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NEW IMMUNOTHERAPY STRATEGIES FOR MELANOMA: CHECKPOINT INHIBITORS, COMBINATION THERAPIES AND mRNA VACCINES

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ABSTRACT

Melanoma remains one of the most aggressive forms of skin cancer; however, the development of modern immunotherapeutic strategies has significantly improved the prognosis for a subset of patients. This review aims to discuss current and emerging treatment approaches based on modulation of the immune response, with particular emphasis on immune checkpoint inhibitors, targeted therapies, and mRNA vaccines. The mechanisms of action of antibodies targeting CTLA-4 and PD-1/PD-L1, their clinical efficacy, and the characteristic immune-related adverse events are presented. The review also discusses targeted therapies directed against BRAF and MEK mutations, as well as the rationale for combining these agents with immunotherapy to overcome treatment resistance. Furthermore, the emerging role of personalized mRNA vaccines designed according to the tumor neoantigen profile and the preliminary results of clinical trials are summarized. The importance of predictive biomarkers for patient selection and future directions in combination therapies are also highlighted. Overall, this review synthesizes the current state of knowledge and outlines promising opportunities for further improving treatment outcomes in patients with melanoma.

KEYWORDS

Melanoma, Immunotherapy, Immune Checkpoint Inhibitors, Targeted Therapy, BRAF Inhibitors, mRNA Vaccines, Combination Therapy, Precision Oncology

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Introduction

Melanoma remains the deadliest form of skin cancer, despite the fact that a substantial proportion of cases could potentially be prevented through reduced ultraviolet (UV) radiation exposure and early detection (Arnold et al., 2022; De Pinto et al., 2024; Wang et al., 2025). In 2020, approximately **325,000** new melanoma cases and **57,000** deaths were reported worldwide. If current trends continue, the global incidence is projected to increase by approximately **50%**, while melanoma-related mortality may rise by nearly **70%** by 2040 (Arnold et al., 2022; Liu et al., 2024). The highest incidence rates are observed among fair-skinned populations in Australia/New Zealand, North America, and Europe, whereas melanoma remains relatively uncommon across many countries in Asia and Africa (Arnold et al., 2022; De Pinto et al., 2024; Wang et al., 2025).

Long-term epidemiological analyses indicate that although melanoma incidence has steadily increased, mortality rates have stabilized—or even declined—in highly developed countries. This trend is attributed to improvements in prevention strategies, earlier diagnosis, and major advances in systemic therapies (De Pinto et al., 2024; Wang et al., 2025; Liu et al., 2024). Nevertheless, data from the *Global Burden of Disease* study demonstrate that the global prevalence of melanoma continues to rise, while the overall disease burden, expressed as disability-adjusted life years (DALYs), remains substantial, particularly in regions with a high sociodemographic index (Wang et al., 2025).

The major therapeutic breakthrough of the past decade has been driven primarily by two classes of agents: **immune checkpoint inhibitors** (anti-PD-1/PD-L1 and anti-CTLA-4 antibodies) and **targeted therapies** directed against the mitogen-activated protein kinase (MAPK) signaling pathway, including **BRAF** and **MEK** inhibitors (Lelliott et al., 2021; Pelster & Amaria, 2019; Dummer et al., 2020; Lengyel et al., 2024). These therapies have substantially prolonged survival and improved response rates in patients with advanced or metastatic melanoma. Moreover, several of these agents have become standard adjuvant treatments following complete surgical resection of high-risk melanoma (Dummer et al., 2020; Lengyel et al., 2024; Sheng et al., 2023). Despite these advances, their clinical efficacy remains limited by both primary and acquired resistance, immune-related toxicities, and the lack of reliable predictive biomarkers (Lelliott et al., 2021; Pelster & Amaria, 2019; Dummer et al., 2020).

Against this background, a third pillar of modern melanoma therapy has rapidly emerged: **mRNA-based anticancer vaccines**, including personalized vaccines targeting patient-specific tumor neoantigens (Sisk et al., 2026; Gao et al., 2026; Fu et al., 2025). Meta-analyses and systematic reviews indicate that mRNA vaccines exhibit a favorable safety profile and are capable of eliciting robust antigen-specific T-cell responses. Preliminary clinical studies in melanoma further suggest that these vaccines may improve disease control, particularly when administered in combination with immune checkpoint inhibitors (Sisk et al., 2026; Gao et al., 2026; Zhang et al., 2023; Fu et al., 2025).

Given the increasing global burden of melanoma and its persistently high mortality, optimizing the use of available immunotherapeutic strategies has become a major clinical challenge. This includes not only the effective application of monotherapies but also the development of combination treatment approaches and the integration of next-generation mRNA vaccines into established therapeutic regimens (Lelliott et al., 2021; Pelster & Amaria, 2019; Dummer et al., 2020; Lengyel et al., 2024; Sisk et al., 2026; Gao et al., 2026; Fu et al., 2025). Accordingly, the aim of this review is to summarize current evidence regarding the use of immune checkpoint inhibitors, targeted therapies, and mRNA vaccines in the treatment of melanoma, with particular emphasis on their clinical efficacy, safety profiles, and the therapeutic potential of combination strategies.

Methodology

A comprehensive literature review was conducted to evaluate emerging therapeutic strategies for melanoma, focusing on **immune checkpoint inhibitors (ICIs), targeted therapies, and mRNA vaccines**.

The literature search was performed using the **PubMed, Embase, Cochrane Library,** and **Web of Science** databases and included publications from the introduction of immune checkpoint inhibitors and targeted therapies in melanoma (approximately 2010) through the end of 2024. Combinations of Medical Subject Headings (MeSH) terms and keywords were used, including *melanoma*, *immune checkpoint inhibitors*, *PD-1*, *CTLA-4*, *targeted therapy*, *BRAF*, *MEK*, *mRNA vaccine*, and *cancer vaccine*. Eligible publications included phase I–III clinical trials, systematic reviews, meta-analyses, and narrative reviews investigating the efficacy, safety, and clinical application of these therapeutic strategies in melanoma.

Clinical Outcomes of Immune Checkpoint Inhibitors in Melanoma Treatment

Immune checkpoint inhibitor (ICI) therapy has revolutionized the treatment of advanced and metastatic melanoma, resulting in substantial improvements in **overall survival (OS), progression-free survival (PFS),** and **objective response rate (ORR)** compared with historical chemotherapy-based treatment standards (Carlino et al., 2021; Sabbatino et al., 2022; Shah et al., 2024; Karlsson & Saleh, 2017; Furue et al., 2018). The principal agents currently used include **anti-CTLA-4 antibodies** (ipilimumab), **anti-PD-1 antibodies** (nivolumab and pembrolizumab), and the recently introduced **anti-LAG-3 antibody** relatlimab. These agents are administered both as monotherapy and in combination regimens (Carlino et al., 2021; Ziogas et al., 2023; Lu & Tan, 2024; Li et al., 2023).

Clinical Efficacy

The introduction of ICIs has enabled durable disease control in approximately **50% of patients** with advanced melanoma, compared with fewer than **10%** prior to the immunotherapy era (Carlino et al., 2021; Shah et al., 2024). Anti-PD-1 monotherapy with nivolumab or pembrolizumab demonstrates superior efficacy and a more favorable safety profile than ipilimumab, while also providing significantly improved overall survival and objective response rates compared with conventional chemotherapy (Sabbatino et al., 2022; Karlsson & Saleh, 2017; Li et al., 2023).

Combined treatment with **nivolumab and ipilimumab** provides the highest reported three- and five-year survival rates, particularly among patients with high tumor burden or brain metastases. However, these clinical benefits are accompanied by substantially increased treatment-related toxicity (Carlino et al., 2021; Willsmore et al., 2021; Karlsson & Saleh, 2017; Li et al., 2023).

Meta-analyses and network meta-analyses have demonstrated that the regimen consisting of **nivolumab (1 mg/kg) plus ipilimumab (3 mg/kg)** provides the greatest improvement in OS, PFS, and disease control rate (DCR), although it is also associated with the highest incidence of severe treatment-related adverse events (Li et al., 2023; Chang et al., 2020). More recently, novel combinations such as **nivolumab plus relatlimab** (anti-LAG-3) have shown significant improvements in PFS while exhibiting lower toxicity than conventional dual checkpoint blockade (Ziogas et al., 2023).

Adjuvant and Neoadjuvant Applications

PD-1 inhibitors have become the standard of care for **adjuvant treatment** following complete resection of high-risk stage III and IV melanoma, significantly prolonging recurrence-free survival (Carlino et al., 2021; Sheng et al., 2023).

Neoadjuvant immunotherapy has also emerged as a promising therapeutic strategy. Early clinical studies have demonstrated high pathological response rates with an acceptable safety profile, suggesting that preoperative checkpoint inhibition may further improve long-term outcomes in patients with high-risk melanoma (Carlino et al., 2021).

Toxicity and Immune-Related Adverse Events

Despite their remarkable efficacy, ICIs are associated with **immune-related adverse events (irAEs)** resulting from excessive activation of the immune system. These toxicities most commonly affect the **skin, gastrointestinal tract, endocrine organs,** and **liver**. The highest incidence of severe irAEs has been reported with combined **CTLA-4 plus PD-1 blockade** (Carlino et al., 2021; Chang et al., 2020).

Network meta-analyses indicate that pembrolizumab and nivolumab monotherapy exhibit the most favorable safety profiles, whereas combination regimens are associated with the greatest risk of grade 3–4 treatment-related complications (Chang et al., 2020).

Special Patient Populations and Melanoma Subtypes

The efficacy of ICIs has also been confirmed in **older adults**, with current evidence indicating that advanced age does not significantly influence treatment effectiveness or safety (Lens & Schachter, 2025; Kim et al., 2022).

In contrast, less common melanoma subtypes—including **mucosal melanoma, acral melanoma,** and **uveal melanoma**—generally exhibit lower response rates than UV-induced cutaneous melanoma. Nevertheless, the best clinical outcomes in these populations have been achieved with combined **anti-PD-1 plus anti-CTLA-4 therapy** (Teo et al., 2024; Li et al., 2020; Klemen et al., 2020).

Table 1. Key Clinical Outcomes of Immune Checkpoint Inhibitors in Melanoma

Treatment regimen	12-month OS (%)	12-month PFS (%)	ORR (%)	Grade 3–4 AEs (%)	Subtype
Nivolumab + ipilimumab	71–75	35–40	50–60	55–60	Advanced/metastatic melanoma
Nivolumab or pembrolizumab	64–70	28–30	36–45	10–15	Advanced/metastatic melanoma
Ipilimumab	33	~10	~13	19–27	Advanced/metastatic melanoma
Nivolumab + relatlimab	~65	>30	>40	<20	Advanced melanoma
Anti-PD-1 + anti-CTLA-4 in mucosal melanoma	~72	~35	>33	>50	Mucosal melanoma

Summary

Immune checkpoint inhibitors currently constitute the cornerstone of systemic treatment for **advanced melanoma** and represent the standard **adjuvant therapy** following complete resection of high-risk disease. The most favorable long-term clinical outcomes have been achieved with combined **anti-PD-1 plus anti-CTLA-4 therapy**, although this approach is associated with substantially greater toxicity than monotherapy. Anti-PD-1 monotherapy provides durable clinical benefit while maintaining a considerably more favorable safety profile. Nevertheless, both primary and acquired resistance remain major clinical challenges. Ongoing research is therefore focused on identifying predictive biomarkers and developing novel combination strategies aimed at further improving patient outcomes (Vukadin et al., 2021; Ziogas et al., 2023; Lu & Tan, 2024; Karlsson & Saleh, 2017; Li et al., 2023; Teo et al., 2024; Lens & Schachter, 2025; Chang et al., 2020; Ziogas et al., 2022; Li et al., 2020).

Clinical Outcomes of Targeted Therapies in Melanoma

Targeted therapies, particularly **BRAF** and **MEK inhibitors**, have transformed the treatment landscape of advanced melanoma, especially in patients harboring **BRAF V600 mutations**. In recent years, targeted therapeutic approaches have also been investigated in other molecular subtypes, including **NRAS-** and **KIT-mutant melanoma**, as well as in combination with immunotherapy. The following section summarizes the key findings from clinical trials and real-world studies regarding the efficacy, safety, and limitations of these therapeutic strategies.

Clinical Efficacy of Targeted Therapy in Patients with BRAF Mutations

Combination therapy with **BRAF and MEK inhibitors**—including **dabrafenib plus trametinib**, **vemurafenib plus cobimetinib**, and **encorafenib plus binimetinib**—has become the standard of care for patients with advanced melanoma harboring **BRAF V600 mutations**. Clinical trials and real-world evidence consistently demonstrate **objective response rates (ORRs) of 50–60%**, while the **median overall survival (OS)** exceeds **20 months** (Luke et al., 2017; Orlova et al., 2021; Pippa et al., 2022; Schadendorf et al., 2018; Ugurel et al., 2020; Pala et al., 2023).

Compared with BRAF inhibitor monotherapy, combined **BRAF/MEK inhibition** provides superior clinical efficacy, including higher ORRs and prolonged progression-free survival (PFS) and overall survival. In addition, combination therapy reduces the incidence of several adverse events commonly associated with BRAF inhibitor monotherapy, thereby improving its overall tolerability (Luke et al., 2017; Orlova et al., 2021; Pippa et al., 2022; Pala et al., 2023).

Recent meta-analyses suggest that the **encorafenib plus binimetinib** regimen demonstrates the most favorable balance between efficacy and safety among currently available BRAF/MEK inhibitor combinations (Pippa et al., 2022).

Targeted Therapies in Other Molecular Subtypes

In patients with **NRAS-mutant melanoma**, the clinical benefit of **MEK inhibitors** is considerably more limited. Reported objective response rates are approximately **14%**, with a median progression-free survival of less than **3 months**, while treatment-related adverse events remain relatively common (Khan et al., 2025; Randic et al., 2021).

Similarly, targeted therapies have shown only modest efficacy in patients harboring **non-V600 BRAF mutations** or **KIT mutations**, although selected molecular subgroups may derive meaningful clinical benefit from these approaches (Menzer et al., 2025).

Resistance to Targeted Therapy

Both **primary and acquired resistance** remain major limitations of targeted therapy. Despite high initial response rates, the majority of patients experience disease progression within the first year after treatment initiation (Arozarena & Wellbrock, 2017; Lim et al., 2017; Patel et al., 2021).

The underlying mechanisms of resistance are complex and include **reactivation of the MAPK signaling pathway** as well as activation of alternative intracellular signaling cascades that enable tumor cells to bypass BRAF and MEK inhibition. Consequently, considerable research efforts are focused on developing novel therapeutic strategies capable of delaying or overcoming treatment resistance (Arozarena & Wellbrock, 2017; Imani et al., 2024; Lim et al., 2017).

Table 2. Key Clinical Outcomes of Targeted Therapies in Melanoma

Therapeutic regimen	Objective response rate (ORR)	Median PFS (months)	Median OS (months)	Major adverse events
BRAF inhibitor monotherapy	35–45%	5–7	13–16	Rash, pyrexia, cutaneous toxicities
BRAF inhibitor + MEK inhibitor	50–65%	9–12	>20	Pyrexia, fatigue, nausea
Encorafenib + binimetinib	Up to 70%	>12	>20	Fewer serious adverse events than other combinations
MEK inhibitor in NRAS-mutant melanoma	~14%	<3	<12	Rash, diarrhea, peripheral edema
BRAF/MEK inhibitors + immunotherapy	Up to 80–90%	>12	Not yet established	Increased incidence of grade 3–4 toxicities

Summary

Targeted therapies have substantially improved the prognosis of patients with **advanced BRAF V600-mutant melanoma**, with combined **BRAF and MEK inhibition** providing significantly higher response rates and longer overall survival than either BRAF inhibitor monotherapy or conventional chemotherapy (Luke et al., 2017; Orlova et al., 2021; Pippa et al., 2022). Nevertheless, the long-term effectiveness of these strategies remains limited by the development of both primary and acquired resistance, as well as their reduced efficacy in patients lacking **BRAF V600 mutations**.

The combination of targeted therapy with immunotherapy represents a promising therapeutic strategy, offering the potential for enhanced antitumor activity. However, current evidence indicates that these combinations are associated with increased toxicity and have not yet demonstrated a consistent overall survival advantage. Consequently, further large-scale randomized clinical trials are required to define their optimal role in melanoma treatment. At the same time, ongoing research continues to explore novel therapeutic approaches for patients with alternative oncogenic mutations and resistance-associated molecular mechanisms.

Clinical Trial Outcomes of mRNA Vaccines in Melanoma

mRNA-based vaccines for melanoma are currently being investigated primarily as **adjuvant therapy** following complete tumor resection and in patients with **advanced disease**, most commonly in combination with immune checkpoint inhibitors. Clinical evidence indicates promising improvements in survival outcomes while maintaining an acceptable safety profile. However, most available data originate from early-phase clinical trials.

Personalized Adjuvant Vaccines (mRNA-4157/V940, KEYNOTE-942)

A randomized phase IIb trial involving patients who had undergone complete resection of **stage IIIB–IV melanoma**demonstrated that the addition of the personalized **mRNA-4157/V940 vaccine** to pembrolizumab significantly improved **recurrence-free survival (RFS)** compared with pembrolizumab alone. The combination therapy reduced the risk of recurrence or death (**hazard ratio [HR] = 0.561**), with an **18-month RFS of 79%** versus **62%** in the pembrolizumab monotherapy group (Khattak et al., 2023; Weber et al., 2024).

The combination regimen also significantly prolonged **distant metastasis-free survival (DMFS)**, reducing the risk of distant metastatic recurrence (**HR = 0.347**). At 18 months, the DMFS rate reached **91.8%** in the combination group compared with **76.8%** among patients receiving pembrolizumab alone (Khattak et al., 2023).

Treatment was generally well tolerated. Most adverse events were **grade 1–2**, whereas grade ≥3 treatment-related adverse events occurred in **25%** of patients receiving the combination therapy compared with **18%** in the pembrolizumab monotherapy group. Importantly, **no vaccine-related deaths** were reported (Weber et al., 2024).

Recent review articles suggest that these findings have the potential to redefine the standard of adjuvant treatment for high-risk melanoma, although confirmation in ongoing phase III clinical trials remains necessary (Zoroddu & Bagella, 2025; Şahin et al., 2020; Blass & Ott, 2021; Latifyan & Haanen, 2024; Broderick et al., 2025; Khaddour & Buchbinder, 2025; Floudas et al., 2025).

Non-Personalized mRNA Vaccines in Advanced Melanoma

The **FixVac BNT111** vaccine, an mRNA-based therapeutic vaccine encoding four shared melanoma-associated antigens, has demonstrated encouraging activity in patients with **advanced melanoma resistant to immune checkpoint inhibitors**.

In a phase I clinical trial, BNT111 induced **durable objective responses** together with robust **$CD4^+$ and $CD8^+$ T-cell activation**. Clinical responses were observed both when the vaccine was administered as monotherapy and in combination with anti-PD-1 therapy (Şahin et al., 2020; Bafaloukos et al., 2023).

A meta-analysis including **32 clinical studies**, of which **13 involved melanoma**, reported an overall **objective response rate of 10%** and a **disease control rate of 34.6%** among patients with solid tumors treated with mRNA vaccines. Severe treatment-related adverse events were uncommon, occurring in approximately **1%** of patients, supporting the favorable safety profile of this therapeutic approach (Zhang et al., 2023).

Table 3. Selected Clinical Outcomes of mRNA-4157/V940 in High-Risk Melanoma

Study / Clinical Setting	Treatment Arms	Key Efficacy Outcome	Grade ≥3 Toxicity
KEYNOTE-942 (resected stage III–IV melanoma)	mRNA-4157/V940 + pembrolizumab vs. pembrolizumab	18-month RFS: **79% vs. 62%**; HR = 0.56	25% vs. 18%
KEYNOTE-942 (DMFS analysis)	mRNA-4157/V940 + pembrolizumab vs. pembrolizumab	18-month DMFS: **91.8% vs. 76.8%**; HR = 0.35	Same as above

Summary

Current clinical evidence demonstrates that the personalized **mRNA-4157/V940 vaccine**, when combined with pembrolizumab, significantly reduces the risk of **disease recurrence** and **distant metastasis** following complete resection of high-risk melanoma while maintaining an acceptable safety profile.

In advanced melanoma, both **personalized neoantigen-based vaccines** and **shared-antigen mRNA vaccines** have shown the ability to induce robust tumor-specific immune responses. In a subset of patients, these immune responses translate into durable clinical remissions, particularly when mRNA vaccination is combined with immune checkpoint blockade.

Despite these encouraging findings, the available evidence is still largely derived from early-phase clinical trials. Therefore, larger randomized phase III studies are required to establish the definitive role of mRNA vaccines within the standard treatment algorithm for melanoma. Nevertheless, current results strongly suggest that mRNA-based immunotherapy represents one of the most promising future directions in precision oncology and may become an integral component of combination treatment strategies for melanoma.

Conclusions

Recent advances in melanoma treatment have been driven by the development of **immune checkpoint inhibitors**, **targeted therapies**, and emerging **RNA-based therapeutic strategies**, including mRNA vaccines. Immune checkpoint inhibitors targeting the **PD-1/PD-L1** and **CTLA-4** pathways have substantially improved survival outcomes in patients with advanced melanoma. Moreover, the introduction of additional checkpoint targets, such as **LAG-3**, and the development of combination immunotherapeutic approaches have further increased response rates, although durable clinical benefit is still achieved in only a subset of patients (Mehta et al., 2025; Sun et al., 2023; Dutta et al., 2023; Sun et al., 2024; Qu et al., 2022; Коротаева et al., 2020). Likewise, targeted therapies—particularly combined **BRAF and MEK inhibition** in patients with **BRAF-mutant melanoma**—provide rapid tumor regression and significant improvements in clinical outcomes. Nevertheless, the emergence of treatment resistance remains a major limitation, supporting the rationale for sequential treatment strategies and combinations with immunotherapy (Mehta et al., 2025; Sun et al., 2023; Dutta et al., 2023).

At the same time, a new generation of **RNA-based immunotherapies** is rapidly emerging. Technologies based on **modified mRNA, self-amplifying RNA (saRNA), small interfering RNA (siRNA), microRNA (miRNA), circular RNA (circRNA),** and other **non-coding RNAs (ncRNAs)** enable not only more precise modulation of immunosuppressive pathways—including **PD-1/PD-L1** and **CTLA-4** signaling—but also the development of personalized neoantigen vaccines capable of enhancing the efficacy of immune checkpoint blockade (Minnaert et al., 2021; Mehta et al., 2025; Touchaei & Vahidi, 2024; Choi et al., 2024; Dutta et al., 2023; Han et al., 2023; Han et al., 2024; Mauricio et al., 2021; Batista-Duharte et al., 2022). In parallel, advances in nanoengineered and bioengineered delivery systems are improving the immunogenicity, stability, and safety of RNA-based therapeutics, thereby accelerating their clinical translation (Minnaert et al., 2021; Choi et al., 2024; Han et al., 2023; Han et al., 2024; Batista-Duharte et al., 2022).

Taken together, the available evidence suggests that the future of melanoma treatment will rely increasingly on **multimodal combination therapies**, integrating multiple immune checkpoint inhibitors, molecularly targeted agents, and RNA-based therapeutics—including personalized mRNA vaccines—to overcome treatment resistance and further individualize patient management. Continued progress in biomarker discovery, optimization of treatment sequencing, and refinement of combination strategies will be essential to maximize therapeutic efficacy while minimizing toxicity and improving the cost-effectiveness of melanoma care.

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