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In this issue:

Abbreviations used in this issue:

cirAE = cutaneous immune-related adverse events; **ICI** = immune checkpoint inhibitor; **IHP** = isolated hepatic perfusion; **MDSC** = melanoma-derived suppressor cells; **PD-1** = programmed death ligand; **TFS** = treatment-free survival.

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Welcome to the 61st issue of Melanoma Research Review

We begin this issue with a randomised controlled trial on isolated hepatic perfusion for patients with isolated uveal melanoma liver metastasis. This is followed by a retrospective analysis of ten patients who relapsed after elective treatment discontinuation with metastatic cutaneous melanoma highlighted the significant role loc-regional therapies play in relapsed patients. An interesting study to look out for in this issue is a comparison of front-line surgery to regular front-line treatment for patients in need of lymph node dissections showing compatibility between high-risk stage III melanoma and patients who underwent lymph node dissections post-neoadjuvant systemic immunotherapies. We conclude this month's issue with a multicentre Dermatologic Cooperative Oncology Group study on the significance of immune checkpoint inhibitors (ICI) and their relationship with *NRAS* mutational status in advanced melanoma.

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

Kind Regards,

Dr Michael Henderson
michael.henderson@researchreview.com.au

Isolated hepatic perfusion with melphalan for patients with isolated uveal melanoma liver metastases

Authors: Bagge RO et al.

Summary: This multicentre, randomised, open-label, phase III trial included 93 randomly assigned patients to either isolated hepatic perfusion (IHP) or control. In the control group, patients had previously received chemotherapy (49%), immune checkpoint inhibitor (ICI) therapy (39%), and locoregional treatment (9%) other than IHP. The overall response rates were 40% versus 4.5% in the IHP and control groups. The median hepatic progression-free survival was 9.1 months compared to 3.3 months for IHP and control groups, respectively, and the median progression-free survival overall was 7.4 months versus 3.3 months, respectively. The researchers acknowledged 11 treatment-related serious adverse events in the IHP group, compared to 7 in the controls.

Comment: Uveal melanoma is characterised by a high rate of liver metastasis (50%) and, despite recent advances, remains a therapeutic challenge. The response rate to ICI therapy is disappointingly low (15%), and the results from a recent randomised trial of the novel agent tebentafusp demonstrated only modest improvement (overall survival 22 versus 16 months). Comparable results from regional therapies, including surgery and radiotherapy, are only found in highly selected subgroups. The current study randomised patients with treatment-naive isolated liver metastases to either isolated hepatic perfusion or investigators' choice, mostly either chemotherapy or ICI therapy. Overall survival has not been reported at this stage, but the objective response rates and progression-free survival are significantly better in the IHP arm (medium follow-up 18 months). Adverse events were seen more commonly in the IHP arm (20% versus 7%), including one patient in the IHP arm who died as a consequence of the surgery. The performance of IHP is a major undertaking and should be limited to major centres. How this procedure may fit in with current systemic therapy options is undefined.

Reference: J Clin Oncol. 2023;41:3042-50
Abstract

Independent commentary by Professor Michael Henderson

Michael A Henderson is Professor of surgery in the University of Melbourne and surgeon in the multidisciplinary Melanoma and Skin Service at the Peter MacCallum Cancer Centre in Melbourne. He is a graduate of the University of Melbourne and after obtaining a Fellowship of the Royal Australasian College of Surgeons spent 2 1/2 years undertaking a fellowship in surgical oncology at the University of Texas MD Anderson Cancer Centre. His clinical practice is confined to surgical oncology. His major clinical interests are in the management of patients with melanoma and maintains an active clinical and translational research interest in melanoma. He led a major international multicentre study of adjuvant radiotherapy after link for melanoma and is currently the principal investigator of a multicentre international trial of margins of excision of intermediate and thick melanoma (MELMART).

Retreatment of patients with metastatic cutaneous melanoma who relapse after elective checkpoint inhibitor discontinuation after a complete remission

Authors: Sadrolashrafi K et al.

Summary: This retrospective analysis included ten patients who relapsed post-elective treatment discontinuation after a radiologically confirmed remission. The researchers found an initial complete response rate of 20% following retreatment. With a median follow-up of 26 months, the study found four additional patients who converted to a second remission, all of whom discontinued therapy again. The study noted three patients who died of metastatic melanoma, whilst another has again recommenced salvage therapies. Sixty per cent of the patients experienced grades 2-3 retreatment-related toxicity. There were no adverse event-related hospitalisations or fatalities.

Comment: This is a small but interesting report which explores the fate of patients finishing immune checkpoint inhibitor therapy after complete remission. They identified ten patients in their institution represented with metastatic disease at a median of 24 months after cessation of ICI therapy. Only two responded to the re-introduction of ICI, but in a novel finding, a further four were rendered and remained disease-free after initially failing reintroduction of ICI with the use of concurrent tBRAF/MEKi therapy, surgery or targeted radiotherapy. The six patients remain disease free at a median follow-up of 26 months. The significance of this study is the role of loc-regional therapies in relapsed patients.

Reference: Oncolcogist. 2023;28:e270-5
Abstract

Surgical outcomes of lymph node dissections for stage III melanoma after neoadjuvant systemic therapy are not inferior to upfront surgery

Authors: Zijlker LP et al.

Summary: This retrospective cohort study included high-risk stage III melanoma patients treated with neoadjuvant anti-PD-1 and anti-CLTA4 therapy in the OpACIN and OpACIN-neo trials. Of the 120 patients, 44 received neoadjuvant systemic therapy, and 76 underwent upfront therapy. The study found no significant difference in the overall rate of postoperative complications or post-operative morbidity between either group. Regarding postoperative morbidity, the overall rate for seroma was 56.8% versus 57.9%, and for lymphoedema, 22.7% versus 13.2% for neoadjuvant systemic therapy and upfront surgery, respectively. The study found no significant differences towards a longer duration of surgery post-neoadjuvant immunotherapy. The researchers concluded that there was compatibility between high-risk stage III melanoma and patients who underwent lymph node dissections post-neoadjuvant systemic immunotherapies.

Comment: One of the major concerns when considering the role for neo-adjuvant therapy for patients with regional lymph node relapse has been the potential for poorer surgical outcomes, possibly due to impaired wound healing, sepsis or operative morbidity related to treatment-related fibrosis. Anecdotally at least one-third of lymphadenectomy procedures after ICI can be technically demanding predominantly due to extensive tissue fibrosis ablating normal tissue planes. This study found no difference in surgical outcomes but noted slightly longer operative times, indicating that from a surgical perspective, neo-adjuvant therapy is safe, but surgeons need to be prepared for increased operative difficulty.

Reference: Eur J Cancer. 2023;185:131-8
Abstract

Nivolumab and relatlimab in patients with advanced melanoma that had progressed on anti–programmed death-1/programmed death ligand 1 therapy

Authors: Ascierto PA et al.

Summary: This phase I/IIa, open-label RELATIVITY-020 trial part D, aimed to assess the efficacy and safety of nivolumab and relatimab in advanced melanoma. This trial included 518 patients who received a combination of nivolumab and relatimab. The study found that responses were enriched in patients with tumours expressing PD-1 or lymphocyte activation gene 3 (LAG-3). From the 354 patients included in D1, the median duration of response was not achieved, the 6-month progression-free survival was 2.1 months, and there were more instances of treatment-related adverse events than in D2. D2 included 164 patients with a median duration to response of 12.8 months, a progression-free survival rate of 27.7% and the incidence of treatment-related adverse events was 12.8%.

Comment: RELATIVITY047 confirmed the safety and effectiveness of relatinib with nivolumab over single-agent nivolumab. The current study RELATIVITY020 is a dose escalation and cohort expansion trial that confirms the safety and effectiveness of a combination of relatinib and nivolumab in patients with advanced disease who had progressed on prior anti-PD-1 therapy (047 enrolled anti-PD-1 naive patients). The overall response rate was just over 10%, and these patients had durable ongoing responses. Response rates were higher in patients with tumours expressing PD-L1 or LAG-3, but their absence did not preclude a response similarly for controlled brain mets, raised LDH or prior anti-CLTA-4 therapy. These results are consistent with the original RELATIVITY 047 study, but the role of anti-LAG-3 therapy remains under evaluation.

Reference: J Clin Oncol. 2023;41:2724-35
Abstract

Influence of melanoma type on incidence and downstream implications of cutaneous immune-related adverse events in the setting of immune checkpoint inhibitor therapy

Authors: Nguyen N et al.

Summary: This retrospective, multi-institutional cohort study included multivariate time-series regressions to utilise the relationship between types of melanoma and cutaneous immune-related adverse events (cirAE) and overall survival. The study included 747 patients who received ICI therapy, 236 of whom developed a cirAE. Patients who were least likely to develop cirAEs were those with acral melanoma compared to nonacral melanoma. By melanoma, those associated with increased mortality were diagnosed with acral, mucosal and uveal melanomas, compared to those with cirAEs. This study concluded that the presence of cirAEs was associated with better survival. The lower incidence of cirAEs may be a marker of immunotherapy response.

Comment: CirAEs are common in patients receiving ICI therapy and vary from pruritus through to extensive pemphigoid reactions. This study also confirms the likelihood that the development of cirAEs is associated with increased responses and survival. cirAEs were less common in patients with noncutaneous melanomas, specifically acral lentiginous and mucosal melanoma. Unlike previous studies, which only investigated vitiligo, this study confirmed that any cirAEs are associated with improved outcomes. All adverse events including cirAEs, were more common in patients receiving combination ICI therapy. This is a small retrospective study, and while this data is of interest and confirms other small studies, it provides advice to clinicians counselling patients with cirAEs.

Reference: J Am Acad Dermatol. 2023;88:1308-16
Abstract

Comparative analysis of adjuvant therapy for stage III BRAF-mut melanoma

Authors: Zhong J et al.

Summary: This real-world retrospective study from China included patients with radical surgery and stage III melanoma harbouring BRAF V600 mutation. The study included 93 patients, 25 who received adjuvant anti-PD-1 immunotherapy, 25 receiving adjuvant dabrafenib plus trametinib, 23 receiving vemurafenib and 20 patients with observation-only. The median relapse-free survival time was not reached in the combination adjuvant therapy group, 15 months in the vemurafenib group, 15 months in the PD-1 group and ten months in the observation-only group. Anti-PD-1 monotherapy showed significantly worse relapse control when compared to dabrafenib plus trametinib and all three therapy groups tended to benefit from relapse-free survival.

Comment: This study involved comparing the genomic landscape of tumours in patients who developed ICI or BRAF-MEKi resistance before and after the development of resistance. ICI-resistant tumours were enriched for immune evasive processes, while BRAF MEKi-resistant tumours demonstrated therapy-related damaged or impaired DNA repair. Organ-specific metastatic signatures for several sites were identified. These and other multiple sites of genomic instability associated with drug resistance indicate avenues for further investigation and may have therapeutic implications.

Reference: Cancer Med. 2023;12:11475-82
Abstract

Treatment-free survival after nivolumab vs pembrolizumab vs nivolumab-ipilimumab for advanced melanoma

Authors: Gupta M et al.

Summary: This multicentre cohort study included participants with advanced melanoma who received first-line ICI therapy. Patients were exposed to standard-of-care or first-line ICI therapies, including nivolumab, pembrolizumab or combination ipilimumab-nivolumab. The study included 316 patients with a mean age of 66 years. The restricted mean treatment-free survival (TFS) rate was longer in the combination group compared to nivolumab single-agent and pembrolizumab single-agent. After a 36-month follow-up interval, patients treated with nivolumab-ipilimumab spent 34.4% of their time not receiving systemic anticancer treatments, whereas, for the single-agent therapies, the rate of not receiving anti-cancer treatments was 30.8% of the pembrolizumab and 24.7% of the nivolumab treatment groups.

Comment: This is a small study (n=316) of patients with advanced melanoma treated with single-agent anti-PD-1 or combined ipilimumab with nivolumab. The novel aspect of this study is the endpoint used, TFS, which is strongly associated with quality of life. Patients receiving combination therapy had longer TFS but were more likely to be younger, have an actionable BRAF mutation and have lower ECOG scores. TFS was higher in the combination therapy group, as might be expected. No patient-reported outcome measures were reported in this study, limiting the data's utility. For example, the higher rates of response in the combined ICI group may be associated with a shorter duration of initial therapy. Nevertheless, TFS is a useful and objective way of assessing the acceptability of treatment.

Reference: JAMA Netw Open. 2023;6:e2319607
Abstract

Early decrease of blood myeloid-derived suppressor cells during checkpoint inhibition is a favorable biomarker in metastatic melanoma

Authors: Gaiβler A et al.

Summary: This study aimed to investigate the potential cellular biomarkers from clinical routine blood counts in patients with stage IV M1c melanoma before and during immune checkpoint blockade therapy. Elevated baseline frequencies of monocytic MDSCs predicted shorter overall survival and progression-free survival. The study also identified a group of patients with highly elevated monocytic MDSCs with a longer overall survival similar to patients with low baseline monocytic MDSCs. In conclusion, the utility of MDSC is paramount, given by patients with longer monocytic MDSC frequencies who exhibited a skewed baseline distribution of certain immune cells.

Comment: At the present time, serum lactate dehydrogenase is the only validated biomarker in patients with advanced melanoma, although there has been considerable interest in immune parameters predicting survival and response to ICI therapy. Several groups have reported poorer outcomes in patients with increased levels of peripheral myeloid-derived suppressor cells, but the novel finding of this study is that patients in whom the levels fell with the initiation of ICI therapy had outcomes similar to patients with low levels i.e. improved outcomes. The patients with high levels of MDSC, which remained elevated, demonstrated a pattern of immune cells consistent with impaired cancer immunosurveillance. The implications for clinical practice at present are limited.

Reference: J Immunother Cancer. 2023;11:e006802
Abstract

Immune checkpoint inhibition in patients with *NRAS* mutated and *NRAS* wild type melanoma

Authors: Zaremba A

Summary: This multicentre Dermatologic Cooperative Oncology Group study included 637 patients from the prospective skin cancer registry ADOREG. The researchers included 637 BRAF wild-type patients, 310 of whom had an *NRAS* mutation. They found no significant differences in progression-free survival and overall survival for PD-1 monotherapy in *NRAS* mutation patients and 41% in NRAS-wild-type mutations. The two-year overall survival for *NRAS* mutation and anti-PD-1 plus anti-CTLA4 therapy was 54% and 57%, respectively. The overall response rate to anti-PD-1 therapy was 26% for *NRAS* mutation patients compared to 35% for *NRAS*-wild-type mutation patients. The study identified that 82 patients had programmed-death ligand-1 expressions, which did not correlate with *NRAS* mutational status.

Comment: Approximately one-quarter of patients with advanced melanoma have tumours with mutated NRAS. The implications for outcome and response to treatment with ICI are controversial, but in this study, no difference was found between *NRAS* mutated and wild-type tumours. This study specifically excluded patients with combined *NRAS* and BRAF mutations. In this relatively large study, *NRAS* mutated tumours were more likely to be located on the lower limbs and have a nodular subtype, and in a small group (n=82), expression of tumour PDI-1 was not found to have any significant implications contrary to previous reports. This study supports current ICI treatment practices.

Reference: Eur J Cancer. 2023;188:140-151
Abstract