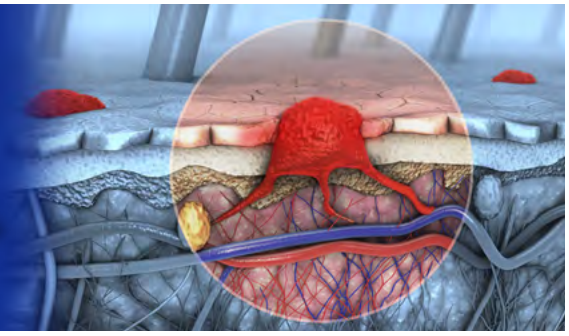
Melanoma Practice Review™



Making Education Easy

Issue 13 - 2023

In this issue:

Abbreviations used in this issue:

ASCO = American Society of Clinical Oncology; **FDA** = US Food & Drug Administration; **FMT** = faecal microbiota transplantation; **NCCN** = US National Comprehensive Cancer Network; **NICE** = English National Institute for Health and Care Excellence; **OS** = overall survival; **PBAC** = Pharmaceutical Benefits Advisory Committee; **PBS** = Pharmaceutical Benefits Scheme; **PD-1** = programmed death 1; **PFS** = progression-free survival; **RFS** = recurrence-free survival; **SLNB** = sentinel lymph node biopsy.

Welcome to the 13th 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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Clinical Practice

NCCN Clinical Practice Guidelines in Oncology - melanoma: Cutaneous and uveal

Recent updates to the US National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology for the management of cutaneous and uveal melanoma have been published (versions 2.2023 and 1.2023, respectively). Since their inception in 1996 the guidelines have undergone at least one update annually.

With respect to cutaneous disease, key revisions in 2023 iterations include changes in the principles of molecular testing and principles of sentinel lymph node biopsy (SLNB), respectively as follows:

- A warning that the prognostic value of novel molecular techniques, including commercially available gene expression profiling tests and circulating tumour DNA tests, have not been conclusively demonstrated and should not be used to inform therapeutic decisions prior to definitive evidence of superiority versus established methods such as multivariable phenotypic SLNB risk prediction models
- Two free risk calculators are provided to assist in risk versus benefit discussions regarding SLNB (Melanoma Institute of Australia's Prediction Tool for Sentinel Node Metastasis Risk and MSKCC melanoma sentinel lymph node metastasis nomogram)

The complete and most recent versions of these guidelines are available free of charge at www.NCCN.org (register to access)

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Systemic therapy for melanoma: ASCO Guideline Update

A full update to the 2018 American Society of Clinical Oncology (ASCO) guideline on systemic therapy for melanoma has been published, encompassing advice from the 2022 rapid update regarding uveal melanoma that was covered in Issue 11 of *Melanoma Practice Review*. Four novel treatment recommendations were provided for adult patients with cutaneous or noncutaneous melanoma and two previous recommendations were rescinded, based on systematic review of data from 21 randomised trials published since the previous iteration.

A strong recommendation was made for the use of neoadjuvant pembrolizumab for resectable Stage 3B-4 cutaneous melanoma. This treatment is to be used in conjunction with adjuvant pembrolizumab following resection and was made based on moderate strength evidence from the phase 2 S1801 trial that found a significant event-free survival benefit when patients received both pre- and post-operative pembrolizumab versus adjuvant pembrolizumab only.

Strong endorsement was given to the expanded use of adjuvant immune checkpoint inhibition with single-agent nivolumab OR pembrolizumab for resected *BRAF* wild-type cutaneous disease, from those with advanced (Stage- 3A-D) disease to include Stage 2B-C. These recommendations were based on moderate evidence quality from an interim analysis of the CheckMate 76K trial that demonstrated a clinically meaningful recurrence-free survival (RFS) benefit to adjuvant nivolumab versus placebo for this indication, consistent with the benefits with post-operative pembrolizumab versus placebo and post-operative nivolumab versus ipilimumab found in EORTC 1325 and CheckMate 238 in advanced resected disease. The advice regarding adjuvant treatment for *BRAF*-mutated resected Stage 3A-D disease remains unchanged (Stage 3: nivolumab, pembrolizumab or dabrafenib plus trametinib for V600E/K mutations; no recommendation is made regarding adjuvant BRAF/MEK inhibition for disease with other *BRAF* mutations).

Based on an informal consensus, combination nivolumab plus ipilimumab followed by nivolumab is added as a possible adjuvant regimen for resected Stage 4 cutaneous disease, based on low quality evidence of improved RFS and overall survival (OS) versus nivolumab monotherapy in IMMUNED.

In the realm of advanced metastatic or unresectable cutaneous melanoma the front-line immunotherapy doublet of nivolumab plus relatlimab is strongly recommended as a therapeutic option, regardless of *BRAF* mutation status. This recommendation was based on the 25% reduced risk of disease progression or death with nivolumab plus relatlimab versus nivolumab monotherapy in the global phase 2/3 RELATIVITY-047 trial (median progression-free survival [PFS], 10.1 vs 4.6 months; hazard ratio 0.75). Other front-line options for this indication, with/without $BRAF^{V600}$ mutations, are nivolumab plus ipilimumab followed by nivolumab OR nivolumab OR pembrolizumab. Dabrafenib plus trametinib OR encorafenib plus binimetinib OR vemurafenib plus cobimetinib are also options for $BRAF^{V600}$-mutated unresectable and/or metastatic cutaneous melanoma.

The recommendations that have been removed from the previous guideline iteration are:

- Talimogene laherparepvec for *BRAF* wild-type disease after progression on anti- programmed cell death protein 1 (PD-1) therapy
- Second- or later-line ipilimumab- and ipilimumab-containing regimens for patients with *BRAF*-mutated disease

The full guidelines can be downloaded from the ASCO website here

J Clin Oncol. 2023;41(30):4794-820

Redesigning sentinel lymph node biopsy guidelines in melanoma cases

Given the adverse prognostic ramifications of melanoma metastasis and the proven accuracy of status in the first draining lymph node to reflect status in the whole draining nodal basin, staging SLNB is a standard practice in patients with primary melanoma to identify the presence of low volume metastatic disease without resorting to potentially unnecessary lymphadenectomy (lymph node dissection). Clinical guidelines regarding candidacy for SLNB stratify by primary melanoma Breslow thickness with an indication threshold of ≥ 1mm and restriction in thin melanomas of at least 0.8 mm to cases with additional risk factors such as ulceration, high mitotic index, microsatellites and lymphovascular invasion. Conflicting advice is given by various professional societies for SLNB in thin nonulcerated melanoma (T1a, < 0.8 mm Breslow thickness), with this population excluded from SLNB in both Cancer Council Australia and European consensus-based interdisciplinary guidelines but considered in the American Academy of Dermatology's and NCCN recommendations if other unfavourable histological features are present or the patient is younger than 40 years.

Now, a systematic review indicates that patient selection for SLNB may be refined to minimise invasive procedures and SLNB negativity rates and optimise prognostication by devising algorithms incorporating additional variables beyond Breslow depth and ulceration across all strata of primary melanoma depth. Analysis of studies used to formulate US melanoma management guidelines confirmed that the strongest predictor of SLNB positivity is tumour depth with risk of SLN involvement increasing with Breslow thickness, but that it may be necessary to increase the number of strata for intermediate or thick melanoma to reflect the variations in prognosis and rates of lymph node involvement observed with every millimetre above 1 mm. The researchers further found that factors used to evaluate risk of melanoma dissemination in thin melanomas (such as younger patient age, ulceration, lymphovascular invasion and satellitosis) also have significance in intermediate and thick melanomas and should be considered, regardless of Breslow thickness. Finally, scrutiny of modifiers outside the current guidelines identified factors that significantly affect the rate of positive SLNB and may be included in formulas for personalised determination of need for SLBN. The novel factors portending higher rate of SLNB positivity included nodular and acral lentiginous melanoma subtypes, trunk and lower extremity anatomical location and immunocompromised status.

Eplasty. 2023 Feb 3;23:e8

NICE 2022 guidelines on the management of melanoma: Update and implications

The English National Institute for Health and Care Excellence (NICE) updated their guidelines for the assessment and management of Stage 1-3 melanoma in July 2022 (available here). Advice regarding genetic testing, staging, surgery, anticancer treatment and follow-up were modernised. Novel recommendations with relevance to clinical practice include:

- Introduction of genetic testing - *BRAF* analysis of primary tissue samples, including immunohistochemistry analysis of $BRAF^{V600E}$, in patients with Stage 2A-4 disease and in potential clinical trial candidates
- Reduced use of SLNB – restricted to primary lesions with a Breslow thickness > 1 mm and lesions 0.8-1 mm with ulceration, lymphovascular invasion or a mitotic index ≥ 2.
- Increased use of imaging – staging of Stage 2B-4 melanoma with whole-body and brain contrast-enhanced-computed tomography or magnetic resonance imaging (MRI) to reduce radiation exposure in pregnant women or younger adults and children and increased use of ultrasound for nodal drainage basin
- Diminished follow-up duration post-treatment with one-year for Stage 1A and five years for Stage 1B-4 melanoma

Updated guidance was also provided regarding adjuvant immunotherapy regimen for advanced or unresectable Stage 3 disease, targeted treatment options for $BRAF^{V600}$ mutation-positive melanoma and alternatives to immunotherapies for *BRAF* wild-type melanoma, but these were not predicted to substantially alter management.

A group from the skin cancer specialist centre at the University Hospitals of Leicester NHS Trust assessed the economic and service provision impact of the guideline changes using a newly diagnosed patient cohort with Stage 1-3 melanoma from 2019 (n=110). Five-year idealised journey pathways were modelled to contrast the experience when old and new guideline iterations were followed. Changes were found in department-specific workloads with lower use of plastic surgeons and dermatologists as a result of lessened SLNB requirement and follow-up length, but a significant increase in radiology and histopathology services. Even with the extra expense of genetic testing and imaging, the new guideline iteration resulted in a cost saving of £141.85 per patient versus the older guidelines.

J Plast Reconstr Aesthet Surg. 2023; 85:401-13

Nivolumab plus relatlimab vs NIVO in previously untreated metastatic or unresectable melanoma: 2-year results from RELATIVITY-047

During the Melanoma/Skin Cancers session at the 2023 ASCO annual meeting positive results were presented for several different immunotherapies for melanoma in different settings.

Dr Hussein Tawbi from the University of Texas MD Anderson Cancer Centre in Texas detailed two-year follow-up data from the RELATIVITY-047 trial of front-line dual lymphocyte-activation gene 3 (LAG-3) and PD-1 inhibition with nivolumab plus relatlimab for metastatic or unresectable melanoma. A total of 714 patients with previously untreated, histologically confirmed Stage 3 or 4 melanoma without brain or leptomeningeal metastases were accrued to the international, double-blind, phase 2/3 study and received fixed-dose nivolumab ± relatlimab (480 mg every four weeks and 160 mg, respectively). The significant PFS benefit exhibited with nivolumab plus relatlimab over single-agent nivolumab at 13-month follow-up (*N Engl J Med.* 2022;386[1]:24-34) was durable on longer follow-up with a more than doubling of median PFS and a 19% reduced risk of disease progression (4.6 vs 10.2 months; hazard ratio 0.81). The combination regimen also demonstrated clinical benefits that extended beyond initial treatment and first progression (median PFS2, 20.1 vs 28.4 months; hazard ratio, 0.79) and a numerical OS advantage. There were no novel safety signals of concern.

J Clin Oncol. 2023;41 (suppl 16; abstr 9502)

Distant metastasis-free survival results from the randomized, phase 2 mRNA-4157-P201/KEYNOTE-942 trial

Secondary endpoint results from KEYNOTE-942, reported by Adnan Khattak from One Clinical Research and Edith Cowan University in Western Australia, are consistent with the previously published primary endpoint in demonstrating superior efficacy with the addition of an investigational personalised mRNA vaccine (mRNA-4157) to pembrolizumab versus the PD-1 inhibitor alone, suggesting it may be a novel adjuvant therapy for high-risk resected melanoma. This personalised neoantigen approach targets tumour mutations specific to each patient with the vaccine encoding up to 34 neoantigens and designed to augment endogenous neoantigen T-cell responses. Following complete surgical resection of high-risk Stage 3B-4 cutaneous melanoma, patients (n=157) received up to 18 cycles of adjuvant pembrolizumab ± up to nine intramuscular doses of mRNA-4157 with stratification by disease stage. The primary trial analysis (presented at the American Association for Cancer Research Annual Meeting 2023; Abstract CT001) found that compared to adjuvant pembrolizumab alone, the combination therapy almost halved the risk of disease recurrence or death (RFS events: 22.4% vs 40%; hazard ratio 0.56), meeting the trials primary end point. These data represent the inaugural clinical trial evidence supporting the efficacy for an mRNA cancer vaccine and may herald a new era of cancer therapy. Additional analyses demonstrated a significant reduction in the risk of developing distant metastases with the vaccine-based combination immunotherapy with an 18-month distant metastasis-free survival rate of 91.8% versus 76.8% with pembrolizumab monotherapy (hazard ratio 0.35). Analysis by recurrence type revealed favourable rates of both local/regional and distant recurrence in the combination treatment arm versus pembrolizumab alone (13.1% vs 18% and 5.5% vs 20%, respectively) and a three-fold reduced rate of distant recurrence or death (8.4% vs 24%). Dr Khattak noted that the improvements in efficacy were obtained without compromising on treatment tolerability or increasing immune-mediated adverse events. The global phase 3 V940-001 trial will further evaluate this combination adjuvant regimen, with a planned accrual of 1089 patients with high-risk resected melanoma. Enrolment in Australia has commenced at sites in Western Australia, Victoria, Queensland and new South Wales. According to a press release from the trial sponsors Moderna and Merck the doublet of mRNA-4157 plus pembrolizumab has been granted a breakthrough therapy designation by the US Food 7 Drug Administration (FDA) for this indication. The full press release can be found here.

J Clin Oncol. 2023;41 (suppl 17; abstr LBA9503)

Fecal microbiota transplantation plus anti-PD-1 immunotherapy in advanced melanoma: a phase I trial

Results from the Canadian world-first phase 1 MIMic trial indicate that restoration of a healthy and diverse gut microbiome through faecal microbiota transplant (FMT) may boost response to immunotherapy in patients with advanced melanoma and is safe. A total of 20 adult patients with previously untreated unresectable or metastatic cutaneous melanoma (*BRAF* wild-type or mutant) underwent a single FMT from a healthy donor with oral administration of stool-derived intestinal bacteria via capsule form (approximately 40 capsules) at least one week prior to single-agent immunotherapy with either pembrolizumab or nivolumab. The trial demonstrated that the procedure was safe with mild to moderate adverse events including transient diarrhoea, flatulence and abdominal discomfort reported in 40% of patients but no grade 3 or worse adverse events attributed to FMT. Almost two-thirds of patients achieved an objective response, including one-fifth with a complete response. Donor strain engraftment was observed in all patients but increased similarity in the gut microbiome to the donor longitudinally was restricted to responding patients, who also exhibited increased and decreased beneficial and deleterious bacteria, respectively. The study also demonstrated the augmented immunotherapy efficacy by FMT in murine models. This research group have commenced a larger phase 2 trial of FMT for melanoma in the front-line setting and are investigating its value in other hard-to-treat malignancies including renal cell carcinoma, pancreatic cancer and lung cancer.

Nat Med. 2023;29(8):2121-32

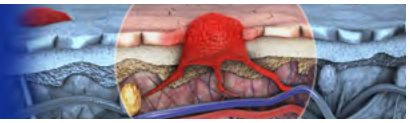
Regulatory News

PBAC recommendations

The Australian Pharmaceutical Benefits Advisory Committee (PBAC) has recently made two positive recommendations:

- To expand the existing Pharmaceutical Benefits Scheme (PBS) listing for pembrolizumab (Keytruda®) for patients with resectable Stage 3B-D malignant melanoma from the adjuvant setting to also include the neoadjuvant setting. This recommendation was made in response to a request from the Melanoma Institute Australia based on data from the S1801 clinical trial published in the New England Journal of Medicine and is the first regulatory authority in the world to approve and subsidise neoadjuvant pembrolizumab for this indication
- the PBS listing of relatlimab and nivolumab (Opdualag®) for unresectable Stage 3 or Stage 4 malignant melanoma under the Section 100 Highly Specialised Drugs Program, while implementation issues relating to a Section 100 Efficient Funding of Chemotherapy listing are being worked through.

Read more here and here



News in Brief

Cancer Council Australia - Clinical practice guidelines for the diagnosis and management of melanoma

Since their inception in 1999 the Australian clinical practice guideline for the diagnosis and management of melanoma, published under the auspices of the Australian Cancer Network, have undergone several iterations. In 2014, modernisation of individual sections was enabled by transitioning to a web-based wiki platform, in-line with Australian guidelines for the management of other malignancies including lung cancer and sarcoma. The evidence-based guidelines provide a valuable resource for healthcare providers to see the most recent recommendations to optimise care for their patients with melanoma.

The regularly updated guidelines are available here

Melanoma Institute Australia partners with Toyota Material Handling

The Melanoma Institute of Australia are collaborating with Toyota material handling, an Australian forklift company, to advocate for sun safety and to improve the awareness of melanoma risk in workers in the transport and logistics industries. This alliance provides funding for essential clinical research and will promote sun safe behaviour in laborers who spend a great proportion of their work day outside and have high UV radiation exposure.

The press release can be read online here

FDA approves melphalan as a liver-directed treatment for uveal melanoma

A melphalan chemotherapy hepatic delivery system (Hepzato, Delcath Systems, Inc.) has been granted FDA approval for the treatment of adult patients with metastatic ocular melanoma with unresectable hepatic metastases affecting less than half of the liver and limited extrahepatic disease amenable to resection or radiotherapy. The system enables locoregional high-dose drug delivery while minimising systemic toxicity by direct drug injection into the liver via percutaneous hepatic perfusion and filtration of blood exiting the liver utilising a bypass circuit. Approval was based on data from the pivotal international FOCUS trial where superior efficacy with improved response rate, duration of response and survival were found with percutaneous hepatic perfusion versus best alternative care in a US/European cohort of both treatment naïve and previously treated patients.

The press release is available here

Racial and ethnic differences in males with melanoma

A retrospective cohort study of 205,125 cases from the National Cancer Database sought to explicate the role of race in men with primary cutaneous invasive melanoma. Analysis utilising Kaplan-Meier curves, log-rank tests and multivariate regression revealed divergence between ethnic and racial groups in anatomic location, with melanoma most commonly found on the trunk in Caucasian men but on the lower extremities in Black, Asian and Hispanic men. A disparity in survival was also noted with Caucasian men having the best five-year overall survival rate of 75.1% and Black men the worst at 51.7%.

JAMA Dermatol. 2023;159(9):1004-06

COVID-19 Resources

European Academy of Dermatology and Venereology

American Academy of Dermatology

European Society of Medical Oncology

American Society of Clinical Oncology

Conferences, Workshops, and CPD

The Australasian College of Dermatologists – Events

DermNet New Zealand – Conferences

COSA – Events

COMS – Conferences and Meetings on Dermatology

Research Review Publications

Dermatology Research Review with Dr Warren Weightman and Clinical Professor Saxon Smith

Melanoma Research Review with Professors Michael Henderson and Peter Hersey

Skin Cancer Research Review with Dr David Simpson

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