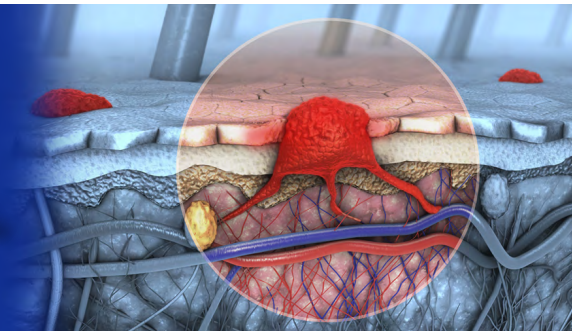
Melanoma Practice Review™



Making Education Easy

Issue 12 - 2023

In this issue:

Abbreviations used in this issue:

CTLA-4 = cytotoxic T lymphocyte antigen-4; **ECOG** = Eastern Cooperative Oncology Group; **EFS** = event-free survival; **HR** = hazard ratio; **ICI** = immune checkpoint inhibitor; **ORR** = objective response rate; **OS** = overall survival; **PBAC** = Pharmaceutical Benefits Advisory Committee; **PBS** = Pharmaceutical Benefits Scheme; **PCM** = patient-centred methodology; **PD-(L)1** = programmed death-(ligand)1; **PFS** = progression-free survival; **RFS** = recurrence-free survival; **SLNB** = sentinel lymph node biopsy; **TIL** = tumour-infiltrating lymphocyte.

Welcome to the 12th issue of Melanoma Practice Review.

This Review covers news and issues relevant to clinical practice in melanoma. It will bring you the latest updates, both locally and from around the globe, in relation to topics such as new and updated treatment guidelines, changes to medicines reimbursement and licensing, educational, professional body news and more. And finally, on the back cover you will find our COVID-19 resources, and a summary of upcoming local and international educational opportunities including workshops, webinars and conferences.

We hope you enjoy this new Research Review publication and look forward to hearing your comments and feedback.

Kind Regards,

Dr Janette Tenne
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Clinical Practice

Vitamin D supplementation increases objective response rate and prolongs progression-free time in patients with advanced melanoma undergoing anti–PD-1 therapy

Preservation of normal vitamin D levels during front-line immune checkpoint inhibitor (ICI) therapy may augment therapeutic responses and improve outcomes in patients with advanced or metastatic melanoma, according to results from this Polish study.

The researchers examined serum vitamin D levels in a cohort of 200 patients with locally advanced, inoperable or metastatic melanoma before and every 12 weeks during single-agent immunotherapy with the anti–programmed death-1 (PD-1) antibodies nivolumab or pembrolizumab. The study design included both prospective and retrospective components depending on trial enrolment date, with the earlier enrolled cohort (prior to July 2018) all receiving vitamin D supplementation and analysed retrospectively based on preserved serum samples. With a 12-month follow-up period, objective response rates (ORRs) were significantly higher in patients with a normal serum vitamin D level - regardless of whether this was a normal baseline level or corrected-to-normal level achieved through supplementation – versus patients with a vitamin D deficiency (56% vs 36.2%; p=0.01). Outcome measures also favoured the cohort with normal vitamin levels with an almost doubling of median progression-free survival (PFS), from 5.75 months in the low vitamin D group to 11.25 months in the normal vitamin D level group (p=0.01) and an absolute extension in overall survival (OS) of over four months (31.5 vs 27 months; p=0.39).

Previous research has demonstrated the modulating function of vitamin D, especially D3 (cholecalciferol), on the immune system and the authors hypothesised that the effect may be exerted through tumour-infiltrating lymphocytes. While the findings need to be confirmed in randomised trials and the mechanism of the effect remains to be elucidated, vitamin D supplementation may offer a relatively easy way to optimise ICI therapy in melanoma.

Cancer. 2023;129(13):2047-55

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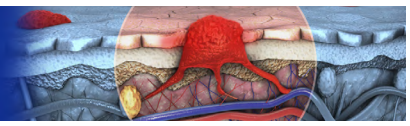


Adjuvant nivolumab versus ipilimumab in resected stage III/IV melanoma

Five-year efficacy and biomarker results from CheckMate 238 (CHECKpoint Pathway and nivoluMAb Clinical Trial Evaluation 238) continue to demonstrate superior efficacy and a more favourable safety profile for nivolumab compared to ipilimumab when used in the adjuvant setting for resected melanoma at high risk of recurrence.

Briefly, the international trial enrolled 905 patients at least 15 years of age with histologically confirmed stage 3b/4 melanoma with metastases to regional lymph nodes or distant metastases (including brain metastases) who had undergone a complete regional lymphadenectomy or resection. Patients received up to 12 months of single-agent nivolumab (n=453; 3 mg/kg every two weeks) or ipilimumab (n=453; 10 mg/kg every three weeks for four doses and then every 12 weeks). In an interim analysis at 18 months of follow-up, PD-1 inhibition with nivolumab exhibited better efficacy, decreasing melanoma recurrence by 10% and conferring a 35% reduced risk of disease recurrence of death compared to cytotoxic T lymphocyte antigen-4 (CTLA-4) blockage with ipilimumab (12-month recurrence-free survival [RFS], 70.5% vs 60.8%; hazard ratio [HR] 0.65). The improved prevention of recurrence with nivolumab versus ipilimumab was durable with significantly increased RFS rates at three- and four-year follow-ups. All analyses also consistently found nivolumab to be less toxic and associated with fewer grade 3/4 treatment-related adverse events versus ipilimumab. As reported by Larkin et al sustained, long-term benefits to nivolumab adjuvant treatment continue to be seen at five-year follow-up with significant improvements in RFS and distant metastasis-free survival over ipilimumab adjuvant treatment (five-year RFS: 50% vs 39%; HR 0.72). Subgroup analyses provided results consistent with findings in the overall population with superior efficacy of nivolumab regardless of disease stage, PD-ligand (L)1 expression or *BRAF* status. OS data remains immature. Biomarker analyses failed to identify factors with clinically meaningful predictive value although several factors associated with improved outcomes across both trial arms were noted, including higher tumour mutational burden and high tumour PD-L1 expression.

Front-line immunotherapy doublets such as nivolumab/ipilimumab and nivolumab/relatlimab (an anti-LAG3 monoclonal antibody) have demonstrated PFS and OS benefits for unresectable melanoma. In the adjuvant treatment setting anti-PD-1 agents (e.g., pembrolizumab) consistently demonstrate improved efficacy, durability and safety versus CTLA-4 blockade with ipilimumab. Whether the treatment landscape in resected melanoma will move towards combination immunotherapy regimens remains to be seen but the choice between ICI monotherapy or combination therapy may be driven by toxicity considerations.

Clin Cancer Res. 2023; Apr 14; Online ahead of print

First-line, fixed-duration nivolumab plus ipilimumab followed by nivolumab in clinically diverse patient populations with unresectable stage III or IV melanoma: CheckMate 401

CheckMate 401, a multinational single-arm phase 3b trial, evaluated a strategy of first-line combination ICIs with nivolumab plus ipilimumab followed by single-agent nivolumab in a diverse population with unresectable advanced metastatic melanoma, reflective of real-world practice, including patients with poor prognosis features. A cohort of 533 patients with previously untreated advanced (stage 3/4) melanoma with metastases not able to be surgically excised were enrolled. The patient population was comprised predominantly of European males and included various melanoma subtypes such as cutaneous, ocular, mucosal and acral with/without asymptomatic brain metastases. Enrolment was not restricted by *BRAF* mutational status but inclusion criteria specified patients be ambulatory and capable of self-care with an Eastern Cooperative Oncology Group (ECOG) performance score of ≤ 2. Patients received four doses of induction therapy with combination nivolumab/ipilimumab (1 mg/kg and 3 mg/kg every three weeks, respectively) followed by nivolumab maintenance monotherapy (240 mg every two weeks) for a total treatment duration of up to two years. Treatment was reported to be tolerable with the most common grade 3-5 treatment-related adverse events gastrointestinal, hepatic and endocrine, reported in 16%, 15% and 11% of patients, respectively. Efficacy outcomes in the all-comer population with a median follow-up of 21.6 months included an ORR of 44%, encompassing 11% with a complete response. The median OS in the overall study population was not reached (two-year OS rate, 44%). Reduced efficacy was noted in ocular/uveal and mucosal disease subtypes with ORRs of 9%/44% and two-year OS rates of 36%/38%, and in patients with poorer performance status (ORR 30%; two-year OS 44%). The authors emphasised that novel efficacious treatment strategies are urgently required for these rarer forms of melanoma.

J Clin Oncol. 2023; Jun 12 [Online ahead of print]

Determinants of overall survival in patients with metastatic uveal melanoma

While treatments for primary uveal melanoma tumours – the most common intraocular cancer - yield high rates of local control, up to one-third of patients develop metastatic disease within ten years and have an abysmal survival with a median of about 12 months. In this context, this study sought to ascertain factors prognostic for survival in metastatic uveal melanoma, leveraging data from two clinical cohorts with long-term follow-up.

Retrospective analysis was based on medical chart review of 89 patients – an initial cohort of 71 patients treated at the Yale New Haven Health Centre in Connecticut between March 2007 and November 2021 and a validation cohort of 18 patients treated between February 2005 and June 2022 at the Memorial Sloan Kettering Cancer Centre ocular oncology service. The patient population was almost exclusively Caucasian, with a median age at first metastasis of over 60 years and a median lag between time of primary tumour diagnosis and development of metastatic disease of almost three years. The median OS from time of first metastasis was less than two years (21.8 months in the initial cohort and 17.6 months in the validation cohort). Cox proportional hazards regression analysis revealed female gender and ICI therapy (both anti-CTLA-4 and anti-PD-1 agents) to be independent factors positively associating with survival, with Kaplan–Meier analysis estimating the risk of death to be more than halved with either factor. Liver metastasis, found in a high proportion of patients in both cohorts (78.9% including 35.7% with a lesion ≥ 30mm in the initial cohort and 94.4% in the validation cohort) was associated with significantly shorter survival, as was poorer performance status (both HR 2.8). These findings suggest that ICIs may be a valid treatment option for this population.

Cancer. 2023; Jun 29. Online ahead of print

Neoadjuvant–adjuvant or adjuvant-only pembrolizumab in advanced melanoma

Patients with clinical stage 3/4 resectable melanoma are at a high risk of regional recurrence and progression to metastatic disease despite surgical resection with lymph node dissection and/or resection of in-transit disease ± adjuvant systemic therapy or radiation. Data from this phase 2 multicentre US trial (S1801) provides direct head-to-head evidence to support a neoadjuvant plus adjuvant immunotherapy approach in this population, demonstrating superior event-free survival (EFS) compared to adjuvant-only therapy. A total of 313 adult patients with clinically detectable stage 3 (N1b-N3c) or 4 resectable melanoma - including of mucosal or acral origin - with or without nodal, satellite, in-transit, distant or recurrent disease were enrolled. Patients were randomised to receive 18 cycles of pembrolizumab monotherapy – administered either as three pre-operative cycles plus 15 post-operative cycles (neoadjuvant-adjuvant arm; n=154) or exclusively post-surgery (adjuvant arm; n=159). The trial demonstrated that receipt of pembrolizumab both before and after surgery significantly prolonged EFS versus adjuvant pembrolizumab alone, with two-year EFS rates of 72% and 49% in the respective treatment arms (p=0.004). In the neoadjuvant-adjuvant cohort surgery was precluded by disease progression or adverse events in less than 10% of patients. Grade 3 or worse treatment-related adverse events were comparable between arms (12% vs 14%) and no new safety concerns were reported.

N Engl J Med. 2023;388(9):813-23

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

This real-world study from Canada reports treatment-free survival outcomes in patients with advanced melanoma who received first-line treatment with a single-agent anti-PD-1 antibody (nivolumab or pembrolizumab) or doublet immunotherapy targeted to both PD-1 and CTLA-4 to characterise time spent free of systemic therapy between regimens. Data derived from the observational Alberta Immunotherapy Database study and included patients (n=316) with locally advanced metastatic melanoma (stage 3 unresectable or stage 4 metastatic) who received front-line nivolumab or pembrolizumab monotherapy, or combination nivolumab-ipilimumab, in an approximately seven-year period up to May 2020. The study defined treatment-free survival as the difference in the 36-month mean survival duration between time from treatment initiation to- termination or death, and time from treatment initiation to subsequent line of systemic therapy or death. Results showed extended treatment-free survival – representing better survival with greater time without treatment - in the cohort who received doublet immunotherapy compared to single-agent anti-PD-1 treatment (12.4 vs 8.9/11.1 months) and the authors concluded that this outcome measure provides an informative end point. With the obvious limitations imposed by the retrospective design of this study the findings indicate that doublet immunotherapy regimens may prolong time without therapy in patients with advanced melanoma, potentially with quality-of-life ramifications.

JAMA Netw Open. 2023;6(6): e2319607

Camrelizumab plus apatinib and temozolomide as first-line treatment in patients with advanced acral melanoma

The CAP 03 phase 2 nonrandomised clinical trial evaluated a front-line triplet regimen incorporating an ICI, an antiangiogenic agent and chemotherapy in treatment-naïve advanced acral melanoma. Patients (n=50) with unresectable stage 3 or metastatic acral melanoma who had not received prior systemic anti-tumour therapy in the advanced setting received open-label continuous 28-day cycles of camrelizumab, apatinib plus temozolomide until prohibitive toxicity or disease progression. At a median follow-up of just over one year 32 patients achieved an objective response per Response Evaluation Criteria in Solid Tumours (RECIST) criteria for an ORR of 64%. Best responses were almost exclusively partial. A further 13 patients attained stable disease for a disease control rate of 88%. Responses were elicited rapidly, with a median time of 2.7 months, including almost one-quarter of patients who attained a partial response by the first radiologic evaluation after two cycles of treatment. Six- and 12-month PFS rates were 84.8% and 65.1%, respectively with an estimated median PFS of 18.4 months. At 12-months the OS rate was 91.6% and the median was not reached. Treatment-related adverse events were common including grade 3 or 4 in 62% of patients, most commonly increased gamma-glutamyltransferase levels, decreased neutrophil count, increased conjugated bilirubin levels and increased aspartate aminotransferase levels. Adverse event onset mostly occurred around four months after treatment initiation. Immune-related adverse events were transient and manageable with alleviation of symptoms in about 10 days. There were no treatment-related fatalities. This research group are planning a randomised trial to confirm the efficacy of this three-drug combination in advanced acral melanoma.

JAMA Oncol. 2023; Jun 1; Online ahead of print

Tebentafusp in combination with durvalumab and/or tremelimumab in patients with metastatic cutaneous melanoma: a phase 1 study

In light of the survival benefit conferred by the first-in-class gp100×CD3 T-cell receptor bispecific antibody tebentafusp in metastatic uveal melanoma - albeit with a modest response rate - an open-label, multicentre, phase 1b, dose-escalation trial was conducted to assess the preliminary safety and efficacy of tebentafusp-based immunotherapy combination regimens in HLA-A*02:01-positive patients with cutaneous melanoma. A heavily pre-treated cohort of patients with cutaneous melanoma were enrolled, most of whom had progressed on prior PD-(L)1 inhibitor therapy (n=85; median three prior lines of therapy). Patients were randomly allocated to one of the three trial arms and received tebentafusp plus durvalumab (arm A; n=43), tebentafusp plus tremelimumab (arm B; n=13) or tebentafusp plus durvalumab and tremelimumab (arm C; n=29). The maximum tolerated dose was not confirmed with any regimen but maximum administered doses of tebentafusp in arms A, B and C were 68 mcg, 30 mcg and 50 mcg with 20 mg/kg durvalumab, 1 mg/kg tremelimumab and 10 mg/kg durvalumab plus 1 mg/kg tremelimumab, respectively. Analysis of efficacy in evaluable patients in arms A and B (tebentafusp plus durvalumab ± tremelimumab) revealed anti-tumour activity for the combination regimens with a response rate of 14% including one complete response attained after tebentafusp plus durvalumab treatment and tumour shrinkage as the best response in another 41% of patients. The median duration of response was over 18 months with one response ongoing at over three years. The estimated median OS duration was 18.7 months. One-year OS rate was 74% with tebentafusp in combination with anti-PD-1 therapy (arm A) and was not improved significantly with the addition of anti-CTLA-4 inhibition (arm C: 79%). Given the clinically meaningful antitumor activity reported with tebentafusp plus ICIs, this combination may be a therapeutic option in this population.

J Immunother Cancer. 2023;11(6): e006747

Regulatory News

PBAC recommendations

At its March 2023 meeting the Pharmaceutical Benefits Advisory Committee (PBAC) recommended the special arrangements under Section 100 (Efficient Funding of Chemotherapy) listing of relatlimab and nivolumab (Opdualag®) for patients with unresectable stage 3 or 4 malignant melanoma

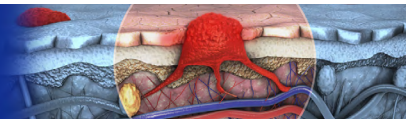
Read more here

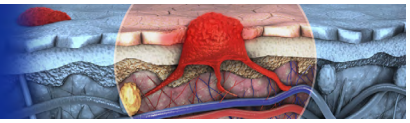
PBS listings

At the November 2022 PBAC meeting a recommendation was made to expand the indication of the combination of **nivolumab plus ipilimumab** (Opdivo®; Yervoy®) to include the treatment of unresectable stage 3 or 4 malignant melanoma in patients who experience melanoma recurrence while receiving, or within six months of completing, adjuvant anti-PD-1 inhibitor monotherapy. This regimen was subsequently subsided for this indication by the Pharmaceutical Benefits Scheme (PBS), effective 1 March 2023.

This expanded PBS listing is projected to save patients more than 99% per treatment course, reducing each script from AU$10,200 to a maximum of AU$30.

Read more here





News in Brief

Deep learning-based scoring of tumour-infiltrating lymphocytes is prognostic in primary melanoma and predictive to PD-1 checkpoint inhibition in melanoma metastases

This study from Germany confirmed the prognostic value of an electronic tumour-infiltrating lymphocytes (TIL) score in stage 1B-2C primary melanoma and its predictive ability with regard to response to PD-1 inhibitor therapy in treatment-naïve metastatic disease. The study utilised digital pathology to enumerate TILs in hematoxylin-eosin-stained slides from 512 primary cutaneous tumour samples or metastatic samples and employed the deep-learning *NN192* algorithm. An electronic TIL score of ≤16.6% was identified in the primary tumour as an adverse prognostic factor, associating with unfavourable RFS and distant metastasis-free survival. Matched primary lesion-to-metastasis analysis found significantly reduced TILs levels in metastases. Finally, higher TIL (> 12.2%) in metastatic sites correlated with improved outcomes after PD-1 targeted immunotherapy.

EBioMedicine. 2023; 93:104644

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

Results from the phase 1/2a RELATIVITY-020 trial indicate that the combination of nivolumab plus relatlimab has activity in advanced melanoma that progressed during PD-(L)1 inhibitor therapy. In a cohort of 518 patients with disease progression during or within three months of at least one anti–PD-1/PD-L1–containing regimen/s who received nivolumab/relatlimab, between 9.2% and 12% attained a response including 2.3%-4.3% with a complete response. Stable disease in roughly another 30% of patients resulted in a disease control rate of approximately 40%. Responses were durable with a median response of over one year. The safety profile was reported to be manageable.

J Clin Oncol. 2023;41(15):2724-35

Improving selection for sentinel lymph node biopsy among patients with melanoma

A first-in-kind hybrid prognostic study/decision analytical modelling analysis has reported improved accuracy of melanoma patients likely to return a positive sentinel lymph node biopsy (SLNB) with a patient-centred methodology (PCM) compared to the current eligibility guidelines, with cost-saving implications. Comparison of probabilities of SLNB positivity created via PCM or conventional logistic regression analysis in Australian (n=3,640) and US cohorts (n=1,342) who underwent SLNB between 2000 and 2014 revealed improved prognostic accuracy of the former, with area under the receiver operating characteristic curves of 0.803 and 0.826 in the two cohorts, respectively. A simulation analysis further found that utilising minimally acceptable PCM-generated probabilities of 8.7% and 23.7% resulted in improvements in the positivity rate to 29.3% and 42.7% while maintaining or reducing the number of SLNBs performed.

JAMA Netw Open. 2023;6(4): e236356

Asian American and Pacific Islander patients with melanoma have increased odds of treatment delays: A cross-sectional study

An analysis of 17 years of data from the US National Cancer Database finds a disparity in timing of surgery by race in patients with melanoma. In a cohort of over 350 thousand patients diagnosed with cutaneous melanoma over the study period, 0.33% were Asian American or Pacific Islander. These patients were significantly more likely to experience delays of up to or longer than three months between diagnosis and definitive surgery than Caucasian patients. Given the known deleterious impact of delayed treatment on mortality, ways to mitigate this race disparity are necessary.

J Am Acad Dermatol. 2023; May 22. Online ahead of print

COVID-19 Resources

Cancer Australia

European Academy of Dermatology and Venereology

American Academy of Dermatology

European Society of Medical Oncology

American Society of Clinical Oncology

Conferences, Workshops, and CPD

The Australasian College of Dermatologists – Events

DermNet New Zealand – Conferences

COSA – Events

MOGA – Events

COMS – Conferences and Meetings on Dermatology

Research Review Publications

Dermatology Research Review with Dr Warren Weightman and Clinical Professor Saxon Smith

Melanoma Research Review with Professors Michael Henderson and Peter Hersey

Skin Cancer Research Review with Dr David Simpson

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