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DERMATOLOGÍA PRÁCTICA

[Translated article] Immunotherapy and Targeted Therapy in Patients With Advanced Melanoma and the V600 BRAF Mutation: Which One First?

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PALABRAS CLAVE

Melanoma;
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Inhibidores de BRAF;
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Abstract Systemic treatment with immunotherapy or targeted therapy can significantly improve survival in patients with advanced (metastatic or high-risk) melanoma. Fifty percent of patients with melanoma have a *BRAF* mutation. Decisions on optimal sequencing of systemic treatments should take into account drug- and tumor-related factors and patient characteristics. Although the combination of ipilimumab and nivolumab is associated with the best survival outcomes, it is associated with significant toxicity. Targeted therapy may be a more favorable option in certain clinical situations. We review the literature on immunotherapy and targeted therapy in melanoma and present an algorithm for guiding decision-making on their use as first-line systemic treatments for advanced *BRAF*-mutated melanoma.

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Inmunoterapia vs. terapia diana en el paciente con melanoma avanzado y mutación BRAF V600, ¿por cuál comenzar?

Resumen El paciente con melanoma avanzado, metastásico o de alto riesgo, cuenta con opciones de tratamiento sistémico, inmunoterapia y terapias dirigidas, que han mejorado significativamente su supervivencia. El 50% de los pacientes con melanoma presentan mutación del gen *BRAF*. La toma de decisiones en cuanto a la secuencia óptima de tratamiento sistémico debe tener en cuenta factores relacionados con el medicamento, factores clínicos del paciente, así como los propios del tumor. Aunque la combinación ipilimumab-nivolumab es la que proporciona mejores resultados de supervivencia en todos los pacientes, la toxicidad asociada y

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Tratamiento
adyuvante;
Anti-PD1;
Anti-CTLA4;
Tratamiento
neoadyuvante

el perfil de las terapias diana las puede hacer recomendables como primera línea en pacientes en determinadas situaciones clínicas. El objetivo de esta revisión es proporcionar un algoritmo de toma de decisiones en cuanto a la primera línea de tratamiento sistémico, inmunoterapia vs. terapias dirigidas, en el paciente con melanoma avanzado con mutación *BRAF*.

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Introduction

Systemic treatments for metastatic melanoma have changed considerably in the past decade. The estimated 5-year survival rate for stage IV melanoma according to the seventh edition of the American Joint Committee on Cancer Staging Manual was less than 20%, but with the use of immunotherapy and targeted therapies (*BRAF* and *MEK* inhibitors), this has now increased to around 50%.^{1,2} Patients with *BRAF*-mutant melanoma can be treated with immunotherapy and/or targeted therapy, whereas immunotherapy is the only option for patients without *BRAF* mutations.

The aim of this review was to synthesize recent evidence-based research to guide decision-making on the use of first-line systemic treatments and optimal sequencing in patients with advanced *BRAF* V600-mutant melanoma.

Treatment Strategies for Advanced Melanoma

Two strategies are currently available for the systemic treatment of melanoma: immunotherapy and targeted therapy (Table 1). Both can be used in the adjuvant setting and the treatment of unresectable metastatic melanoma.

Cutaneous melanoma is a highly immunogenic tumor, derived from a high mutational burden due to cumulative sun exposure.³ This immunogenicity results in the release of tumor autoantigens, which are processed by antigen-presenting cells and interact with lymphocyte receptors to trigger an immune response. These receptors, *CTLA-4* and *PD-1*, are known as immune checkpoints. In melanoma, *CTLA-4* and anti-*PD-1* checkpoint immunotherapy blocks these antagonistic receptors and favors the antitumoral action of T cells.⁴

The goal of targeted therapy is to counter the effects of somatic mutations in tumor cells that promote uncontrolled cell proliferation.⁵ *BRAF* mutations are present in approximately 50% of cutaneous melanomas; the most common mutation is the *BRAF* V600E mutation, found in 90% of cases.^{6,7} Targeted therapy thus can only be used to treat half of all patients with melanoma, and it is currently only effective when *BRAF* and *MEK* inhibitors are administered simultaneously.

Clinical and Treatment Factors Guiding Decisions on First-line Systemic Treatments

When choosing a first-line systemic treatment, it is important to consider the differences between immunotherapy

and targeted therapy and additional factors such as drug-related factors, individual patient characteristics (e.g., comorbidities), and tumor-related factors (e.g., behavior, progression) (Table 2).

Drug-Related Factors

Long-term follow-up data from clinical trials of anti-*PD1* monotherapy with nivolumab or pembrolizumab and combination therapy with *BRAF* and *MEK* inhibitors show 5-year overall survival rates of approximately 50%.² Ipilimumab plus nivolumab, however, offers the best long-term survival outcomes, making it the general first choice for unresectable metastatic melanoma.^{8–10} It is, however, also associated with an increased risk of severe toxicity. Accordingly, first-line anti-*PD1* monotherapy with nivolumab or pembrolizumab is also an acceptable choice.^{10,11}

Immune checkpoint inhibitors (ICIs) and targeted agents are associated with considerably different treatment response patterns. Because of their mechanism of action, *BRAF* and *MEK* inhibitors produce faster responses than anti-*PD1* or anti-*CTLA-4* antibodies. The differences are evident in survival curves from clinical trials, which show a stronger initial plateau and better short-term survival in patients on targeted therapy and a sharper initial drop in survival, followed by clear survival benefits, in those on immunotherapy² (Fig. 1). ICIs elicit more sustained responses, even after they are discontinued, whereas discontinuation of targeted agents is usually followed by rapid disease progression; *BRAF* and *MEK* inhibitors are therefore generally considered the treatment of choice for maintenance regimens.^{12,13} ICIs and *BRAF* and *MEK* inhibitors also have different safety profiles. ICIs often cause grade 3 or 4 adverse events, with incidence rates of 14% observed for anti-*PD1* antibodies and 45% for the anti-*CTLA-4* agent ipilimumab; in addition, these immune-mediated effects are often irreversible.^{14,15} *BRAF* and *MEK* inhibitors, by contrast, cause moderate to severe adverse events (grade 3–4 in 41% of patients) that are frequently reversible with dose adjustments or treatment discontinuation.¹⁶

Finally, ICIs and *BRAF* and *MET* inhibitors have different administration routes, an important consideration in the context of patient preferences (Table 1).

Individual Patient Characteristics

Individual patient-related factors, such as comorbidities or concomitant treatments, must be considered when evaluating first-line treatments for advanced melanoma. Presence

Table 1 Drugs Currently Available for the Systemic Treatment of Melanoma in Clinical Practice.

Treatment strategy	Drug	Mechanism of action	Route	Clinical practice dosage
Immune checkpoint inhibitors	Ipilimumab	CTLA-4 blockade	IV	Ipilimumab 3 mg/kg every 3 wk up to 4 doses
	Nivolumab	PD-1 blockade	IV	Nivolumab 240 mg every 2 wk or 480 mg every 4 wk
	Pembrolizumab	PD-1 blockade	IV	Pembrolizumab 200 mg every 3 wk or 400 mg every 6 wk
	Ipilimumab plus nivolumab	CTLA-4 plus PD-1 blockade	IV	Nivolumab 1 mg/kg and ipilimumab 3 mg/kg every 3 wk for the first 4 doses. Nivolumab 240 mg every 2 wk or 480 mg every 4 wk
Targeted therapy	Dabrafenib plus trametinib	BRAF and MEK inhibition	Oral	Dabrafenib 150 mg/12 h Trametinib 2 mg/24 h
	Vemurafenib plus cobimetinib	BRAF and MEK inhibition	Oral	Vemurafenib 960 mg/12 h Cobimetinib 60 mg/24 h for 21 d, followed by 7 days of rest, in continuous repeated cycles
	Encorafenib plus binimetinib	BRAF-MEK inhibition	Oral	Encorafenib 450 mg/24 h Binimetinib 45 mg/12 h

Table 2 Factors To Consider When Deciding on First-line Systemic Treatment for Patients With Advanced Melanoma.

Drug-related factors	Tumor-related factors	Patient-related factors
<ul style="list-style-type: none"> • Survival results • Time to response • Duration of response • Toxicity • Administration route • Regulatory issues 	<ul style="list-style-type: none"> • Tumor burden • Progression rate • Location of metastases: brain • Manifestations 	<ul style="list-style-type: none"> • Autoimmune disease • Immunosuppressive agents: corticosteroids, other • Solid organ tumors • Performance status • Personal preference

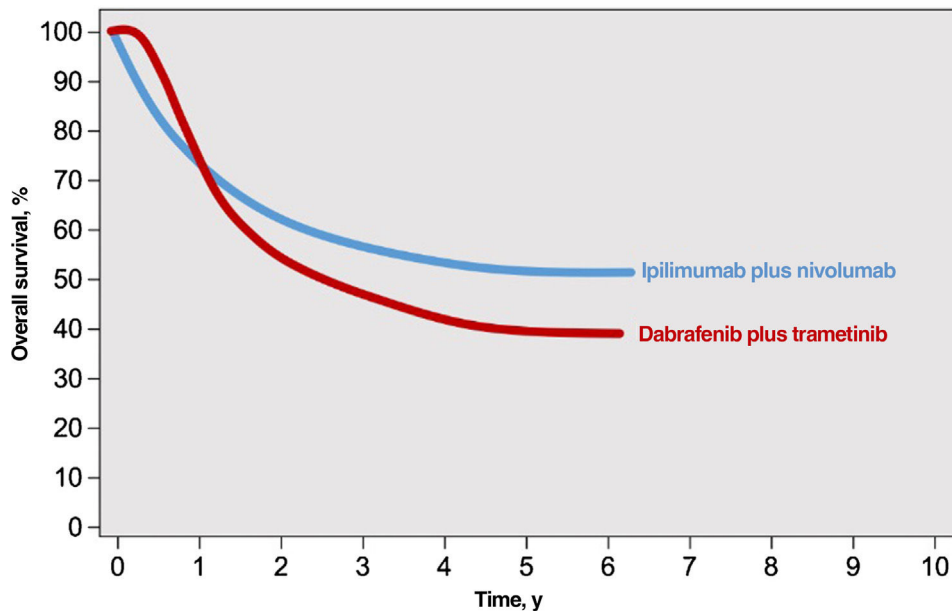


Figure 1 Responses to combined anti-CTLA-4 immunotherapy and targeted therapy with BRAF and MEK inhibitors. Source: Adapted from Michielin et al.²

of an underlying autoimmune disease has been associated with a significantly increased risk of immune-mediated adverse events in patients with melanoma receiving immunotherapy.¹⁷ Similar findings have been observed for anti-PD-1 agents in the treatment of advanced cancer, including melanoma. In particular, the authors observed a higher frequency of immune-related adverse events in patients with a previous autoimmune disease (65.9% vs. 39.9%), although the severity of effects (grade 3-4) was similar to that observed in patients without a history of autoimmune disease.¹⁸ In another study, ipilimumab plus nivolumab triggered a flare in 33% of patient with a pre-existing autoimmune disease; the flares were particularly common in patients with inflammatory bowel disease or a rheumatologic disorder and in those on immunosuppressive therapy.¹⁹

An increased risk of disease progression and death has been observed in patients with cancer being treated with an ICI and corticosteroids for any reason (palliative treatment, brain metastases, etc.) (HR, 1.54; 95% CI, 1.24-1.91; $P = .0001$). A similar risk was observed for patients with melanoma (HR, 1.75; 95% CI, 1.07-2.88; $P = .03$).²⁰ Another study reported a 50% organ rejection rate in kidney transplant recipients under treatment with ICIs, although a reduced immunosuppressive regimen was used in most patients.²¹ When immunosuppression was maintained, however, there was a striking reduction in organ rejection (6% retrievable allograft rejection with tumor response and 6% irretrievable allograft rejection with tumor response). The findings suggest that maintaining immunosuppression during ICI therapy might not diminish the effectiveness of immunotherapy and might even reduce the risk of allograft rejection.²¹ Nonetheless, and considering the available data, first-line targeted therapy could be a prudent choice for patients with *BRAF*-mutant melanoma who have an underlying autoimmune disease and/or are receiving immunosuppressive treatment, providing there are no other clinical factors that take precedence.

Performance status (PS) has been studied as a predictor of treatment response in melanoma, but clinical trials do not include patients with reduced functional status (a score of ≥ 2 on the Eastern Cooperative Oncology Group Performance Status [ECOG PS] Scale). One meta-analysis showed that ICIs improved survival regardless of ECOG PS.²² Studies of combined treatment with dabrafenib and trametinib, however, have found significant differences in progression-free survival in patients with reduced functional status ($PS \geq 1$ vs. $PS = 0$).^{23,24}

Tumor-Related Factors

Tumor burden or volume and speed of progression and related symptoms must also be taken into account when evaluating first-line systemic treatments for patients with advanced melanoma.

A pooled analysis of data from clinical trials evaluating combination therapy with dabrafenib and trametinib showed that normal lactate dehydrogenase (LDH) levels, fewer than 3 metastatic sites, and less measurable disease were associated with better survival at 2 years.²⁴ ICIs, however, have also been associated with survival benefits

in patients with low tumor burden.^{25,26} The toxicity profile of *BRAF* and *MEK* inhibitors and the option of switching to immunotherapy in the event of progression are factors in favor of using first-line targeted therapy in patients with low tumor burden. A recent editorial on the role of *BRAF* and *MEK* inhibitors in melanoma defended the use of these agents in patients with low tumor burden, including candidates for adjuvant therapy. In this scenario, the results are similar to those observed with immunotherapy and, in addition, anti-PD-1 therapy is highly effective in patients who experience recurrence during *BRAF*-targeted therapy.²⁷

Fast-acting *BRAF* and *MEK* inhibitors, however, could also be prioritized in the event of rapid, life-threatening symptomatic growth. Although response is short lasting, the priority is to bring the disease under control as quickly as possible. The European Association of Dermato-Oncology clinical guideline for melanoma recommends frontline *BRAF* and *MEK* inhibitors for patients with mutant tumors, high tumor burden, an aggressive course, or high LDH levels.¹¹

The impact of tumor progression and associated symptoms is also influenced by the site of metastatic disease. A patient with progressive brain metastases, for example, will usually be administered symptomatic treatment with corticosteroids, most likely improving candidacy for first-line *BRAF* and *MEK* therapy.²⁸ Combination immunotherapy with ipilimumab and nivolumab would be the first choice in patients with highly disseminated melanoma, even in non-life-threatening situations, as it has proven survival benefits.^{8,9,29,30}

Proposals for Guiding Decisions on Systemic Treatments for Patients With *BRAF*-Mutant Melanoma

Adjuvant and Neoadjuvant Therapy

Disease-free survival benefits have been demonstrated for adjuvant immunotherapy and targeted therapy following complete resection of metastasis. Clinical practice guidelines thus recommend first-line adjuvant therapy with anti-PD1 antibodies for all patients with stage IIIA-IIID melanoma, regardless of *BRAF* status. For patients with *BRAF* V600-mutant melanoma, they recommend *BRAF* and *MEK* inhibitors^{10,11} (Table 3).

Based on the results of phase III trials, the US Food and Drug Administration has authorized adjuvant therapy for patients with primary, nonmetastatic, high-risk tumors (stage IIB-IIC). The National Comprehensive Cancer Network has already incorporated the recommendation to use pembrolizumab monotherapy in such cases in its clinical practice guidelines (Table 3).^{10,31} This indication is not authorized in Spain.

In the more recent field of neoadjuvant therapy for advanced melanoma, preliminary studies reported that ipilimumab plus nivolumab before lymph node dissection was associated with major pathologic responses in 61% of metastatic lymph nodes, although 22% of patients showed grade 3 to 4 toxicity.³² A very recent phase II trial showed a clear 2-year survival benefit for neoadjuvant plus adjuvant pembrolizumab compared with pembrolizumab only after lymph node dissection (72% vs. 49%, $P = .004$).³³

Table 3 Indications and Regulatory Situation for Currently Available Immunotherapy and Targeted Therapy Drugs.

Drug	Adjuvant treatment	Unresectable metastasis
Ipilimumab	Not authorized	AEMPS: treatment of advanced melanoma (unresectable or metastatic) in adults and adolescents aged ≥ 12 years
Nivolumab	AEMPS: adults with melanoma and lymph node metastasis after complete resection Indication limited to patients with stage IIIC or IIID melanoma after complete resection ^a FDA: patients with stage IIB-IIC melanoma after complete resection	AEMPS: treatment of advanced (unresectable or metastatic) melanoma in adults
Pembrolizumab	AEMPS: melanoma and lymph node metastasis after complete resection Indication limited to patients with stage IIIC or IIID melanoma after complete resection ^a FDA, EMA: adults and adolescents aged ≥ 12 years with stage IIB, IIC, or III melanoma after complete resection	AEMPS: treatment in adults and adolescents aged ≥ 12 years with advanced (unresectable or metastatic) melanoma
Ipilimumab plus nivolumab	FDA, EMA, AEMPS: not authorized	AEMPS: treatment of advanced (unresectable or metastatic) melanoma in adults
Dabrafenib plus trametinib	FDA, EMA: stage III melanoma with BRAF V600 mutation after complete resection Not funded in Spain ^b	AEMPS: adults with unresectable or metastatic melanoma with a BRAF V600 mutation
Vemurafenib plus cobimetinib	FDA, EMA, AEMPS: not authorized	AEMPS: adults with unresectable or metastatic melanoma with a BRAF V600 mutation
Encorafenib plus binimetinib	FDA, EMA, AEMPS: not authorized	AEMPS: adults with unresectable or metastatic melanoma with a BRAF V600 mutation

Abbreviations: AEMPS, Spanish Agency for Medicines and Medical Devices; EMA, European Medicines Agency; FDA, US Food and Drug Administration

^a The General Directorate of the Common Portfolio of Services of the Spanish National Health Care System has ruled that the use of pembrolizumab and nivolumab is limited to the adjuvant treatment of patients with stage IIIC or IIID melanoma with lymph node involvement who have undergone complete resection.

^b The General Directorate of the Basic Portfolio of the Spanish National Health Care System and Pharmacy has ruled that adjuvant trametinib plus dabrafenib for the treatment of stage III BRAF V600-mutant melanoma is not funded by the state.

Decisions on treatment strategies for BRAF-mutant melanoma should also be based on comorbidities and expected drug toxicity. In countries where adjuvant therapy with dabrafenib plus trametinib is authorized, and following the recommendation to use BRAF and MEK inhibitors in patients with low tumor burden, targeted therapy would appear to be the adjuvant treatment of choice for BRAF-mutant melanoma.²⁷

Sequence of Initial Systemic Treatment for Patients with BRAF-Mutant Melanoma and Unresectable Metastases

Evidence derived from indirect comparisons, mechanisms of action, safety profiles, and administration routes to guide decisions on treatment sequencing for BRAF-mutant melanoma was recently complemented by direct evidence from the phase III DREAMseq clinical trial. In this trial, patients with unresectable metastatic BRAF V600-mutant melanoma who had not received previous treatment for metastatic disease or adjuvant therapy were assigned to 2 groups: one that started with ipilimumab plus nivolumab followed by dabrafenib plus trametinib in the event of disease progression, and another that started with dabrafenib plus

trametinib followed by ipilimumab plus nivolumab in the event of progression (Fig. 2). Overall 2-year survival rates clearly favored treatment initiation with ipilimumab plus nivolumab (71.8% vs. 51.5%, $P = .01$). This survival advantage was maintained in all subgroups, even in patients who would supposedly have a better initial response to dabrafenib plus trametinib (ECOG PS = 0, normal LDH levels, and low tumor burden with < 3 metastatic sites).³⁴ Furthermore, the overall objective response rate was similar in patients initiated on ipilimumab plus nivolumab vs. dabrafenib plus trametinib (46.0% vs. 43.0%). However, the switch to dabrafenib plus trametinib at disease progression achieved a similar objective response to that achieved with the first-line treatment (47.8%). Ipilimumab plus nivolumab, by contrast, was less effective than the first-line option when used to treat progression (objective response, 29.6%). These results suggest that ipilimumab plus nivolumab after progression in patients receiving dabrafenib plus trametinib is less effective than first-line treatment.³⁴ Differences in the frequency of grade 3 adverse events were not significant between the 2 sequences, but grade 4 events were more common in patients started on ipilimumab plus nivolumab.³⁴

The above results led the authors to conclude that the optimal sequence for most patients with BRAF-mutant

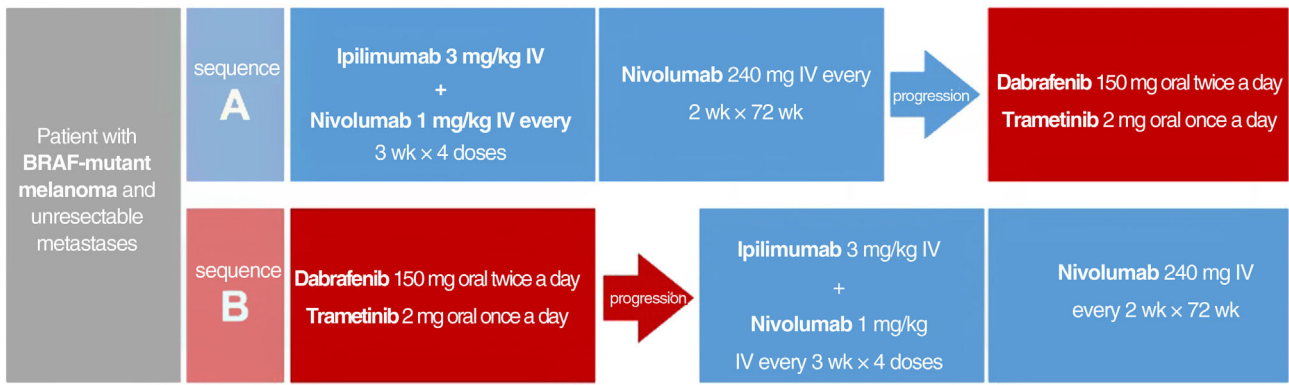


Figure 2 Treatment sequences compared in the DREAMseq clinical trial of patients with unresectable metastatic *BRAF*-mutant melanoma.³⁴ IV indicates intravenous.

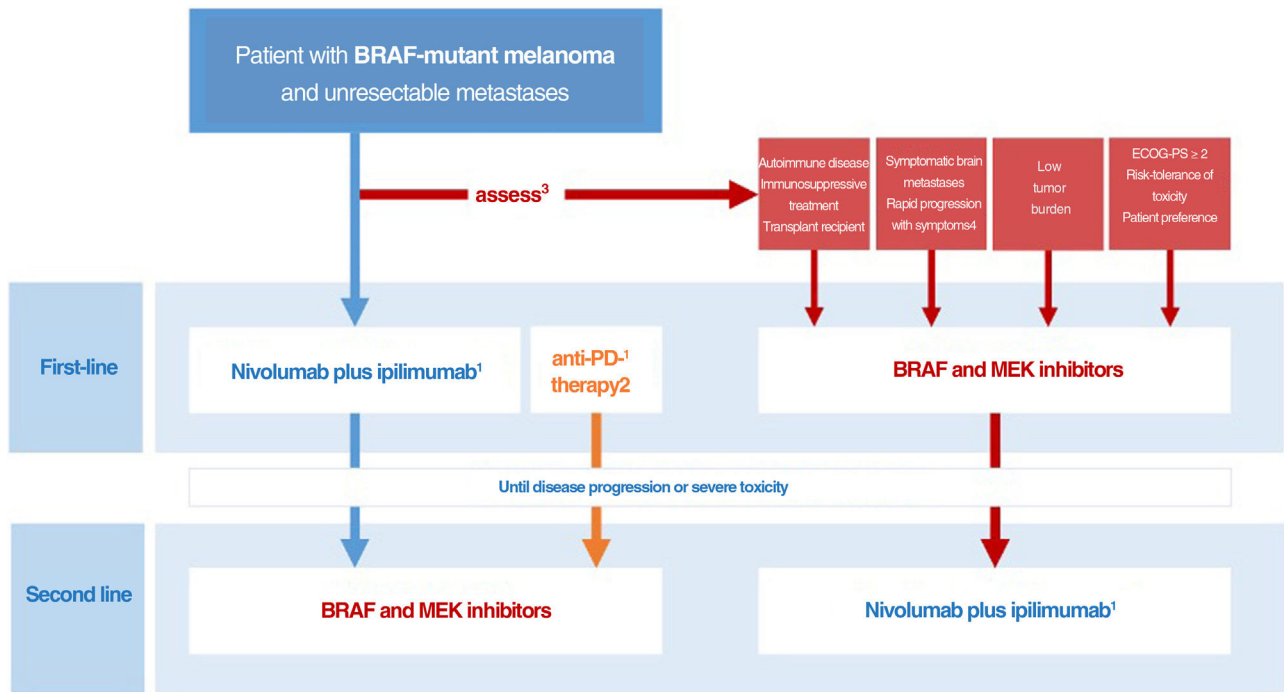


Figure 3 Decision-making algorithm for first-line systemic treatment of *BRAF*-mutant cutaneous melanoma. 1. Ipilimumab plus nivolumab should be considered the first-line treatment in most clinical situations. 2. Indirect comparisons from pivotal trials and clinical registry data suggest that anti-PD1 monotherapy with nivolumab or pembrolizumab may offer the same results as initial anti-CTLA-4 plus anti-PD1 immunotherapy. 3. The multidisciplinary committee should consider clinical and progression-related factors that would favor initiation of systemic BRAF and MEK inhibitor therapy. 4. The need for high-dose corticosteroids to treat symptomatic brain metastases is a limiting factor for immunotherapy. 5. Objective parameters indicative of low tumor burden: normal lactate dehydrogenase levels, ≤ 3 metastatic sites, sum of longest diameters of target lesions < 44 mm. ECOG-PS indicates Eastern Cooperative Oncology Group performance status.

melanoma is ipilimumab plus nivolumab, followed by BRAF and MEK inhibitors if necessary. This may, however, not be applicable to patients previously treated with immunotherapy or patients treated with adjuvant anti-PD1 or anti-CTLA4 immunotherapy or BRAF and MEK inhibitors, as these were excluded from the clinical trial.³⁴ Although comparative clinical trials have not been conducted, indirect long-term comparative data from pivotal trials and clinical registry data may also support initial treatment with anti-PD1 monotherapy.

In the phase II SECOMBIT trial, although no formal comparisons were made, first-line ipilimumab plus nivolumab followed by encorafenib plus binimetinib was associated with the best overall survival at 3 years (62%).³⁵ The best overall response rate for ipilimumab plus nivolumab (57.9%) was observed when the combination was administered using a “sandwich” strategy consisting of encorafenib plus binimetinib for 8 weeks followed by nivolumab plus ipilimumab, and, in patients who experienced disease progression, encorafenib plus binimetinib.³⁵ The authors

mentioned that this strategy could boost initial responses while maintaining long-term benefits (phase II EBIN-EORTC trial ClinicalTrials.gov identifier: NCT03235245).

Drawing on the conclusions of the DREAMseq clinical trial, indirect evidence, and prior experience with BRAF and MEK inhibitors, we have designed an algorithm for guiding decisions aimed at tailoring treatment to all concurrent conditions, optimizing survival outcomes, and reducing variability in clinical practice (Fig. 3). This proposal, however, will need to be revised as clinically relevant data from ongoing clinical trials examining different treatment sequences become available.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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