A COMPREHENSIVE REVIEW OF NIVOLUMAB AND IPILIMUMAB COMBINATION THERAPY IN ADVANCED MELANOMA

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Abstract

Melanoma is the most aggressive form of skin cancer and carries a poor prognosis in advanced stages. Until 2011, systemic treatments such as dacarbazine and high-dose interleukin-2 offered limited and short-lived survival benefits. The introduction of immune checkpoint inhibitors has revolutionized the management of metastatic melanoma. The mechanistic rationale for dual immune checkpoint blockade is discussed, highlighting complementary enhancement of antitumor T-cell activation and effector function. Clinical evidence from pivotal randomized trials, including CheckMate 067 and CheckMate 511, is critically appraised alongside real-world observational data. Combination therapy with nivolumab plus ipilimumab consistently demonstrates higher objective response rates and improved long-term survival compared with monotherapy, with durable responses extending beyond 10 years in selected patient subgroups. However, these benefits are accompanied by a substantially increased incidence of immune-related adverse events, necessitating careful patient selection, close monitoring, and proactive toxicity management. Emerging strategies, including modified dosing schedules and novel checkpoint combinations such as PD-1 plus LAG-3 blockade, aim to improve the benefit–risk balance. Overall, nivolumab plus ipilimumab represents a cornerstone first-line option for advanced melanoma, offering the potential for long-term disease control in a subset of patients, while ongoing research seeks to optimize safety and broaden durable responses. This review summarizes the global burden and epidemiology of melanoma, the evolution of systemic therapy from chemotherapy to immunotherapy, and the pharmacological profiles of Nivolumab (anti-PD-1) and Ipilimumab (anti-CTLA-4).

Key words: Melanoma; immune checkpoint inhibitors; nivolumab; ipilimumab; combination immunotherapy;immune-related adverse events.

Introduction

Melanoma is a malignant tumor of melanocytes that typically appears on the skin. The prognosis for metastatic illness has always been quite poor for this most aggressive type of skin cancer. Before 2011, there were few treatments available: the FDA-approved alkylating drug dacarbazine and high-dose interleukin-2 (IL-2) only produced modest objective response rates (≈10–15%), and the median overall survival (OS) was about 8–12 months[15,19]. Therapy was revolutionized by developments in immunology and tumor biology. Targeted medications (BRAF/MEK inhibitors) were developed as a result of the finding that melanoma often contains targetable mutations and new immunotherapies were made possible by a better knowledge of immunological checkpoints[12].

Ipilimumab (anti-CTLA-4) was the first checkpoint inhibitor medication to be approved by the FDA in 2011 after showing improved overall survival in metastatic melanoma. Approved in 2014, nivolumab (Opdivo) is a completely human IgG4 monoclonal antibody against PD-1. By binding to PD-1 on T cells and preventing it from interacting with PD-L1/PD-L2, it restores antitumor immunity and T-cell activation [4,15].

Ipilimumab (Yervoy) is a fully human IgG1κ antibody against CTLA-4, which is a negative regulator of T-cell activation. By preventing CTLA-4 from binding to its ligands (CD80/CD86), ipilimumab enhances early T-cell priming [4,5,6]. In advanced melanoma, these drugs showed modest single-agent activity (ipilimumab ORR ~10–15%, nivolumab ORR ~40%) and long-term survivors; however, their combination proved synergistic, with early studies showing that dual blockade achieved rapid and deep tumor regressions in many patients, surpassing responses with either drug alone [13,1]. This review will cover the burden of melanoma and the evolution of therapy, the profiles of nivolumab and ipilimumab, as well as comprehensive data on their combination in advanced melanoma .

Global Scenario and Epidemiology

The incidence of melanoma varies greatly by population and geography. The highest rates are found in populations with fair complexion; for instance, melanoma ASIRs >30 per 100,000 are found in Australia and New Zealand. An estimated 303,105 new cases of malignant melanoma (ASIR ~3.56/100,000) were reported globally in 2021 [7,20]. Although

melanoma accounts for roughly 58% of skin cancer-related disability-adjusted life years, this reflects only 4.6% of all skin cancer cases. High-Income North America (12.86/100k), Central Europe (12.52), and Australasia had the highest age-standardized incidences . In recent years, melanoma death and DALY rates have decreased (estimated annual decline ~0.67%), showing therapeutic advancements, despite an increase in incidence worldwide (probably due to aging populations and UV exposure) [7,20.]

Melanoma is still a major public health concern, nevertheless, as seen by the approximately 2.89 million DALYs and 63,000 melanoma-related fatalities that occurred worldwide in 2021. The burden is uneven: Western nations have the highest incidence, whilst Asian and African populations have far lower rates (because of melanin protection). It is anticipated that incidence will rise slightly on a regional level. For instance, according to American Cancer Society forecasts, there will be around 7,650 fatalities and 99,780 new cases of melanoma in the US in 2025. Although lower, the rates are rising throughout India and parts of Asia. With a 5-year survival rate of less than 10% prior to contemporary medicines and a historical median overall survival of less than a year, advanced (Stage IV) melanoma is still difficult to treat overall. These epidemiologic patterns highlight the global need for efficient systemic therapies [7,20.]

Current Therapeutic Landscape

Immunocheckpoint inhibitors and targeted treatments for molecular subtypes now dominate the treatment landscape for advanced melanoma. Whether used alone or in conjunction with ipilimumab, the anti-PD-1 antibodies nivolumab and pembrolizumab are common first-line treatments [17]. Because dual therapy with nivolumab+ipilimumab has a better long-term survival rate (median OS >70 months) [2,14,16], it is now frequently regarded as the preferred strategy for eligible patients. BRAF inhibitors (vemurafenib, dabrafenib) in combination with MEK inhibitors (trametinib, cobimetinib) provide alternative high-response regimens for patients with BRAF^V600 mutations (~40–50% of melanomas), albeit remissions are typically shorter-lived. Intralesional T-VEC for specific individuals and high-dose interleukin-2, which is rarely used because of toxicity, are other authorized treatments.

Clinical decision-making is now individualized; treatment selection is influenced by variables such as BRAF status, PD-L1 expression, performance status, the existence of brain metastases, and previous adjuvant therapy . Nivolumab+ipilimumab offers the highest durable response rate for the majority of individuals with satisfactory performance status [12].

Many people find that pembrolizumab or single-agent nivolumab work well and are less harmful. Another ICI possibility is the combination of nivolumab (recently approved) with relatlimab (anti-LAG-3) [9.] Key nivolumab/ipilimumab clinical trials are summarized in Table 1 (below).

Study (Year)	**Phase**	**Patients**	**ORR(%)**	**Grade 3–4 AES(%)**	**Grade 3–4 AES(%)**
CheckMate-067 (2015)	III	945	58.3	59	59
CheckMate-511 (2019)	III/IV	360	45.6	34	34
Real-world multicenter (2022)	-	697	48.5	44.9	44.9

Mechanism of Action

Ipilimumab and nivolumab target two different immunological checkpoints to improve T-cell-mediated anti-tumor immunity. Nivolumab attacks T cells' PD-1 (programmed death-1). PD-1 normally inhibits T-cell activation (increasing tolerance) by binding PD-L1/PD-L2 (on tumor or immune cells). This interaction is stopped by nivolumab, a human IgG4 monoclonal antibody that binds PD-1 with great affinity [5,19]. T lymphocytes are free to assault tumor cells as a result of this. On T cells, ipilimumab binds CTLA-4. Early in T-cell priming, CTLA-4 is increased and competes with CD28 for binding to antigen-presenting cells' B7 receptors (CD80/CD86). With a greater affinity, CTLA-4 inhibits T-cell activation by sending out signals. By preventing CTLA-4 from interacting with B7, ipilimumab (fully human IgG1κ) maintains the CD28 costimulatory signal . In sum, ipilimumab amplifies initial T-cell activation in lymph nodes, while nivolumab reinvigorates exhausted T cells in the tumor microenvironment [4,16].

These systems work in combination. While PD-1 blockade improves effector and natural-killer cell activities, CTLA-4 blockage increases memory T cell numbers in preclinical and translational studies. Combination therapy produces different immunological

profiles in patients: dual blockade enhances tumor T-cell infiltration more than each agent alone and raises many cytokines and chemokines in plasma . As a result, nivolumab+ipilimumab produces synergistic anti-tumor activity by engaging T cells at successive checkpoints. Nonetheless, the increased frequency of immune-related side effects linked to the combination can also be explained by this wide immunological activation [4,5].

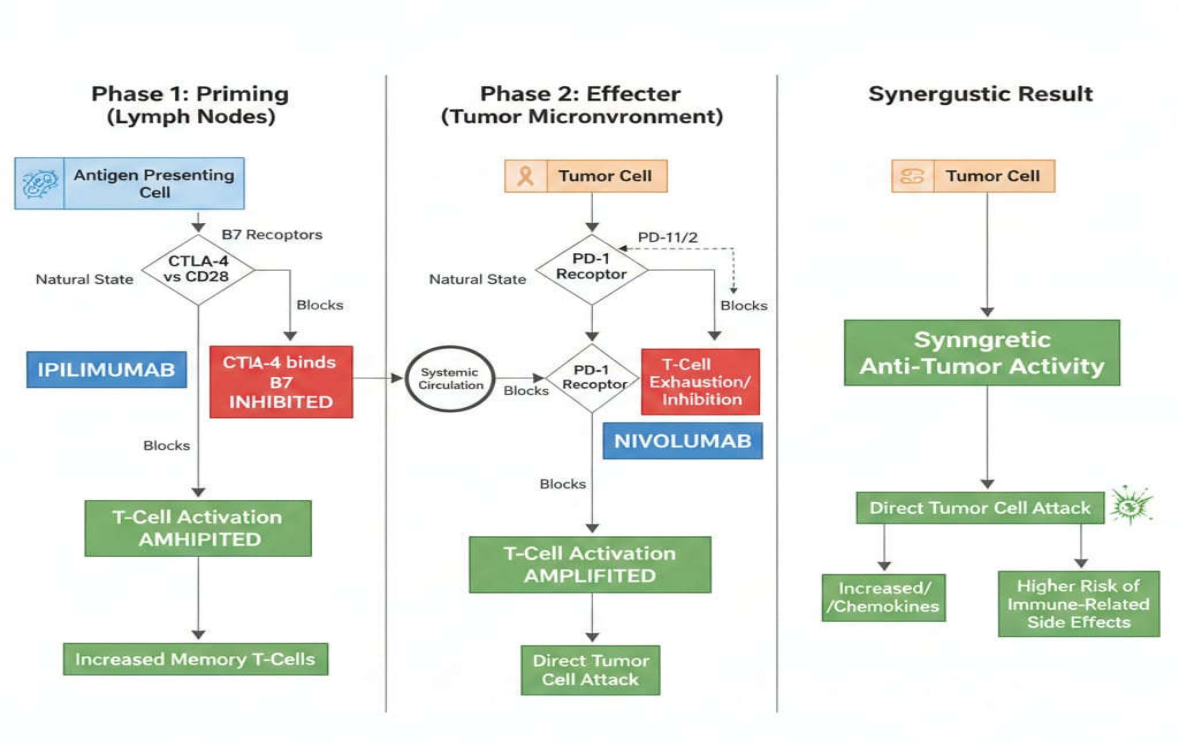

Fig.1.Shows the Mechanism Of Action of the combined checkpoint blockade (Ipilimumab+nivolumab)

Clinical Trials

The efficacy and safety of nivolumab+ipilimumab in advanced melanoma have been established in multiple pivotal trials:

• **CheckMate-067** – A pivotal randomized phase III trial in treatment-naïve unresectable stage III/IV melanoma comparing nivolumab plus ipilimumab, nivolumab monotherapy, and ipilimumab monotherapy. The combination produced substantially superior antitumor activity. The unconfirmed objective response rate (ORR) was 58.3% with dual therapy versus 44.9% with nivolumab alone, with deeper and more durable responses. Median progression-free survival (PFS) was 11.5 months for the combination compared with approximately 6.9 months for nivolumab monotherapy, while median overall survival (OS) was not reached in

the initial analysis. Long-term follow-up confirmed durable survival benefit: 5-year OS rates were ~52% with the combination versus ~44% with nivolumab alone, and the final 10-year analysis demonstrated a median OS of ~72 months for nivolumab plus ipilimumab compared with ~37 months for nivolumab and ~20 months for ipilimumab. Importantly, clinical benefit was observed irrespective of PD-L1 expression or BRAF mutation status, indicating broad applicability of dual checkpoint blockade across molecular subgroups. [13,14]

• **CheckMate-511** – A phase IIIb/IV trial evaluating alternative dosing schedules of nivolumab and ipilimumab to improve tolerability without compromising efficacy. The modified regimen (nivolumab 3 mg/kg + ipilimumab 1 mg/kg; NIVO3+IPI1) significantly reduced high-grade immune-related toxicity compared with the standard regimen (nivolumab 1 mg/kg + ipilimumab 3 mg/kg), with grade 3–5 adverse events occurring in 34% versus 48% of patients at 12 months ($p = 0.006$). Efficacy outcomes were broadly comparable between regimens (ORR 45.6% vs 50.6%; median PFS 9.9 vs 8.9 months), supporting adoption of the NIVO3+IPI1 schedule in routine practice to optimize the risk–benefit balance. [10]

• **Other trials and special populations** – Phase II evidence from **CheckMate-069** first demonstrated the marked activity of nivolumab plus ipilimumab over ipilimumab alone, with ORRs approaching 60%, helping to establish proof of concept for dual checkpoint blockade. Subsequent studies extended these findings to clinically challenging subgroups, including patients with brain metastases in **CheckMate-204** and the adjuvant setting in **CheckMate-238**. Collectively, prospective trials and retrospective real-world analyses demonstrate that combination immunotherapy retains meaningful intracranial activity, benefits heavily pretreated patients, and yields consistent efficacy across diverse clinical subgroups, reinforcing the robustness and generalizability of outcomes observed in pivotal trials. [13]

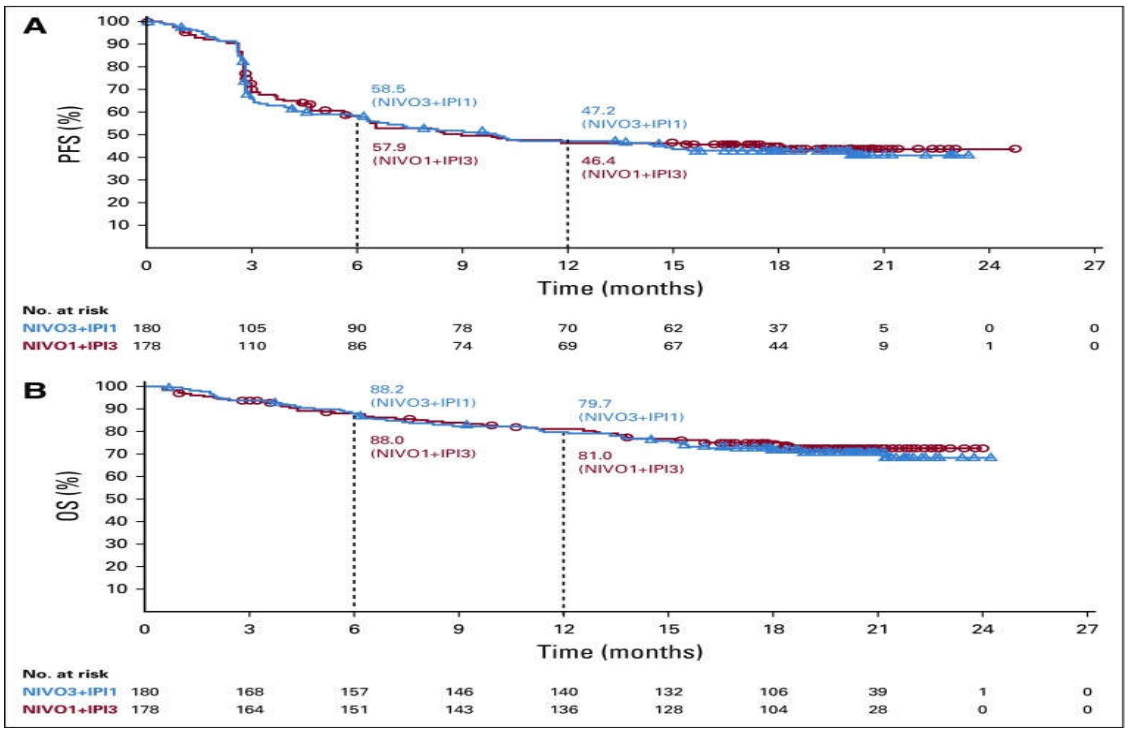

Fig.2: Kaplan–Meier curves from the CheckMate-511 trial (nivolumab 3 mg/kg + ipilimumab 1 mg/kg vs 1 mg/kg + 3 mg/kg). Panel A: progression-free survival; Panel B: overall survival. Curves are nearly overlapping, reflecting similar efficacy (12-mo PFS ≈47%; OS ≈88% for both regimens).

Efficacy

In advanced melanoma, nivolumab+ipilimumab leads to excellent survival and significant tumor response rates. The combination produced ORRs of approximately 50–60% in pivotal studies, which is significantly higher than historical rates when using chemo or ipilimumab alone. In contrast to 26% with ipilimumab, CheckMate-067 found a 5-year OS of 52% with nivolumab+ipilimumab ,43% of patients who had combination treatment were still alive at the end of the 10-year analysis , and many of them are still disease-free, which may indicate a cure. After ten years, the combo group's median melanoma-specific survival and response duration were not attained [2,14,16].

When compared to monotherapy, PD-1 blockage by itself also produces a long-lasting effect (5-year OS ~44%), but combination therapy usually outperforms it. For example, 5-

year melanoma-specific survival was 44% with nivolumab and 52% with combination. Additionally, the combination is especially advantageous for specific subgroups. Nivolumab+ipilimumab patients with BRAF-mutated melanoma demonstrated more significant 10-year survival increases (56% vs. 42% with nivolumab alone) . Early surrogate signs also predict outcomes: patients who were progression-free at 3 years had a 10-year survival rate of ≥96% for melanoma-specific causes .

The clinic is consistent with these efficacy findings. There was a median overall survival of about 38.7 months and an ORR of 48.5% in a large real-world retrospective (n=697) [12,14] . The ORR and median PFS among treatment-naive patients without brain mets were 56.6% and 13.7 months, respectively. 3-year OS was around 54% (in non-brain-met patients) and 3-year PFS was 35% in that series. Crucially, survival curves in the actual world match trial outcomes [3.]

Safety Profile

Nivolumab+ipilimumab's strong effectiveness is accompanied by a high risk of immune-related adverse events (irAEs). Approximately 55–60% of participants in trials experience grade 3–4 toxicity. The spectrum, which reflects widespread immunological activity, includes colitis/diarrhea, hepatitis, dermatitis/rash, endocrinopathies (thyroiditis, hypophysitis), and pneumonitis. For instance, hepatitis (all grades 27%, grade 3–4 16.1%) and skin rash (28%, grade 3–4 3.9%) were also common in a retrospective analysis; diarrhea/colitis occurred in 30% (all grades) with grade 3–4 colitis in 20.9% . Pneumonitis and endocrine consequences (such as hypothyroidism and hypophysitis) were less common but still noticeable [10,19.]

High-dose corticosteroids and treatment interruption are frequently necessary for grade 3–4 AEs; approximately 80% of patients who experience grade ≥3 irAEs in studies are given immunosuppression. Remarkably, there seems to be a correlation between the onset of high-grade toxicity and response: patients who experienced early grade 3–4 episodes and needed to stop were more likely to get very long-lasting remissions . Although fatal irAEs are uncommon (<1%), caution is required. No new severe toxicities have surfaced with extended follow-up [3.]

Reduced ipilimumab dosage or dosing schedules are methods to reduce toxicity. Without sacrificing efficacy, CheckMate-511 discovered that nivolumab 3 mg/kg + ipilimumab 1 mg/kg decreased grade 3–5 adverse events from 48% to 34% . The toxicity rates in ordinary practice (about 44% grade 3–4) are comparable to those in trials, according

to real-world data [10]. The incidence of high-grade irAEs was considerably higher with nivolumab+ipilimumab than with anti-PD-1 monotherapy in a real-world population, as shown in Fig.3(below), which highlights the disproportionate toxicity burden of combination therapy.

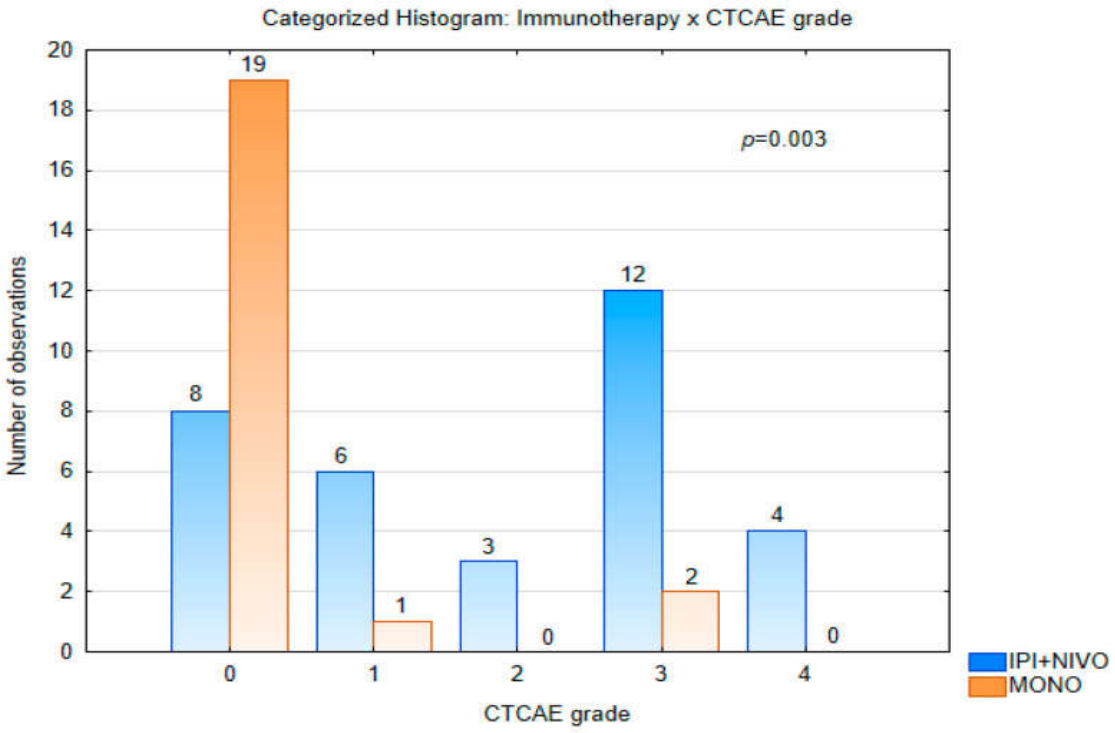

Fig.3: Distribution of CTCAE grades in a real-world cohort (ipilimumab+nivolumab vs anti–PD-1 alone). The combination (blue bars) shows many more grade ≥3 events than PD-1 monotherapy (orange) – 48% vs 9% of patients had grade 3–4 irAEs.

Real-World Evidence

Results from clinical trials have mostly been supported by real-world research. 697 individuals treated with ipilimumab+nivolumab in multiple countries were included in the biggest multicenter retrospective to date. The observed effectiveness was comparable to trials in this "real-life" population (many of whom had brain metastases or had received previous therapy): ORR was 48% overall, median PFS was approximately 7.9 months, and median OS was approximately 38.7 months. Similar to trial outcomes, the median PFS was 13.7 months and the ORR was 56.6% among treatment-naïve patients without brain mets. Significantly, about 23% of patients had no advancement after three years, and those patients had outstanding long-term survival. Additionally, safety was comparable to trials: 44.9% of

patients experienced grade 3–4 events, while 76.3% of patients experienced any-grade harm. Hepatitis (16.1%), rash (3.9%), and colitis/diarrhea (20.9%) were the most frequent high-grade events .

These patterns are supported by several real-world data (such as single-center uveal melanoma cohorts), which show that combination therapy produces a greater response and survival than PD-1 alone, albeit with noticeably more severe toxicity . Overall, empirical data supports the broad-spectrum activity of the nivolumab+ipilimumab combo and the manageability of its side effects when following prescribed protocols [3,11].

Conclusion

Moreover, Ipilimumab has revolutionized the treatment of advanced melanoma by converting short-term chemotherapeutic responses into long-term, sustainable disease control. A subset of patients achieve long-term survival, indicating the potential for a functional cure in metastatic illness. Evidence from pivotal trials and real-world research demonstrates higher and more sustained response rates with combination therapy than with monotherapy. A greater frequency of immune-related toxicities counteracts these advantages, emphasizing the necessity of proper patient selection, early toxicity detection, and consistent multidisciplinary care. Dosing optimization has increased tolerability without sacrificing effectiveness. Biomarker-guided patient selection, innovative checkpoint combinations (such PD-1/LAG-3 blockade), and the use of real-world data to improve sequencing and tailor treatment are some future prospects. Overall, the standard first-line treatment for metastatic melanoma is still nivolumab plus ipilimumab.

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