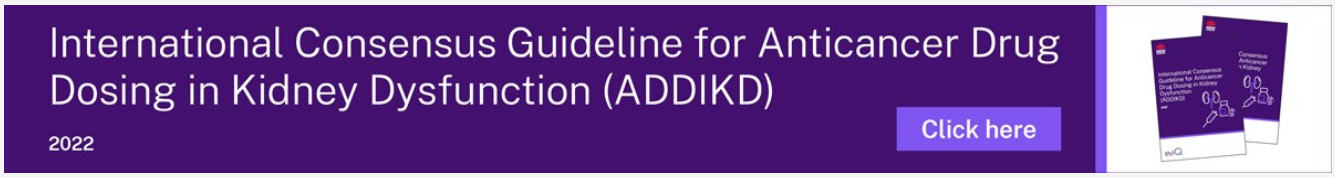
Melanoma metastatic cOBIMEtinib and vemurafenib

ID: 2037 v.2 **Endorsed**

Check for clinical trials in this patient group. Link to Australian Clinical Trials website

The anticancer drug(s) in this protocol may have been included in the ADDIKD guideline. Dose recommendations in kidney dysfunction have yet to be updated to align with the ADDIKD guideline. Recommendations will be updated once the individual protocol has been evaluated by the reference committee. For further information refer to the ADDIKD guideline. To assist with calculations, use the eviQ Estimated Glomerular Filtration Rate (eGFR) calculator.



Related pages:

- Melanoma metastatic daBRAFEnib and tRAMEtinib
- Melanoma metastatic biNIMEtinib and encorafenib

Treatment schedule - Overview

Cycle 1 and further cycles

Drug	Dose	Route	Day
cOBIMEtinib	60 mg ONCE a day	PO	1 to 21
Vemurafenib	960 mg TWICE a day *	PO	1 to 28

*It is the consensus of the reference committee that a starting dose of 720 mg twice a day for vemurafenib may be appropriate in select patients, with the view to increasing the dose to 960 mg twice a day if well tolerated

Frequency: 28 days

Cycles: Continuous until disease progression or unacceptable toxicity

Notes:

- Combination treatment with a BRAF inhibitor and a MEK inhibitor is preferred over single agents.[1, 2, 3]
- Clinicians should be vigilant for toxicities (especially skin toxicities) when switching from combination immunotherapy (ipilimumab-nivolumab) to vemurafenib-cobimetinib.

Drug status: Vemurafenib is PBS authority. Vemurafenib is available as a **240 mg** tablet

Cobimetinib is PBS authority: Cobimetinib is available as a **20 mg** tablet

Note: To be eligible to receive cobimetinib on the PBS, patients must also be receiving PBS-subsidised vemurafenib concomitantly.

Cost: ~ $13,480 per cycle

Treatment schedule - Detail

The supportive therapies (e.g. antiemetics, premedications, etc.), infusion times, diluents, volumes and routes of administration, if included, are listed as defaults. They may vary between institutions and can be substituted to reflect individual institutional policy.

*Antiemetics if included in the treatment schedule are based upon recommendations from national and international guidelines. These are **defaults only** and may be substituted to reflect individual institutional policy. Select here for recommended doses of alternative antiemetics.*

Cycle 1 and further cycles

Day 1 to 21		
cOBIMEtinib	60 mg (PO)	ONCE a day (3 x 20 mg tablets). Tablets can be taken with or without a meal.
Vemurafenib	960 mg (PO)	TWICE a day (4 x 240 mg tablets morning and evening 12 hours apart), at least one hour before, or at least two hours after a meal.
Day 22 to 28		
Vemurafenib	960 mg (PO)	TWICE a day (4 x 240 mg tablets morning and evening 12 hours apart), at least one hour before, or at least two hours after a meal.

*It is the consensus of the reference committee that a starting dose of 720 mg twice a day for vemurafenib may be appropriate in select patients, with the view to increasing the dose to 960 mg twice a day if well tolerated

Frequency: 28 days

Cycles: Continuous until disease progression or unacceptable toxicity

Indications and patient population

- Unresectable stage III or stage IV malignant melanoma with a BRAF V600 mutation.

Clinical information

Caution with oral anti-cancer drugs	Select links for information on the safe prescribing, dispensing and administration of orally administered anti-cancer drugs. Read more about the COSA guidelines and oral anti-cancer therapy
Hypersensitivity	Serious hypersensitivity reactions, including anaphylaxis, have been reported with vemurafenib. Read more about Hypersensitivity reaction
Emetogenicity minimal or low	No routine prophylaxis required. If patients experience nausea and/or vomiting, consider using the low emetogenic risk regimen. Read more about preventing anti-cancer therapy induced nausea and vomiting
Cardiac toxicity	Cobimetinib may be associated with a reduction in the left ventricular ejection fraction (LVEF). Most reductions in ejection fraction are asymptomatic and occur in a low proportion of patients treated with cobimetinib. Consider baseline cardiac assessment including echocardiogram (ECHO) or multigated acquisition (MUGA) in high risk patients (e.g. history of cardiac failure) and repeat throughout treatment as clinically indicated. If LVEF dysfunction occurs, treatment interruption, dose modification or treatment discontinuation may be required. Consider review by a cardiologist. Read more about cardiac toxicity associated with anti-cancer drugs

Prolongation of QT interval	Vemurafenib may prolong the QT interval and increase the risk of cardiac arrhythmia. Patients with QTc > 500 ms should not be commenced with vemurafenib. Risk factors (e.g. electrolyte abnormalities) should be corrected, where possible, prior to commencement of vemurafenib and the concurrent use of drugs that may prolong the QT interval should be avoided. In patients with cardiac comorbidities and other risk factors monitor ECG at baseline and periodically throughout treatment as clinically indicated. If QT prolongation occurs, treatment interruption, dose modification or treatment discontinuation may be required. Consider review by a cardiologist. Read more about drugs that may prolong QTc interval at crediblemeds.org (registration required).
Dermatologic toxicities	Single agent vemurafenib is associated with skin toxicities including photosensitivity, secondary cutaneous malignancies such as squamous cell carcinomas (SCC) and keratoacanthomas, dry skin, pruritus, rash and hypersensitivity reactions. When used in combination with cobimetinib, the incidence of cutaneous SCC, keratocanthomas and Bowen's disease is reduced, however the risk of photosensitivity is not altered by the addition of cobimetinib. All patients should be advised to avoid sun exposure, wear protective clothing and use a broad spectrum UVA/UVB sunscreen and lip balm (SPF 50+) when outdoors to minimise photosensitivity. Management of the adverse skin reactions may include dose reduction or interruption of vemurafenib and cobimetinib. Dermatologic evaluation prior to the initiation of therapy and while on therapy is not routinely required, but should be promptly sought if toxicities occur. Read more about the skin toxicities associated with BRAF and MEK inhibitors
Other malignancies	New primary malignant melanomas have been reported in clinical trials with BRAF inhibitors. Additionally, based on its mechanism of action, BRAF inhibitors may cause progression of cancers associated with RAS mutations (e.g. pancreatic adenocarcinoma). BRAF inhibitors should be used with caution in patients with a prior or concurrent cancer associated with a RAS mutation.
Concurrent radiation therapy	Vemurafenib appears to be radiosensitising with excess toxicity when given with concurrent radiation therapy. Both vemurafenib and cobimetinib should be withheld during radiation therapy, however concurrent stereotactic radiation therapy to brain metastases can be provided with minimal additional toxicity. Read more about how the "Combination of BRAF Inhibitors and Brain Radiotherapy in Patients With Metastatic Melanoma Shows Minimal Acute Toxicity" Rompoti et al 2013[4] Read more about how "On demand Gamma-Knife strategy can be safely combined with BRAF inhibitors for the treatment of melanoma brain metastases" Gaudy-Marqueste et al 2014[5]
Ocular toxicity	Patients should be routinely monitored for signs and symptoms of uveitis (e.g. blurred vision, photophobia, eye redness and pain) and serous retinopathy (e.g. blurred vision, loss of vision). Any visual disturbance reported on treatment should be promptly assessed by an ophthalmologist, with treatment withheld until review.
Diarrhoea	Antidiarrhoeals (e.g. loperamide) are usually prescribed with this treatment. Read more about treatment induced diarrhoea
Blood tests	FBC, EUC, eGFR and LFTs at baseline and repeat monthly during treatment or as clinically indicated.
Hepatitis B screening and prophylaxis	Screening for HBsAg and anti-HBc is NOT usually recommended for patients receiving this treatment. Screening could be considered in high risk individuals prior to initiation of treatment. Read more about hepatitis B screening and prophylaxis in cancer patients requiring cytotoxic and/or immunosuppressive therapy

Fertility, pregnancy and lactation	Cancer treatment can have harmful effects on fertility and this should be discussed with all patients of reproductive potential prior to commencing treatment. There is a risk of foetal harm in pregnant women. A pregnancy test should be considered prior to initiating treatment in females of reproductive potential if sexually active. It is important that all patients of reproductive potential use effective contraception whilst on therapy and after treatment finishes. Effective contraception methods and adequate contraception timeframe should be discussed with all patients of reproductive potential. Possibility of infant risk should be discussed with breastfeeding patients. Read more about the effect of cancer treatment on fertility

Dose modifications

Evidence for dose modifications is limited, and the recommendations made on eviQ are intended as a guide only. They are generally conservative with an emphasis on safety. Any dose modification should be based on clinical judgement, and the individual patient's situation including but not limited to treatment intent (curative vs palliative), the anti-cancer regimen (single versus combination therapy versus chemotherapy versus immunotherapy), biology of the cancer (site, size, mutations, metastases), other treatment related side effects, additional co-morbidities, performance status and patient preferences.Suggested dose modifications are based on clinical trial findings, product information, published guidelines and reference committee consensus . The dose reduction applies to each individual dose and not to the total number of days or duration of treatment cycle unless stated otherwise. Non-haematological gradings are based on Common Terminology Criteria for Adverse Events (CTCAE) unless otherwise specified. Renal and hepatic dose modifications have been standardised where possible. For more information see dosing considerations & disclaimer .

The dose recommendations in kidney dysfunction (i.e.renal impairment) displayed may not reflect those in the ADDIKD guideline and have been included for historical reference only. Recommendations will be updated once the individual protocol has been evaluated by the reference committee, with this version of the protocol then being archived. Clinicians are expected to refer to the ADDIKD guideline prior to prescribing in kidney dysfunction.
International Consensus Guideline for Anticancer Drug Dosing in Kidney Dysfunction (ADDIKD).

Note:

- Dose reductions resulting in a dose of vemurafenib below 480 mg twice daily are not recommended.
- Dose modification of cobimetinib may be independent of vemurafenib dose modification. The decision to dose reduce either or both drugs should be based on clinical assessment.
- Dose modifications or interruptions are not recommended for cutaneous squamous cell carcinoma (cuSCC).

Renal impairment	
Creatinine clearance (mL/min)	
30 to 50	No dose reductions necessary
less than 30	Limited data; use cobimetinib and vemurafenib with caution in patients with severe renal impairment

Hepatic impairment	
Hepatic dysfunction	
At baseline:	
Mild	No dose reductions necessary
Moderate	No dose reductions necessary
Severe	Limited data; use cobimetinib and vemurafenib with caution in patients with severe hepatic impairment
During treatment:	
Bilirubin , Transaminases (ALT/SPGT and AST/SGOT) , Alkaline phosphatase (ALP)	
Grade 1	Continue cobimetinib and vemurafenib at current dose

Hepatic impairment	
Grade 2 or Grade 3	Withhold cobimetinib and vemurafenib treatment until toxicity has resolved to Grade 1 or less and reduce the dose as follows: 1st occurrence: Reduce vemurafenib to 720 mg twice a day. Continue cobimetinib at current dose 2nd occurrence: Reduce vemurafenib to 480 mg twice a day. Continue cobimetinib at current dose 3rd occurrence: Cease cobimetinib and vemurafenib
Grade 4	Withhold cobimetinib and vemurafenib treatment until toxicity has resolved to Grade 1 or less and reduce the dose as follows: 1st occurrence: Reduce vemurafenib to 480 mg twice a day and reduce cobimetinib to 40 mg once a day 2nd occurrence: Cease cobimetinib and vemurafenib

QT prolongation	
QTc > 500 ms at baseline	Treatment with vemurafenib not recommended
QTc > 500 ms during treatment and change from pre-treatment value remains ≤ 60 ms	Withhold cobimetinib and vemurafenib treatment until QTc decreases to < 500 ms and reduce the dose as follows: 1st occurrence: Reduce vemurafenib dose by 240 mg both morning and night. Continue cobimetinib at current dose 2nd occurrence: Reduce vemurafenib dose by 240 mg both morning and night and continue cobimetinib at current dose (or consider cessation of cobimetinib and vemurafenib if the dose of vemurafenib has already been lowered to 480 mg twice daily) 3rd occurrence: Consider cessation of cobimetinib and vemurafenib
QTc increase meets values of both > 500 ms **and** > 60 ms change from pre-treatment values	Withhold cobimetinib and vemurafenib treatment and seek review by a cardiologist. Consider cessation of cobimetinib and vemurafenib

Left ventricular ejection fraction (LVEF) reduction	
Asymptomatic, left ventricular ejection fraction (LVEF) < 50% (or 40 – 49% and ≥ 10% absolute decrease from baseline)	Withhold cobimetinib and vemurafenib treatment and seek cardiology opinion. Once cardiac function has recovered consider continuing vemurafenib at current dose and reduce the dose of cobimetinib as follows with close monitoring: 1st occurrence: Reduce cobimetinib to 40 mg once a day 2nd occurrence: Reduce cobimetinib to 20 mg once a day 3rd occurrence: Cease cobimetinib. Consider continuing vemurafenib monotherapy
Symptomatic left ventricular dysfunction or if LVEF does not recover	Withhold cobimetinib and vemurafenib treatment and seek cardiology opinion. Consider cessation of cobimetinib. Once cardiac function has recovered consider continuing vemurafenib monotherapy

Photosensitivity	
Grade 1 or Grade 2 (tolerable)	Continue with cobimetinib and vemurafenib treatment. Advise thorough sun protection and symptomatic treatment
Grade 2 (intolerable) or Grade 3	Withhold cobimetinib and vemurafenib treatment until toxicity has resolved to Grade 1 or less and reduce the dose as follows: 1st occurrence: Reduce vemurafenib to 720 mg twice a day. Continue cobimetinib at current dose. 2nd occurrence: Reduce vemurafenib to 480 mg twice a day. Continue cobimetinib at current dose 3rd occurrence: Consider cessation of cobimetinib and vemurafenib
Grade 4	Consider cessation of cobimetinib and vemurafenib or withhold treatment until toxicity has resolved to Grade 1 or less and reduce the dose as follows:

Photosensitivity	
	1st occurrence: Reduce vemurafenib to 480 mg twice a day. Continue cobimetinib at current dose 2nd occurrence: Consider cessation of cobimetinib and vemurafenib.

Rash maculo-papular (link to Skin toxicities associated with BRAF inhibitors)	
Grade 1 or Grade 2 (tolerable)	Continue with cobimetinib and vemurafenib treatment. Symptomatic treatment e.g. topical corticosteroids
Grade 2 (intolerable) or Grade 3	Symptomatic treatment e.g. topical corticosteroids Withhold cobimetinib and vemurafenib treatment until toxicity has resolved to Grade 1 or less and reduce the dose as follows: 1st occurrence: Reduce vemurafenib to 720 mg twice a day. Continue cobimetinib at current dose 2nd occurrence: Reduce vemurafenib to 480 mg twice a day. Continue cobimetinib at current dose 3rd occurrence: Consider cessation of cobimetinib and vemurafenib

Rash acneiform	
Grade 1 or Grade 2 (tolerable)	Continue with cobimetinib and vemurafenib treatment. Symptomatic treatment e.g. topical corticosteroids, topical or systemic antibiotics
Grade 2 (intolerable), Grade 3 or Grade 4	Symptomatic treatment e.g. topical corticosteroids, topical or systemic antibiotics Withhold cobimetinib and vemurafenib treatment until toxicity has resolved to Grade 1 or less and reduce the dose as follows: 1st occurrence: Reduce cobimetinib to 40 mg once a day. Continue vemurafenib at current dose 2nd occurrence: Reduce cobimetinib to 20 mg once a day. Continue vemurafenib at current dose 3rd occurrence: Consider cessation of cobimetinib. Consider continuing vemurafenib monotherapy

Serous retinopathy	
Any occurrence	Prompt referral for ophthalmological review Withhold cobimetinib and vemurafenib treatment until visual symptoms have resolved to Grade 1 or less. Consider dose modification or treatment discontinuation

Interactions

The drug interactions shown below are not an exhaustive list. For a more comprehensive list and for detailed information on specific drug interactions and clinical management, please refer to the specific drug product information and the following key resources:

- *MIMS - interactions tab (includes link to a CYP-450 table) (login required)*
- *Australian Medicines Handbook (AMH) – interactions tab (login required)*
- *Micromedex Drug Interactions (login required)*
- *Cancer Drug Interactions*
- *Cytochrome P450 Drug Interactions*

For more information see References & Disclaimer.

Cobimetinib

	Interaction	Clinical management
CYP3A4 inhibitors (e.g. amiodarone, aprepitant, azole-antifungals, ritonavir, lapatinib, nilotinib, sorafenib, macrolides, ciclosporin, grapefruit juice etc.)	Increased toxicity of cobimetinib possible due to reduced clearance	Avoid combination or monitor for cobimetinib toxicity
CYP3A4 inducers (e.g. carbamazepine, phenytoin, phenobarbitone, rifampicin, St John's wort, dexamethasone etc.)	Reduced efficacy of cobimetinib possible due to increased clearance	Avoid combination or monitor for decreased clinical response to cobimetinib
CYP3A4 substrates (e.g. atorvastatin, benzodiazepines, calcineurin inhibitors, clarithromycin, dihydroergotamine, simvastatin, etc.etc.)	Reduced efficacy of these drugs possible due to induction of CYP3A4 by cobimetinib resulting in increased clearance	Avoid combination or monitor for reduced efficacy of the interacting drugs.

Vemurafenib		
	Interaction	**Clinical management**
Drugs that may prolong the QTc interval (e.g. azole antifungals, tricyclic antidepressants, antiarrhythmics etc.)	Additive effect with vemurafenib; may lead to torsades de pointes and cardiac arrest	Avoid combination or minimise additional risk factors (e.g. correct electrolyte imbalances) and monitor ECG for signs of cardiac arrhythmia
CYP3A4 and P-gp inhibitors (e.g. amiodarone, aprepitant, azole-antifungals, ritonavir, lapatinib, nilotinib, sorafenib, macrolides, cyclosporin, grapefruit juice etc.)	Increased toxicity of vemurafenib possible due to reduced clearance	Avoid combination or monitor for vemurafenib toxicity
CYP3A4 and P-gp inducers (e.g. carbamazepine, phenytoin, phenobarbitone, rifampicin, St John's wort, dexamethasone etc.)	Reduced efficacy of vemurafenib possible due to increased clearance	Avoid combination or monitor for decreased clinical response to vemurafenib
Drugs metabolised by CYP3A4 (e.g. atorvastatin, benzodiazepines, calcineurin inhibitors, clarithromycin, dihydroergotamine, simvastatin, etc.)	Reduced efficacy of these drugs possible due to induction of CYP3A4 by vemurafenib resulting in increased clearance	Avoid combination or monitor for reduced efficacy of the interacting drugs (esp. antimicrobials, anti-virals, anti-parasitics)
Drugs undergoing P-gp-mediated elimination (e.g. dabigatran, loperamide, phenytoin etc.)	Increased effects/toxicity of these drugs possible due to inhibition of P-gp by vemurafenib resulting in reduced clearance	Avoid combination or monitor for increased effect/toxicity of interacting drugs
Ipilimumab	Increased risk of hepatotoxicity	Combination not recommended outside of a clinical trial
Warfarin	Increased anticoagulant effect/increased bleeding risk; possibly due to inhibition of CYP2C9 by vemurafenib	Monitor INR regularly and adjust warfarin dosage as appropriate; consider alternative anticoagulant (e.g. LMWH, unfractionated heparin)
Nephrotoxic drugs (e.g. aminoglycosides, amphotericin, contrast dye, frusemide, NSAIDs)	Additive nephrotoxicity	Avoid combination or monitor kidney function closely

Administration

eviQ provides safe and effective instructions on how to administer cancer treatments. However, eviQ does not provide every treatment delivery option, and is unable to provide a comprehensive list of cancer treatment agents and their required IV line giving set/filter. There may be

alternative methods of treatment administration, and alternative supportive treatments that are also appropriate. Please refer to the individual product information monographs via the TGA website for further information.

Days 1 to 21 (cobimetinib)

This is an oral treatment

Safe handling and waste management (reproductive risk only)

Safe administration

General patient assessment prior to each treatment.

Any toxicity grade 2 or greater may require dose reduction, delay or omission of treatment and review by medical officer before recommencing treatment.

Pre treatment medication

Administer antiemetics if required

Treatment - Time out

Cobimetinib

- administer orally ONCE a day on **days 1 to 21**
- to be swallowed whole with a glass of water; do not crush or chew
- can be taken with or without food

Note: missed doses should not be taken if it is less than 12 hours until the next dose; if vomiting occurs after a dose, administer the next dose at the next scheduled time.

Continue safe handling precautions (reproductive risk only) for 7 days after completion of drug(s).

Days 1 to 28 (vemurafenib)

This is a continuous oral treatment

Safe handling and waste management (reproductive risk only)

Safe administration

General patient assessment prior to each treatment.

Any toxicity grade 2 or greater may require dose reduction, delay or omission of treatment and review by medical officer before recommencing treatment.

Pre treatment medication

Administer antiemetics if required

Treatment - Time out

Vemurafenib

- administer orally TWICE a day (morning and evening, approximately 12 hours apart)
- to be swallowed whole with a glass of water; do not crush or chew
- to be taken on an empty stomach, one hour before or two hours after food.

Note: If a patient misses a dose, the missed dose may be taken up to 4 hours prior to the next scheduled dose. If it is within 4 hours of the next scheduled dose, administer the next dose at the regular schedule. Both doses should not be taken at the same time. If vomiting occurs after a dose is taken, do not take an additional dose; continue with the next scheduled dose.

Continue safe handling precautions (reproductive risk only) for 7 days after completion of drug(s).

Discharge information

Cobimetinib tablets

- Cobimetinib tablets with written instructions on how to take them.

Vemurafenib tablets

- Vemurafenib tablets with written instructions on how to take them.

Antidiarrhoeals

- Antidiarrhoeals as prescribed.

Patient information

- Ensure patient receives patient information sheet.

Side effects

The side effects listed below are not a complete list of all possible side effects for this treatment. Side effects are categorised into the approximate onset of presentation and should only be used as a guide.

Early (onset days to weeks)	
Photosensitivity	Increased sensitivity to ultraviolet (UV) light resulting in an exaggerated sunburn-like reaction accompanied by stinging sensations and urticaria.
Skin rash	Anti-cancer drugs can cause a number of changes in the skin with maculo-papular rash the most common type of drug-induced skin reaction. Read more about skin rash
Diarrhoea	Read more about treatment induced diarrhoea
Fatigue	Read more about fatigue
Arthralgia and myalgia	Generalised joint pain or and/or stiffness and muscle aches, often worse upon waking or after long periods of inactivity. Can improve with movement. May be mild or severe, intermittent or constant and accompanied by inflammation. Read more about arthralgia and myalgia
Nausea and vomiting	Read more about prevention of treatment induced nausea and vomiting
Skin toxicities	Skin toxicities including secondary cutaneous malignancies, hyperkeratosis and maculo-papular rash are associated with dabrafenib, vemurafenib and encorafenib. When treatment is combined with a MEK inhibitor (trametinib, cobimetinib or binimetinib respectively), the prevalence of these toxicities is reduced. Read more about skin toxicities associated with BRAF inhibitors and MEK inhibitors
Ocular changes	Retinal vein occlusion or central serous retinopathy can occur in patients on a MEK inhibitor (trametinib, cobimetinib, binimetinib) and uveitis can occur with BRAF inhibitors (dabrafenib, vemurafenib, encorafenib).
Hepatotoxicity	Anti-cancer drugs administered either alone or in combination with other drugs and/or radiation may cause direct or indirect hepatotoxicity. Hepatic dysfunction can alter the metabolism of some drugs resulting in systemic toxicity.

Late (onset weeks to months)	
Cardiotoxicity	Cardiotoxicity may manifest as asymptomatic reduction in left ventricular ejection fraction (LVEF), arrhythmia, cardiomyopathy, hypertension, cardiac ischaemia and congestive heart failure (CHF). The risk of cardiotoxicity is increased by a number of factors, particularly a history of heart disease and electrolyte imbalances. Read more about cardiotoxicity associated with anti-cancer drugs
Alopecia - partial	Hair thinning and/or patchy hair loss. Patients can also experience mild to moderate discomfort of the hair follicles, and rarely pain as the hair is falling out. Read more about alopecia and scalp cooling

Delayed (onset months to years)	
Dupuytren's contracture	Fibrosing disorder that results in slow, progressive thickening and shortening of the palmar fascia, leading to debilitating contractures of the fingers. This causes one or more fingers to bend in towards the palm of the hand, limiting hand function. Cases of Dupuytren's contracture have been reported with vemurafenib treatment.

Evidence

The evidence supporting this protocol is provided by a phase 3 multicentre, international, randomised controlled trial (coBRIM) involving 495 patients with previously untreated, unresectable locally advanced or metastatic BRAF V600 mutant melanoma. Patients were randomised 1:1 to receive either vemurafenib 960 mg twice daily for 28 days and cobimetinib 60 mg once daily for 21 days followed by 7 days off (combination group) or vemurafenib 960 mg twice daily for 28 days and placebo once daily for 21 days followed by 7 days off (control group).[3]

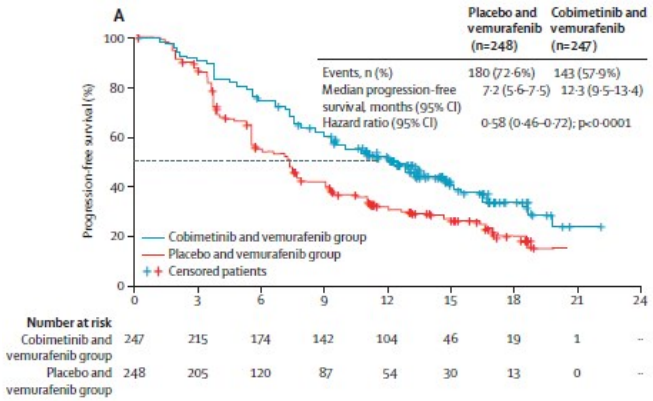
The primary end point was investigator-assessed progression free survival (PFS). Secondary end points included overall survival (OS), objective response rates, duration of response, PFS by independent review, and safety.

Efficacy

The combination of vemurafenib and cobimetinib resulted in a significantly prolonged PFS according to investigator assessment compared to the control arm.[3]

After a median follow up of 14.2 months, the updated investigator assessed median PFS remained superior in the combination arm compared to the control arm (median PFS 12.3 vs 7.2 months, HR 0.58, 95% CI 0.46-0.72, p<0.0001). [6]

Kaplan-Meier analysis of progression free survival (PFS)[6]



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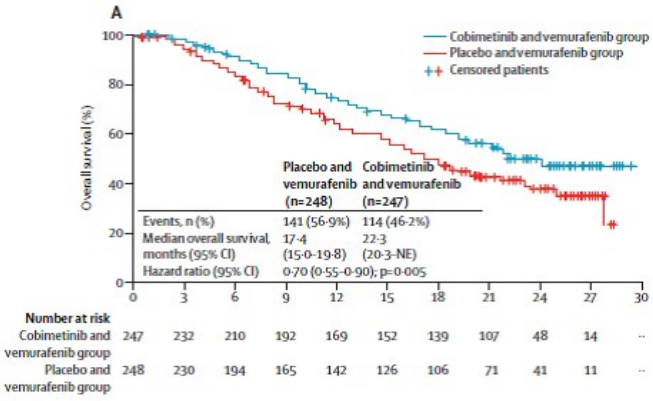
In the final analysis of OS, median OS was superior in the combination arm compared to the control arm (median OS 22.3 vs 17.4 months, HR 0.7, 95% CI 0.55 - 0.9, p=0.005).[6]

Kaplan-Meier analysis of overall survival (OS) [6]



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Best response to treatment [6]

	Placebo and vemurafenib (n=248)	Cobimetinib and vemurafenib (n=247)
Complete response, n (%)	26 (10%)	39 (16%)
Partial response, n (%)	98 (40%)	133 (54%)
Stable disease, n (%)	92 (37%)	44 (18%)
Progressive disease, n (%)	25 (10%)	19 (8%)
Not done*	6 (2%)	12 (5%)
Complete or partial response, n (%; 95% CI)	124 (50%; 43·6–56·4)	172 (70%; 63·5–75·3)
p value	Reference	<0·0001

*Responses could not be assessed for patients who withdrew consent, were withdrawn by the site investigator, died, or started new anticancer therapy before the first tumour assessment.

Health related quality of life outcomes were similar in the combination arm compared to the control arm (difference <5%).[7]

Toxicity

In the updated analysis, 147 (60%) of patients in the combination arm and 128 (52%) of patients in the control arm experienced a grade 3 or 4 treatment-related event.[6]

In the combination arm, the most common grade 3 and 4 toxicities were rash (17%), y-glutamyltransferase concentration rise (15%), blood creatine phosphokinase rise (12%) and alanine aminotransferase concentration rise (11%). In the control arm, the most common grade 3 and 4 toxicities were rash (16%), cutaneous squamous cell carcinoma (13%) and y-glutamyltransferase concentration rise (10%).[6]

Adverse events [6]

	Placebo and vemurafenib (n=246)		Cobimetinib and vemurafenib (n=247)	
	All grades	Grade ≥3	All grades	Grade ≥3
Most common adverse events (occurring in ≥20% of patients in either group)				
Rash*	166 (68%)	40 (16%)	179 (73%)	42 (17%)
Arthralgia	103 (42%)	12 (5%)	94 (38%)	6 (3%)
Diarrhoea	82 (33%)	2 (1%)	150 (61%)	16 (7%)
Fatigue	82 (33%)	7 (3%)	91 (37%)	11 (5%)
Alopecia	75 (31%)	1 (<1%)	41 (17%)	1 (<1%)
Hyperkeratosis	67 (27%)	6 (3%)	25 (10%)	1 (<1%)
Nausea	64 (26%)	2 (1%)	105 (43%)	3 (1%)
Pyrexia	59 (24%)	0	71 (29%)	3 (1%)
Decreased appetite	50 (20%)	1 (<1%)	50 (20%)	0
Photosensitivity reaction	48 (20%)	0	84 (34%)	8 (3%)
Alanine aminotransferase concentration increase	44 (18%)	15 (6%)	65 (26%)	28 (11%)
γ-glutamyltransferase concentration increase	44 (18%)	25 (10%)	54 (22%)	36 (15%)
Vomiting	34 (14%)	2 (1%)	63 (26%)	4 (2%)
Aspartate aminotransferase concentration increase	31 (13%)	5 (2%)	60 (24%)	22 (9%)
Serous retinopathy†	9 (4%)	0	67 (27%)	7 (3%)
Blood creatine phosphokinase level increase	7 (3%)	1 (<1%)	87 (35%)	30 (12%)
Other selected adverse events (selected based upon known association with BRAF or MEK inhibition)				
Cutaneous squamous cell carcinoma	31 (13%)	31 (13%)	10 (4%)	9 (4%)
Keratoacanthoma	23 (9%)	21 (9%)	4 (2%)	3 (1%)
Decreased ejection fraction	13 (5%)	3 (1%)	29 (12%)	5 (2%)
QT prolongation	13 (5%)	3 (1%)	11 (5%)	3 (1%)

52 patients (11%) discontinued treatment due to treatment related adverse events, including 35 (14%) in the combination arm and 17 (7%) in the vemurafenib arm. The most common reason for discontinuation was liver function test derangement.

8 patients (2%) died during the study. 5 patients died in the combination arm due to pneumonia, Clostridium difficile colitis, coma, cardiac arrest and death (unspecified). 3 patients in the vemurafenib group died due to cardiac failure, atelectasis and death (unspecified).[6]

References

1 Long, G. V., D. Stroyakovskiy, H. Gogas, et al. 2014. "Combined BRAF and MEK inhibition versus BRAF inhibition alone in melanoma." N Engl J Med 371(20):1877-1888.

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History

Version 2

Date	Summary of changes
12/03/2021	Protocol reviewed at Medical Oncology reference committee meeting. Evidence updated to include health related quality of life information. Version number changed to V.2. Next review in 2 years.
21/12/2021	Changed antiemetic clinical information block to minimal or low, to align with new categories. See ID 7 Prevention of anti-cancer therapy induced nausea and vomiting (AINV) V.5.
12/05/2023	Protocol reviewed electronically by Medical Oncology Reference Committee. No changes. Next review 2 years.

Version 1

Date	Summary of changes
05/02/2018	New protocol discussed by Medical oncology reference committee (discussed electronically via email)
10/04/2018	Protocol approved and published on eviQ. Review protocol in 1 year
31/05/2019	Protocol reviewed electronically by Medical Oncology Reference Committee. No changes. Next review in 2 years.
06/08/2019	ID 3600 Melanoma metastatic binimetinib and encorafenib added as a related page. 'Not traditional chemotherapy drug' information added to patient information.

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Patient information - Melanoma metastatic - Cobimetinib and vemurafenib

Patient's name:

Your treatment

It is important to understand that cobimetinib and vemurafenib are not traditional chemotherapy drugs and have a different way of working. They work by targeting the cancer cells to stop them growing and spreading. The treatment schedule below explains how the drugs for this treatment are given.

Cobimetinib and vemurafenib		
This treatment cycle is repeated every 28 days. Your doctor will advise you how long to take the treatment for.		
Day	**Treatment**	**How it is given**
1 to 21	**Cobimetinib** *(KOE-bi-ME-ti-nib)*	Take orally ONCE a day on days 1 to 21 only with a glass of water, with or without food. Swallow whole - do not break, crush or chew the tablets. If you forget to take a dose, and if it is more than 12 hours before your next dose, take it as soon as you remember. If it is less than 12 hours before your next dose, skip that dose and take your normal dose the next time it is due. Do not take an extra dose. If you vomit after taking your dose, do not take the same dose again. Then take the next dose at the usual time.
1 to 28	**Vemurafenib** (*vem-ue-RAF-e-nib)*	Take orally TWICE a day (morning and evening, about 12 hours apart) with a glass of water. Take on an empty stomach, at least one hour before food or two hours after food. Swallow whole - do not break, crush or chew the tablets. If you forget to take a dose, and if it is more than 4 hours before your next dose, take it as soon as you remember. If it is less than 4 hours before your next dose, skip that dose and take your normal dose the next time it is due. Do not take an extra dose. If you vomit after taking your dose, do not take the same dose again. Then take the next dose at the usual time.
22 to 28	**Do not** take **cobimetinib** tablets from day 22 to 28.	

- Tell your doctor if you have any heart, liver, kidney or eye problems.

When to get help

Anticancer drugs (drugs used to treat cancer) can sometimes cause serious problems. It is important to get medical help immediately if you become unwell.

Let your doctor or nurse know if you notice any of the following changes to your skin:

- a new wart
- a skin sore or reddish bump that bleeds or does not heal

- a change in size or colour of a mole

Contact your doctor immediately if you have any of the following side effects:

- a rash all over your body
- blisters on your skin or sores in your mouth
- redness or swelling of your face, hands, or soles of your feet.
- any eye pain, swelling or redness
- blurred vision or other vision changes
- your skin or whites of your eyes turn yellow
- you feel your heart beating irregularly or fast.

Your doctor will advise you if you should stop taking cobimetinib and vemurafenib.

IMMEDIATELY go to your nearest hospital Emergency Department, or contact your doctor or nurse if you have any of the following at any time:	**Emergency contact details** Ask your doctor or nurse from your treating team who to contact if you have a problem
• a temperature of 38°C or higher • chills, sweats, shivers or shakes • shortness of breath • uncontrolled vomiting or diarrhoea • pain, tingling or discomfort in your chest or arms • you become unwell.	Daytime:..... Night/weekend:..... Other instructions:..... ....

Other information about your treatment

Changes to your dose or treatment delays

Sometimes a treatment may be started at a lower dose or the dose needs to be changed during treatment. There may also be times when your treatment is delayed. This can happen if your doctor thinks you are likely to have severe side effects, if you get severe side effects, if your blood counts are affected and causing delays in treatment, or if you are finding it hard to cope with the treatment. This is called a dose reduction, dose change or treatment delay. Your doctor will explain if you need any changes or delays to your treatment and the reason why.

Blood tests and monitoring

You will need to have a blood test before you start treatment and regularly throughout your treatment. Your doctor or nurse will tell you when to have these blood tests.

Squamous cell carcinoma

This treatment may occasionally cause a type of skin cancer called squamous cell carcinoma (SCC). This usually does not spread to other parts of your body. Your doctor or nurse should check your skin for any new skin cancers before you start taking this treatment and regularly while you are on this treatment. They may continue to check your skin for six months after your treatment has stopped.

Other medications given during this treatment

- **Antidiarrhoeals:** you may be given some medication to treat diarrhoea. Your doctor or nurse will tell you how and when to take your antidiarrhoeal medication.

Side effects

Cancer treatments can cause damage to normal cells in your body, which can cause side effects. Everyone gets different side effects, and some people will have more problems than others.

The table below shows some of the side effects you may get with this treatment. You are unlikely to get all of those listed and you may also get some side effects that have not been listed.

Tell your doctor or nurse about any side effects that worry you. Follow the instructions below and those given to you by your doctor or nurse.

Early (onset days to weeks)	
Skin that is more sensitive to the sun (photosensitivity)	• After being out in the sun you may develop a rash like a bad sunburn. • Your skin may become red, swollen and blistered. • Avoid direct sunlight. • Protect your skin from the sun by wearing sun-protective clothing, a wide-brimmed hat, sunglasses and a sunscreen of SPF 50 or higher. • **Tell your doctor or nurse if you get any of the symptoms listed above.**
Skin rash	• You may get a red, bumpy rash and dry, itchy skin. • Moisturise your skin with a gentle non-perfumed moisturising cream like sorbolene or aqueous cream. • Do not scratch your skin. • Protect your skin from the sun by wearing sun-protective clothing, a wide-brimmed hat, sunglasses and sunscreen of SPF 50 or higher. • **Talk to your doctor or nurse about other ways to manage your skin rash.**
Diarrhoea	• You may get bowel motions (stools, poo) that are more frequent or more liquid. • You may also get bloating, cramping or pain. • Take your antidiarrhoeal medication as directed by your doctor. • Drink plenty of fluids (unless you are fluid restricted). • Eat and drink small amounts more often. • Avoid spicy foods, dairy products, high fibre foods, and coffee. • Ask your doctor or nurse for eviQ patient information - Diarrhoea during cancer treatment. • **Tell your doctor or nurse immediately, or go to your nearest hospital Emergency Department if your diarrhoea is not controlled, you have 4 or more loose bowel motions per day, and if you feel dizzy or light-headed.**
Tiredness and lack of energy (fatigue)	• You may feel very tired, have no energy, sleep a lot, and not be able to do normal activities or things you enjoy. • Do not drive or operate machinery if you are feeling tired. • Nap for short periods (only 1 hour at a time) • Prioritise your tasks to ensure the best use of your energy. • Eat a well balanced diet and drink plenty of fluids (unless you are fluid restricted). • Try some gentle exercise daily. • Allow your friends and family to help. • **Tell your doctor or nurse if you get any of the symptoms listed above.**
Joint and muscle pain and stiffness	• You may get muscle, joint or general body pain and stiffness. • Applying a heat pack to affected areas may help. • Talk to your doctor or nurse about other ways to manage these symptoms. You may need medication to help with any pain.

Nausea and vomiting	• You may feel sick (nausea) or be sick (vomit). • Take your anti-sickness medication as directed even if you don't feel sick. • Drink plenty of fluids (unless you are fluid restricted). • Eat small meals more frequently. • Try food that does not require much preparation. • Try bland foods like dry biscuits or toast. • Gentle exercise may help with nausea. • Ask your doctor or nurse for eviQ patient information - Nausea and vomiting during cancer treatment. • **Tell your doctor or nurse immediately, or go to the nearest hospital Emergency Department if you have uncontrolled vomiting or feel dizzy or light-headed.**
Skin changes	• You may notice skin changes like: ◦ dry skin or redness ◦ changes to sunspots or moles ◦ new sunspots or moles ◦ thickening of skin on palms of hands or soles of feet. • Moisturise your skin with a gentle non-perfumed moisturising cream like sorbolene or aqueous cream. • Use a soap-free wash. • Avoid direct sunlight. • Protect your skin from the sun by wearing sun-protective clothing, a wide-brimmed hat, sunglasses and sunscreen of SPF 50 or higher. • Tell your doctor or nurse if you notice skin changes or have symptoms that cause discomfort or pain.
Eye problems	• You may get: ◦ eye pain or irritation ◦ red or swollen eyes ◦ blurred vision ◦ floating spots ◦ changes in your eyesight. • Protect your eyes from the weather (sun and wind) by wearing sunglasses, especially if you have lost your eyelashes. • **Tell your doctor or nurse immediately if you get any of the symptoms listed above.**
Liver problems	• You may get: ◦ yellowing of your skin or eyes ◦ itchy skin ◦ pain or tenderness in your stomach ◦ nausea and vomiting ◦ loss of appetite • You will have regular blood tests to check how well your liver is working. • **Tell your doctor or nurse as soon as possible if you notice that your urine is a dark colour, the whites of your eyes look yellow, or if you have stomach pain.**

Late (onset weeks to months)	
Heart problems	• You may get: ◦ chest pain or tightness ◦ shortness of breath ◦ swelling of your ankles ◦ an abnormal heartbeat. • Heart problems can occur months to years after treatment. • Tell your doctor if you have a history of heart problems or high blood pressure. • Before or during treatment, you may be asked to have a test to see how well your heart is working. • **Tell your doctor or nurse immediately, or go to the nearest hospital Emergency Department if you get any of the symptoms listed above.**
Hair thinning	• Your hair may become dry and may break easily. • You may lose some of your hair. • Use a gentle shampoo and a soft hairbrush. • Take care with hair products like hairspray, hair dye, bleaches and perms. • Protect your scalp from the cold with a hat or scarf. • Protect your scalp from the sun with a hat and sunscreen of SPF 50 or higher. • Ask your doctor or nurse about the Look Good Feel Better program (www.lgfb.org.au)

Delayed (onset months to years)	
Deformity of the hand (Dupuytren's contracture)	• This side effect is very rare and usually develops very slowly over many years • It can affect one or both of your hands. • Over time you may notice: ◦ thickening of the skin on the palm of your hand(s) ◦ the skin may start to appear dimpled ◦ small lumps (called nodules) may form under the skin at the base of your finger(s) in the palm of your hand(s) ◦ one or more of your fingers (or thumb) may gradually become bent and pulled towards your palm ◦ it may become difficult to straighten your finger(s) completely • You may find it hard to perform daily activities using your hand (e.g. holding objects) • Tell your doctor or nurse if you get any of the symptoms listed above.

General advice for people having cancer treatment

Blood clot risk

- Cancer and anticancer drugs can increase the risk of a blood clot (thrombosis).
- Tell your doctor if you have a family history of blood clots.
- A blood clot can cause pain, redness, swelling in your arms or legs, shortness of breath or chest pain.
- If you have any of these symptoms go to your nearest hospital Emergency Department.

Medications

- Before you start treatment, tell your doctor about any medications you are taking, including vitamins or herbal supplements.
- Don’t stop or start any medications during treatment without talking to your doctor and pharmacist first.

Other medical and dental treatment

- If you go to hospital or any other medical appointment (including dental appointments), always tell the person treating you that you are receiving anticancer drugs.
- Before you have any dental treatment, talk to your doctor.

Diet

- While you are receiving this treatment it is important that you try to maintain a healthy diet.

- Grapefruit and grapefruit juice can interact with your medication and should be avoided while you are on this treatment.
- Speak to your doctor or nurse about whether drinking alcohol is safe with your treatment.
- If you have any concerns about recent weight loss or weight gain or questions about your diet, ask to speak to a dietitian.

Fertility

- Some cancer treatments can reduce your fertility. This can make it difficult or impossible to get pregnant or father a child.
- Talk to your doctor or nurse before you start any treatment. Depending on your situation there may be fertility sparing options available to you and/or your partner, discuss these with your doctor or nurse.

Pregnancy and breastfeeding

- Some cancer treatments can be dangerous to unborn babies. Talk to your doctor or nurse if you think there is any chance that you could be pregnant.
- Do not try to get pregnant or father a child during this treatment. Contraception should be used during treatment and after stopping treatment. Ask your doctor or nurse about what type of contraception you should use.
- If you are planning pregnancy/fatherhood after completing this treatment, talk to your doctor. Some doctors advise waiting between 6 months and 2 years after treatment.
- Do not breastfeed if you are on this treatment, as anti-cancer medications can also pass into breast milk.

Sex life and sexuality

- The desire to have sex may decrease as a result of this treatment or its side effects.
- Your emotions and the way you feel about yourself may also be affected by this treatment.
- It may help to discuss your concerns with your partner and doctor or nurse.

Quitting smoking

- It is never too late to quit smoking. Quitting smoking is one of the best things you can do to help your treatment work better.
- There are many effective tools to improve your chances of quitting.
- Talk to your treating team for more information and referral to a smoking cessation support service.

Staying active

- Research shows that exercise, no matter how small, has many benefits for people during and after cancer treatment.
- Talk to your doctor before starting an exercise program. Your doctor can advise whether you need a modified exercise program.

For more information about cancer treatment, side effects and side effect management see our Patient and carers section.

Where to get more information

Telephone support

- Call Cancer Council on 13 11 20 for cancer information and support

Melanoma information

- Melanoma Institute Australia – melanoma.org.au
- Melanoma Patients Australia – melanomapatients.org.au

General cancer information and support

- Australian Rare Cancer (ARC) Portal – arcportal.org.au/
- Beyond Blue – beyondblue.org.au
- Cancer Australia – canceraustralia.gov.au
- Cancer Council Australia – cancer.org.au
- Cancer Voices Australia – cancervoicesaustralia.org
- CanTeen – canteen.org.au
- Carers Australia – carersaustralia.com.au
- Carer Help - carerhelp.com.au
- CHILL Cancer related hair loss - scalpcooling.org
- eviQ Cancer Treatments Online – eviQ.org.au
- LGBTQI+ People and Cancer - cancercouncil.com.au/cancer-information/lgbtqi

- Look Good Feel Better – lgfb.org.au
- Patient Information – patients.cancer.nsw.gov.au
- Radiation Oncology Targeting Cancer – targetingcancer.com.au
- Redkite – redkite.org.au
- Return Unwanted Medicines – returnmed.com.au
- Staying active during cancer treatment – patients.cancer.nsw.gov.au/coping-with-cancer/physical-wellbeing/staying-active

Quit smoking information and support

Quitting smoking is helpful even after you have been diagnosed with cancer. The following resources provide useful information and support to help you quit smoking. Talk to your treating team about any other questions you may have.

- Call Quitline on 13 QUIT (13 78 48)
- iCanQuit –iCanQuit.com.au
- Patient Information – patients.cancer.nsw.gov.au/coping-with-cancer/physical-wellbeing/quitting-smoking
- Quitnow – quitnow.gov.au

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