Melanoma Research Review™

Making Education Easy

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In this issue:

Abbreviations used in this issue:

ctDNA = circulating tumour DNA; **DDIs** = drug-drug interactions; **SN** = sentinel node; **TILs** = tumour infiltrating lymphocytes; **TMB** = tumour mutation burden.

Welcome to the 69th issue of Melanoma Research Review

This review begins with a 10-year follow-up study that compared nivolumab plus ipilimumab to nivolumab monotherapy and ipilimumab monotherapy, revealing some promising results. Another noteworthy study included is a multicentre, observational, retrospective study in which researchers aimed to determine the impact of drug-drug interactions on clinical outcomes, particularly among patients with metastatic melanoma being treated with BRAF/MEK inhibitors. This review concludes with an open-label, randomised, phase 2 study that examined the efficacy of ipilimumab plus nivolumab over a 7-year period, producing more promising results.

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

Kind Regards,

Professor Michael Henderson
michael.henderson@researchreview.com.au

Final, 10-year outcomes with nivolumab plus ipilimumab in advanced melanoma

Authors: Wolchok JD et al.

Summary: In this study, 10-year follow-up data comparing nivolumab plus ipilimumab with nivolumab monotherapy and ipilimumab monotherapy were reported. Participants were randomly allocated (1:1:1) to receive either nivolumab plus ipilimumab every three weeks for four doses followed by an additional dose of nivolumab every two weeks, nivolumab plus placebo, or ipilimumab plus placebo. After the 10-year follow-up, patients receiving both nivolumab and ipilimumab had a median OS of 71.9 months, compared to 36.9 months for nivolumab monotherapy and 19.9 months for ipilimumab monotherapy. Compared to ipilimumab monotherapy, those in the nivolumab plus ipilimumab group had an HR for death of 0.53 (95% CI 0.44 to 0.65), and when comparing nivolumab with ipilimumab it was 0.63 (0.52 to 0.76). These findings indicate that nivolumab plus ipilimumab, as well as nivolumab monotherapy, provide an ongoing survival benefit for advanced melanoma.

Comment: The Checkmate 067 study was a landmark in the development of the current management of advanced melanoma, and the current article is the final report detailing outcomes with a minimum 10-year follow up. Given the prolonged survival seen with ICI therapy, the 10-year follow up is significant although the final data are consistent with the previous reports notably improved outcomes with combination ipilimumab and nivolumab over single agent nivolumab (and both over ipilimumab). No new toxicity with the prolonged follow up was reported, with most AEs occurring early. Survival benefits were seen even in patients who developed significant AEs in the first six months, patients receiving combination therapy who stopped during the induction phase or patients receiving immune modulating therapy in the first six months. This report confirms previous data that patients who remained progression free at three years had a very high probability of surviving to 10 years for both combination and single agent nivolumab. Further analysis indicated pronged control for patients with at least an 80% best reduction in tumour burden. These two findings provide a basis for planning an appropriate follow-up regime for patients who respond to ICI therapy.

Reference: N Engl J Med. 2025;2;392(1):11-22.
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).

Pretreatment and on-treatment ctDNA and tissue biomarkers predict recurrence in patients with stage IIIB–D/IV melanoma treated with adjuvant immunotherapy: CheckMate 915

Authors: Long GV et al.

Summary: Within this study, CheckMate 915, researchers compared nivolumab monotherapy to nivolumab plus ipilimumab in those with resected stage III/IV melanoma. A total of 1,844 participants were included, receiving either nivolumab 480 mg every 4 weeks or nivolumab 240 mg every 2 weeks plus ipilimumab 1 mg/kg every 6 weeks. Several tumour and peripheral biomarkers in 60–96% of patients were examined, such as circulating tumour DNA (ctDNA). At baseline, 16.2% of patients had ctDNA positivity, with on-treatment increasing the risk of recurrence in comparison to ctDNA negativity (HR 1.97, 95% CI 1.57 to 2.46). Furthermore, when examining factors such as ctDNA status, tumour mutational burden (TMB), and interferon gamma-RNA signature scores together, they were more predictive of survival in contrast to ctDNA alone. These biomarkers could aid in monitoring the risk of recurrence for this patient population.

Comment: This is a very large and complex study evaluating ctDNA and other biomarkers including CD8+ T cell levels, TMB, % tumour cells PD-L1 positive and interferon gamma RNA signature scores using patients from the Checkmate 915 study (n=1,844 completely resected stage III/IV patients randomised to nivolumab or ipilimumab and nivolumab). ctDNA levels were assessed post resection prior to IO and during treatment. ctDNA, which was predictive of poorer RFS, was detected in 16.7% overall at baseline with increasing incidence with increasing stage of disease. Compared to the biomarkers all of which individually and combined predicted poorer RFS, ctDNA positive patients were more likely to relapse early. The authors suggest serial ctDNA measurements may permit rational decision making to de-escalate or cease IO. The large numbers in this study allowed subgroup analysis with ctDNA negative, high TMB and high IFN ɣ score patients faring particularly well. A number of other associations were described, which justify further evaluation. Features of this report included the large patient cohort and the novel tumour directed ctDNA assay.

Reference: J Immunother Cancer. 2025;11;13(7):e012034.
Abstract

Circulating tumor DNA predicts tumor progression and poor survival in patients with stage III melanoma

Authors: Palacios-Diaz RD et al.

Summary: This prospective, multicentre study examined the usefulness of ctDNA and whether it can predict tumour progression. Those included had stage III cutaneous melanoma and provided blood samples at various time points, including the following: after detecting a positive lymph node by sentinel lymph node biopsy; preoperatively in patients with lymph node metastasis; prior to any treatment in those with confirmed unresectable lymph node metastasis or in-transit metastasis; 4 weeks post-lymph node surgery; and every 3 or 6 months after baseline. Using these samples, researchers isolated cell-free DNA and then searched for ctDNA. Overall, 21 of 48 patients (43.8%) had detectable ctDNA. Detection of plasma ctDNA at any point was associated with progression (p=0.011), overall mortality (p<0.001), and melanoma-specific death (p<0.001). Those with detectable postsurgical ctDNA had lower recurrence-free survival, OS, and melanoma-specific survival. These findings suggest that blood sampling for ctDNA could provide valuable information on recurrence and survival in this patient population.

Comment: This is a much smaller study of ctDNA in stage III patients than the study by Long et al (see above). The detection method involved identification of BRAF, NRAS and TERT promoter mutations and patients were followed after a baseline sample and 3 - 6 monthly thereafter. ctDNA was not reliably found in patients with lymph node involvement or in transit metastasis whereas patients with metastatic disease, particularly with two or more distant sites, had detectable ctDNA. As noted by others, ctDNA was uncommonly seen in patients with soft tissue and brain metastasis. As noted by Long et al, the presence of ctDNA after resection of stage III disease was associated with poorer outcomes. Both the studies confirm the potential utility of ctDNA but highlight several issues including the optimal technology, timing and the issue of low sensitivity but high specificity.

Reference: Melanoma Res. 2025;1;35(4):259-267.
Abstract

Impact of drug–drug interactions on clinical outcomes in metastatic melanoma patients treated with combined BRAF/MEK inhibitors: A real-world study

Authors: Mezi S et al.

Summary: The impacts of drug-drug interactions (DDIs) on clinical outcomes were examined in this multicentre, observational, retrospective study. Patients included had metastatic melanoma and were being treated with BRAF/MEK inhibitors. To determine DDIs, researchers utilised the Drug-PIN software, which examined the association between the Drug-PIN continuous score, Drug-PIN light, and treatment outcomes to specific drugs involved in the DDIs. A total of 177 participants were enrolled, of whom 94 (55.9%) were exposed to a complex drug regimen related to factors such as comorbidities, supportive care, and symptom management. A large change in Drug-PIN scores was observed, particularly before and after therapy initiation. Those with a low-grade DDI had significantly longer median OS and PFS compared to those with high-grade DDIs (log-rank p=0.0045 and p=0.012, respectively). Moreover, when combining both clinical and DDI data, four patient subgroups were identified, showing statistically significant differences in OS and PFS (log-rank p<0.0001). Participants with the highest clinical risk and high DDI had the worst outcomes (HR 2.87, 95% CI 1.7 to 4.8, p<0.001). In summary, minimising the risk of DDIs should be prioritised to optimise treatment efficacy.

Comment: This is a small retrospective study of BRAF/MEK inhibitors and potential drug interactions using a drug interaction software tool. 56% of the 177 patients were receiving complex drug regimes. The number of patients with potentially serious drug interactions increased significantly from before initiation of treatment to the end of treatment. Significantly, outcome measures (OS and PFS) were poorer in patients with potentially high-risk drug interactions, which appeared to be independent of other prognostic factors.

Reference: Pigment Cell Melanoma Res. 2025;38(4):e70026.
Abstract

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Australian College of Rural and Remote Medicine (ACRRM) Professional Development Program (PDP) participants can claim Educational Activity hours in the self-directed learning category for reading Research Reviews. More info.

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Global applicability of a risk prediction tool for sentinel node positivity in patients with primary cutaneous melanoma

Authors: Lo SN et al.

Summary: In this retrospective, multicentre cohort study, the validity of the Melanoma Institute Australia sentinel node (SN) metastasis risk prediction tool was examined. Data were derived from four continents, including the national Danish Melanoma Database and cancer centres in the UK (n=3), US (n=2), New Zealand (n=1), Sweden (n=1), and Brazil (n=1). Those included were 18 years or older with a SN biopsy completed for an invasive primary cutaneous melanoma. In total, 15,731 patients were included, 4,989 of whom had all 6 parameters available. For those with all parameters available, the AUC was 73.0% (95% CI 70.6 to 75.3), compared to 70.8% for those with 1 parameter missing, 71.5% for 2 parameters missing, and 70.1% for 3 parameters missing. The calibration had an intercept and calibration slope of 0.01 (-0.02 to 0.03) and 1.03 (0.90 to 1.16), respectively. Overall, these findings support the robustness, precision, and applicability of this calculator.

Comment: In the absence of effective biomarkers, several groups have published nomograms predicting the risk of a positive SN in patients with T2-T4 tumours. The MIA prediction tool is the most well-known and was initially based on a large cohort of patients treated at the Melanoma Institute Australia. Validation of the mammogram with European and North American cohorts has demonstrated the validity of the prediction tool. The current study, which employed an updated version of the prediction tool, incorporates six parameters (age, thickness, ulceration, lymphatic vascular invasion, tumour type and mitotic rate) and provides significantly improved confidence intervals for the risk of a positive node. An international cohort including patients from Australia, New Zealand, South America, North America and Europe has again confirmed the validity of the updated version. Given that alternate methods of SN status prediction, e.g. gene expression, remain unproven, the improvements in the MIA nomogram are significant. In addition, the potential for combination of the nomogram and other prediction tools remains untested.

Reference: JAMA Dermatol. 2025;1;161(6):589-596.
Abstract

Effective TIL therapy for patients with checkpoint-resistant melanoma without lymphodepleting regimens requires IFNα

Authors: Verdegaal EME et al.

Summary: Within this study, the impact of pegylated IFNα conditioning and a support regimen on the safety and efficacy of tumour-infiltrating lymphocytes (TILs) plus nivolumab was investigated. Those included had immune checkpoint blockade-resistant stage III/IV melanoma and were allocated to receive TIL plus nivolumab either with (n=25) or without (n=9) the addition of IFNα. After analysis, the treatment was found to be safe; however, 16% of patients experienced IFNα-induced lymphopenia and 12% had neutropenia, though no febrile neutropenia or grade 4 AEs were reported. In the non-IFNα group, 11.1% of patients achieved disease control (95% CI -14.5 to 36.7), compared to 41.7% (20.4 to 62.9) in the IFNα-treated group. A significant reduction in circulating leukocytes and neutrophils was observed in those receiving IFNα support. In summary, these results suggest that IFNα is safe and could be a suitable option for this patient population.

Comment: Given issues with the current AJCC staging system, e.g. stage IIIa survival is superior to stage IIc, more nuanced stratification variables have been proposed. This paper explored whether staging could be improved with the incorporation of TILs which reflect the local immune response and appear to have prognostic value. TILs are classified as none, non-brisk and brisk. (Non-brisk is diffuse scattering of TILs among melanoma cells rather than brisk which signifies widespread extensive infiltration). Unlike the staging system which did not effectively discriminate prognosis in stage IIb,c melanoma, 80% of patients with non-brisk TILS eventually progressed. The authors argue that incorporation of TILs into the staging system may provide increased discrimination among their heterogenous group of patients with stage IIb,c melanoma. Potential advantages include selection of patients with stage IIb,c disease who are more likely to progress but also respond to IO approaches.

Reference: Clin Cancer Res. 2025;1;31(13):2628-2638.
Abstract

The risk of ultraviolet exposure for melanoma in Fitzpatrick skin types I–IV: A 20-year systematic review with meta-analysis for sunburns

Authors: Kwa M et al.

Summary: The risk of melanoma development after UV exposure in Fitzpatrick skin types I–IV over the last 20 years was reviewed in this systematic review. A total of 19,852 studies were identified, 26 of which met the inclusion criteria. These studies were derived from national and multinational cohorts (USA, Europe, Australia, Asia, and South America). Of the 26 studies, 20 (77%) identified an association between UV exposure and melanoma incidence, with sunburn being the most frequently reported risk factor, encompassing 3,417 melanomas. An unadjusted OR of 1.66 (1.40 to 1.97) was identified for the risk of melanoma with sunburn, along with an adjusted OR of 1.23 (1.04 to 1.46). Furthermore, cumulative sun exposure was the second most frequently reported risk factor, encompassing 913 melanomas, with a significant positive OR ranging from 1.1 (1.0 to 1.2) to 5.2 (2.1 to 12.5). These results highlight the risk of UV exposure for melanoma among those with fairer skin.

Comment: It is commonly assumed there is little to learn about UV exposure and risk of melanoma, however a deep understanding particularly for fair skinned individuals as described in this report is vital in counselling patients and directing public health campaigns. This study is the first in 20 years to comprehensively examine melanoma and UV exposure. The study was essentially a meta-analysis, and the major conclusion was that sunburn particularly in childhood and defined as pain lasting more than two days or associated with peeling or blistering was the strongest predictive variable. The analysis was limited by the heterogeneity of the studies in large measure due to a lack of standardisation or quantification of variables such as time spent outdoors, living in a high UV environment etc. The authors argue that all patients with a melanoma should be asked about a history of sunburn, particularly as a child.

Reference: J Eur Acad Dermatol Venereol. 2025;39(7):1239-1253.
Abstract

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Relation between dabrafenib plus trametinib-induced pyrexia and age in BRAF V600-mutated metastatic melanoma patients: A post hoc analysis of the real-world ELDERLYMEL study

Authors: González-Barrallo I et al.

Summary: This multicentre, noninterventional, retrospective, real-world study, ELDERLYMEL, compared the efficacy and safety of dabrafenib plus trametinib in older (≥75 years) and younger (<75 years) patients. Those included had BRAF V600-mutated advanced melanoma, were derived from Spain, and were divided into two age-based groups: elderly (n=29) and younger (n=130). Analysis revealed that patients younger than 75 years had 4.59 times higher odds of developing pyrexia compared to elderly patients. Furthermore, the likelihood of developing pyrexia increased by 1.03 with each 1-year decrease in age. The optimal cutoff value for predicting the onset of pyrexia was 61.5 years; individuals younger than this had 2.53 times higher odds of developing pyrexia compared to those aged 61.5 years or older. In summary, these results suggest that age significantly affects the occurrence of pyrexia in this patient population and should be considered during management.

Comment: This is a small study which looked at the incidence of pyrexia in a real-world environment (ELDERLYMEL study) which identified older age specifically with a cut off of 62 years as having a lower incidence. Although the numbers of patients are small, the magnitude of the effect was high (x2.5). This finding, less nausea in the elderly, is contrary to what has been reported previously in the landmark trials of dabrafenib and trametinib. Possible reasons for this difference include different patient populations, e.g. this study included patients with comorbidities that would have prevented enrolment in the landmark studies. This and other factors such as use of steroids and dosage had no relationship to pyrexia in the older patients. It was not possible to analyse the severity of pyrexia as there were very few patients in either age group with grade 3 or more pyrexia.

Reference: Melanoma Res. 2025;1;35(3):170-175.
Abstract

Ipilimumab plus nivolumab versus nivolumab alone in patients with melanoma brain metastases (ABC): 7-year follow-up of a multicentre, open-label, randomised, phase 2 study

Authors: Long GV et al.

Summary: In this open label, randomised, phase 2 study, the efficacy of ipilimumab plus nivolumab compared to nivolumab monotherapy after 7 years was examined. Those included were 18 years or older with active, immunotherapy-naive melanoma brain metastases. Asymptomatic patients were randomly allocated (5:4) to either cohort A (n=36; intravenous ipilimumab plus nivolumab every 3 weeks for 4 doses followed by nivolumab every 2 weeks), cohort B (n=27; intravenous nivolumab every 2 weeks), or cohort C (n=16; intravenous nivolumab every 2 weeks). After a median follow-up of 7.6 years, 18 patients in cohort A (51% [95% CI 34 to 69]), 5 in cohort B (20% [7 to 41]), and 1 in cohort C (6% [0 to 30]) had an intracranial response. The 7-year intracranial PFS rates were: cohort A, 42%; cohort B, 26%; and cohort C, 13%. Overall, these findings suggest that ipilimumab plus nivolumab maintains its efficacy for at least up to 7 years in this patient population.

Comment: This report describes the 7-year results of the ABC trial of ICI therapy in patients with asymptomatic brain metastases with or without other extracranial sites of disease. Response rates at 12 weeks were superior for combined ipilimumab and nivolumab compared to single agent nivolumab (51% versus 20%) and improved 7-year survival (48 versus 26%). Although an intracranial response at 12 weeks predicted improved survival, 25% died of melanoma. Outcomes were poorer for patients with BRAF mutations who had previously received BRAF MEK inhibitors. A further group of patients with neurological symptoms, previous surgery or radiotherapy or leptomeningeal disease received single agent nivolumab with a 3-year survival of 19% and PFS of 6%. Improved QoL has been reported for this group. The authors argue the superior results for treating asymptomatic brain metastases rather than symptomatic patients justifies close MRI surveillance of high-risk patients.

Reference: Lancet Oncol. 2025;26(3):320-330.
Abstract