Melanoma Research Review™

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Issue 67 - 2024

In this issue:

Abbreviations used in this issue:

DMFS = distant metastasis-free survival; **HRQOL** = health-related quality of life; **ICB** = immune checkpoint blockade; **ICI** = immune checkpoint inhibitor; **PPI** = proton pump inhibitor; **SLNB** = sentinel lymph node biopsy; **TT** = targeted therapies.

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Welcome to the 67th issue of Melanoma Research Review

We open this month's issue with a retrospective analysis of histopathic regression in patients with cutaneous melanoma, this study assessed patients who underwent sentinel lymph node biopsy (SLNB) between 2010 and 2015 to assess the significance of histopathologic regression. This is followed by a clinical study on the impact of proton pump inhibitors and other co-medications on advanced melanoma patients treated with BRAF/MEK inhibitors. We also highlight a study on smoking status and survival in early stage primary cutaneous melanoma and finally we conclude this issue with a real world study on health-related quality-of-life outcomes with adjuvant anti-PD1 therapy.

We hope that you enjoy this month's issue of Melanoma Research Review and we look forward to welcoming your feedback.

Kind Regards,

Professor Michael Henderson
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Histopathologic regression in patients with primary cutaneous melanoma undergoing sentinel lymph node biopsy is associated with favorable survival and, after metastasis, with improved progression-free survival on immune checkpoint inhibitor therapy

Authors: Wagner NB et al.

Summary: This study retrospectively analysed 1179 patients with primary cutaneous melanoma who underwent SLNB between 2010 and 2015 to assess the significance of histopathologic regression. Results showed that regression was associated with favourable relapse-free, distant metastasis-free, melanoma-specific survival, and negative SLNB status. Moreover, regression was linked to improved PFS in patients progressing to an unresectable stage and receiving immune checkpoint inhibitors. However, it didn't show similar benefits in patients treated with targeted therapy or chemotherapy. Although the study identified limitations, such as its retrospective design, it suggested that regression of cutaneous melanoma is a promising prognostic factor for patients undergoing SLNB and those receiving systemic therapy with ICIs.

Comment: This is yet another small retrospective study that aimed to resolve the ongoing controversy about the significance of tumour regression, which was found in 22% of cases with stage 1 and 2 melanoma (n= 295). In an attempt to overcome an issue seen in many studies of regression, the authors used a rigorous definition of what they regarded as late regression, attempting to disregard the effects of tumour infiltrating lymphocytes. The authors found a relationship with the male sex, thinner, non-ulcerated superficial spreading melanomas located on the trunk and associated with a pre-existing naevus. Progression-free survival, relapse-free survival, and melanoma-specific survival were related to regression. Sentinel node biopsy was routinely performed, including in patients with T1B melanoma. Negative SNB status was associated with regression, which was seen less commonly in SNB-positive patients (10 vs 20%). In support of the general hypothesis that regression indicates an immune response, patients with regression in the primary were more likely to respond to ICI therapy and had better long-term outcomes, while regression had no impact on outcomes for patients receiving targeted therapies. The prognostic significance of regression was poor compared to more standard prognostic factors, which does not support the author's contention that regression could be a reliable biomarker.

Reference: J Am Acad Dermatol. 2024;90:739-48.
Abstract

Melanoma Research Review™

Independent commentary by Professor Michael Henderson

Michael A Henderson is Professor of surgery in the University of Melbourne and surgeon in the multidisciplinary Melanoma and Skin Service at the Peter MacCallum Cancer Centre in Melbourne. He is a graduate of the University of Melbourne and after obtaining a Fellowship of the Royal Australasian College of Surgeons spent 2 1/2 years undertaking a fellowship in surgical oncology at the University of Texas MD Anderson Cancer Centre. His clinical practice is confined to surgical oncology. His major clinical interests are in the management of patients with melanoma and maintains an active clinical and translational research interest in melanoma. He led a major international multicentre study of adjuvant radiotherapy after link for melanoma and is currently the principal investigator of a multicentre international trial of margins of excision of intermediate and thick melanoma (MELMART).

Clinical impact of proton pump inhibitors and other co-medications on advanced melanoma patients treated with BRAF/MEK inhibitors

Authors: Ramel E et al.

Summary: This study aimed to investigate the impact of co-medication on the efficacy and toxicity of targeted therapies (TT) for advanced melanoma, specifically BRAF/MEK inhibitors. Conducted at Bordeaux University Hospital from 2013 to 2020, the observational study analysed data from 192 patients. Co-medications taken within one month before and three months after TT initiation were categorised, and their influence on OS and PFS was assessed. Proton pump inhibitors (PPIs) emerged as significantly affecting OS and/or PFS in multivariable analysis. However, co-medications did not affect TT-related toxicity. Factor analysis of mixed data further linked to their impact on oncological outcomes. The study underscores the importance of evaluating co-medications, particularly PPIs when initiating TT for melanoma.

Comment: It is generally accepted that PPIs should be prescribed with caution in patients receiving ICI therapy, but data on these drugs and BRAF MEK inhibitor therapies is scarce. This was a retrospective review and, unfortunately, highlighted some of the issues with this type of study. Many of the patients who started on targeted therapy eventually received ICI therapy and tended to be taking multiple medications, making analysis of the results difficult. Nevertheless, both overall survival and PFS were poorer in patients receiving PPIs and targeted therapies. Given the limitations of this study it is impossible to make any definitive recommendations about the use of PPI's and targeted therapies, but a conservative approach would be appropriate.

Reference: Eur J Cancer. 2024;197:113477
Abstract

Association of antibiotic treatment with survival outcomes in treatment-naïve melanoma patients receiving immune checkpoint blockade

Authors: Chorti E et al.

Summary: The study aimed to investigate the impact of antibiotic exposure on the efficacy of first-line anti-PD-1 based immune checkpoint blockade (ICB) in treatment-naïve patients with advanced melanoma. Conducted as a multicentre retrospective cohort study, it analysed data from patients treated between June 2013 and September 2018. Of the 578 patients receiving ICB, 7% received antibiotics within 60 days prior to ICB and 19% after starting ICB. Antibiotic exposure before ICB was associated with poorer PFS and OS, while antibiotic use after the start of ICB showed no significant effect on PFS or OS. The study concluded that findings suggest that antibiotic exposure before ICB may negatively impact treatment outcomes in melanoma patients, highlighting the potential importance of considering antibiotic use in treatment planning.

Comment: In recent years, more than a dozen reports of immune checkpoint inhibitor therapy and antibiotic use confirm poorer outcomes in these patients. These studies are compromised by small size, selection bias, multiple tumour types, previous treatment, etc. This study investigated previously untreated patients with metastatic melanoma receiving first-line immune checkpoint inhibitor therapy, either single agent or combination therapy. This study again confirmed poor outcomes for patients receiving antibiotics within 60 days of commencement of ICI therapy but no effect for patients requiring antibiotics during ICI therapy. Patients who did not receive antibiotics fared better than those receiving antibiotics at any time. In the absence of high-level data, this study again confirms that it would be reasonable to avoid antibiotic treatment, when possible, prior to initiation of ICI therapy.

Reference: Eur J Cancer. 2024;200:113536
Abstract

Population-based validation of the MIA and MSKCC tools for predicting sentinel lymph node status

Authors: Olofsson Bagge R et al.

Summary: The study aimed to assess the clinical utility of predictive models developed by the Memorial Sloan Kettering Cancer Center (MSKCC) and Melanoma Institute Australia (MIA) for selecting patients with melanoma for SLNB. The study analysed data from 10,089 patients with cutaneous melanoma undergoing SLNB from the Swedish Melanoma Registry and found that both models were well-calibrated and had similar accuracy in predicting sentinel lymph node positivity. Decision curve analysis indicated that neither model provided added net benefit compared to performing SLNB for all patients at a risk threshold of 5%. However, at thresholds of 10% or higher, both models showed benefit, particularly in patients with T2 melanomas. These findings underscore the importance of considering risk thresholds when using predictive models to guide SLNB selection, especially for patients with T2 melanomas.

Comment: In the absence of effective biomarkers or other predictive tools, the standard recommendation is for sentinel node biopsy in all patients with T2 or greater melanoma and selective use in patients with T1 melanoma and poor prognostic factors. Two nomograms from Memorial Sloan Kettering and Melanoma Institute Australia have been developed and validated. This validation study of over 10,000 patients from a Swedish population database compared the two nomograms. The authors used decision curve analysis, which highlights the harms of not performing an SNB against the harms of not performing it in a patient with a positive SNB. The NCCN guidelines recommend SNB for patients with a risk greater than 10%, and for this group, the nomograms worked reasonably well. For patients with a 5% risk, there was no clinical benefit. Both nomograms performed equally well; however, as the Swedish database did not include mitotic rate or lymphatic-vascular invasion, a modified MIA model was used, and it could be argued that the full model might have been expected to perform better. In routine clinical practice, the confidence intervals around SNB positivity for thinner melanomas are wide and need to be considered.

Reference: JAMA Surg. 2024;159:260-8
Abstract

Pembrolizumab versus placebo as adjuvant therapy in resected stage IIB or IIC melanoma

Authors: Schadendorf D et al.

Summary: This *post hoc* analysis examined the efficacy of adjuvant pembrolizumab in resected stage IIB or IIC melanoma, focusing on subtypes defined by histopathologic characteristics. Among 976 patients randomised to pembrolizumab or placebo, pembrolizumab significantly improved RFS and distant metastasis-free survival (DMFS) across subgroups. Regardless of melanoma subtype (nodular vs non-nodular), tumour thickness, presence of ulceration, mitotic rate, or tumour-infiltrating lymphocytes, pembrolizumab consistently showed benefit. Cox multivariate analysis identified treatment arm, tumour thickness, and mitotic rate as significant independent factors for RFS, and treatment arm and mitotic rate for DMFS. The study concluded that findings support adjuvant pembrolizumab use in patients with resected stage IIB or IIC melanoma, irrespective of histopathologic characteristics.

Comment: This report is a *post hoc* analysis of important subgroups from the keynote 716 trial for stage 2B-2C melanoma. Not surprisingly the benefits of adjuvant pembrolizumab previously documented apply to the high risk subgroups investigated in this analysis. Of note histological subtype, nodular versus non nodular had no impact on DMFS. The benefits of adjuvant therapy was seen in all the high risk subgroups examined and the authors have also highlighted that patients with lower risk scenarios will also benefit from treatment.

Reference: J Immunother Cancer. 2024;12:e007501
Abstract

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CSCC=cutaneous squamous cell carcinoma; laCSCC=locally advanced CSCC; mCSCC=metastatic CSCC.

References: 1. LIBTAYO (cemiplimab) approved Product Information. **2.** Cancer Council Australia Keratinocyte Cancer Guidelines Working Party. Clinical Practice Guidelines for Keratinocyte Cancer. Section 12.2: Systemic therapies for metastatic cutaneous squamous cell carcinoma. https://wiki.cancer.org.au/australia/Clinical_question:Protocol_to_treat_local_regional_SCC (accessed 24 January 2024).

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MAT-AU-2400677-1.0. Ward7 SALI32602M. Date of preparation: April 2024.

The effect of surgical timing in nonmetastatic melanoma

Authors: Kakish H et al.

Summary: This study aimed to assess the impact of surgical timing on nodal upstaging in high-risk cutaneous melanoma patients undergoing SLNB. Analysing data from the National Cancer Database (2004–2018), 53,355 patients with T2–T4, N0, and M0 melanomas were included. Patients underwent surgery within 2–19 weeks post-diagnosis, with a median of 5 weeks. The rate of positive lymph nodes increased with a longer time to surgery, with a significant rise observed after nine weeks. Multivariable analysis revealed a 2.4% increased risk of nodal positivity per week of delay. Notably, patients with T2–3 tumours showed a significant increase in nodal positivity with delayed surgery, while no significant trend was observed for T4 melanomas. The study's findings suggest that surgery within nine weeks of diagnosis is not associated with an increased risk of nodal positivity, providing valuable guidance for clinical decision-making regarding surgical timing in melanoma patients.

Comment: The issue of time to surgery from diagnosis on outcomes which has been evaluated in a number of studies remains controversial given conflicting results at least partly related to small sample sizes, population heterogeneity and study end points. The current study again is a relatively small retrospective study which specifically evaluated the time to sentinel node biopsy and used the rate of sentinel node biopsy positivity as a surrogate for survival. In summary the authors found that if the patient came to surgery within nine weeks of initial diagnosis there was no difference in the rate of sentinel node positivity but after nine weeks the proportion increased significantly indicating the potential for poorer outcomes in patients in this delayed group. The very limited evidence suggests that in patients requiring a central node biopsy the procedure should be performed relatively soon after diagnosis and certainly within nine weeks.

Reference: J Surg Oncol. 2024;129:509-16
Abstract

Individualised neoantigen therapy mRNA-4157 (V940) plus pembrolizumab versus pembrolizumab monotherapy in resected melanoma (KEYNOTE-942)

Authors: Weber JS et al.

Summary: This study investigated the efficacy of mRNA-4157 (V940), a novel mRNA-based individualised neoantigen therapy, in combination with pembrolizumab versus pembrolizumab monotherapy in resected high-risk melanoma patients. Conducted as an open-label, randomised phase 2b trial, 157 patients with completely resected high-risk cutaneous melanoma (stage IIIB–IV) were enrolled. The primary endpoint was RFS. Results showed a longer RFS with the combination therapy compared to monotherapy, although statistical significance was not reached (HR 0.561, p=0.053). Most treatment-related adverse events were grade 1–2, with manageable safety profiles. Immune-mediated adverse event frequency was similar between the groups. The study concluded that adjuvant mRNA-4157 plus pembrolizumab could potentially improve outcomes in resected high-risk melanoma, indicating the potential benefit of mRNA-based individualised neoantigen therapy in the adjuvant setting.

Comment: This paper highlights a potential evolving strategy for managing patients with melanoma. A unique feature of this study is the use of mRNA vaccine technology, which evolved during the Covid pandemic. mRNA vaccines are now a well-developed technology which is relatively straightforward, can be produced in a timely fashion, incorporates multiple antigens and has been shown to induce effective CD4 and CD8 T cell responses. Rather than combining immunotherapy with a vaccine raised against a single neo-antigen, (a strategy which has failed repeatedly) up to 34 neo-antigens identified from the patient's tumour were employed. This is a phase 2b study with limited numbers and relatively short follow-up, but there is a significant and clinically important benefit for the patient receiving a combination mRNA vaccine and anti-PD-1 therapy. The presence of circulating tumour DNA was strongly associated with the outcome in both arms of the study. Toxicity in the anti-PD-1 arm was as expected, and in the combination arm, flu-like illness related to the vaccine injection was noncommon but easily managed. No increase in immune-related adverse events was seen. A variety of exploratory biomarker and immunogenicity studies were undertaken. Although the numbers were small the benefit of combination treatment was seen in patients regardless of PDL-1 status nor was the extent of tumour mutational burden related to outcome.

Reference: Lancet. 2024;403:632-44
Abstract

Smoking status and survival in patients with early-stage primary cutaneous melanoma

Authors: Jackson KM et al.

Summary: This study aimed to investigate the impact of smoking status on those with early-stage primary cutaneous melanoma. Among 6279 patients, 17.2% were current smokers, 27.0% were former smokers, and 55.9% were never smokers. Current smoking was associated with male sex, younger age, trunk site tumours, thicker tumours, tumour ulceration, and SLNB positivity. Multivariable analysis showed that current smoking was associated with a higher risk of melanoma-specific mortality (HR, 1.48; 95% CI, 1.26-1.75; P < .001). The increased risk was highest among patients with SLNB-negative melanoma (HR, 1.85; 95% CI, 1.35-2.52; P < .001) but was also present in patients with SLNB-positive melanoma (HR, 1.29; 95% CI, 1.04-1.59; P = .02) and those undergoing nodal observation (HR, 1.68; 95% CI, 1.09-2.61; P = .02). Smoking at least 20 cigarettes per day doubled the risk of melanoma-specific mortality in patients with SLNB-negative disease (HR, 2.06; 95% CI, 1.36-3.13; P < .001).

Comment: In many tumour systems cigarette smoking is associated with poorer outcomes except for melanoma where the data has been controversial but possibly suggesting a protective effect. Although a post hoc analysis, this study is based on prospectively accrued data from the MSLT studies. The numbers are large (6729 patients), and follow-up is over five years. A strength of this study was the collection of extensive smoking behaviour at baseline, unlike previous studies, which mainly rely on patient recollection of previous smoking status. The patient cohort is described as clinical Stage 1 and 2 but excluded patients with melanomas less than 1 mm in thickness potentially limiting the applicability of these results to this large group of patients. However, current smoking but not past was associated with poorer prognosis tumours and increased risk of death due to melanoma. The risk of death was higher in the sentinel node-negative group, where 20 cigarettes a day doubled the risk of dying. This study is another reason to counsel melanoma patients about smoking cessation. (Disclosure: the author participated in the MSLT2 study).

Reference: JAMA Netw Open. 2024;7:e2354751
Abstract

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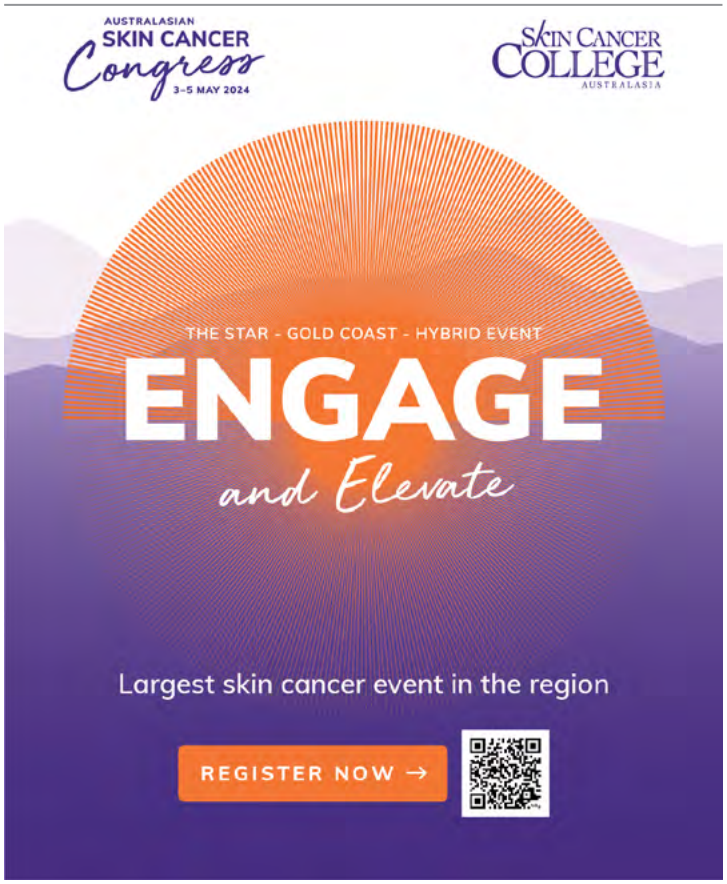

Health economic consequences associated with COVID-19–related delay in melanoma diagnosis in Europe

Authors: Maul LV et al.

Summary: This study investigated the repercussions of COVID-19 lockdowns on melanoma detection, posing public health and economic burdens. Lockdown scenarios involved halting routine medical exams and limiting follow-up access for at least four weeks. Primary outcomes encompassed the total burden of delayed melanoma diagnosis, measured in direct (USD) and indirect costs (YLL, YLD and DALYs) for Europe. Indirect treatment costs predominated, constituting 94.5% of the total $7.65 billion additional costs. YLD estimates ranged from 15,360 to 40,660 years, contributing to overall disease burden ranging from 59,682 to 335,711 DALYs. The study highlighted the significant impact of delayed melanoma detection during COVID-19 lockdowns, stressing the importance of timely medical care to mitigate public health and economic consequences.

Comment: This study, while focused on a European population, highlights the significant economic burden to the community from the cessation of screening, delays in diagnosis with potential upstaging and instituting treatment for patients with melanoma due to the COVID pandemic. In the Australian context, population registries suggested a significant decrease in the rate of diagnosis of melanoma during that period, and an Australian study of costs of care for major cancers highlighted the increased morbidity and future costs (see Asia Pac J Clin Oncol. 2021 Aug;17(4):359). The authors in this study describe a 17% upstaging in melanoma and estimate the extra cost to the European economies of nearly $8 billion. The authors make the point that based on other studies that have documented an increase in late-stage presentations, the cost due to the pandemic in health and economic terms is likely to continue. The authors acknowledge a large number of assumptions have gone into their modelling.

Reference: JAMA Netw Open. 2024;7:e2356479
Abstract

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Real-world health-related quality of life outcomes for patients with resected stage III/IV melanoma treated with adjuvant anti-PD1 therapy

Authors: Egeler M et al.

Summary: This study utilised data from melanoma registries in Australia and the Netherlands to examine the health-related quality of life (HRQOL) of patients with resected stage III/IV melanoma receiving adjuvant anti-PD1 therapy. Among 92 patients, mean symptom and functioning scores generally improved or remained stable at 12 months post-treatment compared to baseline. However, a significant proportion experienced clinically significant declines in role (39%), social (41%), or emotional (50%) functioning at 12 months. Younger patients were more likely to experience deteriorations in role and social functioning. These findings underscore the HRQOL challenges during adjuvant anti-PD1 therapy, necessitating supportive care interventions. The study concluded that the importance of addressing HRQOL issues may improve the overall well-being of patients undergoing adjuvant therapy for advanced melanoma.

Comment: This is a small but important study that addressed HRQOL in patients 12 months after completing immune checkpoint inhibitor therapy for stage 3B/4 disease. The strength of this study is that it describes real-world experience and highlights the observation that although mean scores improved from baseline at 12 months a significant proportion of patients (39%) particularly younger patients had a measurable decrease in role, social and emotional functioning. The authors conclude that clinicians should be aware of the ongoing potential for the impact of treatment on quality of life and the importance of patient-reported outcome measures in clinical trials. Disclosure, this study included patients from the authors institution.

Reference: Eur J Cancer. 2024;200:113601
Abstract

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