritic cells (DCs) in PBMCs.<sup>4</sup> Importantly, the prostate TME was not evaluated in these studies; therefore, it is difficult to know

whether enzalutamide had similar effects on intratumoral DCs and lymphocytes. Subsequently, in the initial report of a phase II trial enrolling metastatic castration-resistant prostate cancer (CRPC) patients who had progressed on enzalutamide, treatment with pembrolizumab resulted in partial responses in two of three patients with measurable disease.<sup>4</sup> It should be noted that one of these patients who responded to the combination had MSI-H disease.<sup>4</sup>

Powles et al. report in *Nature Medicine* the results of a randomized phase III trial of enzalutamide with or without atezolizumab (anti-PD-L1) in 759 men with metastatic CRPC who progressed on abiraterone (androgen synthesis inhibitor).<sup>1</sup> The study was terminated early due to lack of efficacy and failed to meet its primary endpoint of overall survival (OS). To define the subsets of patients who may have benefited from the combination, the authors conducted biomarker analyses on pre-treatment tumor tissues that were primarily archival. Although retrospective analysis of pre-treatment tissues can identify prognostic biomarkers and candidate mechanisms of *primary* resistance, they cannot reveal mechanisms of *adaptive* resistance to therapy (Figure 1B).

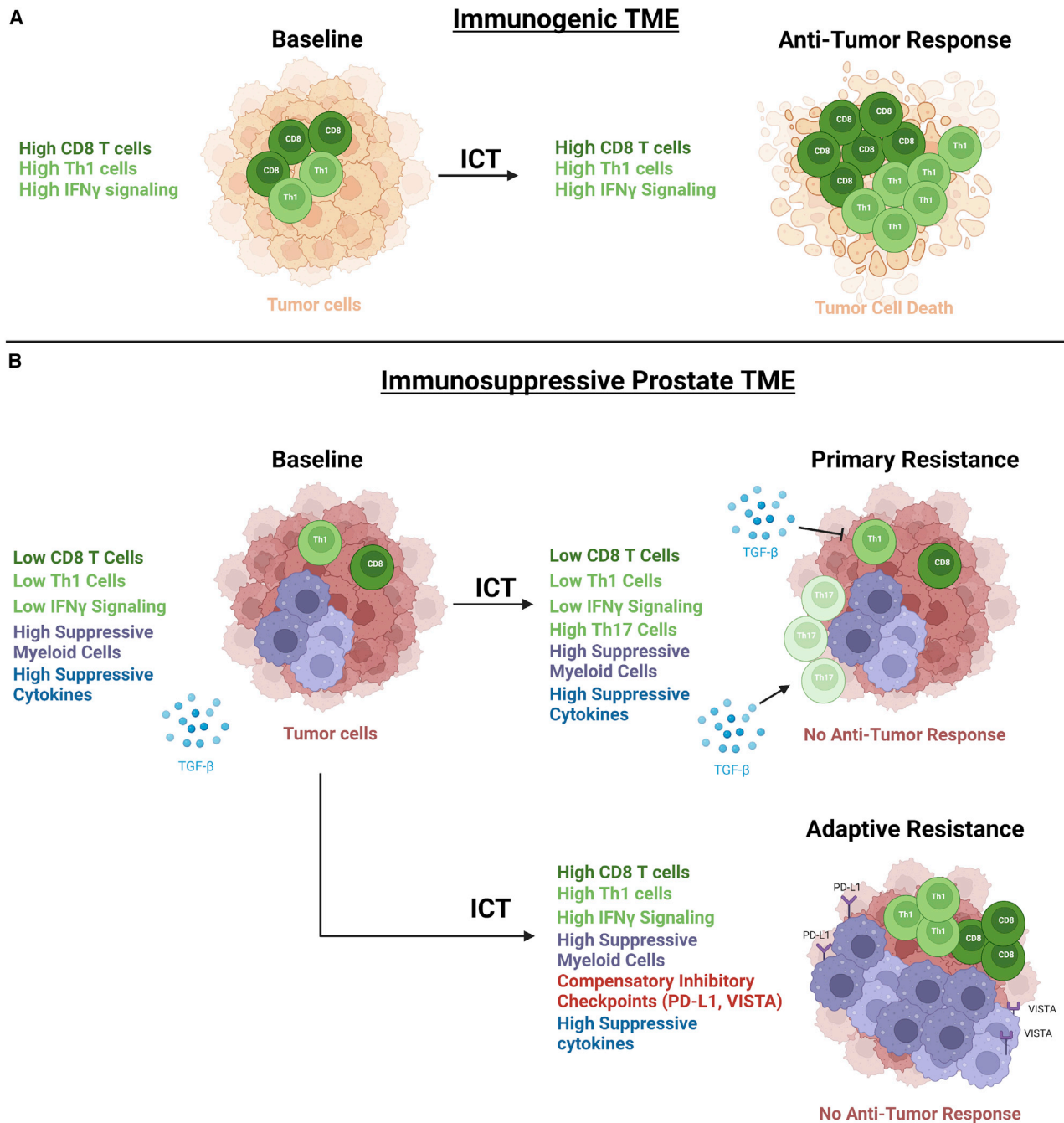
The authors evaluated several candidate biomarkers of response to ICTs. Consistent with previous reports, the tumors from the overall population displayed low CD8 T cell infiltration, PD-L1 expression on immune cells, TMB ( $n = 9$  for TMB  $\geq 10$  muts/Mb) and prevalence of MSI-H status ( $n = 2$ ).<sup>2,3</sup> In the current study, CD8 T cell infiltration and effector

T cell ( $T_{eff}$ ) gene signature levels above or equal to the median were associated with improved progression-free survival (PFS) with combination therapy.<sup>3</sup> Elevated PD-L1 expression correlated with improved PFS, but not OS with the combination. Given that OS (the primary endpoint of this trial) was not prolonged, PFS has limited clinical impact in this setting. These data highlight the issues of heterogeneous expression and dynamic changes in expression that affect the use of PD-L1 as a reliable biomarker.

Immunogenetics has also been shown to improve patient selection for ICTs; although in this study, the results were variable. For example, a clinical study evaluating prostate tumors demonstrated that *PTEN* loss was associated with increased T cell density.<sup>6</sup> Consistent with this finding, the authors observed that *PTEN* loss correlated with prolonged PFS with atezolizumab plus enzalutamide. On the other hand, the authors found conflicting results with TMB cutoffs of  $\geq 4.5$  muts/Mb versus  $\geq 2.52$  muts/Mb. The lower cutoff was associated with greater PFS, which is surprising given that higher TMB is linked to increased neoantigen load and T cell density. The variable performance of these individual biomarkers suggests a need for combinatorial biomarkers incorporating tumor, immune, and host factors derived from biological mechanisms.

The low proportion of patients with a T cell-inflamed TME partly explains the negative results of this study, as ICTs block inhibitory pathways on intratumoral T cells. It has been shown that hormonal therapies can recruit T cells to the TME;





**Figure 1. Characteristics of immunogenic and immunosuppressive tumor microenvironments.**

(A) Characteristics of an immunogenic tumor microenvironment (TME) associated with response to ICTs.

(B) Mechanisms of primary and adaptive resistance within the immunosuppressive prostate TME limit responses to ICTs. Created with [BioRender.com](https://www.biorender.com).

however, prior trials combining ADT with ipilimumab (anti-CTLA-4) in localized and metastatic prostate cancers failed to demonstrate a clinical benefit.<sup>4</sup> This was likely due in part to adaptive upregulation of inhibitory pathways, PD-L1 and VISTA, on myeloid cells within the TME (Figure

1B).<sup>7</sup> In addition, castration itself has been shown to induce infiltration of suppressive myeloid cells into the prostate TME.<sup>8</sup>

The path forward to developing rational combinations with ICTs in prostate cancer will require data from pre- and on-

treatment tumor tissues to generate hypotheses about relevant biological mechanisms of response and resistance that can be tested in pre-clinical models. For example, we reported that restraint of Th1 anti-tumor responses by TGF- $\beta$  and suppressive myeloid cells was a

predominant feature of the bone TME, even after treatment with ICTs.<sup>9,10</sup> Future studies will be needed to address these and identify other mechanisms of resistance across disease sites.

In summary, this randomized phase III trial showed that anti-PD-L1 plus enzalutamide did not improve OS compared to enzalutamide alone in patients with metastatic CRPC progressing on abiraterone. Comprehensive analysis of pre-treatment tumors identified markers associated with response and confirmed previous findings of an immunosuppressive prostate TME. The authors should be commended for conducting and completing this large phase III trial, which was based on the best available data at the time. Prior to initiating large clinical trials, especially when resources are limited (e.g., patient participation, financial support), it will be imperative to consider smaller studies with matched pre- and on-treatment tumor biopsies. Utilizing this approach can clearly define how therapeutic agents impact the immune TME and identify potential mechanisms of response and resistance. This strategy will be critical to efficiently develop rational combinations to improve outcomes in patients with lethal prostate cancer.

#### DECLARATION OF INTERESTS

The authors declare no competing interests.

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