



## Combination therapy for metastatic melanoma: a pharmacist's role, drug interactions & complementary alternative therapies

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### Practice points

- Metastatic melanoma is a very chemotherapy-resistant disease with a dismal prognosis.
- Nivolumab and pembrolizumab have a more distant mechanism of action than ipilimumab.
- Drug resistance to anti-BRAF therapy is known to develop quite quickly.
- Inhibiting the MEK kinase of the MAPK pathway, by MEK inhibitors, and by associating them with anti-BRAF<sup>V600</sup> therapy, can delay the development of resistance.
- The nature of drug–drug interactions can either be pharmacokinetic, pharmacodynamic or pharmaceutical.
- During patient counseling, it is essential to do a complete medication history and medication reconciliation.
- The use of complementary and alternative medicine is on the rise in the oncology population.
- Natural products and herbs are not regulated in as stringent and rigorous a fashion as traditional drugs used in medicine.

The incidence of metastatic melanoma has been increasing dramatically over the last decades. Yet, there have been many new innovative therapies, such as targeted therapies and checkpoint inhibitors, which have made progress in survival for these patients. The oncology pharmacist is part of the healthcare team and can help in optimizing these newer therapies. There will be discussion about combination therapies, the oncology pharmacist's role, and issues at the core of his interest, such as drug interactions and complementary and alternative therapies.

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The incidence of metastatic melanoma has been dramatically increasing over the last 40 years [1]. Historically, metastatic melanoma has been a very chemotherapy-resistant disease with a dismal prognosis. Prior to the development of targeted therapies and immunotherapies, survival rates were in the order of 6 months with or without treatment with chemotherapy, where agents such as dacarbazine, temozolomide or chemotherapy associations such as paclitaxel and carboplatin have been used with disappointing results [2–4].

The stimulation of the immune system for the treatment of melanoma has shown in the past a couple of success stories: IFN- $\alpha$  was for many years a standard of treatment for the adjuvant treatment of melanoma, and a minority of patients treated with IL-2 for metastatic melanoma showed very interesting longstanding and durable responses [3]. Unfortunately, very low response rates in the order of approximately 6% of patients, an important side effect profile, and indirect costs associated with hospitalizations, have rendered IL-2 an option for very few patients [3,4]. Yet these experiences have generated an interest in continuing to define the importance of the immune system as a potential target for the treatment of metastatic melanoma [3].

During the last decade, we have had the opportunity of witnessing dramatic improvements in the treatment of metastatic melanoma. In patients that express a BRAF<sup>V600</sup> mutation, we have seen that targeted therapy inhibiting the MAPK pathway with either vemurafenib or dabrafenib has generated high response rates [5–7]. The use of

**Table 1. Phase III combination trials for the treatment of metastatic melanoma. Checkpoint inhibition and immunotherapy: anti-CTLA-4 and anti-PD-1 combination in the Checkmate 067 study.**

Treatment	Number of patients	Response rates (%)	mPFS (months)	Grade 3–4 AEs (%)
Nivolumab + ipilimumab	314	57	11.5	55.0
Nivolumab	316	44	6.9	16.3
Ipilimumab	315	19	2.9	27.3

AE: Adverse event; mPFS: Median progression-free survival.  
Data taken from [2,30–33].

ipilimumab, an anti-CTLA-4 inhibitor that restores T-cell function targeting tumor cells has yielded much needed overall survival improvements and durable responses of 3 years in approximately 20% of patients; certain patients achieving this milestone reach a stable plateau of response that has been reported to last up to 10 years in a certain number of patients [8–11]. Checkpoint inhibition or anti-programmed death-1 (PD-1) therapy with nivolumab or pembrolizumab that also restores T-cell function at a more peripheral level and at the tumor site was developed to try to increase the number of response rates while improving the toxicity profile of anti-CTLA-4 therapy [12–16].

In this article, we will define a recent trend in the treatment of metastatic melanoma which is the use of combination therapy: in patients with a BRAF<sup>V600</sup> mutation, we will discuss BRAF inhibition in association with an MEK inhibitor, either trametinib or cobimetinib; we will also discuss the association of anti-CTLA-4 and anti-PD-1 therapy [2,17–19]. We will discuss the role of the oncology pharmacist in treating patients that have metastatic melanoma. We will focus our attention on pharmacy issues of drug interactions, and the use of natural products or complimentary and alternative medicine (CAM) in this patient population. We will not discuss side effect management of these newer combination therapies because this issue has been discussed extensively elsewhere [4,20–26]. We will try to make this article more of a practical tool for pharmacists and other healthcare practitioners than a theoretical one.

### Combination therapy for the treatment of metastatic melanoma: Phase III trials Immunotherapy: anti-CTLA-4 therapy & anti-PD-1 therapy

In recent years, many innovations have demonstrated benefits in the treatment of metastatic melanoma that have rendered the use of classic chemotherapy nearly obsolete [2–4]. The development of immunotherapy with ipilimumab, an anti-CTLA-4 inhibitor, or the checkpoint inhibitors which are anti-PD-1 inhibitors, such as nivolumab or pembrolizumab have made a major impact on metastatic melanoma survival [3].

Ipilimumab was the first molecule since approximately 45 years of use of dacarbazine to demonstrate an increase in progression-free and overall survival [2–4,6]. A meta-analysis has clearly shown overall survival rates of 20% at 3 years and if a patient is fortunately alive at this 3-year mark, he has a good chance at a potential long-term survival where patients have been reported alive and well 10 years post-therapy [10]. The issues with ipilimumab are that it is a very costly therapy with low response rates and no biomarker which may help us in defining beforehand which patient might well respond to this therapy [1].

Checkpoint inhibitors, or anti-PD-1 receptors, either nivolumab or pembrolizumab, have a more distant mechanism of action than ipilimumab [27–29]. Anti-PD-1 therapy restores T-cell function peripherally and at the tumor site. The idea behind this difference is that we may improve response rates with these molecules and improve the toxicity profile compared with ipilimumab [13]. These goals have been attained for nivolumab and pembrolizumab in comparative Phase III trials to ipilimumab that have been described elsewhere and are outside the scope of this article [2].

The Checkmate 067 was a 3-arm randomized Phase III trial that offered treatment to 945 patients with unresectable stage III or stage IV melanoma as a first line of therapy. Patients were randomized either to ipilimumab monotherapy (n = 315), nivolumab monotherapy (n = 316) or the combination of ipilimumab and nivolumab (n = 314). The results of this trial (see Table 1) demonstrated that the combination therapy had a statistically significant superiority over either agent alone with regard to median progression survival and objective response rates. The downside to this combination therapy is the important increase in grade 3–4 toxicity rates with the combination therapy versus either agent being used alone used as monotherapy [30].

At this time, there are no published Phase III trials involving pembrolizumab in combination therapy for the treatment of unresectable or metastatic melanoma.

**Table 2. Phase III combination trials for the treatment of metastatic melanoma. Targeted therapy: BRAF<sup>V600</sup> inhibitors and MEK inhibitors combination.**

Study	Treatment	Number of patients	Response rates (%)	Duration (months)	mPFS (months)	OS	>Grade 3 AEs (%)
COMBI-d	Dabrafenib + trametinib	211	69	12.9	11.0	25.1 months	32
	Dabrafenib + placebo	212	53	10.6	8.8	18.7 months	32
COMBI-v	Dabrafenib + trametinib	352	64	13.8	11.4	–	52
	Vemurafenib	352	51	7.5	7.3	–	63
Co-BRIM	Vemurafenib + cobimetinib	247	68	ND	9.9	81% <sup>†</sup>	65
	Vemurafenib + placebo	248	45	7.3	6.2	73% <sup>†</sup>	59

<sup>†</sup> Overall survival rate at 9 months.

AE: Adverse event; mPFS: Median progression-free survival; ND: Not determined; OS: Overall survival. Data taken from [2,30–33].

### Targeted therapy: BRAF<sup>V600</sup> inhibitors & MEK inhibitors

Patients that express BRAF<sup>V600</sup> positive, or mutated, metastatic melanoma now have the possibility of being treated with targeted therapy. Patients can now be treated with BRAF<sup>V600</sup> inhibitors, either vemurafenib or dabrafenib, which inhibit the intracellular MAPK pathway by inhibiting the BRAF kinase which ultimately leads to cell death. Anti-BRAF<sup>V600</sup> therapy has demonstrated in Phase III trials improvements in overall survival rates and progression-free survival compared with classic chemotherapy [2,4,6,7,4].

The first issue that must be taken into consideration with treatment with BRAF<sup>V600</sup> inhibitors is that drug resistance to anti-BRAF therapy is known to develop quite quickly. The second issue is that once anti-BRAF therapy resistance is known, metastatic melanoma appears to progress very rapidly and it is very difficult to regain control of the disease at this point. Despite these drawbacks, anti-BRAF<sup>V600</sup> therapy is an excellent choice in patients that present with aggressive BRAF<sup>V600</sup>-positive disease because patients usually respond quickly to anti-BRAF<sup>V600</sup> therapy [2,4,6,7,4].

In order to overcome drug resistance which may develop over time to vemurafenib or dabrafenib therapy, the idea of targeting a different kinase of the MAP pathway may prove to be beneficial. Therefore, inhibiting the MEK kinase of the MAPK pathway, by MEK inhibitors such as trametinib or cobimetinib, and associating one of them with an anti-BRAF<sup>V600</sup> agent may bring a benefit and delay the development of resistance to treatment. Different Phase III trials have looked at this issue [2,4,6,7,4].

The Co-BRIM trial is a Phase III trial that studied the association of vemurafenib to either cobimetinib (n = 247) or a placebo (n = 248) in patients with untreated unresectable or metastatic melanoma with BRAF<sup>V600</sup> mutations. This trial (see Table 2) demonstrated that the association of cobimetinib to vemurafenib compared with vemurafenib alone improved the rate of progression-free survival (9.9 vs 6.2 months, p < 0.001), response rates (68 vs 45%, p < 0.001) and 9-month overall survival rates (81 vs 73%, p = 0.046) [31].

The COMBI-d trial (see Table 2) looked at combining dabrafenib to either trametinib (n = 211) or a placebo (n = 212) in previously untreated patients with unresectable stage IIIc or metastatic melanoma with BRAF mutation disease. The combination therapy demonstrated over anti-BRAF<sup>V600</sup> monotherapy an improvement in progression-free survival (11.0 vs 8.8 months, p = 0.0004), in overall response rates (69 vs 53%, p = 0.0014) and overall survival (25.1 vs 18.7 months, p = 0.0107) [32].

The Phase III COMBI-v trial evaluated the association of dabrafenib and trametinib (n = 352) to vemurafenib monotherapy (n = 352) in patients with previously untreated BRAF-mutated metastatic melanoma. The combination therapy compared with anti-BRAF<sup>V600</sup> monotherapy showed an improvement in response rates (64 vs 51%, p < 0.001), in progression-free survival (11.4 vs 7.3 months, p < 0.001) and 12-month overall survival rate (72 vs 65%) [33].

### The role of the oncology pharmacist

The role of the oncology pharmacist in treating patients is multifold (see Table 3). The first step would be at the validation of the prescription, whether the treatment is chemotherapy, immunotherapy or targeted therapy. It is here where we validate appropriate treatment choice versus clinical indication, appropriate dose of treatment versus renal and hepatic function and if any dosage recommendations are required. A medication reconciliation should be done to make sure that the patient is not taking any other medications, which may interfere with the efficacy

**Table 3. Roles of the oncology pharmacist in treating patients with metastatic melanoma.**

Role	Details
Prescription validation	<ul style="list-style-type: none"> <li>Validating clinical indication and appropriate therapy, validating dose, route of administration and dosing schedule, validation of dosage adjustment versus toxicities and renal or hepatic function</li> </ul>
Treatment preparation	–
Education	<ul style="list-style-type: none"> <li>Other healthcare professionals</li> <li>Patients: medication history, medication reconciliation, patient counseling, side effect prevention and management, managing drug interactions, counseling on complimentary or alternative therapies (natural products)</li> </ul>
Side effect management and supportive care, if required	–
Facilitator role for drug access or access to compassionate programs, if required	–
Research and managing clinical trials	–
Linking with other healthcare practitioners in the community (e.g., community pharmacists)	–
Data taken from [4,34].	

of the chosen antimelanoma therapy. During medication reconciliation, it is always very important to define if the patient is taking any CAM, which may also have an impact on the efficacy of treatment.

The oncology pharmacist plays an important role in the preparation of the antimelanoma treatment. Independently of what type of therapy will be given to the patient, he must make sure that the chosen treatment is prepared in the safest fashion possible and in accordance with and with respect to current manipulation of hazardous products recommendations (e.g., NIOSH) or basic aseptic technique recommendations (e.g., USP). The techniques of preparation of these products are often delegated to pharmacy technicians or technical assistants. Their tasks are delegated tasks under the supervision of an oncology pharmacist: they must well understand their responsibilities, use the most current techniques of preparation which are validated, evaluated periodically and controlled by the oncology pharmacist.

Education is an important role of the oncology pharmacist. It can be towards other healthcare professionals or residents or even students. But the most important educational role is towards the patient. Each patient starting antimelanoma therapy should be met with and have the chosen treatment explained. Issues of appropriate dosage and how to take the medication the most efficiently (e.g., in the context of oral targeted anti-BRAF<sup>V600</sup> and anti-MEK therapy). The dosing schedule should be clear for the patient and so should be the treatment plan. It is important to discuss side effects of the chosen therapy and what can be done either to prevent, if possible, or to control them; this issue is very important with anti-CTLA-4 or anti-PD-1 therapy where the side effects are more frequent with combination therapy, they may also present at any given time and sometimes even after the treatment has stopped. All of this information should be reinforced with a written handout and clear information on where to call about any questions, issues, or worries.

During the patient counseling described above, it is essential to do a complete medication history and medication reconciliation to detect any contraindications or discrepancies with regards to the current medication list or potential drug interactions, and to validate if the patient is taking or seeking any CAM.

The oncology pharmacist is an important player in the multidisciplinary approach to optimizing treatment of the patient with metastatic melanoma; he may bring his expertise to the healthcare team and be of value to others by his skills in education, communication of knowledge to others and his thorough and keen knowledge about current therapies and how to maximize their therapeutic benefit and minimize toxicities and how to best manage them [4,34,35].

### *Drug interactions*

During the last 20 years, we have witnessed a trend of classic chemotherapy being challenged by newer therapies such as monoclonal antibodies and targeted therapy. There has also been a trend to develop oral therapies in order to simplify therapies for patients and to try to decrease the number of patients being treated in ambulatory oncology clinics [36,37]. This is also true for the treatment of metastatic melanoma. Yet, this brings on issues of potential drug–drug interactions which need to be challenged because they are a major concern in oncology, due to a narrow therapeutic index of molecules and toxicity of anticancer therapies. This is at the heart of what an

oncology pharmacist does on a daily basis whether it be during prescription validation, medication reconciliation or patient counseling [38,39].

Drug–drug interactions happen when two drugs that are either inducers, inhibitors or substrates of the same metabolic enzyme are administered together and could lead to an unexpected metabolism of one or the two drugs. This could lead potentially to a lack of efficacy or severe toxicity [40,41]. The nature of drug–drug interactions can either be pharmacokinetic, pharmacodynamic or pharmaceutical. Pharmacokinetic interactions happen when one drug alters another drug by affecting either its absorption, distribution, metabolism or excretion. Pharmacodynamic interactions occur when drugs influence each other's effect directly due to competing at a receptor site on the same physiological system. Pharmaceutical interactions take place when drugs are combined in solution or admixed during infusion that is issues of physical or chemical compatibilities [40–43].

Pharmacokinetic drug–drug interactions altering drug metabolism are common. The CYP450 is a metabolic enzyme system whose purpose is to eliminate drugs from the body. Many enzyme families have been identified within this entity; yet, the CYP3A4 is the most common involved in the metabolism of current medications. There are other isoenzymes which should be taken into consideration: CYP1A2, CYP2C9 and CYP2D6. A drug that inhibits the CYP450 enzymes will generally decrease the metabolism of a given drug, thus leading to potentially higher drug concentrations and therefore potential increased toxicity. This phenomenon happens quickly. The opposite phenomenon, where a drug induces the CYP450 system, would result in an increased clearance of the other drug, decreasing its serum concentration and potentially its efficacy. This phenomenon presents itself in a slower fashion. If a drug is metabolized to an active drug via the CYP450 system and is given with an inducer, we would see an increased serum concentration of the active metabolite, which could cause potentially serious toxicities [40,44–46].

We will try to define potential drug interactions with anti-CTLA-4, anti-PD-1, anti-BRAF<sup>V600</sup> and anti-MEK therapies. We will try to address this issue in a practical fashion and try to offer tools that may help out oncology pharmacists in their current practice.

### Immunotherapy, checkpoint inhibitors: ipilimumab, nivolumab, pembrolizumab

Ipilimumab is a monoclonal antibody and is not metabolized by the CYP450 enzyme system. A Phase I combination trial of ipilimumab and vemurafenib had been stopped prematurely due to hepatotoxicity; this association is therefore not recommended [11,47].

No formal drug interaction trials have been conducted with regard to nivolumab or pembrolizumab. The risk of drug interactions for these monoclonal antibodies is considered very low [48,49].

The question that arises frequently with immunotherapy is whether immunosuppression with corticosteroids renders the immunotherapy less effective [20]. Some authors believe that the use of prior or concomitant immunosuppression can make this happen [26]. Immunosuppression is often used to treat immune-related adverse events and studies so far have demonstrated that the use of immunosuppression has not had a negative impact on response rates or on time to response compared with patients treated with immunotherapy not requiring at any given time immunosuppression [20,24]. Recommendations from the manufacturers are that immunotherapy should not be started if the patient is on active immunotherapy with corticosteroids because of the potential interference with the pharmacodynamic activity of the immunotherapy [47–49]. Some authors will put the immunotherapy on hold while treating an immune-related adverse event and will only restart the immunotherapy once the corticosteroids are tapered down to equal or less than 10 mg/day [50].

### Targeted therapy: anti-BRAF<sup>V600</sup> & anti-MEK therapy

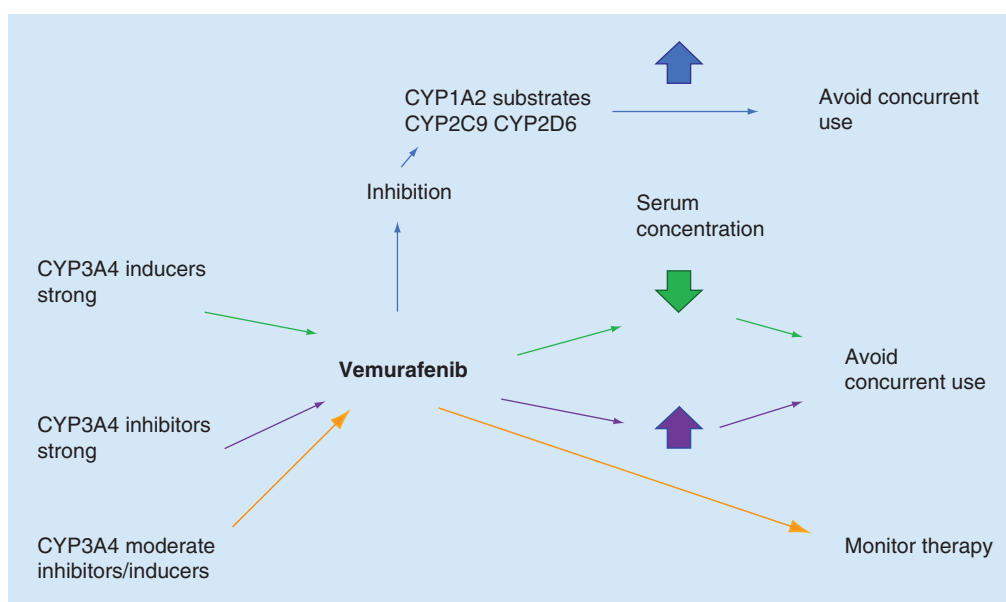
#### *Vemurafenib*

Vemurafenib is a substrate of BCRP and p-glycoprotein, and a major substrate of CYP3A4. Therefore, drugs that are either strong inducers or inhibitors of CYP3A4 (see Table 4) should be avoided if to be used concomitantly with vemurafenib; or an alternative to the inducer or inhibitor should be considered [36,51–55]. Strong inducers may decrease the serum concentration of vemurafenib and have an effect on the efficacy of the molecule. Strong inhibitors would increase the serum concentration of vemurafenib and may put the patient at risk of significant toxicity (see Figure 1) [36,52,55].

Vemurafenib is also known for causing inhibition of the metabolism of drugs that are substrates of the CYP1A2 (e.g., caffeine) and can cause an increase in the serum concentration of the substrate. Vemurafenib can also inhibit

Table 4. Strong inducers and inhibitors of CYP3A4/CYP2C8.	
Category	Compound
CYP3A4 inhibitors	Amiodarone, cimetidine, clarithromycin, ciprofloxacin, diltiazem, erythromycin, fluconazole, ketoconazole, posaconazole, voriconazole, fluoxetine, fluvoxamine, grapefruit juice, indinavir, nelfinavir, lopinavir/ritonavir, saquinavir, itraconazole, norfloxacin <sup>36</sup>
CYP3A4 inducers	Barbiturates, carbamazepine, dexamethasone, efavirenz, griseovulfin, phenytoin, primidone, rifabutin, St John's wort
CYP2C8 inhibitors	Montelukast, demfibrozil
CYP2C8 inducers	Rifampicin

Please note that this list is not exhaustive.  
Data taken from [36,51].



**Figure 1. Potential drug interactions with vemurafenib.**  
Data taken from [36,55,52].

CYP2C9 (e.g., warfarin) and CYP2D6 (e.g., dextromethorphan). An alternative should be considered or the substrate should be avoided if it has a narrow therapeutic index [36,46,52,55].

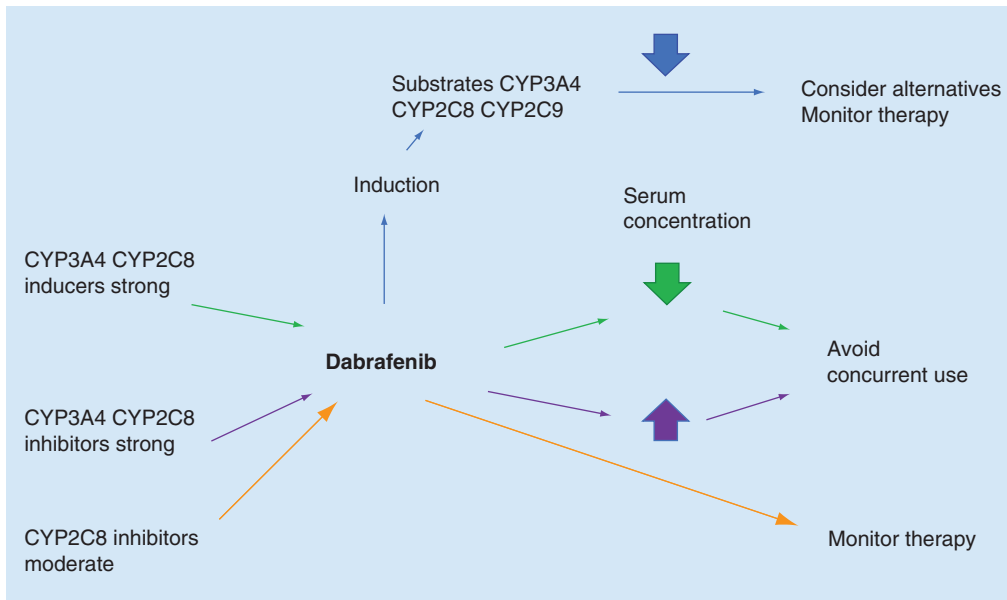
### Dabrafenib

Dabrafenib is a BRAF<sup>V600</sup> inhibitor which is metabolized to hydroxy-dabrafenib, desmethyl-dabrafenib and carboxy-dabrafenib. The clinical activity is essentially defined by the parent molecule and the first two metabolites; the role of carboxy-dabrafenib is considered to be minimal with regard to clinical activity [56–58]. Drug interactions have the potential to affect the serum concentrations of dabrafenib and its metabolites [58].

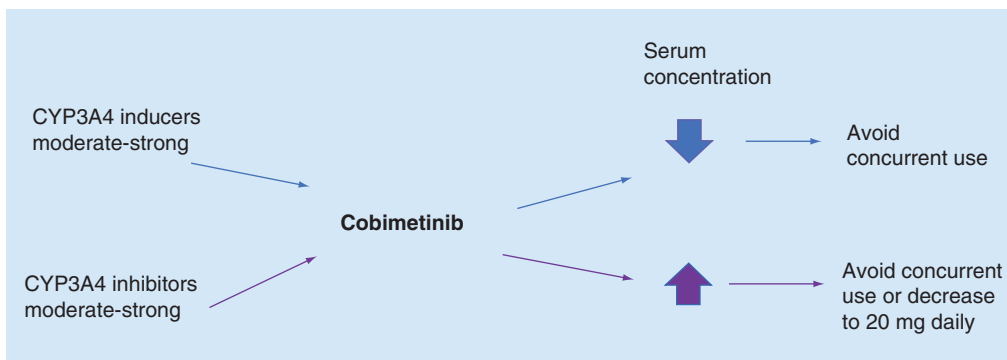
Dabrafenib is considered to be a major substrate of CYP2C8 and CYP3A4. Drugs that are either strong inhibitors or inducers of CYP2C8 should not be used concomitantly with dabrafenib (see Table 4) [36,46,52,56]. Strong CYP3A4 inducers may decrease the serum concentration of dabrafenib and one should monitor therapy closely; strong CYP3A4 inhibitors should be avoided because they may cause increased serum concentration of dabrafenib and exacerbate toxicities [52,56].

Dabrafenib is also known to be a moderate inducer of CYP2C8, CYP2C9 and CYP3A4. Dabrafenib may decrease the serum concentration of CYP2C8, CYP2C9 and CYP3A4 substrates; alternative therapies should be considered to the given substrate and concomitant therapy should be avoided; if this is not feasible, patients should be monitored closely for efficacy of the substrate [52,56]. Dabrafenib is known to decrease serum concentrations of warfarin, hormonal contraceptives and dexamethasone; substitution should be considered (see Figure 2) [58].





**Figure 2. Potential drug interactions with dabrafenib.**  
Data taken from [36,52,55,58].



**Figure 3. Potential drug interactions with cobimetinib.**  
Data taken from [36,46,52,60].

### Trametinib

Trametinib is a MEK inhibitor that does not inhibit CYP1A2, CYP2A6, CYP2B6, CYP2D6 and CYP3A4 and the inhibition of CYP2C8, CYP2C9 and CYP2C19 which is weak occurs at much higher concentrations than the therapeutic level. Trametinib is an inducer of CYP3A4 *in vitro* but at a low level. Therefore, interactions with substrates are not anticipated [46,52,56,59],56.

### Cobimetinib

Cobimetinib is another anti-MEK molecule which is a known major substrate for CYP3A4; inducers should be avoided because they may decrease the serum concentration of cobimetinib and potentially have an impact on therapeutic efficacy. CYP3A4 inhibitors should be avoided if used concomitantly with cobimetinib because they may increase the serum concentration of cobimetinib and may lead to increased toxicity. Some authors recommend decreasing the cobimetinib dose to 20 mg daily (regular dosage is 60 mg p.o. daily; see Figure 3) [46,52,60].

Cobimetinib has been shown *in vitro* to be an inhibitor of CYP3A and CYP2D6 but this effect has not been seen at clinically relevant doses in clinical practice [46,60,46].

**Box 1. Useful tools for the oncology pharmacist to help in dealing with drug interactions.**

- <https://online.lexi.com>
- Drug monographs and package inserts
- [www.uptodate.com](http://www.uptodate.com)
- [www.drugs.com](http://www.drugs.com)
- [www.wolterskluwer CDI.com](http://www.wolterskluwer CDI.com)
- [www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/UCM292362.pdf](http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/UCM292362.pdf)
- [www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm](http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm)
- <http://medicine.iupui.edu/clinpharm/ddis/main-table/>

Please note that this list is not exhaustive. Some of these websites may require a subscription.  
Data taken from [42,46,52,61].

**Box 2. Position statements and useful websites which may help in counseling patients with regard to use of complementary and alternative medicine or natural products.**

**Position statements**

- British Columbia Cancer Agency  
[www.bccancer.bc.ca/drug-database-site/Documents/NHPandCancerTherapy\\_1Jan06.pdf\(0:bold\)/\(0:bold\)](http://www.bccancer.bc.ca/drug-database-site/Documents/NHPandCancerTherapy_1Jan06.pdf(0:bold)/(0:bold))
- Cancer Care Ontario <https://archive.cancercare.on.ca/common/pages/UserFile.aspx?fileId=13376>
- Clinical Oncology Society of Australia [78]

**Useful Websites**

- [www.canada.ca/en/health-canada/services/drugs-health-products/natural-non-prescription.html](http://www.canada.ca/en/health-canada/services/drugs-health-products/natural-non-prescription.html)
- [www.cancer.ca/~media/cancer.ca/CW/publications/Complementary%20therapies/Complementary-therapies-EN.pdf](http://www.cancer.ca/~media/cancer.ca/CW/publications/Complementary%20therapies/Complementary-therapies-EN.pdf)  
Complementary therapies: a guide for people with cancer
- [www.mskcc.org/cancer-care/diagnosis-treatment/symptom-management/integrative-medicine/herbs](http://www.mskcc.org/cancer-care/diagnosis-treatment/symptom-management/integrative-medicine/herbs)  
Memorial Sloan-Kettering, about herbs, great mobile application
- [www.uptodate.com](http://www.uptodate.com)  
Herbs, intended uses, toxicities, and interactions with chemo, complementary and alternative therapies for cancer.
- <https://online.lexi.com>
- <http://naturaldatabase.therapeuticresearch.com/home.aspx?cs=&s=ND&AspxAutoDetectCookieSupport=1>
- <https://naturalmedicines.therapeuticresearch.com/>
- <https://nccih.nih.gov/>  
National Center for Complementary and Integrative Health
- <https://nccih.nih.gov/health/herbsataglance.htm>  
Herbs at a glance.
- [www.cancer.gov/publications/patient-education/thinking-about-cam](http://www.cancer.gov/publications/patient-education/thinking-about-cam)  
Thinking about complementary and alternative medicine.
- [www.cancer.org/treatment/treatments-and-side-effects/complementary-and-alternative-medicine/complementary-and-alternative-methods-and-cancer.html](http://www.cancer.org/treatment/treatments-and-side-effects/complementary-and-alternative-medicine/complementary-and-alternative-methods-and-cancer.html)
- [www.medscape.com/viewarticle/458306\\_3](http://www.medscape.com/viewarticle/458306_3)

Please note that this list is not exhaustive. Some of these websites may require a subscription.  
Data taken from [74,78–80].

The above recommendations should be considered and individualized to the patient and his clinical condition, co-morbidities and other medications or CAM he may be taking. We recommend using the following tools in helping the oncology pharmacist in his decisional process (see Box 1).

*Complementary & alternative medicine*

CAM is defined as:

*"A group of diverse medical and healthcare systems, practices, and products that are not generally considered to be part of conventional medicine."*

This is a very large definition and for the sake of the oncology pharmacist's interest, we will limit this definition to that of natural products that encompass herbs, vitamins and minerals, probiotics, homeopathic products [62,63].



A newer concept which is growing in popularity is that of integrative medicine where alternative therapies are integrated to science-based medicine and offer the patient the integration of two very different approaches to their treatment. The use of CAM is on the rise in the oncology population and this is probably also true in patients with metastatic melanoma [64–66].

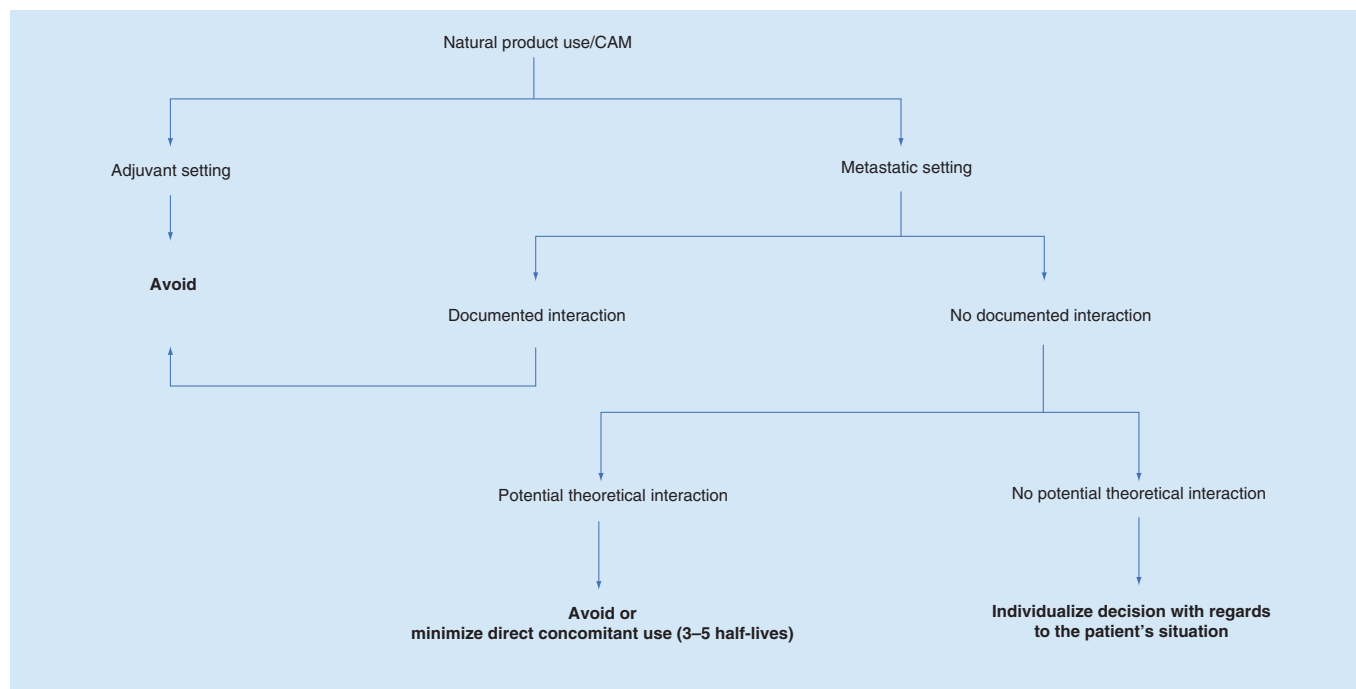
Studies have shown that CAM use is higher in patients of the female sex, patients with a higher level of education, in non-Hispanic white race patients, in patients with diminished functional status and patients of a younger age [67]. A survey has demonstrated that fewer than half of oncologists engage discussions with their patients about herbs and supplements because of a lack of knowledge and education that inhibits an open discussion about the topic. Oncologists are yet worried about herbs and supplements interfering with the efficacy of a patient's chemotherapy treatment or increasing the risk of toxicities or unwanted complications. The oncology pharmacist is the ideal healthcare practitioner to deal with this issue because of his knowledge in pharmacotherapy, his interest in optimizing the cancer treatment and his focus on patient care [68,69].

Many issues must be taken into consideration when dealing with patients that have metastatic melanoma or any other cancer that are using CAM or natural products. These products are not regulated in a stringent and rigorous fashion as traditional drugs used in medicine. This brings on issues with regard to contamination of the products that have been reported with either metals or bacteria; issues of variations of quantity or concentrations for a same product between different lots, which could have an effect on efficacy or toxicities of a given CAM. There may also be variations between a same product made by different manufacturers [64,66,70]. There is also a lack of well-done rigorous clinical trials demonstrating in a convincing manner the efficacy of a given CAM or either documenting the given toxicity profile of CAM [63,67]. From an oncology perspective, there is also the important issue of CAM interacting with potentially curable chemotherapy regimens and leading to a lack or decrease of efficacy of the chemotherapy [69].

It is very easy as an oncology pharmacist when counseling a patient that has metastatic melanoma using CAM to take the 'tough approach' and simply tell the patient that these products have not demonstrated any efficacy and may be a serious waste of time. Being oncology pharmacists with the background that we have, the education and knowledge we have about drug integrity, manufacturing processes, it is in our nature to take this 'tough approach'; for the oncology pharmacist, this is a simple way of dealing with the problem. And so the patient does not put himself at risk of a lack of efficacy of treatment, potential drug interactions caused by CAM or unwanted and unpredictable toxicities potentially attributed to CAM. Therefore, the oncology pharmacist is at ease with this approach: better safe than sorry. Yet, knowing that many cancer patients use these products and are afraid to disclose this fact with their healthcare professional for many reasons, being rigid when discussing about CAM with your patients may simply put at risk the relationship the patient has with his healthcare practitioner; and then you have jeopardized the relationship of confidence that should exist between a patient and the practitioner [66,68,71,72].

There are few clinical trials evaluating the interactions between CAM and targeted therapy or immunotherapy [73]. Some natural products are well-known inhibitors of the CYP enzyme system, such as St John's Wort that is well documented to interact with irinotecan but can interact with other substrates of the CYP system; as do garlic, Ginkgo Biloba, kava, ginseng, Echinacea, milk thistle and evening primrose oil [36,53,70,74,75]. These natural products most likely do not interact with immunotherapy for reasons we discussed earlier [48,49]. Yet, there is a potential for interaction with the CYP system and it would probably be safer to not use these CAM with vemurafenib, dabrafenib or cobimetinib since there are no data justifying the safe use of these combinations and also because we do not know to which intensity this interaction may take place. Grapefruit juice or derivatives are not CAM but are known to be an important inducer of the CYP system. It should be avoided in combination with vemurafenib or cobimetinib [55,56,60,73,76].

When counseling a patient receiving active therapy and the patient is considering or using CAM one must first consider if the patient is in the adjuvant versus palliative setting; if the patient is receiving curative adjuvant therapy, you probably will not want to jeopardize the efficacy of the treatment or induce unwanted toxicities by taking natural products. In the metastatic setting, you may be more tolerant with regard to natural product use, especially if there is no documented interaction. If ever there is a documented interaction (e.g., St John's Wort), you should base your decision on the available scientific literature. If you are in the 'unknown,' which is often the case with natural products, you may need to make your decision by individualizing the situation, keeping in mind issues such as the patient's age, co-morbidities, performance status. There is an interesting concept that we use in our practice occasionally: in a situation where a patient adamantly wants to take a natural product and requires active anticancer therapy, stopping the natural product three to five half-lives before the chemotherapy treatment



**Figure 4.** Decision algorithm to help counseling patients receiving anticancer therapy wanting to use complementary and alternative medicine alongside natural products.

and restating it three to five half-lives after the chemotherapy treatment minimizes dramatically, around 80%, of a potential pharmacodynamic interaction [73,77]. This is an easy concept to put into practice and worth mentioning; unfortunately, it is not applicable to the subject we are studying, combination therapy in metastatic melanoma, because targeted therapy is given continuously, and immunotherapies have very long half-lives. We propose an algorithm tree to help in deciding with the use of natural products and concomitant cancer therapy (see Figure 4); this process is a guide and should be adapted to each patient’s situation. There are many position statements with regard to the use of CAM and natural products and useful websites which may aid the oncology pharmacist in how to counsel and give direction to the melanoma patient considering to use or taking CAM (see Box 2).

### Conclusion & future perspective

Metastatic melanoma is still considered an incurable disease with a dismal prognosis and very resistant to chemotherapy. Yet, the last decade has seen the advent of targeted therapy and immunotherapy that has rendered chemotherapy nearly obsolete for the treatment of metastatic melanoma. There have also been some gains in survival by using combination therapies: combination of anti-BRAF<sup>V600</sup> with anti-MEK therapy in order to overcome resistance to monotherapy with anti-BRAF<sup>V600</sup> in patients with BRAF positive disease; combination of anti-CTLA-4 with anti-PD-1 therapy in order to increase response rates seen with anti-CTLA-4 monotherapy.

In this article, we have examined the results of the Phase III clinical trials looking at the treatment of metastatic melanoma with combination therapies. We have also defined briefly the role of the oncology pharmacist and how he may help melanoma patients and bring value to a multidisciplinary team. We have examined issues that are part of the daily activities that the oncology pharmacy is faced with and are quite controversial: drug interactions and CAM. These are exciting times for the treatment of metastatic melanoma where patients have hope of increased quality of life and now even hope for longstanding overall survival responses.

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