

Dabrafenib: a new opportunity for the treatment of BRAF V600-positive melanoma

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Abstract: Prior to 2011, the 1-year survival rates for patients suffering from advanced or metastatic melanoma was as low as 33%, with a median overall survival of about 9 months. Several chemotherapeutic regimens have been applied, either as monochemotherapy or as polychemotherapy, overall not resulting in an improvement of progression-free or overall survival. Novel insights into the epidemiology and biology of melanoma allowed the development of newer therapies. The discovery of mutations in BRAF, a part of the mitogen-activated protein kinase, allowed the development of two BRAF inhibitors, vemurafenib and dabrafenib, which significantly improved the outcome of metastatic melanoma treatment. This article reviews the mechanism of action, efficacy, and safety profile of dabrafenib. An in-depth knowledge of this medication will encourage clinicians to select the appropriate therapeutic strategy for each patient, as well as to prevent or adequately manage side effects, optimizing, thus, the drug's applicability.

Keywords: melanoma, BRAF, target therapy, dabrafenib, melanoma survival

Introduction

Despite an increase in the incidence of advanced melanoma, little progress has been made over recent decades in addressing the poor prognosis of patients or the limited treatment options available.^{1–3} The “traditional” treatments for metastatic melanoma were associated with low response rates and complicated by severe toxicities. Dacarbazine was one of the first chemotherapies approved for metastatic melanoma, achieving a response rate of about 20% and a median response duration of 5–6 months. However, studies assessing the efficacy of dacarbazine revealed no benefit in overall survival (OS).⁴ High-dose interleukin (IL)-2 has been reported to achieve a 6%–16% response rate, with a progression-free survival (PFS) of 13.1 months.^{5,6} However, the response rate of IL-2 in patients with brain metastasis is only 5%.⁷ A slightly improved response rate and PFS has been reported with the combination of high-dose IL-2 therapy and the peptide vaccine gp-100. However, the use of high-dose IL-2 is restricted by its severe toxicity, consisting of capillary leak syndrome, arrhythmias, hypotension, and neurologic disturbances.^{5,6} Although lacking an OS benefit and associated with severe toxicity, IL-2 remained for years a first-line treatment for metastatic melanoma, on the basis of the prolonged PFS of responding patients.⁵ Temozolomide is an oral alkylating agent with a cytotoxic effect similar to dacarbazine. Based on its ability to penetrate the blood–brain barrier, temozolomide has been tested in previously untreated patients with brain metastases, achieving a response rate of ~7% and a median PFS of 1.2 months.⁸ Combination chemotherapy has also been tested in several studies, without showing any improvement in response rates.⁹

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During the last years, the prognosis of metastatic melanoma substantially changed with the introduction of kinase inhibitors vemurafenib, dabrafenib, and trametinib and the immune checkpoint inhibitor ipilimumab, an anti-CTLA-4 antibody.^{10–13} More recently, clinical trials testing the efficacy of the programmed cell death-1 receptor inhibitors nivolumab and pembrolizumab showed a further improvement in OS of metastatic melanoma patients.^{7,8}

Targeted therapy

Several key genetic mutations have been shown to contribute to melanoma development and progression. Approximately 40%–50% of melanomas harbor activating mutations in the *BRAF* oncogene, most of them found in exon 15, codon 600 (*V600*). The most frequent mutation event is the substitution of valine by glutamic acid (*V600E*), occurring in ~75% of the cases. Other, less frequent, substitutions include valine by lysine (*V600K*) and valine by arginine (*V600R*).

BRAF is a key molecule of the rat sarcoma gene (*RAS*), which activates several pathways, such as the mitogen-activated protein kinase (*MAPK*) pathway that induces cell growth and cell proliferation. Indeed, mutations in the *MAPK* signaling pathway may be detected in melanoma patients.¹⁴ Intracellular signaling is triggered by growth factors that enhance the binding of a GTP protein (*RAS*) to cell membranes, which, subsequently, promotes the formation of dimers leading to the activation of *RAF* kinases.¹⁵ *RAF* kinases stimulate the phosphorylation of MEK proteins, which in turn phosphorylate and activate the protein kinase ERK. ERK, finally, stimulates the signals for progrowth within the nucleus, leading to cell proliferation and differentiation and to an inhibitory feedback toward upstream components of the pathway.^{15–17} Therefore, the uncontrolled activation of the *MAPK* pathway is associated with the proliferation of malignant cells. This pathway is physiologically activated when extracellular signals bind to their cognate membrane receptor, typically a receptor tyrosine kinase.

BRAF mutations have been reported also in most of the melanocytic nevi, suggesting that the mutation is not responsible for malignancy in melanocytic proliferations. This indicates that *BRAF* mutations may contribute to an early increased proliferation of melanocytes, but not necessarily

a malignant transformation.¹⁰ In fact, the formation of nevi might result from melanocytic proliferation driven by *BRAF* mutations and followed by oncogene-induced senescence. In contrast, melanoma formation requires that senescence does not occur.^{18–20} Most melanoma cells derive directly from transformed melanocytes, without a previous formation of a nevus, possibly resulting from other genetic alterations (eg, alterations in the p53 and Rb pathways) additional to the oncogenic *BRAF* mutations.

BRAF mutations in melanoma are significantly more frequent in younger patients, while *BRAF* mutational status has been shown to correlate to the anatomic site of primary melanoma, the histological subtype, the evidence of chronic sun damage and, partially, the geographic region (Table 1).^{21,22} For example, *BRAF* mutations are much less frequent in acral and mucosal melanoma, while they have never been documented in uveal melanoma.^{23,24}

Two different combinations of *BRAF* inhibitors have been developed and tested for advanced melanoma: type 1 *BRAF* kinase inhibitors, which bind and inhibit the effect of *BRAF* mutation, and type 2 *BRAF* inhibitors, binding to the inactive kinase.¹⁷ Wild-type *BRAF* status represents an absolute contraindication for such compounds, due to paradoxical activation of *MAPK*.¹⁵

Sorafenib, a nonselective *BRAF* inhibitor, acts as a pan-inhibitor of *BRAF* and has largely failed in melanoma treatment. In contrast, drugs that selectively target a mutated and activated form of the *BRAF* kinase have been shown to be appropriate for *BRAF* mutant melanoma treatment.

Vemurafenib (Zelboraf[®]) was the first molecular agent targeting the mutated *BRAF* kinase that demonstrated an improved OS in a Phase III randomized trial. Vemurafenib is an orally administered small-molecule showing a remarkable antitumor activity against *BRAFV600E* mutant melanoma cell lines. On the basis of the documented efficacy of vemurafenib in Phase I and II studies,^{17,25} a Phase III randomized clinical trial (BRIM-3) compared vemurafenib to dacarbazine in patients with unresectable stage III or IV melanoma.²⁶ In this trial, 675 previously untreated patients with *BRAFV600E* mutation-positive advanced melanoma were randomized to receive either 960 mg of vemurafenib orally twice a day or 1 g/m² of dacarbazine intravenously

Table 1 Frequency, type, and clinical characteristics associated to *BRAF* mutation

Cancer type	Mutation frequency and type	Clinical characteristics
Melanoma	46%–48%; <i>V600E</i> more common than <i>V600K</i> ; other rare exon 15 mutations reported	<i>BRAFV600E</i> mutations more common in younger persons and in tumors arising from intermittently sun-exposed skin. Mutually exclusive with <i>NRAS</i>

every 3 weeks. The endpoints of the study were PFS and OS. After a median follow-up period of 3.8 months for patients treated with vemurafenib and 2.3 months for those receiving dacarbazine, vemurafenib was associated with a relative reduction of 63% in the risk of death and of 74% in the relative risk of disease progression, as compared with dacarbazine ($P < 0.001$). Vemurafenib was also associated with a higher disease control rate and a higher response rate. The safety and efficacy of vemurafenib and dacarbazine in this Phase III study were updated at a median follow-up of 12.5 and 9.5 months, respectively, with median OS reaching 13.6 months with vemurafenib compared to 9.7 months with dacarbazine. The hazard ratio (HR) for death in the vemurafenib group was 0.70 (95% confidence interval [CI]: 0.57–0.87; $P = 0.0008$).¹⁰ The vemurafenib group showed significantly longer PFS than the dacarbazine group (6.9 vs 1.6 months; HR 0.38 (95% CI: 0.32–0.46); $P < 0.0001$). The relative impact of vemurafenib with respect to mutated *BRAF* subtypes was also assessed by the updated analysis, showing comparable efficacy and toxicity in patients with *BRAFV600E* and *BRAFV600K* mutation.¹⁰

The recommended dose of vemurafenib is 960 mg to be taken orally twice each day. The most common adverse events (AEs) recorded in the BRIM-3 registration trial included arthralgia, fatigue, nausea, rash, photosensitivity, and development of cutaneous squamous cell carcinoma (cSCC) or keratoacanthoma (KA) (25).¹⁰ The most frequent grade 3 or 4 AEs were cSCC/KA, transaminitis, and rash.¹⁴ The dose of vemurafenib was modified or interrupted due to AEs in 38% of patients,²⁶ while the drug was permanently discontinued in only 7% of the patients treated.¹⁰

The second selective *BRAF* inhibitor approved for treatment of *BRAF*-mutated metastatic melanoma is dabrafenib (Tafinlar[®]), which is a highly potent adenosine triphosphate-competitive inhibitor of *BRAFV600E* kinase with proven antitumor activity within the brain and systemically. The recommended dose is 150 mg twice a day.

Dabrafenib monotherapy

The approval of dabrafenib was mainly based on the BREAK trial, which began in 2009; the initial results of the Phase I trial were presented in 2010 and the final results in 2012.^{19,20} The trial in Phase I included 184 patients, 156 suffering from melanoma and 28 from other solid tumors, with an Eastern Cooperative Oncology Group performance status of 0 or 1. The main aim of the study was to evaluate the safety and tolerability of dabrafenib, as well as to determine the recommended dose for Phase II. Secondary aims were to investigate

the pharmacokinetic/pharmacodynamic profile of the drug and the tumor response. The treatment was continued until disease progression, intolerable toxic events, or withdrawal of consent. The tumor response was assessed by the Response Evaluation Criteria in Solid Tumours version 1.0. The most common AEs included development of cSCC (20 patients, 11%), fatigue (14, 8%), and pyrexia (11, 6%). A reduction in drug dose was required in 13 (7%) patients, while no deaths or discontinuations due to AEs occurred. On the basis of safety and the pharmacokinetic profile of dabrafenib, the dose of 150 mg twice daily was determined as the recommended dose for Phase II. Among the 36 patients with *BRAFV600*-mutant melanoma receiving the recommended dose, 18 (50%, 32.9–67.1 CI 95%) had confirmed response, while the response rate for patients with *BRAFV600E* was 56% (15 out of 27, 56%, 35.3–74.5).²⁷ The median duration of response was 6.2 months (95% CI, 4.2–7.7) and the PFS was similar for patients with *BRAFV600E* and *V600K* mutations (5.5 and 5.6 months, respectively).

After establishment of the optimal dose, three expanded cohorts were added; one with metastatic melanoma, one with asymptomatic untreated brain metastases (3 mm or larger), and one with nonmelanoma solid tumors. In the BREAK-2, single-arm, open-label, Phase II trial, 76 patients with melanoma and *BRAFV600E* and 16 with *BRAFV600K* mutation were enrolled.²⁸ The response rate was much better in the *V600E* group (59% with 7% complete response) than the *V600K* group (13%). PFS and OS were also longer in the *V600E* group (6.3 and 13.1 months, respectively), compared to patients with *V600K* (4.5 and 12.9 months, respectively).

Although the different response between patients harboring the *V600E* and those with *V600K* mutation cannot be adequately explained, it provides evidence supporting that these genotypes correspond to biologically distinct subtypes of melanoma, with *V600K* mutation associated with a significantly shorter disease-free interval but no difference in survival thereafter.²²

In the Phase I study, a reduction in the size of brain metastases was reported in nine of ten patients, four of whom experienced a complete remission.¹⁹ Based on this observation, the BREAK-MB Phase II study was designed to assess the efficacy of dabrafenib in patients with *BRAFV600E*-mutant melanoma with untreated or recurrent/progressing after local treatments on brain metastases. The study found dabrafenib to be effective in both groups of patients (with previously treated brain metastasis and untreated ones). The reported survival was approximately three times longer

compared to the temozolomide study (patients were not *BRAF* genotyped).^{8,29} The safety profile was acceptable; the three most frequent serious AEs were pyrexia (6%), intracranial hemorrhage (6%, one treatment related), and development of cSCC (6%).

The pivotal Phase III trial¹¹ (BREAK-3) compared dabrafenib with dacarbazine (DTIC) in patients with stage IV or unresectable stage IIIC *BRAFV600E* melanoma with an Eastern Cooperative Oncology Group performance status of 0 or 1. The trial enrolled patients with a 3:1 randomization to receive either dabrafenib 150 mg or DTIC (1,000 mg/m² every 3 weeks). Patients receiving DTIC crossed over to dabrafenib in case of disease progression. The primary endpoint of the study was PFS as assessed by a local investigator. Secondary endpoints were the following: PFS assessed by an independent review committee (IRC); OS; objective response rate (ORR) according to revised Response Evaluation Criteria in Solid Tumours guidelines, version 1.1,³⁰ as assessed by an investigator and IRC; PFS after crossover from DTIC to dabrafenib, response duration, quality of life, safety, and tolerability. Confirmed responses by an IRC were recorded in 50% of dabrafenib patients (3% complete, 47% partial) and 6% of DTIC patients (2% complete, 4% partial). The median time to response in the dabrafenib group was 6.2 weeks. Similarly to the previous vemurafenib Phase III trial, a median PFS of 6.9 months was found for dabrafenib treatment versus 2.7 months for DTIC.

The most recent update at 16.9 months median follow-up³¹ reported a median OS of 20.0 months for dabrafenib versus 15.6 months for DTIC (59% of DTIC patients crossed over to dabrafenib arm). Of note, 18 patients (10%) remain on dabrafenib without disease progression.

Toxic AEs and cSCC are reported less frequently in patients treated with dabrafenib compared to those treated with vemurafenib, but a direct comparison has never been conducted.

Dabrafenib in combination

Although *BRAF*i were the first agents achieving a significant efficacy in metastatic melanoma, their beneficial effect is limited by the frequent development of acquired resistance, while ~15% of patients do not respond at all. Therefore, several challenges remain to be addressed to optimize the efficacy of these drugs and minimize treatment failures. Resistance to targeted therapy with *BRAF*i is a result of reactivation of the MAPK pathway, limiting the PFS benefit to 6–8 months. *BRAF* inhibitors have also been suggested

to induce secondary primary tumor development through a paradoxical activation of the *MAPK* pathway in cells lacking *BRAF* mutations.

The estimated crucial role of the *MAPK* pathway in the development of resistance to *BRAF*i generated the hypothesis that its blockage by an *MEK* inhibitor might improve the efficacy of *BRAF*i. This led to the first combination treatment of a *BRAF* inhibitor (dabrafenib) with an *MEK* inhibitor (trametinib). Trametinib, an *MEK1/2* inhibitor targeting the kinase downstream of *BRAF* in the *MAPK* pathway, is also active in monotherapy in *BRAF*-mutated melanomas but with lower efficacy than *BRAF* inhibitors. As opposed to dabrafenib, the metabolism of trametinib is predominantly nonhepatic, involving deacetylation as well as secondary modifications including oxidation and glucuronidation. Trametinib does not appear to have significant inhibitory activity toward CYP isozyme or transport proteins, limiting, thus, the possibility of interactions with dabrafenib.

The efficacy of the combination treatment has been tested in different schemes, including synchronous and sequential initiation of the two agents. It has been shown that inhibition of *MEK* by a single agent has limited value in patients with melanoma after progression on a *BRAF* inhibitor.³² Instead, the response rate to *MEK* inhibition was higher when this agent was given first, followed by the initiation of dabrafenib.¹² However, all sequential regimens were shown to be inferior to the synchronous initiation of the two drugs.

Analytically, a Phase I/II study explored the combination of dabrafenib and trametinib in patients affected by advanced melanoma harboring mutations in *BRAFV600E/K*. Combination treatment with 150 mg of dabrafenib twice per day and 2 mg of trametinib daily was compared with monotherapy with 150 mg of dabrafenib twice per day. A significantly higher response rate (76% vs 54%, $P=0.03$) and a prolonged PFS was observed in the combination arm, compared to dabrafenib monotherapy.³³ Furthermore, combination therapy was associated with a lower rate of cSCC development (7% vs 19%), whereas pyrexia was more frequent in the combination arm (71% vs 26%). Based on these promising data, US Food and Drug Administration approved the combination treatment of dabrafenib and trametinib for metastatic melanoma. Subsequently, the superiority of the combination regimen was further documented by the results of two Phase III trials. In COMBI-V study,³⁴ dabrafenib plus trametinib were compared to vemurafenib plus placebo as first-line treatment for *BRAF*-mutant metastatic melanoma. The study was terminated early since, at the preplanned

interim analysis, the combination treatment was assessed as significantly superior. In detail, patients receiving the combination treatment had a longer OS (median OS not reached vs 17.2 months), a longer PFS (11.4 vs 7.3 months; HR 0.56 [95% CI 0.46–0.69]; $P < 0.001$), a prolonged response duration (13.8 vs 7.5 months) and a higher response rate (64% vs 51%; $P < 0.001$).³⁵ The last data cutoff was then performed at 349 events, with the combination treatment associated with a higher 2-year OS compared to vemurafenib (51% and 38%, respectively), a higher median OS (25.6 vs 18.0 months (HR 0.66; $P < 0.001$), a prolonged PFS (12.6 vs 7.3 months, HR 0.61; $P < 0.001$), and improved ORR and deep of response. Good prognostic features at baseline, associated with durable response and prolonged OS, were the following: lactate dehydrogenase, with a 2-year OS rate of 66% and a median PFS of 17.5 months, earlier-stage melanoma, and fewer metastatic sites.³⁶

Furthermore, this study showed that treatment with the combination of dabrafenib plus trametinib does not result in deterioration of quality of life, adding a clear benefit over monotherapy with the *BRAF* inhibitor vemurafenib.³⁴ The latter finding is highly relevant in clinical practice, since, in addition to the survival benefit, the minimization of disease-associated symptoms and drug-associated AEs also represent pursued goals.

In the second Phase III study, COMBI-D, untreated *BRAF*-mutant patients were randomized to receive either dabrafenib and trametinib or dabrafenib plus placebo. The median OS for the combination group was 25.1 months (95% CI 19.2 to not reached) versus 18.7 months (15.2–23.7 95% CI) for the monotherapy group, while 1- and 2-year survival rates were also higher in the combination group. Among patients receiving the combination of dabrafenib, 87% experienced treatment-related AEs, compared to 90% of patients in the dabrafenib group. Fever was the most common AE (52%) in the combination group and hyperkeratosis (33%) in the monotherapy group, while grade 3 or 4 AEs were similar in the two groups (32% and 31%).³⁷

Finally, a Phase III randomized, double-blind and placebo-controlled trial (COMBI-AD) is underway, assessing the efficacy of the combination of dabrafenib plus trametinib as an adjuvant therapy, following surgical excision, of high-risk *BRAF* mutation-positive melanoma (NCT0909453).

Since targeted therapy has an important effect on the immune system, the possibility of combining a *BRAF* or *MEK* inhibitor with immunotherapy is an interesting approach. However, Phase I data showed that combined administration of vemurafenib and ipilimumab increases liver toxicity (although

this was not reported with dabrafenib plus ipilimumab),³⁸ while the triple combination of ipilimumab plus dabrafenib and trametinib was reported to increase the risk of bowel perforation. The development of anti-*PD-1/PD-L1* agents, which appear to be more effective and less toxic than ipilimumab, reintroduces the possibility of a combined approach with *BRAF* or *MEK* inhibitor. Indeed, a Phase I study reported data on the combination of the anti-*PD-L1* antibody, MEDI14736 (durvolumab) with dabrafenib and trametinib in patients with clinical stage IIIC or stage IV melanoma. The triple combination resulted in an ORR of 69% and disease control rate of 100%, showing also a manageable safety profile. However, longer follow-up will be necessary to determine the efficacy and safety of the triple drug combination.³⁹

Safety evaluation

Cumulative experience with the two *BRAF*i, vemurafenib and dabrafenib, has shown that, although some toxicities such as skin toxicity, joint pain, and fever are common with both inhibitors, their type and severity vary considerably and may influence the choice of the drug (Table 2). For example, photosensitivity is common in patients treated with vemurafenib and much less frequent in patients treated with dabrafenib, whereas fever and chills are much more frequent with dabrafenib treatment. Skin toxicities are the most common AEs associated with *BRAF*i, experienced by up to 57% of patients, and appearing within days after therapy initiation (Figures 1–4).

Overall, dabrafenib is well tolerated by the patients, including those with brain metastases, since its side effects are common but usually manageable. The toxicities in the Phase III trial were similar to those observed in early-phase trials.¹¹ The most common grade 2 or higher AEs were cutaneous manifestations (hyperkeratosis, papillomas, palma-plantar erythrodysesthesia), pyrexia, fatigue, headache, and arthralgia. In the BREAK-3 trial,¹¹ 7% of patients developed cSCC/KA, three patients (2%) developed new primary melanomas, while phototoxicity was rare (3%), as were grade 3 AEs. Dose reductions were necessary in 28%

Table 2 Skin toxicity

Vemurafenib	Dabrafenib
Rash: 49%	Hyperkeratosis: 39%
Photosensitivity: 31%	Photosensitivity: rare
SCC: 19%	SCC: 10%
Alopecia: 26%	Alopecia: rare
Others (pruritus, dry skin, papillomas): frequent	Others (pruritus, dry skin, papillomas): not frequent

Abbreviation: SCC, squamous cell carcinoma including keratoacanthoma.



Figure 1 Acantholytic dyskeratosis.



Figure 3 Verrucous keratosis.

of patients, and therapy was permanently discontinued due to toxicity in only 3% of patients. In the BREAK-MB study, 82% of patients experienced at least one grade 2 or higher side effect and 22% had grade 3 or higher AE. However, only 2% discontinued dabrafenib due to toxicity.

Although vemurafenib is considered to be well tolerated as well, adverse effects are frequent, with skin toxicity representing the most common problem. Among several skin AEs reported in the literature, the most common are alopecia, photosensitivity, pruritus, hand-foot skin reactions (HFSR), cutaneous manifestations resembling hyperkeratotic and dyskeratotic diseases (Figure 1), follicular-centered eruption resembling keratosis pilaris (Figure 2),⁴⁰ seborrheic dermatitis-like eruptions, and Darier or Grover-like eruptions. Less frequent events include pyogenic granuloma, gingival hyperplasia, and lupus erythematosus-like skin eruption.⁴¹⁻⁴³

The development of keratosis pilaris-like eruptions associated with facial erythema and HFSR in patients treated

with vemurafenib validate the association of facial erythema with the *BRAF* pathway and indicate VEGF inhibition as the molecular mechanism responsible for HFSR. The specificity of vemurafenib for BRAF suggests that inhibition of the BRAF pathway alone is sufficient to induce HFSR.⁴⁰ The occurrence of malignant and benign hyperproliferative skin lesions like cSCC, KA, warty dyskeratoma, and verrucous keratosis (Figure 3) has also been documented. The paradoxical phenomenon of vemurafenib-induced SCCs suggests that transformation of sensitive cells, harboring clinically silent *RAS* mutations, is regulated by *BRAF*-inhibitor-induced *MAPK* signaling via noninhibited *RAF* isoforms, highlighting the complexity and redundancy of kinase signaling.⁴⁴ Notably, cSCCs and KAs associated with vemurafenib therapy are easily treated by simple excision, without requiring discontinuation of vemurafenib. Another peculiar side effect of vemurafenib is the darkening of existing nevi and the appearance of new nevi within 2 months after drug initiation (Figure 4).⁴⁵⁻⁴⁷ Skin toxicities generally cannot be



Figure 2 Keratosis pilaris.



Figure 4 New and enlarging melanocytic nevi.

prevented, but rarely require permanent discontinuation of the treatment, being usually adequately managed with dose modification and appropriate therapy.^{48,49}

The absence of photosensitivity with dabrafenib and the lower frequency of cutaneous AEs suggest dabrafenib as an appropriate alternative treatment option for patients who are intolerant to vemurafenib due to skin toxicity.

The combination of dabrafenib plus trametinib and vemurafenib plus cobimetinib resulted in similar clinical efficacy. Therefore, the selection of combination regimen might mainly be based on its expected toxicity. Pyrexia is the most frequent AE reported with the combination of dabrafenib and trametinib (51%–53%; G3: 4%–6%), representing the most common reason for dose interruptions, dose reductions, and permanent discontinuation.^{34,35,37} No baseline features have been identified to predict pyrexia, and it does not seem to be associated with the clinical outcome.⁵⁰ Other frequent AEs include fatigue (35%), nausea (30%–35%), headache (30%), chills (30%–31%), diarrhea (24%–32%), arthralgia (24%), rash (22%–23%), and hypertension (22%).^{34,35,37}

Cardiac-related AEs may occur when trametinib is administered as a single agent or in combination with dabrafenib. Specifically, trametinib has been reported to decrease LVEF. In clinical trials, the median time to the first occurrence of left ventricular dysfunction, cardiac failure, and LVEF decrease was between 2 and 5 months. Integrated safety data from COMBI-D (N=209) and COMBI-V studies (N=559) suggest a decreased ejection fraction as a common AE, whereas LVEF dysfunction and cardiac failure were not reported during COMBI-D, but were noted as uncommon events in the integrated safety analysis.

Pyrexia was reported also in patients treated with the combination of vemurafenib and cobimetinib, although to a much lesser extent as regarding frequency and severity (26%; G3: 2%).⁵¹ On the other hand, photosensitivity reaction (28%), diarrhea (56%; G3: 6%), increased aspartate/alanine aminotransferase (22%–23%; G3: 8%–11%) and increased creatinine kinase (27%; G3: 7%) are more frequent and severe with vemurafenib plus cobimetinib than dabrafenib plus trametinib. Ocular toxicity is also more commonly reported in patients treated with vemurafenib and cobimetinib (chorioretinopathy: 1%), though most of these events were low-grade and reversible without any treatment, or with dose reduction/withdrawal of cobimetinib.⁵²

The most striking safety difference between combination therapy and monotherapy is the decreased incidence of new skin cancers and other hyperproliferative skin lesions. As discussed earlier, this finding is consistent with the

suggested pathogenesis of these tumors, which includes a paradoxical activation of the *MAPK* pathway with upstream activation of signaling by preexisting *RAS* mutation.⁵³ The addition of an *MEK* inhibitor leads to a block of *RAS* signaling along the *MAPK* pathway and prevents the cellular proliferation.

Conclusion

BRAF inhibitors (vemurafenib and dabrafenib) have become worldwide standards of care for patients with *BRAF*-mutant metastatic melanoma, especially those with high tumor burden or progression after immunotherapy. Both agents improve survival, compared with chemotherapy, and have acceptable toxicity profiles. Combined *BRAF* and *MEK* inhibition achieves a statistically significant further improvement in response rate, PFS, and OS compared to monotherapy. However, the majority of the patients develop resistance and tumor progression similar to that observed with *BRAF* inhibitor monotherapy. Preclinical evidence, a Phase I trial,⁴⁵ reported promising data indicating that a multitargeted upfront approach, including immunotherapy, might have the potential to achieve the greatest survival benefit for patients with metastatic melanoma.

Definitely, the appropriate selection of systemic therapy for metastatic melanoma remains an evolving field and requires further elucidation. For instance, long-term data on the combination therapy with dabrafenib and trametinib revealed that long-term survival and durable responses are associated with good prognostic features at baseline, including factors related to low-volume disease.⁵⁴ However, such baseline factors are classically considered a reason to choose front-line immunotherapy. The need to develop specific predictive molecular markers for each therapy is now more important than ever. Another issue requiring further clarification is the determination of the optimal sequence of administered therapeutic agents, since it remains unknown whether treating patients with ipilimumab and nivolumab followed by dabrafenib and trametinib is more effective than treatment with dabrafenib and trametinib followed by ipilimumab and nivolumab (ongoing trial NCT02224781).

Finally, neoadjuvant *BRAF*-targeted therapy in advanced locoregional *BRAFV600* mutant melanoma patients represents a novel challenge to be addressed, with a relevant clinical trial urgently required.

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Disclosure

The authors report no conflicts of interest in this work.

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