Melanoma Research Review™

Making Education Easy

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In this issue:

Abbreviations used in this issue:

HSC = hepatic stellate cell; **LSEC** = liver sinusoidal endothelial cell; **NGS** = next-generation sequencing; **MF** = metabolic flare; **MR** = metabolic response; **SRS** = stereotactic radiosurgery.

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Welcome to the 68th issue of Melanoma Research Review

This month's review includes several studies that focus on strategies for treating patients who have failed targeted treatments or immunotherapy. We also feature studies demonstrating a new drug targeting NRAS and RAF dimers-resistant melanoma. There is a description of a simple nomogram that will help select stage II patients for immunotherapy and the innovative use of iPhones and artificial intelligence from images generated from primary melanoma for use in primary care settings. Several multicentre studies are included that largely confirm results from single-centre studies.

We hope you enjoy this month's update in melanoma research and look forward to welcoming your feedback.

Kind Regards,

Professor Peter Hersey
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Anti-PD-1 alone or in combination with anti-CTLA-4 for advanced melanoma patients with liver metastases

Authors: Pires da Silva I et al.

Summary: This international multicenter retrospective study compared the efficacy of anti-PD-1 monotherapy versus a combination of anti-PD-1 and anti-CTLA-4 in advanced melanoma patients with liver metastases. With a median follow-up of 47 months, the objective response rate was higher in the combination therapy group (47%) compared to monotherapy (35%) ($p = 0.0027$). While progression-free survival and overall survival were not significantly different between groups, multivariable analysis showed that combination therapy was associated with improved objective response (OR 2.21, $p < 0.001$), progression-free survival (HR 0.73, $p = 0.009$), and overall survival (HR 0.71, $p = 0.018$) compared to monotherapy.

Comment: Confirming the efficacy of combination immunotherapy in melanoma patients with liver metastases in a large multicentre study. As stated by the authors, the liver is a known site of immune tolerance through multiple mechanisms, such as poor antigen presentation by non-professional antigen-presenting cells such as liver sinusoidal endothelial cells (LSEC), kupffer cells and hepatic stellate cells (HSC). These have low expression levels of MHC class II, low costimulatory molecules and high levels of PD-L1, generating regulatory T cells and partially activated CD8+ T cells. There is also evidence that the presence of liver metastases negatively impacts the response at other sites of metastases. This large, multicentre international study of a representative cohort of patients with advanced melanoma confirmed better response rates with a combination of checkpoints. They acknowledge that failure to include subsequent therapy was a weakness of the study. Nevertheless, the analysis included the most important prognostic clinical variables, including ECOG PS, M1 staging and LDH.

Reference: Eur J Cancer. 2024;205:114101

Abstract

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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.

Exploring molecular genetic alterations and RAF fusions in melanoma

Authors: Kim KH et al.

Summary: This study analysed the molecular landscape of melanoma in East Asian patients at a South Korean tertiary centre using next-generation sequencing (NGS). Among 192 patients, the most common alterations were in the RAS/RTK pathway, with BRAF mutations in 22.4% and NRAS mutations in 17.7% of cases. NGS also identified fusion mutations, including 6 BRAF and 1 RAF1 fusion. Sixteen patients with NRAS or RAF alterations received the pan-RAF dimer inhibitor belvarafenib through an Expanded Access Program. Disease control was achieved in 50% of these patients, with 2 showing remarkable responses.

Comment: Promising results in NRAS and BRAF inhibitor failures with a new RAF kinase dimer inhibitor. Although targeted therapies with combinations such as dabrafenib and trametinib are available for patients with BRAF mutations, few agents are available to treat NRAS BRAF fusions and other RAF mutations. In the present study, NGS was used to identify patients with these mutations who were treated with belvarafenib and were known to inhibit both BRAF and CRAF monomers, homodimers and heterodimers. Studies on 16 patients showed partial responses or stable disease in 8 patients, many of whom had had extensive pretreatment with other therapies. Their studies were ongoing, and three other ongoing NCI trials, including belvarafenib, are referred to.

Reference: Oncologist 2024;29:e811-21
Abstract

Clinical predictors of survival in patients with $BRAF^{V600}$ -mutated metastatic melanoma treated with combined BRAF and MEK inhibitors after immune checkpoint inhibitors

Authors: Kahn AM et al.

Summary: This retrospective single-institution study analysed 40 metastatic melanoma patients treated with combined BRAF/MEK inhibitors after progressing on immunotherapy. The median overall survival (OS) from the start of BRAF/MEK inhibitors was 20.3 months (95% CI 13.3-30.7). Key clinical variables associated with worse survival included age over 60 years (median OS 14 vs. 28 months, HR 2.5, p = .023), ECOG-PS greater than 2 (median OS 7 vs. 33 months, HR 2.89, p = .018), and the presence of bone metastases (median OS 9 vs. 52 months, HR 3.17, p = .002). These factors remained significant in multivariate analysis.

Comment: How effective is targeted therapy after failure of immunotherapy, and who does not benefit? Clinical variables associated with treatment outcomes with combined BRAF/MEK inhibition have been identified in the first-line setting but have not been investigated when targeted therapies are administered after progression on immune checkpoint inhibitors. This retrospective study on 40 patients with a median follow-up of 33 months showed that despite progression on immunotherapy, some patients receiving BRAF/MEKi have prolonged OS, including some that maintain durable responses even after discontinuing BRAF/MEKi. It was examined whether tumour regression from prior immune therapy, despite ultimate overall disease progression, may have better outcomes from second-line targeted therapy, perhaps due to modulation of the immune-suppressive environment. No clear associations were identified. Limitations of the study, such as failure to analyse concomitant treatments with radiotherapy, were acknowledged. Nevertheless, they concluded that this data would assist in stratification for future randomised trials.

Reference: Oncologist. 2024;29:e507-13
Abstract

Long-term intracranial outcomes with combination dual immune-checkpoint blockade and stereotactic radiosurgery in patients with melanoma and non-small cell lung cancer brain metastases

Authors: Vaios EJ et al.

Summary: This study evaluated melanoma and NSCLC patients treated with stereotactic radiosurgery (SRS) from 2014 to 2022, comparing outcomes between those receiving dual immune checkpoint inhibitors (D-ICPI), single ICPI (S-ICPI), or SRS alone. Among 288 patients with 1,704 brain metastases, the 12-month local control rates were highest with D-ICPI (94.73%) compared to S-ICPI (91.74%) and SRS alone (88.26%). D-ICPI significantly reduced local recurrence (p = .0032) and intracranial progression (p = .0408). Multivariate analysis showed D-ICPI was associated with better local control (HR 0.4003, p = .0239) and reduced intracranial progression (HR 0.595, p = .0300). The 12-month cumulative incidence of intracranial progression was lowest with D-ICPI (41.27%). Median overall survival was longest for D-ICPI (26.1 months), followed by S-ICPI (21.5 months) and SRS alone (17.5 months). No significant differences in hospitalisations or neurologic adverse events were observed between cohorts.

Comment: This large study with long follow-up times provides further support for the use of dual ICI with IPI and anti-PD1 in the treatment of brain metastases. They acknowledge limitations of the study - interpretation of these results is limited by the nonrandomised, retrospective nature of this study and the potential for unobserved covariates contributing to differences in local and intracranial control despite efforts to account for imbalances between cohorts. Importantly, the inclusion of patients with melanoma and NSCLC brain metastases may obfuscate histology-specific clinical responses to immunotherapy. Nonetheless, in a subgroup analysis of our study, D-ICPI remained associated with improved intracranial progression-free survival for patients with either melanoma (P = .038) or NSCLC (P = .058) compared with SRS alone. Although our findings support results from the CheckMate-204 and CheckMate-9LA trials, future investigations should consider evaluating SRS with dual ICPI exclusively in patients with NSCLC or melanoma. They conclude, "D-ICPI plus SRS appears to be an effective treatment option for patients with NSCLC and melanoma brain metastases, including those with symptomatic disease and larger intracranial disease burden. The clinical benefit of this approach is independent of fractionation, tumour histology, and whether immunotherapy is delivered concurrently or sequentially with SRS, suggesting that this strategy has implications for a large proportion of patients with brain metastases. Results from ongoing trials evaluating outcomes with dual ICPI and SRS will be informative."

Reference: Int J Radiat Oncol Biol Phys. 2024;118:1507-18
Abstract

Evaluation of artificial intelligence-based decision support for the detection of cutaneous melanoma in primary care

Authors: Papachristou P et al.

Summary: This study evaluated the diagnostic performance of an AI-based clinical decision support tool for detecting cutaneous melanoma used by primary care physicians via a smartphone app. The study was conducted at 36 primary care centres in Sweden and involved 253 skin lesions from 228 patients. The app provided a dichotomous decision support text based on dermoscopic photographs. All lesions underwent standard diagnostic procedures regardless of the app's outcome. Among the lesions, 21 were confirmed as melanomas, including 11 thin invasive melanomas and ten melanomas in situ. The app demonstrated high accuracy, with an area under the receiver operating characteristic (AUROC) curve of 0.960, achieving 95.2% sensitivity and 84.5% specificity. For invasive melanomas, the AUROC was 0.988, with 100% sensitivity and 92.6% specificity. The tool showed high diagnostic accuracy, suggesting significant clinical value for primary care physicians in assessing skin lesions for melanoma.

Comment: An innovative approach to improve the diagnosis of suspected melanoma in general practice. AI in medical imaging of dermoscopic images for melanoma recognition using various image databases consistently reports levels of diagnostic accuracy comparable to those achieved by experienced dermatologists. However, few studies have investigated the prospective performance of AI with patients in real-life primary care clinical settings. This study in 36 primary care centres examined an AI-based clinical decision support tool for melanoma detection, operated by a smartphone application (app), used prospectively by PCPs to assess 'skin lesions of concern' due to some degree of melanoma suspicion. They report that this approach had a negative prediction value of 100% for invasive melanoma and 99.5% for all melanomas. This would substantially decrease the need for dermatologist and histopathology assessment if confirmed. They conclude that the next step should be to proceed with a randomised study design, evaluating the app when it is actually being used to guide a PCP in the diagnostic process and comparing it with an ordinary clinical routine.

Reference: Br J Dermatol. 2024;191:125-33.
Abstract

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

OPDUALAG is PBS listed.
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).

FDG PET/CT imaging 1 week after a single dose of pembrolizumab predicts treatment response in patients with advanced melanoma

Authors: Anderson TM et al.

Summary: This study explored whether early FDG PET/CT imaging, performed about one week after starting pembrolizumab, could predict response in patients with advanced melanoma. Nineteen patients were enrolled, and scans were evaluated for changes in SUVmax, with a metabolic flare (MF) defined as a >70% increase and a metabolic response (MR) as a >30% decrease. Results showed that 6 of 11 (55%) responders exhibited MF or MR, whereas none of the eight nonresponders did. The objective response rate was 100% in the MF-MR group versus 38% in the stable metabolism group. Additionally, MF or MR correlated with T-cell reinvigoration and tumour immune infiltration. At three years, overall survival was 83% in the MF-MR group versus 62% in the stable metabolism group, and median progression-free survival was over 38 months in the MF-MR group compared to 2.8 months in the stable metabolism group (P = 0.017). Thus, early FDG PET/CT can potentially predict pembrolizumab response and is significantly associated with progression-free survival.

Comment: The ideas are okay, but the study has inadequate valuation to support the idea. Although there are potential benefits from early detection of responses on no responses in melanoma patients being treated with anti-PD1, the present study has so many limitations it is highly unlikely that clinicians would act on this from the evidence presented in the study. For example, there is a small sample size, variable intervals between PET and therapy initiation, no patients with stable disease, no liver metastases, and so on. Puzzling how the paper was accepted for publication.

Reference: Clin Cancer Res. 2024;30:1758-67.
Abstract

Neoadjuvant dual checkpoint inhibitors vs anti-PD1 therapy in high-risk resectable melanoma

Authors: Mangla A et al.

Summary: This pooled analysis compared neoadjuvant therapy options for high-risk resectable melanoma patients. Among 573 participants from six clinical trials, dual checkpoint inhibition showed significantly higher rates of achieving pathologic complete response (CR) compared to anti-PD1 monotherapy (OR 3.16, p < .001). However, DCPI also carried higher odds of grade 3 or 4 immune-related adverse events (OR 3.75, p < .001). Comparing different dosing regimens of ipilimumab and nivolumab, no significant differences were found in radiologic responses or pathological CR rates. Conventional-dose IPI-NIVO was associated with increased grade 3 or 4 adverse events compared to anti-PD1 monotherapy (OR 4.76, p < .001), but also higher rates of radiologic overall objective response and pathological CR (OR 1.95, p = .046 and OR 2.99, p < .001 respectively).

Comment: Confirmation of the efficacy of neoadjuvant immunotherapy for melanoma in multiple studies. The neoadjuvant approach to the management of patients with high-risk resectable melanoma was first pursued with interferons in 2006. It is hypothesised that neoadjuvant therapy with ICIs leads to a better immune response due to the delivery of immunomodulators when the tumour is still present in measurable (generally nodal) resectable disease. Neoadjuvant therapy also allows for assessing the pathologic response of tumours, which provides information about the immunologic activity of the various interventions and can have a congruent effect on relapse-free survival, distant metastasis-free survival, and overall survival. The results from this pooled analysis of 6 clinical trials confirm the published data from the individual trials that show increased CR with a combination of ipilimumab and nivolumab compared to anti-PD1 alone. This was associated with increased adverse effects in grades 3-4. The latter was less with alternative combinations using lower doses of IPI without loss of efficacy. In conclusion, they suggest translating immunologic assessment into treatment is needed, and a comparison with similar studies on relatlimab-nivolumab combinations is needed.

Reference: JAMA Oncol. 2024;10:612-20
Abstract

Predicting recurrence-free and overall survival for patients with stage II melanoma

Authors: Varey AHR et al.

Summary: This study aimed to develop a prognostic tool for stage II melanoma patients to predict recurrence-free survival and OS. Using data from the Melanoma Institute Australia database (n = 3,220), multivariable Cox regression models were created and validated externally with U.S. and Dutch datasets. The developed MIA models outperformed traditional AJCC-8 staging models in predicting 5- and 10-year recurrence-free survival and OS. The C-statistics for MIA models were 0.70 and 0.73 for 5-year and 10-year recurrence-free survival and 0.71 and 0.75 for 5-year and 10-year OS, respectively. In contrast, AJCC-8 stage models showed lower C-statistics. The study concluded that, MIA models were calibrated and provided more accurate prognostic estimates, aiding patients in weighing the risks and benefits of adjuvant therapy for stage II melanoma.

Comment: A simple well, evaluated nomogram can potentially improve the management of stage II melanoma. The background to this study includes the results of 2 large clinical trials (Keynote -716 and Checkmate -76) in patients with stage IIB or IIC in SN-negative melanoma, which showed improved distant metastasis-free survival compared to placebo. However, as reported by the authors, the side effects included a grade 3-4 adverse event rate of up to 16%, which may include hepatitis, colitis, pneumonitis, and occasionally myocarditis and a mortality rate of up to 0.5%. There is also a permanent endocrinopathy rate of around 20%, most commonly hypothyroidism (15%), but occasionally hypophysitis (2%-5%) or type I diabetes (<0.5%). It is also estimated that only 50% of patients are undergoing SNB, so there was a need to better predict patients most at risk from metastases. They concluded that the nomograms provide accurate and personalised estimates of both OS and recurrence-free survival for patients with stage II melanomas, both for patients who are SN-negative and those who did not have an SNB.

Reference: J Clin Oncol. 2024;42:1169-80
Abstract

BRAF/MEK inhibitor rechallenge in advanced melanoma patients

Authors: Van Not OJ et al.

Summary: This study analysed data from the Dutch Melanoma Treatment Registry to assess the outcomes of BRAFi(/MEKi) rechallenge in advanced melanoma patients. They included 468 patients who underwent at least two treatment episodes. Following the rechallenge, the ORR was 43%, the median PFS was 4.6 months (95% CI, 4.1-5.2), and the median OS was 8.2 months (95% CI, 7.2-9.4). Patients who discontinued first treatment due to progression had shorter median PFS (3.1 months) than those who discontinued for other reasons (5.2 months). Factors associated with poorer outcomes included elevated lactate dehydrogenase (LDH) levels and symptomatic brain metastases, while a longer treatment interval between first treatment and rechallenge correlated with better.

Comment: Is rechallenging with targeted treatments an effective strategy? Most patients with BRAF-mutant melanoma develop resistance to targeted therapy, leading to disease progression. Several new treatment strategies are being investigated, such as switching to immune checkpoint inhibition in response to targeted therapy. The present study examined whether retreating patients with BRAFi(/MEKi) after prior treatment with BRAFi(/MEKi) may also be an effective strategy. "They report that patients can benefit from rechallenging with BRAFi(/MEKi). Response to rechallenge was not associated with response to or duration of the first BRAFi(/MEKi) treatment. However, patients with elevated LDH levels, symptomatic brain metastases, and those who discontinued prior BRAFi(/MEKi) due to progression benefit less from rechallenge. In contrast, a prolonged treatment interval is associated with better outcomes after BRAF/MEK rechallenge. They suggest that future studies should focus on finding the optimal rechallenge strategy in terms of treatment interval in the first challenge and use of intermittent treatments in the first challenge to optimise survival after rechallenging in advanced melanoma patients."

Reference: Cancer. 2024;130:1673-83.
Abstract

Does patient sex affect the treatment outcome of immune checkpoint inhibitors?

Authors: Petersen SK et al.

Summary: This study utilised the Danish Metastatic Melanoma Database to assess treatment outcomes based on biological sex in patients with metastatic melanoma undergoing first-line immune checkpoint inhibitor (ICI) therapy. Analysing data from 1378 patients, females demonstrated significantly improved overall survival (OS) compared to males in both univariable ($p = 0.003$) and multivariable analyses (adjusted pOS = 0.002). This trend was consistent across progression-free survival (PFS = 0.014) and melanoma-specific survival (pMSS = 0.03) metrics. Five-year OS rates were 47% for females and 38% for males, with corresponding melanoma-specific survival rates of 50% and 45%. The study concluded that the female sex independently predicts better treatment outcomes, though the underlying reasons-whether biological or treatment-related-require further investigation.

Comment: Do women show better responses to checkpoint immunotherapy than men? Female patients in several Western countries are known to have longer survival from melanoma compared to males. This is particularly evident in Australia, where death rates for women in 2012 were 2/100000 to 5/100000 for men. Response rates and survival from targeted treatments have also been much better in women than men. In view of this, it has been puzzling that some large studies have shown better responses and survival of males treated with ICI than equivalent women. The present study is therefore of interest in showing better outcomes for women with melanoma in Denmark treated by ICI than equivalent men. It was considered in previous studies that immune responses in men were poor to start with, and hence, ICI induced relatively better outcomes. Whether other factors, such as mutation burden, may play a part remains to be examined.

Reference: Eur J Cancer. 2024 Jul:205:114099
Abstract

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