Melanoma Research Review™

Making Education Easy

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In this issue:

Abbreviations used in this issue:

AR = acquired resistance; **CI** = confidence interval; **ED** = emotional distress; **ICI** = immune checkpoint inhibitor; **LMM** = lentigo maligna melanoma; **NM** = nodular melanoma; **MIS** = melanoma in-situ; **ORR** = overall response rate; **OS** = overall survival; **SLNB** = sentinel lymph node biopsy.

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Welcome to the 66th issue of Melanoma Research Review

This month's melanoma research reviews includes a detailed look at the importance of emotional distress in outcomes from ICI immunotherapy. Also included are early studies on immunostimulatory antibodies against CD40 and a confirmatory study of benefit from ICI in stage IIB/IIC melanoma. Good outcomes are described in treatment of patients with acquired resistance to ICI and lentigo maligna melanoma may be associated with better survival. Genetic analyses of nodular melanoma suggest there may be a role for sonic hedgehog inhibitors in treatment.

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

Kind Regards,

Professor Peter Hersey
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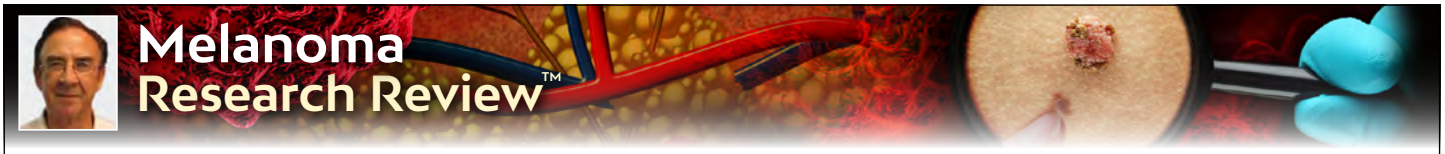
Association between pretreatment emotional distress and neoadjuvant immune checkpoint blockade response in melanoma

Authors: Fraterman I et al.

Summary: This study analysed neoadjuvant immune checkpoint blockade in stage IIIB-D melanoma; researchers conducted a *post hoc* analysis on patients from the PRADO trial (NCT02977052) to investigate the impact of pretreatment emotional distress (ED) on clinical responses. Using the European Organisation for Research and Treatment of Cancer scale for emotional functioning, 28 patients with ED were compared to 60 without. The analysis revealed that pretreatment ED was significantly associated with reduced major pathologic responses, 2-year relapse-free survival, and 2-year distant metastasis-free survival. Adjusting for interferon-gamma signature and tumour mutational burden, the findings suggested that ED may be a marker linked to poorer outcomes after neoadjuvant immune checkpoint blockade in melanoma. Further investigation is recommended. The study did not identify specific β-adrenergic- or glucocorticoid-driven mechanisms associated with these outcomes.

Comment: Will treatment of emotional distress become part of treatment in melanoma? The message in this abstract is likely to fall on receptive ears as many clinicians have anecdotes, particularly of recurrences of melanoma in patients undergoing stress of some nature. The difficulty in such analyses has been a repeatable measure of stress and a defined population of patients. This study used the EORTC QLQ-C30 subgroup, which scores ED as emotional and physical functioning, anxiety and depression and sleep disorders. Many measures are subjective, and insomnia may be the least subjective. A definite plus for the study is their selection of a well-defined subgroup of patients and the inclusion of pathology and immunology measures. The lack of a clear association with effector responses is well-discussed and adds to the study's validity. Unlike several other studies on stress, the authors have suggested that treatments like beta blockers might improve outcomes. As stated by the authors, this study can only be seen as hypothesis-generating because of several limitations and because no exact mechanism of action could be identified. Therefore, confirmation in a larger trial like the NADINA neoadjuvant trial would be very interesting.

Reference: Nat Med 2023;29:3090-9
Abstract



Independent commentary by Professor Peter Hersey

Peter Hersey is an honorary Professor of Immuno Oncology in the University of Sydney and a faculty member of the Melanoma Institute Australia. He has conducted a number of phase I to III trials of immunotherapy in melanoma, including use of modified peptide antigens and dendritic cell vaccines. He has taken a leading role in studies investigating properties of melanoma cells that make them resistant to treatment and new treatment approaches to overcome these properties. He is generally recognized as a pioneer of immunotherapy for melanoma in Australia and has participated in most of the key clinical trials on immunotherapy with immune checkpoint inhibitors. He continues translational research on melanoma in the Centenary Institute as joint holder of a NHMRC program grant on melanoma.

The features and management of acquired resistance to PD1-based therapy in metastatic melanoma

Authors: Hepner A et al.

Summary: This study focused on patients initially responding to anti-PD-1 therapy for melanoma; subsequent disease progression was investigated in a study involving 299 individuals from 16 centres. While high initial response rates were observed, 20% with a complete response and 30% with a partial response within 12 months experienced acquired resistance by six years. The median time to acquired resistance was 12.6 months, with most progressing in a single organ site (65%) and a solitary lesion (51%), frequently in lymph nodes (38%) and the brain (25%). Management strategies for acquired resistance included systemic therapy (45%), local therapy plus systemic therapy (31%), local therapy alone (21%), or observation (3%). Survival outcomes were favourable, especially in cases of single-site progression. The study suggested that acquired resistance to PD1 therapy in melanoma is often oligometastatic, and salvage treatment may lead to favourable survival outcomes.

Comment: Is acquired resistance to ICI immunotherapy not the end of the road? This international study on large numbers of patients is a good news story. It shows that patients developing acquired resistance (AR) to anti-PD1 or anti-PD1/CTLA treatment respond well to subsequent treatment. Median overall survival (OS) from the start of the AR was three years, and 2-year survival for patients with oligometastatic disease was 70%. The article is well-written and illustrated. A critical statistical analysis from the article states, "On univariable analysis, solitary progression, fewer progressing organs, progression in existing lesions, no brain and/or leptomeningeal metastases progressing at AR, ECOG status 0, and AR off immunosuppression therapy were associated with improved OS. Only ECOG status 0 and *BRAF*-mutant melanoma were associated with improved OS on multivariable analysis".

Reference: Eur J Cancer. 2024;196:113441
Abstract

A phase II trial of the CD40 agonistic antibody sotigalimab (APX005M) in combination with nivolumab in subjects with metastatic melanoma with confirmed disease progression on anti-PD-1 therapy

Authors: Weiss SA et al.

Summary: In this phase II trial, the combination of sotigalimab, a CD40 agonist antibody, and nivolumab, an anti-PD-1 inhibitor, was evaluated in 38 patients with advanced melanoma who had confirmed disease progression on a PD-1 inhibitor. The primary objective was to determine the objective response rate (ORR). Thirty-three patients were evaluable; the ORR was 15%, with five confirmed partial responses. Two responders maintained ongoing responses at 45.9+ and 26+ months, while the other three relapsed at 41.1, 18.7, and 18.4 months. The median duration of response was at least 26 months. The combination demonstrated a favourable safety profile, and adverse events were manageable. The study concluded that these promising results suggest that sotigalimab plus nivolumab may be effective in patients with anti-PD-1-resistant melanoma, warranting further investigation.

Comment: A fresh look at immune stimulatory Aabs in treatment of melanoma. The most successful treatments in melanoma have been with Mabs (like Nivolumab) that block inhibitory receptors on lymphocytes. Sotigalimab is a class of Mabs that act on immune-stimulatory receptors. As reviewed by others (see link here), this class of Mabs has a less than impressive history, such as the six deaths in normal people with Mabs against CD28. Mabs against 4-1BB (sarilumab) induced fatal hepatotoxicity in 2 patients. Those against ICOS, OX40 and GITR in phase 1 studies were unexciting. A number of other Mabs against CD40, such as Selicrelumab, are under development. Overall, the response rate from the combination of sotigalimab and nivolumab compared favourably to that of nivolumab plus relatlimab (ORR 11%) in a similar PD-1 refractory patient population. Particular interest is whether biomarkers can be identified to select patients, with most focus being on subsets of dendritic cells responding to anti-CD40.

Reference: Clin Cancer Res. 2024;30:74-81
Abstract

Adjuvant nivolumab in resected stage IIB/C melanoma

Authors: Kirkwood JM et al.

Summary: The CheckMate 76K trial was a phase 3, double-blind study that assessed 790 patients with resected stage IIB/C melanoma, comparing nivolumab (480mg every four weeks for 12 months) to a placebo. At 7.8 months of follow-up, nivolumab significantly improved investigator-assessed recurrence-free survival compared to placebo (HR = 0.42; 95% confidence interval (CI): 0.30-0.59; P < 0.0001), with a 12-month recurrence-free survival of 89.0% versus 79.4%. Benefits were observed across subgroups, and distant metastasis-free survival improved (HR = 0.47; 95% CI: 0.30-0.72). Treatment-related grade 3/4 adverse events occurred in 10.3% (nivolumab) and 2.3% (placebo), with one treatment-related death (0.2%) in the nivolumab group. The findings suggest that nivolumab is an effective and generally well-tolerated adjuvant treatment for patients with resected stage IIB/C melanoma.

Comment: A second major international trial showing benefit from immune checkpoint inhibition in earlier stages of melanoma. The abstract says it all. This large study is the second to show that adjuvant anti-PD1 given for 1 year after surgical removal of stage IIB/IIC melanoma significantly increases relapse-free and distant metastasis survival. The first trial was the phase 3 KEYNOTE-716 study using pembrolizumab, which led to FDA approval of adjuvant treatment of patients with high-risk stage II and III melanoma. In both studies, the distant recurrences were approximately 50% of that in patients on placebo. OS data is now awaited in both studies.

Reference: Nat Med. 2023;29:2835-2843
Abstract

Assessing the genetic risk of nodular melanoma using a candidate gene approach

Authors: Stark MS et al.

Summary: This study focused on nodular melanoma (NM), a challenging type to diagnose early, contributing significantly to melanoma mortality. Whole-exome sequencing of 131 NM and 194 non-NM patients aimed to analyse rare-variant alleles in 500 candidate melanoma-related genes. Phenotypic analysis revealed NM patients were predominantly older males with fair skin and red hair. Common melanoma polygenic risk scores were distributed similarly between NM and non-NM cases. Carriage of familial/high-penetrant melanoma gene variants showed no significant difference. Filtering 500 genes identified 39 with higher NM frequency, including PTCH1, ARID2, and GHR, suggesting Hedgehog pathway involvement. Cumulative RVAs in NM-associated genes showed a 14.8-fold increased ratio for NM. The study considers rare-variant alleles frequency to identify NM risk beyond known high-penetrance genes.

Comment: What are the genes driving nodular melanoma? The difficulties in early diagnosis of nodular melanoma (NM), particularly amelanotic forms, have been well described. Despite the phenotypic and clinical differences from other primary melanomas, outstanding genetic differences are hard to find. The authors have therefore examined whether rare variant alleles, when considered a collective difference, may account for the development of NM. Perhaps the most interesting finding was that PTCH1, a receptor for sonic hedgehogs, was more frequent in patients with rare variant alleles. Aberration in the sonic hedgehog pathway has been implicated in multiple cancers, including basal cell carcinoma and squamous cell carcinoma, and inhibitors of this pathway are in clinical use. They suggest, therefore, that these inhibitors may have a role in treating some NM.

Reference: Br J Dermatol. 2024;190:199-206
Abstract

Risk factors for subsequent primary melanoma in patients with previous melanoma

Authors: Smith J et al.

Summary: This systematic review and meta-analysis were conducted to identify risk factors for subsequent primary melanoma in individuals with a history of melanoma. Data from 27 studies involving 413,181 participants revealed several independent risk factors for developing additional primary melanomas. Pooled analyses identified male sex (HR 1.46), increasing age per 10 years (HR 1.19), light skin colour (HR 1.44), family history (OR 1.79), CDKN2A mutation (OR 5.29), high or moderate naevus count (OR 2.63 and 1.64, respectively), one or more atypical naevi (OR 3.01), first lesions on the head or neck, lentigo maligna subtype (HR 1.16), other subtype (HR 1.14), and inadequate sun protection (HR 1.85) as significant risk factors. The findings provide valuable information for stratifying subsequent melanoma risk, guiding surveillance schedules, and enhancing patient education. However, based on GRADE criteria, confidence in pooled effect estimates varied from high to very low.

Comment: A look at whether genetic testing of patients with primary melanoma is justified. As stated by the authors, it is well known that having a history of melanoma places an individual at markedly increased risk of developing subsequent primary melanomas vs the general population. Given the substantial resources required for long-term surveillance of people diagnosed with melanoma, they state it is important to stratify their risk to guide follow-up. The risk factors to consider are well described and include CDKN2A mutations. However, they state that the feasibility, cost, and utility of genetic testing, including MC1R, remain evolving considerations, and there is no consensus about the utility of wide-panel genetic testing in clinical settings. CDKN2A mutations were recommended in several countries when indicated by high pretest probability.

Reference: Br J Dermatol. 2024;190:174-83
Abstract

Survival in patients diagnosed with melanoma *in situ* compared to the general population

Authors: Naeser Y et al.

Summary: This population-based study in Sweden aimed to assess the OS in individuals diagnosed with melanoma *in situ* (MIS) compared to the general population. Analysing data from 7963 MIS cases and 39,662 matched comparators, the study found a ten-year OS of 77% in women and 72% in men with MIS compared to their counterparts. MIS patients had a higher socioeconomic status and lower comorbidity burden. Even after adjusting for these factors, women with MIS had a significantly lower mortality risk (HR 0.88), whereas the difference was not statistically significant in men (HR 0.94). Although MIS patients face an increased risk of developing cutaneous malignant melanoma, their overall survival appears to be better than the matched general population, emphasising the importance of communicating these reassuring findings to patients.

Comment: Melanoma *in situ* (MIS) may increase overall survival. This large, well-conducted population study reinforces the idea that MIS is a benign condition, with only 3.5% of patients developing invasive melanoma over at least 10 years of follow-up. What is not so well known is that death from all causes was less in patients with MIS compared to non-MIS comparators. Cardiovascular disease was the main cause of death (37% versus 40%) other malignancies (27% versus 23%); dementia (5.9% versus 7.7%). These differences were partially accounted for by a higher socioeconomic status in MIS patients (as reported previously in CMM patients). Multivariate analysis, however, indicated other factors were responsible for the improved survival, especially in women, again consistent with the known improved survival of women from CMM. They conclude by saying that these reassuring results should be conveyed to patients with recent diagnoses of MIS.

Reference: EClinicalMedicine. 2023:65:102284
Abstract

The limited value of sentinel lymph node biopsy in lentigo maligna melanoma

Authors: Elshot YS et al.

Summary: In this nationwide cohort study, researchers sought to identify lentigo maligna melanoma (LMM) patients at an increased risk of positive sentinel lymph node biopsy (SLNB), considering the limited reported positivity in such cases. Analysing data from 1989 LMM patients meeting SLNB criteria, SLNB was performed in 16.7%, with 7.5% showing positivity. A penalised logistic regression identified age, ulceration, T4-stage, male sex, (lymph)angioinvasion, and microsatellites as factors predictive of SLNB-positivity. A nomogram incorporating these features demonstrated a C-statistic of 0.75. The false-negative rate was 21.9%, and regional lymph node recurrences were detected in 4.2%, with most having no baseline LN metastases. The study confirmed the limited positivity in LMM patients, providing a nomogram to predict the risk of positive SLNB.

Comment: Questions relating to the value of SLNB in patients with LMM. This retrospective study appears important for several reasons. One is that it is based on a large patient group of 333 LMM patients. A second is that the recommended nomogram for SLNB developed by the authors differs from that for non-LMM in including only T4 as a predictive variable and microsatellites as well as ulceration, age less than 60 and male sex. Microsatellites were a strong independent predictor. Even with these more stringent criteria, the positive rate for SLNB was only 7.5%, which contrasted with a rate of 21% for non-LMM head and neck melanoma. They conclude by stating, "Our findings might be a good reason to consider alternative options for the early detection of regional metastases in LMM with a focus on lymph nodes at risk; ultrasound surveillance of LN following lymphoscintigraphy could be considered a valuable alternative in selected patients." Also, "A diagnostic excisional biopsy, if cosmetically acceptable, should be considered before evaluating if SLNB is indicated. Future research should focus on validating our nomogram's predictive value and determining its value compared to currently available tools."

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

Lower frequencies of circulating suppressive regulatory T cells and higher frequencies of CD4+ naïve T cells at baseline are associated with severe immune-related adverse events in immune checkpoint inhibitor-treated melanoma

Authors: Kovacsovics-Bankowski M

Summary: In this study, researchers aimed to identify immune features in peripheral blood associated with developing severe immune-related adverse events (irAEs) in melanoma patients undergoing immune checkpoint inhibitor (ICI) therapy. Using a 43-marker mass cytometry panel, they analysed peripheral blood mononuclear cells from 28 patients before treatment, before irAE onset, and at the peak of irAEs. Patients with severe irAEs exhibited a higher frequency of CD4+ naïve T cells and a lower frequency of CD16+ natural killer (NK) cells at all time points. Additionally, patients with severe irAEs had fewer T cell immunoreceptors with Ig and ITIM domain (TIGIT+) regulatory T cells at baseline and more activated CD38+ CD4+ central memory T cells and CD39+ and human leukocyte antigen-DR isotype+ CD8+ TCM at the peak of irAEs. The differentiating immune features at baseline were predominantly seen in patients with gastrointestinal and cutaneous irAEs and type 1 diabetes. Higher frequencies of CD4+ naïve T cells and lower frequencies of CD16+ NK cells were also associated with the clinical benefits of ICI therapy.

Comment: Can immune phenotyping identify patients at risk of irAE before treatment? This is largely a descriptive study that reproduces findings from several previous studies. The discussion on CD4 T cells is well reasoned, and the findings of an association with low numbers of TIGIT CD155 T regulatory cells appear feasible. They conclude that "additional studies with larger cohorts will need to be done to further expand on and independently validate these findings to assess their performance and use as clinical biomarkers. They considered that integrating mass cytometry data with other methods in a larger data set would increase the impact and breadth of their findings. Combining multi-omic approaches, including machine-learning algorithmic analysis, may help these aims." The study, as presented, is a good source of references but not complete enough to help in biomarker or treatment analysis.

Reference: J Immmunother Cancer. 2024;12:e008056
Abstract

Dabrafenib plus trametinib versus anti-PD-1 monotherapy as adjuvant therapy in BRAF V600-mutant stage III melanoma after definitive surgery: a multicenter, retrospective cohort study

Authors: Bai X et al.

Summary: In this multicenter, retrospective cohort study involving 15 melanoma centres across several countries, the efficacy and toxicity outcomes of adjuvant therapies dabrafenib/trametinib (D/T) and anti-PD-1 were compared in patients with resected stage III *BRAF V600*-mutant melanoma. Among 598 included patients, 393 received adjuvant D/T, and 205 received PD-1. The study found that the median relapse-free survival was significantly longer in the D/T group (51.0 months) compared to PD-1 (44.8 months). The OS was comparable between D/T and PD-1. D/T had a higher incidence of treatment modification due to adverse events but fewer persistent adverse events. The study suggests that D/T may provide better recurrence-free survival than PD-1 in this patient population, but longer follow-up and prospective trials are needed for conclusive evidence.

Comment: Surprisingly, no direct comparisons have been made between adjuvant treatment of *BRAF* plus stage III melanoma with D/T and anti-PD1 monotherapy. The results from this large retrospective study suggest that D/T may still offer at least comparable overall survival for up to four years. "In subgroup analyses, they noted that although D/T was associated with substantial RFS benefit across ethnicities, strongest effects were seen in younger patients, females, with non-acral (NAC/UP) subtype, V600E mutation, stage IIIC, and those who received sentinal lymph node biopsy rather than CLND'. Previous studies have shown that males respond less well to D/T compared to females but respond better to anti-PD1. They conclude that the data suggest that D/T may be superior to PD-1 in female patients with resected stage III *BRAF* mutant melanoma, given its substantial recurrence free survival benefit and lower persistent toxicity. Longer follow-up is required to be certain of these results, given these therapies' very different mechanisms of action.

Reference: EClinicalMedicine. 2023;65:102290
Abstract

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