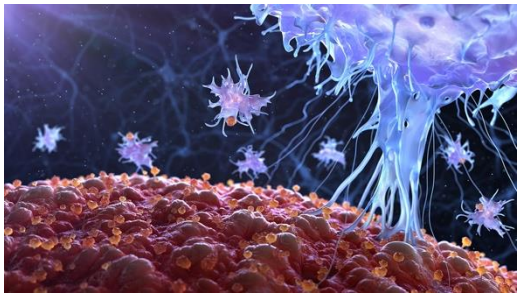
I-O CHALLENGER: IMMUNOTHERAPY BACKGROUNDER

What are immune checkpoints?



A core concept in cancer immunotherapy is that tumor cells, which would normally be recognized by T cells, have developed ways to "hide under the radar" of the host immune system. It is now recognized that established tumors possess several mechanisms of suppressing the antitumor response including production of inhibitory cytokines, recruitment of immunosuppressive immune cells and upregulation of co-inhibitory receptors known as immune checkpoints.

In 2018, Dr. James P. Allison and Tasuku Honjo were awarded jointly the Nobel Prize for their discovery of cancer therapy by inhibition of negative immune regulation. James P. Allison discovered that the CTLA-4 functions as a brake on T cells and set out to prove that CTLA-4 blockade disengage the T-cell brake and unleashes the immune system to attack cancer cells. Tasuku Honjo, discovered the PD-1, another protein expressed on the surface of T-cells. His results showed that PD-1, like the CTLA-4, functions as a T-cell brake but using a different mechanism. Both these discoveries led to the discovery of checkpoint inhibitors in the treatment of cancer.

How do checkpoint inhibitors work?

The immune checkpoint proteins, CTLA-4 and PD-1, are receptors expressed on the surface of cytotoxic T-cells that interact with their ligands CD80/CD86 and programmed death ligand-1 (PDL-1) on antigen-presenting cells, respectively, which helps the cancer cell evade T-cell-mediated death. **(Figure 2)**

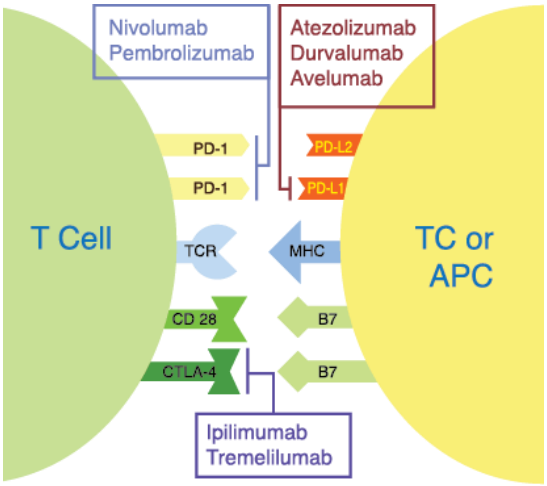


Figure 2. This figure was used under the Creative Commons license: CC BY-NC 4.0. Source: Endocrine Connections May 2018; 7(5):R196-R211.

Monoclonal antibodies blocking the PD-1 or its ligand (PD-L1) are a group of immune checkpoints inhibitors with proven anti-tumor efficacy. In the context of bladder cancer immunotherapy, the programmed cell death (PD) pathway, which consists of PD-1 and PD-L1, is the most researched pathway. PD-1 is a protein receptor commonly found on the cell surface of tumor infiltrating immune cells or (activated) T-cells. PD-L1 is expressed on antigen-presenting cells in the human body (e.g., dendritic cells or macrophages). PD-1 interacts with PD-L1 to "switch off" the immune response and prevent T-cells from attacking normal, healthy cells. In bladder cancer, tumor cells can escape detection because they too produce large amounts of immune markers like PD-L1 proteins that deactivate immune response, leading to the proliferation of cancer cells and T-cell exhaustion.

Which checkpoint inhibitors have been approved for bladder cancer?

Five checkpoint inhibitors have been approved for the treatment of advanced metastatic urothelial carcinoma. Immunotherapy is an option for patients who progress after standard platinum-based chemotherapy. In cisplatin-ineligible patients, atezolizumab and pembrolizumab have been approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA). Checkpoint inhibitors approved for second-line treatment in patients who have progressed on cisplatin-based chemotherapy include pembrolizumab, atezolizumab, durvalumab, nivolumab, and avelumab. These drugs and their targets are shown in **Figure 2**.

Biomarkers in Bladder Cancer

Several studies have shown that PD-L1 expression, as measured by immunohistochemistry in bladder tumors is associated with increased pathologic stage at resection and increased all-cause mortality suggesting that high levels may be associated with a more aggressive disease. These studies demonstrated the prognostic value of PD-L1 expression in terms of outcome, which is also important when considering its predictive value in the context of PD-1/PD-L1 targeted treatment.

Both the FDA and the EMA recommend that pembrolizumab therapy should only be used in patients whose tumors express PD-L1 with a combined positive score (CPS) assessing PD-L1 staining of ≥ 10%, and atezolizumab be used for patients whose tumors have PD-L1 expression of ≥ 5%. Patients already receiving these two drugs can continue treatment regardless of PD-L1 status.

Further studies are required to determine standardized reproducible biomarkers that will optimally guide treatment decisions.

References

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Test your knowledge on immunotherapy for bladder cancer. Take the I-O Challenge!

There are 3 levels to the game. Your mission: To beat the tumor and get as many correct answers as possible in the least amount of time. Wrong answers lead to damage points. The player with the least amount of damage points in the least amount of time will be declared the winner. Prizes will be awarded to the top player at the end of each day.