Narrative Review Article

Personalized Medicine in the Treatment of Melanoma: Advances and Current Approaches

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ABSTRACT

Melanoma remains a major global health concern due to its high mortality rate and resistance to conventional therapies. While standard approaches such as surgery, radiation, chemotherapy, and radiation are effective in early stages, they are insufficient in cases of advanced disease. Personalized medicine, which tailors interventions to the unique molecular and immunological profile of each tumor, has transformed melanoma management. Molecular profiling has identified key driver mutations, including *BRAF* and *NRAS*, as biomarkers guiding targeted therapies. In parallel, immunotherapies, and particularly immune checkpoint inhibitors, have significantly improved survival, although resistance remains a major challenge. Combination strategies, such as pairing immunotherapy with targeted therapy or radiotherapy, have been explored to enhance treatment efficacy and overcome resistance, but their safety profiles require further evaluation. Collectively, these advances demonstrate that personalized medicine has shifted the field of melanoma treatment and will continue to play a central role in improving patient outcomes. This review aims to summarize recent advances in personalized medicine for melanoma, with a particular focus on molecular profiling, targeted therapies, immunotherapy, and combination strategies.

Keywords: Melanoma; Personalized Medicine; Skin Cancer; Immunotherapy; Targeted Therapies; Combination Treatments

INTRODUCTION

Skin cancer is among the most common types of cancer, largely attributable to the skin's large surface area and its continual exposure to environmental risk factors. In 2018, over 1 million new cases of non-melanoma skin cancer (NMSC) were diagnosed globally, resulting in approximately 65,000 deaths. In the same year, more than 280,000 new cases of malignant melanoma (MM) were diagnosed, leading to around 60,000 deaths (1).

The majority of skin cancers are associated with both non-modifiable, and modifiable risk factors. Non-modifiable risk factors include age, sex, and genetic predisposition. Hereditary mutations can increase susceptibility, increasing the individual's risk of developing cancer. Modifiable risk factors include lifestyle and environmental exposure, with ultraviolet (UV) radiation being the most significant (2). UV radiation induces cellular damage through apoptosis and interference with DNA repair mechanisms, leading

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to the accumulation of mutations. Over time, these mutations can initiate carcinogenesis. Further, UV exposure suppresses the immune system's ability to detect and eliminate malignant cells, therefore creating a dual mechanism that favors the transformation of normal cells into cancerous cells (3).

There are three major types of skin cancer: basal cell carcinoma (BCC), squamous cell carcinoma (SCC), and melanoma. BCC and SCC, collectively classified as non-melanoma skin cancers, originate in the middle and upper layers of the epidermis. BCC is the most common form of skin cancer, with an estimated 3.6 million cases annually in the U.S., followed by SCC with approximately 1.8 million cases (4). These subtypes generally exhibit limited metastatic potential, making them more treatable.

Melanoma, by contrast, arises from the malignant transformation of melanocytes, cells responsible for the production of melanin. By accumulating above the nuclei within the epidermis, melanin normally protects nuclear DNA in keratinocytes from UV-induced damage (5). When melanocytes become dysregulated, however, they proliferate uncontrollably to form malignant tumors (6). Although melanoma accounts for just 4% of all skin cancer cases, it is responsible for 65% of deaths related to skin cancer (7).

Conventional treatments for skin cancer include surgery, chemotherapy, and radiation therapy. When the tumour is localized, surgical removal is often effective, as it allows the complete removal of the tumor, with minimal damage to the surrounding tissue. However, these methods have limited effectiveness in advanced stages, particularly when metastasis occurs. This is due to the lack of selectivity of treatments such as chemotherapy and radiotherapy, with healthy cells being damaged alongside malignant ones (3). Further, as these treatments apply a "one-size-fits-all" approach they do not take into account the unique biological features and molecular heterogeneity of individual tumors. Recent innovations in technology and medicine have led to the development of personalized medicine, which moves away from blanket treatments to more targeted approaches that consider the specific genetic, molecular and cellular characteristics of a person's tumor.

In the context of skin cancer, personalized medicine primarily encompasses molecular profiling, targeted therapies and immunotherapies. Molecular profiling allows clinicians to uncover the genetic, transcriptomic and proteomic makeup of a patient's tumor, guiding the selection of optimal therapeutic interventions. Targeted therapies, such as BRAF and MEK inhibitors, directly interfere with dysregulated signaling pathways central to melanoma pathogenesis (8). Immunotherapy represents another powerful personalized treatment approach. It works by enhancing the immune system's ability to recognize and eliminate malignant cells. Clinical trials have shown that immunotherapy can increase systemic antitumor responses and increase survival in patients with metastatic disease (9).

The main advancements in personalized melanoma treatment strategies are outlined in this review, with an emphasis on molecular profiling, targeted therapies, immunotherapies, and combination approaches. We also highlight present issues and potential paths forward to improve patient outcomes via personalized treatment.

MOLECULAR PROFILING AND DIAGNOSTIC TECHNIQUES

Molecular Profiling

Molecular profiling represents one of the most critical tools in personalized skin cancer therapy, enabling clinicians to characterize the genetic, transcriptomic and proteomic makeup of a patient's tumor. This molecular insight informs individualized treatment strategies by identifying driver mutations and dysregulated pathways, thereby guiding the selection of the most effective therapies. In melanoma, several oncogenic mutations serve as key biomarkers, most notably in the *BRAF*, *NRAS* and *KIT* genes.

Mutations in *BRAF*, particularly the V600E variant, occur in approximately 35-60% of malignant melanomas, and drive melanomagenesis (the formation and development of melanomas) through constitutive activation of the mitogen-activated protein kinase (MAPK) pathway, which results in uncontrolled cell proliferation (5). *BRAF* mutations are clinically significant because they predict responsiveness to targeted BRAF and MEK inhibitor therapy. *NRAS* mutations, present in approximately 20% of melanoma cases, generally occur independently of *BRAF* mutations. Although less common, *KIT* mutations are observed in specific melanoma subtypes, including mucosal, acral and chronically sun-damaged melanoma.

Next generation sequencing

The identification of these mutations has been greatly facilitated by advances in sequencing technologies. Next generation sequencing is particularly valuable, as it allows the detection of mutations, insertions,

deletions and copy number variations across the entire genome with high precision (10). Compared with Sanger Sequencing, which has been the gold-standard for the past 25 years, NGS is faster, more cost-effective and gives more precise results (11). In melanoma, targeted NGS gene panels are often used to assess common mutations, such as those in *BRAF* and *NRAS*. These panels have shown great concordance with real-time PCR (RT-PCR) and mass-spectrometry, while also detecting variants that other single-gene tests might miss (12). Further, NGS allows for the measurement of tumor mutational burden (TMB), defined as the total number of somatic mutations per megabase (Mb) of DNA within the tumor genome. A high TMB reflects the accumulation of mutations and has emerged as a potential biomarker for immunotherapy responsiveness. Notably, melanoma is one of the human cancers with the highest TMB levels, mainly due to the accumulation of mutations caused by UV-induced DNA damage (13).

Liquid Biopsies

Liquid biopsies, specifically the analysis of circulating tumor DNA (ctDNA) from blood, are a minimally invasive and highly informative approach for molecular profiling in melanoma. ctDNA fragments are released by tumor cells into the bloodstream and contain the same genetic mutations present in the primary and metastatic lesions, including mutations like *BRAF* V600E, *NRAS* and *KIT*. Thus, ctDNA is a valuable biomarker for disease monitoring, prognosis, and treatment decision-making (14). Moreover, clinical studies have shown strong correlations between baseline ctDNA levels, overall response rate (ORR) and progression-free survival (PFS). For example, in the phase II BREAK-2 trial, which evaluated the safety and efficacy of the BRAF inhibitor dabrafenib, higher baseline ctDNA levels were associated with reduced ORR and shorter PFS (15). These results were further validated in a larger pooled analysis of 836 patients from the BREAK-3, BREAK-MB, and METRIC trials, which confirmed the predictive significance of pre-treatment levels of ctDNA (16). Collectively, these results emphasize the value of ctDNA as a predictive biomarker for response to targeted therapies in melanoma. In addition to ctDNA, liquid biopsies can detect other tumor-derived materials, such as microRNAs (miRNAs). MiRNAs are small non-coding RNA molecules circulating in the blood and play a crucial role in oncogenesis. In patients with cancer, expression of miRNAs is altered: oncogenic miRNAs become overexpressed, while tumor-suppressive miRNAs are underexpressed (17). Overall, liquid biopsy-based detection of ctDNA and miRNAs holds significant promise for early detection, which is crucial for melanoma.

TREATMENT APPROACHES

Targeted Therapies

Targeted therapies are pharmacological approaches that disrupt specific signaling pathways or molecular drivers of tumorigenesis. They may act by blocking aberrant signal transduction pathways, inhibiting oncogenic proteins, triggering apoptosis, boosting the immune response or specifically delivering chemotherapeutic agents to cancer cells while sparing normal tissue (18). Melanoma is particularly suited to targeted therapies because it is mostly driven by well-defined mutations like *BRAF* and *NRAS*. The most common BRAF mutation in melanoma, *BRAF V600*, constitutively activates the mitogen-activated protein kinase (MAPK) pathway which leads to abnormal proliferation of melanocytes, inhibits apoptosis and accelerates melanoma progression. A previous study showed that BRAF inhibitors such as vemurafenib and dabrafenib produce strong initial responses. However, about 15% of patients exhibited primary resistance, and nearly half of the initial responders developed acquired resistance within six to eight months (19). Resistance typically develops through MAPK reactivation (via NRAS, MEK, or BRAF changes), as well as adaptive mechanisms such as ERK reactivation and compensatory PI3K-AKT signaling, which further reduce long-term efficacy (19).

To improve outcomes, combined therapies have been developed. These involve two or more simultaneous treatments to increase effectiveness, reduce resistance, and target complementary pathways (20). In melanoma, combining BRAF and MEK inhibitors has demonstrated superior results. For example, the combination of dabrafenib with the MEK inhibitor trametinib significantly prolonged PFS compared with dabrafenib alone in patients with metastatic melanoma (21). Mutations in *NRAS* are the second most common oncogenic driver after BRAF. However, direct pharmacological inhibition of NRAS has proven difficult due to its high affinity GTP binding and lack of druggable pockets for small molecules. MEK inhibitors remain the most commonly used targeted approach for NRAS-mutant melanoma, although their benefit as a

monotherapy is limited. Combination approaches are being explored, pairing MEK inhibitors with CDK4/6, PI3K or metabolic inhibitors such as PDK and PHGDH, but most of these are still in the preclinical stage (22)

Immunotherapy

The treatment of melanoma with immunotherapy has been a topic of research since the 1980s. Immunotherapy utilizes the body's own immune system to recognize and eliminate malignant cells. Multiple strategies have been developed, including cytokine stimulation, tumor vaccines, adoptive cell transfer, immune checkpoint inhibition and oncolytic viruses. Melanoma is particularly responsive to immunotherapy due to its high immunogenicity and elevated mutation burden (23). The first clinical breakthrough occurred when Rosenberg and colleagues showed that the injection of immune cells activated with IL-2 could induce regression of metastatic melanoma. This finding led to subsequent trials involving direct IL-2 administration, *ex vivo* expansion and reinfusion of tumor-infiltrating lymphocytes (TILs) or natural killer (NK) cells, and other strategies such as the use of radiation to enhance immunogenicity (24). Later, the discovery of melanoma-associated antigens, such as MAGE proteins and recognition of mutated proteins (e.g. mutant CDK4) by T cells enabled the development of antigen-specific immunotherapies, including peptide vaccines, cytokine therapies, and RNA-based approaches (25). Although promising responses were observed in individual patients, these early modalities did not improve overall survival rates compared with chemotherapy (e.g. dacarbazine). A major advance came with the development of immune checkpoint inhibitors (ICIs), which target inhibitory pathways of the immune system in order to promote cancer-cell killing by CD8 positive T-cells (26). ICIs have significantly changed the prognosis of metastatic melanoma, extending median survival from approximately six months to almost six years (23). Clinical evidence demonstrated that blockade of the programmed cell death-1 (PD-1) pathway using monoclonal antibodies, such as pembrolizumab and nivolumab yields durable responses. In a previous clinical trial, which included 655 patients with advanced melanoma, pembrolizumab achieved an ORR of 33% overall and 45% in treatment naive patients, with a 12-month PFS rate of 35%, with only 4% of patients discontinuing treatment due to treatment-related adverse events (27). Similarly, blockade of cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) with ipilimumab has been shown to improve median survival in advanced melanoma. In a clinical trial carried out in 2010 by Hodi *et al*., 676 patients with stage III or IV melanoma were randomly given ipilimumab alone, ipilimumab plus gp100 vaccine (a peptide cancer vaccine consisting amino acids of glycoprotein 100 melanoma antigen), or gp100 alone in a 1:3:1 ratio. The results demonstrated that median overall survival improved from 6.4 months (vaccine alone) to 10 months (ipilimumab alone) (28).

Mechanistically, PD-1 and its ligand PD-L1 suppress antitumor immunity by reducing T-cell activation and proliferation (Figure 1). Tumor cells often upregulate PD-L1, which binds to PD-1 receptors on T cells to promote immune evasion (29). Meanwhile, CTLA-4, expressed on regulatory T cells (Tregs), binds CD80/CD86 on antigen-presenting cells (APCs) to limit T-cell

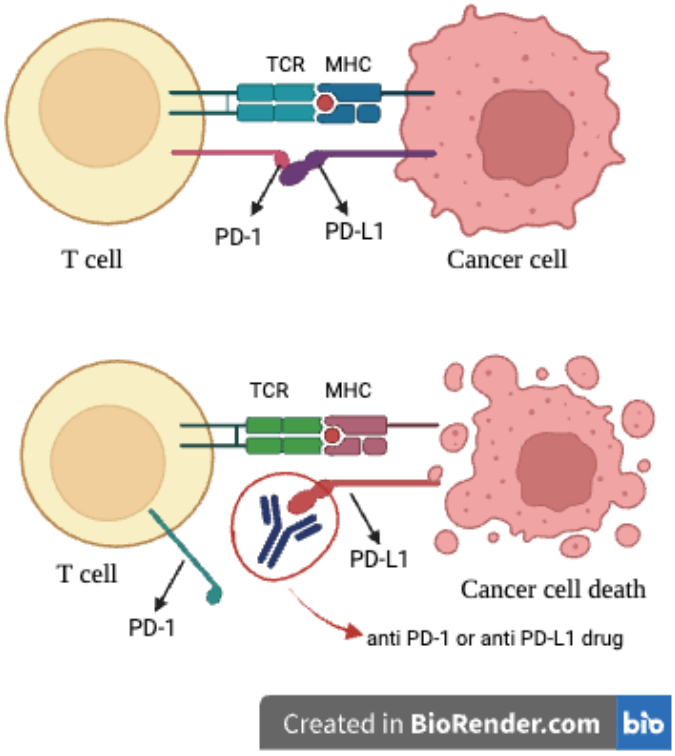

Figure 1. Mechanism of PD-1/PD-L1 inhibition in cancer immunotherapy. (Top) T-cell activation is inhibited by the interaction between PD-1, expressed on T-cells, and its ligand, PD-L1, expressed on cancer cells. This interaction enables immune evasion. (Bottom) By blocking this interaction, therapeutic antibodies that target PD-1 or PD-L1 restore T-cell activity and enable tumor cell death. Created with BioRender.

priming (Figure 2). Inhibition of these checkpoints restores T-cell function, allowing sustained immune-mediated tumor control (30).

Despite their success, ICIs face the challenge of primary and acquired resistance. Primary resistance, observed in up to 40% of patients with stage IV melanoma treated with PD-1 inhibitors, is often due to poor immunogenicity (insufficient tumor-associated antigens) (31) or impaired T-cell trafficking, as tumors downregulate chemokines required for T-cell homing (32). Secondary (acquired) resistance arises when patients initially respond to the treatment but later relapse frequently due to loss of T-cell function or downregulation of tumor antigens, including neoantigens that originally served as immune targets (33). To address these challenges in immunotherapies, combination therapies are being explored. These approaches, which combine two or more treatments, aim to enhance response rates, prolong durability and overcome resistance.

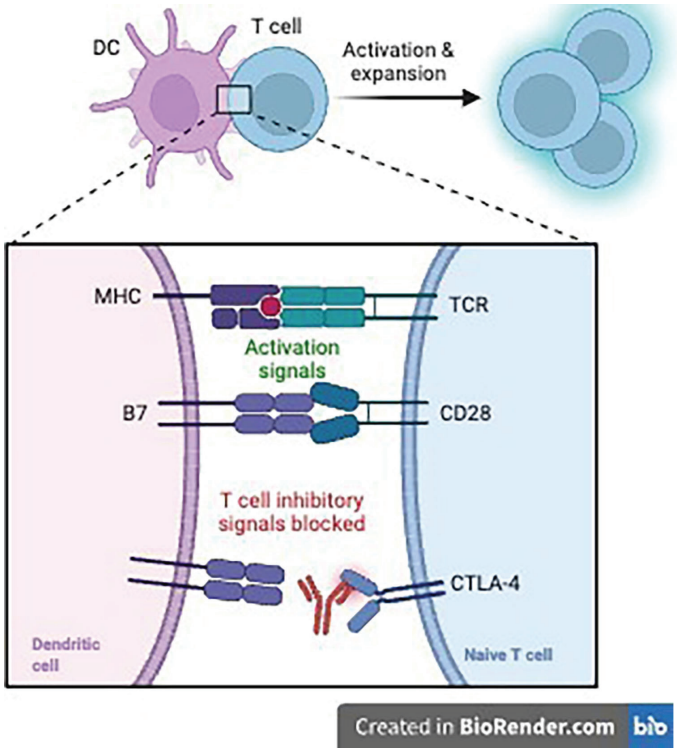

Figure 2. Mechanism of CTLA-4 immune checkpoint blockade. Under normal conditions, B7-CD18 interactions activate T cells, while CTLA-4 competes with CD28 to inhibit activation. Blocking CTLA-4 with immune checkpoint inhibitors prevents this suppression, enhancing T-cell activation and proliferation. Created with BioRender.

COMBINATION TREATMENTS

Combination therapy is a key strategy in the treatment of melanoma, designed to enhance treatment efficacy, overcome resistance and improve durability. These regimens may involve combining two different therapeutic modalities (e.g. targeted therapy plus immunotherapy) or administering two drugs from the same class (e.g. dual checkpoint blockade with ipilimumab and nivolumab). The rationale is that while individual treatments may have limitations, their combination can produce synergistic effects, reduce drug resistance and sustain antitumor activity (34) (Table 1).

Immunotherapy combinations

Dual immunotherapy has shown particular promise in melanoma. The combination of ipilimumab (CTLA-4 inhibitor) and nivolumab (PD-1 inhibitor) provides complementary mechanisms of action and has demonstrated improved outcomes compared to monotherapy. In a key trial of 945 untreated patients with stage III or IV melanoma, patients were randomized to nivolumab alone, ipilimumab alone or ipilimumab and nivolumab in combination. Median PFS was 11.5 months with the combination treatment, compared to 6.9 months for nivolumab alone and 2.9 months for ipilimumab alone. However, the combination treatment showed substantially higher toxicity, with 55% of patients experiencing treatment-related adverse events, versus 16.3% with nivolumab alone and 27.3% with ipilimumab (35). Thus, while efficacy improves, increased risk must be carefully managed. Another strategy involves combining cytokine therapy with immune checkpoint inhibitors. IL-2, the most extensively studied cytokine in melanoma, stimulates T-cell proliferation and modulates the tumor microenvironment (TME) (36). Preclinical studies in chronic viral models showed that while IL-2 or PD-L1 blockade alone produced modest benefits, their combination markedly expanded and restored CD8+ T-cell function, improved epitope recognition, and enhanced viral clearance (37). These findings provide a rationale for testing cytokine-checkpoint inhibitor combinations in cancer therapy, including melanoma.

Targeted therapy plus immunotherapy

Combining targeted therapies with immunotherapies has gained momentum as a strategy to merge the rapid responses induced by BRAF/MEK inhibitors

with the durable effect of checkpoint inhibitors (27). Preclinical studies demonstrate that BRAF/MEK inhibition promotes T-cell infiltration, enhances antigen presentation, and modulates the tumor microenvironment to support the immune response (35). Moreover, preclinical evidence suggests that MAPK inhibition exerts immune-modulating effects that can help overcome resistance to checkpoint blockade (36). Clinically, triplet combinations of BRAF inhibitors, MEK inhibitors, and PD-1/PD-L1 blockade have shown encouraging results. In 2020, the FDA approved atezolizumab (anti-PD-L1), vemurafenib (BRAF inhibitor) and cobimetinib (MEK inhibitor), which significantly prolonged PFS compared with BRAF/MEK inhibition alone (37, 38). These findings show the potential of combination therapy to extend response durability and resistance in advanced melanoma.

Table 1. Comparison of Different Therapy Approaches in Melanoma

Approach	Examples	Clinical Benefits	Limitations/ Resistance	Key Trial Outcomes
BRAF/MEK inhibitors	Vemurafenib, Dabrafenib + Trametinib	Rapid tumor regression, improved PFS	Acquired resistance (MAPK reactivation)	Clinical studies demonstrated significant early responses in patients with BRAF V600 mutations, confirming the central role of MAPK pathway inhibition in melanoma treatment (19).
Immune Checkpoint Inhibitors (ICIs)	Pembrolizumab, Nivolumab, Ipilimumab	Durable responses, long-term survival	Primary/acquired resistance, immune toxicity	Early IL-2–based therapies demonstrated tumor regression; later, pembrolizumab showed a 33% overall response rate and ipilimumab improved median survival from 6.4 to 10 months (27).
Combination ICI therapy	Nivolumab + Ipilimumab	Higher ORR and PFS	High grade- ¾ toxicity	Combination of ipilimumab and nivolumab improved median PFS to 11.5 months vs. 6.9 (nivolumab) and 2.9 (ipilimumab) but caused higher toxicity (55% adverse events); cytokine–checkpoint combinations show synergistic potential (35).
Targeted + Immunotherapy	Vemurafenib + Cobimetinib + Atezolizumab	Synergistic effect, prolonged PFS	Safety, immune-related adverse events	Triplet therapy with atezolizumab, vemurafenib, and cobimetinib significantly prolonged progression-free survival compared with BRAF/MEK inhibition alone, highlighting the potential of combined targeted–immunothera py approaches (37, 38).
Radiotherapy + Immunıtherapy	RT + ICIs	Enhanced systemic antitumor response, improved response rates and overall survival; acceptable toxicity	Abscopal effect	The Swedish metastatic melanoma study (2015–2020) showed that RT combined with ICIs increased response rates in irradiated lesions (70.7% and 67.5% vs 43.1%) and non-irradiated metastases (36.1% and 14.8% vs 0%), and prolonged median overall survival (18.2 and 15.0 months vs 7.2 months) compared to RT alone, with no increase in toxicity (43).
Liquid biopsy guided therapy	ctDNA, miRNA biomarkers	Early detection therapy monitoring	Standardization needed, low abundance	Emerging clinical studies highlight potential for real-time monitoring of tumor evolution and therapy response (15-17).

Radiotherapy and immunotherapy

Radiotherapy (RT) has also been combined with immunotherapy. Radiotherapy induces immunogenic cell death, releasing damage-associated molecular patterns (DAMPs)(signals produced by dying or injured cells that stimulate the innate immune system), exposing calreticulin, and enhancing antigen presentation, which in turn improves T cell priming. Although RT alone can have immune suppressive effects, when combined with immunotherapy, it can potentiate systemic antitumor responses. Of the most notable phenomena that occur as a result of this combination, and particularly with immune checkpoint inhibitors, is the abscopal effect, in which localized irradiation results in tumor regression in distant, non-irradiated tumor sites by converting irradiated lesions into an in situ vaccine (39). A Swedish study of metastatic melanoma patients (2015-2020) compared RT alone with RT plus ICIs. Patients receiving RT+ICI demonstrated higher response rates in irradiated lesions (70.7% and 67.5% vs. 43.1%) and improved overall responses in non-irradiated metastases (36.1% and 14.8% vs. 0.0%). Median overall survival was significantly longer with RT+ICI (18.2 and 15.0 months) compared to RT alone (7.2 months). Importantly, toxicity rates remained acceptable, with no increase in RT-related adverse events. These results show the therapeutic potential of combining RT with ICIs to enhance systemic immune responses in melanoma (43).

CONCLUSION

Personalized medicine has redefined the landscape of melanoma treatment by moving beyond uniform approaches to strategies informed by the genetic and immunological features of individuals tumors. Targeted treatment against BRAF and MEK mutations, along with immune checkpoint inhibitors, have greatly improved patient survival and quality of life.

Despite these achievements, a number of challenges still remain. Resistance to both targeted therapies and immunotherapies continues to limit long-term efficacy. The lack of standardized liquid biopsy techniques and biomarker variability further complicate patient selection and treatment monitoring. Further, combination treatments, though promising, often increase toxicity and cost, highlighting the need for improved predictive tools to balance efficacy and safety.

Future research is needed to concentrate on overcoming resistance mechanisms, monitoring real-time liquid biopsies and maybe the usage of artificial intelligence to predict models to optimize therapy selections and predict future outcomes. Clinical trials investigating combinational therapy approaches are required for these approaches to be more widely used. As molecular profiling technologies and therapeutic innovations advance, personalized medicine is poised to redefine the future of melanoma treatment, offering hope for improved survival in patients with this condition.

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CONFLICT OF INTERESTS

The author declares that there are no conflicts of interests related to this work.

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