Melanoma Research Review™

Making Education Easy

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In this issue:

Abbreviations used in this issue:

ICI = immune checkpoint inhibitor; **EOL** = end-of-life; **LN** = lymph node; **MUM** = metastatic uveal melanoma; **OS** = overall survival; **ORR** = objective response rate; **PFS** = progression-free survival; **TME** = tumour microenvironment.

Welcome to the 64th issue of Melanoma Research Review

The articles in this month's review of melanoma research include several studies on practical management of melanoma. Such as how frequently should imaging be carried out in long-term progression-free patients after immune checkpoint inhibitor (ICI) treatment. Is PET scanning reliable enough to detect metastases in lymph nodes? Should ICI treatments be continued in patients near the end of life? In addition, the power of randomised trials is shown by the negative outcome of treatment with pegylated IL-2 despite positive phase 2 results. It raises questions regarding the need for more stringent criteria for phase 2 studies. Studies on tumour microenvironment pretreatment with ICIs also query whether stratification based on tumour microenvironment (TME) may be useful in selecting appropriate treatments in unfavourable TME patients. Uveal melanoma continues to attract much attention, and new data indicate that loss of chromosome Y may be a factor in some patients.

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

Kind Regards,

Dr Peter Hersey
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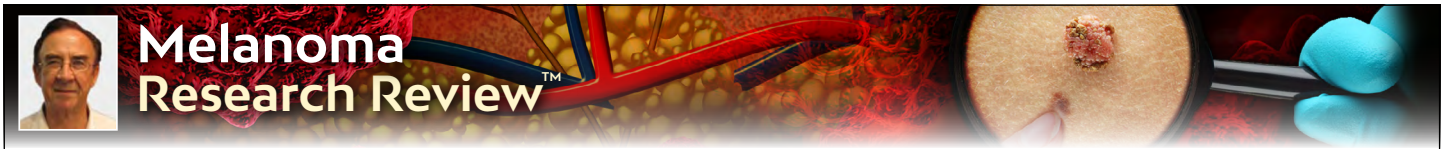
Classification of the tumor immune microenvironment and associations with outcomes in patients with metastatic melanoma treated with immunotherapies

Authors: Adegoke NA et al.

Summary: In this study on metastatic melanoma patients receiving anti-PD-1 therapy alone or combined with anti-CTLA-4, researchers examined immune cell compositions in tumour regions using complex immunohistochemistry and quantitative pathology-derived assessments. They classified patients into three distinct TME categories based on immune cell presence: immune-scarce, immune-intermediate, and immune-rich. Patients with immune-rich tumours exhibited lower melanoma cell proportions and higher immune cell levels, particularly elevated PD-L1 expression, leading to superior treatment response rates and longer progression-free survival (PFS) compared to immune-intermediate and immune-scarce tumours. At an 18-month median follow-up, patients with an immune-rich TME had a 1-year PFS of 76%, contrasting with 56% for immune-intermediate and 33% for immune-scarce TME patients. Furthermore, the combination therapy (ipilimumab+PD-1) displayed better response rates in immune-scarce or intermediate TMEs compared to PD-1 treatment alone.

Comment: This rather lengthy paper complements and adds important information to the literature concerning the importance of TME in the prognosis and response of patients to treatment with ICIs. Features of the study include the large patient numbers involved, its focus on pretreatment biopsies and the digitisation of the data. They suggest the 3 TME classes defined in the study, including distinct intratumoral and peritumoral patterns, may be useful in stratifying patients prior to treatment for standard treatments or for more novel strategies in clinical trials. Digitisation of the data means that subsequent analysis could involve artificial intelligence to help in the analysis of the massive amount of data such studies generate.

Reference: J Immunother Cancer. 2023;11:e007144
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.

Bempegaldesleukin plus nivolumab in untreated advanced melanoma

Authors: Diab A et al.

Summary: The phase III PIVOT IO 001 trial aimed to evaluate the efficacy of bempegaldesleukin (BEMPEG), a pegylated IL-2 cytokine prodrug, in first-line treatment for unresectable or metastatic melanoma. Of the 783 patients, those treated with BEMPEG plus nivolumab exhibited an objective response rate (ORR) of 27.7%, slightly lower than the 36.0% ORR in the nivolumab monotherapy group. The median PFS was 4.17 months with the combination compared to 4.99 months with nivolumab, and the median OS was 29.67 months versus 28.88 months, respectively. However, no significant differences in PFS or OS were observed between the two groups. The combination therapy also led to higher rates of severe adverse events when compared to nivolumab alone.

Comment: BEMPEG is a pegylated IL-2 cytokine prodrug engineered to activate the clinically validated IL-2 pathway in a controlled and sustained fashion, with the goal of preferentially activating and expanding effector CD8+ T cells and natural killer cells over immunosuppressive regulator T cells in the TME. Despite the promising results in the previous phase 2 study, this well-executed randomised study on 783 patients did not reveal any benefits above nivolumab alone, but there was increased toxicity. They discuss the need for more rigorous phase II studies and suggest that further analysis of the biomarker results from the study might help in future studies on other engineered IL-2 products.

Reference: J Clin Oncol. 2023;41:4756-67
Abstract

PET-CT underestimates the true pathological extent of disease at lymphadenectomy for melanoma patients after systemic therapy

Authors: Mor E et al.

Summary: This study aimed to assess the oncological validity of PET-CT-guided lymphatic resection following systemic therapy for melanoma. Researchers retrospectively reviewed 39 patients who underwent lymphadenectomy after systemic therapy, analysing demographic, clinical, and perioperative parameters alongside PET-CT findings compared to pathological outcomes. They categorised outcomes as "as or less than expected" or "more than expected" based on pathology. Among the findings, 71.8% had pathology matching the PET-CT predictions, while 28.2% showed unexpected results. The group with "more than expected" outcomes had more advanced disease at presentation (75% with regional/metastatic disease) compared to the "as or less than expected" group (42.9%). However, the study found that poor response to therapy and the extent of disease on imaging did not reliably predict pathological concordance.

Comment: The background to this study is the current use of neoadjuvant treatment of melanoma, where the pathological response of index lymph nodes (LNs) after neo-adjuvant therapy is used to tailor subsequent surgical management of the LN basin and subsequent adjuvant therapy (e.g. in the PRADO and OPACIN trials). The present study examined whether PET-CT can help predict true LN basin involvement after systemic therapy and thus could potentially identify patients who can undergo a more conservative approach, such as targeted dissection of only the remaining clinical/radiographic disease after systemic therapy rather than complete lymphadenectomy without leaving residual disease. The results appeared clear cut in that pathological responses were greater than PET scan detection in 30% of the patients, particularly in patients who had a less favourable response to systemic therapy.

Reference: Eur J Surg Oncol. 2023;49:106950
Abstract

Risk of further progression or death among durable progression-free survivors with melanoma or non-small-cell lung cancer in PD-1 blockade trials

Authors: Deng L et al.

Summary: This study focused on patients with melanoma or non-small-cell lung cancer who had durable PFS for at least two years after PD-(L)1 therapy, examining the risk of progression beyond this period and determining the ideal imaging surveillance frequency. Data from PD-1 blockade trials were analysed, identifying 474 melanoma patients (31.7%) and 586 non-small-cell lung cancer patients (15.6%) as durable PFS survivors. The analysis revealed that over three subsequent years, the probability of continued PFS was 76.4% for melanoma and 48.1% for non-small-cell lung cancer. The study proposed surveillance intervals based on risk thresholds, suggesting that melanoma durable PFS could be scanned every six months in the third year and annually in years 4 and 5 at a 10% risk threshold, whereas non-small-cell lung cancer patients should be scanned every three months in the third year and every four months in years 4 and 5, with less frequent scans allowed at higher risk tolerances of 15% or 20%.

Comment: This is a study of practical utility that presents evidence for the optimal frequency of imaging to detect recurrences in patients treated with anti-PD1 who have durable PFS after two years of follow-up. In melanoma, the probability of PFS in such patients for the next three years was 76.4%, and no more than 8% had recurrences in any quarter at that time. Based on this analysis, they discuss recommended imaging intervals based on individual risk tolerance. Based on their study, the lowest risk tolerance of 10% imaging at 6-month intervals would still be adequate.

Reference: JCO Oncol Pract. 2023;19:871-81
Abstract

Prognostic risk stratification and end-of-life care outcomes in patients with metastatic melanoma treated with immune checkpoint inhibitors

Authors: Grad RN et al.

Summary: The study focused on 398 patients with advanced melanoma undergoing ICI treatment to identify prognostic factors and their association with end-of-life (EOL) outcomes. Factors impacting OS included LDL, neutrophil/lymphocyte ratio, performance status, prior therapies, and sites of metastases. Using risk scores derived from these factors, patients were categorised into low, medium, and high-risk groups. Among deceased patients, higher-risk individuals (73% of high-risk versus 34% of low-risk) were more likely to receive ICIs within 14, 30, and 90 days of death. However, no significant associations were found between risk groups and hospice referrals or the location of death.

Comment: As experience with the use of ICI in melanoma grows, the question arises as to whether their use near the EOL is appropriate. The use of chemotherapy near EOL is now seen often as low-value care due to minimal benefits and worsening quality of life. The authors have used an algorithm based on readily available clinical information to categorise patients into low, medium and high risk of dying. The article points out that EOL planning is more complex due to responses even in high-risk subgroups. To quote, “our study demonstrates that 27% of high-risk patients in our cohort did not die, and approximately 34% of high-risk patients survived over one year from ICI therapy, with most patients receiving first-line therapy. Thus, given the inherent uncertainty of response to treatment in patients with poorer prognoses, our study does not suggest denying patients the opportunity to receive ICIs; it instead emphasises that potentially beneficial cancer treatment should be balanced with improved efforts for co-management with integrated palliative care.”

Reference: Oncologist. 2023;28:911-6
Abstract

Determinants of overall survival in patients with metastatic uveal melanoma

Authors: Demkowicz P et al.

Summary: This study examined 89 metastatic uveal melanoma (MUM) patients from Yale (initial cohort) and Memorial Sloan Kettering (validation cohort). Cox regression analysis was used to identify factors influencing OS, including sex, performance status, lab measures, metastasis sites, and immunotherapy. Results showed a median OS of 21.8 months in the initial cohort, with female sex and use of ICI (anti-CTLA-4 and anti-PD-1) correlating with better survival (hazard ratio 0.40, 0.44 and 0.42, respectively). Worse outcomes were associated with hepatic metastases and ECOG score ≥1 (hazard ratio 2.86 and 2.84, respectively). Both cohorts demonstrated that ICIs significantly improved OS after adjusting for sex and performance status (hazard ratio 0.22 and 0.04, respectively), underscoring their impact on MUM patient survival.

Comment: The authors have carried out retrospective studies on two large series of patients with uveal melanoma. They point out that 27-34% of patients develop metastases within ten years and that OS is then less than one year. Immunotherapy with tebentafusp bispecific gp100/CD3 has been of modest benefit in patients with HLA A2 alleles. They discuss the limitations of retrospective studies, but their conclusions appear well based on their analyses. "We found that the absence of hepatic metastases, lower LDH, increased performance status, treatment with anti-CTLA–4 or anti-PD-1 therapy, and female sex was associated with improved OS in patients diagnosed with MUM. The findings suggest that ICIs are a viable treatment option for such patients." It is worth noting that the female sex was associated with better responses compared to male patients. This is not the case in ICI treatment of patients with cutaneous melanoma, where responses are better in males. The associated article on the loss of the Y chromosome in MUM may be relevant to these findings.

Reference: Cancer. 2023;129:3275-86
Abstract

Contribution of MEK inhibition to BRAF/MEK inhibitor combination treatment of *BRAF*-mutant melanoma

Authors: Ascierto PA et al.

Summary: The COLUMBUS study's second part focused on patients with advanced *BRAF*^{V600}-mutant melanoma and evaluated the role of binimetinib in treatment combinations. Patients received either encorafenib 300 mg daily plus binimetinib 45 mg twice daily (COMBO300) or encorafenib 300 mg daily alone (ENCO300). Combined data from ENCO300 in parts 1 and 2 were assessed for PFS as a key secondary endpoint. The median PFS was notably longer in COMBO300 at 12.9 months compared to 9.2 months in ENCO300 (parts 1 and 2) and 7.4 months in ENCO300 (part 2). COMBO300 demonstrated a higher ORR (68%) versus ENCO300 (parts 1 and 2) at 51%. Additionally, COMBO300 showed better relative dose intensity and fewer severe adverse events compared to ENCO300.

Comment: There is not very much that is new in this publication. In practical terms, it confirms that combining the popular *BRAF* inhibitor encorafenib with an MEK inhibitor (binimetinib) results in higher ORR and PFS. There is also the bonus of fewer grade 3/4 adverse effects. These comments also apply to the combined treatment with dabrafenib and trametinib.

Reference: J Clin Oncol. 2023;41:4621-31
Abstract

Loss of chromosome Y in primary tumours

Authors: Qi M et al.

Summary: This study investigated the prevalence and implications of loss of Y (LOY) in over 5,000 primary tumours from male patients in TCGA and aimed to highlight the importance of understanding LOY tumours, particularly in the ageing male population. The research revealed varying LOY rates by tumour type and suggested its dual role as a passenger or driver event, depending on the context. In MUM, LOY correlated with age and survival, independently predicting poorer outcomes. Furthermore, the study identified LOY-related vulnerabilities in male cell lines, suggesting potential therapeutic targets such as DDX3X and EIF1AX.

Comment: This article is included as it appears relevant to the relatively poor survival of males from melanoma compared to females. This also applies to a range of other cancers. LOY is getting attention as an associate of a range of disorders in males. This article indicates that it is relatively common in cancers. In the case of uveal melanoma, it is an early event and is considered most probably a driver event in the development of uveal melanoma. Whether these findings will lead to more effective therapies for LOY uveal melanoma remains to be seen, but several targetable abnormalities were identified.

Reference: Cell. 2023:S0092-867400646-3
Abstract

Predictors of sentinel lymph node metastasis in very thin invasive melanomas

Authors: Kakish H et al.

Summary: This study assessed the association between high-risk features and sentinel LN positivity in very thin melanomas. Analysing data from the National Cancer Database and encompassing melanomas with Breslow thickness < 0.8 mm, this study found that among the patients who underwent sentinel LN biopsy, 5.0% had positive nodal metastases. Factors significantly linked to nodal positivity included lymphovascular invasion, ulceration, mitoses, and nodular subtype. Patients with positive sentinel LN exhibited a lower five-year OS of 75%, compared to 92% for those with negative sentinel LN. The presence of certain high-risk characteristics, particularly ulceration, showed a strong association with sentinel LN positivity.

Comment: The authors indicate that earlier detection of melanoma has resulted in an increase in the presentation of patients with thin melanoma < 0.8mm Breslow thickness. Although the positivity for LN metastasis is low when detected, nodal positivity is associated with lower OS (at five years, 92% versus 75%). The rates of nodal positivity were found to be higher in primary melanoma that had factors such as lymphovascular invasion, ulceration, mitoses and nodular histology. The incidence with any one of the features ranged from > 6% to 23% of patients. When two or more factors are present, the rates increase; e.g. lymphovascular invasion plus ulceration was associated with 40.6% positivity, and these plus a nodular pattern was associated with 52.2% positivity. They suggest that "this analysis can help practitioners to counsel patients through the shared decision-making process that is recommended even for these very thin melanomas when sentinel LN biopsy needs to be considered."

Reference: Br J Dermatol. 2023;189:419-26
Abstract

Identification of tumor-intrinsic drivers of immune exclusion in acral melanoma

Authors: Augustin RC et al.

Summary: This study extensively examined acral melanoma tumours to understand their immune landscape and response to ICIs. Among 892 tumours, 72.5% displayed low expression of T cell-inflamed genes, with 23.9% categorised as non-T cell-inflamed. Patients with low intratumoral T-cell density had poorer prognoses. The analysis identified 11 upregulated oncogenic pathways in non-T cell-inflamed tumours, consistent across acral melanoma cohorts, demonstrating association with ICI non-response in various cancers. Single-cell RNA sequencing highlighted higher pathway scores in low T cell-infiltrated tumours. These pathways were linked to suppressed antigen presentation, with fatty acid synthase and CXCL8 identified as potential therapeutic targets across the diverse cancers studied.

Comment: This paper examined data from immunohistochemistry and RNAseq studies in 109 patients with acral melanoma identified in 3 datasets. As reported by others, there was a strong association between a T cell inflamed signature and response to ICI. From RNAseq data, they identified 11 signal pathways associated with non-T cell inflamed pathways, some of which were associated with suppression of type I and II IFN signalling. These pathways were associated with non-response to ICI. The potential role of the 11 pathways is well discussed. IL-8 gets a mention as a possible target of the pathways. Given the lack of effective treatment options for patients with acral melanoma, they propose further investigation into targeting these pathways as a way to improve immunotherapy outcomes in acral melanoma.

Reference: bioRxiv. 2023:2023.08.24.554717.
Abstract