

EDITORIAL

Finding an Immunologic Beachhead in the Prostate Cancer Microenvironment

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Trials in prostate cancer with immune checkpoint inhibitors have yielded disappointing results relative to other genitourinary malignancies. This includes two negative phase III trials with ipilimumab that did not meet an overall survival (OS) endpoint and several smaller studies with PD-1/PD-L1 inhibitors that have suggested clinical benefit only in a small percentage of patients (1–3). It has been noted that the prostate cancer immune microenvironment may be inhospitable to immune cells, thereby limiting the potential of immunotherapy in prostate cancer. In this issue of the Journal, Dr. Zhao et al. provide an extensively detailed genomic interrogation via gene expression data from 9393 prostatectomy samples (7826 of which were prospectively evaluated) (4). This is the largest study of its kind and the authors should be commended for their efforts, as the data may provide valuable insight which could optimize immunotherapeutic strategies in prostate cancer.

The analysis focused on prespecified variables including four immune checkpoints (CTLA-4, PD-1, PD-L1, and PD-L2) and seven cell types including mast cells, natural killer (NK) cells, dendritic cells (DCs), T-cells, regulatory T-cells (Tregs), macrophages, and B-cells (4). Commercially available assays were used for genome-wide assessments and associations were made with the primary endpoint of distant metastasis-free survival (DMFS), biochemical recurrence-free survival (bRFS), prostate cancer-specific survival (PCSS), and OS. The results indicated several cytokine pathways (IL-6, IL-2, interferons alpha and gamma, inflammatory responses, and complement) were highly correlated and formed an immune cluster of genes. Mast cells and NK cells were associated with better DMFS, while B-cells and neutrophils had no association with prognosis. Interestingly, along with macrophages, T-cells appeared to be associated with worse DMFS while T-reg cells did not appear to impact long-term outcomes. Of the immune checkpoints evaluated, PD-L2 appeared to be associated with worse bRFS, DMFS, and PCSS, whereas PD-1 was found in patients with better bRFS, DMFS, and PCSS (PD-L1 was not associated with

outcomes, perhaps because, as the authors suggest, it is not highly expressed) (4).

Ultimately, what can be gleaned from this vast amount of gene expression data and how can that be used to improve immunotherapy development in prostate cancer? Perhaps the most important caveat for this study, as the authors fully acknowledge (4), is that this analysis was done in prostatectomy specimens in men who are presumably noncastrate and thus likely have disease amenable to androgen deprivation. Thus, extrapolating these data into the metastatic castration-resistant prostate cancer (mCRPC) setting, where testosterone is maximally suppressed and tumors largely reside in bone, as opposed to within the prostatic capsule, requires caution despite the fact that mCRPC patients provide the largest clinical datasets for immunotherapy in prostate cancer and PD-L1 expression may be higher in that population (5). Nonetheless, the data are valuable and may provide a rationale for future therapeutic development across all stages of prostate cancer.

Regardless of the immunotherapeutic wave in recent years, biomarkers predicting responses remain dubious across tumor subtypes. In lung cancer, tumor mutational burden appears critical, while in other diseases, such as renal cancer, that does not appear to be the case (6,7). PD-L1 expression within bladder cancer has yielded confounding results in trials with atezolizumab (8). These data suggest that perhaps the immune predictive biomarkers will vary across tumor types and consist more of a panel of markers rather than a binary readout. In that regard, as Zhao et al. suggest, PD-L2 may well have a role as a candidate biomarker in prostate cancer. Interestingly, Zhao et al. noted associations with genes in radiation response pathways, possibly suggesting that these patients may benefit from radiation-based therapies or immune-combinations (4). That provocative hypothesis could be prospectively evaluated in the newly diagnosed or localized setting and could provide therapeutic guidance.

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Perhaps most surprising among the data presented in this large analysis is that T-cells appear to be associated with worse outcomes (4). This is critical, because currently immune checkpoint inhibitors most frequently target PD-1 and CTLA-4 on T-cells. As Zhao et al. note, the literature on T-cells in prostate cancer has not always indicated that they are beneficial, but the data are somewhat conflicting and mostly centered on the localized/newly diagnosed setting (9). Thus, it would be best to not presume what this means for later-stage disease. Also, as the authors acknowledge, this seems to conflict with their data suggesting PD-1—often associated with activated T-cells—is associated with better prognosis. Although Zhao et al. hypothesized that PD-1 expression could be related to chronic inflammation, which in turn could be tolerogenic, and thus immune permissive of oncogenesis, more data on this and the functional role of T-cells in the microenvironment of early- and late-stage disease is required.

The negative impact of macrophages on the patients' DMFS is less surprising (4). Data have suggested that after treatment with ipilimumab, prostate cancer patients have increased VISTA expression, another inhibiting immune checkpoint, on CD68+ macrophages (10). Additional data suggests that tumor-associated macrophages promote tumor angiogenesis, which has been associated with poor prognosis in prostate cancer (11).

Ultimately, the data by Zhao et al. (4), combined with other emerging data, paints a multifaceted, pleotropic immune tumor microenvironment (in early-stage prostate cancer) without a clear therapeutic target. Indeed, this is likely why immunotherapy has had limited success, not just in prostate cancer, but the majority of cancer patients. Targeting T-cells, macrophages, or PD-L2 alone may not be therapeutically sufficient for the majority of patients. This perhaps highlights the greater need for immunotherapy to move beyond targeting one molecule (ie, PD-L1) and focus on generating robust in vivo immune responses that ultimately can resculpt the immune microenvironment and shift the dynamic away from immune tolerance of tumors or alter protumor properties of certain multifunctional immune cells. The byproduct of a robust immune response would include cytokines that have the potential to convert pleotropic immune suppressive cells into antitumor killing cells. Furthermore, an array of immunocytokines is now starting to enter the clinic and may be integral components to demonstrate this hypothesis. NKTR-214 is a CD122-binding cytokine agonist that stimulates IL-2-mediated pathways and Alt-803 is an IL-15 superagonist, both of which can induce NK and T-cell activation have preliminary clinical data suggesting clinical impact in either PD-1 negative or anti-PD-1 refractory patients (12,13). Additional immunocytokines are being developed to

specifically target the tumor microenvironment to alter the pleotropic immune balance towards a more antitumor effect. The data by Zhao et al. accentuates the complexity of the tumor immune microenvironment and perhaps defines the need for equally diversified immunotherapeutic combination strategies.

Notes

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