by being the first drug in 30 years of clinical research to improve survival of metastatic melanoma and becoming paradigm shift for this disease. Although CTLA4 was the first molecule to be targeted by blocking antibodies, other targetable checkpoint molecules are PD1 and its ligand PDL1. Anti-PD1 antibody nivolumab was recently approved in Japan for the treatment of metastatic melanoma based on improvement in survival compared to chemotherapy. Pembrolizumab is another mAb against PD1 expressed by activated or exhausted T cells residing at the site of the tumor, showing strong anti-tumor activity in metastatic melanoma. Both antibodies exhibit clinical activity in metastatic NSCLC, renal cell cancer, gastric cancer, Hodgkins lymphoma, bladder cancer and others. Also anti-PDL1 mAb MPDL3280A, an engineered human antibody, has broad activity against a large number of human cancers.

In order for immune checkpoint inhibitors to work a T cell infiltrate is required. Currently, much effort is being put in trying to understand how T cells recognize cancers. Apart from T cells specific for shared tumor antigens, for which tolerance is incomplete, it has been shown that T cells can recognize antigens that arise as a result of tumor-associated DNA damage. Interestingly, cancers with a large number of somatic mutations, such as melanomas and smoking associated cancers, have a higher likelihood of being recognized by the immune system compared to cancers with only few mutations, and appear quite sensitive for immune checkpoint inhibition. This knowledge may be further exploited to improve the results of cancer immunotherapy in the near future.