

## Advances in the treatment of melanoma

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Malignant melanoma is an aggressive form of skin cancer arising from malignantly transformed melanocytes. The incidence and mortality from melanoma are currently rising, placing significant demands on healthcare provision and representing a major public health issue. Surgical excision remains the standard of care for the treatment of primary melanomas. Excision of thin tumours less than 1 mm in thickness can result in an over 95% five-year survival rate.<sup>1</sup>

Despite this however, 20% of primary melanomas will progress to metastatic disease for which the treatment options are limited and the prognosis poor with a median survival of 8-18 months.<sup>1</sup> Over the last year significant progress has been made in the treatment of advanced stage disease with the reporting of large phase III studies demonstrating improved survival in patients with metastatic melanoma, followed by Food and Drug Administration (FDA) approval of new therapeutic agents (Table 1).

### Longstanding conventional therapies for melanoma

#### Chemotherapeutics

The need for development of novel therapeutics is highlighted by the fact that

**Table 1. Food & Drug Administration approved agents for the treatment of melanoma.**

Year of approval	Agent	Type of agent and actions
2011	Vemurafenib	BRAF V600E kinase inhibitor
2011	Ipilimumab	Humanised mAB targeting the inhibitory molecule CTLA-4
2011	Pegylated IFN- $\alpha$ 2 $\beta$	Modified (pegylated) IFN has actions as for IFN- $\alpha$ 2 $\beta$ , with increased half life and enhanced therapeutic efficacy
1998	High dose IL-2	Cytokine therapy aimed at promoting T-cell activation and proliferation
1995	IFN- $\alpha$ 2 $\beta$	Interferon enhances the antitumour immune response in addition to having anti-angiogenic and pro-apoptotic properties
1975	Dacarbazine	Alkylating agent inducing cell cycle arrest and tumour cell apoptosis

mAB = monoclonal antibody; IFN = interferon; IL = interleukin.

standard chemotherapeutic regimens have little impact on survival for advanced disease. An analysis of randomised controlled trials demonstrated no superiority of chemotherapy over supportive care and, for patients who do respond, the remissions are usually of short duration.<sup>2</sup> The alkylating agent dacarbazine (DTIC) is currently widely used as part of standard care for the treatment of unresectable stage IV disease, in spite of a response rate of only around 20% and a median response duration of 4-5 months.<sup>2</sup>

Other chemotherapeutic agents including temozolomide, cisplatin, carboplatin, vinca alkaloids and taxanes are associated with poor outcomes and significant adverse side effects.

#### Interleukin-2

Interleukin (IL)-2 is thought to have antitumour effects both by inducing T-cell activation and proliferation and by stimulating host antitumour responses. The treatment of advanced disease with IL-2 alone, however, has shown limited responses in around 15% of cases, although durable remissions have been reported in some patients.<sup>3</sup> The use of IL-2 in high doses is associated with considerable mortality, with the development of gastrointestinal, cardiovascular, renal and neurological toxicities, including the vascular leak syndrome

with accumulation of fluid within the lung and liver.

#### Interferon

The type 1 interferons (IFN- $\alpha$ , IFN- $\alpha$ 2 $\beta$ ) have been evaluated in numerous clinical trials and shown in some studies to be beneficial in prolonging disease-free survival when used in the adjuvant setting. Recent promise has been demonstrated with a modified form of IFN, pegylated IFN- $\alpha$ 2 $\beta$ ; this has a longer half-life, enhanced therapeutic efficacy and improved tolerability. A phase III study investigating the use of this agent versus observation alone as adjuvant therapy for resected stage III disease (metastatic disease within the draining lymph node basin) showed a significant improvement in relapse-free survival.<sup>4</sup>

### New agents for the treatment of melanoma

It is well recognised that melanoma is an immunogenic tumour with the demonstration of T lymphocyte infiltrates within the tumour that correlate with improved patient survival. Despite the presence of demonstrable antitumour immune responses, tumours are able to evade the immune response and progress, a process known as immune escape. Multiple immunotherapeutic strategies have been adopted with a view

to overcoming the immunosuppressive tumour environment and boosting antimelanoma immunity. Overall response rates have been poor in previous studies investigating immunotherapeutic modalities despite showing some tantalising results – for example, a limited number of patients developed durable responses with T- and dendritic cell autologous cell therapies.

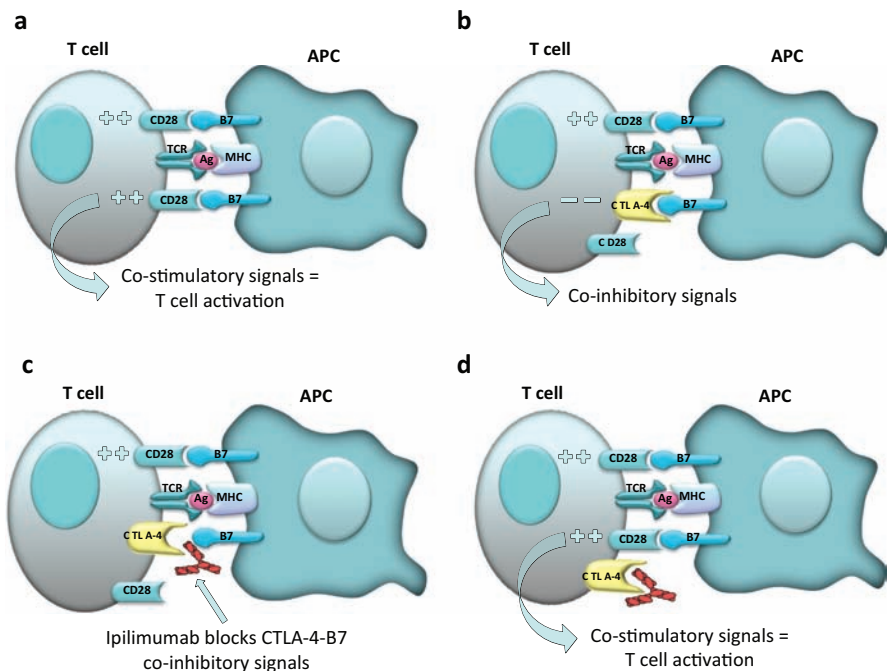
### Ipilimumab

Interest in immunotherapeutic approaches has been reinvigorated over the last year following promising results with ipilimumab, a human monoclonal antibody (mAb) targeting CTLA-4. CTLA-4 is expressed on the cell surface of activated T lymphocytes, acting as an inhibitory molecule by competing for binding to B7 with CD28, a co-stimulatory molecule also expressed on T lymphocytes (Fig 1).

In a recent phase III trial in patients with stage III or IV disease, ipilimumab therapy improved the median overall survival (10.1 months) compared with a peptide vaccine (gp100) (6.4 months).<sup>5</sup> A subsequent phase III trial compared treatment with ipilimumab and DTIC versus DTIC alone, with improved survival in the group treated with ipilimumab (11.2 months vs 9.1 months).<sup>6</sup> Importantly, although there was relatively modest improvement in overall survival, durable responses were seen in a number of patients.

Studies are now also underway to evaluate the use of ipilimumab in combinations with other therapies such as IL-2. The utility of the drug in the adjuvant setting is also being assessed.

**Side effects.** Side effects of ipilimumab include development of immune-related adverse effects including colitis and dermatitis that are commonly responsive to systemic steroids. However, improved clinical responses are seen in patients who develop autoimmune complications, highlighting the fine balance that needs to be achieved between stimulating antitumour responses and the development of unwanted autoimmunity with subsequent toxicities.



**Fig 1. Mechanism of action of ipilimumab.** Melanoma antigens (Ag) bound to the major histocompatibility complex (MHC) on the surface of antigen-presenting cells (APC) are presented to T-cells through the T-cell receptor (TCR): (a) T-cell activation is achieved by co-stimulatory signals to T-cells by CD28 receptor recognition of B7 ligands on APCs; (b) an important immunoregulatory signal is that of the cytotoxic T lymphocyte antigen-4 (CTLA-4) on T-cells which competes with CD28 for binding to B7 molecules, blocking the necessary co-stimulatory signals by APCs; (c) ipilimumab blocks binding of CTLA-4 to B7 on the surface of APCs; (d) this allows CD28-B7 complex assembly and co-stimulation, restoring T-cell activation.

### Mutation targeted therapies for melanoma: agents targeting BRAF mutations

Newly emerging therapeutics that target oncogenes thought to be critical in the

pathogenesis of melanoma are currently under evaluation. Around 60% of melanoma tumours are thought to have mutations in the BRAF gene, the commonest of which is V600E. BRAF gene mutations result in activation of

## Key points

Melanoma incidence and mortality are increasing

Melanoma is relatively resistant to therapy with standard chemotherapeutic regimens

The small molecule inhibitor vemurafenib that targets melanomas with a common and specific mutation (BRAF V600E) has shown promise in the treatment of melanoma, representing a successful form of truly personalised therapy based on molecular testing of individual tumours

Success with the anti-CTLA-4 monoclonal antibody ipilimumab highlights the therapeutic potential of targeting antitumour immune responses

Numerous other agents are currently under development and may provide alternative therapeutic options in the future

Combinations of treatments that target different pathways involved in melanoma progression require further evaluation

**KEY WORDS:** immunotherapy, melanoma, small molecule inhibitor, tumour mutation

downstream signalling through the mitogen-activated protein kinase (MAPK) pathway (Fig 2). Initial trials using the non-selective BRAF kinase inhibitor sorafenib were disappointing, but data from studies evaluating the effects of vemurafenib, a potent selective inhibitor of mutated BRAF, have shown exciting results with clinical responses in patients with BRAF V600E mutations. A recently published large multicentre phase III trial showed improved overall survival compared with patients treated with DTIC, leading to FDA approval.<sup>7</sup> Overall survival at six months was 84% versus 64% in the vemurafenib and DTIC treated groups, respectively, with response rates of 48% versus 5%.<sup>7</sup>

Studies are also ongoing to assess the efficacy of another BRAF inhibitor, dabrafenib (GSK2118436), thought to target tumours with both BRAF V600E and BRAF V600K mutations. Early studies have shown this agent to be effective for the treatment of brain metastases<sup>8</sup> and a large Phase III study is currently underway.

*Side effects.* The most common side effects with BRAF inhibitors include the development of cutaneous squamous cell carcinomas in 18–24% of patients, photosensitivity, rash, arthralgia, fatigue, alopecia and pruritus. Unfortunately, it is now well recognised that after initial impressive responses, tumours often develop drug resistance with reactivation of the MAPK pathway. Attempts to overcome drug resistance are now underway with the introduction of MEK (mitogen activated protein kinase) inhibitors. MEK is a downstream target of BRAF in the MAPK pathway. Preliminary studies with the combined use of dabrafenib and the MEK inhibitor GSK1120212 have shown promise, with delayed emergence of resistance to dabrafenib and decreased incidence of squamous cell carcinoma development.<sup>9</sup>

**New therapeutic agents currently in development**

*Inhibitors targeting cKIT mutations*

Mutations in cKit, the receptor tyrosine kinase for stem cell factor, although

uncommon in cutaneous melanomas, have been identified in up to 20% of acral and mucosal melanomas.<sup>10</sup> Accumulating evidence suggests that certain small molecule inhibitors of c-KIT, including imatinib, nilotinib and dasatinib, may be of benefit in patients with c-KIT mutations. These are currently under evaluation in clinical trials.<sup>11-12</sup>

*Antibodies targeting vascular endothelial growth factor*

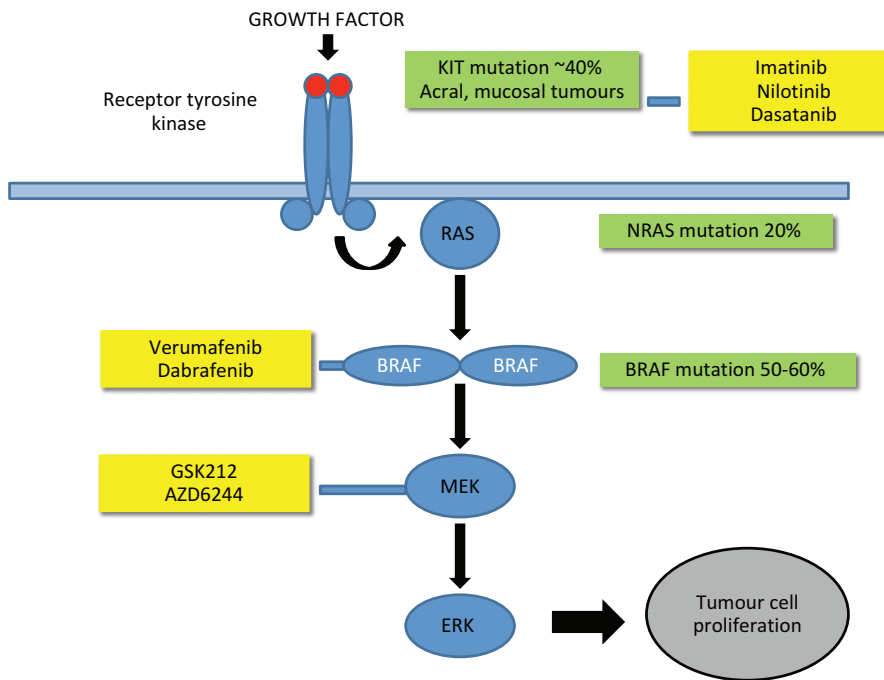
It is well recognised that the formation of new blood vessels within tumours can help to promote metastasis and tumour growth. The humanised mAb bevacizumab targets vascular endothelial growth factor (VEGF) by blocking its binding to the VEGF receptor, and is thought to inhibit angiogenesis. Bevacizumab is FDA approved for the treatment of metastatic colorectal cancer, breast cancer and non-small cell lung cancer in combination with chemotherapy. Its use in the treatment of melanoma is currently under evaluation. Phase II studies have shown some activity against melanoma in combination with IFN and fotmustine.<sup>13</sup> A large Phase III study is ongoing to assess efficacy of response to therapy with bevacizumab in the adjuvant setting for surgically resected advanced disease (AVAST-M study).

*Antibodies targeting programmed death-1*

Programmed death-1 (PD-1) is an inhibitory cell surface molecule expressed on T lymphocytes and has homology to CTLA-4. Its ligand PD-L1 is upregulated on tumour cells and thought to be associated with poor prognosis. In addition, senescent/exhausted T lymphocytes (such as those seen within the tumour microenvironment) demonstrate increased expression of PD-1. mAbs targeting PD-1 are currently in development for the treatment of melanoma.<sup>14</sup>

*Oncolytic vaccine therapy*

Promise has recently been demonstrated with a genetically modified herpes



**Fig 2. The mitogen-activated protein kinase (MAPK) pathway and potential therapeutic targets in melanoma.** Activation of the receptor tyrosine kinase receptor by growth factors results in activation of the MAPK pathway and subsequent tumour cell proliferation. A significant proportion of melanomas contain activating mutations (green boxes) that result in activation of protein kinases (blue boxes). Various agents have been developed that target activated protein kinases with specific mutations (yellow boxes).

simplex virus with selectivity for malignantly transformed cells, in addition to the insertion of a coding sequence for the production of granulocyte-macrophage colony-stimulating factor (GM-CSF) known as OncoVEX<sup>GM-CSF</sup>. An overall response rate of 26% was observed in a phase II study.<sup>15</sup> A phase III study is now being performed. The agent is injected locally into melanoma metastases and is thought to induce both localised and systemic immune responses with a limited toxicity profile.

## Conclusions

Exciting progress has been made in the treatment of advanced melanoma over the last year. Although overall limited responses have been observed, the responses to treatment with the agents ipilimumab and vemurafenib represent true progress in the treatment of a cancer previously resistant to numerous conventional chemotherapeutic regimens. Knowledge and clinical experience with the application of these agents will most likely pave the way for improved targeted therapies with enhanced efficacy and safety profiles.

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