Melanoma Research Review™

Making Education Easy

Issue 47 - 2021

In this issue:

Abbreviations used in this issue:

CLND = completion lymph node dissection; **CPI** = checkpoint inhibitor; **DFS** = disease-free survival; **ICB** = immune checkpoint blockade; **ICI** = immune checkpoint inhibition; **KPS** = Karnofsky Performance Status; **LRC** = locoregional disease control; **MBM** = melanoma brain metastases; **MKP** = melanoma of known primary; **MUP** = melanoma of unknown primary; **NED** = no evidence of disease; **NPRD** = non-progressive residual disease; **OS** = overall survival; **pCR** = pathological complete response; **PFS** = progression-free survival; **PRD** = progressive residual disease; **RFS** = recurrence-free survival; **sAEs** = severe adverse events; **SNB** = sentinel lymph node biopsy; **SLN** = sentinel lymph node; **SRS** = stereotactic radiosurgery; **TIL** = tumour-infiltrating lymphocyte; **T-VEC** = talimogene laherparepvec; **WBRT** = whole brain radiation therapy.

Welcome to the 47th issue of Melanoma Research Review

Dear Readers,

This month's excerpts from the melanoma literature have several important findings relating to treatment of brain metastases. The Peter Mac study in particular provides scope for further advances in their treatment. The radiotherapy studies explore the best ways of combining ICI treatments with radiotherapy but good clinical trials are still needed. There is also a substantial study from the Melanoma institute of Australia surgeons showing the effectiveness of their craft in salvage treatment of melanoma failing standard treatments. Unknown primaries get a mention and an interesting study on plasminogen activator inhibitors may be worth following.

Best to all

Kind Regards,

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

Concurrent vs. sequential stereotactic radiosurgery and immune checkpoint inhibition in melanoma brain metastases: An international cooperative group study

Authors: Lehrer EJ, et al

Summary: The study cohort comprised of 254 patients with 1,322 melanoma brain metastases (MBM) treated across 10 institutions. The median follow-up was 12.9 months, BRAF mutation was present in 46.6% of patients, active extracranial disease was present in 70% of patients, and the median Karnofsky Performance Status (KPS) was 90. Stereotactic radiosurgery (SRS) and immune checkpoint inhibitors (ICI) were administered concurrently in 46.5% of patients. The authors reported radiation necrosis occurred in 14.2% of patients. Overall survival (OS) at 1-year was 77.4% versus 72.1%, and at 2-years was 63.1% vs. 46.1% (P = 0.048) for concurrent and sequential therapy, respectively. Local control at 1-year was 91.5% versus 84.6%, and at 2-years was 84.9% versus 75.6% (P = 0.12) for concurrent and sequential therapy, respectively. Total treated brain metastasis volume (OR: 1.11; P = 0.008) was associated with a higher risk of development of radiation necrosis; however, sequential therapy (OR: 0.97; P = 0.94), and V12 (OR: 0.98; P = 0.22) were not statistically significant. Sequential therapy (HR: 1.58; P = 0.03) and KPS (HR: 0.96; P < 0.001) were prognostic factors for OS, while the presence of extracranial disease (HR: 1.03; P = 0.90) and age (HR: 1.01; P = 0.25) were not prognostic.

Comment: This study on a large number of patients puts forward fairly convincing evidence that concurrent SRS and ICI was more effective than sequential SRS and ICI. Radiation necrosis was 14% in the concurrent and apparently not significant to that in the sequential. The full paper will be needed to examine this more fully.

Reference: Int J Radiat Biol. 2021 Nov;111(3):571-572

Abstract

Independent commentary by Peter Hersey, FRACP, D Phil

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.

Brain metastases in metastatic cutaneous melanoma: Patterns of care and clinical outcomes in the era of immunotherapy and targeted therapy

Authors: Chin RI, et al

Summary: This retrospective study included 123 patients with MBMs with 55% BRAF-mutant. Before MBM diagnosis, 30% had prior ICI and 18% had prior BRAF inhibitors. For the upfront MBM treatment, 64% received SRS, 27% received whole brain radiation therapy (WBRT), 9% received upfront ICI/BRAF inhibitors. The median follow-up was 8.7 months for all patients and 32 months for living patients. For patients who received upfront ICI/BRAF inhibitors, 73% underwent salvage SRS and 27% with salvage WBRT at a median of 5.7 months after MBM diagnosis. The researchers found fewer number of MBMs, higher KPS, and craniotomy were significant predictors of SRS use. For the upfront SRS cohort, treatment after 2016, BRAF-wild type status, and prior ICI exposure were associated with higher likelihood of concomitant ICI use with SRS. After adjusting for the number of MBMs, upfront SRS+ICI was associated with higher intracranial control than upfront SRS without ICI (HR: 0.43; P = 0.02). Furthermore, upfront SRS+ICI trended towards a higher intracranial control than upfront ICI/BRAF inhibitors with salvage radiation therapy (HR: 0.54; P = 0.07) after adjusting for the number of MBMs.

Comment: This study on 123 patients was not a randomised study but came to similar conclusions to the previous article by Lehrer EJ, et al - that concurrent SRS and immune checkpoint inhibitors (CPIs) gave better intracranial control than SRS followed by CPI or CPI followed by salvage SRS. Radiation necrosis was not discussed. Both studies illustrate the need for randomised trials on these issues.

Reference: Int J Radiat Biol. 2021 Nov;111(3):565-566
Abstract

Melanoma brain metastases that progress on BRAF-MEK inhibitors demonstrate resistance to ipilimumab-nivolumab that is associated with the Innate PD-1 Resistance Signature (IPRES)

Authors: Lau PKH, et al

Summary: The researchers investigated the utility of ipilimumab-nivolumab after MBM progression on BRAF-MEKi and explored mechanisms of resistance. The retrospective study included patients who received first (n = 25) and second/third line (n = 30) ipilimumab-nivolumab. Intracranial response rate was 75.0% (12/16), and median progression-free survival (PFS) was 41.6 months for first-line ipilimumab-nivolumab. Efficacy of second/third line ipilimumab-nivolumab after BRAF-MEKi progression was poor with an intracranial response rate of 4.8% (1/21) and median PFS of 1.3 months. The researchers performed whole transcriptome sequencing to identify mechanisms of drug resistance. They identified a set of 178 differentially expressed genes between naïve and MBMs with progression on BRAF-MEKi treatment. In addition, they identified enrichment of differentially expressed genes from the Innate Anti-PD1 Resistance Signature (IPRES).

Comment: This is a very impressive study with important treatment implications. The most significant finding was the poor efficacy of second-line ipilimumab-nivolumab following intracranial progression on first-line BRAF-MEKi with median PFS of less than 6 weeks and response rates of less than 5%. As summarised in their discussion the poor intracranial PFS with BRAF-MEKi suggest that ipilimumab-nivolumab rather than BRAF-MEKi should be given as first-line treatment for MBMs given the poor second-line activity of combination immunotherapy. Given intracranial response rates did not differ between BRAFV600 mutant and wildtype MBMs to ipilimumab-nivolumab in CHECKMATE 204, this infers PFS between the two molecular groups are likely to perform similarly.

The finding that the resistant MBM had the IPRES prompted the authors to suggest other agents that might be given in treatment of the resistant MBM such as lenvatinib with activity against VEGFR 1-3 or radiotherapy to increase adaptive responses.

Reference: J Immunother Cancer. 2021 Oct;9(10):e002995
Abstract

Multicenter, double-blind, placebo-controlled trial of seviprotimut-L polyvalent melanoma vaccine in patients with post-resection melanoma at high risk of recurrence

Authors: Slingluff CL, et al

Summary: The three-part multicentre, phase III trial assessed the efficacy of seviprotimut-L in patients with post-resection melanoma. This article reports the results of Part B1. Patients (n = 347) with stage IIB-III cutaneous melanoma after resection were randomised 2:1 to seviprotimut-L 40 mcg or placebo. For the primary intent-to-treat endpoint of recurrence-free survival (RFS), the estimated HR was 0.881. The authors noted the estimated HRs were not uniform over the stage randomised strata, with HRs for stages IIB/IIC, IIIA, IIIB/IIIC of 0.67, 0.72, and 1.19, respectively. In the stage IIB/IIC stratum, the effect on RFS was greatest for patients <60 years old (HR = 0.324) and those with ulcerated primary melanomas (HR = 0.493). They also noted treatment-emergent adverse events were similar for seviprotimut-L and placebo.

Comment: Cancer vaccines offer promise to prevent melanoma recurrence by enhancing melanoma-specific immune responses. However, no cancer vaccine has yet proven effective for prolonging RFS or survival after melanoma resection. Seviprotimut-L (formerly POL-103A) was developed based on data from a prototype polyvalent melanoma vaccine comprised of shed antigens from four melanoma cell lines, administered with alum and developed by Bystryn et al. Part B1 of the trial was to identify a signal of clinical efficacy, prior to initiating Part B2 which would be the definitive evaluation of clinical efficacy.

The subgroup analyses in this report showed a trend for prolonged RFS and prolonged OS in stage IIB/IIC patients in those who received seviprotimut-L. The reasons for these different results based on stage are not clear. These findings supported limiting the design of the future Part B2 trial to patients with stage IIB/IIC melanoma, who are those for whom no systemic adjuvant therapy is currently recommended. They also identified young age and ulcerated melanoma as having favourable responses and speculated that patients over age 60 may benefit by combining vaccine and PD-1 blockade.

Reference: Immunother Cancer 2021. Oct;9(10):e003272
Abstract

RIPK3 and AXL expression study in primary cutaneous melanoma unmasks AXL as predictor of sentinel node metastasis: A pilot study

Authors: Nicolè L, et al

Summary: The investigators evaluated the clinical impact of the expression of AXL and RIPK3 in 108 primary cutaneous malignant melanomas. Immunoreaction in tumour cells was detected in 30 cases (28%) and in 17 cases (16%) for AXL and RIPK3, respectively. Metastases in the sentinel lymph nodes (SLNs) were detected in 14 out of 61 patients, and these were associated with AXL-positive immunoreactivity in the primary tumour ($P < 0.0001$). No association between AXL and tumour-infiltrating lymphocytes (TILs) was found. RIPK3 immunoreactivity was not associated with any variables. Breslow and AXL-positive immunoreactivity were predictors for positive sentinel node status.

Comment: Sentinel lymph node biopsy (SNB) is important for staging of melanoma and access to adjuvant treatments. The incidence of positive nodes can be predicted to some extent by characteristics of the primary melanoma such as tumour thickness, ulceration and mitotic rate. Algorithms using these characteristics such as that published by the Melanoma Institute of Australia (MIA) (*Lo SN et al. Improved Risk Prediction Calculator for Sentinel Node Positivity in Patients With Melanoma: The Melanoma Institute Australia Nomogram. J Clin Oncol. 2020 Aug 20;38(24):2719-2727*) improve the accuracy of detection and reduce the number of unnecessary SNBs. Similar results were obtained by use of a 31 gene expression profile (*Whitman ED et al. Integrating 31-Gene Expression Profiling With Clinicopathologic Features to Optimize Cutaneous Melanoma Sentinel Lymph Node Metastasis Prediction. JCO Precis Oncol. 2021 Sep 13;5*). The present study was based on immunochemical analysis of AXL expression in 61 cases; 14 had proven lymph node metastases. Only 1 positive SLN had negative staining for AXL and when positivity for AXL was combined with melanoma thickness they reported very low false positivity and ROC curve prediction of 0.96 under the curve. They were aware of the limitations of the study such as very low patient numbers and its retrospective nature. Presumably the main reason for its publication was the interesting biology of AXL especially in relation to metastasis.

Reference: Front in Oncol 21. October 2021; Online ahead of print
Abstract

c-Kit inhibitors for unresectable or metastatic mucosal, acral or chronically sun-damaged melanoma: A systematic review and one-arm meta-analysis

Authors: Steeb T, et al

Summary: The authors reviewed the efficacy and safety of c-Kit inhibitors for unresectable or metastatic mucosal, acral or chronically sun-damaged melanoma. The meta-analysis included 19 single-arm studies with 601 patients. The studies investigated imatinib (n = 8), nilotinib (n = 7), dasatinib (n = 3) and sunitinib (n = 1). They reported the pooled objective response rate (ORR) for all inhibitors was 15%. Subgroup analysis revealed the highest ORR (20%) for nilotinib. The ORR for mucosal melanoma was 14% and 22% for acral lentiginous melanoma. At least one severe adverse event (sAE) was reported in 42% of patients.

Comment: This was a well conducted large review of treatment with c-KIT inhibitors. The authors emphasised the low ORR of 13% and the relatively high toxicity with 42% having at least one sAE. The median OS ranged from 5.2-6.9 months. They compared this data with results from immune checkpoint blockade (ICB) in major trials that achieved 6.4 months for ipilimumab alone 11.3 months for anti-PD1 alone and up to 20.7 months for the combination. They qualified the poor results from c-KIT inhibitors by saying that early studies included all mutations rather than just mutations in exon 11 and 13 known to be more responsive. The article refers to a number of phase I/II trials combining c-KITi and ICB. They conclude – "Overall, our results highlight that c-Kit inhibitors represent valuable treatment options for patients with KIT mutations. Furthermore, high-quality research is urgently needed to investigate the combination of specific targeting with immunotherapy".

Reference: Eur J Cancer 2021. Nov;157:348-357
Abstract

Inhibition of PAI-1 blocks PD-L1 endocytosis and improves the response of melanoma cells to immune checkpoint blockade

Authors: Tseng Y, et al

Summary: The researchers demonstrated that cell surface retention of PD-L1 is inversely correlated with plasminogen activator inhibitor-1 (PAI-1) expression in vitro, in vivo, and in clinical specimens. In addition, extracellular PAI-1 induced the internalisation of surface-expressed PD-L1 by triggering clathrin-mediated endocytosis. The endocytosed PD-L1 was transported to lysosomes for degradation by endolysosomal systems, resulting in the reduction of surface PD-L1. They noted inhibition of PAI-1 by pharmacological inhibitor with tiplaxtinin led to elevated PD-L1 expression on the plasma membrane, both in vitro and in vivo. Targeting PAI-1 by tiplaxtinin treatment synergised with anti-PD-L1 ICB therapy in a syngeneic murine model of melanoma.

Comment: This study shows that PAI-1 leads to internalisation and degradation of PD-L1 which appears to be a previously unreported mechanism of regulation of PD-L1 levels at the plasma membrane. Given that the therapeutic efficacy of immune checkpoint blockade–based immunotherapy relies on the expression of PD-L1 in melanoma cells their findings that an inhibitor of PAI-1 increases PD-L1 may have significance in increasing treatment responses to anti-PD1. In addition, their murine model showed that the PAI-1 inhibitor alone had anti-tumour activity perhaps by effects on tumour vasculature. They suggest the combination of PAI-1 inhibition and immunotherapy with anti-PD-L1 as a promising strategy for overcoming resistance to anti-PD-L1 therapy in treating melanoma.

Reference: J Invest Dermatol. 2021 Nov;141(11):2690-2698.e6
Abstract

Survival outcomes of salvage metastasectomy after failure of modern-era systemic therapy for melanoma

Authors: Li AT, et al

Summary: Stage 3 or 4 melanoma patients (n = 190) with extracranial disease progression after at least 4 weeks of systemic treatment were categorised as resected to no evidence of disease (NED), non-progressive residual disease (NPRD), or progressive residual disease (PRD). Among all the patients, the 5-year OS from metastatectomy was 52%, the 3-year PFS was 21%, and the 5-year locoregional disease control (LRC) was 61%. After resection to NED, NPRD, and PRD, the 5-year OS values were 69%, 62% and 8%, respectively. It was noted fewer lines of preoperative therapy, use of preoperative immunotherapy, and resection to NED were predictors of improved OS. After resection to NED, NPRD, and PRD, the 3-year PFS values were 23%, 24% and 10%, and the 5-year LRC values were 61%, 72% and 34%, respectively.

Comment: This is a large well conducted retrospective study on 190 patients that confirms that salvage metastasectomy after failure of modern systemic therapy for melanoma is safe and associated with durable survival and LRC for carefully selected patients. The results are consistent with similar studies although survival outcomes were superior to many of the other studies. They suggest this may be due to a policy of stringent patient selection for metastasectomy after discussion at multidisciplinary team meetings, even though there were no prospectively defined indications or contraindications. Given these results some care may be needed in deciding whether surgery is preferable to trials with newer treatments targeting melanoma that has failed standard treatments.

Reference: Ann Surg Oncol 2021. Oct;28(11):6109-6123
Abstract

Surveillance of sentinel node-positive melanoma patients who receive adjuvant therapy without undergoing completion lymph node dissection

Authors: Broman KK, et al

Summary: This retrospective study evaluated the association between adjuvant treatment and location of first recurrence (locoregional, nodal, distant, or multisite) in a cohort of SLN-positive melanoma patients managed with nodal surveillance. Among 177 nodal surveillance patients, 66 (37%) received adjuvant therapy. Median follow-up was 24 months, during which 48 patients (27%) recurred. The researchers found adjuvant treatment did not alter patterns of initial recurrence ($P = 0.76$). Adjuvant therapy recipients more often had both nodal ultrasound and cross-sectional imaging surveillance ($P < 0.01$). Among 13 isolated nodal recurrences, 85% were within the first year and 85% were detected by examination and/or ultrasound. They noted increasing surveillance intensity was not associated with recurrence detection rates but increased overall cost and cost per detected recurrence.

Comment: These findings have implications for how surveillance is performed for SLN-positive patients receiving adjuvant treatment without undergoing completion lymph node dissection (CLND). SLN-positive melanoma patients managed with nodal surveillance and adjuvant therapy had comparable patterns of recurrence, including isolated nodal relapse, supporting use of similar surveillance strategies. Most nodal basin recurrences occurred within the first year and were initially detected by clinical assessment and/or ultrasound, even when serial cross-sectional imaging was performed. The relative cost of high-intensity surveillance was more than five times greater than low-intensity surveillance and even if earlier lesions were detected the treatment outcomes were unlikely to justify the added costs.

Reference: Ann Surg Oncol. 2021 Nov;28(12):6978-6985
Abstract

Clinical outcome of patients with metastatic melanoma of unknown primary in the era of novel therapy

Authors: Verver D, et al

Summary: This study used Dutch registry data to compare the characteristics and OS of patients with advanced and metastatic melanoma of unknown primary (MUP) and melanoma of known primary (MKP). The study cohort had a diagnosis of stage IIIc unresectable or IV cutaneous MKP (n = 2,321) or MUP (n = 385) and treatment with ICI and/or targeted therapy. In comparative analysis, MUP patients more often presented with advanced and metastatic disease at primary diagnosis with poorer performance status, higher LDH, and CNS metastases. In crude analysis, median OS of cutaneous MKP or MUP patients was 12 months and 14 months, respectively ($P = 0.278$). In adjusted analysis, OS in MUP patients was superior (HR: 0.70; $P < 0.001$). As compared to patients with advanced and metastatic cutaneous MKP, MUP patients have superior survival in adjusted analysis, but usually present with poorer prognostic characteristics. In crude analysis, OS was comparable indicating that patients with MUP benefit at least equally from treatment with novel therapies.

Comment: Presentation with metastatic melanoma and no history of primary melanoma is relatively common (14% in this Dutch series). It is generally thought this may be due to immune responses against the primary and if so such patients may have better outcomes when they develop overt metastatic disease. This appeared to be born out by the present study in that even though the disease at presentation was more advanced, patients with MUP had better OS and responded better to anti-PD1 treatment.

Reference: Cancer Immunol Immunother. 2021 Nov;70(11):3123-3135
Abstract

Claim CPD/CME points Click here for more info.

Neoadjuvant talimogene laherparepvec plus surgery versus surgery alone for resectable stage IIIB–IVM1a melanoma: A randomized, open-label, phase 2 trial

Authors: Dummer R, et al

Summary: The open-label, phase 2 trial randomised patients with resectable stage IIIB-IVM1a melanoma to receive talimogene laherparepvec (T-VEC) followed by surgery (n = 76) or surgery alone (n = 74). The authors reported 2-year RFS was 29.5% in the T-VEC group and 16.5% in the surgery alone group (overall HR: 0.75). The 2-year OS was 88.9% for the T-VEC group and 77.4% for surgery alone (overall HR: 0.49). The RFS and OS differences between arms persisted at 3 years. In the T-VEC group 17.1% achieved a pathological complete response (pCR). Increased CD8+ density correlated with clinical outcomes in an exploratory analysis. They noted adverse events were consistent with previous reports for T-VEC.

Comment: This study was commenced before approval of ICIs or BRAF inhibitors for adjuvant treatments of melanoma so at that time the study was quite novel which probably accounts for why it was published in Nature. The treatment was given into lymph nodes or subcutaneous or dermal metastases over a 3 month period before surgery and hence was more complex than giving anti-PD1 or BRAF inhibitors. The control group had surgery within 6 weeks from randomisation so that there was a longer period for the treatment group to develop recurrences before surgery. The results were inferior to the neoadjuvant studies with the standard agents. They conclude by saying "Although the results of our trial are not sufficient to justify routine use of neoadjuvant T-VEC outside the protocol setting at this time, they support further investigation of T-VEC in the neoadjuvant setting for resectable high-risk melanoma".

Reference: Nat Med. 2021 Oct;27(10):1789-1796
Abstract

Talimogene laherparepvec (T-VEC) for the treatment of advanced locoregional melanoma after failure of immunotherapy: An international multi-institutional experience

Authors: Carr MJ, et al

Summary: The retrospective study reviewed 112 stage IIIB-IV melanoma patients treated with T-VEC after failure of systemic immunotherapy. Before T-VEC, 57% patients received one systemic immunotherapy regimen, 42% received two or more, with most patients (n = 74, 66%) receiving T-VEC sequential to immunotherapy. Most were stage 3C (n = 51, 46%) at T-VEC initiation, 29 (26%) received injections to nodal disease. Over median follow-up of 14 months, in-field response at final T-VEC injection was 37% complete response, 14% partial response. T-VEC initiation sequentially or concurrently did not significantly affect in-field response (P = 0.26). Median in-field PFS was 15 months. Median overall disease-free survival (DFS) after complete response was 32 months.

Comment: This study demonstrated that intralesional T-VEC for unresectable, metastatic melanoma is an effective and safe treatment option for patients with disease progression on ICIs. In-field ORR of 51% was observed over a median follow-up time of 14 months but patients with stage IV disease derived less overall response from T-VEC injection after ICI failure and those with lower burden of disease derived better overall responses. Furthermore, this study demonstrated that response did not differ significantly whether T-VEC therapy was initiated sequentially after discontinuation of ICI or added on concurrently. ORR remained similar between these two defined treatment groups (sequential 52% vs. concurrent 50%). This study is subject to the inherent limitations of retrospective studies, including selection bias, incomplete medical records and nonuniform reporting of treatment responses given the number of institutions involved. Nonetheless, this study builds on prior research supporting the synergistic effect of intratumoural T-VEC and ICI. We demonstrated that T-VEC is effective not only in combination with ICI, but also after failure of these agents either added in conjunction to or after discontinuation of systemic treatment.

Reference: Ann Surg Oncol. 2021 Oct 14. Online ahead of print.
Abstract

Australian Research Review subscribers can claim CPD/CME points for time spent reading our reviews from a wide range of local medical and nursing colleges. Find out more on our CPD page.

Research Reviews are prepared with an independent commentary from relevant specialists. To become a reviewer please email geoff@researchreview.com.au.
Research Review Australia Pty Ltd is an independent Australian publisher. Research Review receives funding from a variety of sources including Government depts., health product companies, insurers and other organisations with an interest in health. Journal content is created independently of sponsor companies with assistance from leading local specialists. **Privacy Policy:** Research Review will record your email details on a secure database and will not release them to anyone without your prior approval. Research Review and you have the right to inspect, update or delete your details at any time. **Disclaimer:** This publication is not intended as a replacement for regular medical education but to assist in the process. The reviews are a summarised interpretation of the published study and reflect the opinion of the writer rather than those of the research group or scientific journal. It is suggested readers review the full trial data before forming a final conclusion on its merits.
Research Review publications are intended for Australian health professionals.