REVIEW
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Melanoma Management

Pharmacist's role in optimizing therapy of the newer agents for the treatment of metastatic melanoma

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Practice points

- Ipilimumab, vemurafenib, dabrafenib and trametinib have demonstrated survival advantages in the treatment of unresectable and metastatic melanoma in randomized controlled Phase III trials.
- Patients must be $BRAF^{V600}$ mutation positive in order to be eligible for treatment with vemurafenib, dabrafenib or trametinib.
- Patients receiving ipilimumab must be made aware of potential immune-related adverse effects and how best to manage them.
- When taking vemurafenib, patients must wear protective clothing, use an effective sunscreen and avoid sunlight for best prevention and management of photosensitivity caused by vemurafenib.
- Ipilimumab is associated with low response rates but the responders have durable responses.
- BRAF inhibitors are associated to high response rates of short duration most likely caused by the development of drug resistance.

SUMMARY Metastatic melanoma is a disease with a historically dismal survival of 6–9 months with treatment. It is considered an incurable disease and resistant to conventional chemotherapy. We have learned much about the role of newer targets in the development of melanoma which has helped us in developing targeted therapy and improving immunotherapy for the treatment of melanoma. These new therapies have a different adverse event profile from conventional chemotherapy. We will define these and their management from the perspective of the oncology pharmacist. We will also discuss the role that the oncology pharmacist can play in optimizing therapy and side effect management in the multidisciplinary team treating patients that have unresectable or metastatic melanoma.

Over the last 60 years, the incidence of melanoma in society has been increasing dramatically by 690% and the mortality rate has also been increasing by 165% [1]. Although metastatic melanoma accounts for only 5% of all skin cancers, it is responsible for 80% of skin cancer related deaths [2]. If melanoma is caught early, the 5-year survival rate is as high as 98%; unfortunately, if patients present with stage IV disease, the 5-year survival rate falls to 15% [3]. Fortunately, only 5% of patients that have melanoma present with metastatic disease at diagnosis [4].

The prognosis of metastatic melanoma remains poor with median historical survival rates of around 6–9 months with treatment [3]. Surgical resection of the melanoma should be offered to all patients whenever complete extirpation of disease is possible, including brain metastases [2,5]. Patients that are present with unresectable metastatic disease should be considered for systemic therapy, including clinical trials or palliative care [2].

KEYWORDS
• BRAF inhibitors
• dabrafenib
• immunotherapy
• ipilimumab • melanoma
• oncology pharmacist
• trametinib • vemurafenib

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Metastatic melanoma is considered a highly chemoresistant disease [2]. Historically, the treatment options were limited to dacarbazine and high-dose IL-2 [6]. Dacarbazine has not shown any survival data in a Phase III trial and is limited by low response rates in the 10–15% range [6,7]. It has also shown overall survival of approximately 8 months and has toxicities that affect the patient's quality of life [6,7]. High-dose IL-2 has also shown very low response rates in the order of 6–10% without demonstrating any survival data in a Phase III trial [7]. IL-2 has a very serious toxicity profile where patients may develop capillary leak syndrome requiring intensive care admission and other severe systemic toxicities [7]. However, anecdotally, rare patients can be put into complete remission with IL-2 and have long-term survival rates and are considered potentially cured of disease [7].

Recently, newer treatment modalities for metastatic melanoma have been developed which have demonstrated survival advantage in randomized Phase III trials. We will present these new molecules, their side-effect profiles and their management from a pharmacist's perspective. The intention of this article is of a practical nature rather than a therapeutic review which may be found elsewhere. The goal is to help oncology pharmacists in their day-to-day practice in being able to help their patients optimize their therapies treating metastatic melanoma since the advent of these newer treatments.

Defining new targets & therapeutic opportunities

Much improvement has been accomplished during the last years regarding newer therapeutic targets in melanoma. Many pathways, certain mutations and the immune system play an important role in the survival of the melanoma cell. The RAS/RAF/MEK pathway plays an important role where an NRAS mutation is present in 20% of cutaneous melanomas and that $BRAF^{V600E}$ mutations are present in 50–60% of cutaneous melanomas. cKit receptor kinase mutations are expressed in around 40% of melanomas, especially the mucosal, acral and sun-damaged subtypes [6,8]. There is also the PI3-K/AKT/mTOR pathway which may play a role in the development of the melanoma cell [6,8]. The immune system also plays a role which has been historically demonstrated with the use of interferon in the adjuvant setting and IL-2 in the metastatic setting and the use of certain vaccine therapies [9].

We will focus on molecules that have become commercially available and clinically indicated for the treatment of unresectable or metastatic melanoma: ipilimumab, the BRAF inhibitors vemurafenib and dabrafenib and the MEK inhibitor, trametinib.

Ipilimumab (YERVOY, Bristol-Myers Squibb)

Ipilimumab is a fully human monoclonal antibody against cytotoxic T-lymphocyte antigen 4 (CTLA-4) that is expressed on the surface of activated T cells [10]. Essentially, ipilimumab blocks the CTLA-4 antigen on T cells which restores and reactivates its proliferation, hence rendering activity to the immune system against the melanoma cells.

Ipilimumab has demonstrated a survival advantage in a pivotal Phase III trial, where pretreated unresectable or metastatic melanoma patients (n = 676) were randomized in a 3:1:1 fashion to ipilimumab 3 mg/kg + gp100 peptide vaccine or Ipilimumab 3 mg/kg + placebo or gp100 peptide vaccine + placebo given q 3 weeks for a total of four treatments. The primary endpoint of the trial was overall survival. The median overall survival in months was 10.0, 10.1 and 6.4 months (p = 0.003), respectively. Of note, 2 year survival rates were 21.6, 23.5 and 13.7%, respectively [11].

Essentially, the adverse effect profile of ipilimumab is, unlike the one of classic chemotherapy, immune related (see **Table 1**). The immune-related adverse events of ipilimumab are of dermatologic nature and seen as diffuse maculopapular rash, pruritis and vitiligo. They can be gastrointestinal and present as diarrhea or colitis. If the event is endocrine, it usually manifests itself as hypophysitis where the patient may experience late onset headache, fatigue, visual changes, confusion and fever. Hepatic immune-related adverse event would manifest itself as increases in alanine aminotransferase, aspartate aminotransferase, hepatitis or right upper quadrant pain [11,12].

The dermatologic immune-related adverse events should be managed symptomatically. For the relief of mild pruritis and rash, patients should be recommended the use of oral antihistaminics, the application of topical steroids and a nonperfumed hydrating cream or emollient, such as urea (see **Tables 2 & 3**). If the patient experiences a severe life-threatening dermatologic condition (Stevens–Johnson reaction), the

Table 1. Ipilimumab immune-related adverse events.

Immune-related adverse event	Percentage of patients†			Average time to presentation‡
	All grades (%)	Grade 3 (%)	Grade 4 (%)	
Any	61.10	12.20	2.30	
Dermatologic	43.50	1.50	0	3–4 weeks
Gastrointestinal	29.00	7.60	0	6–7 weeks
Endocrine	7.60	2.30	1.50	9–11 weeks
Hepatic	3.80	0	0	6–7 weeks

†Data taken from [11].
‡Data taken from [10].

patient may require systemic steroid therapy followed by an oral steroid taper and should discontinue ipilimumab therapy [10–12].

Gastrointestinal immune-related adverse events are diarrhea or colitis. If the symptoms are mild, the events may be treated symptomatically with antidiarrheals, such as loperamide or diphenoxylate/atropine and rehydration. If ever the symptoms are severe or persistent despite symptomatic therapy, a trial of systemic steroids should be enforced. If this option is ineffective, a trial of infliximab is the standard treatment in presence of corticosteroid-refractory disease, which becomes a quite costly option. There is conflicting data on the use of prophylactic budesonide, an oral steroid with poor oral absorption, to prevent ipilimumab-induced colitis but at this time the results of this trial were negative and budesonide cannot be recommended at this time as a prophylactic measure [10,12].

Hypophysitis is a late-onset immune-related adverse event of ipilimumab which presents itself as a syndrome with fatigue, headache, nausea, vomiting, visual changes, altered mental status and hypotension. The pituitary gland is enlarged and this can be confirmed by magnetic resonance imaging. The treatment of this rarer adverse event is with systemic steroid therapy and appropriate hormone replacement. The treatment of this adverse event can be of a long-term nature where certain patients may need follow-up for years [10,12].

Ipilimumab immue-related hepatitis is a rare adverse event and manifests itself as an increase in liver enzymes, right upper quadrant pain, nausea and vomiting. If severe, this condition should be treated with systemic steroids followed by an oral steroid taper. If ever the hepatitis is refractory to steroid therapy, other immunosuppressants such as mycophenolate mofetil may be considered as another therapeutic option [10,12].

There is a pattern of predictability to the apparition and resolution of the immune-related adverse events of ipilimumab. The immune-related skin reactions would be the first adverse event to present at 3–4 weeks after initiation of treatment, then the gastrointestinal and hepatic immune-related adverse events would present at 6–7 weeks and the endocrine adverse events later at 9–11 weeks. If these adverse events are caught quickly and managed appropriately, they will resolve normally within 2–4 weeks. An exception is hypophysitis which may require prolonged steroid treatment and resolution of this adverse event may even take years [10–12].

It is important for the oncology pharmacist to discuss during patient teaching counseling the concept of immune-related adverse events with ipilimumab, how they present and how best to manage them. We normally focus on the ones that may manifest quickly and affect the patient's quality of life: the dermatologic and gastrointestinal adverse events. Patients are given a verbal counseling with supportive written literature and contact information for the oncology pharmacy. The pharmacist must also be available (by phone or in person) for follow-up in order to confirm tolerance and adherence to treatment.

Ipilimumab has demonstrated durable responses in patients with melanoma but unfortunately the response rates are low [13]. It will be interesting to see during upcoming years if we will be able to predefine which patients will respond to this expensive therapy and if any biomarkers will be able to help guide us in selecting the right patient for this treatment [14].

BRAF^{V600} inhibitors : vemurafenib (ZELBORAF, Roche), dabrafenib (TAFINLAR, GlaxoSmithKline, Inc.)

Vemurafenib is a BRAF^{V600} inhibitor which targets the RAS/RAF/MEF/ERK pathway, the MAPK pathway, where 50–60% of patients that have melanoma harbor a BRAF mutation. By inhibiting this intracellular serine threonine

Table 2. Management of ipilimumab immune-related adverse events.

Immune-related adverse event	Management strategies	
	Grade	
	Mild	Severe
Dermatologic – Rash – Vitiligo – Pruritis	Oral antihistaminics Topical steroids Urea/hydrating cream	Systemic steroids + oral taper
Gastrointestinal – Diarrhea – Colitis	Antidiarrheals Hydration Electrolyte substitution	Systemic steroids + oral taper Infliximab
Endocrine – Hypophysitis	–	Systemic steroids + oral taper + hormone replacement
Hepatic – Hepatitis	–	Systemic steroids + oral taper Immunosuppressive therapy

Data taken from [10,12].

kinase receptor, the signaling via this pathway is disrupted and the melanoma cell cannot survive nor proliferate. A validated test is required to determine if patients harbor the mutation and BRAF positivity must be confirmed in order for the treatment to be warranted [15].

Vemurafenib has also demonstrated a survival advantage in a randomized, placebo-controlled Phase III trial. In the pivotal BRIM3 trial, 675 patients with previously untreated $BRAF^{V600E}$ mutation-positive unresectable stage IIIc or IV melanoma were randomized to vemurafenib 960 mg po b.i.d. or dacarbazine 1000 mg/m^2 iv. q 3 weeks. The primary objectives of the trial were overall survival and progression-free survival. Overall survival at 6 months was 84% in the vemurafenib group and 64% in the dacarbazine group and progression-free survival was 5.3 months in the vemurafenib group and 1.6 months in the dacarbazine group [16].

The adverse event profile of vemurafenib is musculoskeletal which manifests itself as arthralgia and myalgia, dermatologic which presents itself in many forms, the potential development of secondary malignancies, gastrointestinal events and fatigue (see Table 4) [17].

The dermatologic reactions of vemurafenib consist of a maculopapular rash which should be treated symptomatically with hydrating creams, antihistamines for pruritis and the use of topical steroids for any redness or inflammation (see Table 5). Photosensitivity reactions are a serious issue with vemurafenib and patients taking this medication should avoid sunlight, wear protective clothing and use a sunblock of at least 30. Patients taking vemurafenib are at risk of developing keratoacanthomas or secondary squamous cell skin cancers which are easily removed by surgical excision; all patients taking vemurafenib will require close monitoring by a dermatologist in order to manage this side effect [17,18]. The most common gastrointestinal toxicities are low-grade nausea and vomiting which may be controlled with as needed antiemetics such as metoclopramide or prochlorperazine and diarrhea which may be symptomatically controlled with supportive therapy such as oral hydration and antidiarrheals [17,18]. Any arthralgia or myalgia may be relieved symptomatically by the use of antipyretics or anti-inflammatory agents [17,18].

When doing a patient counseling to a patient initiating vemurafenib therapy, it is important to insist on the importance of the potential severity of the photosensitivity adverse event which may manifest itself very quickly (sometimes even during the first day) and very severely. A patient may experience sunburn even if it is not very sunny outside, even if they are simply in their house and even if they are exposed to the sun for a short period of time (e.g., going from the front door of their house to the car). We counsel patients using written information documents and making ourselves available for any questions or concerns. We will also insist on the importance of using an effective sunblock, wearing clothing that does not reveal too much skin and also to avoid sun exposure if possible.

Vemurafenib has demonstrated in a Phase III randomized trial very important and significant response rates but unfortunately in most patients they are of a short duration. The problem is the development of resistance mechanisms to the BRAF inhibitor. There are many hypotheses for the mechanism of this resistance and there are ongoing studies looking at ways to overcome this issue with vemurafenib [15,17].

Dabrafenib is another $BRAF^{V600}$ mutated inhibitor. The patient must present a BRAF-positive mutation in order to being eligible for this medication [19,20].

Dabrafenib has also demonstrated a survival advantage in a Phase III randomized controlled trial, the BREAK-3 trial. Patients with metastatic melanoma or unresectable melanoma were randomized to dabrafenib 150 mg po b.i.d. or dacarbazine 1000 mg/m^2 iv. q 3 weeks and the primary endpoint was progression-free survival. The progression-free survival was superior in the dabrafenib arm than the dacarbazine arm, 5.7 versus 2.7 months respectively. The response rate was also superior in the dabrafenib arm, 50 versus 6% respectively [19].

The most common adverse effects of dabrafenib are cutaneous in nature, such as hyperkeratosis, papillomas, palmar-plantar erythrodysesthesia, photosensitivity and others such as headache, pyrexia, fatigue and arthralgia and the management of theses adverse events are similar to those of vemurafenib (see **Table 5**) [19].

A side effect that is specific to dabrafenib which requires intervention is pyrexia. If a patient presents with a fever of 38.5–40°C, treatment should be interrupted until fever resolves, that

Table 3. Dosing examples of therapeutic options for managing ipilimumab immune-related adverse events.

Immune-related adverse event	Management strategies	
	Grade	
	Mild	Severe
Dermatologic	Diphehydramine 25–50 mg po q6h prn Hydrorxyzine 25–50 mg po q6h prn Urea 10–22% loc appl prn Hydrating cream loc appl prn Hydrocortisone 1% or betamethasone 0.1% loc appl prn	Prednisone/equivalent 1–2 mg/kg po die ×4 weeks then taper over at least 30 days
Gastrointestinal	Loperamide 2 mg po prn max 16 mg/day Diphenoxylate/atropine 1–2 tabs po q6–8 h prn Hydration Electrolyte substitution	Methylprednisolone 125 mg iv. × 1 then Prednisone 1–2 mg/kg or Dexamethasone 4 mg po q4h then taper over at least 30 days Infliximab 5 mg/kg iv. q2 weeks until relief then steroid taper over 45–60 days
Endocrine	–	Methylprednisolone 1–2 mg/kg iv. ×1 then prednisone 1–2 mg/kg po die then taper over 4 weeks + hydrocortisone po
Hepatic	–	High dose glucocorticoid iv. ×24–48 h then dexamethasone 4 mg po q4h or prednisone 1–2 mg/kg taper over at least 30 days Mycophenolate mofetil Tacrolimus Infliximab

die: Daily; po: Per os; prn: If needed; q6h: Every 6 h.
Data taken from [10,12].

Table 4. Vemurafenib adverse events reported from the BRIM III trial.

Adverse event	All grades (%)	Grade 3 (%)	Grade 4 (%)
Dermatologic			
Rash	37	8	–
Photosensitivity reaction	33	3	–
Alopecia	45	<1	–
Muscoloskeletal arthralgia	53	4	–
Gastrointestinal			
Nausea	35	2	–
Vomiting	18	1	–
Diarrhea	28	<1	–
Constipation	12	<1	–
Secondary malignancies			
Skin papilloma	21	<1	–
Squamous cell skin cancer	24	22	–
Keratoacanthoma	11	10	–
Other			
Fatigue	38	2	–

Data taken from [16] and product monograph ZELBORAF Vemurafenib Roche Canada, 19 December 2013.

an infection has been excluded; treatment may be reinitiated at the same or reduced dose and antipyretic prophylaxis may be considered. If ever a patient presents with a fever superior to 40°C, or the fever is associated with rigors, hypotension, dehydration or renal failure, treatment may be discontinued permanently or interrupted until resolution of symptoms; if treatment is to be reinitiated, dose should be reduced and antipyretic prophylaxis may be required [20].

As with vemurafenib, dabrafenib has demonstrated promising response rates that are short lived because of the quick development of drug resistance [7].

Trametinib (MEKINIST, GlaxoSmithKline, Inc.)

Trametinib is an inhibitor of the MEK1 and MEK2 kinases which is downstream from the BRAF kinase. Once again, patients must be BRAF mutant positive to receive this medication [21].

Trametinib has also shown a survival advantage in a randomized, controlled Phase III trial, the METRIC trial. Pateints with stage IIIc unresectable or IV melanoma with a positive $BRAF^{V600}$ mutation were randomized to a second-line therapy of trametinib 2 mg po daily or chemotherapy consisting of either dacarbazine 1000 mg/m^2 iv. q 3 weeks or paclitaxel 175 mg/m^2 iv. q 3 weeks. The primary objective of the trial was progression-free survival and secondary objectives were response rates, overall survival. The progression-free survival was 4.8 months in the trametinib group and 1.5 months in the chemotherapy group. The 6 month survival rate was 81 versus 67% respectively and the response rates were 22 versus 8% respectively [22].

The most common adverse events with trametinib consist of rash, diarrhea, peripheral edema and fatigue and acneiform dermatitis. The acneiform rash is similar in nature to an EGFR-inhibitor type rash and should be dealt with the same way: hydrating creams or lotions, topical steroids and if needed, the addition of a systemic antibiotic of the tetracycline family, such as doxycycline or minocycline [23]. Trametinib has been associated with decreased ejection fraction and ocular events consisting essentially of dry eye, blurred or impaired vision. The incidence of diarrhea is relatively important, around 45%, yet it is mild in nature and can be relieved symptomatically as described previously with basic hydration and antidiarrheals. Hypertension can be a problem with trametinib where 12% of patients will develop grade 3 hypertension which can be controlled simply by following basic guidelines for the treatment of hypertension.

The role of the oncology pharmacist

The role played by the oncology pharmacist in the optimal treatment of patients with metastatic melanoma with the newer treatment modalities discussed within this article is a multifactorial one which goes beyond the basic preparation of

the patient's medication. The oncology pharmacist plays a key role with regard to patient education where it is very important for these patients to understand the importance of proper adherence to their therapies, to recognize associated side effects of their treatments and how best to manage them. The educative role of the oncology pharmacist can also be preventative in fashion with regard to optimal sun protection.

The oncology pharmacist can also have an impact in optimal dosing of these new therapies with regard to the patients' functional status, that is their renal and hepatic function. At this time, there is a lack of data for clear dosing adjustment guidelines in the presence of hepatic or renal impairment with these newer molecules. Caution may be required in the presence of severe renal or hepatic impairment and the interaction between oncology pharmacist and prescribing oncologist is of utmost importance in this situation where the goals of therapy must be clearly defined. The pharmacist can also optimize therapeutic dosing according to dosage adjustment guidelines that take into account treatment toxicities.

The oncology pharmacist also has a role in doing medication histories. This is very important in this patient population because the newer oral therapies for the treatment of metastatic melanoma have many potential drug interactions that have to be taken into consideration. Drug interactions are an important issue with the newer oral therapeutic modalities and a discussion of this topic is outside of the scope of this article [15]. An analysis of complimentary therapies is also warranted while doing a medication history; patients often minimize the impact of these drugs on their antineoplastic treatment and the pharmacist can clarify if there is any negative impact on the treatment.

The oncology pharmacist can play an active role in the multidisciplinary team in treating patients with metastatic melanoma by bringing his expertise to the optimal use of the newer cancer agents for treating this horrible disease.

Conclusion & future perspective

Unresectable or metastatic melanoma was historically a disease with a dismal prognosis and known to be very chemo-resistant. Much progress has been achieved during the last decade in our gaining knowledge about melanoma and the development of defining therapeutic modalities effective against therapeutic targets. These newer agents have adverse event profiles which are much different from the classic chemotherapy that has been used to treat melanoma. The oncology pharmacist needs to be aware of these

Table 5. Management of $BRAF^{V600}$ inhibitor toxicities.

Toxicity	Management
Skin toxicities	
Rash	Diphehydramine 25–50 mg po q6h prn Hydrorxyzine 25–50 mg po q6h prn Urea 10–22% loc appl prn Hydrating cream loc appl prn Hydrocortisone 1% or betamethasone 0.1% loc appl prn
Photosensitivity	Protective clothing, avoid sunlight Sun block of at least 30 SPF
Secondary malignancies	
Squamous cell skin cancer	Close follow-up by dermatologist
Keratoacanthoma	
Gastrointestinal	
Diarrhea	Loperamide 2 mg po prn max 16 mg/day Diphenoxylate/atropine 1–2 tabs po q6–8h prn
Nausea, vomiting	Metoclopramide 10 mg po q6h prn Prochlorperazin 10 mg po/pr q6h prn
Musculoskeletal	
Arthralgia	Acetaminophen 325–650 mg po q4–6h prn Ibuprofen 200–400 mg po q6h prn[†]

[†]Or equivalent.
po: Per os; Prn: If needed; q6h: Every 6 h; SPF: Sun protection factor.

new molecules and how to manage their optimal use with regard to appropriate treatment and side-effect management.

Despite all these accomplishments, many vital questions remain unanswered. We need to be able to better define the potential responders to anti-CTLA-4 molecules in order to use this expensive molecule in a more optimal fashion. We need to be able to find ways to overcome resistance that develops with the use of anti-BRAF therapy. During the upcoming years we will gain more knowledge with regard to these questions, where combination of agents may offer solutions, newer therapies (anti-PD-L1 therapies) or the exploitation of other pathways (the PI3K pathway) or redefining the role of angiogenesis, or apoptosis or restoring tumor suppressor function may offer new possibilities for managing this disease.

We are on the verge of a new era for the treatment of unresectable or metastatic melanoma where there is a hope for a brighter future for these patients fighting a devastating disease.

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