Drug treatment for melanoma: progress, but who pays?

Making cancer drugs affordable requires coherent policy and cannot be left to market forces

Richard F Kefford
AM, PhD, FRACP,
Professor of Medicine,[1] and
Co-Director of Research[2]

1 University of Sydney at Westmead Hospital, Sydney, NSW.

2 Melanoma Institute Australia, Sydney, NSW.

richard.kefford@sydney.edu.au

doi: 10.5694/mja12.10955

Melanoma is 10 times more common in Australia than in most countries,[1] and kills more than 1300 Australians every year.[2] The good news is that we now have effective drug treatments for metastatic melanoma. Two drugs, ipilimumab[3,4] and vemurafenib,[5] are now approved by the United States Food and Drug Administration and the Australian Therapeutic Goods Administration in recognition of convincing evidence for prolongation of life in treated patients, at least in the short term. Australia has played an important role in the development of drug treatment for melanoma,[6,7] including the practice-changing discovery of the effectiveness of drug therapy against brain metastases.[8]

The bad news is that, like all new cancer drugs, these drugs are expensive, with price tags in the six-figure realm for each treated patient. Vemurafenib, which targets the mutated BRAF oncogene present in 50% of melanomas, produces dramatic tumour regressions in most cases. However, the average duration of the response is just 6 months, with a median extension in overall survival of just under 4 months. Ipilimumab, a potent but non-specific immunostimulant, rarely induces tumour regressions, but the disease stabilises for 3 or more years in a subset of around 10% of patients. This subset cannot yet be presumptively identified by biomarkers or other tests, so most treated patients do not benefit. Although these advances

appear modest, they must be viewed against a background of dismal treatment outcomes for people with this disease, for whom even toxic chemotherapy combinations have had minimal benefit and failed to prolong life.[1] These drugs are therefore enthusiastically welcomed by melanoma oncologists, patients and their carers as the first in a predicted series of stepwise advances that promise considerable improvements in survival time for patients with metastatic melanoma.

Not surprisingly, however, the Australian Pharmaceutical Benefits Advisory Committee (PBAC), which advises the federal government on reimbursement of drug costs, has baulked at the cost–benefit equation for ipilimumab, which is currently marketed in Australia at $120 000 for four injections. The PBAC considered the case for vemurafenib at its July meeting in 2012. Even if the PBAC recommends that vemurafenib be approved for subsidy, it must also be approved by the Health Minister, and this is never automatic.

The Australian reaction is not unique. Reimbursement for ipilimumab was rejected in the United Kingdom. Only patients in certain European countries, or who are insured in the US, or wealthy, have ready access to the drug (although means-tested access programs also exist in the US). It appears to be the size of the cohort of patients with projected ability to pay that largely determines business modelling for the initial drug price in the international marketplace.

This problem is about to become much worse, and not just for melanoma. The molecular biology revolution is now delivering a rapidly expanding cascade of rational designer anticancer drugs that target cancer-specific molecular changes, or cleverly reverse immunological tolerance to the disease. The strategy of combining these approaches is in its infancy, but promises advances that are complementary and synergistic across multiple tumour types, with toxicity profiles far lower than those of traditional chemotherapy. Oncologists will rapidly adopt double and triple drug treatments in multipronged therapy for metastatic cancer. This strategy holds the real promise of being able to convert metastatic melanoma from a rapidly fatal illness to a chronic disease within the next decade. A doublet of two highly effective targeted drugs, dabrafenib and trametinib,[9] will, like vemurafenib, shortly be tested as adjuvant therapy for high-risk melanoma after surgical excision, and the results of a similar trial of ipilimumab are anticipated in mid 2013. If these therapeutic strategies work as well as we anticipate, years may be added to the lives of patients who have undergone resection of lymph node metastases. A large proportion of these patients are young adults.

However, the price of this success will be an exponential escalation of drug costs. Even if the extension of life is measured in years with these strategies, and some cures are seen, it seems that not even the top end of the US market can sustain this development.

Drug development is already a high-risk investment, with a 1% chance of any candidate molecule surviving the rigours of preclinical and clinical testing and making it into the marketplace. The cost of this pathway for a single successful cancer drug is often over $1 billion, and many fail at the final challenge of large-scale Phase 3 testing. The precedent of the failure to sell ipilimumab in countries like Australia and the continuing pressure for inevitable price cutting and lower returns may influence the board rooms of pharmaceutical companies to move away from cancer drugs and towards potentially easier, faster and safer investments.

The stakes for human health seem too high to trust the solution entirely to the marketplace. Certainly, growing competition between new drugs may drive down prices. Smarter, smaller, more selective cancer-drug trials may reduce drug development costs by improving the accuracy with which patients who are likely to benefit are identified. There will be increased incentive to cut layers of unnecessary legalistic and bureaucratic flab from the gigantically inefficient clinical trials and drug-approval machinery.

But there are only so many things the market can do, and wider policy decisions are urgently needed. How do therapies for advanced cancer stack up as a priority against some of the other big-ticket items for the Australian Pharmaceutical Benefits Scheme (PBS), like statins and protein-pump inhibitors? How much of the health dollar should be justifiably expended on cancer drugs? Is a smarter, less toxic, incrementally beneficial, but expensive, drug, such as PBS-approved paclitaxel protein-bound for metastatic breast cancer, a justifiable priority over older, cheaper, off-patent drugs?

If public funding cannot withstand the impost of effective high-cost drugs, should there be inducements for specific private health insurance that does? (This, of course, would not resolve the issue for the uninsured.) Can governments work internationally with the pharmaceutical industry to sustain strategic invention, subsidise the costs of drug development and minimise its risks and costs?

Patients, carers, the medical profession, governments, the pharmaceutical industry, private health insurers and taxpayers need to contribute to solving this dilemma. One in every three Australians will need cancer treatment at some time. Many of them will need drug treatment. There is now an urgent need for an informed public debate about how to pay for it.

Competing interests: I have received institutional reimbursement for membership of advisory boards on drug development from Roche, GlaxoSmithKline and Bristol-Myers Squibb and travel assistance from GlaxoSmithKline to present clinical trial data.

Provenance: Commissioned; externally peer reviewed.

1 Thompson JF, Scolyer RA, Kefford RF. Cutaneous melanoma. *Lancet* 2005; 365: 687-701.

2 Australian Institute of Health and Welfare. Australian cancer incidence and mortality (ACIM) books. Melanoma of the skin. Canberra: AIHW, 2011. http://www.aihw.gov.au/acim-books/ (accessed Jul 2012).

3 Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. *N Engl J Med* 2010; 363: 711-723.

4 Robert C, Thomas L, Bondarenko I, et al. Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. *N Engl J Med* 2011; 364: 2517-2526.

5 Chapman PB, Hauschild A, Robert C, et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. *N Engl J Med* 2011; 364: 2507-2516.

6 Bollag G, Hirth P, Tsai J, et al. Clinical efficacy of a RAF inhibitor needs broad target blockade in BRAF-mutant melanoma. *Nature* 2010; 467: 596-599.

7 Flaherty KT, Puzanov I, Kim KB, et al. Inhibition of mutated, activated BRAF in metastatic melanoma. *N Engl J Med* 2010; 363: 809-819.

8 Falchook GS, Long GV, Kurzrock R, et al. Dabrafenib in patients with melanoma, untreated brain metastases, and other solid tumours: a phase 1 dose-escalation trial. *Lancet* 2012; 379: 1893-1901.

9 Weber JS, Flaherty KT, Infante JR, et al. Updated safety and efficacy results from a phase I/II study of the oral BRAF inhibitor dabrafenib (GSK2118436) combined with the oral MEK 1/2 inhibitor trametinib (GSK1120212) in patients with BRAFi-naive metastatic melanoma. 2012 ASCO Meeting Abstracts. *J Clin Oncol* 2012; 30 (15 Suppl): 8510. http://www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst_detail_view&confID=114&abstractID=97785 (accessed Jul 2012). ❑