Melanoma Research Review™

Making Education Easy

Issue 65 - 2023

In this issue:

Abbreviations used in this issue:

CLND = completion lymph node dissection; **LMM** = lentigo maligna melanoma; **MIA** = Melanoma Institute of Australia.

Welcome to the 65th issue of Melanoma Research Review

This review begins with an open-label, phase 3 trial that explored the long-term survival benefits of tebentafusp in HLA-A*02:01 positive melanoma patients. Another interesting study aimed to determine the significance of incipient ulceration, and whether it is an independent prognostic feature for cutaneous melanoma. This review concludes with a paper that assessed the global burden of melanoma and what the quality of care is like around the world.

We hope you enjoy this update in melanoma research, and we look forward to receiving comments and feedback.

Kind Regards,

Professor Michael Henderson
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Three-year overall survival with tebentafusp in metastatic uveal melanoma

Authors: Hassel JC et al.

Summary: Within this open-label, phase 3 trial, researchers analysed the long-term survival benefits of tebentafusp in patients positive for HLA-A*02:01 with unresectable or metastatic uveal melanoma. Patients included were randomly assigned (2:1) to receive either tebentafusp or the investigator's choice of therapy (pembrolizumab, ipilimumab or dacarbazine). The minimum follow-up was 36 months, with a median OS of 21.6 months for those receiving tebentafusp and 16.9 months for the control group (HR for death 0.68, 95% CI 0.54 to 0.87). Patients receiving tebentafusp had an estimated 3-year survival of 27% compared to 18% in the control group, with the most common treatment-related AEs being rash (83%), pyrexia (76%), pruritus (70%) and hypotension (38%). No AEs were reported due to long-term administration of tebentafusp, however, any AEs were observed early in treatment, and few patients discontinued treatment in both groups due to AEs (2% in tebentafusp group, 5% in control group). Results suggest that tebentafusp could have long-term benefits for this patient population.

Comment: This report updates initial data on tebentafusp, a novel T-cell receptor bispecific molecule. The drug was compared (2:1) with pembrolizumab, ipilimumab or DTIC, but not combination ICI. Patients were previously untreated. 19% had an objective response, but the follow up period of three years is too short to determine if a survival plateau has been reached. Both radiological assessment and PFS underestimated survival benefit, indicating even patients with progressive disease benefited from the therapy. No new toxicity was identified which is predominantly cutaneous (related to anti GP 100 effects on melanocytes) or T-cell activated cytokine mediated toxicity. AEs were manageable and occurred early in treatment.

Reference: N Engl J Med 2023; 389:2256-2266
Abstract

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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).

Adjuvant nivolumab in resected stage IIB/C melanoma: primary results from the randomized, phase 3 CheckMate 76K trial

Authors: Kirkwood JM et al.

Summary: In this phase 3, double-blind CheckMate 76K trial, researchers assessed the safety and efficacy of nivolumab in resected stage IIB/C melanoma patients. 790 patients were included and were randomly allocated (2:1) to receive nivolumab (480 mg) or placebo every 4 weeks for 12 months total. A minimum of 7.8 months for follow-up was obtained, and an improvement in recurrence-free survival occurred for those receiving nivolumab compared to placebo (HR 0.42, 95% CI 0.30 to 0.59, p<0.0001). 12-month recurrence-free survival rates of 89.0% (nivolumab) and 79.4% (placebo) were reported, as well as an improvement in distant metastasis-free survival (0.47, 0.30 to 0.72). 10.3% of patients receiving nivolumab had a treatment-emergent grade 3 or 4 AE, compared to 2.3% of patients in placebo. Overall, findings suggest that nivolumab could be an effective and well-tolerated adjuvant treatment for this patient population.

Comment: This report is an early, but pre-specified, interim analysis of the CheckMate 76K adjuvant nivolumab study, and in summary, confirms the benefits of anti PD-1 adjuvant therapy in patients at high risk of recurrence (stage 2B and 2C). The median follow-up is 16 months with a minimum of 8 months. 49% of patients in the treatment arm completed 12 months of therapy and 12% are still on treatment. OS has not yet been reported but RFS significantly improved (RFS HR 0.49). The results are similar to the Keynote 716 adjuvant pembrolizumab study, although given the different endpoints, eligibility criteria etc, are not directly comparable. No difference in the frequency of new primary melanomas or pattern of local, regional, and distant recurrences between the two study arms was seen. Treatment effect was seen in all subgroups including BRAF status (V600 v wild type).

Reference: Nature Medicine. 2023;29:2835–2843.
Abstract

The limited value of sentinel lymph node biopsy in lentigo maligna melanoma: A nomogram based on the results of 29 years of the nationwide Dutch pathology registry (PALGA)

Authors: Elshot YS et al.

Summary: This nationwide cohort study aimed to identify lentigo maligna melanoma (LMM) patients who had an increased risk for sentinel lymph node biopsy positivity. Data derived from the nationwide network and registry of histo- and cytopathology in the Netherlands, including 1,989 patients. 16.7% of patients received a sentinel lymph node biopsy, 7.5% of which had a positive result, and 21.9% had a false-negative. 1.3% of patients had clinically detectable regional node metastases, and characteristics such as age (OR 0.95, 95% CI 0.91 to 0.99), ulceration (1.59, 0.44 to 4.83), T4-stage (1.81, 0.43 to 6.2), male sex (1.97, 0.79 to 5.2&) angioinvasion (5.07, 0.94 to 23.31) and microsatellites (7.23, 1.56 to 32.7) were all predictive of sentinel lymph node biopsy positivity. Regional lymph node recurrences were identified in 4.2% of patients at follow-up. These results suggest that there is a limited positive yield of sentinel lymph node biopsy in LMM patients when utilised with current melanoma guideline-recommended indications.

Comment: The incidence of LMM is increasing as the population ages. Although a retrospective study, the data comes from a large Dutch national registry. Only 333 patients had a sentinel node biopsy, and of these, only 7.5% (n=25) had a positive sentinel node. The sample size is therefore relatively small and there is significant missing data e.g. at five years, only 64% of patients had data available. The data on SNB in patients with LMM is variable complicated by the age of patients, usually older, which is associated with a lower risk of a positive SNB and technical difficulties including multiple lymph node basins in the head and neck where most LMM are found. This study confirmed younger age, tumour thickness, lympho-vascular invasion and microsatellites as associated with a positive sentinel node biopsy. A nomogram developed by the authors shares many but not all variables with, for instance, the MIA nomogram, but remains to be validated and compared with existing nomograms.

Reference: Eur J Surg Oncol. 2023;49(11):107053.
Abstract

Omission of completion lymph node dissection in sentinel node biopsy positive head and neck cutaneous melanoma patients

Authors: Kesmodel SB et al.

Summary: In this study, utilising a head and neck melanoma cohort, researchers aimed to determine the survival differences between patients receiving lymph node basin surveillance and completion lymph node dissection (CLND). 634 patients from the National Cancer Database were included, and either underwent sentinel lymph node biopsy or sentinel lymph node biopsy plus CLND. After analysis, no difference in OS was observed between cohorts (HR 1.13, 95% CI 0.71 to 1.81, p=0.610) and characteristics such as; Charlson-Deyo score 1 versus 0 (1.70, 1.10 to 2.63, p=0.016), pN2+ versus pN1 (1.74, 1.23 to 2.45, p=0.002) and lymphovascular invasion versus no invasion (2.07, 1.34 to 3.19, p=0.001) led to a worse prognosis. There was no OS benefit for CLND in pN1 (1.04, 0.51 to 2.10, p=0.922) or pN2+ (1.31, 0.67 to 2.57, p=0.427) patients, nor in patients that underwent immunotherapy (1.32, 0.54 to 3.22, p=0.549). Overall, results suggest no difference in OS benefit between the two therapies, however, further studies are warranted to determine the role of CLND.

Comment: Universally, treatment guidelines recommend sentinel node biopsy for patients with melanomas > 1mm thick, based on the German DECOG study and the MSLT2 study, despite patients with head and neck melanomas being excluded from the German study and accounting for only a small proportion (14%) of the MSLT2 study. Furthermore, MSLT2 patients with head and neck melanoma had a non-significant trend towards improved survival with CLND. As several other studies have demonstrated, this report confirmed no advantage to CLND with one of the largest cohorts and longest follow-up yet reported. Compared to the 2 randomised studies, a significant proportion of patients had more advanced lymph node disease and approximately 1/3 received adjuvant ICI therapy. This study confirms the role of SNB in patients with H+N melanoma.

Reference: Ann Surg Oncol. 2023;30(12):7671-7685.
Abstract

Prognostic significance of incipient ulceration in primary cutaneous melanoma

Authors: Paver EC et al.

Summary: Within this case-control study, cutaneous melanoma patients were evaluated to determine the significance of incipient ulceration. Data derived from 340 patients (median age 69 years, 68% men, median follow-up 7.2 years) with melanoma in the Melanoma Institute Australia research database, where they were then matched with nonulcerated and ulcerated controls (2:1). After analysis, a difference in median Breslow thickness was observed between cases and controls (incipient cases; 2.8 [1.7 to 4.1]mm, nonulcerated; 1.0 [0.6 to 2.1]mm, ulcerated; 5.3 [3.5 to 8.0]mm, respectively) and patients median tumour mitotic rate was 5.0 (3.0 to 9.0) per mm^2 for incipiently ulcerated cases versus 1 (0 to 3.0) and 9 (5.0 to 14.0) for nonulcerated and ulcerated controls. A better OS was obtained in patients with nonulcerated tumours (HR 0.49, 95% CI 0.27 to 0.88, p=0.02) as well as an improved recurrence-free survival (0.37, 0.22 to 0.64, p<0.001) compared to incipiently ulcerated cases, and ulcerated tumours had a worse recurrence-free survival compared to incipiently ulcerated cases (1.67, 1.07 to 2.60, p=0.03). These findings suggest that incipient ulceration could be an adverse prognostic feature for this patient population.

Comment: Tumour ulceration has been a feature of the AJCC staging system for over 20 years, but given the subjective nature of the histological findings, diagnosis can be difficult for the pathologist. The extent of ulceration is generally considered to be associated with prognosis and this report examines the significance of incipient ulceration (defined as attenuation of the overlying epithelium with a host response) which is often seen in the periphery of a melanoma adjacent to histologically defined ulceration. Tumour thickness, elevated mitotic rate, lymphatic vascular invasion, sentinel lymph node metastasis and satellites were all associated with incipient ulceration, as would be expected. It was associated with OS on univariate but not multivariate analysis, possibly because of the relatively small number of patients. The clinical significance of these findings awaits further confirmation, which in practical terms, may upstage a small group of patients eligible for adjuvant therapy.

Reference: JAMA Dermatol. 2023;1:e234193.
Abstract

IMPORTANT SAFETY INFORMATION

- OPDIVO, YERVOY and OPDUALAG can cause immune-related adverse reactions (irARs) which can be severe or fatal, and can occur in any organ system and tissue.[1–3]
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Before prescribing, please review the full Product Information and black triangle for OPDUALAG (click HERE).

AE = adverse event; **I-O** = immuno-oncology; **LDH** = lactate dehydrogenase; **TRAE** = treatment-related adverse event.

References: **1.** OPDUALAG (nivolumab/relatlimab) Product Information (rss.medsinfo.com.au/bq/pi.cfm?product=bqpopdu). **2.** OPDIVO (nivolumab) Product Information (rss.medsinfo.com.au/bq/pi.cfm?product=bqpopdiv). **3.** YERVOY (ipilimumab) Product Information (rss.medsinfo.com.au/bq/pi.cfm?product=bqpyervo). **4.** Larkin *et al. New Engl J Med* 2019;381:1535–46 (including supplementary appendix). **5.** Cancer Council Australia. Cancer Guidelines Wiki. Clinical practice guidelines for the diagnosis and management of melanoma. Available at: wiki.cancer.org.au. Accessed July 2023. **6.** Long *et al. Lancet Oncol* 2018;19:672–681. **7.** Atkins *et al. J Clin Oncol* 2013;41:186–97. **8.** Wolchok *et al. J Clin Oncol* 2022;40:127–37 (including supplementary appendix).

Histologic margin status is a predictor of relapse in lentigo maligna melanoma

Authors: Hoang MP et al.

Summary: The question of whether histologic margin status is a predictor of disease progression was investigated in this study. 268 invasive lentigo maligna melanoma cases that were diagnosed from 1990-2019 were included for analysis, 75% of lesions being located on the head and neck. Patients obtained a range of follow-up of 0 to 31.8 years (median 10.2 years), and a time to local recurrence range of 0 to 20 years (3 years). Fifty-four of 268 patients (20.1%) had progression, with local recurrence occurring in 36 (13.4%), local recurrence and subsequent metastasis occurring in 7 (2.6%) and metastasis only occurring in 11 (4.1%) patients. Worse PFS was associated with a positive histologic margin status (and close/<3mm), as well as tumour site (head and neck). Overall, histologic margin status could be the strongest predictor of progression for this patient population.

Comment: Excision margins for lentigo maligna melanoma are based on very limited evidence. Most international guidelines recommend 10 mm possibly more for large or head and neck lesions. The guidelines are based on a clinical margin and this study sought to evaluate histological margins. Factors associated with recurrence included tumour thickness, ulceration, and mitotic rate as well as margin width, but on multivariate analysis, margin width was the strongest predictor of recurrence. Patients with a margin ≤ 3 mm had high rates of recurrence, but even among patients with a 3 mm margin (equivalent to a 6.5 mm clinical margin in this study), the risk of recurrence was 12%. The majority of recurrences were local and perhaps to highlight the heterogeneity of the condition, 7% of patients with a positive margin did not reoccur.

Reference: J Am Acad Dermatol. 2023;89(5):959-966.
Abstract

External validation of the Melanoma Institute Australia sentinel node metastasis risk prediction tool using the national cancer database

Authors: Freeman SC et al.

Summary: In this study, the validity of the Melanoma Institute of Australia (MIA) predictive model to improve patient selection for sentinel node biopsy was explored. 60,165 were included from the National Cancer Database, where their sentinel node positivity was then calculated. Different clinicopathologic characteristics were observed between the original MIA data set and the National Cancer Database cohort, however, the MIA nomogram sustained a high predictive accuracy (C-statistic 0.733 [95% CI 0.726 to 0.739]). Furthermore, calibration seemed to weaken for the highest risk decile. These findings suggest that the MIA nomogram could predict sentinel node positivity, thus reducing the number of negative sentinel node biopsies.

Comment: Interest in refining the indications for sentinel node biopsy has developed of recent due to adjuvant therapy data and recognition of certain groups at high or low risk of lymph node involvement who might be spared the procedure. The MIA sentinel node biopsy nomogram is widely used and has been validated against at least two international comparisons. This study sought to evaluate the nomogram in a large US database (National Cancer Database 60,165 patients). Although there were some differences between this very large database and the original MIA database, overall, the MIA nomogram performed well, confirming its robust nature and applicability.

Reference: J Am Acad Dermatol. 2023;89(5):967-973.
Abstract

The impact of the COVID-19 pandemic in 2020 on the diagnosis, treatment, and outcomes of invasive cutaneous melanoma: A retrospective national cohort study

Authors: Xiong DD & Bordeaux J

Summary: The SEER registry, a retrospective, population-based cohort study, aimed to characterise melanoma patients that were diagnosed during the COVID-19 pandemic (2018-2020). Patients who were diagnosed in the year 2020 had an increased likelihood of a greater Breslow depth as well as more ulceration, nodular tumours, and more advanced stage at diagnosis. A larger proportion of patients were from wealthier, more urban areas and the primary surgical treatment was likely to be with Mohs surgery. A 15.5% drop in melanoma diagnosis was observed in the year 2020, and a diagnosis in this year was not associated with overall or disease specific survival. Thicker, more ulcerated and advanced tumours were reported in patients diagnosed in 2020, however, further studies are warranted to better characterise outcomes for patients in this time period.

Comment: This large US study (SEER database) confirms that patients who presented with melanoma during the recent COVID pandemic (2020) presented with more advanced disease i.e. thicker tumours, more frequently ulcerated but also tended to be from patients of a higher socio-economic background. This data coincided with the lowest incidence of melanoma presenting for care for a number of years. Interestingly, the time to treatment was reduced, suggesting that once patients had presented, their care was appropriately managed. The very limited data at this stage suggests that overall, the outcome for patients treated during the COVID pandemic was not impacted. Based on registry and other data sources, the Australian experience was very similar to that seen in the US. Similarly, concerns have been raised that patients with poor health literacy, limited economic means, the elderly and rural/regional patients combined with reduced face to face primary care appointments were more likely to delay treatment. It will be some years before the impact of the pandemic on melanoma survival becomes apparent.

Reference: J Am Acad Dermatol. 2023;89(6):1167-1176.
Abstract

Assessing the quality of care for skin malignant melanoma on a global, regional, and national scale: a systematic analysis of the global burden of disease study from 1990 to 2019

Authors: Liu M et al.

Summary: Within this study, the global burden of melanoma and the quality of care provided to patients was evaluated. Researchers systematically analysed the Global Burden or Disease Study (1990-2019), assessing patients' quality of care. A further comprehensive literature review was conducted, gathering data on melanoma incidence, mortality and disability-adjusted life years. After analysis, it was identified that the overall quality of care improved from 82.81 to 91.29 in 2019 (as deemed by the Quality-of-Care Index) and a positive correlation was observed with socioeconomic status across regions. The highest quality of care score was obtained by Australia (99.96), with Central African Republic and Kiribati having the lowest scores, and China and Saudi Arabia having the most significant improvements. Scores in the Democratic People's Republic of Korea, Zimbabwe and Guam all decreased from 1990 to 2019. Quality of care was greatest for those 20-39 years old (93.40 to 94.65), and gender disparities narrowed globally in this time period. Overall, these results provide guidance on how to implement focussed interventions, and where quality of care should be improved.

Comment: Overall, the incidence of melanoma worldwide continues to increase. Snapshots from this global survey, which examined quality of care, indicates overall it has improved over the last decade, with Australia ranking highest. Not surprisingly, care was related to national socio-economic status. Females, particularly younger, tended to receive better care than males and overall younger patients received better quality care than older individuals. The value of this survey the authors point out is the potential to transfer the successful strategies of countries with higher quality care to those with lower quality care, eg. SunSmart Campaign.

Reference: Arch Dermatol Res. 2023;315(10):2893-2904.
Abstract