Melanoma research gathers momentum

Every year, 160 000 people are diagnosed with melanoma and 48 000 die from the disease. More than 9000 deaths are in the USA, where, according to an analysis by Gery Guy and colleagues in *Morbidity and Mortality Weekly Report* on June 2, melanoma has become the fifth most common cancer for men and the seventh for women. The reported incidence of melanoma in the USA has doubled in a generation and is increasing at a rate faster than that for any other solid tumour. Therefore, the report's predictions on incidence and costs to 2030 are a stark warning.

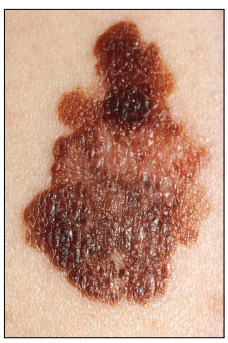
Melanoma can be challenging to diagnose and to treat. Results from research have not kept pace with clinical need. Innovations in surgery, the traditional first line of treatment, have not extended survival, and vaccine trials are disappointing. However, advances in molecular biology and improved understanding of cell pathways offer new insights and therapeutic opportunities. In particular, the combination of molecularly targeted agents and immunotherapy has transformed a once pessimistic outlook to one of expectant optimism. Writing in a Seminar on cutaneous melanoma for *The Lancet* in 2014, Alexander Eggermont and colleagues concluded: "Drug development in melanoma has never been more exciting."

That excitement was palpable during the annual meeting of the American Society of Clinical Oncology (ASCO) in Chicago, IL on May 29–June 2, where two active-comparator phase 3 randomised controlled trials showed synergy for combined treatments. Both studies involved people with untreated, unresectable stage III or IV melanoma. In one study, nivolumab (an anti-programmed death 1 checkpoint inhibitor) and ipilimumab (an anti-cytotoxic T lymphocyte-associated antigen 4 antibody) increased median progression-free survival to 11·5 months. In the other, which recruited patients who had stage IIIC or IV disease and the BRAF Val600Glu or Val600Lys mutation, the combination of dabrafenib (a BRAF inhibitor) with trametinib (an inhibitor of mitogen-activated protein kinases MEK_1 and MEK_2) resulted in 50% overall survival at 2 years. Systemic reactions were common in both studies, especially with the combination of nivolumab and ipilimumab, in which 95% of participants reported treatment-related adverse events. The gains of these studies might seem modest in terms of survival, but are dramatic in this population, and enormous in terms of insight and providing a new platform for further combination treatments in melanoma and other cancers.

The increase in melanoma incidence is as much a challenge for public health as for oncology. Although genetic associations are recognised, more than 90% of melanomas are attributable to skin damage by ultraviolet (UV) radiation, which accumulates over time. The real opportunity to conquer melanoma lies in prevention, rather than treatment. For instance, in the USA, 40% of people report sunburn each year, and 30% of non-Hispanic white women aged 16–25 years use indoor tanning facilities, despite the classification of such facilities as a group 1 carcinogen by the International Agency for Research on Cancer. Such behaviours are believed to account for the more rapid rise of melanoma incidence in women than men.

Guy and colleagues estimate that prevention could reduce the incidence of melanoma by 20%. Australia leads the world in melanoma incidence, and has been a pioneer in public health measures to reduce risk, such as banning commercial indoor tanning in the state of Victoria. SunSmart promotes education, collaboration, and infrastructure to reduce the burden of skin cancers, and is estimated to save AUS$2·30 for every $1·00 invested. The economics of melanoma are important, since changes in the environment and travel mean that more people in less wealthy countries will be exposed to greater UV risk in the future. The cost of care for melanoma is already US$3·3 billion per year in the USA. Therefore, the excitement of new drug combinations at ASCO is tempered by the potential cost of these agents and invites reflection on the economic and human benefits from investment in prevention.

Melanoma provides a snapshot of contemporary cancer research by emphasising the importance of combined approaches: not only at a therapeutic level, but also for shared scientific insights across disciplines to translate molecular observations into clinical care. It shows the importance of opportunistic patient education by all health professionals to reduce risk. Above all, research into melanoma illustrates those moments—witnessed at ASCO—when perseverance and ingenuity make undoubted headway against once insurmountable cancers. ■ *The Lancet*



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For ***Morbidity and Mortality Weekly Report*** see http://www.cdc.gov/mmwr/preview/mmwrhtml/mm64e0602a1.htm

For the **Seminar on cutaneous melanoma** see **Seminar** *Lancet* 2014; **383:** 816–27

For **combined nivolumab and ipilimumab or monotherapy in untreated melanoma** see *New Engl J Med* 2015; published online May 31. http://www.nejm.org/doi/full/10.1056/NEJMoa1504030

For **dabrafenib and trametinib versus dabrafenib and placebo for Val600 BRAF-mutant melanoma** see **Articles** *Lancet* 2015; published online May 31. http://dx.doi.org/10.1016/S0140-6736(15)60898-4/fulltext

For **SunSmart** see http://www.sunsmart.com.au/about/sunsmart-program