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ADJUVANT THERAPY IN MELANOMA: A REVIEW OF CONTEMPORARY TREATMENT STRATEGIES

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ABSTRACT

Melanoma is a highly aggressive skin cancer with a steadily increasing annual incidence. Although it accounts for only 1% of diagnosed skin cancers, it has the highest mortality rate among them. Therefore, it is essential to continuously develop treatment methods and improve long-term outcomes. In recent years, a breakthrough has been the introduction of adjuvant therapy following surgical treatment, which has become the standard of treatment. This has led to an increase in recurrence-free survival and overall survival in high-risk patients. Immunotherapy with anti-CTLA-4 and anti-PD-1 antibodies, as well as targeted therapy for patients with BRAF mutations, have become part of the standard of care. These are recommended for patients with stage IIB–IV melanoma at high risk of recurrence to eliminate micrometastases. Various treatment regimens targeting different patient subgroups are still being investigated to optimize outcomes and minimize adverse effects. This paper reviews and discusses current adjuvant treatment strategies for melanoma. In addition, it highlights the emerging role and future potential of these therapies in the neoadjuvant setting.

KEYWORDS

Melanoma, Adjuvant Therapy, Targeted Therapy, Immune Checkpoint Inhibitors

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Introduction

Melanoma is a malignant skin tumor that develops and progresses due to both environmental factors – primarily ultraviolet (UV) radiation and genetic predisposition (Tasdogan et al., 2025). Excessive exposure to radiation is associated with a high risk of melanoma development, as it causes DNA damage, and the accumulation of damaged DNA ultimately contributes to the emergence of numerous genetic mutations in skin cells (Young et al., 1998). Melanoma develops from altered melanocytes, i.e., cells that produce the pigment melanin. Melanocytes are surrounded by epidermal cells – keratinocytes. Both cell types interact with each other, forming a signaling network that is sensitive to UV radiation (Green et al., 2024). Melanin production is one of the protective mechanisms involved in maintaining the homeostasis of these cellular interactions. Melanin acts as a photoprotectant capable of broad-spectrum UV absorption, and it also functions as an antioxidant, participating in the removal of free radicals produced by UVA (Brenner & Hearing, 2008). It is also worth noting here that inherited risk factors, such as fair skin, blue/green eyes, or red/light hair, are closely linked to decreased melanin production by the body's cells (Olsen et al., 2019).

Although inherited genetic mutations account for a smaller proportion of melanoma cases, they remain a risk factor. In most of these cases, mutations occur in the gene encoding cyclin-dependent kinase 2A (*CDKN2A*) (Goldstein et al., 2006). This gene encodes two proteins that interact with two tumor suppressors – retinoblastoma protein (Rb) and p53 (González-Gil et al., 2021). Both proteins are important regulators of the cell cycle and are responsible for controlling cell proliferation. The protein products of the *CDKN2A* gene inhibit the MDM2 protein (which is a p53 inhibitor) and the cyclin D-CDK4/6 complex (responsible for inhibiting Rb protein via phosphorylation), thereby leading to the activation of cycle regulators and the arrest of the cell cycle upon detection of abnormalities, such as cellular DNA damage (Brown et al., 2004). Mutations in the *CDKN2A* gene can be of various types and may lead to the synthesis of an incomplete protein or the inhibition of protein synthesis. Loss of this function leads to excessive activation of p53 and Rb inhibitors, impaired cell cycle control, excessive cell proliferation, and tumor development (Kreuger et al., 2023).

In the United States, skin cancer is one of the most commonly diagnosed types of cancer. Despite these high rates, most cases are benign forms of the disease, and only 1% are melanoma. Nevertheless, melanoma has the highest mortality rate among them (American Cancer Society, 2026).

The risk of developing melanoma increases with age. Older adults (over 50 years of age) are more prone to developing various types of skin cancer. The link between age and cancer stems from the increased number of old and aging cells, which are at greater risk of developing cancerous mutations. Furthermore, with age, there is also a decline in DNA repair capacity (Torres et al., 2017) and a disruption of energy metabolism due to mitochondrial dysfunction, which induces oxidative stress through increased production of reactive oxygen species (ROS), thereby indirectly promoting cancer (Neagu et al., 2025). Interestingly, the lower incidence among young people may be linked to younger generations' awareness of preventive measures such as using UV filters, wearing protective clothing, reducing exposure to radiation, and regularly checking for skin lesions (American Cancer Society, 2026).

Although UV radiation is the primary risk factor for melanoma, the risk is also increased by: skin color (Fitzpatrick Skin Phototype Classification 1–3), immunosuppression, gender (women under 40 and men over 65), age, a history of other skin cancers, or a family history of melanoma. In recent years, the survival rate of melanoma patients has increased significantly, driven by the use of sentinel lymph node biopsy and the resulting accurate staging, as well as the development of adjuvant therapies following surgical treatment, such as immunotherapy or targeted therapy (Caraviello et al., 2025).

Diagnosis, Classification, and Treatment of Melanoma

The diagnosis of melanoma was systematized in the 1960s by dermatologist Wallace Clark, who suggested that melanoma should be classified based on histological features and can be assigned to three types: superficial spreading melanoma (SSM), lentigo maligna melanoma (LMM), and nodular melanoma (NM) (Scolyer et al., 2011). Over time, the number of distinct types of this cancer was expanded, and Clark himself developed the diagnostic system to include an assessment of the depth of cancer cell invasion into the dermis and subcutaneous tissue (Rebecca et al., 2012). Based on his observations, he identified five levels of melanoma penetration – from the epidermis (level I) to the subcutaneous tissue (level V) – which led to changes in patient treatment depending on the degree of skin penetration by melanoma cells (Davis et al., 2019). Another researcher, Breslow, in 1970 identified five stages of melanoma based on the thickness of the skin lesion, where stage I was ≤ 0.75 mm and stage V was > 3.0 mm, which allowed for the selection of appropriate surgical resection depending on the stage of the tumor (Breslow, 1970). The current classification is based on the TNM system (tumor, lymph nodes, metastasis) and allows for a more precise assessment of the prognosis for patients with melanoma (TNM staging for melanoma skin cancer | Cancer Research UK, 2025).

The primary treatment for melanoma is the surgical removal of the tumor along with the surrounding healthy tissue. In addition, when the tumor is larger than 0.8 mm, a sentinel lymph node biopsy is also performed, and if melanoma cells are present in it, the remaining lymph nodes in the area of the tumor are removed (Lee et al., 2013).

Adjuvant therapy

Adjuvant therapy used in the treatment of melanoma aims to eliminate micrometastases and reduce the risk of recurrence following primary treatment, which is surgical removal of the lesion (Eljilany et al., 2023; "Front Matter" 2020). Adjuvant therapy is most commonly recommended for patients following complete resection of stage IIB–IV tumors (Garbe et al., 2025). There are many different types of adjuvant therapies recommended for the treatment of melanoma (Natarelli et al., 2024).

Immunotherapy

The first drugs used in immunotherapy were interleukin-2 and high-dose interferon-α (HDI), while ipilimumab, an anti-CTLA-4 antibody, was used to block the immune system's checkpoint. Although they demonstrated improvements in progression-free survival and overall survival, their use was discontinued due to significant toxicity in favor of newer drugs: nivolumab and pembrolizumab, anti-PD-1 antibodies, and dabrafenib-trametinib, used in targeted therapy directed at *BRAF* mutations in melanomas with this mutation. These drugs had lower toxicity and, consequently, fewer side effects, and were associated with better survival rates. As a result, they have become the new standard of care for patients (Testori et al., 2020). The aim of this study is to compare and discuss available adjuvant treatment methods and to present new potential treatment strategies with future development potential.

Cytokine immunotherapy – interferon- α

Before the introduction of immune checkpoint inhibitors, IFN-α was the mainstay of adjuvant therapy for high-risk melanoma. This drug was approved by the FDA in 1995 (Kirkwood et al., 1996). Interferon-α causes nonspecific activation of the immune system, resulting in the induction of apoptosis in cancer cell lines. In addition, it exhibits immunomodulatory, antiproliferative, and antiangiogenic effects (Tarhini & Kirkwood, 2009). It also plays a role in increasing STAT1 protein expression while simultaneously reducing STAT3 expression, which may affect abnormal T-cell signaling, causing their infiltration into lymph node metastases (Kirkwood et al., 2004; Kobeissi & Tarhini, 2022). Over the years, Kirkwood et al. and the Eastern Cooperative Oncology Group have conducted large randomized clinical trials using high doses of interferon-α in patients with AJCC stage IIB and III melanoma following surgical resection (Kirkwood et al., 1996, 2000; Kirkwood, Ibrahim, Lawson, et al., 2001; Kirkwood, Ibrahim, Sosman, et al., 2001). Three of these studies demonstrated an improvement in recurrence-free survival, and two showed an improvement in overall survival (E1694, E1684). In 2010, a meta-analysis was published demonstrating improvements in both recurrence-free survival and overall survival with the use of interferon-α. However, the study did not identify the optimal dose of the drug, the duration of treatment, or the patient groups likely to respond better to this adjuvant therapy (Mocellin et al., 2010). The most commonly reported adverse effects include fatigue, nausea, vomiting, fever, muscle pain, myelosuppression, and neuropsychiatric symptoms such as depression and anorexia. Interferon-α may also exhibit cardiotoxic and hepatotoxic effects, cause erectile dysfunction, hypothyroidism, or retinopathy (Hauschild et al., 2008). Due to its numerous adverse effects and the availability of newer drugs with a better safety profile, interferon-α is currently not recommended for adjuvant treatment of melanoma (Garbe et al., 2025).

Anti-CTLA-4 Immunotherapy – ipilimumab

Ipilimumab is a human monoclonal antibody that works by inhibiting the CTLA-4 receptor, thereby enhancing the anticancer immune response. In 2011, the FDA approved the use of ipilimumab for the treatment of metastatic melanoma. This approval was based on a study showing an improvement in median survival rates in patients treated with ipilimumab and ipilimumab combined with a peptide vaccine compared to a control group that received only the vaccine. It was noted that 10–15% of patients experienced grade 3 or 4 adverse events (Hodi et al., 2010). In 2019, the U.S. Intergroup E1609 trial evaluated the efficacy of two doses of ipilimumab (10 mg/kg and 3 mg/kg) compared to high doses of interferon alfa in the treatment of high-risk melanoma following resection. Final results showed that lower doses of ipilimumab significantly prolonged overall survival compared to interferon, whereas this was not observed with higher doses. Furthermore, fewer treatment-related adverse events of grade III or higher were reported with lower doses of ipilimumab compared to higher doses (37% vs. 58%), which led to treatment discontinuation. No differences were observed between drug doses in terms of progression-free survival or overall survival (Tarhini et al., 2020). Currently, ipilimumab is recommended for use in combination with nivolumab only for selected high-risk patients with stage IV melanoma, while continuing to take into account the high toxicity of this treatment (Garbe et al., 2025).

Anti-PD-1 Immunotherapy – nivolumab, pembrolizumab

The IgG4 monoclonal antibodies targeting the PD-1 receptor used in therapy are nivolumab and pembrolizumab. Blocking this receptor results in the reactivation of CD8+ T cells, thereby increasing their number and efficacy (Eljilany et al., 2023). In 2017, the CheckMate-238 study (Weber et al., 2019) and in 2019 the KEYNOTE-054 trial (Eggermont et al., 2018) led to the FDA's approval of these drugs as adjuvant therapy for patients with locally advanced disease who had undergone complete surgical resection.

The CheckMate-238 trial evaluated the efficacy of nivolumab in adjuvant therapy for stage IIIB-IV melanoma. It demonstrated a longer recurrence-free survival rate of 51.7% compared to 41.2% with ipilimumab, as well as a more favorable safety profile associated with a reduction in the number of serious adverse events (14.4% compared to 45.9%) (Weber et al., 2019). Research has begun on the use of nivolumab in stage IIB/C melanoma following resection with a high risk of recurrence. In 2023, the CheckMate 76K study was published, demonstrating a significant 58% reduction in the risk of recurrence compared to placebo, with a 12-month recurrence-free survival rate of 89% vs. 79%.

The KEYNOTE-054 trial (Eggermont et al., 2018) evaluated the efficacy of adjuvant pembrolizumab therapy in high-risk patients with resected stage III melanoma who had sentinel lymph node metastases larger than 1 mm. The study results showed a longer recurrence-free survival rate of 59.8% (95% CI: 55.3–64.1) compared to the placebo group, where the rate was 41.4% (37.0–45.8), with no significant reduction in quality

of life (Bottomley et al., 2021). In 2023, the KEYNOTE-716 study was published, which evaluated the efficacy of pembrolizumab in stage IIB and IIC melanoma following resection over a median follow-up period of 39.4 months. The results demonstrated the drug's superiority over placebo in both recurrence-free survival (RFS) and distant metastasis-free survival (DMFS) (Luke et al., 2023).

Combination immunotherapy – nivolumab and ipilimumab

The randomized, double-blind IMMUNED trial compared the efficacy of combination therapy with nivolumab and ipilimumab, nivolumab alone, and placebo in patients with stage IV melanoma who showed no signs of disease following prior radiation therapy or surgical resection. After one year, recurrence-free survival in the group receiving nivolumab plus ipilimumab was 75% (95% CI 61.0–84.9), and after two years, 70% (55.1–81.0); in the nivolumab-alone group, it was 52% (38.1–63.9), and after 2 years, 42% (28.6–54.5); in the placebo group, it was 32% (19.8–45.3) after one year and 14% (5.9–25.7) after 2 years. Grade III and IV treatment-related adverse events occurred in 71% of patients receiving combination therapy and in 27% of patients treated with nivolumab alone. In both the combination therapy group and the nivolumab-only group, progression-free survival was prolonged compared to placebo (Zimmer et al., 2020).

In contrast, the CheckMate 915 trial evaluated the efficacy of nivolumab alone and in combination with ipilimumab in patients with stage IIIB–D and stage IV melanoma following resection. After 24 months of follow-up, no significant difference was observed between the patient groups; in the combination therapy group, the recurrence-free survival rate was 64.6%, while in the nivolumab monotherapy group it was 63.2%. More grade 3 and 4 treatment-related adverse events were reported in the combination therapy group (Weber et al., 2023).

Targeted therapy (BRAF/MEK)

The mitogen-activated protein kinase (MAPK) signaling pathway is responsible for intracellular processes such as cell differentiation, proliferation, and apoptosis. It also plays a significant role in melanoma oncogenesis, as abnormalities in its function are most commonly caused by a mutation in the *BRAF* gen. This mutation, however, is found in up to half of melanoma cases, mainly in the form of *BRAF* V600E or V600K. A fact suggesting its early role in the neoplastic process is its presence in approximately 80% of melanocytic nevi, even though only a small fraction of them will progress to melanoma (Sun et al., 2020). For this to occur, additional mutations such as deletions of the *CDKN2A* or *PTEN* genes are necessary (Shtivelman et al., 2014). This mutation became the target of targeted therapy (Akbani et al., 2015). BRAF inhibitors were developed, which irreversibly changed the outcomes of melanoma treatment, yielding satisfactory clinical results. However, growing resistance to this treatment was quickly observed, which was associated with the reactivation of the MAPK pathway. The addition of a MEK inhibitor, a molecule activated later in the MAPK pathway, allowed for the delay of resistance development (Sun et al., 2020).

The BRIM8 trial evaluated the efficacy of vemurafenib compared to placebo in patients with stage IIC–IIIB and IIIC melanoma harboring a *BRAF* mutation. Patients with stage IIC–IIIB melanoma treated with vemurafenib did not reach the median disease-free survival, whereas the median for the placebo group was 36.9 months. In stage IIIC patients receiving the drug, the median disease-free survival was 23.1 months versus 15.4 months in the placebo group. The results of the one-year treatment suggested that, although the drug was well tolerated, it did not constitute an optimal treatment regimen in this patient population (Maio et al., 2018). This study did not meet the primary endpoint specified in the statistical plan. The drug was ultimately not approved for use in adjuvant therapy (Garbe et al., 2025).

The efficacy of combination therapy with dabrafenib, a BRAF inhibitor, and trametinib, a MEK inhibitor, was also studied in patients with stage III melanoma and a *BRAF* mutation. Both at the one-year and three-year follow-up, the treatment significantly reduced the risk of disease recurrence in patients compared to placebo, without being associated with new adverse effects (Dummer et al., 2020; Long et al., 2017). The satisfactory results of treatment with dabrafenib and trametinib led to their use in clinical practice for patients with stage III melanoma and a *BRAF* mutation (Garbe et al., 2025).

Neoadjuvant therapy

Neoadjuvant therapy has been the subject of extensive research in recent years. The goal is to improve treatment outcomes by using drugs typically reserved for adjuvant therapy in induction regimens prior to surgical removal of tumors.

Large studies such as OpACIN-neo and PRADO focused on the use of ipilimumab with nivolumab in neoadjuvant therapy for patients with stage III melanoma. Treatment approaches varied. After the OpACIN-neo study suggested that pathological response serves as a predictor of long-term treatment outcomes, the PRADO study tailored treatment based on this indicator (Reijers et al., 2022; Versluis et al., 2023). Therapeutic lymph node dissection was performed in all OpACIN-neo patients, with adjuvant therapy omitted. In contrast, in the PRADO study, it was performed only in patients who did not achieve a major pathological response (MPR), in conjunction with adjuvant therapy. The 3-year survival rates in these studies were compared. The collected data indicated that lymph node dissection and adjuvant therapy could be omitted in patients who achieved a major pathological response (MPR) after neoadjuvant treatment. Both lymph node resection and adjuvant therapy, however, had a positive impact on recurrence-free survival and distant metastasis-free survival in patients who did not achieve this response. The results of these studies still require further verification, but they provide a basis for developing new melanoma treatment methods (Reijers et al., 2025). The phase III NADINA III trial compared the use of neoadjuvant therapy with ipilimumab and nivolumab followed by resection in patients with resectable stage III melanoma against a group of patients who first underwent resection followed by 12 cycles of nivolumab. Neoadjuvant therapy resulted in a longer estimated 12-month recurrence-free survival rate of 83.7% compared to 57.2% with adjuvant therapy (Blank et al., 2024).

SWOG S1801 was another large Phase II trial focusing on the use of pembrolizumab before and after surgery compared to its use only after resection in patients with resectable Stage III and IV melanoma. The primary endpoint was recurrence-free survival, which at 2 years was 72% in the neoadjuvant treatment group and 49% in the adjuvant treatment group (Patel et al., 2023). However, these results should be interpreted with caution, given the study's limitations, such as arbitrary rules for assigning adverse events over time or the inherent limitations of Phase II trials (Olivier & Prasad, 2024).

Available studies evaluating the efficacy of neoadjuvant treatment methods in clinical practice indicate significant potential benefits from the use of new therapies. They also highlight the ongoing need for broader studies to confirm these results and identify response patterns in larger patient cohorts (Blumenröther et al., 2025).

Summary

Although public awareness of melanoma prevention and early diagnosis continues to grow, new advanced cases continue to emerge that require a comprehensive approach. Based on the studies mentioned above, it can be clearly concluded that the introduction of adjuvant therapy has significantly improved the prognosis for patients with high-risk melanoma. However, there are still areas for improvement, such as the level of treatment toxicity and the selection of patient profiles that could benefit the most. This presents an opportunity for further research and refinement of existing therapies.

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