Sipuleucel-T is a cell based therapy for metastatic, castration-resistant prostate cancer (mCRPC) that was approved by the U.S. FDA in 2010. Data from randomized Phase III trials of this agent, as well as Phase II data from second active immunotherapy for prostate cancer (ProstVac VF) provide strong evidence that prostate cancer may be sensitive to immune pressure, although objective responses (ORs) are quite rare. An alternative approach to immunotherapy focuses on a series of molecules known as immune checkpoints, which are expressed on the cell surface of tumor-infiltrating lymphocytes in multiple tumor types. Blocking immune checkpoint molecules with monoclonal antibodies can promote T cell activation and lead to ORs in patients with melanoma, kidney cancer and NSCLC. Immune checkpoint blockade has been less effective in prostate cancer, with a recent randomized Phase III study, anti-CTLA-4 failing to meet its primary (OS) endpoint. The reasons for this are not well-understood, but may involve a differential sensitivity of visceral versus non-visceral metastases to immunotherapy. Ongoing studies in our laboratory are centered around a more precise understanding of the molecular phenotype of the T cells that infiltrate high-grade tumors, based on the hypothesis that checkpoint molecules involved in attenuating an ant-tumor immune response in prostate cancer might be different than those involved in other tumor types.