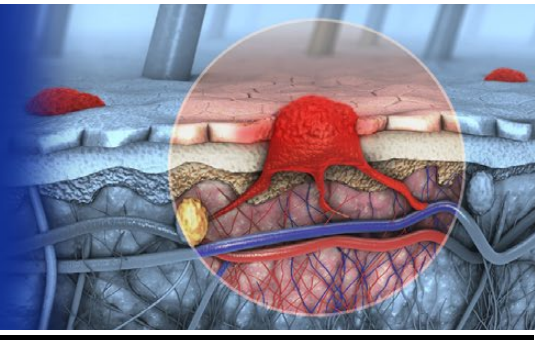
Melanoma Practice Review™



Making Education Easy

Issue 8 - 2021

In this issue:

Abbreviations used in this issue:

EANO = European Association of Neuro-Oncology
ESMO = European Society of Medical Oncology
SITC = Society for Immunotherapy of Cancer

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Welcome to the 8th issue of Melanoma Practice Review.

This Review covers news and issues relevant to clinical practice in melanoma. It will bring you the latest updates, both locally and from around the globe, in relation to topics such as new and updated treatment guidelines, changes to medicines reimbursement and licensing, educational, professional body news and more. And finally, on the back cover you will find our COVID-19 resources, and a summary of upcoming local and international educational opportunities including workshops, webinars and conferences.

We hope you enjoy this new Research Review publication and look forward to hearing your comments and feedback.

Kind Regards,

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Medical Research Advisor
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Clinical Practice

A practical guide on the use of imiquimod cream to treat lentigo maligna

Clinical practice guidelines on the use of imiquimod in the treatment of lentigo maligna (LM) have not been developed due to varying methodologies and short follow-up of trials to date. These authors propose practical clinical strategies for the use of imiquimod for treating LM based on their experience and review of the literature. They describe optimal administration procedures in various clinical settings and long-term management.

LM is a form of melanoma in situ that occurs on exposed sun-damaged skin and mostly affects the head and neck region. The estimated incidence of LM in Australia is more than 15 per 100,000.

Surgery has traditionally been used to treat LM, but localisation in cosmetically sensitive areas, challenge in obtaining wide resection margins, and patient factors such as advanced age and comorbidities have required less invasive strategies. Alternative treatment options include radiotherapy and topical imiquimod.

Treatment of LM with topical imiquimod cream is also not without difficulties, due to the often large treatment area required, variegated appearance of LM, involvement of adnexal structures, poorly defined peripheral edge, disease localisation close to areas such as the eyes and lips, and elderly patients with multiple comorbidities. Ongoing inflammatory side effects and treatment compliance with a self-delivered therapy also presents challenges.

The authors of this paper suggest three main settings where imiquimod can be useful: 1) a patient with multiple comorbidities or multiple recurrence; or 2) patients with repetitive histologic positive margins, where extensive surgical widening of scar is limiting functionality or disfiguring; or 3) fit patients who have cosmetic concerns with surgery.

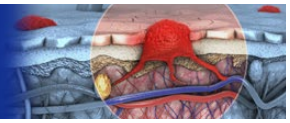
Patient education of side effects is key; patients should be advised that a local inflammatory reaction is required for the treatment to be effective. Practical information is given on administration, including near special sites such as the eyes and mouth. Continued application to achieve a total of 12 weeks of inflammation is recommended. In the case of a patchy result, the authors advise changing the dose to ensure an appropriate inflammatory reaction across the lesion. This may mean increasing the dose in some areas and reducing it in others.

Advice on how patients can manage inflammatory reactions including changing dosing frequency and taking a break from treatment should be discussed. Possible local reactions include thick crusts and infections. In the case of thick crusts, softening with petroleum jelly is recommended. Cotton gauze debridement may be necessary. When the scab has resolved, restart treatment at a lesser dose. Patients should avoid covering the area with a bandage. Regarding infections, swab for bacteriologic or herpes culture and treat accordingly. Imiquimod should be stopped during infection management then resumed.

Systemic side effects may include malaise, fever, rigours, fatigue, arthralgias, chills, myalgias, and nausea. Imiquimod should be withdrawn until complete recovery of systemic side effects (generally less than 48 hours). In the case of recurrence of systemic reactions, therapy should be interrupted and alternative therapy considered.

Six months after the conclusion of treatment, patients should have their lesion evaluated by dermoscopy and Wood's lamp to target a biopsy of any suspicious pigmentation or other changes. Yearly follow-up of all patients with LM is recommended due to the risk of a second melanoma.

Australas J Dermatol. 2021 Sep 16. doi: 10.1111/ajd.13720



Development and validation of a modified pathologic nodal classification system for cutaneous melanoma

The staging system created by the American Joint Committee on Cancer (AJCC) is the gold standard for melanoma and several other cancers. Due to the changing patterns of lymph node evaluation for cutaneous melanoma, it is unclear whether the current nodal classification system will remain accurate in the modern era. The current nodal staging system was developed mainly for patients undergoing completion lymph node dissection (CLND) for node-positive disease and does not produce groups with continuously increasing mortality.

The authors of this article propose a new staging system for patients with lymph node involvement with more distinct and more stepwise N-category groups than the AJCC system.

They found that, in a cohort of 105,785 patients with cutaneous melanoma, factors independently associated with mortality included the number of positive nodes, clinically detected metastasis, and in-transit metastasis.

A recursive partitioning analysis showed continuously increasing mortality for each proposed lymph node classification group. In contrast, a more haphazard mortality risk was seen with nodal staging via AJCC criteria. The proposed system continued to accurately stratify patients when excluding those undergoing CLND for microscopic lymph node metastases. The proposed system was validated in 85,499 patients from the SEER database.

JAMA Surg. 2021 Sep 1:e214298

BRAF-MEK inhibitors as steroid-sparing bridge prior to checkpoint blockade therapy in symptomatic intracranial melanoma

The advent of immune checkpoint inhibitors and BRAF-MEK inhibitors has considerably improved survival for patients with metastatic melanoma. However, the efficacy of immune checkpoint inhibitors is compromised in patients with symptomatic intracranial metastatic melanoma who are immunosuppressed due to the use of steroids to control brain oedema. Furthermore, despite the good efficacy of BRAF-MEK inhibitors in *BRAF*-mutant intracranial metastatic melanoma, most patients will eventually progress. Standard of care is lacking regarding the best approach in treating patients with symptomatic intracranial *BRAF*-mutated melanoma. Using a short course of BRAF-MEK inhibitors in this setting may permit the discontinuation of steroids and lead to higher intracranial response, optimising the effect of immunotherapy if started prior to progression of the disease.

These authors described a patient with *BRAF*-mutant symptomatic intracranial metastatic melanoma who was successfully treated with BRAF-MEK inhibitors as a bridge to allow discontinuation of steroids before immune checkpoint inhibitor therapy.

A 50-year-old female presented with new neurological symptoms. Her previous history included stage IA melanoma treated with wide local excision and stage IB melanoma treated with wide local excision and sentinel lymph node biopsy. Brain MRI revealed metastatic disease. The patient was started on dexamethasone due to oedema. CT and biopsy revealed a pulmonary malignant melanoma which was confirmed by NGS to have a $BRAF^{V600E}$ mutation and *CDKN2A* copy number loss. The patient completed WBRT.

Dexamethasone was tapered after starting a BRAF inhibitor (encorafenib) and MEK inhibitor (binimetinib) as a bridge to control the symptomatic brain lesions prior to initiation of immune checkpoint inhibitor therapy. Treatment was well tolerated and at 8 weeks imaging showed a partial response in both the brain and lung, with no new neurological symptoms. Brain oedema continued to resolve. Encorafenib and binimetinib were discontinued after 8 weeks and the patient switched to ipilimumab and nivolumab. After two cycles, almost complete resolution was observed on brain MRI and complete resolution was seen on pulmonary CT. Grade 3 hepatitis required holding immunotherapy and high-dose prednisone taper. The patient later started maintenance nivolumab therapy and had significant clinical and radiographic response ongoing at 8 months after initiating therapy.

While this case report provides proof-of-concept, additional clinical trials are required.

Melanoma Manag. 2021;8(2):MMT55

Effects of active cancer treatment on safety and immunogenicity of COVID-19 mRNA-BNT162b2 vaccine

The Vax-On observational study evaluated the effects of active anticancer treatment on safety and immunogenicity of the COVID-19 mRNA vaccine (Pfizer-BioNTech) in patients with solid tumours. The study prospectively enrolled 366 patients who started the 3-week vaccine schedule from 9 March to 12 April 2021 (timepoint 1). Patients on active anticancer treatment within the previous 28 days accounted for the exposed cohort (n=285). Patients who had discontinued anticancer treatment by at least 28 days represented the control cohort (n=81). Safety analysis and quantification of anti-SARS-CoV-2 Spike IgG were performed before the second dose (timepoint 2) and 8 weeks thereafter (timepoint 3).

The most common adverse events were mild injection site reactions. Systemic adverse events occurred in less than 17% of patients and were significantly associated with female sex, ECOG performance status 2 or G-CSF use. Severe adverse events occurred in 1% of patients.

Humoral response to the first dose was low, but the second dose resulted in an exponential increase in IgG titre and high rate of seroconversion. At timepoint 2, the median IgG titre (131 AU/mL vs 62 AU/mL; P=0.029), median log IgG titre (P=0.033), and seroconversion rate (65% vs 52%; P=0.048) were significantly higher in the control cohort. At least 15-fold increase in median IgG titres and seroconversion rates up to 91% were observed from timepoint 2 to 3 within the same cohorts (P<0.001). Humoral response did not differ significantly between cohorts at timepoint 3.

Multivariate analysis showed that ECOG performance status 2 and G-CSF use were significantly associated with lower IgG titre and lack of seroconversion after either dose of vaccine.

Ann Oncol. 2021 Sep 20:S0923-7534(21)04488-4

Melanoma mortality declining in the US

Mortality from cutaneous melanoma decreased in the US from 2014 to 2018 but the incidence increased, according to an annual report from The American Cancer Society, Centers for Disease Control and Prevention, the National Cancer Institute, and the North American Association of Central Cancer Registries. It is thought that mortality declined following introduction of new therapies, including targeted and immune checkpoint inhibitors, the first of which was approved by the US FDA in 2011.

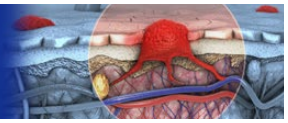
The annual report updates the incidence and mortality of the most common cancers and examines short- and long-term trends since 2001.

Melanoma mortality rates started a considerable decline in 2012 among females (4.4% per year) and in 2013 among males (5.7% per year). The incidence of melanoma, however, showed an opposite trend, increasing 1.9% per year for females and 2.2% for males, from 2001 to 2017. Furthermore, melanoma incidence by ethnicity, reported for 2013-2017, revealed that melanoma was much more common among white non-Hispanics (24.5 per 100,000 for females and 37.4 per 100,000 for males), followed by non-Hispanic American Indians/Alaska Natives (6.7 for females and 10.8 for males), Hispanics (4.5 and 5.1), non-Hispanic Asians/Pacific Islanders (1.3 and 1.6), and non-Hispanic Blacks (1.0 and 1.2). Mortality rates for melanoma, reported for 2014-2018, followed a similar trend with regards to ethnicity. White females (1.8 per 100,000) and males (4.2 per 100,000) had the highest mortality, then American Indians/Alaska Natives (0.5 and 1.0) and Hispanics (0.5 and 0.9), while rates were the same for Blacks and Asians/Pacific Islanders (0.3 and 0.4).

According to the authors, the substantial recent decline in mortality reflects the considerable increase in survival for metastatic melanoma. Two-year survival in distant-stage disease increased by 3.1% per year for patients diagnosed during 2009-2014. Many patients received newer treatments through clinical trials and expanded access programs prior to approval. Two-year survival for nonmetastatic melanoma increased by 0.4% per year for regional-stage disease and 0.03% per year for localised-stage cases diagnosed from 2001-2014.

J Natl Cancer Inst. 2021 Jul 8:djab131

Media release



KEYTRUDA®
(pembrolizumab)

KEYTRUDA AS AN ADJUVANT TREATMENT: HELPING PATIENTS WITH RESECTED MELANOMA LIVE THEIR LIVES WITHOUT RECURRENCE*[1,2]

*RECURRENCE-FREE SURVIVAL was significantly improved for KEYTRUDA vs placebo in KEYNOTE-054 in patients with melanoma with involvement of lymph node(s) following complete resection, number of events 135/514 (26%) vs 216/505 (43%), HR 0.57 (98.4% CI: 0.43–0.74), p<0.001, overall median follow-up of 15.1 months.

PSB LISTED[3]
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SELECTED SAFETY INFORMATION

- Immune-mediated adverse reactions (ImAEs), including severe and fatal cases, have occurred in patients receiving KEYTRUDA. These have included but are not limited to: pneumonitis, colitis, hepatitis, nephritis, endocrinopathies, severe skin reactions and severe infusion reactions. ImAEs have occurred after discontinuation of KEYTRUDA, may affect more than one body system and can occur simultaneously.[1]
- The safety of KEYTRUDA was evaluated in 2799 patients with unresectable or metastatic melanoma or metastatic NSCLC. The most common treatment-related serious AEs were: pneumonitis, colitis, diarrhoea, and pyrexia. The most common treatment related adverse reactions (reported in >10% of patients) were: fatigue, pruritus, rash, diarrhoea, and nausea. The overall safety profile of pembrolizumab for the adjuvant treatment of melanoma was generally similar, with ImAEs the predominant significant toxicity.[1]
- In KEYNOTE-054, the most common adverse reactions (occurring in ≥15% of patients who received KEYTRUDA) were fatigue/asthenia, diarrhoea, pruritus and rash.[2]

The Product Information is available at www.msdinfo.com.au/keytrudapi

Study design: KEYNOTE-054 was a multicentre, randomised, double-blind, placebo-controlled trial in patients aged >18 years of age with completely resected stage IIIA (>1 mm lymph node metastasis), IIIB or IIIC melanoma with no in-transit metastases as defined by AJCC 2009 (7th edition). Exclusion criteria included active autoimmune disease, a medical condition that required immunosuppression, mucosal melanoma, ocular melanoma, ECOG PS >1, uncontrolled infections, use of systemic glucocorticoids, and previous systemic therapy for melanoma. In part 1 of the trial (adjuvant), patients were randomised to receive KEYTRUDA 200 mg Q3W (n=514) or placebo IV Q3W (n=505). Patients were treated for 18 doses or until disease recurrence, unacceptable toxicity, protocol violation or withdrawal of consent. The primary efficacy endpoints were RFS in the whole population and RFS in the subgroup with PD-L1 positive tumours.[1,2]

References: 1. KEYTRUDA Approved Product Information, http://msdinfo.com.au/keytrudapi. **2.** Eggermont AMM *et al.* Adjuvant Pembrolizumab versus Placebo in Resected Stage III Melanoma. *N Engl J Med* 2018; 378(19): 1789–801. **3.** Australian Government Department of Health. Pharmaceutical Benefits Scheme (PBS). Available at: www.pbs.gov.au Accessed 1 January 2021.

AEs: adverse events. **AJCC:** American Joint Committee on Cancer. **ECOG PS:** Eastern Cooperative Oncology Group performance status. **NSCLC:** non-small-cell lung cancer. **PD-L1:** programmed death-ligand.

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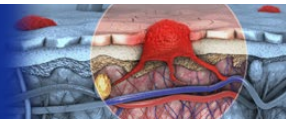

News in Brief

Society for Immunotherapy of Cancer clinical practice guideline on immune checkpoint inhibitor-related adverse events

The Society for Immunotherapy of Cancer has developed recommendations for managing immune-related adverse events associated with immune checkpoint inhibitors. Recommendations state that patients should: receive educational materials on immune-related adverse events; be encouraged to use contraception while undergoing immunotherapy; undergo tests including CBC with differential, comprehensive metabolic panel, thyroid-stimulating hormone and free thyroxine before initiating therapy, with urinalysis to evaluate for kidney disease; and be considered for baseline ECG if they have a higher risk for myocarditis. Specific considerations for immune-related adverse effects affecting a variety of organs and systems are also discussed.

J Immunother Cancer. 2021;9(6):e002435

Risk of developing melanoma with systemic agents used to treat psoriasis

This literature review of 35 studies evaluated the risk of developing melanoma among patients on systemic therapies for psoriasis. There was an association between melanoma risk and the use of TNF-alpha inhibitors adalimumab, infliximab, and etanercept in retrospective studies and multiple case reports. This increased risk was not found in all studies. Cyclosporine, methotrexate, and apremilast were not associated with an increased risk of melanoma. There were no reports of a significantly increased risk of melanoma or recurrence of melanoma in patients on IL-12/23 inhibitors, IL-23 inhibitors, or IL-17 inhibitors.

J Cutan Med Surg. 2021 Aug 15:12034754211038509

Acral lentiginous melanoma: Population, treatment, and survival

This paper describes the characteristics of acral lentiginous melanoma (ALM) in a US cohort of 4796 patients. Survival was poorer among patients with ALM compared with non-ALM cutaneous melanoma patients when stratified by stage, particularly among stage III patients. In ALM patients, lower 5-year survival rates were associated with older age, male sex, higher comorbidity, increased tumour thickness and ulceration, positive lymph nodes, and positive metastasis. Surgery combined with systemic therapy and/or radiation therapy was associated with higher survival rates in stage III patients, but not in patients with other stages of disease.

Pigment Cell Melanoma Res. 2021 Jul 17. doi: 10.1111/pcmr.12999

EANO–ESMO guidelines for diagnosis, treatment and follow-up of patients with brain metastasis from solid tumours

This ESMO clinical practice guideline describes important recommendations for the management of patients with brain metastases from solid tumours, including those from melanoma. The guideline encompasses clinical and pathological diagnosis, staging and risk assessment, treatment and follow-up. A useful treatment algorithm is provided, with recommendations based on available scientific evidence and the authors' expert opinion.

Ann Oncol. 2021:S0923-7534(21)02214-6

ESMO guidelines for care of the adult cancer patient at the end of life

This ESMO guideline describes important recommendations for end-of-life care for patients with advanced cancer. It discusses management that is focused on comfort, quality of life and approaching death of patients with advanced cancer. The recommendations were developed by a multidisciplinary group of experts and are based on available evidence and the authors' expert opinion.

ESMO Open. 2021;6(4):100225

COVID-19 Resources

The Australasian College of Dermatologists
Clinical Oncology Society of Australia
Cancer Australia
European Academy of Dermatology and Venereology
American Academy of Dermatology
European Society of Medical Oncology
American Society of Clinical Oncology

Conferences, Workshops and CPD

Please click on the links below for upcoming local and international melanoma meetings, workshops and CPD.

The Australasian College of Dermatologists - Events
DermNet New Zealand - Conferences
COSA - Events
MOGA - Events
COMS - Conferences and Meetings on Dermatology

Research Review Publications

Melanoma Research Review
with Professor Michael Henderson and Peter Hersey
https://tinyurl.com/y95oloy7

Skin Cancer Research Review
with Dr David Simpson
https://tinyurl.com/y9v4htzj

Dermatology Research Review
with Dr Warren Weightman and Clinical Assoc Prof Saxon D Smith
https://tinyurl.com/y7b6m4e3

ASCO 2021 Conference Review focus on Melanoma
https://tinyurl.com/28jtu4cc