**Core tip:**

The major functions of immune checkpoint receptors are to maintain self-tolerance, prevent immunopathology, and regulate overall immune homeostasis. However, skewed activation of these receptors by cancer cells may lead to suppression of nascent anti-tumor immunity and promote tumor cell growth. Clinical studies demonstrated that blocking of inhibitory immune checkpoint receptors induced durable clinical responses and unprecedented therapeutic benefits in multiple types of malignancies. The present Editorial addresses some of the major immune checkpoint receptor targets in cancer immunotherapy, discusses some of the side effects and limitations in their utilization, and highlights some of the future challenges in the field.