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Targeting the Immune System: How Checkpoint Inhibitors Changed the Prognosis for Advanced Melanoma

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Abstract. Melanoma is a type of aggressive skin cancer that can become very difficult to treat, once it spreads beyond the original site. Surgery is the key to treat melanoma in its earlier stages, such as localized melanoma, and the melanoma has great potential to be successfully removed. On the other hand, once melanoma becomes advanced and enters the metastatic stage, it has historically resulted in limited treatment options as well as poor outcomes. This analysis combines findings from existing research and clinical trials to investigate how immune checkpoint inhibitors can be used for treating and early detection of advanced melanoma. Before the development of immune checkpoint inhibitors, existing treatments included chemotherapy and cytokine-based immunotherapies. Unfortunately, these past treatments produced limited responses and a small chance of leading to durable disease control. First, this paper explains the essential biological characteristics of melanoma, including its high number of mutations and its ability to evade the immune system, which contributes to melanoma progression. The next topic it elaborates on is how checkpoint inhibitors target two pathways that normally limit T-cell activity, which are PD-1 and CTLA-4. By applying checkpoint inhibitors, new drugs such as nivolumab, ipilimumab, and pembrolizumab, improves T-cells' ability to identify and target melanoma cells. Clinical evidence from major trials of ipilimumab, pembrolizumab, and nivolumab, shows improvements in overall survival, response rates, and long-term disease control compared with earlier treatments. While checkpoint inhibitors do not work for every patient and can cause significant immune-related side effects, they have made it possible for a large percentage of patients to survive from advanced melanoma.

Keywords: melanoma, immunotherapy, immune checkpoint inhibitors, PD-1/CTLA-4 blockade

1. Introduction

Cancer poses a major threat to public health, with a projected 2,114,850 new cancer cases and 626,140 cancer deaths in 2026 [1]. Melanoma is a type of rare skin cancer. Although it is responsible for only a small percentage of total skin cancer cases, it has caused a large number of deaths [2, 3]. Early detection of melanoma can often lead to successful treatments. However, the rate of successful prognosis degrades significantly after melanoma spreads to distant organs [2, 3]. As discussed in [4], while the 5-year relative survival rate is 97.6% when melanoma remains localized, the survival rate

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decreases to 60.3% when the cancer has invaded nearby tissues. Moreover, when melanoma has metastasized to distant sites, the survival rate degrades to only 16.2% [4]. This significant decrease in survival clearly illustrates why the treatment of advanced melanoma remains crucial and challenging [2, 5].

Traditional methods for metastatic melanoma treatment include chemotherapy and cytokine-based immunotherapies such as interferon-α and high-dose interleukin-2 (IL-2) [6]. Chemotherapy was the standard treatment for advanced melanoma for a long time, which directly targets rapidly dividing cells. However, response rates remained low, with only about 10-20% of patients experiencing measurable tumor shrinkage [6, 7]. Alternatively, IL-2 and interferon-α aimed to strengthen the body's immune response against the tumor. High-dose of IL-2 stimulated the accumulation and activation of natural killer cells ad T lymphocytes, while interferon-α improved the immune system's ability to attack melanoma cells [6-8]. Although these methods have provided a small proportion of patients with limited benefits, their clinical success remained limited due to severe side effects [6-8]. As a result, most patients with metastatic melanoma continued to struggle with low long-term survival [6, 7]. For many years, there has been a lack of effective long-term treatments for advanced melanoma until immune checkpoint inhibitors were introduced [5-7].

By enabling the immune system to attack cancer cells much more effectively, immune checkpoint inhibitors have emerged as a breakthrough for advanced melanoma treatment. Ipilimumab, a CTLA-4 inhibitor, was first shown to have a significant benefit in treating metastatic melanoma, while subsequent studies of PD-1 inhibitors such as nivolumab and pembrolizumab also demonstrated promising improvements in survival and response rates [9-12]. The introduction of checkpoint inhibitors marked a major milestone in the treatment of advanced melanoma, as some patients were able to achieve very encouraging long-lasting responses that were rarely seen with earlier treatments [9-12]. Checkpoint inhibitor immunotherapy has fundamentally changed the treatment outcomes for advanced melanoma and is becoming the new standard treatment options [10-12].

This paper investigates how immune checkpoint inhibitors can be used for early detection and treatment of advanced melanoma by analyzing findings from existing research and clinical trials. The essential biological characteristics of melanoma progression is described in Section 2, including its high number of mutations and the ability to evade the immune system [2-7]. Section 3 details the mechanisms that checkpoint inhibitors apply to promote T-cells' capability of identifying and targeting melanoma cells are detailed, including the PD-1 and CTLA-4 pathways [8-15]. Clinical results from existing major trials of several new drugs applying checkpoint inhibitors are summarized in Section 4, demonstrating significantly improved overall survival and long-term response rates [9-12]. Finally, some concluding remarks are given in Section 5.

2. What is melanoma, and why is it hard to treat

2.1. Overview of melanoma

Melanoma is a type of malignant tumor that originates from melanocytes, which are the cells that produce melanin in the skin [2]. The melanocytes are often found in the outermost layer of the skin. Melanoma will account for the majority of skin cancer deaths by 2026, as it is estimated that there will be 112,000 new cases and 8510 deaths due to melanoma [3]. The age-adjusted incidence rate for melanoma in the U.S. is 22.3 new cases of melanoma per 100,00 people per year, while the age-adjusted mortality rate for melanoma is 2.0 deaths per 100,000 people per year. These rates are based on melanoma incidence cases during 2019-2023 and melanoma deaths occurring during 2020-2024 [3].

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Surgical removal of melanoma tumors is often effective when cancer is detected and removed at an early stage with localized growth. Removing such a growth can prevent cancer from spreading and in many cases can result in a good long-term outcome. However, it is much more difficult to treat melanoma, if it has spread to other lymph nodes, organs, or tissues [2, 3]. Even if all cancer in the local area has been removed by surgery, cancer that has spread to distant sites in the body is not cured by surgery alone. Treatment may instead require systemic therapies, which are medications that travel through the bloodstream and can target cancer cells throughout the body [2]. Immunotherapy and targeted therapy are becoming more common as treatments for melanoma, while chemotherapy was more commonly used before these newer treatments became available. As a result, the treatment approaches for the progression from localized to metastatic melanoma are vastly different, resulting in patients with localized melanoma having a better prognosis than those with metastatic melanoma [2, 3].

2.2. Biology of melanoma

Another factor that makes melanoma difficult to treat is its high number of genetic mutations, as it has one of the highest mutation rates among human cancers. Many of these are induced by damaged DNA caused by ultraviolet (UV) radiation from the sun or tanning beds [5, 13]. Mutations in BRAF, NRAS, and NF1 genes are frequent events in melanoma that can contribute to uncontrolled cell growth and tumor formation [4]. The large number of mutations in melanoma can also lead to the production of abnormal proteins, or neoantigens, which can make the tumor more recognizable to the immune system [5, 13]. Because melanoma is highly immunogenic, effective treatments can be focused on inducing an anti-tumor immune response [5, 13].

2.3. Why advanced melanoma was historically difficult to treat

Historically, the treatment of metastatic melanoma has been challenging due to the aggressive nature of the cancer to spread distantly [2]. When melanoma has spread and can no longer be cured by surgical removal of the tumor successfully, other treatment options are used. For instance, when chemotherapy was used to treat patients with advanced melanoma, they showed relatively low response rates and little long-term control of the disease. a limited number of patients treated using therapies like high-dose IL-2 or interferon-α showed a durable complete remission. However, due to severe side effects, these treatments were not suitable for the majority of patients. As a result, patients with metastatic melanoma historically had few effective treatment options and generally poor long-term outcomes [6, 7].

3. How do checkpoint inhibitors actually work

3.1. The immune system and cancer

The immune system protects the body by detecting and removing harmful or abnormal cells, including cancer cells. T cells, which are a type of white blood cell that make up part of the immune system, are especially important in this process. These cells can recognize abnormal proteins, such as antigens, on the surface of cells, and as a result, they become activated to attack the harmful cells. The activities of T cells, however, must be controlled so that the immune system does not mistakenly start to attack healthy cells [8, 14].

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In order to control this activity, T cells have proteins that form the immune checkpoints, which typically act like brakes for the immune system, preventing it from becoming too active and attacking healthy tissue [8, 14]. However, cancer cells use the same pathways to make themselves immune to T-cell attack. Melanoma cells use these pathways to reduce the activity of T-cells, thus allowing them to survive even when they are recognized by the immune system. Checkpoint inhibitors are a class of drugs that block these signals, thus allowing the T-cells to remain active to kill cancer cells [8, 14, 15].

3.2. CTLA-4 blockade

One of the first of the immune checkpoints to be targeted in cancer treatment was the protein CTLA-4 on T cells. This protein is used by T cells to switch off T cell activation during an immune response. It is a competitor with another protein called CD28 for binding to molecules on antigen-presenting cells. When CTLA-4 is activated, it delivers inhibitory signals that reduce T-cell activity [8, 14].

Ipilimumab is a drug that blocks CTLA-4. As TGF-β is a checkpoint for T-cell activation that is removed by ipilimumab, instead of directly killing the melanoma cells, ipilimumab can augment the ability of the immune system to attack and kill the tumor cells [8, 9, 14]. Ipilimumab, a drug that blocks the CTLA-4 checkpoint, has improved the survival of patients with advanced melanoma, indicating that cancer can be treated with immune checkpoint blockade [9]. However, CTLA-4 is part of the normal regulation of the immune system, so blocking it can cause immune-related side effects, such as inflammation and autoimmune disease [8].

3.3. PD-1/PD-L1 blockade

Another important checkpoint pathway involves PD-1, a protein found on T cells, and PD-L1 and PD-L2, which can bind to PD-1. Normally, this pathway helps control the immune response and prevents T cells from causing unnecessary damage to healthy tissue [8, 9]. When PD-1 binds to one of its ligands, it sends a signal that decreases T-cell activity. Cancer cells can take advantage of this pathway by expressing PD-L1 or creating an environment that suppresses T-cell activity. This can make T cells less effective at attacking the tumor [8, 14, 15].

Nivolumab and pembrolizumab are two forms of PD-1 inhibitors [8]. These drugs prevent the interaction of PD-1 with its ligands. The signal that normally reduces the activity of T cells is prevented, and as a result, T cells are able to continue to attack cancer cells [8, 14]. There are several major clinical trials that prove the effectiveness of the above-mentioned cancer treatments [10]. Results from the KEYNOTE-006 trial found that pembrolizumab had advantages over ipilimumab for progression-free and overall survival. Similarly, the CheckMate-067 trial provided substantial evidence of the clinical benefits of nivolumab in patients with advanced melanoma, when used as a single agent or combined with ipilimumab [10, 11]. Long-term benefit was reported in some patients participating in the CheckMate-067 study, years after study closure [12].

Other agents targeting the checkpoint pathway, such as PD-1 inhibitors, have gained increasing attention since they appear to be better tolerated than agents targeting the CTLA-4 pathway [8, 10, 11]. Firstly, since CTLA-4 plays a major role in controlling T-cell activation, blocking CTLA-4 can result in more widespread immune-related side effects. Secondly, although PD-1 inhibitors can cause side effects, they have a more favorable safety profile than CTLA-4 inhibitors [8, 10, 11]. Nivolumab and pembrolizumab are two of the most effective first-line treatments for patients with advanced melanoma. However, this combination also increases the risk of side effects [11, 12].

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3.4. Why checkpoint inhibitors are especially effective in melanoma

One reason that melanoma may be very sensitive to immunotherapy is because of the large number of genetic mutations that typical melanoma cells have. These mutations can occur due to a variety of causes, but are often a result of DNA damage from ultraviolet (UV) radiation. Some mutations will cause changes in the proteins that the melanoma cells express and therefore create abnormal markers that are different from the normal cells, and these will be recognized by the immune system as foreign and are called neoantigens [8, 13, 14].

The large number of mutations found in the melanoma genome can result in many different neoantigens being recognized by T cells [8, 13, 14]. This could explain why melanoma can be so sensitive to treatments that release the immune checkpoints before treatment. In these situations, the checkpoint proteins on the tumor cells can prevent T cells from fully attacking the tumor, even if they can recognize melanoma cells. When checkpoint inhibitors block these inhibitory signals, T cells can become more active and attack cells carrying these abnormal markers. Therefore, checkpoint inhibitors do not necessarily create an entirely new immune response. This does not mean that checkpoint inhibitors create a completely new immune response. Instead, they can amplify an existing immune response that has been blocked by a tumor by specific mechanisms of immune suppression [8, 14].

Overall, the way checkpoint inhibitors work is closely connected to the biology of melanoma. Melanoma tumor cells display a high number of mutations leading to many tumor-specific targets for the immune system to recognize, while checkpoint pathways can prevent T cells from attacking those cells effectively. By blocking CTLA-4 or PD-1, checkpoint inhibitors remove these immune "brakes" and allow T cells to respond more strongly against the tumor. This helps explain why checkpoint inhibitors have become such an important part of treatment for advanced melanoma [8, 13, 14].

4. Clinical evidence: how checkpoint inhibitors transformed prognosis

4.1. The shift from chemotherapy to immunotherapy

The development of immune checkpoint inhibitors marked a major shift from the treatments available for metastatic melanoma in the past. Before checkpoint inhibitors, chemotherapy and other treatments such as high-dose interleukin-2 (IL-2) had shown limited effectiveness. Chemotherapy generally produced responses only in a small portion of patients, and long-term control of metastatic melanoma was uncommon [6, 7]. In comparison, checkpoint inhibitors produced higher response rates and, more importantly, allowed some patients to survive for many years after treatment [9-12]. Early studies of ipilimumab provided the first major evidence of this change and showed that blocking an immune checkpoint could improve survival in patients with advanced melanoma [9].

4.2. Landmark clinical trials

4.2.1. Ipilimumab: the first breakthrough

An important early trial using ipilimumab, a CTLA-4-inhibitor, was conducted in patients with metastatic melanoma who had failed prior treatment [9]. The trial was a comparative study of patients who had received ipilimumab alone, melanoma alone, and ipilimumab combined with a melanoma vaccine. Patients receiving ipilimumab had a median overall survival of 10.0 months,

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compared with 6.4 months with the control treatment. The one-year survival rate was also higher in the ipilimumab group, with 46.4% of patients alive after one year compared with 25.3% in the control group [9]. A difference in median survival of only a few months can still be very relevant for individual patients [9]. For example, in the treated group, some patients may have had a long-lasting treatment effect.

The trial with numbers far beyond the simple statistics provided great insight into the possibilities offered by cancer treatment. Before ipilimumab, the past treatments had offered very poor prospects for long-term survival. The trial provided some of the first strong clinical evidence that blocking an immune checkpoint could improve survival in advanced melanoma [9]. Ipilimumab is very different from typical chemotherapy. Instead of directly killing cancer cells, Ipilimumab can cause the body's own immune system to better attack melanoma cells. In this case, Ipilimumab caused the patient's melanoma to go into complete remission [9]. The basis of treatment by immune checkpoint blockade was established in their work and, consequently, other immune checkpoints were investigated, including PD-1 [8, 9].

4.2.2. PD-1 inhibitors and further improvements

The KEYNOTE-006 study demonstrated the benefits of using checkpoint inhibitors by comparing pembrolizumab (a PD-1-inhibitor) to ipilimumab (a CTLA-4 inhibitor) in patients with metastatic or advanced melanoma. Recently updated information revealed that after one year, 74% of patients on pembrolizumab were alive compared to 58% of patients on ipilimumab. Patients treated with pembrolizumab had a longer progression-free survival (time to cancer progression) than patients treated with ipilimumab [10]. Because pembrolizumab had better clinical outcomes and a favorable safety profile than ipilimumab, patients can now consider the use of pembrolizumab and other PD-1 inhibitors as potential treatment options for their disease [10].

Additional information was obtained from the CHECKMATE-067 trial, which compared nivolumab to ipilimumab and the combination of both drugs [11]. After two years, the overall survival rate for patients treated with nivolumab and ipilimumab was 63.8%, while nivolumab alone was 59.5% and ipilimumab alone was 45.4%. The response rates for the different groups of patients also followed a similar pattern: 57.6% of patients treated with the combination of nivolumab and ipilimumab responded to treatment, whereas 43.7% of patients treated with nivolumab alone and 19.0% of patients treated with ipilimumab alone responded to treatment [11]. In addition to offering significant single-agent benefits of PD-1 inhibition, in certain situations, the clinical benefits can be increased by the combination of a PD-1 pathway inhibitor with a CTLA-4 pathway inhibitor. However, the combination also caused more treatment-related side effects [11].

These long-term benefits extend beyond the initial few years of adjuvant treatment and are further described from the ongoing follow-up of patients and data from CheckMate-067. Long-lasting control of advanced melanoma can be obtained by checkpoint inhibition. Some patients even benefit from treatment long after the end of therapy and are still alive today [12].

4.3. Improvements in patient outcomes

These trials have demonstrated several key changes for the treatment of advanced melanoma, including longer survival, higher response rates, durable benefits, and generally manageable tolerability [9-12]. First, checkpoint inhibitors showed improved overall survival compared to past treatment methods, with subsequent trials continuing to demonstrate overall survival benefits [9-12]. Second, a greater proportion of patients experienced tumor shrinkage than with conventional

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treatment, meaning that a greater proportion of patients are likely to experience meaningful treatment effects with checkpoint inhibitors [9-11]. Third, long-term follow-up of CheckMate-067 provided evidence of long-lasting clinical benefit in some patients even years after with checkpoint inhibitors, establishing that responses to checkpoint inhibitors aren't temporary, unlike past treatment methods [12]. Lastly, there are potential serious immune-related side effects with checkpoint inhibitors. Although they can happen with any checkpoint inhibitor, in general the PD-1 inhibitors (pembrolizumab and nivolumab) are better tolerated than ipilimumab, helping make them important treatment options for advanced melanoma [10, 11].

Overall, the clinical evidence provided by these trials supports the notion that checkpoint inhibitors have effects beyond the shrinkage of tumors for a period of time. They improved survival and increased the number of patients with tumors that responded to treatment. Some patients even maintained long-term control of their metastatic melanoma for years, and in some cases decades [9-12]. It is not the case that every patient will have a sufficient response to every treatment, as treatments can cause serious side effects, but advanced melanoma is no longer a disease in which long-term survival is extremely uncommon. Now, for a meaningful number of patients with advanced melanoma, long-lasting survival can be achieved with the help of checkpoint inhibitors. This fundamentally changes the expected outcome for these patients with advanced melanoma.

5. Conclusion

For many years, metastatic melanoma was difficult to treat because of its ability to spread and the limited effectiveness of available therapies. The development of immune checkpoint inhibitors changed this by shifting the focus from directly attacking cancer cells to helping the immune system recognize and destroy them. By blocking CTLA-4 or PD-1, these treatments allow T cells to remain active against melanoma cells rather than being suppressed by the tumor.

Immune evasion in cancer can be targeted for significant clinical effects on patient outcomes. There is early clinical evidence that the trial of ipilimumab led to the development of the checkpoint blockade approach, which is increasing the survival of patients with melanoma. Landmark trials, such as the trial of ipilimumab, have demonstrated the potential of checkpoint blockade to improve survival. In the trial, the median overall survival was increased from 6.4 months to 10.0 months and one-year survival from 25.3% to 46.4% compared with the control treatment. Many subsequent studies with PD-1 inhibitors have shown continued improvements. In the KEYNOTE-006 study, 74% of patients with advanced melanoma were alive at 1 year after receiving pembrolizumab, compared to 58% of patients with advanced melanoma who were on ipilimumab as part of the study. Importantly, long-term follow-up of patients with durable disease control after treatment with checkpoint inhibitors showed that these patients continued to benefit from treatment for many years thereafter. These results highlight the dramatic change in the treatment of patients with metastatic melanoma, as compared to the outcomes before the use of checkpoint inhibitors.

Immunotherapy is not a cure for every single patient. Some patients do not respond to treatment. Others develop resistance to treatment. Furthermore, the immune-related side effects can sometimes even be serious for patients. There are, however, several important questions left to be answered. For example, the reasons for individual patients' treatment response and resistance to treatment can be explained. In addition, the issue of resistance to treatment needs to be addressed, and reliable biomarkers for treatment response need to be identified. Future studies that aim to identify additional predictive biomarkers, to elucidate mechanisms of treatment resistance, and to develop novel anticancer therapies, will be critical to render increasing benefits to an ever-increasing number of patients.

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Overall, the development of immune checkpoint inhibitors marks a paradigm shift in the treatment of advanced melanoma. Rather than adding to the long list of cancer treatments, such as chemotherapy, radiation, hormone therapy, targeted therapy, and immunotherapy, the introduction of checkpoint blockade to cancer treatment has allowed for the possibility of treating patients with previously untreatable diseases. It also demonstrated the potential of using the immune system itself as a powerful tool against cancer.

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