Melanoma Research Review™

Making Education Easy

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In this issue:

Abbreviations used in this issue:

AI = artificial intelligence; **CI** = confidence interval; **CR** = complete response; **CTLA4** = cytotoxic T-lymphocyte associated protein 4; **H&E** = haematoxylin and eosin; **ICI** = immune checkpoint inhibitor; **IFN** = interferon; **ITIM** = immunoreceptor tyrosine-based inhibitory motif; **ITT** = intention to treat; **LAG3** = Lymphocyte-Activation Gene 3; **LDH** = lactate dehydrogenase; **MPR** = major pathological response; **ORR** = objective response rate; **OS** = overall survival; **PD-1** = programmed cell death protein 1; **PD-L1** = programmed cell death ligand 1; **PFS** = progression-free survival; **PR** = partial response; **RFS** = recurrence-free survival; **SD** = stable disease; **SRT** = stereotactic radiotherapy; **TRAE** = treatment-related adverse event.

Welcome to the 70th issue of Melanoma Research Review

This month's melanoma research review has a strong focus on treatment of the 30-40% of patients who are resistant to immune checkpoint inhibitors and of biomarkers that can be used to identify and select such patients. Several intralesional studies on Toll receptor agonists and intralesional modified herpes virus get a mention. The latter has certainly attracted some interest, but needs the rigour of randomised studies for further evaluation. A number of bispecific antibodies that target T cells to tumour antigens are of interest and the present review gives a long-term follow-up on the first of these that targeted gp100 on uveal melanoma cells. Biomarker analysis to select and tailor treatment to individual patients has taken a step forward with multiomic studies from researchers at the university of Zurich. Several lesser retrospective biomarker studies are also reported on a number of trials that provide insight into the action of the anti-LAG3 relatlimab. A challenging idea is that deep AI analysis of H&E-stained slides might provide substantial information in the management of melanoma.

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

Kind Regards,

Professor Peter Hersey

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Combined immunotherapy with nivolumab and ipilimumab with and without sequential or concomitant stereotactic radiotherapy in patients with melanoma brain metastasis: An international retrospective study

Authors: Mandalà M et al.

Summary: This retrospective study examined outcomes of 453 patients with melanoma brain metastases receiving ipilimumab plus nivolumab alone (n=190) or with concomitant (n=107) or sequential (n=156) SRT. Multivariate analysis suggested that on baseline measures, OS was associated with line of treatment (>1st vs 1st; HR 2.60; 95% CI 1.93–3.50), sequential (HR 0.45; 95% CI 0.32–0.64) or concomitant SRT (HR 0.48; 95% CI 0.33–0.69) versus no radiotherapy, use of steroids (HR 1.56; 95% CI 1.17–2.08), age (HR 1.01; 95% CI 1.00–1.02) and number of brain metastases (≥3 vs 1 HR 1.55; 95% CI 1.11–2.17; 2 vs 1 HR 1.53; 95% CI 1.02–2.31). There was no difference between concomitant and sequential SRT. After a median 29-month follow-up, median OS was 17.8 months; in sequential SRT recipients OS was 27.3 months (95% CI 15.3–39.4) and in concomitant SRT recipients it was 22.2 months (95% CI 12.7–31.7). Radio-necrosis incidence was 10.3%.

Comment: Although this is a retrospective study, its strength is data from large patient numbers (453) from 18 centres experienced in treatment of brain metastases. All patients were treated with ipilimumab plus nivolumab and included data on timing of SRT for all patients, and number and size of brain metastases associated with outcome. Its value is in providing strong evidence for long-term benefit from adding SRT to ipilimumab plus nivolumab treatment regardless of the timing and the number of brain metastases. They qualified their results concerning radio-necrosis as collection of these data was apparently sometimes not undertaken. It remains sobering that the best survivals were approximately 68%, 48% and 36% at 1, 2, and 3 years. Having provided and discussed the results, they emphasised that prospective, randomised trials, such as the ABC-X study and the ETOP 19–21 USZ-STRIKE study were warranted to validate these findings and optimise treatment protocols.

Reference: Eur J Cancer. 2025:225:115567

Abstract

Independent commentary by Professor Peter Hersey

Peter Hersey is a past Professor of Immuno Oncology at the University of Sydney and is a 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 recognised 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 an NHMRC program grant on melanoma.

Feasibility of multiomics tumor profiling for guiding treatment of melanoma

Authors: Miglino N et al.

Summary: This analysis of data from the prospective, multicentre, observational Tumor Profiler (TuPro) precision oncology project examined the feasibility of using multiomics and functional technologies to inform treatment decisions for 116 patients based on 9 technologies analysing 126 samples. A molecular tumour board selected 54 markers to inform treatment recommendations with TuPro-based data judged useful in informing recommendations in 75% of cases. The objective response rate in 37 difficult-to-treat palliative patients receiving highly individualised, poly-biomarker-driven treatments was 38% with a disease control rate of 54%. PFS with TuPro-informed therapy decisions was 6.04 months (95% CI 3.75-12.06) and 5.35 months (95% CI 2.89-12.06) with ≥3rd-line therapy.

Comment: This is a very ambitious high-level study that has set itself several criteria to assess just how feasible such combined multiomic techniques would be in the treatment of melanoma. They considered the study did indeed show that incorporation of multiomics into clinical medicine was possible and feasible. They found that conduct of multiomics and their analysis could be carried out within 4 weeks and used to select appropriate treatment for patients. The multitude of omics used would frighten most funders, but surprisingly they assessed costs as only about 1.8-fold the amount refunded per patient by the Swiss government of 4600 Swiss francs. This is about AU$9000. Most benefit was seen in patients regarded as beyond standard of care. They point out that matching the cohorts in or out of the study is difficult and that randomised trials are now needed to establish the significance of multiomics in melanoma treatment. They also suggest that AI techniques are likely to assist in adoption of the most meaningful multiomics. Hopefully their ongoing studies will identify which of the multiomics is most useful in patient selection as very few institutions would be able to support the range of multiomics used in the study.

Reference: Nat Med. 2025;31(7):2430-2441
Abstract

Long-term follow-up of real-world adjuvant anti–PD-1 checkpoint inhibition and targeted therapy in patients with stage III melanoma

Authors: Lodde GC et al.

Summary: This German, multicentre study examined the use of adjuvant therapy with immune checkpoint inhibition (PD-1) or targeted therapy (TT) with BRAF and MEK inhibitors in 589 patients with stage III melanoma in real-world conditions. At 48 months, recurrence-free survival (RFS) was 42.9% (95% CI 38.5–47.8) among PD-1 recipients and 52.6% (95% CI 43.6–63.3) in TT recipients. In *BRAF* mutation patients, rate of recurrence was higher in PD-1 versus TT recipients (HR 1.57; 95% CI 1.09–2.26). OS at 4 years in PD-1 recipients with *BRAF* mutation was 80.8% (95% CI 73.6–88.7) and in TT recipients was 87.3% (95% CI 81.0–94.0). After macroscopic lymph node metastasis resection, adjuvant PD-1 recipients had a greater risk of rapid recurrence (1-year RFS; 58%) versus TT recipients (87%). Recurrence rate was higher after premature discontinuation (≤6 month) versus continued treatment with TT (HR 1.47; 95% CI 0.67–3.23), but not PD-1 (HR 1.07; 95% CI 0.73–1.55).

Comment: This study is a real-world 4-year follow-up analysis of results presented initially after a 2-year follow-up from 11 centres in Germany. It is a very detailed study and focuses particularly on patients with *BRAF*-mutated melanoma. The main take-home message is that patients with *BRAF*-mutated melanoma receiving TT may have better efficacy of adjuvant therapy with PD-1 under real-world conditions. This was more evident in patients with bulky lymph node metastases. This was due to higher relapse rates in the anti-PD-1-treated patients. The results with TT were dependent on treatment for longer than 6 months. Patients in either arm who relapsed responded poorly to subsequent treatments with either TT or anti-PD-1. Despite the present move to neoadjuvant approaches, the results from this adjuvant study may still have relevance to treatment of patients failing neoadjuvant treatments.

Reference: J Clin Oncol. 2025;43(25):2793-2805
Abstract

Improved survival in advanced melanoma patients treated with fecal microbiota transplantation using healthy donor stool in combination with anti-PD1: Final results of the MIMic phase 1 trial

Authors: Hadi DK et al.

Summary: The multicentre, phase I MIMic trial assessed the use of faecal microbiota transplantation (FMT) to overcome primary or acquired resistance to anti-PD1 using healthy donor stools in 20 patients with advanced melanoma, and identified an objective response rate (ORR) of 65%. After 3 years of follow-up, 8 patients remained alive and 7 patients had not progressed; no patients were still receiving anti-PD1 therapy and only 2 patients had received additional therapy. Median PFS was 29.6 months and median OS was 52.8 months. Estimated survival rates were 95% at 1 year, 74% at 2 years, and 53% at 3 years. *Post hoc* analyses suggested improved median PFS in responders and patients with FMT-specific toxicity.

Comment: The influence of the gut microbiome on immune responses is now well established and it is logical to examine whether manipulation of this microbiome can enhance treatment with anti-ICT. The authors question whether this study can answer this question. As described in their discussion, "*Limitations of this trial are the small sample size, lack of an anti-PD-1 alone comparator arm, and patient selection for single-agent anti-PD-1 therapy over combination therapy. This small cohort does not have the statistical power required to determine differences in outcomes, and the results are only hypothesis generating. Without a control arm, it is not possible to account for factors other than FMT that may have impacted results. The patients enrolled were not appropriate for combination immunotherapy, possibly leading to bias in patient selection.*" The article is still worth reading though as it has an excellent discussion about the microbiome and products that are probably mediating effects on immune responses. It also provides evidence for the feasibility of this treatment approach.

Reference: J Immunother Cancer 2025;13(8):e012659
Abstract

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BO-112 plus pembrolizumab for patients with anti–PD-1–resistant advanced melanoma: Phase II clinical trial SPOTLIGHT-203

Authors: Márquez-Rodas I et al.

Summary: The phase II SPOTLIGHT-203 clinical trial assessed the use of intratumoral BO-112 (a synthetic, double-stranded RNA nanoplexed with polyethylenimine) plus intravenous pembrolizumab in 42 patients with anti-PD-1-resistant melanoma. In modified ITT (n=40) analysis, the ORR was 25%, with 4 complete responses (CRs), 6 partial responses (PRs), and 16 stable disease (SD) responses, with median duration of response not reached. In ITT analysis (n=42), median PFS was 3.7 months (95% CI 2.2–9.2) and median OS was not achieved, with 54% of patients alive at 24 months. Adverse events of grade ≥3/4 occurred in 16 (38.1%) patients, 4 (9.5%) of which were drug-related; there were no treatment-related deaths.

Comment: This is one of several phase II trials using intralesional treatments to treat patients with anti-PD-1 resistant melanoma. BO-112 is a double stranded RNA and is believed to interact with toll receptor TLR3, the pattern receptor for viruses that activates production of type 1 IFNs. The study was carried out carefully with strict criteria for anti-PD-1 resistance. Although the ORR was only 25% the responses appeared to have some durability. *NRAS* or *BRAF* mutations were associated with clinical benefit (p=0.02), which was more evident for patients without *MYC* amplifications. Both injected and non-injected lesions showed responses. Patients with acral melanoma and/or lactate dehydrogenase >3 × upper limit of normal had no benefit in terms of response. However, 2 of the 3 patients with mucosal melanoma achieved a PR and one had SD. The mechanisms involved were not clear. Twenty-four patients had baseline and paired baseline/on-treatment biopsies. However, baseline PD-L1 expression and basal and post-treatment CD8 expression in paired biopsies did not correlate with benefit. The authors believe the results justify randomised studies in this patient group. See also results from an agonist of Toll-like receptor 9 (vidutolimod), which appears to induce similar response rates in anti-PD-1 resistant patients (Milhem MM et al. Cancer 2025;131(15)e70022).

Reference: J Clin Oncol. 2025;43(25):2806-2815
Abstract

Long-term survival and biomarker analysis evaluating neoadjuvant plus adjuvant relatlimab (anti-LAG3) and nivolumab (anti-PD1) in patients with resectable melanoma

Authors: Burton EM et al.

Summary: This update provided 4-year clinical follow-up data from a phase II clinical trial of neoadjuvant systemic treatment followed by adjuvant nivolumab and relatlimab in patients with stage III/IV surgically resectable melanoma. The initial result of the study was a major pathologic response (≤10% viable tumour) rate of 63%. The updated, median 47 months, data shows that 80% of patients remain event-free, including 95% of major pathologic responders. Gene expression analysis identified baseline upregulation of immune modulatory pathways was associated with major pathologic response, while increased B7-H3 expression was associated with resistance.

Comment: This is a longer follow-up of a previously published phase II study that now also includes the biomarker studies on the patients. It has the limitations of phase II studies and relatively small patient numbers. Although 40 patients consented, only 30 patients started the neoadjuvant component and 27 the adjuvant component; 15 patients completed the planned treatment. Given these limitations, the results showing durability of the combination in patients achieving major pathological responses are important for future studies on the combination. The biomarker studies were carried out on 27 patients and included 19 patients with pre-treatment tissue samples. Major pathological response was associated with well recognised immune regulatory pathways with increased B and CD8 T cells, IFN gamma and other inflammatory cytokines. A potentially important finding was that non-major pathological response (MPR) responses had increased B3-H7 in the tissues. B7-H3 has been associated with melanoma invasion and 'Cold' tumour infiltrates. The authors conclude that B7-H3 is potentially targetable and it may be a unique biomarker of resistance to anti-PD-1 and anti-LAG-3. They believe further investigation is needed to optimise personalised treatment. See also a more detailed biomarker study on this combination (Lipson EJ et al. Clin Cancer Res. 2025;31(17):3702–3714).

Reference: J Clin Oncol. 2025;43(26):2856-2862
Abstract

NeoACTIVATE Arm C: Phase II trial of neoadjuvant atezolizumab and tiragolumab for high-risk operable stage III melanoma

Authors: Hieken TJ et al.

Summary: The phase II NeoACTIVATE trial compared neoadjuvant atezolizumab plus tiragolumab (T-cell immunoglobulin and ITIM domain [TIGIT] immune checkpoint inhibitor [ICI]) after therapeutic lymph node dissection (TLND) in 34 patients (76.5% >1 metastatic lymph node, 73.5% were Stage IIIC) with high-risk resectable stage III melanoma. Over a median 19.9-month follow-up, MPR was achieved by 16 (47.1%) patients, 12-month event-free survival was 72.0% (95% CI 57.9-89.5), 12-month RFS was 73.3% (95% CI 56.9–94.5), and 12-month distant metastasis-free survival (DMFS) was 86.0% (95% CI 72.2–100). In patients with an MPR, 12-month RFS and DMFS were both 91.7% (95% CI 77.3–100). Possibly treatment-related grade ≥3 adverse events occurred in 2 (5.9%) patients.

Comment: TIGIT is a co-inhibitory receptor found on activated T cells and NK cells and is often co-expressed with PD-1. One of the questions being asked was whether the combination of anti-PD-1 with TIGIT may be as or more effective than other checkpoint inhibitors such as anti-LAG3 or CTLA4. Keeping in mind that there were only 34 patients in their study, the MPR rate of 47% may have been less than the 57% recorded for nivolumab plus ipilimumab and 63% for nivolumab plus relatlimab. The lower rate may also have been due to accrual of patients with more advanced disease, as over 70% of patients had stage IIIC disease. Grade 3 toxicity was seen in 2 patients, but overall toxicity was acceptable. Biomarker studies were not included in the study, but a response in a comparable study in lung cancer was associated with upregulation of chemokines CXCR3, CXCR6 and CLL5. They conclude "*This regimen merits testing in future clinical trials. Predictive biomarkers are needed so that the most efficacious and least toxic neoadjuvant regimen can be identified for individual patients.*"

Reference: Eur J Cancer 2025:227:115688
Abstract

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RP1 combined with nivolumab in advanced anti–PD-1–failed melanoma (IGNYTE)

Authors: Wong MK et al.

Summary: The IGNYTE trial examined RP1 (vusolimogene oderparepvec), a herpes simplex virus type 1-based oncolytic immunotherapy, in combination with nivolumab in 140 patients with anti-PD-1-failed melanoma. Confirmed ORR was 32.9% (95% CI 25.2–41.3) with a CR in 15.0% of patients. Median duration of response was 33.7 months (95% CI 14.1 to not reached) and OS rate at 1 year was 75.3% (95% CI 66.9–81.9) and at 2 years was 63.3% (95% CI 53.6–71.5). Biomarker analysis suggested broad immune activation with increased CD8+ T-cell infiltration and PD-L1 expression. TRAE rates were grade 1/2 77.1%, grade 3 9.3%, and grade 4 3.6%.

Comment: Is this the most effective intralesional treatment of anti-PD-1 resistant melanoma so far reported? This is a detailed quality study on 140 patients who had failed treatment with anti-PD-1. As discussed in the paper, this patient population has a low 5-6% response when retreated with anti-PD-1, so the 33% response reported can be safely attributed to the combination with intralesional injection of RP1 (vusolimogene). Responses were also seen in non-injected lesions. Toxicity was probably not greater than as expected for nivolumab. Biomarker studies showed upregulation of 313 differentially expressed genes most of which were related to immune responses. These gene expression changes were not seen in non- responders. Changes in the RP1 virus that differ from that used in talimogene laherparepvec studies are well described. Based on the results of this phase II study, a randomised phase III confirmatory study evaluating RP1 combined with nivolumab versus treatment of physician's choice in patients with advanced cutaneous melanoma is underway and enrolling (IGNYTE-3; NCT06264180). Despite the encouraging results it is worth noting that Replimunes application to the FDA for fast-track approval has so far not been successful due to a number of factors including the adequacy of controls. The company is currently the subject of a class action by investors.

Reference: J Clin Oncol. 2025 [Epub ahead of print]
Abstract

Analysis of treatment-free survival of patients with advanced melanoma receiving nivolumab as monotherapy or in combination with relatlimab in RELATIVITY-047

Authors: Regan MM et al.

Summary: This analysis compared treatment-free survival (TFS) for nivolumab plus relatlimab versus nivolumab monotherapy in 714 patients with advanced melanoma from the randomised, controlled, phase II/III RELATIVITY-047 trial. After 48 months, OS was 52% for nivolumab plus relatlimab and 43% for nivolumab monotherapy; 38% and 33% were free of subsequent systemic therapy. 48-month mean TFS was longer by 2.9 months (95% CI 1.0–4.9) with nivolumab plus relatlimab (9.7 months) than nivolumab (6.8 months). For time without grade ≥3 TRAEs, the 48-month mean TFS was longer by 2.6 months (95% CI 0.8–4.5) with nivolumab plus relatlimab (9.1 months) than nivolumab (6.5 months). 48-month mean total TFS was longer with nivolumab plus relatlimab in subgroups including *BRAF* mutant (9.4 vs 6.5 months), *BRAF* wild-type (9.9 vs 6.9 months), PD-L1 ≥1% (12.3 vs 7.7 months), and PD-L1 <1% (7.9 vs 6.2 months) patients.

Comment: TFS was used as a complementary assessment and as a patient-centred endpoint that characterises the time spent free of systemic anticancer therapy. This reinforced the clinical benefit of the ICI combination of nivolumab plus relatlimab already reported in the RELATIVITY-047 trial. They found on average, TFS was 2.9 months longer with nivolumab plus relatlimab than with nivolumab (9.7 vs 6.8 months). In particular, patients on the combination were treatment-free for 20% of the 4-year follow-up time since randomisation, compared with 14% in the nivolumab group. TFS benefits observed in the combination group persisted during the entire 48-month follow-up period highlighting the potential for improved quality of life in patients with advanced melanoma with nivolumab plus relatlimab. The authors conclude that TFS is a valuable additional measure that should be used in future clinical trials on ICI.

Reference: J Immunother Cancer 2025;13(9):e012747
Abstract

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Real-life data on tebentafusp in metastatic uveal melanoma patients from four EURACAN Expert Centres

Authors: van der Kooij MK et al.

Summary: This European, retrospective, multinational study, assessed tebentafusp in 175 patients with metastatic uveal melanoma. Transient grade 3-4 toxicity, mostly rash, occurred in 32 (18%) patients and 5 (2.9%) patients experienced grade 3 cytokine release syndrome. Overall, 1 patient had a CR, 7 (4%) patients had a PR, and 82 (47%) patients had SD. Median PFS was 4 months (95% CI 2.7–5.3) and median OS was 20 months (95% CI 15.3–24.6); the 1-year OS rate was 63.6%. Survival was poorer in patients with elevated LDH or extrahepatic metastases.

Comment: The use of bispecific antibodies that target T cells to antigens on cancer cells was pioneered by studies on uveal melanoma that targeted T cells to the gp100 on uveal melanoma and is now referred to as tebentafusp. The present study was on 175 patients treated in 4 expert centres in Europe. The real-life experience in these centres was found to reproduce the results of randomised trials and resulted in clinical benefit including stabilisation of disease in about 50% of patients including those over 70 years of age. The authors discuss the best methods to evaluate treatment benefits as classical response criteria such as RECIST 1.1 did not reflect the clinical benefit of tebentafusp. In particular efficacy could be observed even after initial disease progression, and survival benefit can be observed even in progressive patients. Selection of patients, including baseline elevations in LDH, the presence of extrahepatic metastases and circulating tumour (ct)DNA might be a valuable addition to classical radiological evaluation to predict the benefit from tebentafusp. They considered the challenge lies in making these analyses available in the clinic and defining the most accurate combination of ctDNA monitoring and tumour imaging to optimise treatment decisions.

Reference: Eur J Cancer 2025:227:115634
Abstract

Risk score stratification of cutaneous melanoma patients based on whole slide images analysis by deep learning

Authors: Bossard C et al.

Summary: This study used a weakly-supervised deep-learning approach (SmartProg-MEL; training cohort n=342) to predict survival outcomes in patients with stage I-III melanoma based on H&E-stained whole slide images of primary cutaneous melanomas. Performance, tested on two external independent datasets (IHP-MEL-2 n=161; The Cancer Genome Atlas Program [TCGA] n = 63). In the training cohort, SmartProg-MEL predicted the 5-year OS with a concordance index (c-index) of 0.78 in cross-validation data and 0.72 in a cross-testing series. With the IHP-MEL-2 dataset a c-index of 0.71 was achieved and with the TCGA dataset the c-index was 0.69. In multivariate analysis, SmartProg-MEL had the most powerful prognostic factor (HR 1.84; p<0.005). The model was able to dichotomise patients into low- and high-risk groups associated with different 5-year OS in IHP-MEL-1 (p<0.001) and IHP-MEL-2 (p=0.01) datasets.

Comment: This is an interesting study that examines H&E slides of melanoma by a 'weakly-supervised deep-learning approach', SmartProg-MEL, to predict survival outcomes in stages I to III melanoma patients. In survival data, the concordance index (c-index) is used to evaluate prognostic models by measuring how well the model's predictions agree with actual observed events. A c-index of 1 means the model perfectly predicts which of two subjects will experience an event first, while a c-index of 0.5 indicates the predictions are no better than chance. Given this information, the c-index described in the study would appear to provide additional prognostication and assist in patient selection for treatments. No information is given about the time taken to scan the slides as this might be a factor in its routine application by histopathologists.

Reference: J Eur Acad Dermatol Venereol 2025;39(8):1500-1509
Abstract

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