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Effectiveness of Nivolumab and Pembrolizumab as PD-1 Inhibitors in Unresectable or Metastatic Advanced Melanoma: A Systematic Review

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Abstract
Introduction: *Advanced melanoma is associated with poor prognosis because of limited effective treatment options, however, programmed cell death protein-1 inhibitors have transformed therapeutic strategies and significantly improved patient survival.* ***Objective:*** *This study aimed to evaluate the clinical effectiveness of nivolumab and pembrolizumab in patients with unresectable or metastatic advanced melanoma.* ***Method:*** *A systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 guidelines using PubMed, ScienceDirect, and Wiley Online Library to identify studies published between 2020 and 2026. Clinical trials, randomized controlled trials, cohort studies, and single-arm studies reporting overall survival, progression-free survival, or objective response rate were included.* ***Result and Discussion:*** *wenty studies were included. PD-1 inhibitor monotherapy significantly improved overall survival versus ipilimumab (pembrolizumab: 32.7 vs. 15.9 months; nivolumab: 36.9 vs. 19.9 months). Nivolumab plus ipilimumab achieved overall survival exceeding 70 months with objective response rates up to 58%. Nivolumab combined with relatlimab improved progression-free survival (10.2 vs. 4.6 months) compared with monotherapy. Nivolumab also remained effective in brain metastases, though some combinations increased toxicity without added benefit.* ***Conclusion:*** *Nivolumab and pembrolizumab provide significant clinical benefits in unresectable or metastatic advanced melanoma by improving survival and treatment response.*

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Introduction

Malignant melanoma is one of the most aggressive forms of skin cancer and accounts for the majority of skin cancer-related deaths worldwide. Patients with unresectable stage III disease or metastatic stage IV disease continue to experience a substantial clinical burden because advanced melanoma is characterized by rapid disease progression, early dissemination, and historically poor survival outcomes when treated with conventional therapies. Before the introduction of immune checkpoint inhibitors, therapeutic options were limited and durable disease control was rarely achieved, resulting in high mortality despite advances in surgical techniques, radiotherapy, and systemic treatment. The emergence of immunotherapy has fundamentally changed the therapeutic landscape by enabling durable antitumor immune responses and extending long-term survival in a proportion of patients. Among the currently available immune checkpoint inhibitors, programmed cell death protein-1 (PD-1) inhibitors have become central components of contemporary melanoma management because they restore T-cell activity through blockade of the PD-1/PD-L1 signaling pathway. Consequently, PD-1 inhibition has redefined treatment expectations for patients with advanced melanoma and established a new standard for systemic therapy (Gutzmer *et al*., 2026; Wolchok *et al*., 2025).

Nivolumab and pembrolizumab are the two PD-1 inhibitors most widely used for patients with unresectable or metastatic melanoma and can be administered either as monotherapy or in combination with other immunotherapeutic agents. Clinical trials have consistently showed meaningful improvements in overall survival, progression-free survival, and objective response rate with these agents compared with previous standard treatments. However, treatment selection is not based solely on efficacy because clinicians must also consider multiple clinical factors, including disease burden, the presence of brain metastases, tumor resectability, patient performance status, comorbidities, and the ability to tolerate immune-related adverse events. Patients with high-risk disease or rapidly progressive tumors may derive greater benefit from combination immunotherapy because of its stronger antitumor activity, whereas monotherapy may be preferred for individuals requiring a more favorable safety profile. Therefore, selecting the optimal therapeutic strategy requires balancing expected clinical benefit against the increased toxicity associated with combination regimens while considering individual patient characteristics (Arance *et al*., 2025; Long *et al*., 2024; Peters *et al*., 2022).

Despite the substantial therapeutic advances achieved with PD-1 inhibitors, treatment responses remain heterogeneous across patients. Primary resistance to anti-PD-1 therapy has been reported in approximately 30-50% of patients, while nearly one-quarter of responders subsequently develop acquired resistance after an initial clinical benefit. Consequently, disease progression remains an important clinical challenge, and patients who fail PD-1 inhibitor therapy generally have poor prognoses, with a median overall survival of approximately one year in routine clinical practice. Furthermore, combination immunotherapy, although often associated with greater clinical efficacy, is accompanied by a higher incidence of immune-related adverse events, making toxicity an important consideration during treatment planning. These variations in therapeutic response, resistance patterns, and treatment-related toxicity show the need to identify the most appropriate treatment approach for different patient populations and clinical scenarios (Wong *et al*., 2025).

The growing number of studies evaluating nivolumab and pembrolizumab has provided extensive evidence regarding their effectiveness across different therapeutic settings, including monotherapy and combination therapy. Nevertheless, differences in study design, treatment regimens, comparator groups, follow-up duration, and patient characteristics have resulted in heterogeneous findings, making direct comparison across studies difficult. For this reason, an updated synthesis of the available evidence is needed to compare the reported clinical outcomes and summarize the overall effectiveness of PD-1 inhibitor therapy in advanced melanoma. Accordingly, this systematic review evaluates the clinical effectiveness of nivolumab and pembrolizumab in patients with unresectable or metastatic advanced melanoma based on overall survival, progression-free survival, and objective response rate. The findings are expected to provide evidence that may assist treatment decision-making and serve as a reference for future studies on melanoma immunotherapy (Arance *et al*., 2025; Long *et al*., 2024; Peters *et al*., 2022).

Method

This study was conducted as a systematic literature review following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines to ensure a transparent and reproducible evidence synthesis process. The literature search was performed using three electronic databases, PubMed, ScienceDirect, and Wiley Online Library, covering publications from January 2020 to March 2026. The search strategy was designed to identify original studies evaluating the clinical effectiveness of programmed cell death protein-1 (PD-1) inhibitors in patients with advanced melanoma. Only studies published within the predefined period and available in full text were considered for further screening. The study selection process included identification, screening, eligibility assessment, and final inclusion according to the PRISMA 2020 flow diagram.

Eligible studies included randomized controlled trials (RCTs), other clinical trials, cohort studies, and single-arm studies involving patients with unresectable stage III melanoma or metastatic stage IV melanoma who received nivolumab and/or pembrolizumab either as monotherapy or in combination with other therapeutic agents. To be included, studies were required to report at least one clinically relevant outcome, including overall survival (OS), progression-free survival (PFS), or objective response rate (ORR). Studies were excluded if they were review articles, systematic reviews, meta-analyses, case reports, preclinical or laboratory investigations, animal studies, economic or cost-effectiveness analyses, or studies involving patients with early-stage melanoma. Studies that reported only biomarker-related outcomes without clinical endpoints were also excluded. Publications with inaccessible full texts or insufficient data for extraction were not considered eligible for inclusion. The eligibility criteria were established to ensure that the synthesized evidence directly addressed the clinical effectiveness of PD-1 inhibitors in advanced unresectable or metastatic melanoma.

Table 1
Eligibility Criteria for Study Selection

Category	Inclusion Criteria	Exclusion Criteria
Study design	Randomized controlled trials (RCTs), clinical trials, cohort studies, and single-arm studies	Reviews, systematic reviews, meta-analyses, case reports, preclinical/laboratory studies, animal studies, economic or cost-effectiveness studies
Population	Patients with unresectable stage III melanoma or metastatic stage IV melanoma	Patients with early-stage melanoma
Intervention	Nivolumab and/or pembrolizumab administered as monotherapy or in combination with other therapies	Studies not evaluating PD-1 inhibitors
Clinical outcomes	At least one of the following: Overall Survival (OS), Progression-Free Survival (PFS), or Objective Response Rate (ORR)	Studies reporting only biomarker outcomes without clinical endpoints
Publication period	January 2020 - March 2026	Publications outside the specified time frame
Language and accessibility	Full-text articles available for review	Inaccessible full-text publications or studies with insufficient data

Result and Discussion

1. Result

Following the literature search and study selection process based on the PRISMA 2020 guidelines, a total of 20 studies fulfilled the predefined eligibility criteria and were included in this systematic review. The included studies comprised predominantly phase II and phase III clinical trials, together with several observational cohort studies investigating the clinical effectiveness of PD-1 inhibitors in patients with unresectable stage III or metastatic stage IV melanoma. These studies evaluated nivolumab and pembrolizumab administered either as monotherapy or in combination with other therapeutic strategies and reported clinically relevant outcomes, including overall survival (OS), progression-free survival (PFS), and objective response rate (ORR). The PRISMA 2020 flow diagram showing the study selection process in Figure 1, while the detailed characteristics of the included studies in Table 1.

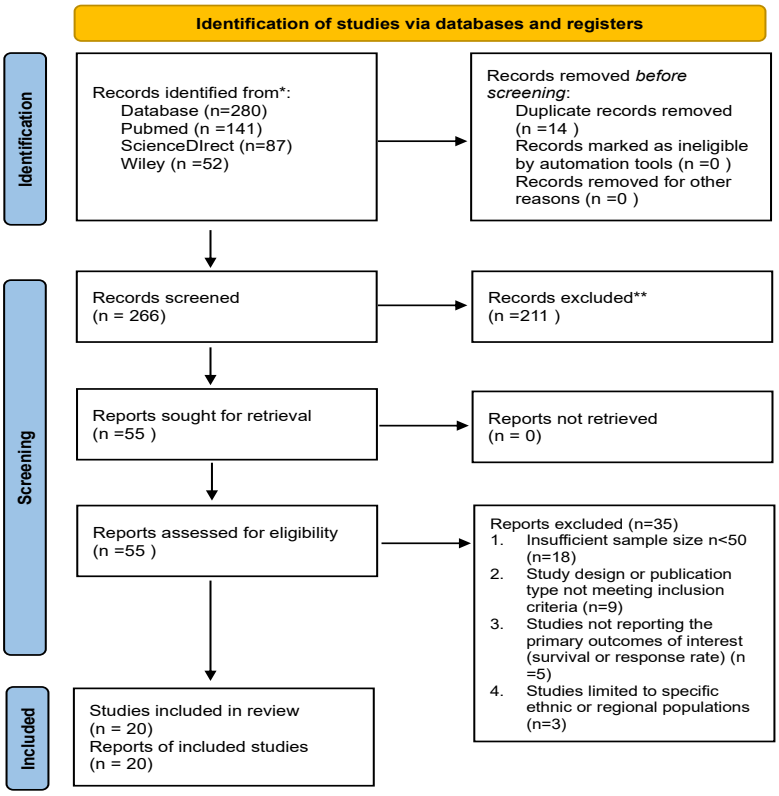

Figure 1. PRISMA 2020 Flow Diagram of the Study Selection Process

Table 2
Characteristics of Studies Included in the Systematic Review

Study	Regimen	Outcomes
Arance A, 2025	Pembro+Lenva vs Pembro	PFS ↔; OS ↔
Wong MK, 2025	RP1+Nivo vs none	ORR 32.9%
Lipson EJ, 2025	Nivo+Relat vs Nivo	PFS ↑; OS ↑; ORR ↑
Tawbi HA, 2025	Nivo+Relat vs Nivo	OS ↑; PFS ↑; ORR ↑
Wolchok JD, 2024	Nivo+Ipi vs Nivo vs Ipi	OS ↑ (combo)
Long GV, 2024	Pembro vs Ipi	OS ↑; PFS ↑
Di Giacomo AM, 2024	Foto vs Ipi+Foto vs Nivo+Ipi	OS ↑ (combo)
Diab A, 2023	Nivo+ Bempeg	ORR ↓; PFS ↓; OS ↔
Chesney JA, 2023	Pembro+TVEC vs Pembro	PFS ↔; OS ↔; ORR ↑
Aktins MB, 2023	Nivo+Ipi vs BRAF+MEK	OS ↑; ORR ↑
Wolchok JD, 2022	Nivo vs Nivo+Ipi vs Ipi	OS ↑ (combo)
Tawbi HA, 2022	Nivo+Relat vs Nivo	PFS ↑
Tawbi HA, 2025	Nivo+Ipi vs none	ORR ↑; PFS ↑; OS ↑
Bloem M, 2025	Nivo+Ipi vs BRAF/MEK	PFS ↔; OS ↑
Robert C, 2025	Nivo+Ipi vs Nivo	ORR ↑; OS ↑
Mandala M, 2024	Nivo+Ipi (subgroup)	ORR ↑ (line 1); OS ↔; PFS ↔
Hilbers M, 2021	Nivo+Ipi vs BRAF+MEK	PFS ↑; OS ↑
Gutzmer R, 2026	Nivo+ Ipi vs Nivo	ORR ↔; OS ↔
VanderWalde A, 2023	Nivo+Ipi vs Ipi	PFS ↑; ORR ↑
Mandala M, 2025	Nivo+Ipi ± SRT(conc/seq)	ORR ↑; OS ↑

Legend:
↑ : Improvement / better outcome (statistically significant)
↓ : Reduction / worse outcome (statistically significant)
↔ : No significant difference (not statistically significant)

A total of twenty studies met the predefined eligibility criteria and were included in this systematic review following the PRISMA 2020 study selection process (Figure 1). The included studies consisted primarily of phase II and phase III clinical trials, supplemented by several observational cohort studies evaluating the clinical effectiveness of PD-1 inhibitors in patients with unresectable stage III or metastatic stage IV melanoma. These studies investigated nivolumab and pembrolizumab administered either as monotherapy or in combination with other immunotherapeutic, targeted, or local treatment modalities. Despite differences in study design, patient characteristics, treatment regimens, and follow-up duration, all studies reported clinically relevant outcomes related to treatment efficacy. The principal endpoints evaluated across the included studies were overall survival (OS), progression-free survival (PFS), and objective response rate (ORR).

The majority of the included studies consistently showed significant improvements in overall survival among patients treated with PD-1 inhibitor-based therapy. Combination therapy with nivolumab plus ipilimumab produced the most favorable survival outcomes, with a median overall survival ranging from 71.9 to 72.1 months, substantially exceeding that observed with ipilimumab monotherapy (19.9 months) and nivolumab monotherapy (36.9 months). These findings indicate that dual immune checkpoint blockade provides superior long-term survival benefits compared with single-agent immunotherapy or CTLA-4 inhibition alone (Wolchok *et al*., 2022; Wolchok *et al*., 2025). Pembrolizumab also showed superior efficacy compared with ipilimumab, achieving a median overall survival of 32.7 months versus 15.9 months and maintaining durable survival benefits over a 10-year follow-up period, with long-term survival rates of 34.0% and 23.6%, respectively (Long *et al*., 2024). In addition, immunotherapy-based strategies showed improved survival compared with targeted therapy, with median overall survival reaching 54.0 months versus 20.0 months in one study, while patients with melanoma brain metastases also experienced longer survival following immunotherapy (44.8 vs. 14.2 months) (Bloem *et al*., 2025; Hilbers *et al*., 2021).

Improvements in progression-free survival were also consistently observed across studies evaluating PD-1 inhibitor therapy, particularly when combination regimens were employed. The combination of nivolumab and relatlimab showed one of the most significant improvements, increasing the median progression-free survival to 10.2 months compared with 4.6 months for nivolumab monotherapy. Moreover, the 12-month progression-free survival rate increased from 36.0% in the monotherapy group to 47.7% in patients receiving dual checkpoint inhibition, indicating sustained disease control during follow-up (Tawbi *et al*., 2022; Tawbi *et al*., 2025). Similar improvements were observed with nivolumab plus ipilimumab, especially among patients with melanoma brain metastases, where the 36-month progression-free survival rate reached 54.1% compared with only 18.9% in comparator groups (Tawbi *et al*., 2021). However, not all combination strategies provided additional clinical benefit, as pembrolizumab combined with lenvatinib or talimogene laherparepvec (T-VEC) failed to demonstrate statistically significant improvements in progression-free survival compared with pembrolizumab alone (Arance *et al*., 2025; Chesney *et al*., 2023).

Objective response rate was important efficacy outcome consistently reported among the included studies. PD-1 inhibitor-based therapies achieved objective response rates ranging from approximately 30% to 60%, showing substantial antitumor activity in advanced melanoma. Combination therapy with nivolumab plus ipilimumab produced higher response rates than nivolumab monotherapy, reaching 58% versus 44% in the

overall study population and 53.5% versus 16.7% among patients with melanoma brain metastases, indicating enhanced therapeutic activity in difficult-to-treat populations (Atkins *et al*., 2023; Robert *et al*., 2025). Similarly, patients with disease refractory to previous PD-1 inhibitor treatment experienced improved objective response rates when treated with nivolumab plus ipilimumab compared with ipilimumab alone (28% vs. 9%), supporting the role of combination immunotherapy after PD-1 treatment failure (VanderWalde *et al*., 2023). Nevertheless, one real-world study reported that nivolumab monotherapy achieved an objective response rate of 61.5%, which was slightly higher than that observed with certain combination regimens (46.2%), suggesting that monotherapy may remain highly effective in selected patient populations (Gutzmer *et al*., 2026).

Taken together, the evidence synthesized from the twenty included studies demonstrates that PD-1 inhibitor-based therapy provides clinically meaningful improvements in survival outcomes and treatment response among patients with unresectable or metastatic melanoma. Combination immunotherapy generally achieved superior efficacy across overall survival, progression-free survival, and objective response rate compared with monotherapy, although not every combination regimen resulted in additional therapeutic benefit. Studies evaluating nivolumab combined with ipilimumab or relatlimab consistently reported the most favorable clinical outcomes, whereas several pembrolizumab-based combinations produced more variable results. Favorable outcomes were observed across different clinical scenarios, including patients with brain metastases and those receiving first-line treatment, supporting the broad applicability of PD-1 inhibitor therapy in advanced melanoma. However, variations in study design, therapeutic combinations, comparator treatments, and patient populations contributed to differences in reported efficacy among individual studies. Consequently, the collective evidence supports PD-1 inhibitors as the current cornerstone of systemic therapy for advanced melanoma while emphasizing the importance of individualized treatment selection based on patient characteristics and therapeutic objectives.

2. Discussion

Nivolumab consistently provides meaningful clinical benefits in patients with unresectable or metastatic melanoma, both as monotherapy and in combination with other immunotherapeutic agents. As a single-agent therapy, nivolumab significantly improves overall survival compared with ipilimumab, achieving a median overall survival of 36.9 months versus 19.9 months while maintaining a more favorable safety profile. These findings support the role of PD-1 blockade as a preferred first-line immunotherapeutic strategy because of its ability to generate durable antitumor immune responses with lower treatment-related toxicity than CTLA-4 inhibition alone. Nevertheless, survival outcomes can be further improved through combination immunotherapy, indicating that simultaneous inhibition of complementary immune checkpoints enhances antitumor activity beyond that achieved with PD-1 blockade alone. Therefore, nivolumab monotherapy remains an effective option for many patients, whereas combination therapy may provide additional benefit in selected populations with high-risk disease. These observations are consistent with long-term clinical evidence showing sustained survival benefits of nivolumab-based therapy in advanced melanoma (Wolchok *et al*., 2022).

The greatest survival benefit identified in this review was observed with the combination of nivolumab and ipilimumab. Long-term follow-up showed median overall survival ranging from 71.9 to 72.1 months, substantially exceeding outcomes achieved with either nivolumab or ipilimumab alone, while durable survival benefits were maintained for more than six to ten years. These findings suggest that dual immune checkpoint inhibition provides synergistic activation of antitumor immunity by simultaneously targeting the PD-1 and CTLA-4 pathways. Furthermore, the combination of nivolumab and relatlimab, which simultaneously inhibits PD-1 and LAG-3, has emerged as another highly effective therapeutic strategy. Results from the RELATIVITY-047 trial and its subsequent three-year and four-year follow-up analyses showed significant improvements in progression-free survival, objective response rate, and long-term overall survival compared with nivolumab monotherapy. The consistent efficacy observed across multiple follow-up periods supports the expanding role of dual checkpoint blockade beyond conventional PD-1 inhibition alone (Tawbi *et al*., 2021; Wolchok *et al*., 2022; Tawbi *et al*., 2022; Tawbi *et al*., 2025; Lipson *et al*., 2025).

The superiority of nivolumab-based immunotherapy over targeted therapy in several clinical settings. Studies comparing nivolumab-containing regimens with BRAF/MEK-targeted therapy showed substantially longer overall survival despite similar progression-free survival in some patient populations, suggesting that immunotherapy provides more durable long-term disease control. This survival advantage is likely attributable to the establishment of long-lasting immune memory capable of maintaining tumor surveillance after treatment initiation. Moreover, nivolumab-based therapy remained clinically effective in patients with melanoma brain metastases, a subgroup traditionally associated with poor prognosis and limited treatment options. These findings show that immunotherapy should be considered an important therapeutic approach even in patients with intracranial disease and other high-risk clinical presentations. Collectively, the available evidence supports the preferential use of nivolumab-based immunotherapy in appropriately selected patients with advanced melanoma (Bloem *et al*., 2025; Hilbers *et al*., 2021; VanderWalde *et al*., 2023).

Patients with melanoma brain metastases represent one of the most challenging populations in clinical oncology because of their historically poor survival outcomes. The evidence included in this review demonstrates that nivolumab combined with ipilimumab remains highly effective in this subgroup, producing objective response rates of up to 53.5% and a 36-month overall survival rate of 71.9% among asymptomatic patients. These encouraging results suggest that effective systemic immune activation can overcome, at least partially, the traditionally unfavorable prognosis associated with intracranial metastatic disease. Furthermore, the addition of stereotactic radiosurgery (SRS) or stereotactic radiotherapy (SRT) appears to further improve treatment outcomes through potential synergistic interactions between radiotherapy and immune checkpoint inhibition. Sequential or concomitant stereotactic radiotherapy was associated with higher objective response rates and prolonged overall survival compared with immunotherapy alone. Consequently, integrating immune checkpoint blockade with local stereotactic radiation may represent an effective multidisciplinary treatment strategy for patients with melanoma brain metastases (Mandalà *et al*., 2024; Mandalà *et al*., 2025).

Management of patients with disease progression after PD-1 inhibitor therapy remains a major therapeutic challenge. The studies included in this review showed that nivolumab combined with ipilimumab improved objective response rate and progression-free survival compared with ipilimumab monotherapy in patients with PD-1-refractory

melanoma, although these benefits were accompanied by increased immune-related toxicity. In addition, combining nivolumab with the oncolytic immunotherapy RP1 produced clinically meaningful antitumor activity, with an objective response rate of 32.9%, suggesting that novel immunotherapeutic combinations may overcome acquired resistance to PD-1 blockade. However, not all combination strategies produced favorable outcomes, as bempegaldesleukin combined with nivolumab failed to show superiority over nivolumab monotherapy. Furthermore, several real-world studies suggested that nivolumab monotherapy may provide efficacy comparable to, or even slightly better than, certain combination regimens while maintaining a lower toxicity burden. These findings show that treatment intensification should be individualized according to patient characteristics, expected therapeutic benefit, and the potential risk of treatment-related adverse events (Wong *et al*., 2025; Diab *et al*., 2023; VanderWalde *et al*., 2023).

Pembrolizumab also showed substantial clinical effectiveness as a first-line PD-1 inhibitor for advanced melanoma. Compared with ipilimumab, pembrolizumab significantly improved overall survival, progression-free survival, and long-term survival outcomes, confirming its role as one of the standard therapeutic options for unresectable or metastatic melanoma. Nevertheless, unlike nivolumab, several pembrolizumab-based combination strategies failed to produce meaningful improvements in major survival outcomes. The combination of pembrolizumab with lenvatinib did not improve overall survival despite modest improvements in progression-free survival, while pembrolizumab combined with talimogene laherparepvec (T-VEC) also failed to significantly improve progression-free survival or overall survival, although slight increases in objective response rate were observed. These findings suggest that pembrolizumab provides its most consistent clinical benefit as monotherapy rather than in certain combination regimens currently available. The evidence synthesized in this review shows that both nivolumab and pembrolizumab remain fundamental components of modern melanoma immunotherapy, with treatment selection guided by disease characteristics, expected efficacy, and safety considerations (Arance *et al*., 2025; Chesney *et al*., 2023; Long *et al*., 2024).

Conclusion

PD-1 inhibitors, particularly nivolumab and pembrolizumab, provide significant clinical benefits for patients with unresectable or metastatic advanced melanoma by improving overall survival (OS), progression-free survival (PFS), and objective response rate (ORR), both as monotherapy and in combination with other therapeutic agents. Combination immunotherapy may provide greater clinical efficacy than monotherapy, however, these benefits are regimen-specific, as only certain combinations consistently showed superior survival and treatment response, whereas others showed limited or no additional clinical benefit. Although combination immunotherapy is generally associated with a higher incidence of treatment-related toxicity, treatment selection should be individualized based on patient characteristics, disease status, the expected benefit of the specific therapeutic regimen, and the balance between efficacy and safety. The current evidence supports nivolumab and pembrolizumab as cornerstone therapies and established standards of care in the management of advanced melanoma.

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