# The Progress of Checkpoint Inhibitors in Melanoma Treatment

Yankun Liu *

College of natural science, Michigan State University, East Lansing, USA

* Corresponding Author Email: yankun.liu.msa@gmail.com

**Abstract.** Melanoma is a type of skin cancer that is considered aggressive and with high metastatic capabilities. The invention of checkpoint inhibitors has revolutionized the approaches to treating melanoma by enhancing anti-tumor immunity and improving survival rates for patients. The first checkpoint inhibitor was approved by the FDA in 2011, targeting CTLA-4 and PD-1, and has shown promising response and provided better quality of life compared to traditional therapies such as chemotherapies. On the other hand, the clinical usage of checkpoint inhibitors is hindered by the development of resistance and immune-related toxicities. Researchers are focusing on novel checkpoint targets that could potentially overcome the current challenges, such as LAG-3 and TIGIT, which can restore cytotoxic T-cell function and enhance immune surveillance. These next-generational immunotherapy targets embrace the potential to achieve more durable control of melanoma while reducing adverse effects and resistance, marking a next step toward a more effective cancer treatment for melanoma.

**Keywords:** Checkpoint Inhibitors, Melanoma, Treatment.

## 1. Introduction

Due to the risk of spreading to more distinct locations of human bodies, melanoma, a type of skin cancer that is considered more severe than many other types.[1] Malignant transformation of melanocytes leads to uncontrolled proliferation, marking the beginning of melanoma progression [1]. Melanocytes are derived from the basal layer of the epidermis, and their primary function is to synthesize melanin, which is responsible for the natural pigment of human skin. The causes of melanoma can vary for patients due to genetics, and the most common cause is UV radiation exposure, such as sunlight exposure or usage of tanning beds [1].

Based on historical records, the incidence rate of melanoma has changed from the start of the 21st century, from 19.8 per 100,000 persons in 2000 to 28.4 per 100,000 persons in 2022, showing an overall increased incidence rate. However, the death rate of melanoma has decreased at the same time, dropping from 2.7% in 2000 to 2.0% in 2022[2].

In this context, the first checkpoint inhibitor drug used to treat melanoma was approved by the FDA in 2011, and it has been regarded as a revolutionary treatment for melanoma and many other malignant cancers [1]. Checkpoint inhibitors have improved both the survival rate and the quality of life of patients with melanoma. Despite its success, checkpoint inhibitor drug usage could induce immune-related adverse effects such as autoimmunity and drug resistance. This article discusses the mechanism of action of checkpoint inhibitor drugs, their advantages and limitations as clinical treatments, and future directions for breakthroughs.

## 2. Mechanism of Checkpoint Inhibitors

The discovery of checkpoint inhibitors as clinical treatment marks a turning point for treating melanoma. Compared to traditional cancer therapy, such as chemotherapy, which offered limited survival benefits and often came with significant toxicity with harmful side effects, checkpoint inhibitors target the body's own immune system and provide sustained long-term anti-tumor responses and less severe adverse effects. The most well-known targets of checkpoint inhibitors are CTLA-4 and PD-1, which dampen T-cell activation [3]. Ipilimumab (a CTLA-4 inhibitor) was the first drug that was approved for clinical usage and followed by the development of PD-1 inhibitors such as nivolumab and pembrolizumab.

Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) is a protein expressed primarily by activated T cells, and its expression and activation regulate the amplitude of T cell activation during its early phase, thereby controlling immune surveillance levels of the body's immune system [3]. CTLA-4 is categorized as an inhibitory receptor and binds to the ligand B7, expressed by B cells and Antigen Presenting Cells (APC). CD28, a co-stimulatory receptor expressed on T cells, also recognizes and binds to B7, and induces T cell activation and proliferation. The binding of CTLA-4 and B7 competitively inhibits CD28 from binding with B7, therefore suppressing T cell activation and preventing further activation of the body's immune responses. Many cancer cells utilize this mechanism, which takes advantage of CTLA-4-mediated suppression to dampen antitumor immunity [3].

CTLA-4 inhibitors are monoclonal antibodies that specifically bind to CTLA-4, and this binding prevents CTLA-4 from binding to its ligands. This action of checkpoint inhibitors removes the “brake,” allowing CD28 to bind to B7 and promoting CD28-mediated costimulatory signaling to be conducted, enhancing T-cell activation and proliferation against tumor cells [3].

The programmed cell death protein 1 (PD-1) is another critical immune checkpoint that is primarily expressed by T cells and natural killer (NK) cells. The function of PD-1 as an inhibitory receptor is to maintain immune tolerance and prevent excessive immune response, which may lead to autoimmunity [3]. PD-L1 and PD-L2 act as the ligands of PD-1 receptors, and they are expressed on antigen-presenting cells such as dendritic cells. The binding of PD-L1/PD-L2 to PD-1 inhibitory receptors induces intracellular responses, which then suppress both T-cell and NK cell activation, thereby reducing immune responses [3]. One of the primary pathways that PD-1 utilizes to suppress the immune system is by reducing cytokine production, which includes IL-2, IFN-γ, and TNF-α. Many cancer cells express PD-L1 or PD-L2, and function in a similar way to dampen the host’s immune surveillance and favor their proliferation and development with fewer immune attacks. Like CTLA-4 inhibitors, PD-1 inhibitors are monoclonal IgG antibodies that specifically target PD-1, and such bindings prevent the ligands PD-L1/PD-L2 from binding to PD-1. This action restores immune response and promotes anti-tumor activities induced by T cells [3].

Another possible and related category of immunotherapy is PD-L1 inhibitors. Unlike PD-1 inhibitors, which bind directly to the receptors on immune cells, PD-L1 inhibitors target the ligands expressed on cancer cells instead and promote an anti-tumor immune response like PD-1 inhibitors. However, some research has suggested that PD-1 inhibitors may not be mechanical equivalent to PD-1 inhibitors in cancer treatments, despite similar mechanisms of action. Additionally, PD-L1 inhibitors also contribute to antibody-dependent cytotoxicity as a possible adverse effect.

## 3. Advantages of Checkpoint Inhibitors in Melanoma

Checkpoint inhibitors have transformed the clinical treatment for melanoma by providing benefits beyond traditional therapies such as chemotherapy or radiation therapy. The ability to harness the patients’ own immune system not only directly improved survival rates clinically but also offered new hope for long-term disease-related control [4]. The following key points highlight the advantages of utilizing checkpoint inhibitors as an option to improve melanoma.

### 3.1. Improved survival outcomes

By comparing chemotherapy and checkpoint inhibitors, they showed a difference in efficacy for treating melanoma. In a network meta-analysis that includes over 6,400 patients, checkpoint inhibitors consistently outperformed chemotherapy in better clinical benefits [4]. Specifically, the analysis showed that complete response (CR) and partial response (PR) were significantly higher when applied to checkpoint inhibitor drugs. For example, Nivolumab 3 mg/kg vs. Chemotherapy showed an odds ratio (OR) of 6.51 for CR, and 2.57 for PR, suggesting that patients were 6.5 times more likely to achieve complete response, and 2.57 times more likely to achieve partial response, when compared to chemotherapy [4].

### 3.2. Fewer adverse effects and better quality of life

Besides the advantage of efficacy for checkpoint inhibitors, the decrease in side effects also highlights the difference between traditional therapy and checkpoint inhibitors [4]. Chemotherapy was more likely to induce adverse effects such as fatigue, pruritus, rash, diarrhea, and nausea than the usage of checkpoint inhibitors. Skin-related adverse effects were especially demonstrated by chemotherapy, such as pruritus and rash. For example, when comparing with Pembrolizumab 10 mg/kg, chemotherapy showed an odds ratio (OR) of 6.92 for pruritus, suggesting that the patients were 6.92 times more frequently getting pruritus after being treated with chemotherapy, compared to the usage of Pembrolizumab, a checkpoint inhibitor drug. These support that checkpoint inhibitors are a better option for melanoma when considering both adverse effects and quality of life after the treatment [4].

### 3.3. Durability of the effects

Durability is also an advantage for checkpoint inhibitors. In a study that included 132 metastatic melanoma patients treated with checkpoint inhibitors, 46 (34.8%) patients had a complete remission and then elected to stop the current checkpoint inhibitor therapy. The treatment effect was long-lasting, with exceptionally high progression-free survival (PFS) - 97.5% at 1 year and 94.7% at 30 months. Only 4 out of 46 patients (8.7%) showed relapses after the discontinuation of the treatment, with a median relapse time of 27 months [5]. This evidence indicates durable cancer control of checkpoint inhibitors, even after treatment discontinuation, and checkpoint inhibitors can provide long-lasting remission support.

## 4. Discussion

One of the challenges that checkpoint inhibitor therapies are facing is the development of resistance after the initial usage, which hinders the performance of such treatment for melanoma. In research conducted in 2017, which contained 488 melanoma patients from 3 different academic centers, 36 out of 488 developed acquired resistance after being treated with PD-1 inhibitors, with a median time to acquire resistance of 11.1 months. Despite the development of resistance in these patients, 89% (32/36) had a partial response; 11% (4/36) had a complete response before developing resistance [6].

The mechanisms for the development of resistance are complicated and multifactorial; they also differ between primary and acquired resistance. For primary (Innate) resistance, which patients never respond to in the first place, the main mechanisms include altered IFN-γ-signaling pathway, insufficient antigen presentation, etc. For acquired resistance, which patients initially respond to (tumor shrinks or stabilizes) but the cancer progresses again after a certain period of benefit, this may be due to the loss of tumor suppressor genes or exhaustion of either T cells or memory cells[7].

Understanding the molecular basis of resistance development is crucial for improving immunotherapies so that the resistance can be prevented or delayed, thereby extending the durable responses for melanoma patients who receive checkpoint inhibitor treatments.

Another challenge that is related to checkpoint inhibitor therapies is immune-related toxicities, or adverse effects. In a recent study that included 4489 patients with melanoma, 418 of those received checkpoint inhibitors as their therapies. After the follow-up, the usage of checkpoint inhibitors was statistically associated with a higher risk of autoimmune-related adverse effects, compared to others receiving other kinds of cancer treatments. Among those, nearly half (207) of the 418 patients had at least one immune-related adverse effect, and one fourth (52) developed 2 different kinds of immune-related adverse effects. The actual progression of such toxicity differs between patients, and the most common adverse effects include diarrhea, sepsis, septicemia, etc[8].

The number of immune-related toxicities is related to the kind of checkpoint inhibitors that have been used, and in general, CTLA-4 blockers usually induce more severe adverse effects than PD-1 blockers. Additionally, CTLA-4 and PD-1 blockers are associated with different kinds of effects. For

example, gut inflammation is much more common in patients with CTLA-4 blocker treatments than PD-1 blocker treatments. On the other hand, PD-1 blockers cause a higher frequency of thyroiditis, pneumonitis, and autoimmune diabetes. Furthermore, a combined therapy with both CTLA-4 and PD-1 blockers causes more significant toxicity than the usage of any alone [9].

Overall, while checkpoint inhibitors provide clinical benefits to treat melanoma, their usage is limited by immune-related toxicities. These findings emphasize the importance of better treatment plans and management to minimize toxicity and optimize therapeutic efficacy.

As the usage of PD-1/PD-L1 and CTLA-4 inhibitors has continued to expand, additional research has also highlighted additional targets for becoming potential checkpoint inhibitors to treat melanoma. These new approaches include LAG-3 and TIGIT and may represent the future direction of immunotherapeutic strategies.

LAG-3 (Lymphocyte Activation Gene-3) is a group of receptors that are expressed on T cells. These receptors bind to MHC II and ligands like Galectin-3, LSECtin, and FGL1. Their main function is to suppress T-cell activation and development, while maintaining immune homeostasis, but allow tumors to evade immune surveillance by this mechanism. As LAG-3 expression is considered more than PD-1, it is considered a potential target for blockage to treat tumors. Blocking LAG-3 restores T-cell activities, enhances infiltration of cytotoxic T lymphocytes, and therefore improves the body's ability to limit tumor development and proliferation [10].

TIGIT (T-cell immunoreceptor with Ig and ITIM domains) is a kind of protein that is expressed mainly on immune cells, including CD4+, CD8+ lymphocytes and natural killer (NK) cells. TIGIT also contributes to immune suppression of the body, mainly through suppressing T cells and NK cells by binding to CD155 and competing with costimulatory receptor CD226's binding capability. Suppressed and stabilized regulatory T cells are achieved through the PI3K/AKT/mTOR pathway inhibition. TIGIT blockage can potentially restore T and NK cells' cytotoxicity and improve anti-tumor immunity [10].

As potential new targets for checkpoint inhibitor therapies, these checkpoints could provide new opportunities to overcome some of the challenges that current immunotherapies have been facing and broaden the treatment options for melanoma patients.

## 5. Conclusion

Checkpoint inhibitors have transformed the therapeutic approaches toward melanoma, providing remarkable improvement in both survival rate and disease control for the patients. By targeting immune inhibitory receptors such as CTLA-4 and PD-1, these inhibitors have restored anti-tumor immunity and offered a great amount of durable immune responses to the patients. However, the achievements of checkpoint inhibitor treatment are challenged by the development of resistance and various immune-related toxicities that can potentially affect multiple organ systems.

The future direction of research is focusing on the exploration of novel checkpoint targets, such as LAG-3, TIGIT, which offer promising potential to overcome resistance and toxicities, while enhancing therapeutic effects. Combining these emerging strategies and precision medicine treatment approaches could further extend the durability and reliability of immunotherapies to treat melanoma while ensuring the quality of life for the patients.

## Referenc


[1] Heistein, J. B., Acharya, U., & Mukkamalla, S. K. R. (2024, February 17). Malignant melanoma. In StatPearls. StatPearls Publishing.

[2] Surveillance, Epidemiology, and End Results (SEER) Program. (n.d.). Cancer stat facts: Melanoma of the skin. National Cancer Institute.

[3] Buchbinder, E. I., & Desai, A. (2016). CTLA-4 and PD-1 pathways: similarities, differences, and implications of their inhibition. American Journal of Clinical Oncology

[4] CiRen, B., Wang, X., & Long, Z. (2016). The evaluation of immunotherapy and chemotherapy treatment on melanoma: A network meta-analysis. Oncotarget

[5] Perez, L., Samlowski, W., & Lopez-Flores, R. (2022). Outcome of elective checkpoint inhibitor discontinuation in melanoma patients with complete remission. Biomedicines

[6] Wang, D. Y., Eroglu, Z., Ozgun, A., Leger, P. D., Zhao, S., Ye, F., Luke, J. J., Joseph, R. W., Haq, R., Ott, P. A., Hodi, F. S., Sosman, J. A., Johnson, D. B., & Buchbinder, E. I. (2017). Clinical features of acquired resistance to anti–PD-1 therapy in advanced melanoma. Cancer Immunology Research

[7] Zielińska, M. K., Ciążyńska, M., Sulejczak, D., Rutkowski, P., & Czarnecka, A. M. (2025). Mechanisms of resistance to anti-PD-1 immunotherapy in melanoma and strategies to overcome it. Biomolecules

[8] Schonfeld, S. J., Tucker, M. A., Engels, E. A., Dores, G. M., Sampson, J. N., Shiels, M. S., Chanock, S. J., & Morton, L. M. (2022). Immune-related adverse events after immune checkpoint inhibitors for melanoma among older adults. JAMA Network Open

[9] Wang, S. J., Dougan, S. K., & Dougan, M. (2023). Immune mechanisms of toxicity from checkpoint inhibitors. Trends in Cancer

[10] Mireștean, C. C., Iancu, R. I., & Iancu, D. P. T. (2025). LAG3, TIM3 and TIGIT: New targets for immunotherapy and potential associations with radiotherapy. Current Oncology