Melanoma Research Review™

Making Education Easy

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In this issue:

Abbreviations used in this issue:

AM = advanced melanoma; **CLL** = chronic lymphocytic leukaemia; **ICI** = immune-checkpoint inhibitor; **MM** = metastatic melanoma; **MMS** = Moh's micrographic surgery; **OS** = overall survival; **PFS** = progression-free survival; **TIL** = tumour infiltrating lymphocytes; **TT** = targeted therapy.

Welcome to the 63rd issue of Melanoma Research Review

The studies included in this month's issue address various aspects of melanoma, exploring treatment approaches, prognostic factors, and patient outcomes. In one study, adjuvant anti-PD1 therapy showed favourable results in high-risk melanoma patients, while another study compared the effectiveness of immune checkpoint inhibitors. A study examined the use of Mohs micrographic surgery for melanoma treatment and its success in preserving healthy tissue. Other studies focused on recurrence rates and factors influencing them, such as tumour thickness, ulceration, and the presence of tumour-infiltrating lymphocytes. The combination of CTLA-4 and PD-1 blockade demonstrated promise in reversing resistance to PD-1 blockade therapy in certain melanoma patients. Overall, these studies contribute valuable insights into melanoma treatment, patient management, and the factors affecting disease outcomes, intending to improve care and long-term survival for individuals with this complex cancer.

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

Kind Regards,

Professor Michael Henderson
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Ipilimumab with or without nivolumab in PD-1 or PD-L1 blockade refractory metastatic melanoma

Authors: VanderWalde A et al.

Summary: This randomised phase 2 trial evaluated the efficacy of combining ipilimumab and nivolumab (CTLA-4 and PD-1 blockade, respectively) in patients with metastatic melanoma who had previously received front-line anti-PD-1 therapy and experienced tumour progression, compared to CTLA-4 blockade alone. Ninety-two eligible patients were assigned to receive either the combination or ipilimumab alone. The study found that the combination therapy significantly improved progression-free survival (hazard ratio = 0.63), with a higher objective response rate (28% vs. 9%) than ipilimumab alone. Treatment-related grade 3 or higher adverse events were observed in 57% of combination therapy patients and 35% of ipilimumab-only patients. While the change in intratumoral CD8 T cell density did not reach statistical significance, this study suggested that combining CTLA-4 and PD-1 blockade can reverse primary resistance to PD-1 therapy in some melanoma patients, providing a potential treatment option for these individuals.

Comment: This report of a randomised phase 2 study is consistent with previous reports of adding anti-CTLA-4 therapy for patients who progress on anti-PD-1 therapy. The objective response rate was 28%, and grade 3 or higher toxicity was 57%, similar to previously reported data. The secondary hypothesis was that CTLA-4 therapy reversed the primary resistance to anti-PD-1 therapy by inducing a specific tumour cytotoxic response as reported by CD8 T cell tumour infiltration. Although anti-CTLA-4 therapy was associated with improved outcomes, the trend to increased CD8 T-cell tumour infiltration was not significant; however, a number of patients without obvious T-cell infiltration had evidence of tumour regression, suggesting the biopsy had missed the peak of the T-cell response (four weeks after initiation of therapy). These results confirm the role of adding anti-CTLA-4 therapy to anti-PD-1 therapy in a proportion of patients, presumably by reversing primary resistance.

Reference: Nat Med. 2023;29:2278-85
Abstract

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Trends and patterns of care of sentinel node biopsy in cutaneous melanoma

Authors: Wong J et al.

Summary: This study analysed data from patients diagnosed with primary invasive cutaneous melanoma in Queensland from 2009 to 2019. High-risk melanoma, defined as being at least 0.8 mm thick or less than 0.8 mm with ulceration, accounted for 33.8% of the 41,412 patients. Of the high-risk group, 20.9% underwent sentinel node biopsy, and this rate increased from 14.2% in 2009 to 36.8% in 2019, with a higher proportion performed in public hospitals over the 11 years. Factors associated with not undergoing sentinel node biopsy included older age, being female, having a head and neck primary site, and having pT1b melanoma. Approximately 26.2% of patients travelled outside their hospital and health services' residence for sentinel node biopsy, although this rate decreased from 24.7% in 2009 to 23.0% in 2019. Those more likely to travel were younger, from remote areas or more affluent backgrounds.

Comment: This study is an extensive review of Sentinel node biopsy performance for high-risk melanoma (defined as at least pT1b or >0.8mm thickness or ulcerated primary). Overall, the rate of sentinel node biopsy was low (21%) but improved over the ten years, from 14% to 37% in 2019, and the authors comment there is anecdotal evidence to suggest it has improved in the last few years. Patients were more likely to receive the procedure in a public hospital rather than a private setting in recent years. Females, older persons, melanomas of the head and neck, pT1b melanomas and remote and low socio-economic status persons were less likely to have the procedure. This study does not contain information on the provider's specialty, which is known to impact the sentinel node biopsy rate. The implications are that a significant number of patients, particularly in remote areas, will be denied standard-of-care adjuvant therapy based on results from a sentinel node biopsy.

Reference: ANZ J Surg. 2023;93:2172-9
Abstract

Deep learning-based scoring of tumour-infiltrating lymphocytes is prognostic in primary melanoma and predictive to PD-1 checkpoint inhibition in melanoma metastases

Authors: Chatziioannou E et al.

Summary: This study examined 321 primary cutaneous melanomas and 191 metastatic samples to identify prognostic factors for relapse-free survival. Tumour thickness, presence of ulceration, and low levels of tumour-infiltrating lymphocytes (TILs) were analysed. Simple Cox regression revealed that tumour thickness, ulceration, and TILs ≤16.6% were significant unfavourable prognostic factors for relapse-free survival. Multiple Cox regression confirmed that TILs ≤16.6% remained significant, even after adjusting for other factors that impacted the current staging. Lower TILs in primary tissue were associated with unfavourable recurrence-free and distant metastasis-free survival. Comparing TILs in primary tissue and corresponding metastases of the same patient revealed that TILs in metastases were lower. In therapy-naïve metastases, TILs >12.2% correlated with longer progression-free survival and melanoma-specific survival in patients treated with anti-PD-1-based immunotherapy. Multiple Cox regression indicated lactate dehydrogenase and TILs ≤12.2% were significantly associated with unfavourable melanoma-specific survival.

Comment: This is an extensive study that evaluates the significance of primary TILs given the recognition that they are associated with improved survival and predict response to immune checkpoint inhibitor therapy. The literature on TILs is contradictory, probably due to a lack of standardisation of the quantification method. This report is interesting as it uses an artificial intelligence deep learning methodology to report the level of TILs in the primary tumour. The authors used a previously validated algorithm, NN192 and standard computerised imaging of routine H and E slides and demonstrated a clear relationship between the presence of TILs and outcome and response to ICI therapy. This data suggests that this standardised methodology is better able to recognise and quantify TILs, distinguishing them from tumour, stomal and other cells.

Reference: EBioMedicine. 2023;93:104644
Abstract

Treatment management for *BRAF*-mutant melanoma patients with tumor recurrence on adjuvant therapy

Authors: Haist M et al.

Summary: This study involved 515 eligible patients, 273 receiving adjuvant anti-PD1 treatment and 242 undergoing adjuvant targeted therapy (TT). After a median follow-up of 21 months, it was observed that 54.6% of patients on anti-PD1 and 36.4% on TT experienced recurrence, with 39.6% (anti-PD1) and 29.3% (TT) developing distant metastasis. The risk of recurrence was significantly lower in the TT group compared to anti-PD1 (adjusted HR 0.52; p<0.001), and the median recurrence-free survival was notably longer in TT-treated patients (31 versus 17 months; p<0.001). For patients who received TT as a second adjuvant treatment upon locoregional recurrence, recurrence-free survival was significantly longer than those receiving adjuvant checkpoint inhibitors (41 versus 6 months; p=0.009). Patients who experienced DM during adjuvant anti-PD1 showed favourable response rates (58.7%) when switching to first-line TT and (35.3%) with first-line ipilimumab plus nivolumab. In general, median progression-free survival (PFS) was significantly longer in patients who switched treatments for stage IV disease (9 versus 5 months; p=0.004).

Comment: This study reported results from a prospectively accrued database of patients receiving adjuvant therapy for *BRAF*-mutated melanoma and described outcomes after ICI or TT and the management of patients who relapse. It demonstrated superior outcomes for patients receiving targeted therapy over ICI. For patients who developed a loco-regional recurrence after targeted therapy, surgical resection resulted in reasonable outcomes, although the number of patients treated was small. Metastatic disease in patients who received adjuvant ICI was best managed by TT or a combination of ipilimumab and nivolumab. For patients with prior anti-PD-1 adjuvant therapy, metastatic disease was best managed by a combination of ipilimumab and nivolumab. This study was a retrospective review of prospectively collected data and confirmed standard practice in an area where there is limited high-level data.

Reference: J Immunother Cancer. 2023;11:e007630
Abstract

Outcomes of invasive melanoma of the head and neck treated with Mohs micrographic surgery

Authors: Beal BT et al.

Summary: This study aimed to assess the outcomes of treating invasive melanoma in the head and neck region with Mohs micrographic surgery (MMS). It involved a retrospective analysis of 785 cases over 12 years. The results indicated that MMS effectively managed these melanomas with low recurrence rates. Local recurrence occurred in 0.51% of cases, nodal recurrence in 1.0%, and distant recurrence in 1.1%. The study also found that the local recurrence rate increased with the tumour's thickness, with T4 tumours having the highest local recurrence rate at 5.26%. The 5 and 10-year disease-specific survival rates were 96.8% and 93.4%, respectively. The study concluded that MMS is a valuable approach for treating invasive melanoma in the head and neck region, resulting in long-term survival outcomes.

Comment: This is yet another retrospective review of MMS for melanoma and, in this case, is limited to primaries arising in the head and neck. Although the numbers are relatively large, 785 patients, the vast majority were thin, low-risk melanomas. A distinguishing feature in this study was the use of MART 1 immunohistochemistry. The local recurrence rate of 0.5% is consistent with results obtained from standard surgical excision. The presence of *in situ* disease is a major issue for head and neck melanomas and is not addressed in the study, nor is there any information on sentinel node biopsy, which does impact local recurrence. The authors fail to make a case for the use of MMS for melanoma nor, as they claim, justify its incorporation into treatment guidelines. Until a randomised comparison with standard-wide excision, particularly given the larger costs, time and resource utilisation of the procedure, the role of MMS for melanoma remains undefined.

Reference: J Am Acad Dermatol. 2023;89:544-50
Abstract

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Before prescribing, please review the full Product Information and boxed warning for OPDIVO (click HERE) and YERVOY (click HERE).

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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).

Seven-year follow-up of the phase III KEYNOTE-006 study

Authors: Robert C et al.

Summary: This study reports the findings of a seven-year follow-up study on pembrolizumab versus ipilimumab in advanced melanoma. Compared to ipilimumab, pembrolizumab demonstrated a significant prolongation of median OS (32.7 months vs. 15.9 months) with a hazard ratio of 0.70. The 7-year OS rates were 37.8% for pembrolizumab and 25.3% for ipilimumab. Pembrolizumab exhibited favourable OS outcomes regardless of BRAF status, prior treatment with BRAF/MEK inhibitors, or certain prognostic characteristics. Median modified PFS is also superior with pembrolizumab (9.4 months vs. 3.8 months). Among patients who completed ≥94 weeks of pembrolizumab, the 5-year OS was an impressive 92.9%, and the 5-year modified PFS was 70.1%. The study further revealed a 56% objective response rate and a 2-year modified PFS of 62.5% with a second course of pembrolizumab.

Comment: In recent months, the CheckMate 067 (nivolumab in advanced melanoma) study was updated, and this report updates the Keynote-006 study (pembrolizumab versus ipilimumab). Both studies report a minimum of seven-year follow-up and continue to demonstrate long-term improved overall survival (pembrolizumab versus ipilimumab, median OS 33m versus 16m). Patients receiving first-line pembrolizumab had similar outcomes to those receiving prior therapy (OS 41% versus 39% at 7 years), and similar benefit was seen regardless of BRAF mutation status.

Reference: J Clin Oncol. 2023;41:3998-4003
Abstract

Efficacy of immune checkpoint inhibitors for the treatment of advanced melanoma in patients with concomitant chronic lymphocytic leukemia

Authors: Cass SH et al.

Summary: In this international multicenter study conducted between 1997 and 2020, researchers retrospectively reviewed clinical databases to identify patients diagnosed with CCL and AM who received ICI treatment. The study included patients from the US-MD Anderson Cancer Center (24 patients), the US-Mayo Clinic (15 patients), and Australia (19 patients). The study assessed ORRs based on RECIST v1.1 criteria and survival outcomes, specifically OS and PFS, in patients with concurrent CLL and AM. The researchers also explored clinical factors associated with improved ORR and survival. Furthermore, they compared ORR and survival outcomes between the Australian cohort with CLL/AM and a control group of 148 Australian patients with AM alone. Notably, the results indicated that patients with a prior history of chemoimmunotherapy treatment for CLL had significantly reduced ORRs, PFS, and OS, while ORRs and survival outcomes were comparable between the CLL/AM and AM control cohorts in Australia.

Comment: CLL, the commonest adult haematological malignancy, is associated with significant immunosuppression (impaired T-lymphocyte function) and is not infrequently seen in older patients with melanoma. Patients with CLL have an increased risk of other malignancies, including melanoma, and these patients commonly present with advanced disease. The role of checkpoint inhibitors in this disease has been uncertain. In this study, the largest investigating use of immune checkpoint inhibitors in CLL patients with advanced disease found responses to treatment similar to patients without CLL. Treatment appears to have no impact on the risk of immune-related adverse events nor alter the prognosis of CLL; however, patients who had received prior treatment for CLL had poorer responses to treatment.

Reference: Ann Oncol. 2023;34:796-805
Abstract

Long-term outcomes to neoadjuvant pembrolizumab based on pathological response for patients with resectable stage III/IV cutaneous melanoma

Authors: Sharon CE et al.

Summary: This is a follow-up study to a phase Ib clinical trial involving 30 patients with stage III/IV cutaneous melanoma. The trial involved neoadjuvant pembrolizumab before surgery and adjuvant pembrolizumab for a year. The study focused on 5-year survival, recurrence-free survival, and recurrence patterns. After five years with a median follow-up of 61.9 months, the study revealed that patients with major or complete pathological responses (less than 10% viable tumour) had no deaths, compared to a 72.8% 5-year survival for the rest of the cohort. Two out of eight patients with major or complete responses experienced recurrence, while 8 out of 22 patients with over 10% viable tumour experienced recurrence. Patients with 10% or less viable tumours had a median time to recurrence of 3.9 years, while those with over 10% viable tumours had a median time of 0.6 years (P = 0.044).

Comment: Several recent reports have highlighted neo-adjuvant superiority over adjuvant approaches for stage three disease. The studies have been small, with limited follow-up. The current study is an update on a small (n=30) trial of adjuvant pembrolizumab (one dose of 200 mg preoperatively followed by 11 months of pembrolizumab) with long-term follow-up - median follow-up 62m. In patients with a major pathological response, recurrences occurred later than among minimal responders (median 3.9 and 0.6m, respectively). The numbers in the study are small and preclude any subgroup analysis, but the findings of only a small risk of delayed recurrence but otherwise durable responses in patients with a maximal pathology response to pre-operative therapy support ongoing investigation of this strategy.

Reference: Ann Oncol. 2023;34:806-12
Abstract

Adjuvant nivolumab versus ipilimumab in resected stage III/IV melanoma

Authors: Weber J et al.

Summary: In this study, resected stage IIIB-C/IV melanoma patients were categorised based on their disease stage and baseline programmed death cell ligand one expression. They were treated with either nivolumab every two weeks or ipilimumab every three weeks for four doses, followed by dosing every 12 weeks intravenously for a year or until disease recurrence, unacceptable toxicity, or withdrawal of consent. The primary outcome measured was recurrence-free survival. After a minimum follow-up of 62 months, the results indicated that nivolumab continued to outperform ipilimumab in terms of recurrence-free survival (hazard ratio = 0.72). The 5-year recurrence-free survival rates were 50% with nivolumab and 39% with ipilimumab. Additionally, the 5-year distant metastasis-free survival rates were 58% for nivolumab and 51% for ipilimumab, while the 5-year OS rates were 76% for nivolumab and 72% for ipilimumab.

Comment: This report updates the early data from the Checkmate 238 study of adjuvant nivolumab versus ipilimumab in patients after completely resected Stage 3 or 4 disease. As anticipated, the recurrence-free survival advantage for nivolumab persisted, be it only a modest difference although durable. No difference in OS has yet been demonstrated. Although a number of factors were identified as associated with outcomes (gamma interferon signature, programmed death cell ligand 1, tumour mutational burden, CD8+ T cells and reduced CRP), the authors concede their value as predictive biomarkers is limited and further biomarker investigation is required.

Reference: Clin Cancer Res. 2023;29:3352-61
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).