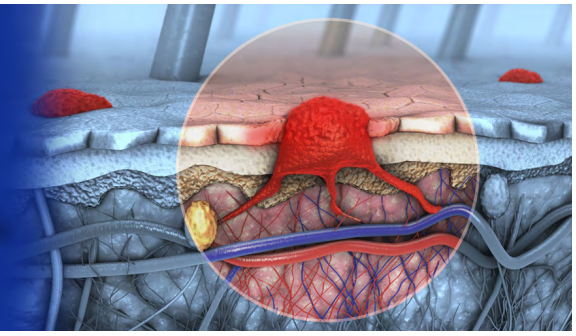
# Melanoma Practice Review™



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Issue 14 - 2024


## In this issue:



**Abbreviations used in this issue:**

**ASCO** = American Society of Clinical Oncology; **CAR** = chimeric antigen receptor; **CTLA-4** = cytotoxic T lymphocyte antigen-4; **FDA** = US Food & Drug Administration; **HLA-A** = human leukocyte antigen A; **HR** = hazard ratio; **OS** = overall survival; **PBAC** = Pharmaceutical Benefits Advisory Committee; **PBS** = Pharmaceutical Benefits Scheme; **PD-1** = programmed death 1; **PPARα** = peroxisome proliferator receptor alpha; **TLPO** = tumour lysate particle only.


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# Welcome to the 14th 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**
**Editor**
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## Clinical Practice

### Society for Immunotherapy of Cancer (SITC) clinical practice guideline on immunotherapy for the treatment of melanoma, version 3.0

In light of the rapidly evolving treatment landscape in melanoma and to ensure optimal therapeutic outcomes as well as quality of life for all patients, the Society for Immunotherapy of Cancer have published recommendations for dermatologists and oncologists regarding the use of immunotherapy in various treatment settings and for special patient populations.

A range of different immunotherapeutic approaches have demonstrated efficacy in various melanoma subtypes including immune checkpoint inhibitors in both resectable and non-resectable metastatic cutaneous disease, oncolytic virotherapy cutaneous melanoma and bispecific T-cell engager therapy for human leukocyte antigen A (*HLA-A*)*02:01 genotype-positive uveal melanoma. The range of immune checkpoint inhibitors continues to expand beyond anti-programmed cell death protein 1 (PD-1) and anti-cytotoxic T lymphocyte antigen-4 (CTLA-4) agents to also include anti-lymphocyte-activation gene 3 (LAG-3) agents.

Developed by an expert panel, the guidelines provide evidence- and consensus-based recommendations based on published data and clinical experience for six patient populations – those with pre-existing autoimmune disease, solid organ transplant recipients, elderly individuals, those living with HIV, pregnant women and those with rare non-cutaneous subtypes of melanoma such as uveal and mucosal. Advice is also provided regarding therapy selection in the neoadjuvant/adjuvant settings, use of immunotherapy in $BRAF^{V600}$-mutated disease, treatment for brain metastases, evaluation of treatment response and survivorship, *inter alia*.

A synopsis of treatment recommendations for special patient populations generally excluded from clinical trials follows:

**Patients with altered immune systems**

Pre-existing altered immunity does not necessarily preclude immunotherapy treatment for melanoma but does necessitate a thorough collaborative multidisciplinary approach to establish whether the risk-benefit profile is favourable in each case. In solid organ recipients and individuals with pre-existing autoimmune diseases the risk of allograft loss and disease flare need to be carefully considered. Advocacy is given to treatment of such cases in specialised cancer centres and adoption of shared decision-making practices involving the patient.

**Patients living with HIV**

Immune checkpoint inhibitor therapy is not contraindicated due to HIV infection, but this patient population requires collaborative care involving an infectious disease specialist. Strong endorsement is also given to initiation of highly active antiretroviral treatment.

**Pregnant women**

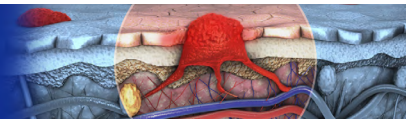
There are no clinical trial data to inform the safety of immunotherapy for melanoma during pregnancy and the Society for Immunotherapy of Cancer therefore discourage commencement of treatment during the gestation period.

**Management of rare non-cutaneous disease subtypes**

The guidelines endorse the use of molecular mutation testing to determine eligibility for targeted therapy in all patients with mucosal or uveal melanoma subtypes and further suggest referral to academic medical centres or enrolment in a suitable clinical trial. Advanced disease may require front-line immunotherapy. It is suggested that treatment for mucosal or uveal melanoma be undertaken at a speciality centre that can appropriately determine the benefits of surgical resection or eye-directed therapy, respectively.

This publication is a valuable resource for clinicians treating patients with melanoma and may aid personalisation of management in a diverse patient population.


J Immunother Cancer. 2023;11(10):e006947



## Longer follow-up from KEYNOTE-942 finds a durable clinical benefit to adjuvant mRNA vaccine in resected melanoma

Positive two-year data regarding the substantial anti-melanoma activity achieved through boosting of innate immunity by combining immunotherapy plus a targeted messenger RNA (mRNA) vaccine from KEYNOTE-942 were first presented at the 2023 American Association for Cancer Research (AACR) and American Society of Clinical Oncology (ASCO) Annual Meetings and subsequently published in *The Lancet*. A robust clinical benefit to the addition of mRNA-4157 - a personalised mRNA-based neoantigen therapy – to standard of care single-agent checkpoint inhibition with pembrolizumab was demonstrated in patients with high-risk resected melanoma, conferring clinically meaningful and statistically significant reductions in the risk of both disease recurrence, and of distant metastasis or death. Based on these results a doublet regimen of mRNA-4157 plus pembrolizumab was granted breakthrough therapy designation by the US Food & Drug Administration (FDA) to expedite its development, and regulatory review and recognition under the Priority Medicines scheme by the European Medicines Agency for this indication.

Now, Merck and Moderna - the trial sponsors - have reported that these benefits are maintained at three-year follow-up. Briefly, patients (n=157) with completely resected Stage 3B-4 cutaneous melanoma enrolled to the trial received up to 18 cycles of adjuvant pembrolizumab ± up to nine intramuscular doses of mRNA-4157. The prolonged recurrence-free survival with mRNA-4157 plus pembrolizumab compared to pembrolizumab monotherapy reported previously was maintained at longer follow-up, with the risk of recurrence or death almost halved (hazard ratio [HR] 0.510). Similarly, a benefit in reduced risk of distant metastasis was found at this time point with a HR of 0.384. Benefits were elicited without significantly increasing the toxicity profile relative to pembrolizumab monotherapy and no novel safety concerns were reported.

The global phase 3 INTerpath program will further evaluate individualised neoantigen therapy with mRNA-4157 plus pembrolizumab in a range of tumour types including resected high-risk melanoma (V940-001; NCT05933577) and non-small cell lung cancer (INTerpath-002; NCT06077760). In a statement made to CNBC's Squawk Box, Moderna's CEO have speculated that the vaccine may be commercially available as soon as next year.

The news release from Moderna can be found here

## FDA approves lifileucel for unresectable or metastatic melanoma

Recently, the tumour infiltrating lymphocyte therapy lifileucel (Amtagvi®) gained FDA approval for the treatment of patients with previously treated unresectable or metastatic melanoma through the Accelerated Approval pathway. The once-off treatment is a tumour-derived autologous T cell immunotherapy and is indicated for patients with advanced (Stage 3C or 4) progressive disease following prior therapy with at least one systemic therapy including a PD-1 blocking antibody and, in *BRAF*$^{V600}$ mutation-positive cases a BRAF inhibitor ± a mitogen-activated extracellular signal-regulated kinase (MEK) inhibitor. Lifileucel is the first tumour-derived T cell immunotherapy to receive FDA approval, although other cellular therapies that employ ex vivo engineering, such as chimeric antigen receptor (CAR) T cell therapy, are utilised in a range of blood malignancies.

US regulatory approval was based on data from the phase 2 C-144-01 trial (NCT02360579) that reported responses to a single lifileucel infusion plus interleukin-2 following a nonmyeloablative lymphodepletion preconditioning regimen in approximately one-third of patients with immune checkpoint inhibitor refractory disease (Chesney J et al. *J Immunother Cancer*. 2022;10[12]:e005755). The confirmatory phase 3 TILVANCE-301 trial will elucidate the efficacy of lifileucel plus pembrolizumab versus pembrolizumab monotherapy in post-PD-1 melanoma and aims to support full FDA approval of lifileucel in this treatment space, as well as establish benefit as an earlier line of therapy.

The full FDA press release can be read here

## Treatment with the PPARα agonist fenofibrate improves the efficacy of CD8+ T cell therapy for melanoma

A research group from the Wistar Institute in Pennsylvania, USA provide preclinical evidence suggesting that metabolic reprogramming of tumour antigen-specific CD8+ T cells may augment their therapeutic efficacy in solid tumours. Despite the resounding success of T-cell-based cellular therapies such as CAR T-cells in liquid cancers, to date their anti-tumour activity against solid tumours has been limited. The study employed patient-derived xenograft melanoma models to evaluate the hypothesis that inducing a switch in T cell cellular metabolism from glycolysis to fatty acid oxidation may mitigate or negate the main underlying mechanism driving apoptosis of transferred T cells and promote *in vivo* persistence. The common cholesterol drug fenofibrate - a peroxisome proliferator receptor alpha (PPARα) agonist was utilised to induce fatty acid oxidation metabolism in *ex vivo* expanded tumour-infiltrating lymphocytes prior to their deployment against melanoma in mice generated using transplanted human tumour fragments or tumour cell lines. Results showed a significant improvement in both the persistence and efficacy of fenofibrate treated versus non-treated tumour antigen-specific CD8+ T cells.

Mol Ther Oncolytics. 2023:31:100744

## Three-year overall survival with tebentafusp in metastatic uveal melanoma

Based on the demonstrated survival benefit of front-line treatment with the bispecific fusion protein tebentafusp (Kimmtrak®) versus standard therapy in previously untreated *HLA-A**02:01–positive, unresectable or metastatic uveal melanoma in Immunocore's global phase 3 IMCgp100-202 trial it was granted various regulatory bodies approval for this indication, including in Australia (TGA listing for tebentafusp), the US and Canada (*N Engl J Med*. 2021;385:1196–206).

Tebentafusp is comprised of an anti-glycoprotein 100 (gp100) T cell receptor (preferentially expressed on melanoma cells) fused to an anti-CD3 antibody fragment. Almost 400 adult patients with advanced uveal melanoma who had not received systemic or liver-directed chemo-, radio- or immune-therapy in the advanced setting were randomised 2:1 to receive tebentafusp or investigator's choice of single-agent immune checkpoint inhibitor or chemotherapy (control; pembrolizumab, ipilimumab or dacarbazine). Primary analysis showed that relative to the control arm front-line tebentafusp boosted the one-year overall survival rate by 14% and almost halved the risk of death (73% vs 59%; HR 0.51).

Now, three-year data from the trial reveals a durable survival benefit to tebentafusp, extending median overall survival (OS) by almost five months versus control (21.6 vs 16.9 months; HR 0.68). The three-year OS rate was reported to be 27% in the tebentafusp arm, compared with 18% in the control arm, suggesting that although an advantage is conferred only a relatively small proportion of patients derive this benefit. At longer follow-up no novel toxicity concerns were observed, with most adverse events noted earlier, low rates of treatment discontinuation due to toxicity and no treatment-related mortality. Efficacy may be enhanced by identification of biomarkers predictive of response. TebeMRD, an academic study, is evaluating tebentafusp in patients with residual microscopic disease following treatment of their primary tumour.

N Engl J Med. 2023;389(24):2256-66

## Overall survival from tebentafusp versus nivolumab plus ipilimumab in first-line metastatic uveal melanoma: a propensity score-weighted analysis

In order to ascertain the relative efficacy of front-line tebentafusp versus nivolumab plus ipilimumab therapy for metastatic uveal melanoma in the absence of direct head-to-head clinical trial evidence a propensity-score weighted analysis was undertaken. Although tebentafusp demonstrated improved survival relative to single-agent checkpoint inhibitor or chemotherapy (investigator's choice of pembrolizumab, ipilimumab or dacarbazine) in adult patients with previously untreated *HLA-A**02:01–positive disease in IMCgp100-202, the efficacy of tebentafusp versus an immunotherapy doublet targeting PD-1 plus CTLA-4 remains unclear.

Data from patients enrolled in the open-label phase 3 IMCgp100-202 trial and the Spanish single-arm GEM-1402 study of nivolumab plus ipilimumab were included in propensity score-based inverse probability of treatment weighting analysis with consideration for seven factors - age, sex, baseline lactate dehydrogenase, baseline alkaline phosphatase, disease location, Eastern Cooperative Oncology Group status and time from primary diagnosis to metastasis. Results revealed a survival benefit with front-line tebentafusp compared to combination nivolumab + ipilimumab with an improvement in one-year OS from 50% to 73% (HR 0.52). This finding was consistent across multiple sensitivity analyses employing diverse weighting methods. In addition, no significant difference in survival was found between single-agent versus doublet immune checkpoint inhibitor immunotherapy (pembrolizumab vs nivolumab + ipilimumab). The study authors concluded that based on these data tebentafusp should remain the standard of care in this patient population.

Ann Oncol. 2023; Dec 2; Online ahead of print

## Association between pretreatment emotional distress and neoadjuvant immune checkpoint blockade response in melanoma

Somatic manifestations resulting from adverse psyche have long been reported, with substantial evidence correlating emotional distress such as depression or anxiety with impaired immune regulation in general and worse outcomes in patients with a range of malignancies. Although the aetiology of this link has not been definitely delineated, psychoimmune regulatory processes such as elevated inflammation, immunosuppressive cytokines and immune cell dysfunction have all been hypothesised to contribute to enhanced tumour evasion of the immune response.

Now, results from a post hoc analysis of data from the phase 2 PRADO trial of neoadjuvant combination nivolumab plus ipilimumab in adult patients with resectable stage 3 melanoma with at least one macroscopic lymph node metastasis find that emotional distress prior to treatment correlates with worse responses to immune checkpoint blockade and a significantly greater likelihood of disease recurrence and distant metastasis. Analysis stratified by the presence/absence of pre-treatment emotional distress per the European Organisation for Research and Treatment of Cancer scale for emotional functioning was undertaken with adjustment for potential biomarkers of response, such as interferon-gamma signature and tumour mutational burden. Results showed that relative to psychologically healthy patients, those with emotional distress had lower odds of attaining a major pathological response to neoadjuvant immunotherapy (46% vs 65%; adjusted odds ratio 0.20; $p$=0.038) and were at significantly greater risk for melanoma recurrence (two-year recurrence-free survival rates, 74% vs 91%; adjusted HR 3.81) and distant metastases (two-year distant metastasis-free survival rates, 78% vs 95%; adjusted HR 4.33; $p$=0.04).

These data suggest that emotional distress may be prognostic for clinical response to neoadjuvant immunotherapy in patients with melanoma and suggest that early psychological interventions to alleviate emotional distress may improve response to immune checkpoint inhibitor therapy and oncologic outcomes.

Nat Med. 2023;29(12):3090-99

# Regulatory News

## PBS listings

From the 1st of February this year the following treatments will be subsided under the Pharmaceutical Benefits Scheme (PBS):

- a fixed-dose combination immunotherapy comprised of nivolumab plus relatlimab (Opdualag®) for patients at least 12 years of age with advanced-stage recurrent or metastatic melanoma.
- Tebentafusp (Kimmtrak®) for unresectable or metastatic uveal melanoma

Without PBS funding, these medications would cost approximately $300,000 and $790,000 per course of treatment, respectively.

More details can be found here & here

Based on Pharmaceutical Benefits Advisory Committee (PBAC) recommendation, the existing PBS listing for adjuvant pembrolizumab (Keytruda®) for patients with resectable Stage 3B-D malignant melanoma will be expanded to also include the treatment in the neoadjuvant setting. Australia is the first country in the world to approve and subsidise neoadjuvant pembrolizumab for this indication.

Read more here

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**AE** = adverse event; **I-O** = immuno-oncology; **LDH** = lactate dehydrogenase; **TRAE** = treatment-related adverse event.


**References: 1.** OPDUALAG (nivolumab/relatlimab) Product Information (rss.medsinfo.com.au/bq/pi.cfm?product=bqpopdu). **2.** OPDIVO (nivolumab) Product Information (rss.medsinfo.com.au/bq/pi.cfm?product=bqpopdiv). **3.** YERVOY (ipilimumab) Product Information (rss.medsinfo.com.au/bq/pi.cfm?product=bqpyervo). **4.** Larkin *et al. New Engl J Med* 2019;381:1535–46 (including supplementary appendix). **5.** Cancer Council Australia. Cancer Guidelines Wiki. Clinical practice guidelines for the diagnosis and management of melanoma. Available at: wiki.cancer.org.au. Accessed July 2023. **6.** Long *et al. Lancet Oncol* 2018;19:672–681. **7.** Atkins *et al. J Clin Oncol* 2013;41:186–97. **8.** Wolchok *et al. J Clin Oncol* 2022;40:127–37 (including supplementary appendix).

## News in Brief

### Phase 3 trial of TLPO vaccine for melanoma to commence in 2024

A tumour lysate particle only (TLPO) vaccine that demonstrated promising efficacy in advanced melanoma in phase 2 testing (*J Immunother Cancer* (2021;9[Suppl 2]:A1054) has received FDA approval to proceed to phase 3 clinical testing. The trial is scheduled to commence this year, pending confirmation of funding, and has a planned accrual of approximately 500 patients.

Press releases from Orbis Health Solutions regarding the TLPO vaccine can be found here

### SEACRAFT-2 to evaluate naporafenib + trametinib for immunotherapy refractory *NRAS*-mutant melanoma

A news release from the Biotech company Erasca reports that a phase 3 trial to evaluate the clinical efficacy of naporafenib + trametinib versus physician's choice of single-agent dacarbazine, temozolomide or trametinib for progressive *NRAS*-mutated metastatic melanoma after anti-PD(L)1-based therapy will commence this year. Naporafenib, a first-in-class pan-RAF inhibitor was previously granted FDA Fast Track Designation for this indication.

The news release can be read here

### Management of metastatic uveal melanoma patients on tebentafusp in a real-world setting

Data from a single-centre Canadian study of patients with metastatic uveal melanoma treated with tebentafusp were presented at the 2023 European Society for Medical Oncology (ESMO) Congress in October last year. Results confirmed the real-world effectiveness of tebentafusp, reporting attainment of disease-control in two-thirds of patients and a one-year OS rate of 68% in a mostly treatment-naïve cohort (n=36).

Ann Oncol 2023;34(Supplement 2_1131P): S679

### ctDNA reduction and clinical efficacy of the darovasertib + crizotinib combination in metastatic uveal melanoma

The therapeutic potential of dual inhibition of protein kinase C plus c-MET warrants further evaluation in metastatic uveal melanoma, with positive preliminary efficacy reported in a phase 1/2 study. Efficacy results in 63 patients treated with darovasertib plus crizotinib included a confirmed partial response in 30% and tumour shrinkage in 92%. Efficacy was reported regardless of *HLA-A2* status and in both treatment-naïve and pre-treated cohorts.

Ann Oncol 2023;34(Supplement 2_10810): S651

## COVID-19 Resources

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

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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