# Melanoma Research Review™

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## In this issue:



**Abbreviations used in this issue:**

**AE** = adverse event; **DCR** = disease control rate; **ICI** = immune checkpoint inhibitor; **IFN-γ** = interferon-γ; **LDH** = lactate dehydrogenase; **MPR** = major pathological response; **ORR** = objective response rate; **PFS** = progression-free survival; **PRS** = polygenic risk score; **RFS** = recurrence-free survival; **SN** = sentinel node; **SNB** = sentinel node biopsy; **SNP** = single-nucleotide polymorphism; **TMB** = tumour mutational burden; **TT** = targeted therapy; **US** = ultrasound.



# Welcome to the 53rd issue of Melanoma Research Review

This month's selections on melanoma research contains articles showing treatment benefit from immune checkpoint inhibitors in stage IIB and IIC melanoma and several articles on combining or sequencing checkpoint inhibitors with targeted treatments. There is also a large epidemiological study reminding us that melanoma remains a global problem. A large screening study is suggesting that screening is not the solution. Another study looks at incorporating polygenetic findings to help in prevention, screening and detection. I have included a Nature article on androgens in melanoma that I think will have important future treatment implications in targeted therapy and immune checkpoint inhibitors in melanoma.

I hope you find the research in this issue useful to you in your practice and I look forward to your comments and feedback.

Kind Regards,


**Professor Peter Hersey**
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## Randomized phase III trial evaluating spartalizumab plus dabrafenib and trametinib for BRAF V600-mutant unresectable or metastatic melanoma

**Authors:** Drummer R, et al


**Summary:** This phase III trial evaluated spartalizumab in combination with dabrafenib and trametinib (sparta-DabTram), versus placebo plus dabrafenib and trametinib (placebo-DabTram) in patients with BRAF V600-mutant unresectable or metastatic melanoma. The authors reported median progression-free survival (PFS) was 16.2 months (95% CI, 12.7 to 23.9 months) in the sparta-DabTram arm versus 12.0 months (95% CI, 10.2 to 15.4 months) in the placebo-DabTram arm (HR, 0.82 [95% CI, 0.66 to 1.03]; P=0.042 [one-sided; nonsignificant]). Objective response rates (ORRs) were 69% (183 of 267 patients) versus 64% (170 of 265 patients), respectively. It was noted Grade ≥ 3 treatment-related adverse events (AEs) occurred in 55% (146 of 267) of patients in the sparta-DabTram arm and 33% (88 of 264) in the placebo-DabTram arm.


**Comment: Concurrent ICI immunotherapy and targeted treatments appears not to have added treatment benefit.** There were many reasons to think that combining RAFi and MEKi with PD-1 or PD-L1 blockade would result in synergistic therapeutic effects. Clinically, the combinations of RAFi plus MEKi resulted in high response rates but of relatively short duration. The PD-1 or PD-L1 blockers, in contrast, were associated with lower response rates but more durable responses. Combination RAFi and MEKi have largely nonoverlapping toxicities with PD-1 and PD-L1 inhibitors and different mechanisms that drive toxicities. As such, it was assumed that combining them would be tolerable. In addition, there was evidence that combination RAFi and MEKi resulted in increased melanoma antigen expression and increased T-cell infiltration in tumours.

The present study is the third randomised study that shows little benefit in combining these two treatment approaches. The other two trials were the IMspire150 study combining vemurafinib plus cobimetinib with atezolizumab. Keynote-022 tested dabrafenib plus trametinib with pembrolizumab. Possible explanations discussed by the authors was the improved performance of the comparator arm versus that observed in historical data with dabrafenib plus trametinib from the phase III COMBI-d/v trials. Treatment-related AEs occurred at a higher frequency in patients receiving sparta-DabTram than in patients receiving placebo-DabTram. Toxicity appeared to be a barrier to patients receiving the full dose, as there were more dose modifications in the sparta-DabTram arm than in the placebo-DabTram arm. In view of the results from these three studies the focus has now switched to whether there will be benefit in sequencing the two different treatments. This is discussed in the abstract.


***Reference: J Clin Oncol. 2022 May 1;40(13):1428-1438***
Abstract

## Biomarkers of treatment benefit with atezolizumab plus vemurafenib plus cobimetinib in BRAF $^{V600}$ mutation-positive melanoma

**Authors:** Robert C, et al

**Summary:** The exploratory biomarker analyses aimed to optimise targeting of patients who are more likely to benefit from triplet combination therapy with atezolizumab, vemurafenib, and cobimetinib. Patients with BRAFV600-mutated advanced melanoma were randomised to atezolizumab (n=256) or control (n=258). The investigators found PFS benefit for atezolizumab versus control was greater in patients with high tumour mutational burden (TMB), [≥10 mutations/Mb; HR 0.73; 95% CI 0.52-1.02; P=0.067] versus low TMB (<10 mutations/Mb; HR 0.92; 95% CI 0.65-1.30; P=0.64) and similar between patients with strong interferon-γ (IFN-γ) (≥median; HR 0.76; 95% CI 0.54-1.06) versus weak IFN-γ (<median; HR 0.79; 95% CI 0.58-1.08). In patients with elevated lactate dehydrogenase (LDH), PFS benefit for atezolizumab versus control was greater in the PD-L1- subgroup (HR 0.53; 95% CI 0.29-0.95; P=0.032) than in the PD-L1+ subgroup (HR 1.16; 95% CI 0.75-1.80; P=0.51).

**Comment: Can patients who benefit from concurrent triplet therapy be identified?** This study is relevant to the triplet therapy study reviewed above (Dummer R, et al) in that the data was analysed to see if biomarkers could be identified to select patients who would most benefit from this treatment approach. PD-L1 expression did not prove to be a predictor of response in triplet versus control but there was some association with TMB and strong IFN-γ gene signatures in this group. LDH remained the primary determinant of PFS regardless of treatment arm. They conclude "the analysis suggests that this triplet combination therapy is most beneficial in the subgroup of patients with elevated LDH and PD-L1– tumors who do not typically benefit from single-agent ICIs". This exploratory analysis should be considered hypothesis-generating given the small numbers of patients in some subsets. Follow-up analyses with more mature overall survival (OS) data from the IMspire150 study are required to confirm the impact of these.

***Reference: Ann Oncol. 2022 May;33(5):544-555***
Abstract

## MAPKinase inhibition after failure of immune checkpoint blockade in patients with advanced melanoma - An evaluation of the multicenter prospective skin cancer registry ADOREG

**Authors:** Kreft S, et al

**Summary:** The study cohort included 108 patients with unresectable stage III or stage IV melanoma progressing on first-line ICI (nivolumab, pembrolizumab or ipilimumab plus nivolumab) and receiving second-line combined BRAF/MEK inhibition. The authors reported 73% of the cohort presented with primary PD-1 resistant disease. Median PFS on ICI was 2.6 (95% CI 2.2-2.9) months. Median PFS on subsequent targeted therapy (TT) was 6.6 (95% CI 5.4-7.8) months. Median OS from start of second-line TT was 16.0 (95% CI 11.2-20.8) months. The 3-year PFS and OS rates on second-line TT were 16% and 30%. The ORR and disease control rate (DCR) to TT were 42.6% and 55.6%. The authors noted in patients with brain metastases, the ORR and DCR were 31.4% and 43.1%. Patients without brain metastases showed an ORR and DCR of 52.6% and 66.7%, respectively. Response to first-line ICI was associated with a numerically higher ORR and DCR to second-line TT and improved OS on TT. Twenty-three patients received third-line ICI of whom two patients showed an objective response.

**Comment: Targeted treatments still effective in patients failing ICI immunotherapy.** Although ICI immunotherapy and TT are both effective treatments for metastatic melanoma there is continuing interest in how to combine these approaches. As reviewed in this series above (Dummer R, et al) concurrent use of both treatments seems to offer no advantages. The so called DREAMseq phase III randomised trial compared starting treatment with ICI or TT and then switching at time of progression. The trial was stopped before full accrual as the 2yr follow up showed a clear survival benefit (72%) for starting treatment with ICI rather than TT (52%). The randomised phase II SECOMBIT trial had similar findings and also included an arm with ICI sandwiched between TT at 8 week intervals.

The present study was a real-world retrospective study which showed that TT in ICI resistant or failed patients was effective treatment and seemed unaffected by upfront immunotherapy. It is of interest that they also included 23 patients who had ICI as thirdline treatment starting with ICI monotherapy then TT and then ICI thirdline. In their series the ICI as thirdline was relatively ineffective. They conclude by drawing attention to the limitations of non-randomised retrospective studies but find that "Rates of long-term benefit and survival were similar to those reported for treatment-naïve patients receiving first-line TT". They also comment that the impact of adjuvant therapies will need assessment in future studies.

***Reference: Eur J Cancer. 2022 May;167:32-41***
Abstract

## Pembrolizumab versus placebo as adjuvant therapy in completely resected stage IIB or IIC melanoma (KEYNOTE-716): A randomised, double-blind, phase 3 trial

**Authors:** Luke JJ, et al

**Summary:** This article reports on the KEYNOTE-716 trial results from the planned first and second interim analyses for RFS. Patients aged 12 years or older with newly diagnosed, completely resected stage IIB or IIC melanoma (TNM stage T3b or T4 with a negative sentinel lymph node biopsy) were randomly assigned to pembrolizumab (n=487) or placebo (n=489; ITT population). At the first interim analysis (median follow-up of 14·4 months in the pembrolizumab group and 14·3 months in the placebo group), 54 (11%) of 487 patients in the pembrolizumab group and 82 (17%) of 489 in the placebo group had a first recurrence of disease or died (HR 0·65 [95% CI 0·46-0·92]; p=0·0066). At the second interim analysis (median follow-up of 20·9 months in the pembrolizumab group and 20·9 months in the placebo group), 72 (15%) patients in the pembrolizumab group and 115 (24%) in the placebo group had a first recurrence or died (HR 0·61 [95% CI 0·45-0·82]). Median RFS was not reached in either group at either assessment timepoint. At the first interim analysis, grade 3-4 treatment-related adverse events occurred in 78 (16%) of 483 patients in the pembrolizumab groups versus 21 (4%) of 486 in the placebo group. It was noted no deaths due to study treatment occurred.

**Comment: Another practice changing trial in melanoma.** Patients with ulcerated 2-4mm thick primaries and primaries greater than 4mm (stage IIB) and ulcerated primaries greater than 4mm (stage IIC) are at high risk of developing recurrent melanoma (10 year survivals 82% and 75% respectively). This large study on 976 patients adds to the results of similar studies on patients with resected stage III disease in showing that 1 year of treatment with pembrolizumab (Keytruda) was associated with a significant reduction in disease recurrence or death. These data led to FDA approval of this treatment as adjuvant treatment for stage IIB, IIC melanoma. Grade 3-4 AEs were similar to previous studies in patients with grade III melanoma. The authors drew attention to the long term endocrinopathies and the need to develop biomarkers that would identify patients at risk of their development. They conclude that adjuvant therapy with pembrolizumab might become a treatment option for patients with resected stage IIB or IIC melanoma, but OS data are awaited.

***Reference: Lancet. 2022 Apr 30;399(10336):1718-1729***
Abstract



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## Global burden of cutaneous melanoma in 2020 and projections to 2040

**Authors:** Arnold M, et al

**Summary:** This population-based study examined global patterns of cutaneous melanoma in 2020 and projected estimates of cases and deaths by 2040. For 2020 researchers estimated a worldwide total of 325,000 new melanoma cases (174,000 males, 151,000 females) and 57,000 deaths (32,000 males, 25,000 females). They noted large geographic variations across regions with the highest incidence rates among males (42 per 100,000 person-years) and females (31 per 100,000 person-years) observed in Australia/New Zealand, followed by Western Europe (19 per 100,000 person-years for males and females), North America (18 per 100,000 person-years for males, 14 per 100,000 person-years for females), and Northern Europe (17 per 100,000 person-years for males, 18 per 100,000 person-years for females). Melanoma was rare in most African and Asian countries, with incidence rates commonly less than 1 per 100,000 person-years. The researchers estimated if 2020 rates continue, the burden from melanoma to increase to 510,000 new cases and to 96,000 deaths by 2040.

**Comment: Is the melanoma problem largely historical or an increasing problem?** Extracts from this study suggest the latter. This population-based epidemiological study found that melanoma constituted a considerable cancer burden in 2020 and was largely concentrated in highly developed countries, predominantly inhabited by people of European origin, with lighter skin pigmentation and therefore higher risk and higher susceptibility to the carcinogenic effects of solar radiation. The number of newly diagnosed cases of melanoma was estimated to increase by more than 50% by 2040, to 510,000. Similarly, melanoma deaths were estimated to increase by approximately 68%, from 57,000 in 2020 to 96,000 in 2040, assuming rates in 2020 remained stable. Melanoma is more common in men than in women in most parts of the world. This, however, differs by age, with rates in women exceeding those in men before 50 years of age. Sex differences also exist with respect to the anatomic localisation of the lesion; melanoma is more frequent on the trunk in men and on the lower limbs in women but whether this can be attributed to gender role–specific behaviours or to biologically intrinsic differences, such as sex hormones is unknown. They conclude melanoma is the most lethal form of skin cancer; this epidemiological assessment found a heavy public health and economic burden, and the projections suggest that it will remain so in the coming decades.

***Reference: JAMA Dermatol. 2022 May 1;158(5):495-503***
Abstract

## Five-year outcomes of a melanoma screening initiative in a large health care system

**Authors:** Matsumoto M, et al

**Summary:** This observational study compared thickness-specific incidence of melanoma in screened versus unscreened patients following a primary care-based skin cancer screening initiative. Among 595,799 analysed screen-eligible patients, 144,851 (24.3%) were screened at least once. The authors reported screened patients were more likely than unscreened patients to be diagnosed with in situ (incidence, 30.4 vs 14.4; HR, 2.6; 95% CI, 2.1-3.1; P<0.001) or thin invasive (≤1 mm) melanoma (incidence, 24.5 vs 16.1; HR, 1.8; 95% CI, 1.5-2.2; P<0.001), after adjusting for age, sex, and race. In addition, screened patients were more likely than unscreened patients to be diagnosed with in situ (incidence, 26.7 vs 12.9; HR, 2.1; 95% CI, 1.7-2.6; P<0.001) or thin invasive (≤1 mm) interval melanomas (incidence, 18.5 vs 14.4; HR, 1.3; 95% CI, 1.0-1.7; P=0.03). Incidence of melanoma thicker than 4 mm in unscreened and screened patients, respectively, was 3.3 and 2.7 (HR, 0.8; 95% CI, 0.4-1.4; P=0.38) for all melanomas and 2.7 and 1.5 (HR, 0.6; 95% CI, 0.2-1.2; P=0.15) for interval melanomas.

**Comment: Is screening for early detection of melanoma the answer to the "melanoma problem"?** Screening for melanoma in an ad hoc or in well organised studies has been part of the Australian scene over several decades. The present US study involved a large number of participants (close to 600,000) and appeared to be well conducted. This extract from the discussion identifies the problem in the screening approach. "While early detection of melanoma is a strategy to reduce melanoma morbidity and mortality, the value of a cancer screening program should most rigorously be measured not by the number of new, early cancers detected, but by its impact on the development of late-stage disease and its associated morbidity, cost, and mortality. The significant increase in melanoma incidence in the US, particularly thin melanoma, without a concomitant decrease in melanoma mortality, raises the concern that early detection efforts, such as visual skin screening, may result in overdiagnosis, meaning the detection of indolent lesions that would not have progressed to fatal melanoma prior to being detected by routine care. While we did observe a lower incidence of thick melanomas in screened patients, particularly in patients 65 years and older, these results were not statistically significant."

***Reference: JAMA Dermatol. 2022 May 1;158(5):504-512***
Abstract

## Independent evaluation of melanoma polygenic risk scores in UK and Australian prospective cohorts

**Authors:** Steinberg J, et al

**Summary:** The investigators analysed invasive melanoma incidence in the UK Biobank (n=395,647; 1,651 cases) and the Melbourne Collaborative Cohort Study (MCCS, Australia), (n=4,765; 303 cases). Three polygenic risk scores (PRSs) were evaluated: 68 single-nucleotide polymorphisms (SNPs) at 54 loci from a 2020 meta-analysis (PRS68), 50 SNPs significant in the 2020 meta-analysis excluding UKB (PRS50) and 45 SNPs at 21 loci known in 2018 (PRS45). The investigators showed predicted absolute melanoma risks based on age and sex alone underestimated melanoma incidence in the UK Biobank (ratio of expected/observed cases = 0·65, 95% CI 0·62-0·68) and MCCS (ratio of expected/observed = 0·63, 95% CI 0·56-0·72). For UK Biobank, calibration was improved by PRS adjustment, with PRS50-adjusted risks ratio of expected/observed = 0·91, 95% CI 0·87-0·95. The discriminative ability for PRS68- and PRS50-adjusted absolute risks was higher than for risks based on age and sex alone (Δ area under the curve 0·07-0·10, P<0·0001), and higher than for PRS45-adjusted risks (Δ area under the curve 0·02-0·04, P<0·001).

**Comment: Can study of genetic variants add to detection and prevention of melanoma in the community?** Polygenic risk scores aggregate the effects of many genetic variants into a single score aiming to reflect an individual's genetic risk of disease. This study examines PRS potential utility for risk-stratified cancer prevention, early detection and screening for melanoma. PRSs were from prospective studies in the UK Biobank and the MCCS. Three PRSs were identified which were associated with traditional phenotypic characteristics such as ease of tanning, skin and hair colour and melanoma incidence. The paper is highly technical but concludes, "newer melanoma PRSs derived from a larger meta-analysis have better risk prediction performance than an earlier PRS and could be used to tailor melanoma prevention and early detection strategies to different risk levels. Recalibration of 10-year absolute risks may be necessary when applied to specific populations. Ensuring that risk prediction models are well calibrated and that they can be applied to diverse populations remain key aspects for future research".

***Reference: Br J Dermatol. 2022 May;186(5):823-834***
Abstract

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**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.

## Long-term control of melanoma adrenal metastasis treated with radiotherapy

**Authors:** McCann B, et al

**Summary:** The single-centre study included 20 patients treated for melanoma adrenal metastasis with radiotherapy (8 delivered by stereotactic ablative body radiotherapy). The most common indication for radiotherapy was oligo-progressive disease (70%) followed by symptom palliation. 60% of patients had concurrent immunotherapy. The authors found 87% of adrenal lesions had an initial response to treatment with 60% maintaining local control until death or end of follow-up. Median adrenal-specific progression-free survival was 13 months. They noted 17% of patients required salvage adrenalectomy. Symptom palliation was achieved in the majority of patients and there were no grade three toxicities.

**Comment: Radiotherapy may be as good as surgery for adrenal metastases?** The adrenal gland is a frequent anatomical site of isolated metastasis, and it is postulated to be an immune-privileged site. The present study examined whether more modern stereotactic ablative radiotherapy has a role in its management and whether it would enhance effects of concurrent ICI. They report excellent local-control rates, with 87% of adrenal lesions responding to radiotherapy and the majority maintaining long-term disease control in the treated site. This was associated with limited toxicity with little risk of adrenal insufficiency. They did not observe abscopal effects in the 12 patients receiving concurrent ICI but believe the study was not adequately designed to assess this. They conclude "Our data support radiotherapy as an acceptable alternative local treatment to patients with melanoma adrenal gland metastasis, reserving surgery for salvage". Future studies with ICI in this potential immune-privileged site may give further insights into its management.

***Reference: Melanoma Res. 2022 Jun 1;32(3):166-172***
Abstract

## Time interval between diagnostic excision-biopsy of a primary melanoma and sentinel node biopsy: Effects on the sentinel node positivity rate and survival outcomes

**Authors:** El Sharouni.MA, et al

**Summary:** The authors sought to determine whether the interval between diagnostic excision of a primary cutaneous melanoma and sentinel node biopsy (SNB) influenced the sentinel node (SN)-positivity rate, recurrence or survival. Data was collected from patients with melanoma who underwent SNB within 100 days of initial diagnosis from a Dutch population-based cohort (n=7,660) and a cohort from Melanoma Institute Australia (MIA) (n=3,478). The authors concluded there was no significant association between time to SNB and SN-positivity in either cohort, nor was there an impact of time to SNB on recurrence-free survival (RFS) or OS in either cohort.

**Comment: Should we worry about interval between diagnosis and SNB?** Sentinel node biopsy is well established as an important staging investigation, but concerns have been raised as to whether a delay in carrying out a SNB could theoretically affect the likelihood of a positive result or survival because cells shed from the primary melanoma have had more time to reach regional lymph nodes or spread to distant sites. This study on 7,660 Dutch and 3,478 MIA patients found that delayed SNB in the Dutch patients was associated with increased diameter of metastasis (>0.6mm in first month to 1.2mm in 3rd month). This was not observed in the MIA cohort possibly because their procedures included ultrasound (US) assessment and early surgical intervention if SN was detected by US. They comment that the results of this study have important clinical implications if the size of SN tumour deposits is used as a criterion for recommending adjuvant systemic therapy. The authors believed however, that delaying a SNB by a few weeks may be largely inconsequential in terms of melanoma outcome compared with the latency between the malignant transformation of a pre-malignant lesion into melanoma and its diagnosis.

***Reference: Eur J Cancer. 2022 May;167:123-132***
Abstract

## Androgen receptor blockade promotes response to BRAF/MEK-targeted therapy

**Authors:** Vellano CP, et al

**Summary:** The study cohort included patients with melanoma who were treated with neoadjuvant BRAF/MEK-targeted therapy (n=51) and found significantly higher rates of major pathological response (MPR; ≤10% viable tumour at resection) and improved RFS in female versus male patients (MPR, 66% versus 14%, P=0.001; RFS, 64% versus 32% at 2 years, P=0.021). The authors report the findings were validated in several additional cohorts of patients with unresectable metastatic melanoma who were treated with BRAF- and/or MEK-targeted therapy (n=664 patients in total), demonstrating improved PFS and OS in female versus male patients. Furthermore, studies in preclinical models demonstrated significantly impaired anti-tumour activity in male versus female mice after BRAF/MEK-targeted therapy (P=0.006), with significantly higher expression of the androgen receptor in tumours of male and female BRAF/MEK-treated mice versus the control (P=0.0006 and P=0.0025). They also report pharmacological inhibition of androgen receptor signalling improved responses to BRAF/MEK-targeted therapy in male and female mice (P=0.018 and P=0.003). In contrast, induction of androgen receptor signalling was associated with a significantly impaired response to BRAF/MEK-targeted therapy in male and female patients (P=0.021 and P<0.0001).

**Comment: Do sex hormones account for differences in survival and response to targeted treatments in melanoma?** Sex differences in survival from melanoma are now well recognised with females having almost half the death rate compared to males. It is less well known that this also applies to response to targeted treatment with BRAF and MEK inhibitors. This was observed in the 5 year follow up study of dabrafenib and trametinib in treatment of metastatic melanoma reported by Robert et al and now by Wargo and colleagues in neoadjuvant BRAF/MEK studies showing higher rates of pathological responses. Pre-clinical studies show higher androgen receptor expression in tumours during treatment with BRAF/MEK inhibitors. Inhibition of androgen receptors improved responses whereas testosterone impaired responses. Equally exciting were studies largely in prostate carcinoma that showed that androgen therapy inhibited CD8 T cell responses induced by inhibition of checkpoint inhibitors. (Guan X, et al. Nature 2022 Jun;606(7915):791-796). One can expect that these findings will flow through to future studies in treatment of melanoma.

***Reference: Nature. 2022 Jun;606(7915):797-803***
Abstract