Making Education Easy

28-31 October, 2021

In this review:

Abbreviations used in this review:

CI = confidence interval
CNS = central nervous system
HR = hazard ratio
LDH = lactate dehydrogenase
LIF = leukaemia inhibitory factor
OR = odds ratio
OS = overall survival
PFS = progression-free survival
VEGF = vascular endothelial growth factor

Claim CPD/CME points Click here for more info.

Welcome to this review of the 18th International Congress of the Society for Melanoma Research (SMR) which was held online in late October, 2021.

The annual Congress provides a forum for the presentation of both clinical and preclinical research and promotes collaboration between researchers. This review provides a snapshot of the latest research, independently selected and reviewed by Dr Katy Harvey, who attended the virtual meeting.

I hope you enjoy these selections and look forward to your comments and feedback.

Kind Regards,

Dr Janette Tenne
Medical Research Advisor
janette.tenne@researchreview.com.au

Skin cancer surveillance behaviours and attitudes among hair professionals and melanoma survivors: A cross-sectional study

Presenter: David C Gibbs

Summary: This US survey-based study examined the attitudes and behaviours of 229 hair professionals and 141 head, neck, and scalp melanoma (HNSM) survivors about skin cancer surveillance in haircare settings. Most hairdressers (75%) and melanoma survivors (79%) considered that hair professionals should be trained to detect skin cancer, while 41% of hairdressers and 44% of melanoma survivors considered that such training should be mandatory. More melanoma survivors (81%) than hairdressers (71%) felt that, regardless of training, hairdressers should refer clients to a physician if they notice an 'abnormal mole'. 52% percent of hairdressers reported referring a client to a physician for an abnormal mole and 20% of head, neck, and scalp melanoma survivors reported being previously referred by a hairdresser. The 'ABCDE' rule for melanoma was recognised by 20% of hairdressers and 40% of melanoma survivors.

Comment: Emory University undertook a cross-sectional study surveying 229 practicing hair professionals in the metropolitan Atlanta area and 141 HNSM survivors. Their aim was to investigate skin cancer behaviours in these groups. The 'Heads Up!' campaign by the Skin Cancer Foundation, promotes the dermatologist-led training of hairdressers to detect and inform clients of suspicious skin lesions. The findings suggest a concordance of opinions, with 75% of hairdressers and 79% of HNSM survivors in support of training hairdressers in skin cancer detection. 81% of melanoma survivors compared to 71% of hairdressers agreed that hairdressers should refer clients to a physician if they notice an abnormal mole, regardless of training. This study is limited by the small sample size, with a low response rate of 15% of HNSM survivors based in one centre. Further training may be of benefit to early detection of HNSMs, which are associated with lower survival rates compared to melanomas on other body sites.

Long-term follow-up of KEYNOTE-029 1B and 1C: Standard-dose pembrolizumab (pembro) + alternate-dose ipilimumab (ipi) in advanced melanoma

Presenter: Georgina V Long

Summary: This report of the long-term follow up of the open-label phase Ib KEYNOTE-029 study, provided details on patients receiving 1 of 2 treatment regimens. In part 1B, pembrolizumab 2 mg/kg (amended to 200 mg) every 3 weeks (Q3W) plus ipilimumab 1 mg/kg Q3W (n = 153) was administered. The median follow-up was 69.0 months and the objective response rate (ORR) was 65.8%, with 52 complete responses (CR) and 44 partial responses (PR). Median duration of response (DOR) was not reached (NR), and 86.2% of recipients had an estimated response duration of ≥4 years. Median OS and PFS were NR, the 5-year OS rate was 68.3%, the 5-year PFS rate was 51.9%, and the 6-year OS rate was 65.3%. Treatment-related adverse events (TRAEs) occurred in 96.1% of patients (grade 3-4 47.1%; grade 5 0%). In part 1C, pembrolizumab 200 mg Q3W plus ipilimumab 50 mg Q6W (arm A; n = 51) or pembrolizumab 200 mg Q3W plus ipilimumab 100 mg Q12W (arm B, n = 51) was administered. The median follow-up was 41.3 months (arm A) and 41.3 months (arm B) and the ORR was 69.6%, with 15 CR and 17 PR in arm A, and 76.7% with 14 CR and 19 PR in arm B. Median DOR was NR in both arms and 82.3% of arm A and 78.7% of arm B recipients had an estimated response duration ≥3 years. Median OS and PFS were NR in both arms, the 3-year OS rates were 74.3% and 70.4%, and 3-year PFS rates were 56.5% and 59.7%. TRAEs occurred in all patients in arm A and 96.1% of patients in arm B (grade 3-5 27.5% and 43.1%, respectively). In arm A, 1 patient died of treatment- related autoimmune myocarditis.

Comment: This open-label trial involves patients with advanced melanoma with no prior CTLA-4, PD-1 or PD-L1 inhibitor treatment. Parts 1B and 1C of KEYNOTE-029 investigated standard-dose pembrolizumab plus alternate-dose ipilimumab, a CTLA-4 inhibitor, to optimise the benefit versus risk of treatment. Dose-dependent toxicity is well documented. The study looks at different ipilimumab dose regimes when combined with pembrolizumab. Pembrolizumab and ipilimumab 1 mg/kg every 3 weeks demonstrated a 5-year OS rate of 68.3%, versus a 3-year OS of 74.3% with an ipilimumab dose of 50 mg every 6 weeks, compared to a 3-year OS of 70.4% when the ipilimumab dose was 100 mg every 12 weeks. The pembrolizumab and ipilimumab combination was well tolerated in all arms of the study, with the lowest ipilimumab dose (50 mg, 6-weekly) associated with the lowest rate of TRAEs (24%).

Real-world outcomes of nivolumab in adjuvant melanoma in Belgium and Luxembourg (PRESERV MEL)

Presenter: Bart Neyns

Summary: The Belgium and Luxembourg observational PRESERV MEL study assessed characteristics, treatment disposition, effectiveness, and safety in 150 patients (median age 60 years) initiating adjuvant nivolumab for adjuvant melanoma treatment in routine practice. Patients had stage IIIA (19%), IIIB (28%), IIIC (33%), IIID (4%), IV (11%), or other (5%) or missing disease; 37% had *BRAF*V600-mutant melanoma, 49% had clinically occult only lymph node involvement, and 35% had a complete lymph node dissection. The median time from resection to start of nivolumab was 1.3 months and the follow-up period was 9.2 months. Overall, 56% of patients discontinued nivolumab. 22% discontinued due to treatment completion, 18% because of TRAEs, 10% due to recurrent disease and 1% for patient decision. One-year relapse-free survival was 83% (95% CI 77-89). TRAEs occurred in 81% of patients and 13% experienced ≥1grade ≥3 TRAE. No treatment-related deaths occurred.

Comment: This observational study of 150 patients assessed the effectiveness and safety of adjuvant nivolumab provided under routine clinical practice in Belgium and Luxembourg. In 2018, nivolumab was approved as an adjunct treatment for melanoma based on the CheckMate 238 study for melanoma patients with lymph node involvement, or with metastatic disease who have undergone complete resection. In the PRESERV MEL study, patients receiving at least one dose of nivolumab were enrolled between 2019- 2021. Follow up is due to continue until 2026 (5 years). The initial results demonstrated a 1-year relapse-free survival that was marginally higher that that observed in the initial CheckMate 238 study (83.3% vs 70.5%). Median follow-up was 9.2 months; longer-term follow-up is required to confirm the findings. This real-world study is largely consistent with the pivotal CheckMate 238 trial and demonstrates the effectiveness of nivolumab as an adjuvant treatment for patients with advanced melanoma with lymph node involvement or metastases.

Role of skin microenvironment in melanomagenesis

Presenter: Shreyans Sadangi

Summary: This study used a keratinocyte-conditioned medium from autologous white Caucasian keratinocytes and allogeneic African-American keratinocytes to assess the role of keratinocyte-derived factors on oncogene-induced senescence in *BRAF* V600E-transduced white and black melanocytes. In the white melanocytes, the medium from both autologous white and allogeneic black keratinocytes suppressed senescence, and targeted proteomic analysis of the spent melanocyte medium revealed upregulated VEGF-A production by transformed white melanocytes with autologous white but not allogeneic black keratinocyte-conditioned medium. White and black melanocytes had differing VEGF-A production in the presence of allogeneic keratinocyte-conditioned medium. Black melanocytes secrete higher levels of LIF with autologous black or allogeneic white keratinocyte-conditioned medium than white melanocytes.

Comment: The *BRAF* V600E mutation is the most common mutation driving melanogenesis, in combination with additional genetic events, including loss of tumour suppressor genes and epigenetic changes. This study investigated the role of keratinocyte-derived factors on oncogene-induced senescence by utilising a keratinocyte-conditioned medium from autologous white Caucasian and allogenic black African-America *BRAF* V600E-induced keratinocytes. It is thought that escape from senescence leads to melanoma development. The findings show that in white melanocytes, keratinocyte-conditioned medium from both autologous white and allogeneic black keratinocytes suppresses senescence development. White and black melanocytes were found to exhibit opposite effects in growth factor VEGF-A production in the presence of allogenic keratinocyte-conditioned medium, with upregulation of VEGF-A production by transformed white melanocytes in the presence of autologous white, but not allogeneic black keratinocyte-conditioned medium. This study found that the skin microenvironment was shown to influence melanocytes that acquire *BRAF*V600E mutation.

Vascular lakes: A new prognostic parameter for uveal melanoma?

Presenter: Hayley M Jones

Summary: This retrospective cohort study examined 132 haematoxylin- and eosin-stained slides from uveal melanoma to assess cell morphology and tumour genetics associated with vascular lakes. Uveal melanoma characterised by lack of nuclear BRCA1-associated protein expressionn (nBAP1; p = 0.034) and chromosome 3 loss (p = 0.013) differed in the number of vascular lakes present and in the vascular lake area within the tumour (p = 0.004; p = 0.035), compared to nBAP1 positive and disomy 3 uveal melanoma. Uveal melanoma samples with extraocular extension had a higher number of vascular lakes than uveal melanoma with no extraocular extension (p = 0.028).

Comment: Vascular lakes are irregular immature blood vessels that contain tumour cells within their 'lumen'. Approximately 50% of patients with uveal melanoma develop metastases, which are typically fatal. This retrospective study looks at 132 haematoxylin-and-eosin stained slides of uveal melanomas. The findings show that uveal melanoma characterised by nBAP1 negative status and Chr3 loss have differences between the number of vascular lakes present and vascular lakes area within the tumour compared to nBAP1 positive and disomy 3 uveal melanoma. Notably, the incidence of vascular lakes is higher, and they are larger in area. Patients with uveal melanoma with higher vascular lake area:tumour size ratio showed a significantly shorter OS, with patients dying within 2 years of diagnosis. Thus, vascular lakes may represent an additional prognostic parameter.

Predictors of sentinel lymph node metastasis in patients with thin melanoma: A multi-institutional collaborative

Presenter: Michail Mavros

Summary: This multinational study sought to identify clinicopathologic factors predicting sentinel lymph node biopsy (SLNB) positivity in 676 patients (median age 56 years; 54% female) with T1b (Breslow depth 0.8-1 mm or <0.8 mm with ulceration) and T1a (<0.8 mm without ulceration) melanomas with high-risk features. Most patients had high-risk features including 78% with Breslow thickness 0.8-1 mm, 8% with ulceration, 43% with a mitotic rate >1/mm^2, 34% Clark's level ≥4, 1% with lymphovascular invasion, 3% nodular histology, and 14% with absence of tumour infiltrating lymphocytes. A positive SLNB was observed in 8%. SLNB positivity was independently predicted by Breslow depth and mitotic rate. Odds of positive SLNB increased by 50% for every 0.1 mm increase in Breslow depth past 0.74 mm (OR 1.50, 95% 1.05-2.13) and by 22% for each mitosis per mm^2 (OR 1.22; 95% CI 1.06-1.41). Patients who had one excised node versus ≥2 were 3-fold less likely to have SLNB positivity (3.6% vs 9.6%; OR 2.9; 95% CI 1.3-7.7).

Comment: This study looked at data from 676 patients who underwent SLNB between 2005-18 in 5 tertiary referral centres in Europe and Canada, aiming to identify clinicopathological factors predicting SLNB positivity. Overall, 8% of patients had a positive SLNB. Mitotic rate and Breslow thickness independently predicted SLNB positivity. The odds of positive SLNB increased by 50% for each 0.1 mm increase in Breslow depth past 0.74 mm and by 22% for each mitosis per mm^2. The number needed to diagnose was 13:1. The proportion of patients with actionable results was very low. Additional work is required to identify accurate predictors of sentinel node positivity.

Independent commentary by Dr Katy Harvey *BMBCh MA (Oxf), DRANZCOG, DCH-SA, FRACGP, Professional Diploma in Skin Cancer Medicine, Professional Diploma in Dermoscopy*

Dr. Katy Harvey graduated from Oxford University with First Class honours (BMBCh, MA) before moving to Melbourne in 2011 to undertake her postgraduate studies. She was awarded the Fellowship of the Royal Australian College of General Practice (FRACGP), Diploma in Obstetrics and Gynaecology (DRANZCOG) and Diploma in Child Health (DCH), and developed a special interest in skin cancer medicine.

Katy holds a Professional Diploma in Skin Cancer Medicine and a Professional Diploma in Dermoscopy, in addition to certificates in Advanced Dermatoscopy and Histopathology and Primary Care Skin Cancer Therapeutics. Since 2015, she has held the position of Senior Lecturer with the University of Queensland School of Medicine, assisting with the Masters of Medicine (Skin Cancer) course. In 2018, she completed the International Short Course in Dermoscopy (ISCD) at the Medical University of Graz, Austria.

Katy also enjoys being a part of the GP Registrar education program in Victoria and also teaches skin cancer skills to doctors and heathcare professionals for HealthCert. She works full time in skin cancer clinics based in Carnegie and Wantirna, Melbourne.

OPDIVO (nivolumab)

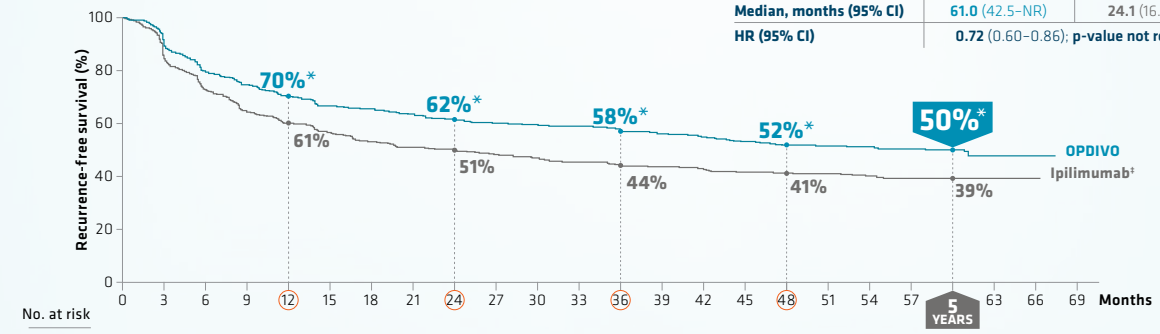
ADJUVANT MELANOMA

50% of patients recurrence free at 5 years[1,2†]

†versus 39% with ipilimumab‡, p-value not reported; median RFS 61.0 months vs 24.1 months‡ (HR 0.72, 95% CI 0.60–0.86, p-value not reported) in patients with completely resected stage IIIB/C or IV melanoma (AJCC 7th Edition)[2]

CheckMate 238: 5-year update of recurrence-free survival (ITT population)[2–4]

	OPDIVO (n=453)	Ipilimumab (n=453)‡
Median, months (95% CI)	61.0 (42.5–NR)	24.1 (16.6–35.1)
HR (95% CI)	0.72 (0.60–0.86); p-value not reported	



No. at risk

OPDIVO	453	395	354	332	311	293	283	271	262	250	245	240	234	225	220	213	202	191	176	147	94	17	4	0
Ipilimumab‡	453	366	316	273	253	234	220	208	201	191	185	178	173	170	165	159	152	145	134	114	78	18	1	0

*p-value for 12-, 24-, 36-, 48- and 60-month recurrence-free survival rate not reported.

‡Ipilimumab is not approved for use in Australia for the adjuvant treatment of melanoma.

Adapted from Weber *et al.* 2021 (SMR oral presentation), Weber *et al.* 2020 (ESMO oral presentation) and Weber *et al.* 2019 (ESMO oral presentation).[2–4]

Q4W **480 mg** EVERY **4** WEEKS

FOR 12 MONTHS[5]

OPDIVO can also be administered fortnightly (Q2W), at 240 mg or 3 mg/kg up to a maximum PBS-reimbursed dose of 240 mg[5,6]

CheckMate 238: Phase 3, randomised, double-blind trial in patients with completely resected stage IIIB/C and IV melanoma (AJCC 7th Edition). In the initial analysis (minimum follow-up 18 months), Grade 3/4 TRAEs and any grade treatment-related discontinuations occurred in 14% and 8%, respectively, of patients treated with OPDIVO.[1] At the 4-year analysis, all patients had been off study treatment for >100 days. Per protocol, safety data were voluntarily reported beyond 18-month follow up. No new safety concerns were noted in the 4-year analysis.[3] The 5-year outcome analysis did not report an updated safety analysis.[2]

OPDIVO is PBS listed. Please refer to http://www.pbs.gov.au for full authority information

Please review the Approved Product Information and Boxed Warnings for OPDIVO (click HERE) before prescribing

AJCC = American Joint Committee on Cancer; CI = confidence interval; ESMO = European Society for Medical Oncology; HR = hazard ratio; ITT = intent-to-treat; NR = not reached; PBS = Pharmaceutical Benefits Scheme; Q2W = every 2 weeks; Q4W = every 4 weeks; RFS = recurrence-free survival; SMR = Society for Melanoma Research.

References: 1. Weber *et al. N Engl J Med* 2017;377:1824–35. **2.** Weber *et al.* Five-year outcomes with adjuvant nivolumab versus ipilimumab in resected stage IIIB–C or IV melanoma (CheckMate 238). Oral presentation at the 18th International Congress of the Society for Melanoma Research (virtual). October 28–31, 2021. **3.** Weber *et al.* Adjuvant nivolumab vs ipilimumab in resected stage III/IV melanoma: 4-year recurrence-free and overall survival results from CheckMate 238. Oral presentation at the 2020 ESMO Virtual Congress. 19–21 September 2020. **4.** Weber *et al.* Adjuvant nivolumab versus ipilimumab in resected stage III/IV melanoma: 3-year efficacy and biomarker results from the phase 3 CheckMate 238 trial. Oral presentation at the 2019 ESMO Congress. 27 September to 1 October 2019; Barcelona, Spain. **5.** OPDIVO® (nivolumab) Approved Product Information (http://www.medicines.org.au/files/bqpopdiv.pdf). **6.** Pharmaceutical Benefits Scheme (http://www.pbs.gov.au).

Bristol Myers Squibb™

Risk factors for central nervous system (CNS) metastasis among stage IV melanoma patients

Presenter: Chantal Saberian

Summary: This analyses of 1936 stage IV melanoma patients sought to identify risk factors for CNS metastasis to rationally personalise CNS surveillance and/or treatment. Cumulative incidence of CNS metastasis was 27% at 1 year, 37% at 2 years and 42% at 5 years. Median time from stage IV diagnosis to CNS metastasis was 8 months. Univariate analysis suggested that the risk of CNS metastasis was associated with melanoma subtype ($p \leq 0.006$; lower for mucosal); mutations ($p < 0.001$) higher for *BRAF* and *KIT* ($p = 0.016$); younger age ($p < 0.001$); higher serum LDH ($p = 0.024$) and neutrophil to lymphocyte ratio ($p = 0.015$); ≥3 non-CNS metastasis sites ($p = 0.004$); and higher with lung metastasis ($p < 0.001$) and lower for liver metastasis ($p = 0.012$). Multivariate analysis indicated that melanoma subtype, *KIT* mutation, and age remained associated with CNS metastasis. *KIT* mutations were associated with a greater risk particularly among mucosal melanoma patients (HR 2.6; $p < 0.006$) versus non-mucosal melanoma patients (HR 1.4; $p = 0.042$).

Comment: This study analyses the cumulative incidence of CNS metastases in 1936 patients with stage IV melanoma (excluding uveal melanoma) at a single centre in the USA between 2012 and 2017. The median time from stage IV melanoma diagnosis to CNS metastases diagnosis was 8 months. The risk of CNS metastases was associated with younger age, *BRAF* and *KIT* mutations, higher serum LDH, higher neutrophil:lymphocyte ratio, melanoma subtype (lower for mucosal melanoma), ≥3 non-CNS metastasis sites. CNS metastases risk was higher for patients with lung metastases and lower for patients with liver metastases. The *KIT* mutation was associated with a higher risk of CNS metastases among mucosal melanoma patients. The hope is that this work will help design a more personalised treatment and surveillance protocol with further research in this area.

MYBL2 is an oncogene in melanoma

Presenter: Kaizhen Wang

Summary: This study examined the role of MYBL2 transcription factor (regulating cell cycle, cell survival, and differentiation) expression in melanoma cell lines using cell proliferation, colony formation assay, and anchorage-independent growth assays in vitro and xenograft models in vivo. MYBL2 expression was upregulated in melanoma cells versus *BRAF*-wildtype and *BRAF*-mutant melanocytes. The Cancer Genome Atlas (TCGA) analysis suggested that higher MYBL2 expression was associated with poorer survival in melanoma patients. In vitro, MYBL2 overexpression in melanoma cells promoted proliferation and increased clonogenic and anchorage-independent growth. MYBL2 knock down in melanoma cell lines reduced melanoma cell proliferation, clonogenic growth and anchorage-independent growth. Silencing of MYBL2 in xenografted A375 melanoma cells in immunodeficient mice slowed tumour growth and decreased tumour weight, while MYBL2 overexpression in WM115 melanoma cells increased tumour growth and weight.

Comment: MYBL2 is a transcription factor that is frequently deregulated in cancer. Previous studies suggest an oncogenic function of MYBL2 in melanoma, but little is known about how it promotes melanoma initiation or progression. This study looked at xenograft models in order to determine the regulation of melanoma tumour growth by MYBL2 in vivo. The results demonstrated that higher MYBL2 expression is associated with poorer survival of melanoma patients, and that overexpression in melanoma cells modestly promoted their proliferation and growth. Moreover, silencing of MYBL2 in melanoma cell xenografts into mice significantly slows tumour growth and decreases tumour weight at end point. This research suggests that MYBL2 is associated with melanoma aggressiveness and could potentially be a future therapeutic target. More work is required to better understand mechanism of the oncogenic role of MYBL2.

The implications of a dermato-pathologists' report on melanoma diagnosis and treatment

Presenter: Nethanel Asher

Summary: This single-centre, retrospective analysis assessed the impact of review of all melanoma biopsy specimens (n = 177) by an expert dermato-pathologist and the critical Breslow score for which a pathology review would be most beneficial. After review, a change in Breslow index was made in 103 (58.2%) cases, most (73.2%) of which were increased cases. T-stage was changed in 51 (28.8%) lesions. The lowest concordance was seen in Tis (57%), T1b (59%), T3a (67%) and T4a (50%). The revised report led changes in the surgical plan in 15.2% of the cases.

Comment: This study, conducted in Israel, utilised an in-house expert dermato-pathologist to review the outside pathology reports of patients referred to their institute between January 2011 and September 2019. It looked at the fundamental histologic and clinical prognostic features of 177 melanoma specimens. Notably, a change to the Breslow thickness was made in 58.2% of cases, with most changes (73.2%) resulting in the revised Breslow being higher than initially reported. As a result, the T-stage was changed in 28.8% of lesions, and the surgical management was subsequently amended in 15.2% of cases. This study supports the recommendation that all routine pathologies of pigmented lesions referred to a dedicated cancer centre for an expert dermato-pathologist. It is most beneficial for melanoma in-situ and thin melanomas (0.6-2.2 mm), where this review may significantly change the management of the patient.

Connection between malignant melanoma and rheumatoid arthritis: Evidence from the NHANES dataset

Presenter: Sri Banerjee

Summary: This analysis of the 2005-10 US National Health and Nutrition Examination Survey (NHANES) was conducted to determine if melanoma is associated with rheumatoid arthritis. A rate of positive melanoma history was higher in males (13.8%) than females (12.6%). Overall there was a higher crude risk of increased melanoma in patients with versus without rheumatoid arthritis (OR 2.72; 95% CI 0.90-8.20; $p = 0.07$). When gender stratified, OR was 5.92 (CI 1.40-25.05; $p = 0.02$) in males and 1.09 (95% CI 0.21-5.51; $p = 0.92$) in females.

Comment: This population-based survey in the US looked at an adult population (aged ≥20 years) between 2005-10. It assessed rheumatoid arthritis and melanoma status by using the arthritis question and cancer question respectively. Complex sample regression was used to assess if gender influenced melanoma outcomes related to rheumatoid arthritis in males and females. The findings demonstrated that the positive melanoma history was higher among males (13.8%) than females (12.6%). The odds ratio of increased melanoma for individuals with rheumatoid arthritis compared to those without the condition was 2.72. Interestingly, the odds ratio was higher for males (5.92) compared to female participants (1.09). Further studies are needed to investigate a potential association between melanoma and rheumatoid arthritis, as little is known. Increased skin surveillance may be of benefit for patients with rheumatoid arthritis, in addition to optimising sun protection education.

