Melanoma Research Review™

Making Education Easy

Issue 57 - 2023

In this issue:

Abbreviations used in this issue:

AE = adverse event; **AJCC** = American Joint Committee on Cancer; **ctDNA** = circulating tumour DNA; **DFS** = disease-free survival; **DMFS** = distant metastasis-free survival; **GM-CSF** = Granulocyte-macrophage colony-stimulating factor; **ICB** = immune checkpoint blockade; **MEK** = mitogen-activated extracellular signal-regulated kinase; **MSS** = melanoma-specific survival; **ObRR** = objective response rate; **ONCOS-102** = oncolytic adenovirus expressing GM-CSF; **OR** = odds ratio; **OS** = overall survival; **PD** = progressive disease; **PFS** = progression-free survival; **RCT** = randomised controlled trial; **RFS** = recurrence-free survival; **SN** = sentinel node.

Welcome to issue 57 of Melanoma Research Review.

This month's review of the melanoma literature describes the outcomes of several large trials on metastatic melanoma which have been reported on previously in conferences, but which are now appearing in print. Several of them had negative outcomes, however the positive side to this is the saving to the public purse in not paying for ineffective treatments. Another theme covers treatment combinations that might be active against melanoma which do not respond to ICB. A very interesting study based on genomic analysis also points to genes that might identify patients likely to have severe side effects when treated by checkpoint inhibitors, which may be the forerunner of more studies like this.

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

Best regards,

Professor Peter Hersey

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Sequencing of ipilimumab plus nivolumab and encorafenib plus binimetinib for untreated *BRAF*-mutated metastatic melanoma (SECOMBIT)

Authors: Ascierto PA et al.

Summary: This randomised, three-arm, open-label, non-comparative phase 2 trial assessed the impacts of sequential immunotherapy and *BRAF*/MEK inhibition on *BRAF*^{V600} mutation-positive melanoma. Eligible patients (n=209) with untreated, metastatic *BRAF*^{V600} mutation-positive melanoma across nine countries were randomised to either arm A (n=69; encorafenib + binimetinib until PD followed by ipilimumab + nivolumab), arm B (n=71; ipilimumab + nivolumab until PD followed by encorafenib + binimetinib) or arm C (encorafenib + binimetinib for 8 weeks followed by ipilimumab + nivolumab until PD, then encorafenib + binimetinib). At a follow-up of 32.2 months, >30 patients remained alive in each arm, and no arm had reached median OS (primary endpoint). The respective OS rates in arms A, B and C at 2 and 3 years were (65%/54%, 73%/62% and 69%/60%), and no novel safety concerns occurred.

Comment: Is a short course of targeted therapy prior to targeted therapy the best sequence? This open-label randomised phase 2 study provides data on survival outcomes with sequential targeted therapy and immunotherapy in patients with treatment-naïve *BRAF*^{V600} mutation-positive melanoma. The survival results are in line with the DREAMseq trial, in which the 2-year survival rates for patients receiving first-line treatment with nivolumab + ipilimumab were 72% vs. 52% for dabrafenib + trametinib. As discussed in the report, the main difference between this study and the DREAMseq study was the inclusion of a sandwich arm, which demonstrated similar clinical benefit. The sandwich approach warrants further investigation, particularly in patients with rapidly progressing disease where the initial induction course of targeted therapy followed by immunotherapy maintenance may enhance initial response rates, while maintaining long-term benefit. This approach of *BRAF*/MEK inhibition followed by combination of anti–CTLA-4 + anti–PD-1 is currently being evaluated in the prospective, randomised, phase II EORTC EBIN trial.

Reference: J Clin Oncol. 2023;41(2):212-21

Abstract

Overall survival with first-line atezolizumab in combination with vemurafenib and cobimetinib in *BRAF*^{V600} mutation-positive advanced melanoma (IMspire150)

Authors: Ascierto PA et al.

Summary: In the primary analysis of the multicentre, double-blind, placebo-controlled, randomised, phase 3 IMspire150 study, patients with previously untreated unresectable stage IIIc/IV *BRAF*^{V600} mutation-positive melanoma had improved PFS with first-line atezolizumab + vemurafenib + cobimetinib (atezolizumab group) vs. placebo + vemurafenib + cobimetinib (control group). This prespecified additional second interim OS analysis assessed long-term OS outcomes for this study population. A total of 514 patients (median age 53 years; 58% men), were randomised 1:1 to the atezolizumab or control arm. At a median follow-up of 29.1 and 22.8 months for the atezolizumab and control groups, respectively, there was a numerical difference in median OS but this was not statistically significant (39.0 vs. 25.8 months; HR 0.84; p=0.14). Serious AEs occurred in 48% and 42% of patients in the atezolizumab and control groups, and grade 5 AEs in 3% and 2%. Two grade 5 AEs in the atezolizumab group were related to the triplet combination (hepatitis fulminant and hepatic failure), and one in the control group was related to cobimetinib (pulmonary haemorrhage). Researchers commented that the final analyses results will reveal whether long-term treatment with the triplet combination will lead to a significant improvement in OS.

Comment: Another study combining targeted and immune checkpoint inhibitors requiring further study. This second interim analysis of IMspire (a randomised trial on 514 *BRAF*^{V600}-positive patients) confirmed the primary analysis showing improved PFS in patients also receiving an immune checkpoint inhibitor. Median OS also pointed to an effect on OS. In discussion they point to a post-hoc analysis on *BRAF*^{V600}E patients that showed there was a significant effect on OS in this subgroup rather than all *BRAF*-mutated patients. Otherwise, they conclude that longer follow up is needed to show an effect on OS. This is supported by the delayed effect on OS evident at 1 year in IMspire and the results of the randomised Keynote-022 phase 2 study where improvement in OS was only confirmed in the longer follow-up of ≈5 years.

Reference: Lancet Oncol. 2023;24(1):33-44
Abstract

Clinical and molecular response to tebentafusp in previously treated patients with metastatic uveal melanoma

Authors: Carvajal RD et al.

Summary: The 1-year OS rate for patients with previously treated metastatic uveal melanoma is 37%, with 7.8 months median OS. In this phase 2 trial, researchers explored the safety and efficacy of tebentafusp, a soluble T cell receptor bispecific (gp100×CD3) in 127 eligible patients (median age 61 years; 50% male) with treatment-refractory metastatic uveal melanoma (96% hepatic involvement) enrolled in 26 centres across five countries. At a median follow-up of 19.5 months, the overall response rate was 5%, with a 1-year OS rate of 62% (95% CI 53–70) and median OS of 16.8 months (95% CI 12.9–21.3). Treatment-related AEs were mild to moderate and experienced by all patients, most commonly including rash (87%), pyrexia (80%) and pruritus (67%), however following the initial three doses the intensity and incidence of toxicity was greatly decreased. Exploratory analyses revealed that OS was strongly associated with early on-treatment decreases in ctDNA, which researchers noted requires confirmation in future randomised studies.

Comment: Some advances in treating uveal melanoma. This study needs little further comment. Uveal melanoma is known to be resistant to most current treatments including immunotherapy, perhaps due to the paucity of uveal melanoma-induced mutations. The bispecific tebentafusp used in this study circumvents this problem to some extent by targeting a differentiation antigen gp100 (CD47) expressed on most uveal melanomas. The study appeared to be well-conducted, and the results appear to justify a randomised trial. Other comments not specific to the study relate to interest in the eye as an immune-privileged site, and possible presence of immunosuppressive factors released by uveal melanoma cells. Studies with mutated gp100 are of interest. CD47 has also been implicated in inhibiting immune responses, so there is much scope for future studies.

Reference: Nat Med. 2022;28(11):2364-73
Abstract

Phase II LEAP-004 study of lenvatinib plus pembrolizumab for melanoma with confirmed progression on a programmed cell death protein-1 or programmed death ligand 1 inhibitor given as monotherapy or in combination

Authors: Arance A et al.

Summary: These researchers investigated the efficacy of pembrolizumab (PD-1 inhibitor) + lenvatinib (multikinase inhibitor) in patients (n=103) with unresectable stage III-IV melanoma. Eligibility criteria included confirmed PD ≤12 weeks after the last dose of a PD-1/L1 inhibitor. All patients were administered 20mg oral lenvatinib once daily + 200mg intravenous pembrolizumab 3-weekly for up to 25 doses until PD or unacceptable toxicity. At a median follow-up of 15.3 months, ObRR (primary endpoint) was 21.4% (95% CI 13.9–30.5), with complete response achieved by three patients (2.9%) partial response by 19 (18.4%), and a median duration of response of 8.3 months (range 3.2-15.9 months). In the 30 patients with PD on prior anti–PD-1 + anti–CTLA-4 therapy, the ObRR was 33.3%. In the total population, median MFS and OS were 4.2 (95% CI 3.8–7.1) and 14.0 months (95% CI 10.8–N/A), respectively. A total of 47 patients (45.6%) experienced grade 3-5 AEs, mainly hypertension (21.4%), with one patient dying due to decreased platelet count which was deemed associated with treatment.

Comment: A well conducted study needing confirmation in further studies. The authors draw attention to the lack of approved treatments for melanoma that progressed on anti–PD-1/L1-based therapy and the high unmet need for treatment of patients who have exhausted targeted therapy (if eligible) and anti–CTLA-4–based regimens. A strong point of their study included the stringent definition of PD on previous anti–PD-1/L1 therapy, in line with recommendations that required PD to be confirmed by iRECIST on a second scan performed ≥4 weeks after initial PD documentation, and to occur on ≤12 weeks of the last dose of anti–PD-1/L1 therapy, which must have been given for ≥2 doses. It was also noted there were *"similar ObRRs regardless of whether patients experienced primary resistance in the adjuvant setting (18.2%) or primary (22.6%) or secondary (22.7%) resistance in the metastatic setting, suggesting that lenvatinib plus pembrolizumab provides a similar likelihood of response across clinical resistance phenotypes".* In the discussion they draw comparisons with treatment utilising lifileucel autologous T infiltrating cells that reported an ObRR of 36% in patients with metastatic melanoma, with confirmed PD on previous anti–PD-1/L1 therapy (n=66). They conclude that these data suggest lenvatinib plus pembrolizumab may be a treatment option for this growing population of high unmet medical need, and that randomised studies are needed to identify a therapy that improves survival for this population.

Reference: J Clin Oncol. 2023;41(1):75-85
Abstract

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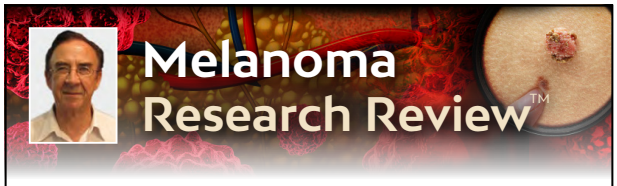
Clinical outcomes and risk stratification of early-stage melanoma micrometastases from an international multicenter study

Authors: Moncrieff MD et al.

Summary: The objective of this study conducted across nine centres in Australia, Europe and North America was to identify which patients with high-risk, SN+, AJCC stage IIIA melanomas would benefit most from adjuvant systemic therapy. A total of 3,607 eligible adult patients (all with pathologic stage pT1b/pT2a primary cutaneous melanomas) were followed for a median of 34 months. There was no significant difference in survival between the N1a and N2a subgroups. The optimal cut-off point for stratifying survival was determined to be a maximum tumour deposit of 0.3mm. Patients with SN metastatic tumour deposits <0.3mm (low-risk cohort) had a significantly higher 5-year disease-specific survival rate than those with tumour deposits ≥0.3mm (high-risk cohort; 94.1% vs. 80.3%, HR 1.26; p<0.0001), with similar results for both overall DFS and DMFS. No survival differences were observed between AJCC IB patients and low-risk <0.3mm AJCC IIIA patients. A total of 271 patients (66.4%) in the AJCC IIIA cohort were identified as high-risk, however only 142 patients (34.8%) had SN tumour deposits >1mm.

Comment: Clarifying the size cut-offs for LN metastases in patients that require no further treatment. A big saving in treatment costs? Several prospective RCTs have shown clinical benefit of adjuvant systemic therapy in terms of RFS for patients with AJCC stage III metastatic melanoma. In general, the phase 3 clinical trials for SN+ patients to date have only included those with a deposit >1 mm or those with ulcerated primaries, as these were judged to be the higher-risk patients in this subgroup. The prognostic relevance of the maximum diameter of the largest tumour deposit was originally described by Dutch investigators and was subsequently validated in the DeCOG-SLT study. In the present study of over 3,600 patients, a threshold analysis algorithm revealed that the breakpoint of maximum clinical significance was 0.3 mm for both overall DMFS and DSS. For those patients with maximum tumour deposits <0.3mm, the 5-year DSS was 94.7%, with this low-risk cohort having an identical prognosis to the N0 cohort. They concluded "*Patients with AJCC IIIA melanoma with SN tumour deposits ≥0.3 mm in maximum dimension are at higher risk of disease progression and may benefit from adjuvant systemic therapy or enrolment into a clinical trial. Patients with SN deposits <0.3 mm in maximum dimension can be managed similar to their SN-negative, AJCC IB counterparts, thereby avoiding regular radiological surveillance and more intensive follow-up.*"

Reference: J Clin Oncol. 2022;40(34):3940-51.
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.

Association of immune-related adverse event management with survival in patients with advanced melanoma

Authors: van Not OJ et al.

Summary: The associations between immunosuppressive treatments for grade ≥3 immune-related AEs and PFS, OS and MSS in patients with advanced melanoma treated with first line ipilimumab + nivolumab were evaluated in this population-based, multicentre cohort study. A total of 771 patients received ipilimumab + nivolumab, 350 of whom (median age 60.0 years; 58.9% male) were administered immunosuppressive mediation for severe immune-related AEs (67.1% steroids alone; 32.9% steroids + second line immunosuppressants). At baseline, there were no significant between-group differences except for type of toxic effects. Compared to patients who received steroids + second line immunosuppressants, those who received steroids alone had significantly longer median PFS (11.3 vs. 5.4 months; p=0.01), OS (46.1 vs 22.5 months p=0.04) and MSS (46.1 vs. 28.8 months; p=0.006).

Comment: A much needed analysis of outcomes in patients being treated for severe immune related AEs. This cohort study investigates whether different immunosuppressive regimens for grade 3 or higher immune-related AEs have an association with OS and PFS in patients treated with immune checkpoint inhibitors. The study was conducted on a homogeneous cohort of patients with advanced melanoma in the Dutch Melanoma Treatment Registry who were treated with first line ipilimumab + nivolumab. The take home message appears to be that treatment with steroids alone had no significant effect on outcome measures, but second-line immunosuppression (largely with anti-TNF agents) for immune-related AEs was associated with impaired PFS, OS, and MSS in patients with advanced melanoma treated with first line ipilimumab + nivolumab. The researchers conclude *"These findings stress the importance of assessing the effects of differential immune-related AE management strategies, not only in patients with melanoma but also in other tumour types."*

Reference: JAMA Oncol. 2022;8(12):1794-1801
Abstract

IL7 genetic variation and toxicity to immune checkpoint blockade in patients with melanoma

Authors: Taylor CA et al.

Summary: This study analysed the associations between genetic variations and risks of immune-related AEs and toxicities in patients (n=214) treated with immune checkpoint blockade (ICB) for melanoma. Patients who were minor allele carriers of rs16906115 intronic to *IL7* had an increased risk of developing grade ≥3 immune-related AEs (OR 2.24; 95% CI 1.03–5.09; p=0.046), with researchers discovering that rs16906115 formed a B cell-specific expression quantitative trait locus to *IL7*. Those who carried the risk allele also had increased B cell *IL7* expression before treatment, increasing the risks of immune-related AEs, more B cell receptor mutations and divergent immunoglobulin expression. Investigations revealed that risk allele carriers demonstrated skewing of T cell clonality, distinct ICB-induced $CD8^+$ T cell responses and increased proportional repertoire occupancy by large clones, as well as improved melanoma survival.

Comment: Identifying genes that predispose to severe AEs during treatment with immune checkpoint blockade. This article needs to be viewed in the context of biomarkers of immune-related AEs that could be used in identifying patients at risk of developing severe side effects during treatment with immune checkpoint inhibitors. Importantly, it has looked at genomic features that may influence immune responses and follows previous studies which had identified three alleles associated with immune-related AEs in genome-wide association studies on 1,751 patients with different cancers treated with immune checkpoint inhibitors (Nat Med. 2022;28(12):2584-91). The present paper identified the risk-associated allele in approximately 7% of melanoma patients being treated with immune checkpoint inhibitors. Such patients had increased *IL-7* expression in B cells, increased size of T cell clones and more mature T cells. Examination of The Cancer Genome Atlas data also showed that patients with the risk alleles had improved survival from melanoma. This is a high-quality study deserving of reading. They conclude *"This study highlights the power of agnostic genetic analyses to provide insights into human immunity of high relevance to disease and delineates a key role for IL-7 in response to ICB, revitalizing previous proposals for incorporating this molecule as a potential adjunct to immunotherapy strategies".*

Reference: Nat Med. 2022;28(12):2592-2600
Abstract

Adjuvant therapy of nivolumab combined with ipilimumab versus nivolumab alone in patients with resected stage IIIB-D or stage IV melanoma (CheckMate 915)

Authors: Weber JS et al.

Summary: The efficacy of adjuvant nivolumab + ipilimumab vs. nivolumab alone in eligible patients (n=1,833) with high-risk resected melanoma was compared in this double-blind, phase III trial. Patients were randomised 1:1 to be administered either 240mg nivolumab 2-weekly + 1mg/kg ipilimumab 6-weekly (n=916; combination group) or 480mg nivolumab 4-weekly (n=917; novolumab group) for up to 1 year. At a follow-up of ≈23.7 months, there were no significant differences in RFS between treatment groups (HR 0.92; p=0.269) or in patients who had PD-L1 expression <1% (HR 0.91). A higher rate of treatment-related AEs occurred in the combination group than in the nivolumab group (32.6% vs. 12.8%), and deaths were reported in 0.4% of the combination group, while none of the nivolumab-treated patients died.

Comment: Adjuvant treatment with combined nivolumab and ipilimumab is no better than nivolumab alone. This unexpected result comes from a well-run large multicentre trial where the results appear clear-cut and of relevance to routine adjuvant treatment of melanoma. Questions raised by the authors in discussion included whether lack of improvement with the combination was due to the shorter time of treatment, or the lower dose and scheduling of treatment with ipilimumab. These questions were well discussed from the literature and appear unlikely explanations. *BRAF* mutation status or expression of PD-L1 also had no effect on the outcome. They conclude *"Combination dosing in the adjuvant setting requires further refinement and investigation to determine the optimal balance between benefit and toxicity."*

Reference: J Clin Oncol. 2023;41(3):517-27
Abstract

Randomized, double-blind, placebo-controlled, global phase III trial of talimogene laherparepvec combined with pembrolizumab for advanced melanoma

Authors: Chesney JA et al.

Summary: Following a phase Ib study which demonstrated improved complete response rates in patients with advanced melanoma treated with talimogene laherparepvec (T-VEC), the safety and efficacy of talimogene laherparepvec + pembrolizumab vs. placebo + pembrolizumab in patients with stage IIIB-IVM1c unresectable melanoma, naïve to anti-programmed cell death protein-1 was assessed in this phase 3, randomised, double-blind, multicentre international study. Eligible patients (n=692) were randomised 1:1 to receive either talimogene laherparepvec + pembrolizumab (n=346) or placebo + pembrolizumab (n=346). There were no statistically significant differences observed in PFS or OS (dual primary endpoints; p=0.13 and p=0.74, respectively). Researchers noted that the safety outcomes in the talimogene laherparepvec + pembrolizumab mirrored the individual safety profiles of each medication.

Comment: Talimogene laherparepvec (T-VEC) + pembrolizumab is no better than pembrolizumab alone. The results from this well-run randomised trial on 692 treatment-naïve unresectable stage IIIB-IVM1C melanomas may save the public purse the cost of adding talimogene laherparepvec to pembrolizumab in this group of patients. As detailed in the discussion, there were some numerical differences between the groups in response rates and their durability, but no differences in PFS or OS. The authors discuss the fine points of difference between patients and treatment with talimogene laherparepvec in the present study and the previous OPTiM phase III trial, but these do not seem important in the outcomes of the study. They conclude *"Although the combination of T-VEC-pembrolizumab did not result in OS benefit compared with placebo-pembrolizumab in the frontline treatment of advanced melanoma, this combination is still under active investigation in patients who are refractory to anti–PD-1 inhibitor therapy for melanoma and other tumor types."*

Reference: J Clin Oncol. 2023;41(3):528-40
Abstract

Pilot study of ONCOS-102 and pembrolizumab

Authors: Shoushtari AN et al.

Summary: The safety and efficacy of ONCOS-102 (oncolytic adenovirus expressing *GM-CSF*) + pembrolizumab (anti-PD-1 therapy) in patients with advanced melanoma progressing after prior PD-1 blockade were examined in this open-label, multicentre pilot study, whereby the researchers suggested that anti-PD-1 resistance may be overcome by remodelling of the tumour microenvironment via intratumoural oncolytic virotherapy. All eligible patients (n=21; median age 73 years; 91% female) were administered a single priming dose of cyclophosphamide before commencing ONCOS-102 + pembrolizumab, in order to decrease regulatory T cells and enhance the effect of GM-CSF-induced natural killer and cytoxic T cells. Patients received either 3 intratumoural doses of ONCOS-102 followed by ≤8 sequential doses of pembrolizumab every 3 weeks (Part 1; n=9), or 4 intratumoural doses of ONCOS-102 followed by ≤8 doses of intratumoural ONCOS-102 + pembrolizumab every 3 weeks (Part 2; n=11). Overall, ONCOS-102 + pembrolizumab had a manageable safety profile (primary endpoint): the majority of AEs were mild/moderate and there were no dose-limiting toxicities. The most common ONCOS-102 treatment-related AEs included chills (43%), pyrexia (43%) and nausea (28%). The median ObRR was 35%, and a systemic effect indicated by a decrease in size of ≥1 non-injected lesion occurred in 53% of patients. A clinical benefit within injected tumours was associated with T cell infiltration and immune-related gene expression. T cell infiltration (especially cytotoxic $CD8^+$ T cells) was enhanced by ONCOS-102, and this effect remained at week 9. Researchers noted that the results support future studies into the Part 2 dosing regimen.

Comment: Another oncolytic virus that may improve treatment with checkpoint inhibitors. This study on 21 patients refractory to anti-PD-1 treatment is another approach showing some promise in this patient group. ONCOS-102 (oncolytic adenovirus expressing *GM-CSF*) is a chimeric oncolytic adenovirus expressing human GM-CSF. Compared with herpes simplex virus, which establishes latency and has diverse mechanisms to overcome immune surveillance, adenovirus is primarily lytic and possesses a limited number of genes with known immune evasion activities. Treatment was over 24 weeks with a 3 week follow up. They summarise as follows "*Treatment was well tolerated. Objective responses were seen in 7 of 20 patients, and size reductions in non-injected lesions suggested local delivery of ONCOS-102 can drive a systemic anti-tumor effect. Serial biopsies of injected tumors at baseline, Week 3 (following ONCOS-102 and prior to pembrolizumab), and Week 9 (following ONCOS-102 and pembrolizumab) indicated that while most tumors experience CD8+ and CD4+ infiltration after ONCOS-102 injection, sustained infiltration at Week 9 was associated with clinical benefit. Future trials of ONCOS-102 and checkpoint inhibition are warranted in anti-PD-1 resistant melanoma. These findings suggest trials utilizing viral agents in anti-PD-1 resistant disease should not solely rely on early onset of cytotoxicity to predict clinical response."*

Reference: Clin Cancer Res. 2023;29(1):100-9
Abstract

