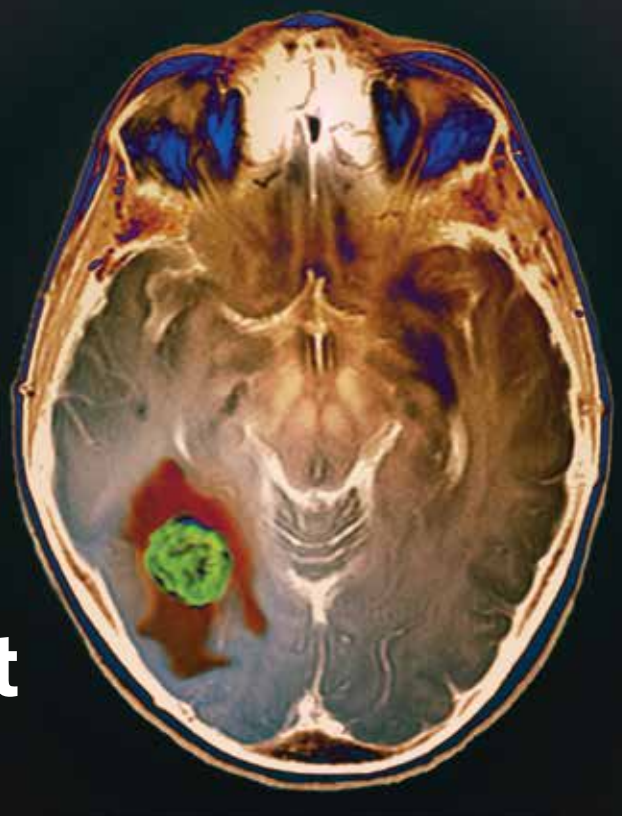

Advanced melanoma

The changing landscape of treatment

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Recently developed immunotherapies and targeted therapies have largely replaced chemotherapy for treatment of patients with metastatic and nonresectable melanoma. These new drugs have improved the prognosis for many patients, but GPs need to be aware of their unique toxicities.

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Over the past few years there have been major advances in the systemic therapeutic options for patients with metastatic or unresectable melanoma. Previously, the mainstay of treatment was chemotherapy, which had low response rates and median survival times of six to nine months. Today, chemotherapy is rarely used and has been superseded as first-line therapy by a number of new targeted agents and immunotherapies. An understanding of these new agents, their unique toxicity profiles and their impact on prognosis will enhance the care of patients with advanced melanoma in primary care.

Immunotherapies for metastatic melanoma

The importance of the interplay between a patient's immune system and the progression of their melanoma has long been acknowledged. Researchers and clinicians have attempted to exploit this complex interaction for decades with very limited success. Finally, a new class of drugs has emerged with clear evidence of efficacy and an acceptable, albeit unique, side effect profile. These are the immune checkpoint inhibitors that act by removing an inbuilt 'brake' on the body's immune response against cancer cells, thus allowing an ongoing antitumour effect from the immune system. The anti-CTLA4 antibody ipilimumab and the anti-PD-1 antibodies pembrolizumab and nivolumab are the furthest advanced of these agents.

Anti-CTLA4 antibodies (ipilimumab)

Ipilimumab is a monoclonal antibody against cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), which is a key regulator of T cell activity. CTLA-4 on the T cell surface interacts with antigen-presenting cells of the immune system, leading to T cell deactivation and downregulation of the immune response. Ipilimumab blocks this interaction, thus preventing the inhibitory signal and enhancing immune activity against the tumour (Figure 1).

In 2010, the results were published of the first trial ever to show a significant overall survival benefit in patients with metastatic melanoma.[1] This trial compared ipilimumab with the melanoma glycoprotein 100 vaccine in previously treated patients. It showed an improvement in median survival for patients treated with ipilimumab, from 6.4 months to 10.1 months (hazard ratio [HR] for death, 0.68; p<0.001). A second study in previously untreated patients confirmed a survival benefit when ipilimumab was added to chemotherapy, from 9.1 months with chemotherapy alone to 11.2 months with combination therapy.[2] Although these survival benefits seem modest, and only 10 to 15% of patients have

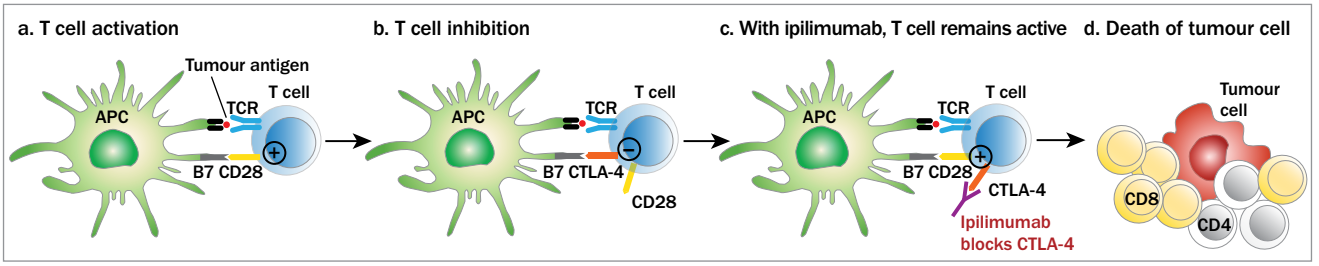


Figure 1. Mode of action of the anti-CTLA-4 antibody ipilimumab. a. Specific antitumour T cells that encounter an antigen-presenting cell (APC) presenting a tumour antigen and expressing B7 costimulatory molecules are activated through T-cell receptor (TCR) and CD28 signalling. b. The T cell response is then attenuated by upregulation of cytotoxic T-lymphocyte-associated protein-4 (CTLA-4), which preferentially binds to B7. c. Ipilimumab blocks CTLA-4, allowing enhanced T cell stimulation. d. Sustained T cell activation enhances immune activity against the tumour, leading to death of tumour cells.

tumour shrinkage with ipilimumab, the enthusiasm surrounding this agent relates to the durability of the response when it is achieved. A recent article reported that about 20% of patients who were treated with ipilimumab in the early trials were alive more than five years from the time of treatment.[3]

The side effects of ipilimumab are quite different to those of chemotherapy and are attributable to overactivation of the immune system against nontumour tissue. These autoimmune-type phenomena have been labelled 'immune related adverse events' (irAEs). Ipilimumab causes irAEs in about 60% of patients, and approximately 20% of these are severe. The most common side effects seen with ipilimumab are itch, rash and diarrhoea (Box). Less common side effects include colitis, autoimmune hepatitis, thyroiditis, hypophysitis and, rarely, a Guillain–Barré type syndrome. Moderate to severe irAEs require prompt treatment with oral or intravenous corticosteroids and occasionally in refractory cases, more potent immunosuppressive drugs such as infliximab.

Ipilimumab was listed on the PBS for the treatment of advanced melanoma in August 2013.

SIDE EFFECTS OF NEW TREATMENTS FOR ADVANCED MELANOMA

Immunotherapies

- Itch
- Skin rash
- Diarrhoea
- Colitis
- Autoimmune hepatitis
- Thyroiditis
- Hypophysitis
- Guillain–Barré like syndrome (rare)

Targeted therapies

- Fever
- Fatigue
- Diarrhoea
- Arthralgia
- Liver biochemistry abnormalities
- Skin changes (e.g. rash, hyperkeratosis, papillomas, squamous cell carcinoma)

Anti-PD-1 antibodies (pembrolizumab and nivolumab)

The second type of immune check point inhibitor that is now entering clinical practice comprises monoclonal antibodies against programmed cell death receptor-1 (PD-1). PD-1 is an immune checkpoint receptor that limits T cell activity. Binding of PD-1 to its ligand on tumour cells (PD-L1) leads to deactivation of the T cells. Upregulation of PD-L1 by tumour cells is a mechanism by which cancers can avoid immune surveillance. The anti-PD-1 antibodies nivolumab and pembrolizumab bind to PD-1, blocking the interaction with PD-L1 and allowing an enhanced antitumour immune response (Figure 2).[4,5]

The first randomised trial of an anti-PD-1 antibody in patients with advanced melanoma was published this year. It compared nivolumab with dacarbazine chemotherapy in previously untreated patients.[6] In this study, 73% of patients treated with nivolumab were alive

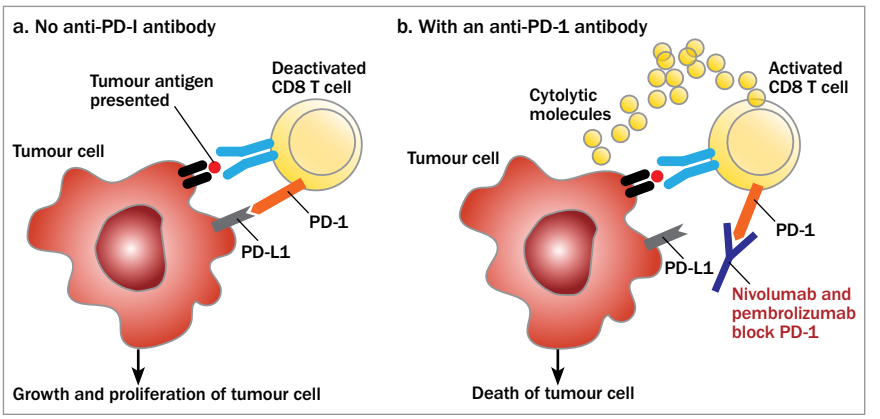


Figure 2. Mode of action of anti-PD-1 antibodies. a. T cells are deactivated by binding of programmed cell death receptor-1 (PD-1) to tumour PD-1 ligand (PD-L1), leading to tumour 'immune escape'. b. Anti-PD-1 antibodies such as nivolumab and pembrolizumab bind to PD-1, preventing deactivation of the T cell and allowing ongoing immune attack of the tumour cell.

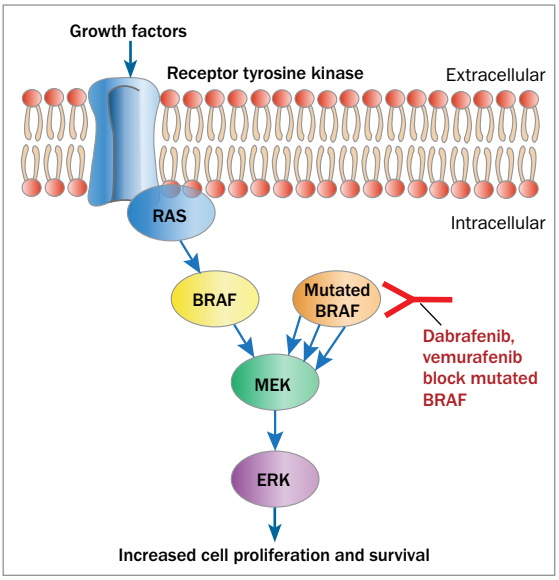


Figure 3. Mode of action of BRAF inhibitors. The mitogen-activated protein (MAP) kinase pathway is a signalling cascade that is activated when growth factors in the extracellular space interact with receptor tyrosine kinase. Activation leads to enhanced cell growth and survival. Mutated BRAF protein (*BRAF*^{V600}) activates the pathway without the need for upstream signalling from receptor tyrosine kinase, leading to tumour growth. BRAF inhibitors such as dabrafenib and vemurafenib block mutated BRAF activity.

Abbreviations: BRAF = a serine/threonine-protein kinase; ERK = extracellular signal-regulated kinase; MEK = mitogen-activated protein kinase.

TABLE. FEATURES OF NEW THERAPIES FOR ADVANCED MELANOMA

Drug therapy	Administration
Immunotherapies	
Anti-CTLA4 antibodies	
Ipilimumab	Intravenous infusion every three weeks for four cycles, with an option for re-induction
Anti-PD-1 antibodies	
Pembrolizumab	Intravenous infusion every three weeks, with treatment continued until disease progresses
Nivolumab	Intravenous infusion every two weeks, with treatment continued until disease progresses
Targeted therapies	
BRAF inhibitors	
Dabrafenib	Oral, twice daily on an empty stomach
Vemurafenib	Oral, twice daily on an empty stomach
Combination BRAF and MEK inhibitors	
Dabrafenib plus trametinib	Oral, dabrafenib as above, trametinib once daily on an empty stomach

Abbreviations: BRAF = serine/threonine-protein kinase B-Raf; CTLA4 = cytotoxic T-lymphocyte-associated antigen 4; MEK = mitogen-activated protein kinase; PD-1= programmed death receptor-1.

at one year compared with 42% of those treated with dacarbazine (HR for death, 0.42; 99.79% CI, 0.25 to 0.73; p<0.001).

Two further randomised trials have since been published showing improved outcomes with the use of an anti-PD-1 antibody compared with the anti-CTLA-4 antibody ipilimumab in untreated patients. The first of these compared pembrolizumab with ipilimumab and demonstrated the superiority of pembrolizumab with respect to response rate (33% versus 12%), progression-free survival and overall survival (HR 0.63; 95% CI, 0.47 to 0.83; p=0.0005); it was also the better tolerated agent.[7] The second trial compared the combination of nivolumab and ipilimumab with single-agent ipilimumab. The combination therapy led to significantly greater activity (response rate of 61% versus 11%), but this came at the cost of 54% of patients experiencing severe toxicity compared with 24% in the ipilimumab-alone arm of the trial.[8] These studies have shown 12-month survival rates for patients treated with anti-PD-1 antibodies in the range of 70 to 80%. Five years ago only 30 to 35% of patients with advanced melanoma survived one year.

The anti-PD-1 antibodies have the same side effects as ipilimumab but are generally better tolerated, with severe irAEs occurring at a lower frequency (about 12%). Early recognition and intervention is important in the management of irAEs. GPs should be especially aware of the potential for colitis presenting as diarrhoea, and consult with the treating oncologist early.

Pembrolizumab was listed on the PBS for the first-line treatment of metastatic melanoma on 1 September 2015. Nivolumab is currently being considered for listing by the TGA. It was also recently considered by the PBAC for PBS listing, but the outcome will not be made public until the TGA outcome is known. Nivolumab is currently available on a compassionate access program for patients with metastatic melanoma.

Targeted therapies

About 40 to 45% of patients with melanoma have a mutation in their tumour cells termed a *BRAF* mutation, which leads to uncontrolled upregulation of the mitogen-activated protein (MAP) kinase pathway. This is an intracellular signalling pathway with a role in promoting cell growth and division. Uncontrolled upregulation of the pathway leads to increased cell division and tumour growth (Figure 3). Blocking this pathway with oral agents that inhibit both the BRAF protein and a further component of the same pathway, mitogen-activated protein kinase (MEK), has led to rapid tumour shrinkage and improved survival in patients whose tumours have a *BRAF* mutation.

These therapies are ineffective in patients whose tumours lack the specific

BRAF mutations. Melanoma tumour tissue should undergo molecular testing for *BRAF* mutation status at diagnosis of stage 4 disease.

Features of these therapies and immunotherapies are summarised in the Table.

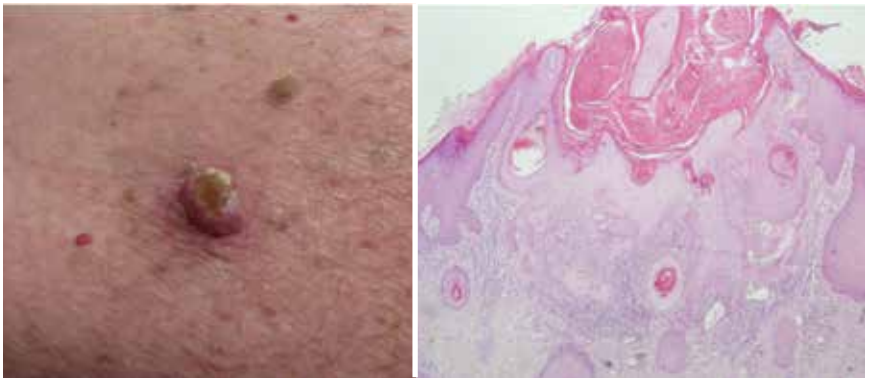
BRAF inhibitors (dabrafenib and vemurafenib)

Initial phase 3 studies compared BRAF inhibitors with chemotherapy. The BRIM-3 study randomised previously untreated patients with *BRAF*-mutant metastatic melanoma to receive the BRAF inhibitor vemurafenib or dacarbazine chemotherapy.[9] The vemurafenib group had a significantly higher response rate (48% versus 5%), progression-free survival and overall survival (despite crossover). The median survival of patients treated with vemurafenib was 13.6 months versus 9.7 months with chemotherapy (HR, 0.70, p=0.0008). A second similar study of the BRAF inhibitor dabrafenib confirmed the BRIM-3 findings.[10] Dabrafenib is now available on the PBS for the first-line treatment of metastatic melanoma.

The most common side effects of BRAF inhibitors are fever, fatigue, diarrhoea, arthralgia, liver biochemistry abnormalities and skin changes (Box). A class effect of single agent BRAF inhibitors, in addition to rash, hyperkeratosis and papillomas, is the development of squamous cell carcinoma (SCC) of the skin (Figure 4). SCCs occur in around 15% of patients, usually within 10 weeks of commencing treatment; they are managed in the same way as nontreatment-induced lesions.

Combination BRAF and MEK inhibition (dabrafenib plus trametinib)

A mechanism of resistance to single-agent BRAF inhibition is reactivation of the MAP kinase pathway with enhanced signalling through the MEK protein. In an attempt to overcome this, BRAF inhibitors have been tested in combination with MEK inhibitors (trametinib or cobimetinib) in three randomised trials.[11-13] In each of these studies, the combination of a BRAF inhibitor and a MEK inhibitor was compared with a single-agent BRAF inhibitor as first-line therapy for *BRAF*-mutant metastatic melanoma. In all three studies, the combination treatment was superior in terms of response and survival endpoints. In a recent update of the COMBI-D trial, the overall survival at two years for patients randomised to the combination of dabrafenib and trametinib was 51%.[14]



Figures 4a and b. Squamous cell carcinoma (SCC) in a patient being treated for melanoma, showing a well-differentiated keratoacanthoma-like lesion. SCC is a side effect of single-agent BRAF inhibitor therapy.

Trametinib became available on the PBS in August 2015. Because of current PBS listings, patients with a *BRAF* mutation can only receive PBS-funded targeted therapies (dabrafenib ± trametinib) as first-line therapies, with immunotherapies available for subsequent treatments.

The predominant toxicity experienced by patients taking the combination of dabrafenib and trametinib is a drug fever, which occurs in approximately 70% of patients. The fever may be associated with chills and myalgias and usually resolves quickly with temporary discontinuation of both drugs. Occasionally, the fever is recalcitrant, and corticosteroid therapy may be needed to allow continued melanoma treatment. If a patient taking dabrafenib and trametinib develops a fever then they should stop taking both drugs and be assessed for possible infective causes.

The hyperkeratotic skin toxicity that often occurs with single-agent BRAF inhibition is rarely seen with combination therapy because of inhibition of the MEK protein.

Conclusion

The past few years have seen the emergence of two important new classes of systemic therapy for metastatic melanoma: immunotherapies and targeted therapies. In Australia, because of current PBS prescribing restrictions, most patients who have advanced melanoma with a *BRAF* mutation receive combination BRAF and MEK inhibition with dabrafenib plus trametinib as first-line therapy, and immunotherapy at progression. Patients who have advanced melanoma without a *BRAF* mutation receive immunotherapy upfront. In countries with unrestricted prescribing arrangements, the sequencing of therapy is tailored to patient and tumour characteristics.

With the changing landscape of treatment for metastatic melanoma, an understanding of these new treatments, their impact on prognosis and the unique toxicities that may occur is important to ensure optimal management of patients with metastatic melanoma by all members of their healthcare team. MT

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A list of references is included in the website version (www.medicinetoday.com.au) and the iPad app version of this article.

COMPETING INTERESTS: None.

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