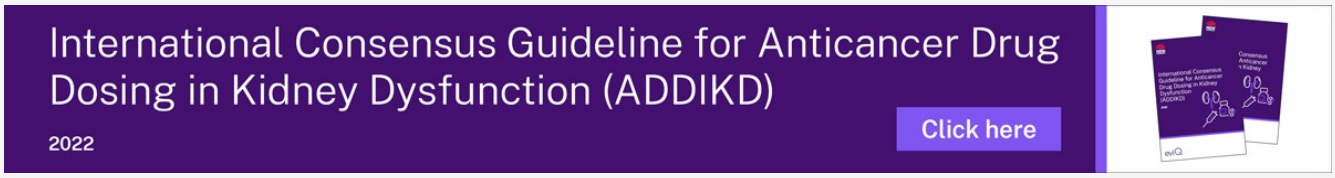
Melanoma metastatic daBRAFEnib and tRAMEtinib

ID: 1619 v.4 **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 cOBIMEtinib and vemurafenib
- Melanoma metastatic biNIMEtinib and encorafenib

Treatment schedule - Overview

Drug	Dose	Route
daBRAFEnib	150 mg TWICE a day	PO
tRAMEtinib	2 mg ONCE a day	PO

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]

Drug status: Dabrafenib is PBS authority. Dabrafenib (Tafinlar®) is available as **50 mg and 75 mg** capsules

Trametinib is PBS authority. Trametinib (Mekinist®) is available as **0.5 mg and 2 mg** tablets

Cost: ~ $14,080 per month

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.*

Continuous treatment		
daBRAFEnib	150 mg (PO)	TWICE a day (2 x 75 mg capsules morning and evening 12 hours apart) at least one hour before, or at least two hours after a meal

Continuous treatment		
tRAMEtinib	2 mg (PO)	ONCE a day at least one hour before, or at least two hours after a meal

Continuous until disease progression or unacceptable toxicity

Indications and patient population

- Unresectable stage III or stage IV metastatic 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
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	Trametinib 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 trametinib. Consider baseline cardiac assessment including echocardiogram (ECHO) 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	Dabrafenib may prolong the QT interval and increase the risk of cardiac arrhythmia. Use with caution in patients with a congenital long QT syndrome, patients treated with a high cumulative dose of anthracycline therapy, patients taking medications that may prolong the QT interval, and those with electrolyte disturbances. Risk factors (e.g. electrolyte abnormalities) should be corrected, where possible, prior to commencement of dabrafenib and the concurrent use of drugs that may prolong the QT interval should be avoided. Periodic monitoring with ECGs and electrolytes (magnesium, potassium, calcium) should be considered in patients at risk of QT prolongation. Read more about drugs that may prolong QTc interval at crediblemeds.org (registration required).
Hypertension	Patients may experience an increased incidence of hypertension with this treatment. Pre-existing hypertension should be adequately controlled prior to commencing treatment and blood pressure should be monitored regularly as clinically indicated.

Fever and fever syndrome	Non-infectious febrile events occur in most patients and can occur at any time, with the majority of events occurring in the first 3 months. The median time to onset is 1 month. Signs and symptoms include rigors, dehydration, hypotension, dizziness, weakness and fatigue. It is important that patients are educated about the prodrome of fever and to cease dabrafenib and trametinib upon symptom onset. Early intervention results in prompt resolution of events, usually within 24 hours of dose interruption. Paracetamol and NSAIDs may alleviate symptoms during pyrexia. A septic work-up is not required for patients with uncomplicated pyrexia and without localizing infective symptoms. Recommencement of dabrafenib and trametinib can safely occur 24 hours after pyrexia resolution. In cases of recurrent or severe pyrexia, an intermittent dosing regimen, and/or corticosteroids (prednisolone 10 to 25 mg daily) may be useful. Unlike other toxicities such as fatigue, dose reduction does not appear to reduce the risk of pyrexia recurrence and is best avoided.
Dermatologic toxicities	Dabrafenib monotherapy is associated with proliferative keratinocytic skin toxicities including squamous cell carcinomas (SCC) and keratoacanthomas (KA) and plantar-palmar hyperkeratosis. Pruritus and rash (Grover's Disease) also occur. The incidence of these is greatly reduced with combination treatment. Dermatologic evaluation prior to the initiation of therapy and while on therapy is not routinely required, but should be sought if toxicities occur. Read more about the skin toxicities associated with BRAF and MEK inhibitors
Concurrent radiation therapy	BRAF inhibitors appear to be radiosensitising with excess toxicity when given with concurrent radiation therapy. Both dabrafenib and trametinib 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]
New primary malignancies	BRAF inhibitors have been associated with new primary non-cutaneous malignancies (e.g. colon and adenocarcinoma pancreatic cancer). Patients should be closely monitored for signs and symptoms during therapy and for up to 6 months after discontinuation of a BRAF inhibitor or until initiation of another anti-cancer therapy. Refer to dose modifications for more information.
Ocular toxicity	Disorders associated with visual disturbance, including central serous retinopathy (CSR) and retinal vein occlusion (RVO), occur rarely with trametinib as monotherapy or in combination with dabrafenib. No cases of RVO have been reported in phase II and III trials of melanoma patients with the daily dose of 2 mg of trametinib. Some patients may develop uveitis with dabrafenib; however, this can be managed with steroid eye drops. For patients with a history of ocular disease, a baseline ophthalmological assessment is recommended. Any visual disturbance reported on treatment should be promptly assessed by an ophthalmologist, with treatment withheld until review.
Fatigue	Profound fatigue is rare but has been reported in patients especially those with multiple brain metastases. Dose reduction has shown to be effective, refer to dose modifications for more information.
Blood tests	FBC, EUC, eGFR, LFTs, calcium and magnesium at baseline. Repeat monthly during treatment, or as clinically indicated. LFTs may become abnormal in the setting of drug-induced fever, and treatment should be withheld until they normalise.

Hepatitis B screening and prophylaxis	Routine screening for HBsAg and anti-HBc is NOT usually recommended for patients receiving this treatment. Read more about hepatitis B screening and prophylaxis in cancer patients requiring cytotoxic and/or immunosuppressive therapy
Vaccinations	Live vaccines are contraindicated in cancer patients receiving immunosuppressive therapy and/or who have poorly controlled malignant disease. Refer to the recommended schedule of vaccination for immunocompromised patients, as outlined in the Australian Immunisation Handbook. Read more about COVID-19 vaccines and cancer.
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. Non-hormonal methods of birth control should be used during this treatment. 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 of dabrafenib resulting in a dose below 50 mg twice daily are not recommended.
- Dose reductions of trametinib resulting in a dose below 1 mg daily are not recommended.
- If adverse events are effectively managed, dose re-escalation following the same dosing steps as de-escalation may be considered with expert guidance.
- Dose modifications or interruptions are not recommended for cutaneous squamous cell carcinoma (cuSCC) or new primary melanoma.

Renal impairment	
Creatinine clearance (mL/min)	
30 to 50	No dose modifications necessary
less than 30	No clinical data; the need for dose modifications cannot be determined

Hepatic impairment

Hepatic dysfunction	
Mild	No dose modifications necessary
Moderate and severe	No clinical data; the need for dose modifications cannot be determined Both dabrafenib and trametinib and their metabolites are eliminated by hepatic metabolism and biliary secretion; patients with moderate to severe hepatic impairment may have increased exposure.

Fever and fever syndrome

- Immediately interrupt treatment with dabrafenib and trametinib at the earliest sign of fever or associated symptoms (e.g. chills, rigors, sweats), regardless of body temperature measurement
- Evaluate with FBC, renal function, LFT and assess for source of infection as indicated
- Paracetamol or ibuprofen and symptomatic treatment. However, prophylactic paracetamol or NSAIDs are ineffective and not recommended. [6]
- Routine use of antibiotics is not appropriate for patients with pyrexia syndrome, they should only be used when the presence of an infection has been confirmed or is highly suspected, or where sepsis cannot be excluded. [6]

Any fever, particularly with signs and symptoms of rigors, dehydration, hypotension, dizziness or weakness	1st occurrence: Withhold dabrafenib and trametinib; restart dabrafenib at 150 mg twice a day and trametinib at 2 mg once a day, 24 hours after fever and symptoms have resolved. 2nd occurrence: Withhold dabrafenib and trametinib; oral prednisolone may be considered depending on the severity of the syndrome. When fever/symptoms resolve, restart dabrafenib at 150 mg twice a day and trametinib at 2 mg once a day. 3rd occurrence: Withhold dabrafenib and trametinib; either commence oral prednisolone 10 to 25 mg/day when infection excluded, and reintroduce therapy at full-dose, consider an intermittent dosing regimen or alternative combination (See Related pages). If starting steroids, slowly wean prednisolone over 2 months. There is limited evidence that indicates dose reductions of dabrafenib do not reduce the frequency of fever.[7] If further episodes of fever occur, consider indefinite maintenance prednisolone and/or an intermittent dosing regimen. Dose reductions of dabrafenib to 100 mg twice a day (or as low as 50 mg twice a day) or trametinib (to 1 mg daily) can be considered if clinically indicated.

Fatigue

- Intermittent regimen (e.g. 5 days on, 2 days off treatment per week) may benefit patients with severely impacted quality of life
- Other causes of fatigue such as disease progression, infection and anaemia should be ruled out[6]

Grade 1	No dose modifications necessary
Grade 2 and Grade 3	Delay treatment until toxicity has resolved to Grade 1 or less and reduce doses as follows: 1st occurrence: Reduce dabrafenib to 100 mg twice a day and trametinib to 1.5 mg once a day 2nd occurrence: Reduce dabrafenib to 75 mg twice a day and trametinib to 1.0 mg once a day 3rd occurrence: Reduce dabrafenib to 50 mg twice a day and cease trametinib 4th occurrence: Cease dabrafenib

New primary malignancies	
New primary cutaneous malignancies	No dose modifications necessary
New primary non-cutaneous malignancies (e.g. colon[8] and adeno-pancreatic cancers[9])	Permanently discontinue dabrafenib in patients who develop RAS mutation positive non-cutaneous malignancies No dose modification necessary for trametinib.

Left Ventricular Ejection Fraction (LVEF) Reduction/Left Ventricular Dysfunction	
Asymptomatic, absolute decrease 10% or more from baseline and below lower limit of normal	Trametinib should be interrupted and cardiology opinion sought Dabrafenib may be continued at the same dose If cardiac function recovers, trametinib may be recommenced at the same dose with close monitoring +/- cardiac medications Alternatively, trametinib may be recommenced at a reduced dose as follows: 1st occurrence: Reduce trametinib to 1.5 mg once a day with careful monitoring 2nd occurrence: Reduce trametinib to 1 mg once a day with careful monitoring
Symptomatic left ventricular dysfunction or if LVEF does not recover	Permanently discontinue trametinib Consider discontinuing dabrafenib until recovery of cardiac function

Retinal Vein Occlusion (RVO) and Central Serous Retinopathy (CSR)	
RVO	Permanently discontinue trametinib Continue with dabrafenib at the same dose
Grade 1 (asymptomatic) CSR	Continue treatment, with retinal evaluation monthly until resolution. If CSR worsens, follow instructions below and withhold trametinib for up to 3 weeks.
Grade 2 or Grade 3 CSR	Withhold trametinib for up to 3 weeks If CSR improves to Grade 1, resume trametinib and reduce the dose by 0.5 mg If CSR does not improve within 3 weeks, permanently discontinue trametinib

Skin toxicities
The prevalence of skin toxicities with combination treatment is low and is usually managed symptomatically without dose modifications. Consultation with a dermatologist is recommended. Read more about the skin toxicities associated with BRAF inhibitors (dabrafenib and vemurafenib).

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 .

Dabrafenib		
	Interaction	**Clinical management**
Drugs that may prolong the QTc interval (e.g. azole antifungals, tricyclic antidepressants, antiarrhythmics etc.)	Additive effect with dabrafenib; 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 inhibitors (e.g. amiodarone, aprepitant, azole-antifungals, ritonavir, lapatinib, nilotinib, sorafenib, macrolides, cyclosporin, grapefruit juice etc.) and CYP 2C8 inhibitors (e.g. gemfibrozil, trimethoprim etc.)	Increased toxicity of dabrafenib possible due to reduced clearance	Avoid combination or monitor for dabrafenib toxicity
CYP3A4 inducers (e.g. carbamazepine, phenytoin, phenobarbitone, rifampicin, St John's wort, dexamethasone etc.) and CYP 2C8 inducers (e.g. rifampicin etc.)	Reduced efficacy of dabrafenib possible due to increased clearance	Avoid combination or monitor for decreased clinical response to dabrafenib
CYP3A4, CYP2C9, CYP2B6, CYP2C8, CYP2C19, UDP glucuronosyl transferase (UGT) substrates (e.g. hormonal contraceptives, dexamethasone, antiretroviral agents, or immunosuppressants etc.)	Reduced efficacy of these drugs possible due to induction of CYP3A4, CYP2C9, CYP2B6, CYP2C8, CYP2C19, UDP glucuronosyl transferase (UGT) by dabrafenib resulting in increased clearance	Avoid combination or monitor for reduced efficacy of the interacting drugs. For hormonal contraceptives, non-hormonal methods should be used during and up to one month after stopping dabrafenib
Warfarin	Reduced anticoagulant efficacy of warfarin due to decreased plasma concentration of S-warfarin	Monitor INR regularly and adjust warfarin dosage as appropriate; consider alternative anticoagulant (e.g. LMWH, unfractionated heparin)
Proton pump inhibitors (e.g. omeprazole), H2 blockers (e.g. ranitidine) and antacids	The solubility of dabrafenib decreases as pH increases. These drugs reduce gastric acid and may reduce the plasma concentration of dabrafenib	Avoid combination or monitor for decreased clinical response to dabrafenib

Trametinib
Due to its mechanism of metabolism it is unlikely that the pharmacokinetics of trametinib will be affected by other drugs through metabolic interactions, or that trametinib will affect the pharmacokinetics of other drugs.

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.

Administration

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

Dabrafenib

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

Note: missed doses should not be taken if it is less than 6 hours until the next dose. If vomiting occurs after dose, administer the next dose at the next scheduled time.

Trametinib

- administer orally ONCE daily
- to be swallowed whole with a glass of water; do not break, crush or chew
- to be taken on empty stomach one hour before or two hours after food

When administered in combination with dabrafenib, take the once-daily dose of trametinib at the same time each day with either the morning or evening dose of dabrafenib

Note: if a patient misses a dose, it should not be taken if it is within 12 hours of the next dose

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

Discharge information

Dabrafenib capsules and trametinib tablets

- Dabrafenib capsules and trametinib tablets with written instructions on how to take them.

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)	
Fever	Non-infectious febrile events are common with BRAF/MEK inhibitors (more common with dabrafenib/trametinib than with encorafenib/binimetinib) and may occur at any time. Educating patients about the prodrome of fever and drug cessation is an important step in managing the fever. Read more about fever and fever syndrome (BRAF MEK inhibitors only)
Anorexia	Loss of appetite accompanied by decreased food intake. Read more about anorexia
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
Diarrhoea	Read more about treatment induced diarrhoea
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
Hair changes	Mild alopecia, slower growth of scalp and body hair, change to wavy or curly, colour change, folliculitis and ingrown hairs may occur with this treatment.
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).

Late (onset weeks to months)	
Pulmonary toxicity	Pulmonary toxicity may include damage to the lungs, airways, pleura and pulmonary circulation. Read more about pulmonary toxicity associated with anti-cancer drugs
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

Evidence

The evidence supporting this protocol is provided by a phase III multicentre international randomised trial (COMBI-D) involving 423 patients comparing combination dabrafenib-trametinib versus dabrafenib-placebo in patients with previously untreated unresectable stage IIIC or IV metastatic melanoma with a BRAF V600E or V600K mutation. Patients were randomised 1:1 to receive combination dabrafenib-trametinib (150 mg PO bd and 2 mg PO daily) versus dabrafenib-placebo (150 mg PO bd).[10]

Further evidence of long-term clinical outcomes in patients treated with combination BRAF and MEK inhibition comes from a pooled analysis of extended survival data from patients who received dabrafenib-trametinib in the intention-to-treat populations of the COMBI-d and COMBI-v trials.[11] COMBI-v was an open-label, randomised phase III trial comparing dabrafenib-trametinib (150 mg PO bd and 2 mg PO daily) with vemurafenib (960 mg PO bd). In the pooled analysis, a total of 563 patients were randomised to receive dabrafenib-trametinib (211 in COMBI-d and 352 in COMBI-v).

The primary end point was progression free survival (PFS) in COMBI-d and overall survival (OS) in COMBI-v. Secondary endpoints were OS, response rate, duration of response, safety and pharmacokinetic features in COMBI-d, and investigator-assessed PFS, response rate, duration of response and safety in COMBI-v.[10, 11]

Efficacy

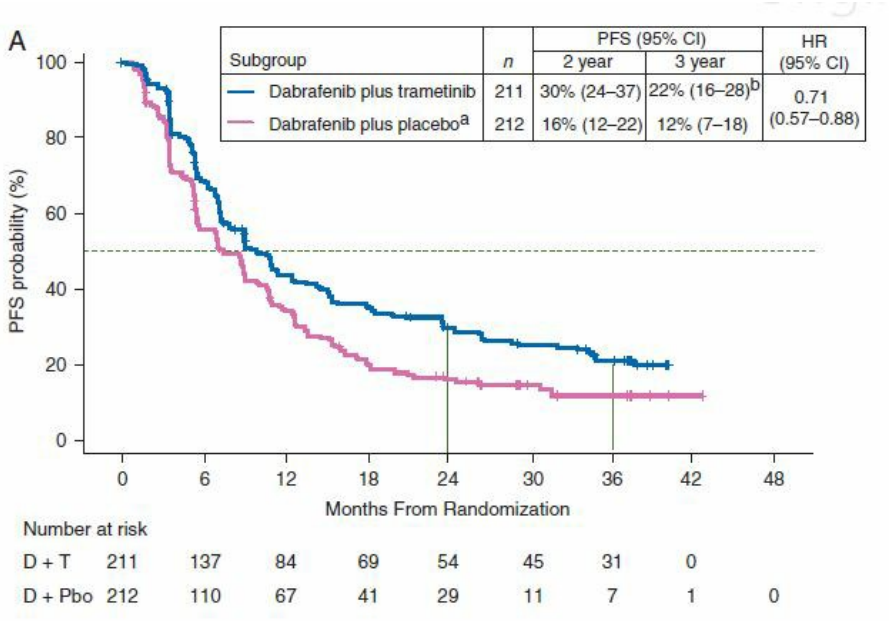
COMBI-d

At data cut-off, 3-year PFS was significantly longer in the combination dabrafenib-trametinib versus dabrafenib-placebo arm (22% vs 12%; HR 0.71, 95% CI, 0.57 to 0.88).[10]

3-year OS analysis showed the combination arm achieved benefit compared to the dabrafenib arm 44% vs 32% respectively (HR 0.75, 95% CI, 058 to 0.96). 25 (12%) patients on the dabrafenib monotherapy arm crossed over to dabrafenib-trametinib and 6 (24%) had progressed on monotherapy before crossover. All crossover patients remained on dabrafenib-trametinib at data cut-off, and survival outcomes continued to be followed up under the monotherapy arm.[10]

Post-progression systemic therapy was greater in the dabrafenib monotherapy arm than with dabrafenib-trametinib (62% vs 48%). In both the dabrafenib-trametinib and monotherapy groups, immunotherapy was the most common subsequent anticancer therapy (56% vs 56%), ipilimumab being the most common immunotherapy (41% vs 50%) with fewer anti-PD-1 treatments with nivolumab (7% vs 5%) and pembrolizumab (13% vs 11%).[10]

Progression free survival[10]



[a]Includes 25 patients who crossed over from monotherapy to the combination.
[b]Of D+T patients who were progression free at 3 years, 28 (90%) remained on D+T.

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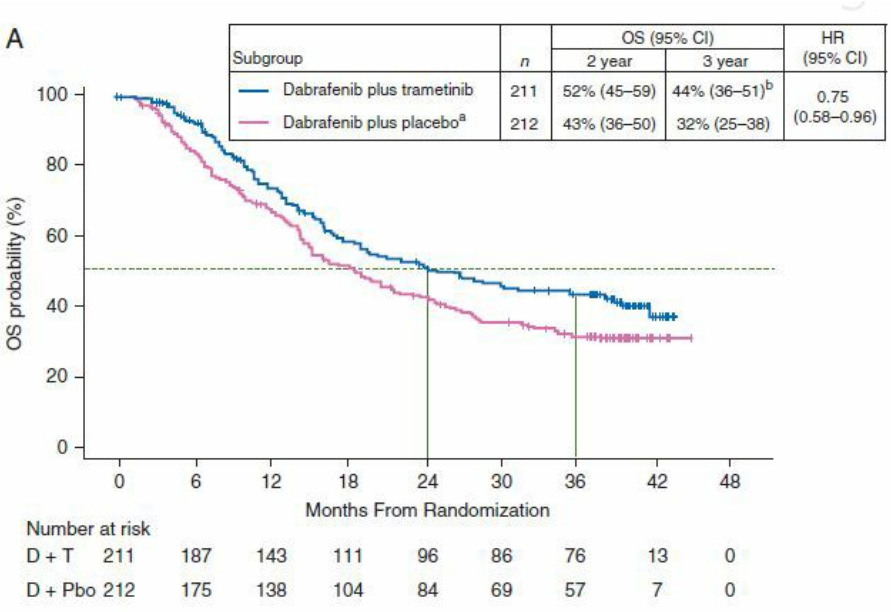
Overall survival[10]



[a]Includes 25 patients who crossed over from monotherapy to the combination.
[b]Of D+T patients who were progression free at 3 years, 28 (90%) remained on D+T.

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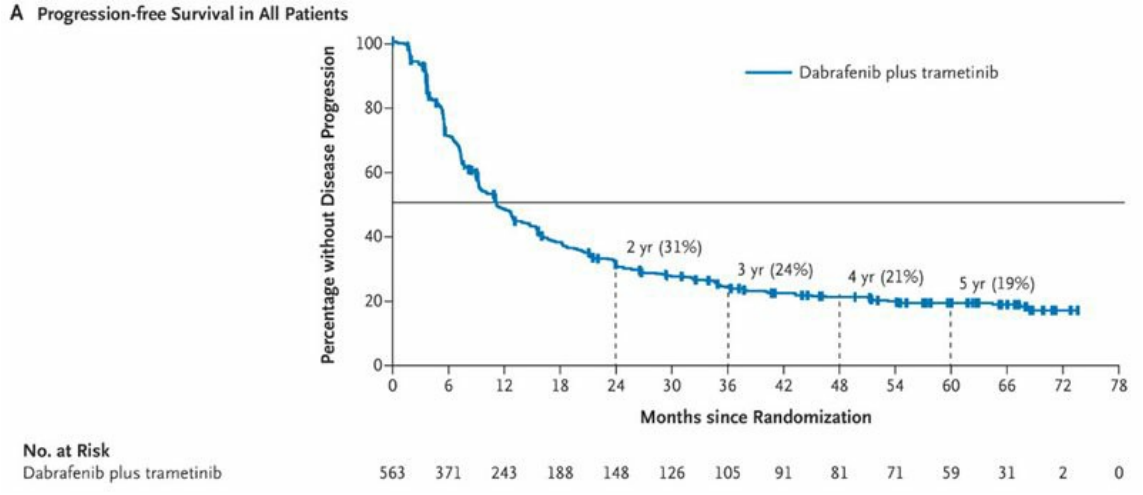
Pooled analysis of COMBI-d and COMBI-v

In the pooled analysis of patients randomised to dabrafenib-trametinib, at a median follow up of 22 months, the median PFS was 11.1 months (95% CI, 9.5-12.8). The PFS rates were 21% (95% CI, 17-24) at 4 years, and 19% (95% CI, 15-22) at 5 years. Patients with a normal baseline lactate dehydrogenase (LDH) had a greater 5-year PFS rate of 25% (95% CI, 20-30), compared to 8% (95% CI, 4-13) in patients with an elevated baseline LDH.[11]

Progression free survival[11]



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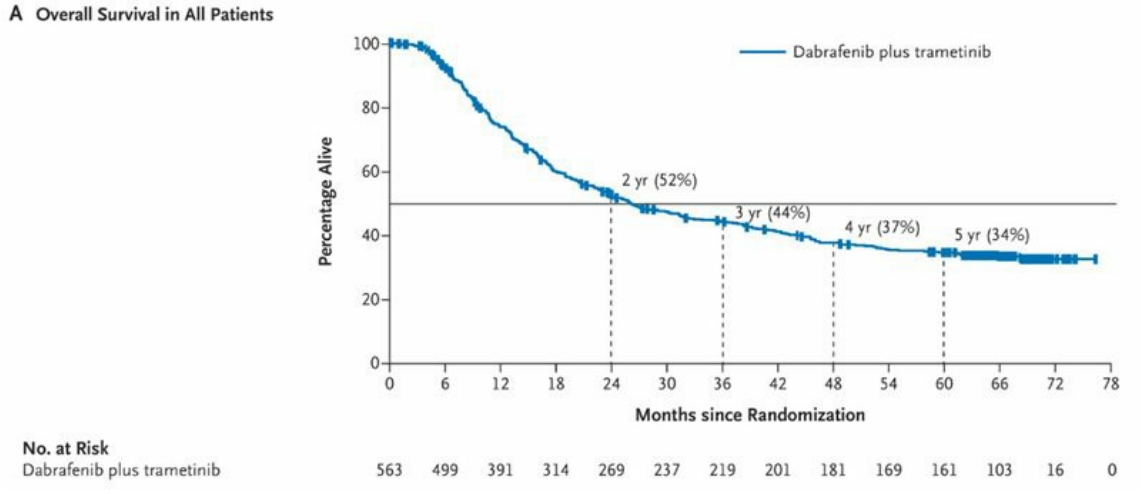
Across the trials, median OS was 25.9 months (95% CI, 22.6-31.5) in patients treated with dabrafenib-trametinib. The OS rates were 37% (95% CI, 33-42) at 4 years, and 34% (95% CI, 30-38) at 5 years. The 5-year OS was 43% in patients with a normal baseline LDH (95% CI, 38-49) compared with 16% in those with elevated LDH (95% CI, 11-22). Patients with normal LDH and fewer than three organ sites of metastasis had an estimated 5-year OS of 55% (95% CI, 48-61). Factors associated with OS by multivariate analysis were consistent with those associated with PFS.[11]

Overall survival[11]



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Objective response to treatment with combination therapy was seen in 68% (n = 383) of patients, with complete response in 19% (n = 109). The 5-year OS was 71% (95% CI, 62-79) in patients with a complete response, 32% (95% CI, 26-37) in those with a partial response and 16% (95% CI, 10-24) in those with stable disease.[11]

Toxicity

COMBI-d

The number of patients with cutaneous squamous cell carcinoma was lower in the dabrafenib–trametinib group than in the dabrafenib-only group (3 vs 10 patients; 1% vs 5% respectively), whereas pyrexia occurred in more patients (59% vs 33%) and was more often severe (grade 3, 7% vs. 2%) in the dabrafenib–trametinib group.[10]

The frequency of the most common dabrafenib-trametinib associated adverse events, including pyrexia, did not increase by>2% with an additional follow-up period of three years. Similarly, the incidence of key skin-related adverse events, including palmoplantar hyperkeratosis, squamous cell carcinoma/ basal cell carcinoma, did not increase by>1% in the combination arm with extended

follow up, and no new primary melanomas were observed.[10]

In the previous data analysis, 11% of patients in the combination arm had discontinued treatment owing to adverse events, versus 7% in dabrafenib arm.[12] The updated 3-year analysis data showed that adverse events leading to permanent discontinuation in the dabrafenib-trametinib arm patients increased by 3% (n=29; 14%) and no new grade 5 adverse events were observed.[10]

Supplementary Table 3. Adverse events (AEs), regardless of study drug relationship, occurring in ≥20% of patients in either treatment arm

	Dabrafenib plus trametinib (*n*=209)		Dabrafenib plus placebo (*n*=211)	
Preferred term, *n* (%)	**All grades**	**Grade 3/4**	**All grades**	**Grade 3/4**
Any AE	203 (97)	100 (48)	205 (97)	106 (50)
Pyrexia	123 (59)	14 (7)	69 (33)	4 (2)
Fatigue	81 (39)	5 (2)	79 (37)	3 (1)
Nausea	76 (36)	1 (<1)	56 (27)	3 (1)
Headache	72 (34)	1 (<1)	62 (29)	3 (1)
Chills	66 (32)	1 (<1)	35 (17)	1 (<1)
Diarrhoea	65 (31)	3 (1)	35 (17)	2 (<1)
Rash	57 (27)	0	46 (22)	2 (<1)
Vomiting	55 (26)	2 (<1)	31 (15)	1 (<1)
Arthralgia	54 (26)	2 (<1)	68 (32)	0
Hypertension	52 (25)	12 (6)	34 (16)	13 (6)
Cough	47 (22)	0	46 (22)	0
Oedema peripheral	46 (22)	2 (<1)	19 (9)	1 (<1)
Hyperkeratosis	15 (7)	0	74 (35)	1 (<1)
Alopecia	19 (9)	1 (<1)	60 (28)	0
Skin papilloma	5 (2)	0	46 (22)	0

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Pooled analysis of COMBI-d and COMBI-v

Adverse events leading to permanent discontinuation occurred in 18% of patients. The most common events leading to permanent discontinuation were pyrexia (n = 23, 4%), decreased ejection fraction (n = 21, 4%) and increased alanine aminotransferase level (n =7, 1%). No grade 5 adverse events related to a trial agent were reported in patients receiving dabrafenib-trametinib.[11]

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History

Version 4

Date	Summary of changes
22/08/2022	Protocol reviewed electronically by Medical Oncology Reference Committee. Evidence updated with pooled analysis of COMBI-d and COMBI-v data. Version number changed to V.4. Next review in 4 years.

Version 3

Date	Summary of changes
12/12/2019	Hypertension and hepatitis B information added to clinical information section. INR monitoring removed from blood tests in clinical information. Dose modifications for LVEF reduction updated. Version number change to V.3.
21/07/2020	Protocol reviewed electronically by Medical Oncology Reference Committee. No changes. Next review in 2 years.
03/09/2020	Cardiac toxicity clinical information updated- assessment recommendations aligned with other MEK inhibitor protocols.
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) v5.

Version 2

Date	Summary of changes
12/09/2014	New protocol taken to Medical Oncology Reference Committee meeting.
17/10/2014	Approved and published on eviQ.
31/05/2016	Protocol reviewed at Medical Oncology Reference Committee meeting on 4 April 2016. Evidence updated. Next review in 1 year.
31/05/2017	Transferred to new eviQ website.
15/06/2017	Information regarding new primary malignancies that was previously in monitoring section transferred to clinical information in new eviQ website.
15/06/2018	Protocol reviewed at Medical Oncology Reference Committee meeting on 15 June 2018. Dose modification information and evidence updated. 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.

The information contained in this protocol is based on the highest level of available evidence and consensus of the eviQ reference committee regarding their views of currently accepted approaches to treatment. Any clinician (medical oncologist, haematologist, radiation oncologist, medical physicist, radiation therapist, pharmacist or nurse) seeking to apply or consult this protocol is expected to use independent clinical judgement in the context of individual clinical circumstances to determine any patient's care or treatment. While eviQ endeavours to link to reliable sources that provide accurate information, eviQ and the Cancer Institute NSW do not endorse or accept responsibility for the accuracy, currency, reliability or correctness of the content of linked external information sources. Use is subject to eviQ's disclaimer available at www.eviQ.org.au

First approved: 17 October 2014
Last reviewed: 8 August 2022
Review due: 30 June 2026

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https://www.eviq.org.au/p/1619
01 Mar 2024

Patient information - Melanoma metastatic - Dabrafenib and trametinib

Patient's name:

Your treatment

It is important to understand that dabrafenib and trametinib 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.

Dabrafenib and trametinib		
This treatment is continuous. Your doctor will advise you how long to take the treatment for.		
Day	**Treatment**	**How it is given**
Continuous	**Dabrafenib** (*da-BRAF-e-nib)*	Take orally (2 x 75 mg capsules) TWICE a day with a glass of water on an empty stomach, at least one hour before or two hours after food. Swallow capsules whole, do not break, crush or chew. If you forget to take a capsule, and if it is less than 6 hours late, take it as soon as you remember. If it is more than 6 hours late, skip that dose and take your normal dose the next time it is due. Do not take an extra dose.
	Trametinib (*tra-ME-ti-nib*)	Take orally ONCE a day with a glass of water, on an empty stomach, at least one hour before or two hours after food. Swallow whole, do not break, crush or chew. Tablets can be taken with **either** the morning or evening dose of dabrafenib. If you forget to take a tablet, and if it is less than 12 hours late, take it as soon as you remember. If it is more than 12 hours late, skip that dose and take your normal dose the next time it is due. Do not take an extra dose.

- Tell your doctor if you have diabetes or any 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.

During treatment if you have any symptoms of a fever (e.g. chills, shivers, dizziness, weakness, or temperature of 38°C or higher):

- stop taking the dabrafenib capsules and trametinib tablets immediately and contact your doctor or nurse for advice
- start taking paracetamol 1 g every 6 hours
- stay well hydrated by drinking plenty of fluids
- monitor your temperature 3 to 4 times a day
- keep a record of your temperatures including the time and date
- if your temperature continues to stay above 38°C despite stopping the medication, go to the nearest Emergency Department.

A short treatment break off dabrafenib and trametinib does not reduce the overall anti-cancer effect.

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, despite stopping the dabrafenib and trametinib • chills, sweats, shivers or shakes, despite stopping the dabrafenib and trametinib • shortness of breath • uncontrolled vomiting or diarrhoea • pain, tingling or discomfort in your chest or arms • severe abdominal pain • eye pain, swelling or redness or any vision changes • 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 cause a type of skin cancer called squamous cell carcinoma (SCC). This usually does not spread to other parts of your body.

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)

Fever	• You may get:
	  ◦ a fever
	  ◦ chills or sweating
	  ◦ muscle pain
	  ◦ headaches.
	• You may also feel:
	  ◦ dizzy or tired.
	• Fever usually occurs within the first few weeks of treatment, but can occur at any time.
	• These symptoms are caused by your treatment.
	• Buy a digital thermometer and take your temperature if you feel unwell.
	• You can take paracetamol if needed.
	• **Stop taking your treatment and tell your doctor or nurse as soon as possible if you notice any of the symptoms listed above, or have a temperature of 38°C or higher.**
	• **Go to the nearest hospital Emergency Department if your temperature continues to stay above 38°C despite stopping the treatment.**

Appetite loss (anorexia)	• You may not feel like eating. • Try to avoid drinking fluids at meal times. • Try to eat small meals or snacks regularly throughout the day. • Try to eat food that is high in protein and calories. • If you are worried about how much food you can eat, or if you are losing weight, ask to speak to a dietitian.
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.
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.**

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.
Hair changes	• Your hair may: ◦ grow darker and thicker than normal on your face and body ◦ become dry, brittle or curly ◦ break easily or fall out. • Use a gentle shampoo and a soft brush. • Take care with hair products for example hairspray, hair dye, bleaches and perms. • Ask your doctor or nurse about the Look Good Feel Better program (www.lgfb.org.au)
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.**

Late (onset weeks to months)	
Lung problems	• Lung problems are rare, but can be serious. They may occur throughout treatment or after the completion of treatment. • You may get: ◦ shortness of breath ◦ fever ◦ dry cough ◦ wheezing ◦ fast heartbeat ◦ chest pain. • Your doctor will monitor how well your lungs are working during your treatment. • **Tell your doctor or nurse immediately, or go to the nearest hospital Emergency Department if you have chest pain or become short of breath.**
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.**

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. Hormonal contraception (such as pills, injections or patches) may not work as well in women having this treatment, and non-hormonal methods of contraception should be used. 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

Additional notes:

This document is a guide only and cannot cover every possible situation. The health professionals caring for you should always consider your individual situation when making decisions about your care. Contact your cancer clinic staff or doctor if you have any questions or concerns about your treatment, or you are having problems coping with side effects. While eviQ endeavours to link to reliable sources that provide accurate information, eviQ and the Cancer Institute NSW do not endorse or accept responsibility for the accuracy, currency, reliability or correctness of the content of linked external information sources. Use of this document is subject to eviQ's disclaimer available at www.eviQ.org.au

First approved: 17 October 2014
Last reviewed: 8 August 2022
Review due: 30 June 2026

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https://www.eviq.org.au/pi/1619
28 Feb 2024