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Immune Checkpoint Inhibition in Advanced Cancer

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In the most basic terms, immunotherapy equates to T-cells killing cancer cells. The first delineation of "checkpoint" blockade involved cytotoxic T lymphocyte antigen 4 (CTLA-4), an immune checkpoint receptor involved in maintaining normal immunologic homeostasis. Antibody blockade of this receptor could result in antitumor immunity as originally defined in preclinical models (reviewed in citation 1).[1] For example, the immune checkpoint inhibitor ipilimumab was found to target CTLA-4 leading to a 5-year survival rate of 18.2% when administered with chemotherapy, compared to a survival rate of 8.8% for standard chemotherapy alone.[2] PD-1 immune checkpoints also became a focus of research in recent years because PD-1 is a negative regulator of T-cell activity that limits the activity at a variety of immune response stages through its interactions with its ligands, PD-L1 and PD-L2 (as reviewed in 1).[1] For example, pembrolizumab is an agent that targets PD-1, and recent data from the KEYNOTE-006 study demonstrated superiority of pembrolizumab over ipilimumab in patients with advanced melanoma in overall survival (OS), progression-free survival (PFS), and overall response rate (ORR); in fact, median OS was not reached for patients who received pembrolizumab vs a median OS of 16.0 months for those in the ipilimumab arm.[3] Currently there are three PD-1/PD-L1-targeting agents approved by the United States Food and Drug Administration (FDA) for use in treating cancer, and the list is evolving rapidly[4]:

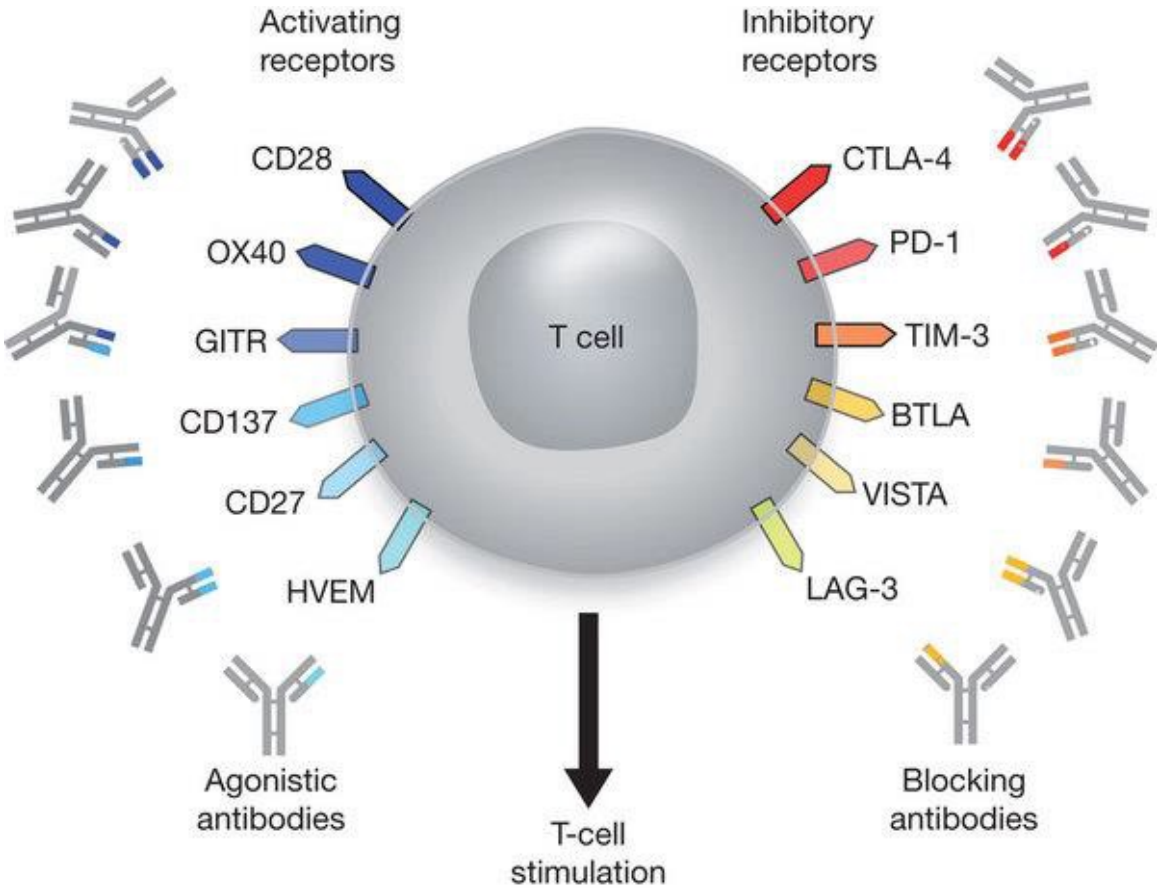
- Pembrolizumab: approved for use in squamous cell carcinoma of the head/neck, melanoma, and non-small cell lung cancer (NSCLC)
- Nivolumab: approved for use in squamous cell carcinoma of the head/neck, melanoma, NSCLC, renal cell carcinoma, and Hodgkin lymphoma
- Atezolizumab: approved for use in urothelial carcinoma and NSCLC

However, with all of these recently-approved immunotherapies, many questions remain. Among the many questions, this talk focused upon[5]:

- How are we considering therapy combinations?
- How can we reconsider toxicity?
- Does radiation really enhance efficacy of immunotherapy?

There are essentially two ways to consider combination immunotherapy. Direct methods involve turning up the activation of T-cells more via agonism of co-stimulatory targets and via antagonism of other negative immune checkpoints. Indirect methods involve killing the tumor with an immunogenic stimulus, such as radiotherapy, chemotherapy, oncolytic viral therapy, or targeted therapy.[5] There are many T-cell co-regulatory targets that may be involved in combination therapy, as seen in this graphic[6]:

T cell targets for immunoregulatory antibody therapy



TURNING UP THE ACTIVATING **BLOCKING THE INHIBITING**

The first experiences using combined CTLA-4 and PD-1 blockade were investigated combining nivolumab plus ipilimumab in advanced melanoma. Initial data demonstrated that more than half (53%) of patients treated with this combination had an objective response, and although toxicity was high, it was manageable.[7] Later data surrounding this combination in patients with untreated melanoma showed that the combination of nivolumab and ipilimumab produced a RR of 61% compared to 11% in patients who received ipilimumab.[8] A major question in all of this research concerns what is actually happening with immune response when these immune checkpoint blocking agents are used and how immunologic results may differ between single and combination checkpoint blockade. Historical data showed that CTLA-4 ligation induces cell cycle arrest.[9] One pharmacodynamic effect of ipilimumab not surprisingly is an increase in Ki67+ T-cells in the peripheral blood; pembrolizumab additionally is believed to increase Ki67+ CD8+ T-cells in the peripheral blood.[10,11] However, data have shown that using ipilimumab and nivolumab in combination results in greater numbers of Ki67+ T cells in the peripheral blood than ipilimumab alone.[12]

However, while the combinations show greater efficacy in achieving better response rates and progression free survival, it is also more likely to produce a greater number of serious side effects. For example, the CheckPoint 067 study assessing nivolumab and ipilimumab alone or in combination found that drug-related adverse events were more common in the combination therapy arm (56.5%) vs either nivolumab (19.8%) or ipilimumab (27.0%) alone.[13] Considering this, the question becomes whether or not the combination is really too toxic. In one pivotal study of the nivolumab/ipilimumab combination, the most commonly reported grade 3/4 toxicities were colitis (17%), diarrhea (11%), increased alanine transferase (11%), and increased lipase (9%). Although lipase was elevated frequently as mentioned, it was almost always asymptomatic.[14] Toxicity assessments in a more granular way (i.e. how many patients received steroids, how many had a dose delay) and beyond only reporting grade 3-4 adverse events are necessary. Because of toxicity concerns, the question then becomes exactly how much immunotherapy is needed for use in combination. There can be a very rapid response even after one dose of

combination therapy.[15] This feature of treatment combined with the fact that patients who discontinue therapy early due to toxicity have favorable long-term outcomes, raises questions about how much immunotherapy needs to be given.[16]

Research now continues into adaptively-dosed combination immunotherapy, with arms that will progress to either maintenance PD-1 blockade (nivolumab) if there is clinical benefit (response) or continued CTLA-4/PD-1-targeted combination therapy with nivolumab/ipilimumab if disease is stable or has progressed.[5] In addition, other immunosuppressive mechanisms in the tumor microenvironment are being studied. Indoleamine-2,3-dioxygenase (IDO) is an intracellular enzyme that acts via tryptophan depletion and production of toxic kynurenine, creating an immunosuppressive effect that facilitates immune escape of tumors.[5,17] CTLA-4 blockade efficacy is enhanced with IDO inhibition. These findings delineate the immunosuppressive role of IDO surrounding immunotherapies targeting immune checkpoints and the potential role of IDO inhibitors in cancer therapy, mostly in combination with checkpoint inhibitors.[18] Data from a study of the novel IDO1 inhibitor epacadostat in combination with the PD-1 inhibitor pembrolizumab in a small group of patients found that the combined blockade demonstrated an ORR of 53%, with 3 complete responses (CRs) and 7 partial responses (PRs) in the combination therapy arm.[19]

In addition to these combinations, radiation enhances multiple inflammatory pathways, including increased cytokines, increased IFNy production, enhanced CD8+ T-cell infiltration into tumors and increased chemokine (CSCL16) production.[5] However, while some anecdotal patient case reports have shown the combined effect of checkpoint inhibition with radiation creating tumor regression at a site distant from the primary radiotherapy site (termed the abscopal effect of radiotherapy), prospective data have yet to deliver convincing data on this concept. In preclinical models, the triple combination of CTLA-4/PD-L1/and radiation has been shown to be more beneficial than CTLA-4 and RT as a doublet.[20,21] Clinical trials testing this triplet are ongoing.

Overall, it must be remembered that the target of immune checkpoint inhibition is the lymphocyte.[6] T-cell receptor diversity is also another key area undergoing investigation. A highly diverse T-cell receptor repertoire is an essential property of an effective healthy immune system. The range of different T-cell receptors expressed in an individual plays a crucial role in host defense against disease.[22]

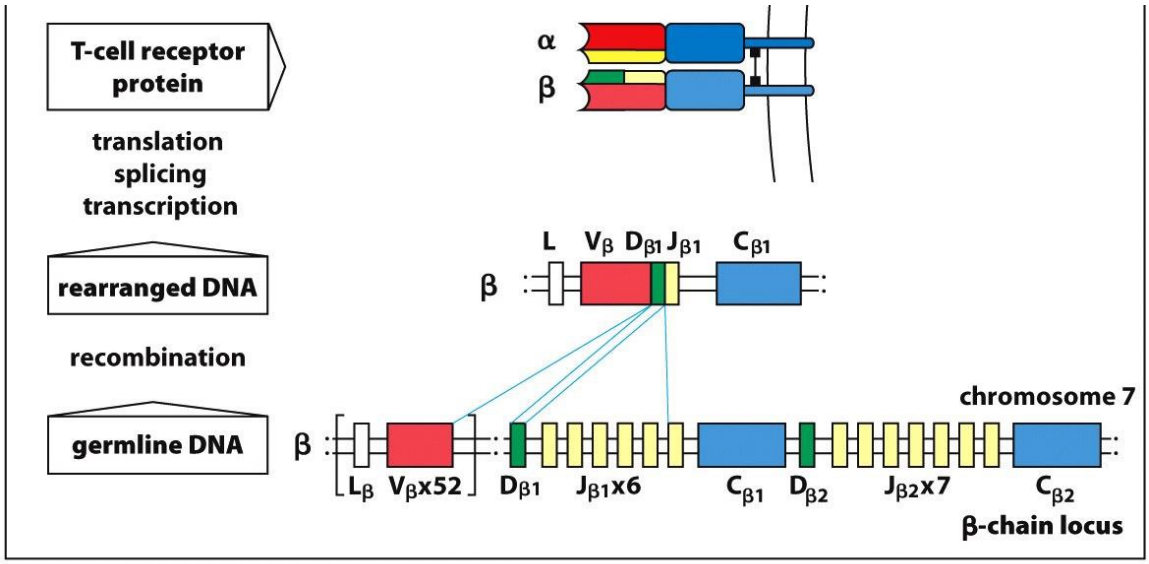


Figure 5.3 The Immune System, 3ed. (© Garland Science 2009)
Graphic courtesy of Michael Postow, MD

T-cell diversity may be considered in terms of greater diversity (more different types of T cells) and greater "clonality" (fewer different types of T cells)[5] Early, preliminary data suggest that T-cell diversity may be associated with clinical outcomes following ipilimumab. A more diverse T-cell receptor repertoire might reflect better immunologic health overall considering T-cell receptor diversity has already been shown to be associated with decreased infection risk after allogeneic stem cell transplantation and, per early data, may be potentially relevant to outcomes following ipilimumab therapy.[23] Radiotherapy has been found to increase intratumoral diversity of T-cells in preclinical models, and this may be a mechanism that is important in potential synergy between radiotherapy and immune checkpoint blockade.[21]

Summary:

Many advances have been made in cancer immunotherapy since the discovery of checkpoint inhibition and use of CTLA-4 and PD-1 blockade. However, there is still much research to be done surrounding combination therapy, including checkpoint inhibition agent combinations, use of radiotherapy as part of combination regimens, and the addition of new targets for therapy such as IDO. Biomarkers, including assessments of T cell receptor repertoire, are needed to more fully understand the mechanism of these drugs. There is still much to be learned about the best combinations of agents and treatments, their targets and timing, and best practices in individualizing treatment to each patient.

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