Melanoma Research Review™

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In this issue:

Abbreviations used in this issue:

ICI = immune checkpoint inhibitor; **HCQ** = hydroxychloroquine; **MPM** = multiple primary melanoma; **OS** = overall survival; **PFS** = progression-free survival; **RN** = radiation necrosis; **SKCM** = skin cutaneous melanoma; **SPM** = single primary melanoma; **SRS** = stereotactic radiosurgery; **SRT** = stereotactic radiotherapy; **TCGA** = The Cancer Genome Atlas; **TT** = tumour treating.

Welcome to the 62nd issue of Melanoma Research Review

The articles in this month's review include studies using genetic analyses to identify patients who may suffer severe side effects from treatment with immune checkpoint inhibitors (ICI), as well as updates on their use in the treatment of mucosal and uveal melanoma. One review even says progress at last in the treatment of uveal melanoma. A retrospective study suggests radiation necrosis may not be so problematic when SRT and ICI are combined. Another article analyses the cost-effectiveness of adjuvant Pembro in stage 2b, 2c melanoma in the US. Is it time for an Australian study using Australian costs?

We hope that you enjoy this update in Melanoma research, and we look forward to hearing your feedback.

Kind Regards,

Professor Peter Hersey
peter.hersey@researchreview.com.au

Efficacy of immune checkpoint inhibition in metastatic uveal melanoma

Authors: Pham JP et al.

Summary: This systematic review and meta-analysis included five databases. Studies included in this review were on ICI therapy and metastatic uveal melanoma that focussed on objective response rate, overall survival and progression-free survival (PFS). The pooled overall response rate was 9.2% and 13.5% for anti-CTLA4 plus anti-PD1 therapy. The median overall survival was 11.5 months compared to 16.0 months for ipilimumab plus anti-PD1 therapy. The median PFS was 3.0 months across all studies. The study recommended further biomarker profiling studies, which may assist in assessing whether patients benefit from ICI therapy, particularly the use of ipilimumab compared to anti-PD1 therapy.

Comment: This is a comprehensive review of studies on the efficacy of ICI in the treatment of metastatic uveal melanoma. It compares results with those obtained in the treatment of cutaneous melanoma and refers to possible reasons why the treatment of uveal melanoma is less effective. E.g., the liver is the common site for metastases which respond poorly even with cutaneous metastases. They review studies showing that there are often many tumour-infiltrating lymphocytes in the liver mets, but these seem to have an exhausted phenotype with high LAG-3 expression. The main importance of this article may be to provide a background for comparison with other treatments currently being evaluated. One mentioned is studies with bispecific abs against gp100 and T cell receptors. In addition, much interest is focused on PKC inhibitors like LXS196, which may be an additional agent to use in combination with immunotherapy. (See review here).

Reference: Melanoma Res. 2023;33:316-25
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.

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Impact of second opinion pathology review in the diagnosis and management of atypical melanocytic lesions

Authors: Massi D et al.

Summary: This prospective study of the Italian Melanoma Intergroup and EORTC Melanoma group reviewed 254 lesions from 230 patients. The most frequent referral diagnoses were atypical melanocytic nevi of different subtypes (29.2%), followed by invasive melanomas (24.0%), atypical melanocytic proliferations (14.6%), AST (8.3%) and *in situ* melanomas (6.7%). Sixty out of ninety patients were major discordances where the patient's clinical management was changed. Fifty-one of sixty cases with major discordances were blindly re-evaluated by EORTC Melanoma pathologists, and a final interobserver agreement was found in 90% of these cases.

Comment: This important article highlights the possible differences in histological diagnoses between pathologists in atypical melanoma and solutions to this problem. They refer to the WHO classification of 9 different pathways needed for optimal treatment but the difficulty of implementing the analysis of different pathways in routine laboratories. To overcome this, they established a national second opinion consultation service. They report, "The present prospective clinical study supports the importance of a real-time expert pathologic review for the diagnostic definition of challenging atypical melanocytic lesions. Their review resulted in 33.8% of diagnostic changes, including 22.5% major discrepancies with predicted clinical impact on patient management. Importantly, Italian Melanoma Intergroup-EORTC interobserver concordance validated the Italian Melanoma Intergroup Second Opinion diagnosis in 90% of cases." Since clinical management was impacted in a significant proportion of patients, they suggest their data strongly support routine second opinion to be included and reimbursed for the effective management of atypical melanocytic tumours.

Reference: Eur J Cancer. 2023;189:112921
Abstract

Potential risk factors, clinicopathological features and determinants of survival for multiple primary melanoma patients compared to single primary melanoma

Authors: Mattavelli I et al.

Summary: This large single-centre Italian study aimed to compare patients' risk factors with multiple primary melanomas (MPM) compared to single primary melanomas (SPM). From 9122 patients with SPM and 944 patients with MPM, there were reports of 1437 deaths in the SPM group and 85 in the MPM group. Of these deaths, 1315 within SPM and 60 within MPM were melanoma-specific deaths. In MPM, patients of higher risk were males, whilst age was not an associated factor. When mitoses and ulceration were present, the risk of MPM decreased by about 45 and 75%, respectively, and by about 50% for Breslow thickness >1mm. The multivariate hazard ratio of death for MPM patients compared to SPM was 0.85. For melanoma-specific death, the corresponding hazard ratio was 0.93.

Comment: Comparisons of survival in patients with multiple versus single primary melanoma has been the topic of a number of studies. Their justification in adding to this was a large number of patients with multiple melanomas in their database (944 patients) and their identification of risk factors for MPM as well as adding to survival data versus single primary melanoma. Their main findings were a higher rate in men but no association with age. Germline mutations in CDKN2A were 19% to 4.4% in SPM. There was a lower risk of MPM on limbs and with nodular melanoma. There was no difference in survival between MPM and SPM. They conclude, "MPM patients are a high-risk population associated with an increased risk of other malignancies due to genetic factors which predispose to several cancers, who should receive a strict and extended follow-up comprehending full skin examination, and genetic counselling when clinically indicated."

Reference: Melanoma Res. 2023;33:309-15
Abstract

SALVO: single-arm trial of ipilimumab and nivolumab as adjuvant therapy for resected mucosal melanoma

Authors: Kottschade LA et al.

Summary: This single-arm, multicentre clinical trial used 'flip-dose' ipilimumab (1 mg/kg q3w × 4 cycles), and nivolumab (3 mg/kg q3w × 4 cycles), then nivolumab (480mg q4w × 11) cycles to complete a year of adjuvant therapy. Twenty-nine of the thirty-five patients had R0 resections, and seven received adjuvant therapy. Recurrence-free survival rates at one and two years were 50% and 37%, respectively. Overall survival at one and two years were 87% and 68%, respectively. The recurrence-survival was 10.3 months. In terms of grade 3 toxicities, the most common were diarrhoea (14%), hypertension (14%) and hyponatraemia (11%).

Comment: Effective treatment of mucosal melanoma remains an unmet need. This clinical trial is apparently the first prospective adjuvant trial focused on mucosal melanoma using dual checkpoint inhibitor therapy. The study included patients from different primary sites of mucosal melanoma and also included patients with *KIT*, *NRAS*, and *BRAF* mutations, reflecting the heterogeneous nature of this rare melanoma subtype. A low dose of Ipi 1mg/kg was used in the study. They conclude- "In our single-arm, multi-centre SALVO trial, the combination of ipilimumab and nivolumab met its primary endpoint of relapse-free survival (median 14.3 months 5.5 months in historical controls) for patients with resected mucosal melanoma. Future randomised trials should be performed to confirm these findings, determine the optimal dosing of adjuvant immunotherapy (i.e. whether ipilimumab should be used at 3mg/kg), address neoadjuvant approaches, and determine long-term outcomes for this rare, extremely high-risk patient cohort". The combination of adjuvant ipilimumab and nivolumab is a potentially valuable addition to the standard of care for patients with mucosal melanoma.

Reference: Clin Cancer Res. 2023;29:2220-5
Abstract

Cost-effectiveness analysis of pembrolizumab as an adjuvant treatment of resected stage IIB or IIC melanoma in the United States

Authors: Zhang S et al.

Summary: This study compared pembrolizumab to observation and evaluated patient transitions among recurrence-free, locoregional recurrence, distant metastasis and death rates. There was an increase in total costs for pembrolizumab by $80,423 compared to observation. Pembrolizumab provided gains of 1.17 quality-adjusted life years and 1.24 life years over a lifetime; this resulted in incremental cost-effectiveness ratios of $68,736 quality-adjusted life year and $65,059 life year. Pembrolizumab was cost-effective versus observation at a $150,000 quality-adjusted life years threshold when 73.9% of probabilistic simulations considered parameter uncertainty.

Comment: Do the gains in survival warrant the costs? This is a very complex analysis modelled on the results from the Keynote-716 trial comparing adjuvant treatment with pembrolizumab versus placebo. In this patient group, 91.2% of relapses occurred in the first five years. Total costs in the pembrolizumab-treated cases were estimated at $492,237 versus $411,813 in the observation group. These estimates included the cost of treating adverse effects. For a total cost of USD $80,423, there was a gain of 1.17 quality-adjusted years. Whether similar results would be obtained in Australia is, of course, unknown as the costs of hospital and physician visits may be less in Australia.

Reference: Adv Ther. 2023;40:3038-55
Abstract

IMPemBra: a phase 2 study comparing pembrolizumab with intermittent/short-term dual MAPK pathway inhibition plus pembrolizumab in patients with melanoma harboring the BRAFV600 mutation

Authors: Rozeman EA et al.

Summary: This study enrolled patients with treatment-naïve $BRAFV^{600E/K}$-mutant advanced melanoma treated with pembrolizumab 200mg every three weeks. By week 6, patients were randomised to either continue pembrolizumab or to receive intermittent dabrafenib 150mg twice daily plus trametinib 2mg once daily. Grade 3 treatment-related adverse events were observed in 12%, 12%, 50%, and 63% of patients in cohorts 1, 2, 3, and four, respectively. The overall response rate at weeks 6, 12, and 18 were 38%, 63% and 63% in cohort 1; 25%, 63%, and 75%, in cohort 2; 25%, 50%, and 75%, in cohort 3; and 0%, 63%, and 50% in cohort 4, respectively. After a median follow-up of 43.5 months, the median PFS was 10.6 months for pembrolizumab monotherapy and was not reached for patients with pembrolizumab combined with intermittent dabrafenib and trametinib. The landmark PFS at 2-years and 3-years were both 25% for cohort one, both 63% in cohort two, 50% and 38% in cohort 3 and 75% and 60% in cohort 4.

Comment: This is an imaginative randomised phase 2 study on 33 patients aimed at determining the best way of combining immune checkpoint inhibitors with MEK pathway inhibitors to reduce toxicity and obtain maximum efficacy. The four cohorts differed in the length of time they were on targeted treatment. The results, with a median follow-up of 43.5 months, showed that toxicity was related to time on targeted treatment. Median PFS was 10.6 months without targeted treatment and 20 months in patients receiving one week of targeted treatment in each cycle. They acknowledged that the small patient number limited interpretation of the study but concluded as follows "IMPemBra demonstrated that addition of short-term intermittent dabrafenib plus trametinib (for two times 1 or 2 weeks) to pembrolizumab is a well-tolerated scheme, with a possible favourable efficacy. Such an approach conserves the possibility for TT as a 'second-line' therapy when patients develop progressive disease, which is not the case for the continuous triple combination schemes. Based on our data, a larger randomised trial evaluating the short-term addition of intermittent BRAF plus MEK inhibition (two times 1 or 2 weeks) to upfront anti-PD-1 should be considered".

Reference: J Immunother Cancer. 2023;11:e006821
Abstract

New algorithms based on autophagy-related lncRNAs pairs to predict the prognosis of skin cutaneous melanoma patients

Authors: Liu Y et al.

Summary: This study analysed skin cutaneous melanoma (SKCM) through autophagy-related long non-coding RNAs. The study aimed to explore the prognostic significance of autophagy-related long non-coding RNAs and apply them to a prognostic model. Four hundred and forty-six qualified samples were enrolled, and 222 autophagy-related genes were obtained. In terms of mutation patterns, similar patterns were observed in high- and low-risk groups, while the low-risk group had a higher mutation frequency. Furthermore, patients in the low-risk group were found to have a better immunological reserve and were more suitable for immunotherapy when compared to those in the high-risk group. The study concluded that their signature had validity when accurately evaluating the prognosis of SKCM.

Comment: This rather abstruse article is based on the idea that autophagy is a prognostic biomarker. References for this are provided, and it seems their main value is in identifying early primary melanoma likely to progress. The second point of interest is whether the autophagy markers depend on long non-coding RNA in the cancer cells. Their analysis is based on examining TCGA data for melanoma and is highly technical and well-illustrated. They conclude as follows "In conclusion, our signature can accurately evaluate the prognosis of SKCM patients, and autophagy-related lncRNA pairs may represent new targets for the development of improved treatment regimens and interventions. More research is needed to confirm the results of this study and provide a basis for individualised therapy." The idea that autophagy is an adverse prognostic indicator is not new, and autophagy inhibitors like hydroxychloroquine (HCQ) remain in clinical trials. Presumably, agents targeting long non-coding RNA, such as histone methylases, might be added to the regimes, but this is not discussed in the article.

Reference: Arch Dermatol Res. 2023;315:1511-26
Abstract

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Germline immunomodulatory expression quantitative trait loci (ieQTLs) associated with immune-related toxicity from checkpoint inhibition

Authors: Ferguson R et al.

Summary: This study identified 42 immunomodulatory expression quantitative trait loci most significantly associated with the expression of 382 immune-related genes. They found that the alternate allele of rs7036417 was strongly associated with an increased risk of grade 3-4 toxicities (odds ratio = 7.46; 95% confidence interval = 2.65-21.03; p = 1.43E-04). This allele was not associated with response (odds ratio = 0.90; 95% confidence interval = 0.37-2.21; p = 0.82). The study concluded that there was an increase in the risk of severe adverse events when patients had an rs7036417 alternate allele. Furthermore, the association between rs7036417 and ipilimumab immune-related adverse events suggested overexpression in developing immune-related adverse events.

Comment: Can genetic tests be done to identify patients who will get severe immune-related adverse events? The ability to identify patients who may undergo a severe immune-related adverse event during treatment with immune checkpoint inhibitors would allow clinicians to plan ahead and possibly change management or treatments. This study identified SYK, a tyrosine kinase involved in TCR signalling, as associated with toxicities during treatment with anti-CTLA4. The authors point to the possible use of inhibitors against this cytokine in treating adverse events. This study followed previous studies of genetics that identify patients likely to undergo severe immune-related adverse events. These are reviewed elsewhere. See link here. Those studies identified alleles associated with increased IL-7 levels which were also associated with a good prognosis in melanoma patients in the TCGA. Both studies are limited by the practicality of getting the tests done in routine management.

Reference: Eur J Cancer. 2023;189:112923
Abstract

Concurrent administration of immune checkpoint inhibitors and single fraction stereotactic radiosurgery in patients with non-small cell lung cancer, melanoma, and renal cell carcinoma brain metastases

Authors: Lehrer EJ et al.

Summary: This study included 657 patients with 4182 brain metastases across 11 institutions treated with stereotactic radiosurgery (SRS) and ICI therapy. The median follow-up was 12.8 months and 14.1 months for patients in the concurrent and nonconcurrent groups, respectively. The risk of radiation necrosis (RN) of any grade at 1- and 2 years were 6.4% and 9.9%, respectively. For patients with symptomatic RN, the rates at 1- and 2 years were 4.8% and 7.2%, respectively. On recursive portioning analysis, the highest fidelity models consistently identified V12 Gy as the dominant predictive of RN. Three risk groups were identified by V12 Gy, (1) <12cm^3, (2) 20cm^3 ≥ V12 Gy ≥ 12cm^3 (3) V12 Gy >20cm^3. For patients with any grade RN, 1-year rates were 3.7%, 10.3%, and 12.6%; the 2-year rates were 7.5%, 13.8%, and 15.4% for groups 1, 2, and 3, respectively.

Comment: The risk of radiation necrosis (RN) during combined SRS and ICI for brain metastases is well-reviewed in this article. They quote rates as high as 20% with concomitant ICI versus 6% without ICI. Pathophysiology is discussed, including the dosimetric predictors of RN, such as the volume of the brain receiving at least 12Gy of radiation (V12 Gy). This was a very large study, and despite its limitations (such as being a retrospective study), their conclusions as follows seem very reassuring- "concurrent administration was not associated with an increased risk of RN. Rates of any grade RN and symptomatic SRN were low at 10% and 6.8%, respectively. Furthermore, rates of any grade RN were noted to be 6.6%, 13.3%, and 20.3% in patients receiving SRS and ICI, where V12 Gy < 12 cm^3, 20 cm^3 ≥ V12 Gy ≥ 12 cm^3, and V12 Gy > 20 cm^3, respectively. Clinicians may consider these dosimetric thresholds in patients who are being treated with SRS and ICI and should consider concurrent use of ICI and SRS to optimise patient outcomes without increasing rates of RN."

Reference: Int J Radiat Oncol Biol Phys. 2023;116:858-68
Abstract

Imaging memory T-cells stratify response to adjuvant metformin combined with αPD-1 therapy

Authors: Goggi JL et al.

Summary: This study used PET imaging to determine whether combining anti-PD1 with metformin lead to an enhanced immunological memory response in preclinical colorectal cancer. Tumour growth showed normal distribution, with each treatment cohort experiencing different response rates and magnitudes. The highest response rate and tumour shrinkage were observed in the combined αPD1 plus metformin treatment group, compared to metformin alone which had no significant effect on tumour growth. The criteria for separating tumours were split into treated responders and non-responders. For treated responder animals, tumour volume was ≤ 740 mm^3 on day 21 (>2 standard deviations lower than the mean control group value on day 21).

Comment: Previous studies on patients with type-2 diabetes have suggested that metformin may have anti-tumour effects. Murine studies on BRAF-mutated melanoma also suggested that metformin may limit melanoma growth and increase responses to treatment with anti-PD1. The authors have therefore examined whether these beneficial effects may be evident in patients entered into the EORTC 1325 adjuvant trial testing anti-PD1. Although it was a good idea, only 54 out of 1019 patients in the trial were on metformin. Given the low patient numbers, it is unsurprising that they could not detect the effects of metformin on outcomes in the study. At least no untoward effects were detected. Therefore, the potential benefits of metformin in melanoma patients remain to be tested.

Reference: Int J Mol Sci. 2022;23:12892
Abstract