

# Medical management of malignant melanoma

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## SUMMARY

The treatment and outcomes for people with metastatic melanoma have changed considerably in the past few years with the introduction of targeted anticancer drugs.

About half of the patients with metastatic melanoma will have activating mutations in the BRAF gene. These people may benefit from a BRAF inhibitor (vemurafenib or dabrafenib) or a MEK inhibitor (trametinib).

Addition of a MEK inhibitor to a BRAF inhibitor improves progression-free survival and alters the adverse effect profile.

Ipilimumab is another drug indicated for metastatic melanoma. It works by altering the patient's own immune response to the tumour.

Toxicities are common with these drugs and include arthralgias, fatigue, photosensitivity, squamous cell carcinomas, fever, diarrhoea, pruritus and immune-related adverse effects.

## Introduction

Metastatic melanoma is the fourth most common cancer diagnosed in Australia and the most common malignancy among 15–24 year-olds.<sup>1,2</sup> Metastatic

disease is incurable and results in a significant loss of life – for example, 365 deaths from metastatic melanoma were registered in Queensland in 2010.<sup>1,3</sup>

The most commonly used drugs in melanoma were dacarbazine and fotemustine. These have been trialled extensively and have complete and partial response rates\* of around 10%. They do not prolong survival.

Until 2010, there were no significant advances in improving survival for metastatic melanoma – the median overall survival of nine months had not changed in 30 years. However, the introduction of targeted anticancer drugs has substantially altered the treatment and outcomes for patients with melanoma.

## Melanoma mutations

Systemic therapy options for metastatic melanoma currently depend on whether the patient's tumour expresses the BRAF mutation. These mutations occur in the mitogen-activated protein (MAP) kinase pathway (see Fig.). Acquired BRAF mutations lead to the expression of an abnormal protein kinase that mediates continuous cell growth and malignant transformation.

BRAF mutations were found to be frequent in melanoma in 2002.<sup>4</sup> About 40–60% of patients have an activating BRAF mutation in their metastatic

\* A complete response is defined as the disappearance of all lesions on imaging, and a partial response is defined as a 30% reduction in the size of target lesions.

## From the Editor



Many new drugs, including those Victoria Atkinson reviews in the article on medical management of malignant melanoma, are expensive. While there is an expectation that money will be found to fund new therapies, millions of dollars are being wasted. Phillip Bergen and colleagues have found that Australians return more than 600 tonnes of unwanted medicines every year.

Antibiotics are among the most commonly discarded drugs. This could contribute to increased antibiotic resistance. Brendan McMullan and Mona Mostaghim also warn against unfettered prescribing of azithromycin because of the risk of macrolide resistance.

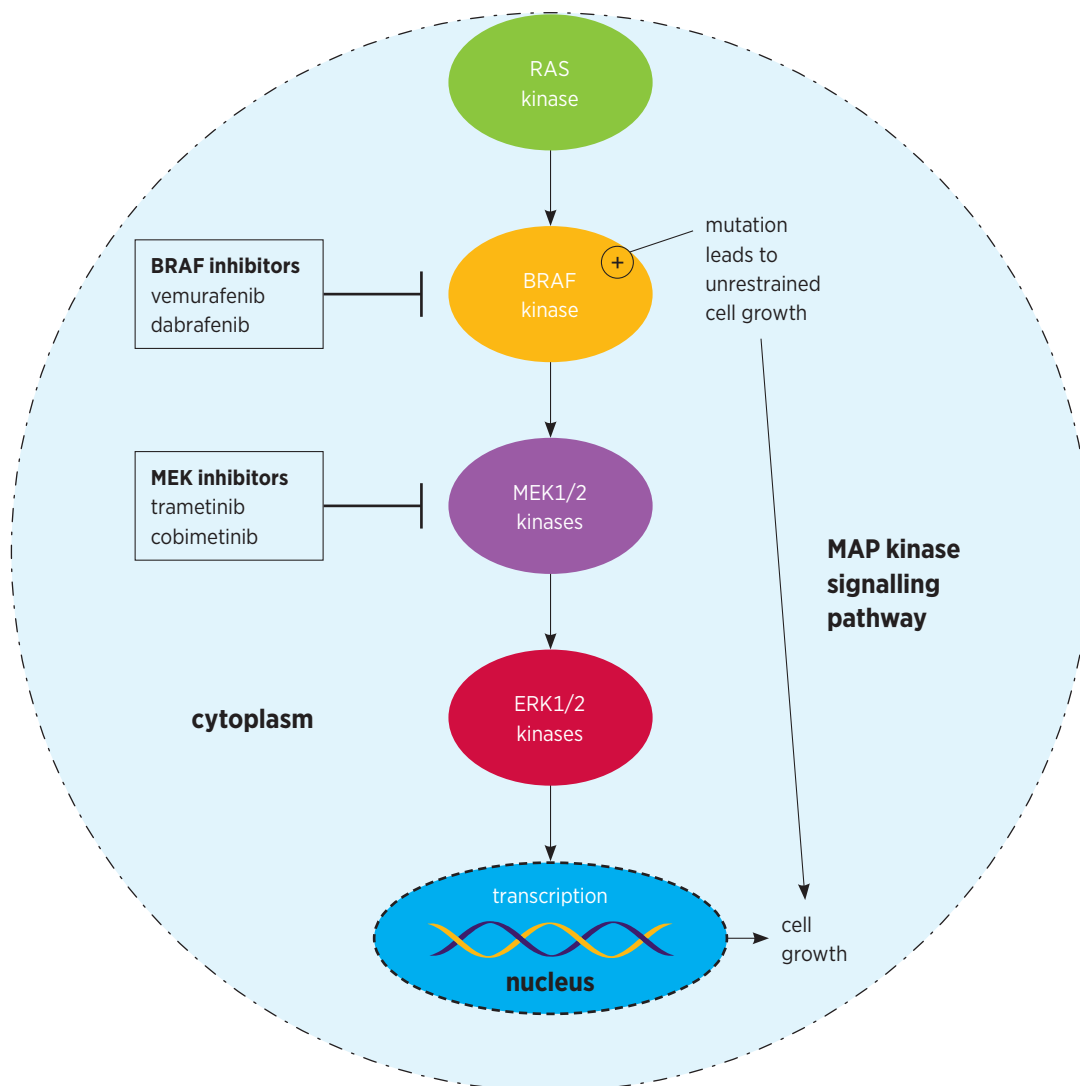
Another drug that requires careful prescribing is quetiapine. Jonathan Brett says the concerns about quetiapine are mainly due to its off-label use. Greta Palmer tells us there is also a lack of evidence for many of the drugs used to treat complex regional pain syndrome.

While the diagnosis of complex regional pain syndrome is clinical, laboratory tests may be needed to exclude other conditions. These could include investigation of inflammation. Michael Harrison discusses the role of measurements of erythrocyte sedimentation rate and C-reactive protein.

The role of oxygen as a drug is reviewed by Janine Pilcher and Richard Beasley. They call for a major change in the acute use of oxygen therapy.

Many other drugs have a role in acute medical conditions. The Editorial Executive Committee hopes the new Australian Prescriber mobile phone app will support health professionals when they are determining the dose of the emergency drugs supplied through the Pharmaceutical Benefits Scheme.

Fig. Action of BRAF and MEK inhibitors in the MAP kinase signalling pathway



melanoma cells.<sup>5</sup> The most common mutation is V600E, then V600K.<sup>6</sup> There are less common mutations including R and D.

Other cellular mutations can be tested for, but are still being investigated in clinical trials. These include NRAS and c-kit mutations. Tumours that do not harbour a BRAF or NRAS mutation are called BRAF wild type.

### BRAF inhibitors

Drugs that block the abnormal BRAF protein kinase aim to slow the growth of melanoma cells (see Fig.).

#### Vemurafenib<sup>7</sup>

The first published report of BRAF inhibitors in metastatic melanoma was in 2010.<sup>5</sup> This phase I dose escalation study looked at vemurafenib in patients with V600E-mutated melanoma. With treatment, 81% of patients had a complete or partial response.

A phase III trial reported in 2011 compared vemurafenib to dacarbazine in 675 randomised patients. Vemurafenib improved both overall and progression-free survival, with an improvement in median survival from 9 to 13.6 months.<sup>8</sup> A phase II trial in 2012 in patients who had had one previous therapy confirmed the survival benefit. The median overall response rate (complete and partial response) was 53% and median overall survival was 16 months.<sup>9</sup>

Vemurafenib is well tolerated, with the most common adverse events being arthralgias, fatigue and photosensitivity. Keratoacanthoma or squamous cell carcinomas developed in 18% of patients. These were usually managed with simple excision.<sup>8</sup>

In early 2012, patients were accessing therapy through compassionate access schemes or clinical trials. Vemurafenib was only approved by the Therapeutic Goods Administration (TGA) in May 2012, but is not

currently reimbursed on the Pharmaceutical Benefits Scheme (PBS).

### **Dabrafenib**<sup>10</sup>

Phase II and III trials of dabrafenib in patients with V600E and V600K-mutated metastatic melanoma found similar results to the trials with vemurafenib.<sup>11,12</sup> The response rate to treatment was 50% and median overall survival improved from 9 to 18 months. The adverse effect profile was similar to vemurafenib apart from an increased incidence of fever, and less photosensitivity.

Dabrafenib was listed on the PBS for selected patients in December 2013 and is currently the only reimbursed BRAF inhibitor in Australia.

### **MEK inhibitors**

MEK1 and MEK2 are enzymes downstream of BRAF in the MAP kinase pathway (see Fig.). In preclinical models, adding a MEK inhibitor to a BRAF inhibitor reduced some resistance to BRAF inhibition.

### **Trametinib**

Trametinib is the first MEK inhibitor to be approved in Australia. It has been shown to improve response rates and progression-free survival compared to chemotherapy.<sup>13</sup> However, the benefits were not of the same magnitude as those of BRAF inhibitors.

A phase III randomised trial of dabrafenib and trametinib versus dabrafenib found improved progression-free survival and response rates for the combination arm (see Table 1).<sup>14</sup> Adding trametinib to dabrafenib reduces the incidence of cutaneous squamous cell carcinomas.<sup>13</sup> These appear because unopposed BRAF inhibition causes paradoxical activation of the MAP kinase pathway.<sup>15</sup>

Dabrafenib combined with trametinib has also been compared to vemurafenib. Improved overall survival has been observed with combination therapy (see Table 1).<sup>16</sup>

These findings establish that combination therapy is a new standard of care for BRAF mutation-positive

metastatic melanoma. Combination therapy with dabrafenib and trametinib was approved by the TGA in March 2014. Trametinib is currently being accessed through a compassionate access program from the supplier.

Adding trametinib does however increase the risk of dabrafenib-induced fever. This is manageable and may require low-dose corticosteroids or dose reduction.

### **Cobimetinib**

Cobimetinib is another MEK inhibitor tested in phase III trials. The superiority of combination therapy was confirmed in a phase III trial of vemurafenib and cobimetinib versus vemurafenib (see Table 1).<sup>17</sup>

### **Immunotherapy**

Given that only about half of people with metastatic melanoma express the BRAF mutation, other treatment options are needed. Immunotherapies have been shown to improve overall survival for patients with metastatic melanoma. They aim to modulate the patient's own immune response to the tumour cells.

### **Ipilimumab**

Targeting cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) has been trialled as an anticancer strategy.<sup>18</sup> It is present on immune cells and is a negative regulator of T cells. Blocking the interaction of CTLA-4 on antigen-presenting cells with cytotoxic T cells leads to ongoing proliferation of T cells, with the hope that these will then target and destroy the melanoma cells.

Ipilimumab is a fully humanised monoclonal antibody that blocks CTLA-4. A phase III trial compared a melanoma vaccine plus ipilimumab (3 mg/kg) to ipilimumab alone and vaccine alone. Median overall survival for both of the ipilimumab arms was around 10 months compared with 6.4 months in the vaccine arm.<sup>19</sup> It must be noted that the median overall survival of 6.4 months in the vaccine arm was shorter than the expected median survival of untreated patients with metastatic melanoma.

**Table 1 Phase III trials of combination BRAF and MEK inhibitors for melanoma**

<b>Trial</b>	<b>Study arms (patients)</b>	<b>Objective response rate</b>	<b>Median progression-free survival</b>
COMBI-D <sup>14</sup>	dabrafenib + placebo (n=212)	51%	8.8 months
	dabrafenib + trametinib (n=212)	67%	9.3 months
COMBI-V <sup>16</sup>	dabrafenib + trametinib (n=352)	64%	11.4 months
	vemurafenib (n=352)	51%	7.3 months
Co-BRIM <sup>17</sup>	vemurafenib + placebo (n=248)	45%	6.2 months
	vemurafenib + cobimetinib (n=247)	68%	9.9 months

Another phase III trial compared a higher dose of ipilimumab (10 mg/kg) combined with dacarbazine, to dacarbazine alone. Median overall survival improved from 9 months in the dacarbazine arm to 11 months when ipilimumab was added. There were no treatment-related deaths in this trial, but elevated liver enzymes were more common with ipilimumab.<sup>20</sup> It is not certain whether this is related to the higher dose of ipilimumab or the addition of dacarbazine.

Objective response rates to ipilimumab were only 10.9%<sup>19</sup> and 15.2%<sup>20</sup> in the phase III trials. However, in the second trial the patients in the ipilimumab arm had a 20.8% chance of being alive at three years compared with 12.2% in the dacarbazine arm.<sup>20</sup> A trial comparing ipilimumab 3 mg/kg and 10 mg/kg has been completed and should be reported this year.

The mechanism of action of ipilimumab leads to unrestrained T cell activation and accounts for the serious (grade 3–4) immune-related adverse events observed in 10–15% patients. The most common events were diarrhoea (27–31%), pruritus (17–24%) and other endocrine insufficiency disorders. Of the deaths in this study, 2.1% were thought to be due to the study drug.<sup>19</sup> Adverse events with ipilimumab can be managed with the appropriate treatment algorithms in clinical practice.

Ipilimumab 3 mg/kg was listed on the PBS for unresectable stage 3C and stage 4 melanoma in August 2013.

### Other immunotherapies

Studies of ipilimumab have shown that the immune system can be manipulated to improve survival in melanoma. Antibodies to other molecules such as programmed death 1 (PD-1) and programmed death ligand (PD-L1) are also being developed and have shown promising phase I results.

Programmed death ligand is a key inhibitory receptor expressed by activated T and B cells. When this receptor binds to tumours that express PD-L1 this leads to T cell downregulation<sup>21</sup> or 'exhaustion'. PD-1 antibodies interfere with this interaction, allowing for ongoing activation of the activated T cells.

Comparative phase III trials of PD-1 antibody (e.g. nivolumab and MK3475) alone or in combination with other therapies are underway. Recruitment to both of these trials was completed in early 2014.

Nivolumab was recently compared to dacarbazine in BRAF wild-type metastatic melanoma (see Table 2). Trials found a significant improvement in response rates and progression-free survival in the nivolumab arm, with fewer adverse events than dacarbazine.<sup>22,23</sup> The most common adverse event with nivolumab was pruritus.

MK3475 and nivolumab are currently available for limited compassionate access use in Australia for patients who meet the eligibility criteria. Patients are encouraged to discuss whether they are eligible with their oncologist.

### Conclusion

The landscape for metastatic melanoma has changed significantly in the last few years with novel drugs that have been shown to prevent progression and improve overall survival. This has reinvigorated research efforts on new targets for drug development and offers hope for further improvement for patients with metastatic melanoma. ◀

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Table 2 Phase III trials of nivolumab for melanoma

Trial	Study arms (patients)	Overall response rate	Median progression-free survival
CheckMate066 (treatment naïve) <sup>22</sup>	nivolumab (n=210)	40%	5.1 months
	dacarbazine (n=208)	13.9%	2.2 months
CheckMate037 (progression after previous therapy) <sup>23</sup>	nivolumab (n=268)	32%	5.3 months
	chemotherapy (n=102)	11%	2 months

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## FURTHER READING

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## Letters to the Editor

### Pharmaceuticals, pharmacists and profits

I am writing in response to the editorials on Pharmaceuticals, pharmacists and profits (*Aust Prescr* 2014;37:146-7 and 148-9). I enjoyed reading the Pharmacy Guild's perspective on troubles facing the industry. However, the editorial failed to mention the financial troubles facing community pharmacists who are not pharmacy owners.

Few people, including those studying to become pharmacists, are aware that the award rate for a full-time pharmacist in charge is \$27.16/hour (equivalent to \$53 674 annual salary).<sup>1</sup> Note that pharmacist interns, pharmacists and experienced pharmacists are all paid less than this. To compare, an unqualified experienced retail employee may earn up to \$44 787.<sup>2</sup> Pharmacists' wages are significantly below the average Australian wage of \$76 804 before tax.<sup>3</sup>

From this wage, a pharmacist must pay to be registered for insurance and course fees for 40 hours of continuing professional development per year. Debt from university fees must also be paid. There is a current oversupply of pharmacists, and jobs for salaried pharmacists are not easy to obtain.

I understand that some pharmacies are currently experiencing a period of hardship. But should salaried pharmacists be the ones to subsidise the industry by being forced to accept these low rates of pay?

Michelle Edwards  
Pharmacist  
Narrabeen

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