

3 Pembrolizumab – a new paradigm in the treatment of cancer

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The programmed death receptor-1 (PD-1) is an inhibitory receptor expressed on activated T-cells as well as B cells, natural killer T cells, monocytes, and dendritic cells. In normal tissues PD-1 acts as an immune checkpoint, enabling self-tolerance and preventing autoimmune reactions. Two ligands for the PD-1 receptor, PD-L1 and PD-L2, have been identified. PD-L1 has been detected on the surface of tumor cells of multiple histologies, including melanoma cells, and when bound, activates PD-1, resulting in suppression of cytotoxic T cell activity. Thus, up-regulation of PD-L1 allows cancer cells to avoid recognition and attack by the immune system. Similar results may occur as a result of expression of PD-L2 by tumor cells.

Pembrolizumab (Keytruda®) is a humanized monoclonal immunoglobulin G4 kappa antibody against PD-1. By blocking ligand interactions, binding of pembrolizumab to PD-1 receptors results in reactivation of tumor-specific T-cells and an anti-cancer immune response. Pembrolizumab was granted breakthrough therapy designation in melanoma

by the US FDA after initial clinical data indicated that it could offer substantial clinical benefit compared with the treatments that were available at the time, and is approved in the US for the treatment of advanced or unresectable melanoma in patients with disease progression following treatment with ipilimumab and, for patients with the BRAF V600 mutation, a BRAF inhibitor. Additional clinical studies have indicated substantial monotherapy activity for pembrolizumab, along with a tolerable safety profile, in several different cancer types, including non-small lung cancer, head and neck cancer, gastric cancer, and bladder cancer. Overall, pembrolizumab is under investigation as a monotherapy in 30 different cancer types, including hematologic malignancies, and is also under investigation in combination with other immune regulatory agents as well as standard-of-care cancer treatments. Activation of the immune system by anti-PD-1 therapies such as pembrolizumab represents a novel and promising therapeutic approach for the treatment of cancer.