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Title

Optimizing combination dabrafenib and trametinib therapy in BRAF mutation-positive advanced melanoma patients: Guidelines from Australian melanoma medical oncologists

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Short title

Dabrafenib & trametinib in BRAF-mutant melanoma

Conflict of interest declaration

VA has sat on advisory boards and received travel support and speaker's fees from BMS, Novartis and MSD.

GVL is a consultant advisor to Amgen, Merck MSD, Novartis and Roche. She has received honoraria from BMS, Novartis and Merck MSD.

AMM has received honoraria from BMS and Novartis, and has sat on advisory boards for MSD and Chugai.

GMcA has no conflicts of interest to declare.

MSC is a consultant advisor to Novartis, BMS, Merck and Amgen. He has received honoraria from Novartis, BMS and Merck.

MM has sat on advisory boards for Novartis.

RRT has received speaker's fees from BMS and Novartis.

BB has sat on advisory boards for Merck and BMS. He has received a BMS travel grant.

RK's institution has received reimbursement for his attendance at advisory boards for Novartis and Roche.

AH has no conflict of interest to declare.

JC has sat on advisory boards for Novartis and GSK, for which his employer has received payment.

Abstract

BRAF mutations occur commonly in metastatic melanomas and inhibition of mutant BRAF and the downstream kinase MEK results in rapid tumor regression and prolonged survival in patients. Combined therapy with BRAF and MEK inhibition improves response rate, progression free survival and overall survival compared with single agent BRAF inhibition, and reduces the skin toxicity that is seen with BRAF inhibitor monotherapy. However, this combination is associated with an increase in other toxicities, particularly drug-related pyrexia which affects approximately 50% of patients treated with dabrafenib and trametinib (CombiDT).

We provide guidance on managing adverse events likely to arise during treatment with combination BRAF and MEK inhibition with CombiDT: pyrexia, skin conditions, fatigue; and discuss management of CombiDT during surgery and radiotherapy. By improving tolerability and in particular preventing unnecessary treatment cessations or reduction in drug exposure, best outcomes can be achieved for patients undergoing CombiDT therapy.

Keywords

Melanoma, BRAF, MEK, dabrafenib, trametinib, pyrexia

Introduction

BRAF mutations occur in approximately 35% to 40% of metastatic melanomas in Australia (1, 2). Inhibition of mutant BRAF or the downstream kinase MEK results in rapid tumor regression and prolonged survival in patients (3-8). In phase III trials (6-8) the BRAF inhibitors vemurafenib and

dabrafenib and the MEK inhibitor trametinib had superior response rates and survival than chemotherapy and these agents were approved in Australia for the treatment of unresectable or metastatic melanoma with BRAF V600 mutation several years ago. BRAF inhibitors are superior to MEK inhibitors as a monotherapy for melanoma (9, 10), and MEK inhibitors have minimal efficacy in patients resistant to BRAF inhibitors (11). Consequently, trametinib monotherapy was initially approved only for patients who are intolerant to or unsuitable for BRAF inhibitors, but is now mainly used as part of combination therapy.

Although most patients initially respond to BRAF inhibitor treatment, the vast majority of patients will develop resistance to therapy shortly thereafter (12, 13). Additionally, oncogenic toxicities occur via paradoxical activation of the MAPK pathway in wild-type BRAF cells (14), e.g. cutaneous squamous cell carcinoma or RAS-mutated gastrointestinal tumors (15). Combination therapy with a BRAF inhibitor and a MEK inhibitor delays the emergence of resistance and reduces skin toxicity compared to single agent BRAF inhibition (9, 16, 17). In previously untreated patients who have metastatic melanoma with BRAF V600E or V600K mutations, combination dabrafenib and trametinib (CombiDT) inhibition improved the response rate, progression-free survival and overall survival compared with dabrafenib or vemurafenib alone (9, 10, 16).

While there was no significant difference in the frequency and grade of toxicity between the CombiDT and BRAF monotherapy arms of the phase III trials, the toxicity profile was different. Cutaneous toxicities with BRAF inhibitor monotherapy, such as hyperkeratosis and the development of cutaneous squamous-cell carcinoma, were less common with the combination, but the rate of pyrexia was higher. In the phase III trials, approximately 50% of patients developed drug-related pyrexia (9, 16), defined as an oral temperature of at least 38.5ºC in the absence of any clinical or microbiological evidence of infection (18). The true extent of this pyrexia syndrome was likely under-represented in the clinical trial data, as patients may experience symptoms without a

documented elevation in body temperature (19). While not compared directly, typical MEK inhibitor toxicities such as acneiform rash were also less common with the combination than with MEK inhibitor monotherapy.

CombiDT was the first combination therapy approved in Australia for the treatment of melanoma by the Therapeutic Goods Administration (TGA), and the only one currently funded via the Pharmaceutical Benefits Scheme (PBS) for the first line treatment of patients who have unresectable Stage III/IV BRAF V600 mutation-positive advanced melanoma (20). Combination therapy with vemurafenib and the MEK inhibitor cobimetinib also has TGA approval for treatment of patients with unresectable or metastatic melanoma with BRAF V600 mutation, however as yet this combination is not listed on the PBS.

Here we offer guidance on managing adverse events that are likely to arise during treatment with CombiDT in order to improve treatment tolerability, in particular to prevent unnecessary treatment cessations or reduction in drug exposure, thus ensuring the best outcome for patients undergoing treatment. The recommendations presented are based on our observations and experiences managing patients on CombiDT in day-to-day, real-world clinical practice as well as on consideration of the relevant published literature.

Pre-assessment considerations

Baseline standard of care assessments should be performed including imaging to assess the extent of disease and blood tests including full blood count, biochemistry, liver function tests and a lactate dehydrogenase (LDH) test. An echocardiogram should be considered for patients with a history of cardiac disease who may be at increased risk of drug-induced cardiomyopathy. An ophthalmological

review should be considered for those with a history of ocular conditions such as retinal vein occlusion or significant retinal pathology.

Concomitant medications that have the potential to affect drug metabolism should also be reviewed (Table 1). Dabrafenib may result in loss of efficacy of warfarin as it has been shown to decrease the systemic exposures of S-warfarin and R-warfarin (21). INR should be monitored more frequently during initiation or discontinuation of dabrafenib, or an alternative anticoagulant should be used. Dabrafenib is mainly metabolized by CYP2C8 and CYP3A4. Strong inhibitors of CYP2C8 or CYP3A4 such as gemfibrozil and ketoconazole are likely to increase dabrafenib concentrations (21) and should be used with caution, and alternative agents used where possible. Inducers of CYP2C8 or CYP3A4 such as rifampin should be avoided as they may reduce the efficacy of dabrafenib. Trametinib is not associated with any significant drug interactions.

Comprehensive patient education should occur covering topics such as the intent of treatment with CombiDT, and the dose and timing of doses, including in relation to meals. Common adverse effects and potentially serious adverse effects should be discussed with the patient, and emergency contact details provided. Written information regarding adverse effects and actions to take may be of benefit. Specific detailed education should be given regarding the management of pyrexia syndrome.

Patients should have baseline staging scans performed. Computed tomography (CT) imaging should cover all areas of known disease. Staging should include imaging of the brain with either MRI or contrast enhanced CT, as brain metastases may require local treatment. Patients should be reviewed shortly after starting CombiDT and have repeat imaging at 8 to 12 weekly intervals. Ongoing review every 4 to 6 weeks should include prior blood tests to assess renal and liver function

together with a full blood count. 12 weekly PET/CT may be useful to monitor response. If the patient is tolerating treatment well with ongoing response, the review interval can be extended.

Adverse event management

Adverse effects most commonly associated with CombiDT include pyrexia (and associated symptoms), nausea, diarrhea, and rash. Rarely cardiac and ocular events may occur.

Pyrexia syndrome

The majority (53%) of patients on CombiDT are likely to experience pyrexia syndrome at least once, and it can be a recurrent problem in some cases (9, 18, 19). A post hoc analysis of a phase I/II study of CombiDT, which included all patients treated at the standard dose (150/2), found that patients experienced a median of two events of pyrexia, and 21% of patients had four or more events (19). The median time to onset from the start of treatment was 19 days (range 1 to 82 days) and the median duration was 9 days (19).

The etiology of CombiDT-related pyrexia is currently unclear. It is not possible before starting treatment to predict who will experience pyrexia or how severe it will be. Without appropriate intervention, pyrexia syndrome has the potential to worsen and can result in hypotension secondary to dehydration and associated organ sequelae.

For the purpose of these guidelines, the pyrexia syndrome is defined as one or more of the following symptoms:

- Fever (≥ 38ºC)
- Chills / rigors / night sweats
- Flu-like symptoms

Because the presence of any of the above symptoms indicates pyrexia syndrome, the presence of high temperature is not required. Patients with will often identify a prodrome prior to the development of fever or significant symptoms of pyrexia, and if this occurs, management should be the same as for established pyrexia syndrome.

Before initiating treatment with CombiDT patients should be reassured that pyrexia is experienced by most, is generally manageable without requiring permanent discontinuation of treatment, and that it is safe and important to temporarily interrupt CombiDT treatment to manage pyrexia. Patients should be provided with written information about the likelihood of experiencing pyrexia, its symptoms and management and when to seek help. Also provide instructions for how to seek advice out of regular working hours. Patients should understand that if they experience the pyrexia syndrome and do not cease dabrafenib and trametinib the symptoms will persist and often intensify.

Recommendations for management of pyrexia syndrome (Figure 1)

1. Advise the patient to immediately stop taking both dabrafenib and trametinib, and contact their medical oncologist or nurse specialist if they feel they need urgent medical attention, if their fevers do not start to improve within 24 hours or if fevers are accompanied by additional or more severe symptoms e.g. rigors, chills, sweats, postural dizziness and oliguria, suggesting dehydration. Prompt treatment interruption as soon as possible after symptom onset will generally result in quicker symptom resolution and enable earlier resumption of treatment.
2. Consider the use of paracetamol or non-steroidal anti-inflammatory drugs (NSAIDs e.g. ibuprofen) to help alleviate symptoms. Prophylactic paracetamol or NSAIDs are ineffective and not recommended (19). Routine use of antibiotics is not appropriate for patients with pyrexia syndrome. Antibiotics should only be used when the presence of infection has been

confirmed or is highly suspected, or in patients who are unwell where sepsis cannot be excluded. Encourage oral fluid intake to avoid dehydration due to insensible water loss with fever.

3. If symptoms do not improve 24 hours after interrupting treatment, or symptoms become more severe or are causing specific concern, the patient should re-contact their medical oncologist or nurse specialist or present to after-hours care immediately for a full assessment.
4. After interrupting treatment, the patient should be reassessed every 2 days until dabrafenib and trametinib are recommenced. This can be in person or over the phone, but if the symptoms have not resolved after a maximum of 5 days, the patient requires a full and immediate assessment.
5. Do not recommence dabrafenib and trametinib treatment until the patient has been symptom free for at least 24 hours.
6. In cases of uncomplicated pyrexia syndrome (that is, fever, chills or fatigue without localizing symptoms and which begin to improve within 24 hours of treatment cessation) patients should recommence CombiDT at the same dose after they have been symptom-free for at least 24 hours; this is often between 2 and 7 days after stopping treatment.
7. Advise patients to seek urgent medical review, which may include presentation to an Emergency Department if they are unable to contact their medical oncologist or nurse specialist, in the event of the following after treatment interruption:
    a. Fever which does not improve within 24 hours
    b. Confusion

c. Localizing symptoms

d. Vomiting and/or dehydration (dizziness, low urine output)

Recommendations for management of recurrent or severe pyrexia syndrome

Consider one or a combination of both of the following strategies in consultation with a medical oncologist who is a melanoma specialist:

1. Use an intermittent dosing strategy, but at full dose. Expert opinion suggests that intermittent dosing is an effective management strategy that is unlikely to impact efficacy and is preferable to dose reduction (19, 22, 23), although randomized clinical trial evidence is lacking. For example, if a patient experiences pyrexia syndrome every 2 to 3 weeks, consider treating for 12 days followed by a 2-day break.
2. Add a corticosteroid as a prophylactic measure. For example, initiate prednisone 10 to 25 mg per day and begin titrating downwards if/when the patient has remained pyrexia free for at least one month. Very occasionally, patients may require a higher dose of prednisone to manage pyrexia.
3. Dose reduction can be considered if intermittent dosing and corticosteroid prophylaxis have failed.

Rash

Rash occurs commonly and within days of starting treatment but is not often particularly troubling to the patient. It has been reviewed comprehensively in other articles (24, 25)

Mild macular or papular rashes caused by BRAF inhibitors only require supportive care, such as twice-daily moisturizing, and treatment with a topical corticosteroid and anti-histamine for itch. Rarely dermatological review may be required. However, dose reduction or interruption may be required if the rash is severe (≥ grade 3).

MEK inhibitors as monotherapy cause an acneiform rash. It is rarely observed in combination with BRAF inhibitor. A mild trametinib-related rash may occur when a patient stops both drugs, because of the longer half-life of trametinib. If a patient experiences a mild acneiform rash on CombiDT, it can be managed with topical antibiotics (e.g. topical clindamycin) or oral antibiotics. A dose interruption or reduction may be required if the rash is severe (≥ grade 3).

Painful lobular panniculitis has been reported in case studies of patients on BRAF inhibitors and combination BRAF and MEK inhibitors (24, 26). Panniculitis and arthralgia can require dose reduction. By initiating treatment early with topical or oral steroids and non-steroidal anti-inflammatory drugs, patients can remain on CombiDT treatment.

Fatigue

Fatigue should be assessed for cause and lifestyle modifications made if appropriate. Drug-induced severe fatigue may benefit from intermittent regimen (for example, 5 days on followed by 2 days off treatment every week) or a dose reduction if treatment is severely impacting the patient's quality of life. Low dose corticosteroids can be used if appropriate to help the very symptomatic patient who does not respond to other interventions. Other causes of fatigue, such as disease progression, infection and anaemia, should be ruled out.

Management of CombiDT therapy during surgery and radiotherapy

Surgery

CombiDT does not require dose interruption pre- or post-surgery. Patients can resume therapy once they are able to take medications orally.

Radiotherapy

There is no published data specifically on CombiDT or combined BRAF and MEK inhibition and radiotherapy, and therefore, recommendations regarding concomitant treatment are based on studies of BRAF inhibitors. In our experience as a group, combination therapy does not increase skin toxicity compared with single agent BRAF inhibition. The addition of a MEK inhibitor to a BRAF inhibitor may ameliorate skin toxicity seen with concomitant BRAF inhibition and radiotherapy.

BRAF inhibitor monotherapy may cause radiosensitization (27, 28). However, there is a lack of definitive toxicity and efficacy data, and there is no standard approach to continuing or interrupting drug therapy while undergoing radiotherapy. The Eastern Cooperative Oncology Group consensus recommendations (29), although not evidence based, include that BRAF inhibitors and MEK inhibitors should be stopped for a minimum of three days before and after fractionated radiotherapy, and for a minimum of one day before and after stereotactic radiotherapy (SRS). The same recommendations are provided for all BRAF inhibitor and MEK inhibitor therapy although most of the evidence assessed was from trials of the BRAF inhibitor vemurafenib.

A study of 70 patients treated with radiotherapy and concomitant BRAF inhibitor therapy in 11 European countries found that after 86 episodes of radiotherapy, 36% of patients had acute radiodermatitis (≥ CTCAE grade 2) and 13% had follicular cystic proliferation (30). In a non-randomised comparison with patients receiving vemurafenib, vemurafenib was associated with significantly higher levels of acute radiodermatitis than dabrafenib (40% vs 26%, p=0.07). There was no radiodermatitis > grade 1 seen with SRS. The occurrence of acute dermatitis ≥CTCAE grade 2 in 32 patients receiving whole brain radiation therapy (WBRT) with concomitant BRAF inhibitor therapy

was higher than in 91 patients treated with WBRT only (44% vs 8%, p<0.001; non-randomised comparison).

Recommendations

There is a lack of published data, and opinion and clinical practice differ regarding therapy interruption when using radiotherapy and combined BRAF and MEK inhibition. Clinicians should consider factors such as disease volume, pace of disease, the location of the lesion and the dose of radiotherapy when deciding the risk benefit of stopping CombiDT for radiotherapy. Caution should be taken with higher doses of radiotherapy as there is even less data available, as most studies are limited to palliative doses.

Dose interruptions are not required for SRS or Gamma Knife therapy.

For WBRT the clinical scenario and need for concurrent therapy must be considered, in the absence of reported data demonstrating safety and efficacy.

The half-life of BRAF and MEK inhibitors and their metabolites is such that if there is concern about concurrent dosing, therapy needs to be ceased at least 5 days before performing radiotherapy.

Second line therapy

- We have provided recommendations to increase tolerability of CombiDT therapy based on our experience and published literature.
- If treatment needs to be discontinued due to disease progression, toxicity or other reason, the washout period of CombiDT should be considered.
- All trials to date have had a 2- to 4-week washout period (31).

- When switching from CombiDT to ipilimumab or combined ipilimumab plus nivolumab a caution is required as the phase I study of trametinib in combination with ipilimumab reported a high rate of bowel perforation. The optimal washout period when switching to ipilimumab is 2- to 4-weeks, however clinical factors such as disease burden and rate of progression may preclude this.
- The phase II study of pembrolizumab in combination with CombiDT was not associated with any new safety concerns. Therefore, when switching from CombiDT to single agent anti-PD1 agent a shorter or no washout can be considered (32).

Summary

The combination of dabrafenib and trametinib is an important therapy for patients with BRAF mutant metastatic melanoma. In order to help prevent unnecessary treatment cessations and to improve patient quality of life for patients on CombiDT, we have provided recommendations for managing common adverse events, and for managing therapy during surgery and radiotherapy.

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Figures

Figure 1: Pyrexia syndrome management algorithm

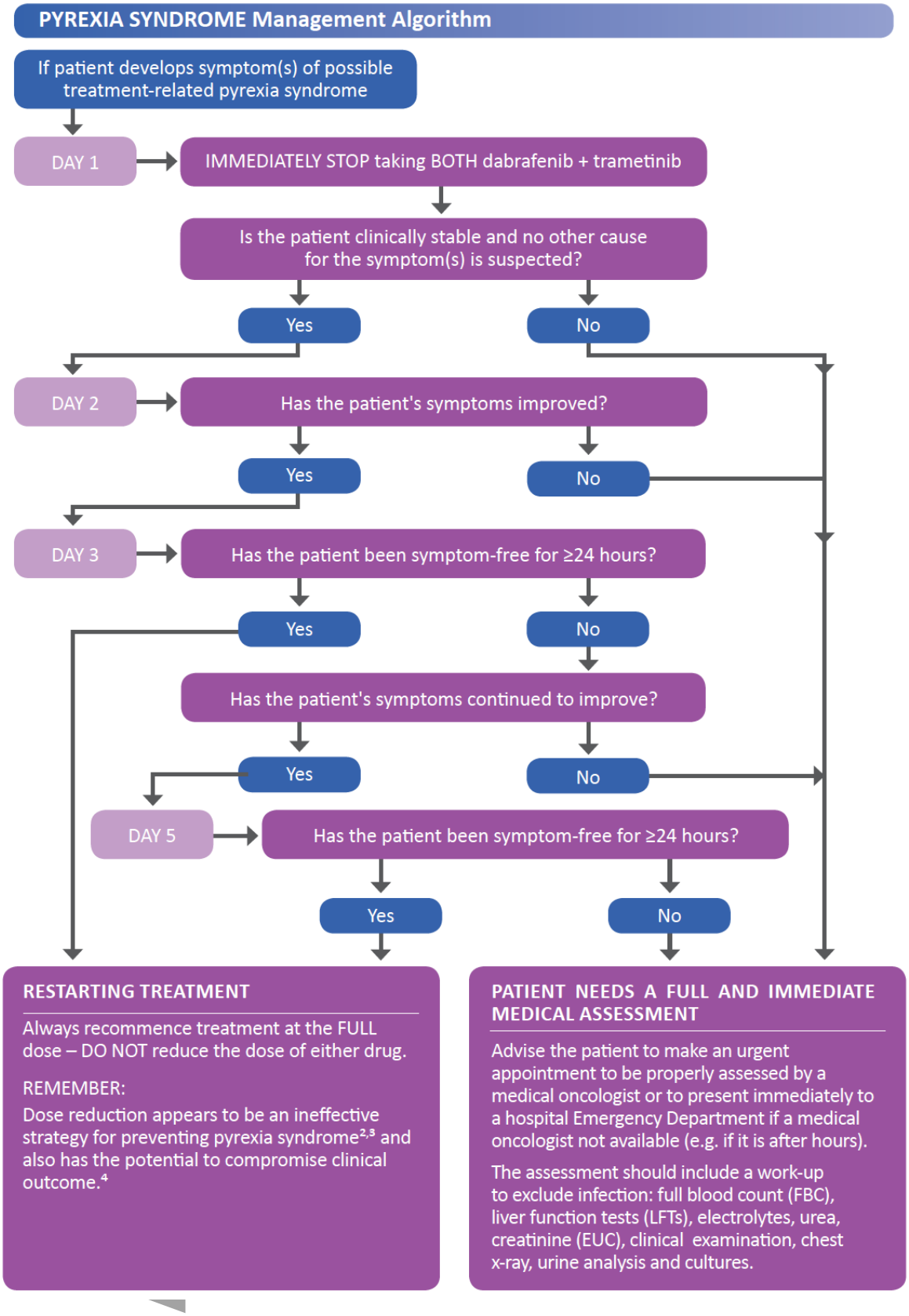

Table 1 Drug interactions (21)

Concomitant medications may result in increased or decreased dabrafenib concentrations
Use caution if coadministering strong inhibitors of CYP3A4 or CYP2C8 which are likely to increase concentrations of dabrafenib e.g. ketoconazole, nefazodone, clarithromycin, ritonavir, saquinavir, telithromycin, itraconazole, voriconazole, posaconazole, atazanir, gemfibrozil
Avoid coadministration with potent inducers of CYP3A4 or CYP2C8 which are likely to decrease concentrations of dabrafenib e.g. rifampin, phenytoin, carbamazepine, phenobarbital, St John's wort (Hypericum perforatum)
There is a theoretical risk that medicines that decrease dabrafenib solubility (increase pH) may decrease oral bioavailability of dabrafenib e.g. proton pump inhibitors
Dabrafenib may result in reduced concentrations of concomitant medications
Dabrafenib induces CYP3A4 and CYP2C9 mediated metabolism and may induce other enzymes. Concomitant use of the following medicines should be avoided if monitoring for efficacy and dose adjustment is not possible e.g. hormonal contraception, dexamethasone, antiretroviral agents, immunosuppressants due to decreased concentrations and loss of efficacy Warfarin may be used with caution. Consider additional International Normalised Ratio (INR) monitoring.

Onset of induction is likely to occur after 3 days of repeat dosing with dabrafenib.