Melanoma Research Review™

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In this issue:

Abbreviations used in this issue:

CP-GEP = clinicopathologic factors with gene expression profiling; **ICI** = immune checkpoint inhibitor; **MPM** = multiple primary melanoma; **MSD** = melanoma-specific death; **NEMJ** = New England Journal of Medicine; **OS** = overall survival; **PD-1** = programmed cell death protein-1; **pPR** = pathological response rate; **PFS** = progression-free survival; **RNA** = ribonucleic acid; **SLN** = sentinel lymph node; **SSM** = superficial spreading melanoma; **TLND** = therapeutic lymph node dissection.

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Welcome to the 59th issue of Melanoma Research Review

This month's collection of research articles has two articles on the neoadjuvant and adjuvant treatment of melanoma. One using single agent anti-PD1 from The New England Journal of Medicine (NEJM). The other is a commentary from Nature Medicine discussing innovative approaches such as those in the PRADO study. It needs to be read in full. Two other articles discuss approaches to select high-risk stage I/II patients for treatment, and both have merit. An innovative study has touched on the role of androgens in treatment outcomes and may become important in small patient subgroups. I trust the articles point to important research progress in melanoma.

I hope you enjoy the articles featured in this month's issue, and as always, we welcome your feedback.

Kind Regards,

Professor Peter Hersey
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Neoadjuvant–adjuvant or adjuvant-only pembrolizumab in advanced melanoma

Authors: Patel SP et al.

Summary: This phase two trial randomly assigned patients with clinically detectable stage IIIB to IVC melanoma. After a median follow-up of 14.7 months, the neoadjuvant-only group had a longer event-free survival than the adjuvant-only group. This study undertook a landmark analysis and found that event-free survival at two years was 72% in the neoadjuvant-adjuvant combined group compared to 49% in the adjuvant-only group. In addition, the percentage of patients with treatment-related adverse events of grade 3 or higher during therapy was 12% in the neoadjuvant-adjuvant combined group and 14% in the adjuvant-only group. This study concluded that among patients with resectable melanoma, event-free survival was significantly longer in those who received pembrolizumab both before and after surgery than in those who received adjuvant pembrolizumab alone.

Comment: Although adjuvant therapy with anti-PD1 is now the standard of care, neoantigen immunotherapy of stage IIIB-IVC is proving so successful that it has raised questions about whether adjuvant therapy after surgery is needed. The current study provides early evidence that treatment results with single-agent anti-PD1 are much improved when combined with anti-PD1 given before surgery. Patients with acral and mucosal melanoma were included in the study. Whether the improvement seen with added anti-PD1 adjuvant therapy will apply to anti-PD1 combined with other agents such as ipilimumab or anti-LAG3 is yet to be tested (see commentary on the PRADO trial in this melanoma research collection). No additional toxicities were noted, but no doubt would include long-term side effects such as hypothyroidism. Combining neoadjuvant and adjuvant treatment will likely be the standard of care for some time. From a historical point of view, the acknowledgement of early studies in this area by Dr Mark Smyth in animal tumour models would be appropriate as these laid the foundation for the neoantigen approach (see link here).

Reference: N Engl J Med. 2023;388:813-23
Abstract

The Australasian College of Dermatologists has approved all **Dermatology Research Reviews** for accreditation as a **Category 1 Level 1 activity = 1 point per hour.**

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Personalizing the approach to neoadjuvant therapy

Authors: Karakousis GC and Mitchell TC.

Summary: This review aimed to personalise the approach to neoadjuvant therapy and create a promising path to improve outcomes of resectable melanoma. This review reported on the PRADO extension cohort of the OpACIN-neo trial. The study presented the survival outcomes of 99 patients with clinical stage III nodal melanoma treated with a personalised approach after six weeks of neoadjuvant dual immune checkpoint inhibitor (ICI) therapy. Patients were assigned to further surgery versus removal of the index lymph node alone and were allocated subsequent adjuvant therapy or no additional therapy. The primary objective of this study was the pathological response rate, which was met with 72%, and a major pathological response was met with 61% in the PRADO group. The second primary objective was to investigate whether therapeutic lymph node dissection (TLND) should remain the standard of care. Sixty patients with major pathological responses had high 2-year recurrence-free and distant metastasis-free survival rates of 93% and 98%, respectively.

Comment: Maybe surgery is not needed for some patients with stage III melanoma, but caution is recommended. The publication of the neoadjuvant/adjuvant study in the NEJM referred to in current melanoma reviews needs to be viewed against ongoing concurrent studies with combinations of ipilimumab and anti-PD1. Perhaps the boldest of these is the so-called PRADO study which aims to personalise treatment based on changes in the draining index lymph node (see link here). This commentary in Nature Medicine summarises progress and identifies questions yet to be answered in these innovative approaches. The following are some extracts from this review that discussed the PRADO study. Specifically, patients who had a major pathological response (MPR; ≤10% viable tumour) on pathological assessment of only the index lymph node received no further surgery or adjuvant systemic therapy. Patients with a partial pathological response (pPR; >10 to ≤50% viable tumour) in the index lymph node underwent TLND but no further adjuvant systemic therapy. Finally, patients with pathological non-response (pPR; >50% viable tumour) in the index lymph node underwent both TLND and systemic adjuvant therapy, with or without adjuvant radiotherapy, to the nodal basin. However, compared to adjuvant therapy, the clinical benefit of neoadjuvant therapy is yet to be determined and is being investigated in randomised phase II and III trials (NCT03698019 and NCT04949113). We must also emphasise the lack of robust OS data for any adjuvant therapy in melanoma in the current era of highly effective therapy for stage IV disease and the lack of recurrence-free survival benefit of adjuvant ipilimumab plus nivolumab compared to the single-agent PD-1 blockade.

Reference: Nat Rev Clin Oncol. 2022;19:679-80
Abstract

Sentinel lymph node biopsy status improves adjuvant therapy decision-making in patients with clinical stage IIB/C melanoma

Authors: Sharon CE et al.

Summary: This population-based analysis aimed to determine the utility of sentinel lymph node (SLN) status in guiding the recommendations for adjuvant therapy. For the 4391 patients included, the 5-year melanoma-specific death (MSD) rate was 46%. The model estimating 5-year MSD risk that included SLN status provided greater net benefit at treatment thresholds from 30% to 78% compared to the model without SLN status. The added net benefit for the SLN biopsy-containing model persisted in a subgroup analysis of patients in different age groups with various T stages. This study concluded that the prognostic model with SLN status estimated that patient risk for 5-year MSD provides superior net benefit compared to a model with primary tumour staging factors alone for threshold mortality rates ≥30%.

Comment: A decision to have adjuvant treatment with checkpoint inhibitors involves assessment of the risk of side effects as well as likely benefit from the treatment as well as cost. These factors can vary, and accurate prognostication with regards to MSD is needed for optimal assessment of the risk-benefit for a particular patient. The statistical analyses in the article demonstrate that the estimation of risk by the inclusion of SLN status has a higher net benefit at treatment thresholds over 30%, wherein adjuvant therapy would typically be considered. Patients with pathologic stage IIB/C from the eighth edition American Joint Committee on Cancer staging dataset may not reach this 30% threshold without appropriate SLN staging. They concluded that "in clinical stage IIB/C primary cutaneous melanoma, a prognostic model with SLN status provides net benefit in guiding adjuvant therapy compared to a model with primary tumour features alone. Foregoing SLN biopsy in these patients precludes the ability to perform complete pathologic staging. It may negatively impact decision-making for providing adjuvant treatment based on accurate risk assessment for melanoma-related death."

Reference: J Am Acad Dermatol. 2023;88:802-7
Abstract

Identification of stage I/II melanoma patients at high risk for recurrence using a model combining clinicopathologic factors with gene expression profiling (CP-GEP)

Authors: Amaral T et al.

Summary: As patients with cutaneous melanoma stage I/IIA disease are currently not eligible for adjuvant therapy, this study aimed to validate the ability of a model combining CP-GEP to identify patients at high risk in this disease group. This study included 543 patients diagnosed between 2000 and 2017 who were treated with sentinel lymph node biopsy (SLNB). CP-GEP stratified 424 stage I/IIA patients, according to their risk for recurrence. The five-year relapse-free survival rates were 77.8% and 93% for CP-GEP high-risk and low-risk patients, respectively. For the patients who did not receive SLNB biopsy, CP-GEP captured 6 out of 7 relapses. Therefore, the study concluded that CP-GEP could be used to identify primary cutaneous melanoma patients with a high risk for disease recurrence.

Comment: Is clinicopathologic plus a gene expression profile test better than a sentinel lymph node biopsy to select patients for adjuvant therapy? The authors point out that early-stage melanoma patients with stage I/IIA cannot access adjuvant treatment options – not even in clinical trials. In contrast, a subgroup of these patients will relapse and have shorter survival. In terms of absolute numbers, more patients with stage I/IIA melanoma die than patients with stage IIB/IIC/III melanoma. These patients can possibly be identified by new technologies and then would be candidates for adjuvant therapeutic options. Overtreatment of early-stage melanoma patients is to be avoided. Application of an 8-gene expression profile developed by the authors was reported to identify patients at high risk and, in a 5-year period, identified 83 of 98 patients who did relapse. They concluded, "Provided this is validated in other cohorts, CP-GEP could be used to predict the risk of recurrence, allowing them to safely forgo the invasive procedure of SLNB. Our results may kick off important developments that could potentially lead to replacing SLNB with standard CP-GEP procedures for patients with stage I/II melanoma – especially in stage I/IIA melanoma patients. A limitation of the current study is its retrospective nature and the fact that data comes from only one centre."

Reference: Eur J Cancer. 2023;182:155-62
Abstract

Apatinib combined with camrelizumab in advanced acral melanoma patients

Authors: Wang X et al.

Summary: This open-label, single-arm phase two trial included patients with pathologically confirmed, locally unresectable or metastatic treatment native acral melanoma treated with 250mg apatinib once daily and camrelizumab 200mg once every two weeks. The results of this study found that the objective response rate was 24.1%, and 7 of 29 patients had an anti-tumour response, including partial response and complete response. The disease control rate was 82.8%, the median PFS was 7.39 months, and the median OS was 3.4 months. The study concluded that apatinib combined with camrelizumab showed a manageable safety profile and reasonable anti-tumour activity in advanced acral melanoma patients as first-line therapy.

Comment: This well-conducted study included whole-exome sequencing to identify gene sets associated with outcomes. The rationale for including inhibitors of VEGFR-2 tyrosine kinase inhibitors with anti-PD1 appears well thought out. They acknowledge the limitations of a single-arm study and the relatively small number of patients. Nevertheless, the identification of mutations that appeared associated with responses appears to be new data and could be built on in future randomised studies. The article did not mention the CRKL associated with insulin signalling (see link here).

Reference: Eur J Cancer. 2023;182:57-65
Abstract

Phase I study of androgen deprivation therapy in combination with anti–PD-1 in melanoma patients pretreated with anti–PD-1

Authors: Robert C et al.

Summary: This study included adult male patients with advanced melanoma who progressed under anti-PD-1 regimens and received 3.75mg every four weeks, nivolumab 3mg/kg every two weeks, and bicalutamide 50mg once daily during the first 28 days. Of the 14 patients included, 4 were locally advanced, and 10 had metastases. Disease control was obtained in 42.8% (RECIST) lower-case 50% (iRESIST). According to RECIST v1.1, the best overall response was partial response in one patient with a pancreas metastasis, stable disease in 5 patients and progressive disease in 8 patients. According to iRECIST, a second partial response occurred after the initial pseudo-progression. This study concluded that the combination was well tolerated.

Comment: Will targeting male hormones become a new treatment for some melanoma? It is well known that female melanoma patients have a better prognosis than male patients. Female patients also have longer survival from treatment with targeted treatments. Several preclinical studies showed increased survival from targeted treatment when androgen receptors were blocked. Androgens were associated with T cell exhaustion of CD8 T cells in colorectal carcinoma and melanoma patients (see link here). Given this background, the present study was an innovative translational study to determine whether androgen receptor blockade and suppression of androgen production as used in the treatment of prostate cancer would improve treatment outcomes in patients failing anti-PD1 treatment. Patient numbers were small, but the results would appear to justify a further examination of this approach.

Reference: Clin Cancer Res. 2023;29:858-65
Abstract

Prognostic significance of age on superficial spreading melanoma after resection

Authors: Sun J et al.

Summary: This study reviewed the lessons from the SEER database, which included 12,536 patients. Among the 12,536 patients with superficial spreading melanoma (SSM), 8664 patients were ≤70 years, and 3872 were >70 years. Patients in the elderly group had a higher incidence of multiple tumours, lymphatic metastasis, larger size primary lesions and worse tumour stage and infiltration degree. On a matched analysis, the elderly group was associated with worse OS and cause-specific mortality was estimated by Cox-regression and completing-risk regression models.

Comment: Is a greater focus on melanoma in the elderly needed? The promised three score and 10 years is now achieved by more and more people in Western countries. This study on SSM outcomes in those above and below 70 years of age in the SEER data identified elderly age as an independent risk for survival and cause-specific mortality. The reasons for this may be similar to other age-related diseases, such as reduced immune responses with age and metabolic changes that are the subject of basic research studies on aging. An individualised approach to treatment, taking into account the patient's age, is recommended.

Reference: ANZ J Surg. 2023;93:227-34
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.

Identification and characterization of circular RNAs as novel putative biomarkers to predict anti-PD-1 monotherapy response in metastatic melanoma patients

Authors: Zhou JG et al.

Summary: This study used knowledge from two independent international studies to identify and characterise circular RNAs as novel putative biomarkers to predict anti-PD-1 monotherapy response in metastatic melanoma patients. Circular RNAs are a conserved novel class of noncoding endogenous RNAs found in eukaryotic transcriptomes and were used based on RNAseq. This study combined the transcriptomic and clinical data of 163 advanced melanoma patients receiving anti-PD-1 from the NIH Melanoma Institute Australia cohort. 74,243 circular RNAs were identified, and 70 were significantly associated with PFS and OS.

Comment: Potential as a blood test in the management of melanoma? Circular RNAs are an evolutionarily conserved novel class of noncoding endogenous RNAs found in the eukaryotic transcriptome and were detected from RNAseq data from 163 advanced melanoma patients in the NIH genome project. Circular RNAs are unusually stable RNA molecules with cell type- or developmental stage-specific expression patterns. They concluded that, "overall, we identified a prognostic circular RNAs signature to reflect the different OS and PFS among advanced melanoma patients who are receiving anti-PD-1 monotherapy, which may be helpful for the risk stratification of these patients. The prognostic circular RNAs signature could therefore be a novel independent prognostic predictor and immunotherapy marker for filtering advanced melanoma patients who may benefit from anti-PD-1 monotherapy. These results offer novel insights into the prognosis evaluation of advanced melanoma and provide a reference for future studies on anti-PD-1 monotherapy in advanced melanoma".

Reference: Neoplasia. 2023;37:100877
Abstract

Multiple primary melanoma in association with other personal and familial cancers

Authors: Yang X et al.

Summary: This retrospective case-control study included cases of gender-matched multiple primary melanoma (MPM) and single primary melanoma (SPM). Of the 378 patients enrolled, 252 had single primary melanoma, and 126 had MPM. In comparison to patients with single primary melanoma, patients with MPM were more likely to have squamous cell carcinoma and prostate cancer. First-degree relatives of patients with MPM had a higher prevalence of melanoma and prostate cancer but not other cancers. In the multivariable analysis, the association remained significant between MPM and squamous cell carcinoma, prostate cancer, and first-degree relative history of melanoma or prostate cancer. The study concluded that patients with MPM had a higher prevalence of personal and first-degree histories of non-melanoma skin cancers and prostate cancer.

Comment: Do melanoma and prostate cancer have similar cancer-predisposing genes? The risk of nonmelanoma skin and non-skin cancers is increased in patients with melanoma due either to shared environmental risk factors or the presence of mutations of certain cancer-predisposing genes. BRCA1-associated protein-1 is another heritable cancer-predisposing gene, and its mutation has been reported to be related to mesothelioma, uveal melanoma, and cutaneous melanoma. Patients with familial atypical multiple mole melanoma, a hereditary cancer syndrome caused by mutation of cyclin-dependent kinase inhibitor 2A, are known to have a significantly higher risk of melanoma and pancreatic cancer. Patients with melanoma are at increased risk of developing subsequent melanomas. Compared to patients with single primary melanoma, patients with MPM are more likely to have a younger age at onset, an earlier stage of melanoma (0 or I), and a family history of melanoma. The present study found that compared to patients with single primary melanoma, patients with MPM showed an increase in prostate cancer in the MPM group and their relatives, suggesting a potential familial association between melanoma and prostate cancer. The paper is well-referenced and makes a case for further analysis of the basis for the association.

Reference: Cancer Med. 2023;12:2474-83
Abstract

Comparing the associations between host and tumor factors with survival outcomes with anti-PD-1 immunotherapy in metastatic melanoma

Authors: Koczka K et al.

Summary: This study identified 174 patients treated with anti-PD-1 immunotherapy. At a median follow-up time of 37.1 months, 135 individuals had died, and 150 had progressed. Elevated LDH had a response rate of 21% versus 41% for those with a normal LDH. Host factors associated with worse median PFS and median OS included liver metastases >3 sites of disease, elevated LDH, thrombocytosis, neutrophilia, anaemia, lymphocytopenia, and an elevated neutrophil/lymphocyte ratio. Primary ulcerated tumours had a worse median OS of 11.8 versus 19.3 months. The study concluded that host factors measuring the general immune function, markers of systemic inflammation, tumour burden and location are the most prognostic for survival.

Comment: A real-life study that questions some previous findings. The authors have examined the host factors associated with the response of 174 patients with melanoma and have defined four subgroups based on the host and tumour characteristics (number of metastases). The study is relatively unremarkable, except that a number of host factors identified by others as important such as neutrophilia were not important. The site of metastasis was also not found to be a determinant. Similarly, BRAF status and TMB were not associated with responses, but ulceration of the primary was associated with poor responses. The subject is critically reviewed. They concluded, "Our findings prove that the host immune system is responsible for surpassing a threshold to mount a sufficient immune response against cancer. Using LDH and a number of sites of metastases, we can objectively prognosticate patient outcomes on anti-PD1 immunotherapy. This model, if validated, can help clinical decision-making in treating advanced melanoma."

Reference: Cancer Med. 2023 12:2427-39
Abstract