Research Review™
PRODUCT REVIEW

Encorafenib (BRAFTOVI®) plus binimetinib (MEKTOVI®) in patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation

Making Education Easy 2020

Independent commentary by Associate Professor Andrew Haydon

Associate Professor Andrew Haydon is a full-time Medical Oncologist at the Alfred Hospital and a member of the Victorian Melanoma Service, having joined the service in 2001. He is also an Adjunct Senior Lecturer at the Department of Epidemiology and Preventive Medicine, Monash University and an Honorary Associate and Member of the NHMRC Clinical Trials Centre, School of Public Health, University of Sydney. Andrew completed his PhD at Monash University/Cancer council Victoria in 2004. Over the last 18 years, he has been the principle investigator for over 30 international clinical trials that he has run at the Alfred Hospital for patients with advanced melanoma, with many of these studies leading to major changes in the treatment of this disease. Dr Haydon has authored or co-authored over 60 peer reviewed journal publications and has given numerous local and international presentations on the management of metastatic melanoma.

Abbreviations used in this issue:

AE(s) = adverse event(s)
AJCC = American Joint Committee on Cancer
BICR = blinded independent central review
CI = confidence interval
CYP = cytochrome P450
DOR = duration of response
ECOG = Eastern Cooperative Oncology Group
HR = hazard ratio
IC_{50} = half maximal inhibitory concentration
ILD =interstitial lung disease
LDH = lactate dehydrogenase
MAPK = mitogen-activated protein kinase
MEK = mitogen-activated extracellular signal regulated kinase
ORR = overall response rate
OS = overall survival
PFS = progression-free survival
P-gp = P-glycoprotein
TGA = Therapeutic Goods Administration
RVO = retinal vein occlusion

This review discusses the evidence in support of the combination of encorafenib (BRAFTOVI®) and binimetinib (MEKTOVI®) for the treatment of adult patients with unresectable or metastatic melanoma with a *BRAF* V600E or *BRAF* V600K mutation, as detected by a validated test. The pharmacology of encorafenib and binimetinib, including their mechanism of action, are outlined, along with the efficacy and tolerability outcomes from the open-label, phase 3 COLUMBUS trial.

Introduction

Cutaneous melanoma arises from the genetic mutations of melanocytes that reside in the epidermal layer of the skin and it represents the most aggressive and the deadliest form of skin cancer due to its propensity to metastasise to vital organs, including the brain, lungs, liver and other visceral organs.[1, 2]

Australia has one of the highest incidences of melanoma in the world.[3] Melanoma is the third most common cancer in Australia for both men and women, and it is the second highest cancer diagnosed in Australians aged 25-49 years.[4] It was estimated that there would be 15,229 diagnoses of melanoma of the skin, and 1,726 deaths from this disease, in Australia in 2019.[4]

BRAF is a key serine-threonine kinase from the mitogen-activated protein kinase (MAPK) signalling pathway, with approximately 50% of all melanomas harbouring a *BRAF* mutation.[5] The most common *BRAF* mutation occurs at amino acid 600, in which the normal valine is substituted, by glutamic acid (*BRAF* V600E), or less commonly, by lysine (*BRAF* V600K).[5, 6] These mutations constitutively activate the BRAF protein and downstream signal transduction in the MAPK pathway, and consequently signal for cancer cell proliferation and survival.[5]

The introduction of the BRAF inhibitors vemurafenib (in 2011)[7] and dabrafenib (in 2012)[8] resulted in significant improvements in progression-free survival (PFS) and overall survival (OS) compared with the standard treatment at that time. However, response durations were short lived due to acquired resistance to these agents.[7-9] Moreover, BRAF inhibitor treatment was associated with the development of squamous cell skin cancer and other skin toxicities related to paradoxical activation of the MAPK pathway.[10, 11] Subsequent clinical trials in patients with *BRAF* V600-mutant melanoma demonstrated that targeting the MAPK pathway with the combination of a BRAF inhibitor plus a MEK inhibitor, rather than with a BRAF inhibitor alone, improved efficacy and was associated with fewer paradoxical MAPK activation-related adverse effects.[12-14] BRAF/MEK inhibitor combinations are now recommended in United States and European guidelines as treatments for patients with advanced *BRAF*-mutant melanoma.[2, 15]

The first BRAF/MEK inhibitor combinations to be approved for use were dabrafenib plus trametinib[16] and vemurafenib plus cobimetinib.[17] Another combination (encorafenib plus binimetinib) has recently been approved based on the initial outcomes from a phase 3 clinical trial (COLUMBUS).[18, 19] An updated efficacy and safety landmark analysis of the COLUMBUS trial has also been published more recently.[20] This review outlines the main efficacy and tolerability endpoints from this trial, as well as reviewing the pharmacological properties of this combination.[21, 22]

Focus on encorafenib and binimetinib

The combination of encorafenib (BRAFTOVI®), an ATP-competitive BRAF inhibitor, plus binimetinib (MEKTOVI®), a MEK inhibitor, is approved for the treatment of adult patients with unresectable or metastatic melanoma with a *BRAF* V600E or V600K mutation (as detected by a validated test) by the Australian Therapeutic Goods Administration (TGA).[21, 22]

Dosage and administration

Full details of dosage and administration of encorafenib (BRAFTOVI®, Product Information) and binimetinib (MEKTOVI®, Product Information) can be found in the respective Product Information of each agent.[21, 22]

The recommended dose of encorafenib is 450 mg once daily when used in combination with binimetinib.[21] The recommended dose of binimetinib is 45 mg twice daily, to be administered approximately 12 hours apart, when used in combination with encorafenib.[22]

Patients must have their *BRAF* V600-mutant melanoma status confirmed by a validated test before encorafenib in combination with binimetinib is initiated.[21, 22] Encorafenib should not be used in patients with wild-type *BRAF* malignant melanoma.[21]

Both drugs should be swallowed whole with water, with or without food.[21, 22] Treatment should continue until the patient no longer derives benefit or unacceptable toxicity develops.[21, 22]

The management of adverse reactions may require dose reduction, temporary interruption or treatment discontinuation.[21, 22] Full details of dose modifications are available in the Product Information of each drug.[21, 22]

Administration of encorafenib at a dose of 450 mg once daily as a single agent is not recommended.[21]

If binimetinib is temporarily interrupted, encorafenib should be reduced to 300 mg once daily during the time of binimetinib dose interruption, as encorafenib is not well-tolerated at the dose of 450 mg as a single agent.[21, 22] If binimetinib is permanently discontinued, encorafenib may be continued (at the reduced dose of 300 mg) depending on the individual clinical benefit.[21, 22] If encorafenib is temporarily interrupted, binimetinib should be interrupted.[21, 22] If encorafenib is permanently discontinued, then binimetinib should be discontinued.[21, 22]

Contraindications

Encorafenib is contraindicated in patients with hypersensitivity to encorafenib or to any of the excipients.[21] Binimetinib is contraindicated in patients with hypersensitivity to binimetinib or to any of the excipients.[22]

Warnings and precautions

- The Product Information for encorafenib and for binimetinib includes a number of warnings and precautions which are summarised below.[21, 22] For additional information on warnings and precautions, the respective Product Information should be consulted.[21, 22]
- Before taking binimetinib plus encorafenib, patients must have their *BRAF* V600-mutant melanoma status confirmed by a validated test to minimise false-positive and false-negative determinations.[21, 22] Binimetinib plus encorafenib should not be used in patients with wild-type *BRAF* malignant melanoma.[21, 22]
- Limited data on the use of the combination of encorafenib plus binimetinib in patients who previously progressed on a prior BRAF inhibitor treatment for unresectable or metastatic melanoma with a *BRAF* V600 mutation indicate that the efficacy of the combination would be lower in these patients.[21, 22]
- There are limited efficacy data on the use of the combination of encorafenib plus binimetinib in patients with a *BRAF* V600-mutant melanoma with brain metastases.[21, 22]
- Left ventricular dysfunction, defined as symptomatic or asymptomatic decreases in ejection fraction, has been reported when encorafenib is used in combination with binimetinib.[21] The Product Information for encorafenib and binimetinib recommends that the left ventricular ejection fraction is assessed by an echocardiogram or a multi-gated acquisition scan before initiating treatment, 1 month after initiating treatment, and then approximately every 3 months, or more frequently as clinically indicated during treatment.[21]
- Haemorrhages, including major haemorrhagic events, can occur when encorafenib is administered in combination with binimetinib.[21, 22] The risk of haemorrhage may be increased with the concomitant use of anticoagulant or antiplatelet therapy.[21, 22]
- Ocular toxicities, including uveitis, iritis and iridocyclitis, can occur when encorafenib is administered in combination with binimetinib.[21, 22] Retinal pigment epithelial detachment has been reported in patients treated with encorafenib combined with binimetinib, and retinal vein occlusion (RVO) can occur when binimetinib is administered.[21, 22] Binimetinib is not recommended in patients with a history of RVO.[22] The Product Information for encorafenib and for binimetinib recommends that patients should be assessed for symptoms of new or worsening visual disturbances at each visit, and an ophthalmologic examination is recommended in patients with new or worsening visual disturbances.[21, 22]
- QT prolongation has been observed in patients treated with BRAF inhibitors.[21] Patients should be monitored and managed in regard to QTc prolongation according to the Product Information for encorafenib.[21,22]
- New primary malignancies, both cutaneous and non-cutaneous, have been reported in patients who received BRAF inhibitors, and can occur with encorafenib when used alone or in combination with binimetinib.[21, 22] Patients should be monitored for malignancies and dermatologic evaluations should be performed prior to treatment, while on therapy, and following discontinuation of treatment.[21, 22]
- Liver function abnormalities (e.g. aspartate aminotransferase, alanine aminotransferase elevations) can occur with either encorafenib or binimetinib.[21, 22] Liver function tests should be performed prior to initiating treatment, and at least monthly for the first 6 months of treatment, then as clinically indicated.[21,22]
- Creatinine elevation has been commonly reported with encorafenib as a single agent or in combination with binimetinib.[21, 22] Encorafenib should be used with caution in patients with severe renal impairment.[21, 22]

Mechanism of action

Encorafenib is a potent and selective ATP-competitive small molecule RAF kinase inhibitor.[21, 23] The half maximal inhibitory concentration (IC_{50}) of encorafenib against *BRAF* V600E, BRAF and CRAF enzymes was 0.35, 0.47 and 0.30 nM, respectively.[21] In *in vitro* and *in vivo* studies, encorafenib inhibited *BRAF* V600E-, D- and K-mutant melanoma cell growth.[21, 24] Encorafenib did not inhibit RAF/MEK/ERK signalling in cells expressing wild-type *BRAF*.[21]

In preclinical studies, encorafenib has a longer on-target dissociation half-life (>30 hours) than dabrafenib (2 hours) or vemurafenib (0.5 hours).[24] Encorafenib also displayed stronger inhibition of proliferation compared with dabrafenib or vemurafenib in *BRAF* V600-mutant cell lines.[24] These pharmacological properties suggest that the sustained target inhibition and higher potency associated with encorafenib may translate into greater clinical efficacy. *In vitro,* encorafenib exhibited a longer period of anti-melanoma activity without paradoxical MAPK reactivation compared with dabrafenib and vemurafenib (paradox index; 50 versus 10 and 5.5, respectively),[25] which suggests that toxicities associated with paradoxical MAPK reactivation (e.g. skin adverse events [AEs]) may occur less frequently with encorafenib.

Binimetinib is an ATP-uncompetitive reversible inhibitor of MEK1 and MEK2 activation.[22] The IC_{50} of binimetinib against MEK1 and MEK2 in a cell-free system was 12-46 nM.[22] In *in vitro* and *in vivo* studies, binimetinib has demonstrated activity against MEK1 and MEK2 enzymes and possesses anti-proliferative activity.[26, 27]

Pharmacokinetics

The pharmacokinetics of encorafenib and binimetinib have been studied in healthy subjects and patients with solid tumours, including advanced and unresectable or metastatic cutaneous melanoma.[21, 22, 24]

The pharmacokinetics of encorafenib and binimetinib are approximately dose linear.[21, 22] Steady-state conditions of both drugs are reached within 15 days.[21, 22] The main pharmacokinetic parameters of these two drugs are shown in **Table 1**.

Absorption

Both drugs are rapidly absorbed after oral administration (**Table 1**).[21, 22] Drug exposure (assessed according to area under the concentration-time curve) of either drug was not altered when administered with a high-fat, high-calorie meal.[21, 22]

Distribution

In vitro studies indicated that encorafenib is moderately (86.1%) bound to human plasma proteins,[21] while binimetinib is 97.2% bound to human plasma proteins.[22]

Metabolism

Both encorafenib and binimetinib are mainly cleared by metabolism.[21, 22] The metabolism of encorafenib involves cytochrome P450 (CYP)3A4, CYP2C19 and CYP2D6. The predominant biotransformation reaction of encorafenib was N-dealkylation.[21] Binimetinib is primarily metabolised by UGT1A1-mediated and UGT2B7-mediated glucuronidation and to a lesser extent by CYP1A2-and CYP2C19-mediated oxidation.[22]

Excretion

Both encorafenib and binimetinib are eliminated in the faeces and urine.[21, 22] Encorafenib was eliminated equally through both routes, while approximately 62% of the binimetinib was eliminated in the faeces, and 31% in the urine.[21, 22]

The terminal half-life of encorafenib and binimetinib is approximately 6 hours and 9 hours respectively (**Table 1**).[21, 22] Only a small fraction of each of the active drugs (<2% of encorafenib and <7% of binimetinib) is excreted in the urine.[21, 22]

Table 1. **Pharmacokinetic parameters of encorafenib and binimetinib**[21,22]

Mean values unless otherwise stated	Encorafenib	Binimetinib
Median T_{max} (h)	1.5-2	1.5
Median $T_{1/2}$ (h)	6.32	8.66
Vz/F (L)	226	374
CL/F (L/h)	27.9	28.2

CI/F = apparent clearance; **h** = hours; **L** = litres; $\mathbf{T_{max}}$ = time to maximum plasma concentration; $\mathbf{T_{1/2}}$ = terminal half-life; **Vz/F** = volume of distribution.

Special patient populations

Since both encorafenib and binimetinib are primarily metabolised and eliminated via the liver, patients with hepatic impairment may have increased drug exposure.[21,22]

A reduced dose of 300 mg encorafenib once daily is advised in mild hepatic impairment (Child-Pugh Class A),[21] and the combination is not recommended in patients with moderate (Child-Pugh Class B) or severe hepatic impairment (Child-Pugh Class C).[21,22]

No dose adjustment of encorafenib or binimetinib is required for patients with mild or moderate renal impairment.[18] There have been no clinical studies with encorafenib in patients with severe renal impairment.[21]

Drug interaction profile

The respective Product Information of encorafenib and binimetinib should be consulted for full information about drug interactions.[21,22]

Since the metabolism of encorafenib involves CYP3A4, CYP2C19 and CYP2D6, there is potential for drug interactions to occur.[21] Since binimetinib is metabolised by multiple enzymes, the possible extent of drug interactions mediated by UGT1A1, UGT2B7, CYP1A2 or CYP2C19 is minimal and unlikely to be clinically relevant.[22]

Concomitant administration of encorafenib with strong CYP3A4 inhibitors (e.g. ritonavir, itraconazole, clarithromycin, telithromycin, posaconazole and grapefruit juice) should be avoided (due to increased encorafenib exposure and a potential increase in toxicity).[21] Caution is required if encorafenib is co-administered with moderate CYP3A4 inhibitors (e.g. amiodarone, erythromycin, fluconazole, diltiazem, amprenavir and imatinib).[21]

A reduction in encorafenib exposure is likely to occur if co-administered with CYP3A4 inducers (carbamazepine, rifampicin, phenytoin and St John's Wort).[21] Alternative agents with no or minimal CYP3A induction should be considered.[21]

Encorafenib is a substrate of P-glycoprotein (P-gp), and because of the predicted high intestinal permeability of orally administered encorafenib, distribution into the central nervous system may be increased by P-gp inhibitors.[21]

Since encorafenib is both an inhibitor and inducer of CYP3A4, co-administration of encorafenib and agents that are substrates of CYP3A4 (e.g. hormonal contraceptives) should proceed with caution.[21] Since encorafenib is an inhibitor of UGT1A1, agents that are substrates of UGT1A1 should be also be co-administered with caution.[21]

Tolerability

The most common adverse events (AEs) of any grade reported in patients receiving combination therapy with encorafenib plus binimetinib were nausea, diarrhoea, vomiting, fatigue, arthralgia, increased blood creatine phosphokinase, headache and constipation.[18-20] The most common grade 3-4 AEs seen in >5% of patients treated with encorafenib plus binimetinib was increased blood creatine phosphokinase (7.8%).[20] Further details of the AE profile of encorafenib plus binimetinib as demonstrated in the COLUMBUS trial are outlined in the Key clinical trials section.

RESEARCH REVIEW™
Australia's Leader in Specialist Publications

Key clinical trials

Encorafenib plus binimetinib versus vemurafenib or encorafenib in patients with *BRAF*-mutant melanoma (COLUMBUS): a multicentre, open-label, randomised phase 3 trial

Authors: Dummer R, Ascierto PA, Gogas HJ, et al. Cut-off 19 May, 2016; primary endpoint (PFS) analysis.[18]

Dummer R, Ascierto PA, Gogas HJ, et al. Cut-off 7 November, 2017; interim OS analysis.[19]

Ascierto PA, Dummer R, Gogas HJ, et al. Cut-off date 19 November, 2018; landmark analysis.[20]

Data have also been obtained from the encorafenib and binimetinib Product Information.[21,22]

Methods: The efficacy and tolerability of encorafenib co-administered with binimetinib were evaluated in a two-part, phase 3, randomised active-controlled, open-label, multicentre trial COLUMBUS in patients with unresectable or metastatic melanoma. The trial was conducted at 162 hospitals in 28 countries (ClinicalTrials.gov, number NCT01909453, and EudraCT, number 2013-001176-38).

Eligible patients were aged 18 years or older and were required to have histologically confirmed locally advanced (American Joint Committee on Cancer [AJCC] stage IIIB, IIIC, or IV), unresectable or metastatic cutaneous melanoma, or unknown primary melanoma; a *BRAF* V600E or *BRAF* V600K mutation; an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; and were treatment naive or had progressed on or after previous first-line immunotherapy. Prior treatment with BRAF/MEK inhibitors was not allowed.

In part 1 of this study, patients were randomised (1:1:1) via interactive response technology to oral encorafenib 450 mg once daily plus oral binimetinib 45 mg twice daily, oral encorafenib 300 mg once daily, or oral vemurafenib 960 mg twice daily. Randomisation was stratified by the AJCC stage, ECOG performance status, and *BRAF* mutation status. Treatment continued until disease progression, unacceptable toxicity, or withdrawal of consent.

The primary efficacy endpoint was PFS in the encorafenib plus binimetinib versus vemurafenib groups, assessed by blinded independent central review (BICR). Secondary endpoints included OS, overall response rate (ORR) and duration of response (DOR).

Results: A total of 577 patients were randomly assigned to receive encorafenib plus binimetinib (n=192), encorafenib (n=194), or vemurafenib (n=191) between 30 December 2013 and 10 April 2015.[18] The data cut-off date for analyses of the primary endpoint (PFS) was 19 May 2016.[18] The data cut-off date for the analysis of OS was 7 November 2017.[19]

The median age of patients was 56 years (range 20 to 89 years), 58% were male, 90% were Caucasian, and 72% of patients had baseline ECOG performance status of 0.[18,21,22] Most patients had metastatic disease (95%) and were Stage IVM1c (64%), 27% of patients had elevated baseline serum lactate dehydrogenase (LDH), 45% of patients had three or more organs with tumour involvement at baseline, and 3.5% had brain metastases.[18,21,22] Most patients were *BRAF* V600E-mutant positive (89%) and 11% were *BRAF* V600K-mutant positive.[18]

At the cut-off date 19 May 2016 (median follow-up 16.6 months), median PFS was 14.9 months with encorafenib plus binimetinib and 7.3 months with vemurafenib (hazard ratio [HR] 0.54; 95% confidence interval [CI] 0.41, 0.71; 2-sided p<0.0001; **Table 2**).[18,21,22]

At the updated landmark analysis (cut-off date 19 November 2018; median follow-up 48.8 months), median PFS remained longer with encorafenib plus binimetinib at 14.9 months versus vemurafenib at 7.3 months (HR 0.51; 95% CI 0.39, 0.67; no p-value stated; **Figure 1**).[20] A total of 36 patients (19%) were continuing to receive encorafenib plus binimetinib, 20 patients (10%) were continuing to receive encorafenib alone, and 9 patients (5%) were continuing to receive vemurafenib alone.[20]

Table 2. **Efficacy endpoints in the COLUMBUS trial (cut-off date 19 May 2016; initial analysis and 19 November 2018; landmark analysis). Endpoints assessed by blinded independent central review.**[18-22]

	Encorafenib plus binimetinib (n=192)	Encorafenib (n=194)	Vemurafenib (n=191)
Median PFS, months (95% CI)			
Initial analysis	14.9 (11.0, 18.5)	9.6 (7.5, 14.8)	7.3 (5.6, 8.2)
Landmark analysis	14.9 (11.0, 20.2)	9.6 (7.4, 14.8)	7.3 (5.6, 7.9)
Overall response rate, n (% patients)			
Initial analysis	121 (63.0)	98 (50.5)	77 (40.3)
Landmark analysis	122 (63.5)	100 (51.5)	78 (40.8)
Duration of response, months (95% CI)			
Initial analysis	16.6 (12.2, 20.4)	14.9 (11.1, NE)	12.3 (6.9, 16.9)
Landmark analysis	18.6 (12.7, 24.1)	15.5 (11.1, 28.6)	12.3 (6.9, 14.5)

CI = confidence interval; **NE** = not estimable; **PFS** = progression-free survival.

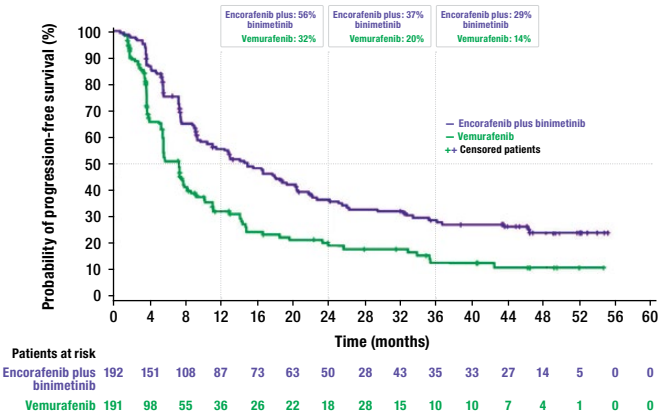

Figure 1. Kaplan-Meier curves of progression-free survival for encorafenib plus binimetinib versus vemurafenib (landmark analysis).[20] Response was assessed by blinded independent central review.[20]
Graph modified from Ascierto PA, et al. Eur J Cancer. 2020;126:33-44. **CI** = confidence interval; **HR**, hazard ratio.

In the interim OS analysis, encorafenib plus binimetinib achieved a median OS of 33.6 months compared with 16.9 months for vemurafenib (HR 0.61; 95% CI 0.47, 0.79; two-sided p<0.0001).[19] In the updated landmark analysis, median OS rates remained consistent – median OS was 33.6 months for encorafenib plus binimetinib compared to 16.9 months for vemurafenib (HR 0.61; 95% CI 0.48, 0.79; no p-value stated; **Table 3; Figure 2**).[20] Compared with vemurafenib, combination therapy with encorafenib plus binimetinib decreased the risk of death by 39% (HR 0.61; 95% CI 0.48, 0.79).[20]

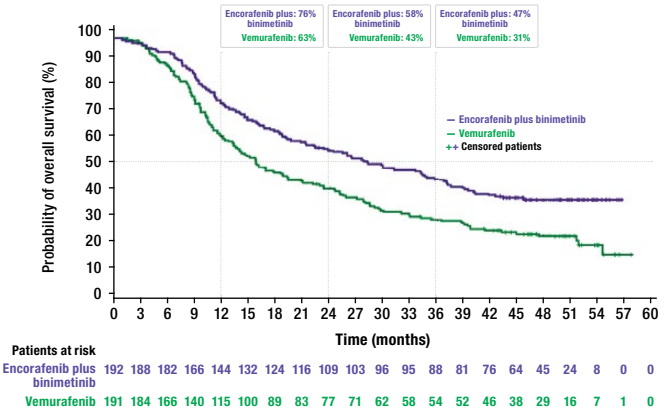

Figure 2. Kaplan-Meier curves of overall survival for encorafenib plus binimetinib versus vemurafenib (landmark analysis).[20] Response was assessed by blinded independent central review.[20]

Table 3. **Survival outcomes in the COLUMBUS trial (cut-off date 19 November 2018); assessed by blinded independent central review**[19-22]

	Encorafenib plus binimetinib (n=192)	Encorafenib (n=194)	Vemurafenib (n=191)
Median OS, months (95% CI)	33.6 (24.4, 39.2)	23.5 (19.6, 33.6)	16.9 (14.0, 24.5)
12-month survival, % patients	76	75	63
24-month survival, % patients	58	49	43
36-month survival, % patients	47	41	31

AEs occurring at an incidence of ≥20% (all grades) with combination therapy reported at the landmark analysis of the phase 3 COLUMBUS trial are shown in **Table 4.**[20] The most common adverse reactions in patients receiving encorafenib plus binimetinib combination therapy were nausea, diarrhoea, vomiting, fatigue, arthralgia, increased blood creatine phosphokinase, headache and constipation.[18-20]

AEs led to discontinuation in 16%, 15% and 17% of patients, and dose reduction/interruption in 55%, 71% and 62% of patients in the encorafenib plus binimetinib, encorafenib and vemurafenib groups, respectively.[20]

AEs that were reported in fewer patients treated with encorafenib plus binimetinib combination therapy than vemurafenib alone (with a difference in proportion of ≥6%) were toxic effects to the skin (including alopecia, photosensitivity, keratosis pilaris, rash, hyperkeratosis, palmoplantar keratoderma, dry skin, palmar-plantar erythrodysaesthesia syndrome), arthralgia, pyrexia and decreased appetite.[20]

At the landmark analysis, the safety profile of encorafenib plus binimetinib combination therapy with encorafenib plus binimetinib was consistent with that in previous reports of the COLUMBUS study.[18-20] No new safety concerns were reported, and patients who remained on combination treatment for at least 24 months had a reduced burden of toxicity in the later years.[2]

Table 4. **Adverse events (≥20% of recipients of combination therapy) reported at the landmark analysis of the phase 3 randomised, active-controlled, open-label, multicentre COLUMBUS trial in patients with unresectable or metastatic *BRAF* V600E- or V600K-mutant melanoma**[20]

% patients	Encorafenib plus binimetinib (n=192)		Encorafenib (n=192)		Vemurafenib (n=186)	
	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4
Total adverse events	98	68	100	68	100	66
Nausea	44	2	39	4	35	2
Diarrhoea	39	3	15	2	34	2
Vomiting	32	2	29	5	16	1
Fatigue	30	2	26	1	31	2
Arthralgia	29	1	45	9	46	6
Increased blood creatinine kinase	26	8	1	0	2	0
Headache	26	2	29	3	20	1
Constipation	25	0	16	0	7	1
Asthenia	22	2	22	3	19	4
Pyrexia	20	4	17	1	29	0

Expert comment

The COLUMBUS study is the fourth international phase 3 study to show the superiority of combination BRAF inhibition plus MEK inhibition over single agent BRAF inhibition in metastatic *BRAF* V600-mutant melanoma. Both the PFS and OS were significantly longer with encorafenib plus binimetinib compared with vemurafenib, and the median survivals (PFS and OS) were the longest reported of all the phase 3 studies comparing combination BRAF inhibition/MEK inhibition to single agent BRAF inhibition. In COLUMBUS, the combination of encorafenib plus binimetinib also demonstrated superiority to vemurafenib, with significantly higher response rates and longer response durations.[18-20] The combination of encorafenib plus binimetinib demonstrates low rates of grade 3/4 pyrexia (which is seen commonly with dabrafenib and trametinib) and any grade of photosensitivity (which occurs frequently with vemurafenib and cobimetinib), which combined with the COLUMBUS efficacy data make it an attractive combination.

Take home messages

- The combination of encorafenib (BRAFTOVI®), a BRAF inhibitor, plus binimetinib (MEKTOVI®), a MEK inhibitor, is approved for the treatment of adult patients with unresectable or metastatic melanoma with a *BRAF* V600E or V600K mutation.
- The clinical activity and safety of encorafenib plus binimetinib were demonstrated in the large randomised COLUMBUS trial.
- In the COLUMBUS trial, patients treated with encorafenib plus binimetinib had longer PFS and OS than those treated with vemurafenib.
- In the COLUMBUS trial, encorafenib plus binimetinib had a manageable safety profile, and patients who remained on treatment for at least two years had a decreased burden of toxicity over time.

Expert's concluding remarks

The COLUMBUS study has clearly demonstrated the superiority of encorafenib plus binimetinib over single-agent vemurafenib, and has established this combination as a standard of care for the treatment of *BRAF* V600-mutant melanoma with targeted therapy. The median OS and PFS for this combination were both approximately double that of vemurafenib, with the combination having a manageable safety profile.

References

1. Schadendorf D, van Akkooi ACJ, Berking C, et al. Melanoma. Lancet. 2018;392:971-84.
2. Garbe C, Peris K, Hauschild A, et al. Diagnosis and treatment of melanoma. European consensus-based interdisciplinary guideline - Update 2016. Eur J Cancer. 2016;63:201-17.
3. Karimkhani C, Green AC, Nijsten T, et al. The global burden of melanoma: results from the Global Burden of Disease Study 2015. Br J Dermatol. 2017;177:134-40.
4. Australian Institute of Health and Welfare. Cancer in Australia: 2019. https://www.aihw.gov.au/getmedia/8c9fcf52-0055-41a0-96d9-f81b0feb98cf/aihw-can-123.pdf.aspx?inline=true. Accessed August 20, 2020.
5. Ascierto PA, Kirkwood JM, Grob JJ, et al. The role of *BRAF* V600 mutation in melanoma. J Transl Med. 2012;10:85.
6. Lyle M, Haydu LE, Menzies AM, et al. The molecular profile of metastatic melanoma in Australia. Pathology. 2016;48:188-93.
7. Chapman PB, Hauschild A, Robert C, et al. Improved survival with vemurafenib in melanoma with *BRAF* V600E mutation. N Engl J Med. 2011;364:2507-16.
8. Hauschild A, Grob JJ, Demidov LV, et al. Dabrafenib in *BRAF*-mutated metastatic melanoma: a multicentre, open-label, phase 3 randomised controlled trial. Lancet. 2012;380:358-65.
9. Poulikakos PI, Zhang C, Bollag G, et al. RAF inhibitors transactivate RAF dimers and ERK signalling in cells with wild-type BRAF. Nature. 2010;464:427-30.
10. Dummer R, Rinderknecht J, Goldinger SM. Ultraviolet A and photosensitivity during vemurafenib therapy. N Engl J Med. 2012;366:480-1.
11. Rinderknecht JD, Goldinger SM, Rozati S, et al. RASopathic skin eruptions during vemurafenib therapy. PLoS One. 2013;8:e58721.
12. Robert C, Karaszewska B, Schachter J, et al. Improved overall survival in melanoma with combined dabrafenib and trametinib. N Engl J Med. 2015;372:30-9.
13. Larkin J, Ascierto PA, Dreno B, et al. Combined vemurafenib and cobimetinib in *BRAF*-mutated melanoma. N Engl J Med. 2014;371:1867-76.
14. Long GV, Stroyakovskiy D, Gogas H, et al. Combined BRAF and MEK inhibition versus BRAF inhibition alone in melanoma. N Engl J Med. 2014;371:1877-88.
15. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology, Cutaneous Melanoma. Upper Dublin Township, PA, USA: National Comprehensive Cancer Network; 2019.
16. NOVARTIS Pharmaceuticals Australia Pty Limited. TAFINLAR® (dabrafenib) capsules - Australian product information. Revised 2 December 2019. https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2013-PI-02126-1&d=201911061016933. Accessed August 20, 2020.
17. Roche Products Pty Limited. Zelboraf® (vemurafenib) - Australian product information. Revised 25 March 2020. https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2012-PI-01949-3&d=202009081016933. Accessed August 20, 2020.
18. Dummer R, Ascierto PA, Gogas HJ, et al. Encorafenib plus binimetinib versus vemurafenib or encorafenib in patients with *BRAF*-mutant melanoma (COLUMBUS): a multicentre, open-label, randomised phase 3 trial. Lancet Oncol. 2018;19:603-15.
19. Dummer R, Ascierto PA, Gogas HJ, et al. Overall survival in patients with *BRAF*-mutant melanoma receiving encorafenib plus binimetinib versus vemurafenib or encorafenib (COLUMBUS): a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol. 2018;19:1315-27.
20. Ascierto PA, Dummer R, Gogas HJ, et al. Update on tolerability and overall survival in COLUMBUS: landmark analysis of a randomised phase 3 trial of encorafenib plus binimetinib vs vemurafenib or encorafenib in patients with *BRAF* V600-mutant melanoma. Eur J Cancer. 2020;126:33-44.
21. Pierre Fabre Australia Pty Limited. BRAFTOVI® (encorafenib) capsules - Australian product information. Revised 1 August 2019. https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2019-PI-01022-1&d=201910311016933. Accessed August 20, 2020.
22. Pierre Fabre Australia Pty Limited. MEKTOVI® (binimetinib) film-coated tablets - Australian product information. 3 January 2019. https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2019-PI-01021-1&d=201911011016933. Accessed August 20, 2020.
23. Holderfield M, Nagel TE, Stuart DD. Mechanism and consequences of RAF kinase activation by small-molecule inhibitors. Br J Cancer. 2014;111:640-5.
24. Delord JP, Robert C, Nyakas M, et al. Phase I dose-escalation and -expansion study of the BRAF inhibitor encorafenib (LGX818) in metastatic *BRAF*-mutant melanoma. Clin Cancer Res. 2017;23:5339-48.
25. Adelmann CH, Ching G, Du L, et al. Comparative profiles of BRAF inhibitors: the paradox index as a predictor of clinical toxicity. Oncotarget. 2016;7:30453-60.
26. Petit V, Raymond J, Alberti C, et al. C57BL/6 congenic mouse NRAS(Q61K) melanoma cell lines are highly sensitive to the combination of Mek and Akt inhibitors in vitro and in vivo. Pigment Cell Melanoma Res. 2019;32:829-41.
27. Lee PA, Wallace E, Marlow A, et al. Preclinical development of ARRY-162, a potent and selective MEK 1/2 inhibitor. Cancer Res. 2010;70:abstract 2515.

BRAFTOVI and MEKTOVI PBS Information:
Authority required (STREAMLINED). Refer to PBS Schedule for full authority information.

Company Commissioned Article

This publication has been commissioned by Pierre Fabre Australia Pty Ltd (PFA). ABN 30 098 999 850. North Sydney NSW 2060. The content is entirely independent and based on published studies and the authors' opinion(s). It may not reflect the views of Pierre Fabre. Please review the full Product Information for BRAFTOVI® and MEKTOVI®, and also review the full Product Information for any other product mentioned in this review via the TGA website https://www.ebs.tga.gov.au before prescribing. Treatment decisions based on these data are the full responsibility of the prescribing physician. Material Prepared: September 2020.