Melanoma Research Review™

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In this issue:

Abbreviations used in this issue:

AE = adverse event; **ATRA** = all-trans retinoic acid; **CI** = confidence interval; **CR** = complete response; **CTLA** = cytotoxic T-lymphocyte-associated protein 4; **DM** = desmoplastic melanoma; **ICI** = immune checkpoint inhibitor; **MBM** = melanoma brain metastases; **MDSC** = myeloid-derived suppressor cells; **MUM** = metastatic uveal melanoma; **NUM** = nail unit melanoma; **OS** = overall survival; **PD-1** = programmed cell death protein-1; **PKC** = protein kinase C; **UM** = uveal melanoma.

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Welcome to the 60th issue of Melanoma Research Review

This month's research has articles on melanomas' neoadjuvant and adjuvant treatment, acceptance of adjuvant immune checkpoint inhibitors (ICI) by patients, and the cost of immune checkpoint immunotherapy. The role of radiotherapy in treating recurrences during ICI gets mentioned. This raises the interesting work from lung and other cancers that shows aneuploidy as a biomarker for radiotherapy in the presence of ICI. Both need to be given concurrently. The subject of recurrent desmoplastic melanoma after surgery gets a review, as does the treatment of nail unit melanoma (NUM). I trust the articles point to important research progress in melanoma.

We hope you enjoy this update in melanoma research, and as always, we welcome your feedback.

Kind Regards,

Professor Peter Hersey
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Targeting MDSC differentiation using ATRA

Authors: Tobin RP et al.

Summary: This phase Ib/II clinical trial included 24 patients, 46% diagnosed with melanoma-1a and 29% diagnosed with melanoma-1c stage disease at enrolment. The study's primary outcome was well tolerated, with the most common all-trans retinoic acid (ATRA) related adverse events (AE) being headache, fatigue and nausea. The mean progression-free survival (PFS) was 20.3 months, and the overall response rate was 71%, with 50% of patients experiencing complete response (CR). The 1-year overall survival (OS) was 80%. The study acknowledged that the combination effectively lowered circulating myeloid-derived suppressor cell (MDSC) frequency.

Comment: Targeting transcription factors involved in differentiation in combination with anti-PD-1. The frequent resistance of melanoma to single-agent anti-PD-1 has given rise to a number of imaginative combinations. This particular combination is based on the idea that ATRA would differentiate and reduce the activity of myeloid-derived suppressor cells. The accompanying article by Olsen and Luke provides a good background to MDSCs and ATRA. In any case, it seems that this combination is worthy of attention in that this single-arm study on 24 patients with melanoma reported responses in 71% of patients and 50% CRs. They were aware of the small patient numbers and previous studies that failed despite early results, such as the failure of the anti-PD-1 plus epacadostat study. A larger study NCT04305041 is in progress.

Reference: Clin Cancer Res. 2023;29:1209-19
Abstract

Local recurrence rates after excision of desmoplastic melanoma

Authors: Ran NA et al.

Summary: This systematic review and meta-analysis identified four studies evaluating Moh's micrographic surgery or staged excision. After wide local excision of desmoplastic melanoma (DM), the overall local recurrence rates were 21%. The local recurrence rate versus negative histological margins was 49% versus 11%, respectively. The study also identified that neurotropism was associated with increased local recurrence rates with a rate of 1.79. Therefore, the study concluded that DM has high local recurrence rates after wise local excision, and the local recurrence risk was greatest with positive excision margins.

Comment: A focus on surgical treatment of DM and the possible need for radiotherapy. This is a systematic review and meta-analysis that characterises locoregional recurrence after excision of desmoplastic melanoma with standard wide-local excision, Mohs surgery, or staged surgery and assesses tumour and treatment risk factors for local recurrence. They reported an incidence of 21% overall and 11% even when margins were negative at wide-local excision or staged surgery. The discussion includes the need for good immunohistochemistry to detect subtle changes in desmoplasia. The well-written paper discusses new treatment guidelines recommending adjuvant radiotherapy for DM with high-risk features. A clinical trial of adjuvant radiotherapy is underway (NCT00975520)

Reference: Dermatol Surg. 2023;49:330-337
Abstract

Brain metastasis and survival outcomes after first-line therapy in metastatic melanoma

Authors: Franklin C et al.

Summary: This prospective, multi-centre real-world study included 1704 patients, 916 were BRAF wild-type (BRAF*wt*), and 788 were BRAF V600 mutant (BRAF*mut*). The primary outcome of this study included the incidence of brain metastasis, which was achieved after 24 months, where therapy with BRAF+MEK resulted in a higher incidence of brain metastasis compared with PD-1±CTLA-4. For brain metastasis-free survival, tumour stage and age were longer. CTLA-4+PD-1 did not result in better brain metastasis-free survival, PFS and OS. The study concluded that in BRAF*mut* patients, therapy with PD-1±CTLA-4 ICI resulted in a delayed and less frequent development of brain metastasis compared to BRAF+MEK target therapy.

Comment: Does the frequency of brain metastases depend on the first-line treatment for metastases? Treatment of patients that develop brain metastases after first-line therapy remains a clinical challenge. The present study is of interest in pointing to different incidences of brain metastases and outcomes according to the first-line therapy used in treatment. Their conclusions were as follows- "Altogether, our analysis of a large real-world cohort of melanoma patients demonstrates a faster and more frequent development of brain metastasis in BRAF*mut* patients treated first-line with BRAF+MEK target therapy, and prolonged OS in BRAF*mut* patients treated first-line with CTLA-4±PD-1 compared with PD-1 or BRAF+MEK. Moreover, we did not detect improved OS or brain metastasis-free survival in BRAF*wt* patients treated with combined ICI compared with PD-1 alone. These findings suggest that survival outcomes have to be assessed separately for BRAF*mut* and BRAF*wt* patients and that ICI, particularly CTLA-4 plus PD-1, should be preferably chosen as first-line therapy in BRAF*mut* melanoma patients without MBM". These conclusions are somewhat controversial and hopefully will lead to similar analyses in other studies.

Reference: J Immunother Cancer. 2023;11:e005828
Abstract

Health care utilization and costs in systemic therapies for metastatic melanoma from 2016 to 2020

Authors: Qian MF et al.

Summary: This study utilised a nationwide commercial claims database between 2016 and 2020 and identified patients with presumed stage IV metastatic melanoma receiving systemic therapy. Among the 2018 patients identified, the mean age was 67 years. The study identified that nivolumab surpassed pembrolizumab as the most prescribed systemic melanoma therapy, whilst combination-ICI and BRAFi+MEKi therapies remained the most stable. The estimated healthcare cost analysis included combination ICI: β = $47,600 pppm, 95%CI $42,200-$53,100; BRAFi+MEKi: β = $3810, 95%CI $365-$7260; pembrolizumab: β = $6450, 95%CI $4420-$8480. The analysis also concluded that combination ICI and BRAFi-MEKi therapies were strongly associated with more inpatient hospital days.

Comment: Costs depend on hospital stays and ease of administration of ICI. An interesting article shows fluctuations in the use of different ICIs in treatment based not so much on efficacy but practical aspects such as dosing frequency. Snippets from the article are reproduced here.- "Compared to nivolumab, combination ICI demonstrated an increase in totals costs, treatment-related costs, and all measures of healthcare resource utilisation, including days hospitalised, number of hospitalisations, emergency room visits, and outpatient visits. These results are consistent with the known treatment-related AEs and toxicities in ipilimumab-containing (anti-CTLA-4) treatment regimens. A notable observation was the rapid rise in nivolumab use in 2018 and the simultaneous decline in pembrolizumab use in 2018. The observed rise in nivolumab uses correlated with its Food and Drug Administration approval to reduce the dosing frequency from every two to every four weeks in March 2018. After a decline in 2018, pembrolizumab monotherapy utilisation increased yearly until 2020, the end of the study period, with an associated decrease in nivolumab use. This shift may be related to pembrolizumab's Food and Drug Administration approval in April 2020 to reduce the dosing frequency from every three to every six weeks."

Reference: Oncologist. 2023;28:268-75
Abstract

Risk of recurrence of nail unit melanoma after functional surgery versus amputation

Authors: Oh BH et al.

Summary: This retrospective analysis reviewed NUM patients between 2008 and 2016. The analysis included 140 cases of NUM with a mean Breslow thickness value of 3.14 ± 2.62mm in the amputation cases and 0.70 ± 1.36mm in the functional surgery cases. For recurrence and distant disease, the occurrence was 21.5% and 7.48% for functional surgery cases, respectively. Furthermore, for the amputation cases, distant disease and occurrence were 30.3% for both outcomes. Finally, patients at further risk of recurrence or distant disease were those of male sex, with greater Breslow thickness, and those with amelanotic colour, ulcers, and nodules.

Comment: Selecting Breslow thickness that can be treated without amputation. This study from Korea was a retrospective analysis of outcomes in 33 patients with amputation of the digit versus 107 patients with functional surgery. The mean Breslow thickness of NUM was 3.14 ± 2.62 mm for the amputation group (range: *in situ* to 11.0 mm), a value markedly greater than that of the functional surgery group at 0.70 ± 1.36 mm (range: *in situ* to 5.0 mm). Patients in the amputation group were more likely to be older and have higher rates of volar involvement, total nail involvement, the Hutchinson sign, ulcers, and nodules than those in the functional surgery group. They reported that 0.8 mm was found to be an optimal cut-off point for stratifying the risk of recurrence and distant disease in NUM. In addition, when 0.8 mm was used as a criterion for determining the surgical strategy, instead of 0.5 mm, amputation could be spared without losing the Youden index sensitivity plus specificity and negative predictive value. However, in the case of NUM with risk factors for recurrence, such as amelanotic colour, ulcers, or nodules, patient counselling and a close follow-up were recommended.

Reference: J Am Acad Dermatol. 2023; 88:1017-23
Abstract

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Survival update of neoadjuvant ipilimumab plus nivolumab in macroscopic stage III melanoma in the OpACIN and OpACIN-neo trials

Authors: Versluis JM et al.

Summary: This analysis compared two trials, OpACIN and OpACIN-neo, and analysed the recurrence-free survival and OS results. This study confirmed that median recurrence-free survival and OS were not reached in either trial in the short-term results. The estimated results for recurrence-free survival at 5-year follow-up were 70% in the neoadjuvant arm and 60% in the adjuvant arm. For OS rates at 5-year follow-up, the estimated results were 90% in the neoadjuvant arm and 70% for the adjuvant arm. After a median follow-up of 47 months for OpACIN-neo, the estimated 3-year recurrence-free survival and OS rates were 82% and 92%, respectively. Of the 12 patients with distant disease recurrence from neoadjuvant therapy, the study identified five patients who responded to subsequent anti-PD-1 and 8 to targeted therapy. However, seven patients showed progression after an initial response.

Comment: Follow-up studies on early neoadjuvant studies. The early short-term results from the OpACIN trials have been presented and reviewed in earlier publications and are now updated after the median follow-up of 5-year data for the OpACIN (20 patients) and three years for the OpACIN-neo trial (86 patients). The discussion needs to be read to understand the finer points in these trials, but the early results seem to be maintained in this longer follow-up in that recurrences after two years were only seen in 4% of the patients. The importance of pathologic responses in the lymph nodes (defined as Major <10% and Partial <50% viable tumour cells) as predictors of outcome was confirmed in the longer follow-up. Three-year recurrence-free survival rates were 80-82%. No doubt, the results of other neoadjuvant studies will follow, such as the NADINA trial, which compares neoadjuvant ipilimumab plus nivolumab with adjuvant nivolumab.

Reference: Ann Oncol. 2023; 34:420-30
Abstract

Decision-making and health-related quality of life in patients with melanoma considering adjuvant immunotherapy

Authors: Atkinson TM et al.

Summary: This study collected data on demographics, healthcare quality of life and attitudes towards adjuvant ICI immunotherapy over one year. The analysis included 34 patients; 41% opted for anti-PD-1 immunotherapy, and 59% opted for observation. From those receiving anti-PD-1 immunotherapy, the health-related quality of life score was higher for social well-being at pre-treatment. They were more likely to endorse positive statements about adjuvant therapy. Furthermore, they had lower decisional regret and higher satisfaction, even if they experienced toxicity or recurrence.

Comment: Uptake of adjuvant ICI immunotherapy not as high as expected. A relatively small study, but the results were interesting in that a high percentage of patients appeared to prefer routine follow-up compared to adjuvant treatment. Some details from the article- "patients entered had stage IIIB-IV cutaneous melanoma, were candidates for adjuvant anti-PD-1 immunotherapy, and had not yet discussed adjuvant treatment options with their oncologist." A 4-minute informational video tailored to their disease stage communicated comprehensive, quantitative information about the risk of relapse both with and without adjuvant treatment and the risks of each immune-related AE. 14 patients received nivolumab. Three of these patients experienced immune-related AEs (one patient with colitis, one patient with hypothyroidism, and one patient with a combination of hypothyroidism, hepatitis, and vitiligo). Twenty patients chose observation. During the year-on-study, melanoma relapse was seen in 6/14 (43%) of patients on adjuvant nivolumab and 10/20 (50%) of patients on observation. 35% of the physicians favoured nivolumab, and there was a tendency for patients seeing these doctors to choose adjuvant treatment.

Reference: Oncologist. 2023;28:251-7
Abstract

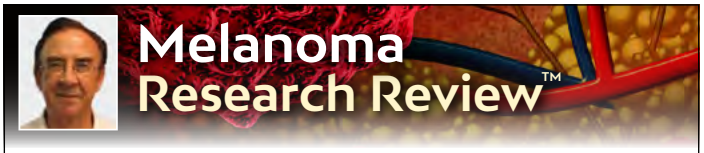
A phase I trial of LXS196, a protein kinase C (PKC) inhibitor, for metastatic uveal melanoma

Authors: Piperno-Neumann S et al.

Summary: This phase I study evaluated the safety, tolerability, pharmacokinetics, pharmacodynamics, and efficacy of oral protein kinase C (PKC) inhibitors in patients with metastatic uveal melanoma (MUM). In the LXS196 once-daily group, first-cycle dose-limiting toxicities were observed in 18.4% of patients, clinical activity was observed in 9.1%, and the median response was 10.15 months, with hypotension being the most common dose-limiting toxicity. For the twice-daily group, the median duration of response was 4.6 months, with 11.1% of patients receiving a complete or partial response. Finally, 45/66 patients had stable disease per RECIST v1.1.

Comment: Looking at PKC inhibition with a new inhibitor. This article describes the results of a phase 1 study in 68 patients with UM with a second-generation, oral PKC inhibitor designed with improved pharmaceutical properties compared with earlier PKC inhibitors. They report that LXS196 has a highly selective kinase profile affording increased tolerability in preclinical studies, with activity restricted to MUM cell lines containing mutant GNAQ or GNA11 and no activity observed in skin-derived melanoma cell lines driven by mutant BRAF or NRAS. Liver metastases were present in 88% of the patients, and baseline lactate dehydrogenase was greater than the upper limit of normal in 56%. The majority of patients (86.8%) had received prior systemic therapy, including immunotherapy in 53%, and had not achieved a response to prior therapy. Exploratory analysis of RasGRP3 revealed it as a potential biomarker for predicting efficacy by PKC inhibition and warrants further investigation. They conclude that "targeting the PKC pathway in MUM should be explored and supports the continued evaluation of LXS196 in combination with other targeted therapies. LXS196, now known as darovasertib (IDE196), is currently being explored by Ideaya biosciences in doublet combinations with the MEK inhibitor binimetinib and the mesenchymal-epithelial transition factor inhibitor crizotinib (NCT03947385)."

Reference: Br J Cancer. 2023;128:1040-51
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.

Highly aneuploid non-small cell lung cancer shows enhanced responsiveness to concurrent radiation and immune checkpoint blockade

Authors: Spurr LF et al.

Summary: This comprehensive molecular analysis of a randomised phase I clinical trial of patients with non-small cell lung cancer aimed to show that concurrent treatment is superior to sequential treatment in augmenting local and distant tumour responses. The study notes that radiotherapy alone may decrease intertumoral cytotoxic T cell and adaptive immune signatures, whereas radiotherapy and immune checkpoint blockade upregulated immune pathways. In conclusion, the study promotes using aneuploidy as a potential biomarker and therapeutic target in personalising treatment for non-small cell lung cancer patients.

Comment: Although this study was on lung carcinoma, similar findings were reported in studies on melanoma and seem relevant to the effect of combining radiotherapy and immune checkpoint blockade. It infers that radiotherapy to the tumour kills existing effector cells, but this results in an influx of effector cells that destroy the tumour. Radiotherapy has to be concurrent and not before or after immune checkpoint blockade to see the effects. The second finding is that it is the aneuploid melanoma that responds and not those with a high tumour mutation burden. Aneuploidy in melanoma is associated with resistance to immune checkpoint blockade (see link here) and is common in late-stage melanoma (see additional link here). These results appear relevant to combining ICI and radiotherapy, particularly brain metastases.

Reference: Nat Cancer. 2022;3:1498-1512
Abstract

Efficacy and toxicity of adjuvant radiotherapy in recurrent melanoma after adjuvant immunotherapy

Authors: Bhave P et al.

Summary: This retrospective study identified 71 patients, 30 were BRAFV600E mutants, and 43 were stage IIIC at diagnosis. The results of this study included a median time to first recurrence of 7 months, with 24 patients receiving adjuvant radiotherapy and 47 patients who did not. The study identified three patients who developed a second recurrence at a median of 5 months. At first-recurrence adjuvant radiotherapy was associated with an improved recurrence-free survival rate, and there was no effect on the risk of distant recurrence or OS. The rate of locoregional relapse at second recurrence was lower in those who received adjuvant radiotherapy when compared to those who did not.

Comment: Radiotherapy is still effective in patients receiving ICI. This study was on 72 patients with a history of surgically resected stage III disease either after sentinel lymph node detection or clinically detected disease (with or without in transit disease) from Europe, Australia and the USA who were subjected to radiotherapy if they developed a locoregional recurrence during (69%) or after (31%) adjuvant radiotherapy. Most recurrences were in regional lymph nodes (75%). Recurrence in 47 patients not receiving radiotherapy was 55% compared to 8% in 7 patients receiving radiotherapy. Further subgroup analysis showed benefit in terms of relapse-free survival at the second recurrence. No benefit was seen in overall recurrence-free survival. The limitations of the study are described. It was concluded that adjuvant radiotherapy continues to provide control of locoregional disease in patients who develop resectable locoregionally recurrent disease during or after adjuvant immunotherapy. As seen in previous studies, adjuvant radiotherapy did not seem to impact distant metastasis-free survival or OS. Larger, prospective studies are required to validate these results. Note - new studies may explain why the benefit of radiotherapy is localised to treated sites as described in Spurr et al.

Reference: J Immunother Cancer. 2023;11:e006629
Abstract

Neoantigen-targeted CD8+ T cell responses with PD-1 blockade therapy

Authors: Puig-Saus C et al.

Summary: This study generated personalised libraries of neoantigen-human leukocyte antigen capture reagents to single-cell isolate the T cells and clone their T cell receptors (neo-T cell receptors). The neo-T cell receptor clonotypes were recurrently detected in the tumours and the blood over time. The study recorded four patients with no response to anti-PD-1 who also demonstrated neoantigen-specific T-cell responses that were not recurrently detected in sequential samples. The study concluded that for effective anti-PD-1 immunotherapy, polyclonal CD8+ T cells are needed in the tumour and blood for immunodominant mutations to be recurrently recognised over time.

Comment: Defining T cell responses against melanoma. This article is from a high-level study of neoantigens involved in responses to checkpoint therapy of 11 patients with metastatic melanoma. The take-home message is that clinical responses were associated with T cell clones recognising a limited number of antigens over repeated samples in both blood and tumours, whereas non-responses were associated with fewer T cell clones that were not repeated in repeat sampling. Transfer of the neo-T cell receptor into donor cells gave them specificity to autologous melanoma. Some of their conclusions were as follows-"The epitope immunodominance observed in the natural T cell responses induced against tumours and unleashed by anti-PD-1 indicates that, despite a large number of potentially immunogenic mutations, the immune system has evolved to target only a small number of immunodominant epitopes, similar to the T cell immune responses induced against viral infections. Even patients without a response to anti-PD-1 therapy have neoantigen-specific T cells that, when expressed in donor T cells, are able to mount an effector response against autologous tumour cell lines and could potentially be used for personalised adoptive cell transfer therapy."

Reference: Nature. 2023;615:697-704
Abstract