

# Encorafenib and Binimetinib Combination Therapy in Metastatic Melanoma

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Authors' disclosures of conflicts of interest are found at the end of this article.

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## Abstract

The treatment landscape for metastatic melanoma has changed dramatically over the past few years as new medications have been developed. Encorafenib, a B-Raf protein kinase inhibitor, and binimetinib, a MEK inhibitor, were approved by the U.S. Food and Drug Administration in 2018 for the treatment of patients with unresectable or metastatic melanoma which harbor a *BRAF* V600E or V600K mutation. These approvals were based on findings from the COLUMBUS trial, which demonstrated improvement in progression-free survival and overall survival with the combination of encorafenib plus binimetinib compared with vemurafenib alone. Encorafenib plus binimetinib is the third *BRAF* plus MEK inhibitor combination to be approved, and there are clinical and practical differences between the combination regimens that should be considered when selecting an appropriate treatment regimen for patients.

**I**ncidence rates of cutaneous melanoma have increased over the past few decades, currently accounting for 1% of all skin cancers. In 2022, an estimated 108,480 new cases will be diagnosed, and 11,990 people are expected to die of melanoma. Metastatic melanoma is associated with high mortality, with 5-year survival rates decreasing from 99% in localized disease to 30% in distant disease (Siegel et al., 2022).

Traditional chemotherapy was previously considered the sole option

for patients with metastatic melanoma, although this was limited by poor response rates of approximately 10% to 20%. Over the past decade, the treatment landscape has evolved to include immunotherapies and small-molecule targeted regimens, which have demonstrated improved survival rates (Michielin et al., 2020; Schvartsman et al., 2019; Sood et al., 2021).

Approximately 50% of patients diagnosed with metastatic melanoma have a protein kinase B-Raf (*BRAF*) point mutation. Mutations at codon 600 of the *BRAF* gene lead

to tumor proliferation through increased signal transduction of the mitogen activated protein kinase (MAPK) pathway. *BRAF* V600E is the most common V600 point mutation, occurring in 84.6% of *BRAF*-mutated melanomas (Cheng et al., 2018).

Advances in the detection of *BRAF* mutations led to the development of targeted agents. Available *BRAF* inhibitors include dabrafenib (Tafinlar), vemurafenib (Zelboraf), and encorafenib (Braftovi; National Comprehensive Cancer Network [NCCN], 2021). Patients treated with *BRAF* inhibitor monotherapy often developed resistant disease as well as secondary malignancies, such as squamous cell carcinoma, through reactivation of the MAPK pathway. The use of combination therapy with an additional inhibitor, targeting the regulator kinases MEK1 and MEK2, may mitigate this resistance pathway. MEK inhibitors include trametinib (Mekinist), cobimetinib (Cotellic), and binimetinib (Mektovi). A MEK inhibitor given in combination with a *BRAF* inhibitor demonstrated a delay in resistance development and reduction in secondary malignancies (Long et al., 2014; Michielin et al., 2020).

Combination regimens targeting *BRAF* and MEK (e.g., dabrafenib plus trametinib, vemurafenib plus cobimetinib, or encorafenib plus binimetinib) are currently recommended as first-line therapy in patients with unresectable or metastatic melanoma with a *BRAF* V600-activating mutation. No head-to-head studies comparing combination therapies currently exist; however, it is important to evaluate the differences in adverse event profiles, dosing schedules, administration considerations, storage, and need for additional patient monitoring (NCCN, 2021). This article will focus on the most recently approved *BRAF*/MEK inhibitor combination regimen, encorafenib plus binimetinib.

## PHARMACOLOGY AND MECHANISM OF ACTION

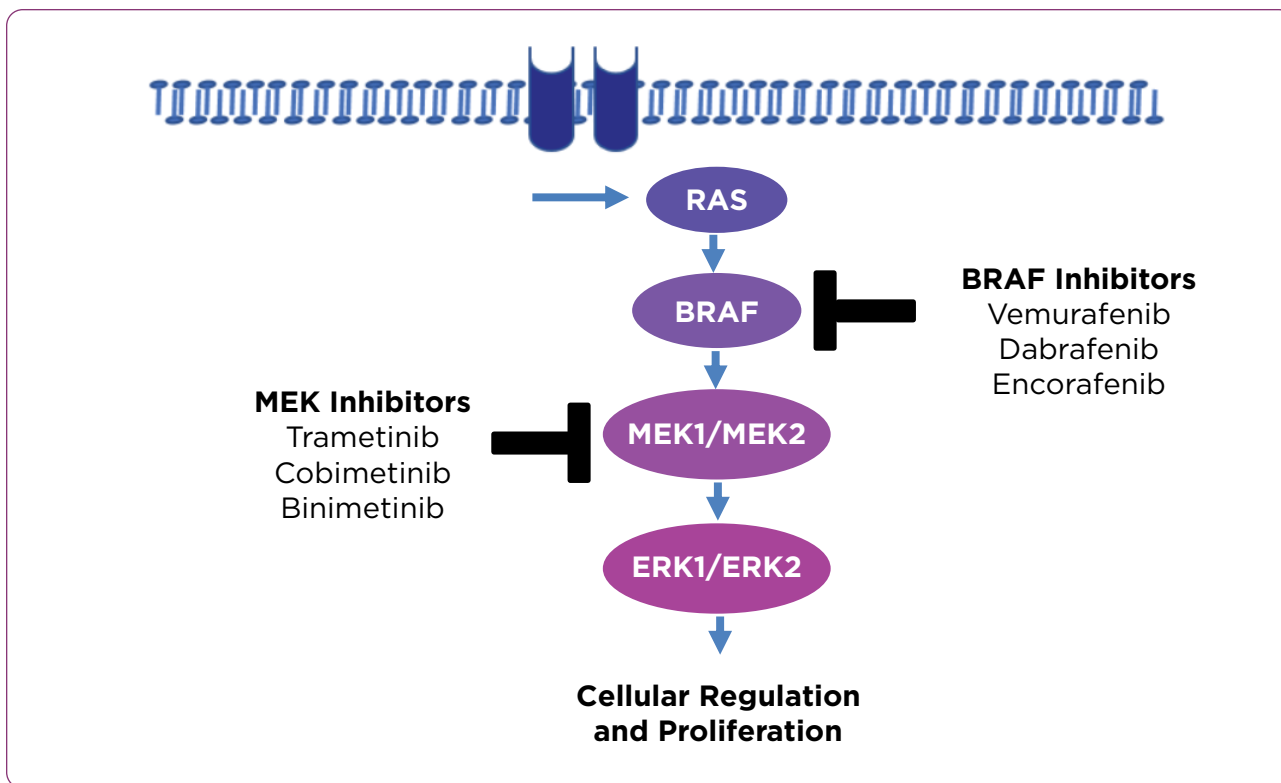
Encorafenib and binimetinib are inhibitors of protein kinases in the MAPK pathway (Figure 1). Encorafenib targets *BRAF* V600E, V600D, and V600K mutant kinases. Binimetinib is a reversible inhibitor of MEK1 and MEK2. The inhibition of *BRAF* and MEK kinases results in inhibition of extracellular signal-regulated kinase (ERK)

phosphorylation, which ultimately leads to decreased cell proliferation. The combination of *BRAF* and MEK inhibition increases antitumor activity, decreases resistance, and attenuates toxicities compared with the activity of either agent alone (Cheng et al., 2018; Sood et al., 2021). Encorafenib and binimetinib are small-molecule, oral agents. Preclinical data demonstrated a dissociation half-life > 30 hours for encorafenib, compared with 2 hours with dabrafenib and 0.5 hours with vemurafenib; thus, encorafenib is dosed once daily. Steady state was achieved by day 15 (Delord et al., 2017). Binimetinib has a mean terminal half-life of 3.5 hours; therefore, it is approved as twice-daily dosing. Encorafenib is primarily metabolized through CYP3A4, CYP2C19, and CYP2D6, and binimetinib is metabolized through glucuronidation (Array Biopharma Inc., 2018a, 2018b).

## CLINICAL TRIALS

Encorafenib plus binimetinib was approved in 2018 for the treatment of patients with unresectable or metastatic melanoma with *BRAF* V600E or V600K mutations. This approval was based on a two-part, randomized, phase III, open-label study. Patients were treatment naive or had progressed on or after previous first-line immunotherapy. Part 1 of the COLUMBUS trial compared encorafenib 450 mg daily plus binimetinib 45 mg twice daily vs. encorafenib 300 mg daily vs. vemurafenib 960 mg twice daily. Median progression-free survival (PFS) in the combination arm was 14.9 months compared with 7.3 months in the vemurafenib monotherapy arm ( $p < .001$ ). Median overall survival (OS) was also longer in the combination arm compared with the vemurafenib arm (33.6 months vs. 16.9 months;  $p < .001$ ). The five-year PFS and OS rates for the combination arm were 22.9% and 34.7%, respectively, compared with 10.2% and 21.4% in the vemurafenib monotherapy arm (Dummer et al., 2018a, 2018b, 2021).

Part 2 of the COLUMBUS trial was conducted to elucidate the true effect of binimetinib in combination with encorafenib. This study confirmed the benefit of combination therapy by demonstrating a significant improvement in PFS with encorafenib plus binimetinib vs. encorafenib monotherapy (Dummer et al., 2018c).



**Figure 1.** MAPK pathway and targets of BRAF/MEK inhibitors. Adapted from Sood et al. (2021).

## ADVERSE EVENTS

The most frequently reported adverse events in the encorafenib plus binimetanib combination arm of the COLUMBUS trial were fatigue, nausea, diarrhea, and vomiting (Table 1). Skin toxicities, increased aminotransferase concentrations, serous retinopathy, left ventricular dysfunction, and pyrexia are commonly associated with BRAF and MEK inhibitor combination therapy. In the phase III trial, skin toxicities were less common in the combination arm compared with the two monotherapy arms. Increased aminotransferase concentrations, serous retinopathy (20% vs. 2% vs. 2% in the combination, encorafenib, and vemurafenib arms, respectively), and left ventricular dysfunction (8% vs. 2% vs. 1% in the combination, encorafenib, and vemurafenib arms, respectively) were more common in the combination arm. Adverse events leading to dose reduction or discontinuation of therapy occurred in 53% of patients in the combination group, 71% of patients in the encorafenib monotherapy group, and 62% of patients in the vemurafenib monotherapy group. The most common adverse event leading to dose

reduction or therapy interruption in the combination arm was nausea. The most common grade 3 and 4 adverse events in the combination arm were increased  $\gamma$ -glutamyltransferase (11%), increased alanine aminotransferase (ALT; 6%), hypertension (6%), and increased creatinine phosphokinase (5%). Safety and tolerability of part 2 was consistent with part 1 results (Dummer et al., 2018a, b, c).

## IMPLICATIONS FOR THE ADVANCED PRACTITIONER

Encorafenib plus binimetinib is FDA approved for patients with unresectable or metastatic melanoma with *BRAF*-activating mutations. Encorafenib is dosed at 450 mg orally once daily and may be taken with or without food. It is available as 75 mg capsules, so patients must take 6 capsules daily. Notably, the initial dose of encorafenib should be reduced to 300 mg once daily when used as monotherapy or if binimetinib is held for toxicity. The recommended dose for binimetinib is 45 mg orally twice daily, which is 3 of the 15-mg tablets twice daily. Binimetinib may also be taken with or without food.

The dose of encorafenib should be reduced with concomitant use of moderate or strong CYP3A4 inhibitors due to increase in encorafenib plasma concentrations and risk of increased adverse reactions. Use of moderate or strong CYP3A4 inducers should be avoided due to the risk of decreased encorafenib plasma concentrations and thus decreased efficacy. No significant drug interactions have been observed with binimetinib; however, a dose reduction is recommended in moderate or severe hepatic impairment. No dose reductions are required in mild or moderate renal impairment for either agent, and the optimal dose has not been established in severe renal impairment (creatinine clearance < 30 mL/min). Adverse events necessitating a dose reduction of encorafenib include uveitis, QTc prolongation, hepatotoxicity, severe dermatologic reactions, and other grade 2 to 4 reac-

tions. The recommended dose is 300 mg for the first dose reduction and 225 mg for the second dose reduction. If the patient is unable to tolerate the 225 mg dose, then encorafenib should be permanently discontinued. Adverse events necessitating a dose reduction of binimetinib include cardiomyopathies, venous thromboembolism, life-threatening pulmonary embolism, renal vein occlusion, uveitis, interstitial lung disease, rhabdomyolysis, severe dermatologic reactions, and other grade 2 to 4 adverse events. The recommended dose reduction is 30 mg twice daily. Binimetinib should be permanently discontinued if 30 mg twice daily is not tolerated (Array Biopharma Inc., 2018a, 2018b).

The three currently FDA-approved BRAF plus MEK inhibitor combinations have not been studied head-to-head, and all three regimens are Category 1 recommendations for the first-line

**Table 1. Efficacy and Safety of BRAF Plus MEK Inhibitor Combination Regimens**

| Trial                     | Vemurafenib plus cobimetinib<br>coBRIM | Dabrafenib plus trametinib<br>COMBI-d, COMBI-v<br>(pooled analysis) | Encorafenib plus binimetinib<br>COLUMBUS |
|---------------------------|--|---|--|
| Median PFS, mo            | 12.6                                   | 11.1  | 14.9                                     |
| PFS, %                    |  |   |  |
| 3 yr                      | 23                                     | 23  | 29                                       |
| 5 yr                      | 14                                     | 19  | N/A                                      |
| Median OS, mo             | 22.5                                   | 25.9  | 33.6                                     |
| OS, %                     |  |   |  |
| 3 yr                      | 38                                     | 44  | 47                                       |
| 5 yr                      | 31                                     | 34  | N/A                                      |
| Select AEs, any grade, %  |  |   |  |
| Fatigue                   | 38                                     | 35  | 43                                       |
| Nausea                    | 44                                     | 37  | 44                                       |
| Diarrhea                  | 61                                     | 36  | 38                                       |
| Vomiting                  | 28                                     | 31  | 32                                       |
| Pyrexia                   | 32                                     | 58  | 20                                       |
| Photosensitivity reaction | 35                                     | NR  | 4  |
| Rash                      | 42                                     | 28  | 16                                       |
| Arthralgia                | 39                                     | 29  | 28                                       |
| Increased ALT             | 27                                     | 48  | 11                                       |
| Increased AST             | 27                                     | 59  | 9  |

Note. Information from Ascierto et al. (2021); Dummer et al. (2018b); Robert et al. (2019); Schadendorf et al. (2017).

**Table 2. Comparison of BRAF/MEK Inhibitor Combinations**

| <b>BRAF inhibitor</b>     | <b>Vemurafenib</b>                                      | <b>Dabrafenib</b>                                   | <b>Encorafenib</b>              |
|---------------------------|---|---|---------------------------------|
| Dose                      | 960 mg (240 mg tab × 4)                                 | 150 mg (75 mg cap × 2)                              | 450 mg (75 mg cap × 6)          |
| Frequency                 | q12h  | q12h  | Daily                           |
| Administration            | With or without food                                    | On an empty stomach                                 | With or without food            |
| Other considerations      | Higher incidence photosensitivity<br>QTc monitoring     | Higher incidence pyrexia                            | High pill burden QTc monitoring |
| <b>MEK inhibitor</b>      | <b>Cobimetinib</b>                                      | <b>Trametinib</b>                                   | <b>Binimetinib</b>              |
| Dose                      | 60 mg (20 mg tab × 3)                                   | 2 mg (2 mg tab × 1)                                 | 45 mg tab (15 mg tab × 3)       |
| Frequency                 | Daily on days 1–21 of 28-day cycle                      | Daily   | q12h                            |
| Administration            | With or without food                                    | On an empty stomach                                 | With or without food            |
| Other considerations      | Dosing schedule (week off)<br>Echocardiogram monitoring | Requires refrigeration<br>Echocardiogram monitoring | Echocardiogram monitoring       |
| Total pill burden (daily) | 11  | 5   | 12                              |

*Note.* Information from Array Biopharma Inc. (2018a, 2018b); Genentech Inc. (2018, 2020); Novartis Pharmaceuticals Corporation (2021a, 2021b).

treatment of *BRAF* V600 mutation-positive unresectable or metastatic melanoma. However, there are clinical and practical considerations for each treatment regimen that can help guide treatment selection (Table 2). Vemurafenib plus cobimetinib has a higher incidence of skin toxicities, particularly photosensitivity, compared with the other combinations, and cobimetinib is taken on days 1 through 21 of a 28-day cycle as opposed to a continuous schedule, which requires patients be able to manage this dosing schedule (Genentech Inc., 2018, 2020). Dabrafenib plus trametinib should be taken on an empty stomach 1 hour before or 2 hours after a meal, and trametinib should be stored in the refrigerator, both of which can be inconvenient and difficult to remember for patients. Dabrafenib plus trametinib has a higher incidence of pyrexia compared with the other combination regimens (Novartis Pharmaceuticals Corporation, 2021a, 2021b). Encorafenib plus binimetinib can be taken with or without food but have a higher pill burden than the other combinations. All three combination regimens require cardiac monitoring with routine echocardiograms per the package inserts; encorafenib plus binimetinib and vemurafenib plus cobimetinib also require routine electrocardiograms (Array Biopharma Inc., 2018a, 2018b; Genentech Inc., 2018, 2020). Patient characteristics and preferences should be considered

when determining the most appropriate treatment regimen.

## SUMMARY AND FUTURE DIRECTIONS

The treatment landscape for melanoma has evolved extensively over the past decade. The introduction of BRAF and MEK inhibitors has led to improved outcomes in patients with unresectable or metastatic melanoma. The combination of encorafenib plus binimetinib has been shown to improve PFS and OS and is relatively well-tolerated in patients. No head-to-head studies comparing BRAF plus MEK inhibitor combination regimens exist, and there is no current preferred combination regimen. Ongoing clinical trials are evaluating the role of BRAF plus MEK inhibitors in patients who previously received BRAF inhibitor monotherapy in the setting of disease progression with an alternative BRAF plus MEK inhibitor combination regimen, and in regards to sequencing with immunotherapy (NCCN, 2021). ●

## Disclosure

Dr. Davis has served on advisory boards for Array BioPharma, Exelixis, Inc., and Sanofi-Genzyme/Regeneron Pharmaceuticals, and on a speakers bureau for Exelixis, Inc. Dr. Wayman has no conflicts of interest to disclose.

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