Skin Cancer Research Review™

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In this issue:

Abbreviations used in this issue:

DedM = dedifferentiated melanoma; **HRQoL** = health-related quality of life; **ICI** = immune checkpoint inhibitor; **MC1R** = melanocortin-1 receptor; **MITF** = microphthalmia-associated transcription factor; **RCH** = red colour hair; **RCM** = reflectance confocal microscopy; **trAEs** = treatment related adverse reactions.

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Welcome to the latest issue of Skin Cancer Research Review.

In this review, researchers conducted a trial to determine the effects of vitamin D levels on anti-PD-1 therapy, and if supplementation can prolong progression-free survival time. Another study evaluates the first-line treatment options for advanced melanoma patients, determining which treatment has the best safety profile. This review concludes with a study that discusses the accuracy of reflectance confocal microscopy, and whether it can identify invasion in lentigo maligna or lentigo maligna melanoma lesions.

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

Kind Regards,

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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 I/IIa RELATIVITY-020 trial

Authors: Ascierto PA et al.

Summary: In this phase I/IIa, RELATIVITY-020 trial, researchers assessed the efficacy and safety of nivolumab and relatlimab in advanced melanoma patients. 518 patients were included and were during or within 3 months of 1 (D1) or ≥ (D2) anti-PD-(L)1-containing regimens. Amongst these patients, the ORR by blinded independent central review was 12.0% (95% CI 8.8 to 15.8) in D1 (n=351) and 9.2% (5.2 to 14.7) in D2 (n=163). Responses were enriched amongst those with tumours expressing programmed death ligand 1 or lymphocyte activation gene 3. D1 patients did not reach the median duration of response, but D2 patients did at 12.8 months (6.9 to 12.9). The median PFS was 2.1 months for D1 patients (1.9 to 3.5) and 3.2 months for D2 patients (1.9 to 3.6), and 6-month PFS rates were 29.1% (24.2 to 34.1) and 27.7% (20.5 to 35.4), respectively. The incidence of grade 3-4 treatment-related AEs was 15.0% in D1 patients and 12.8% in D2 patients, with no deaths. Results support the safety profile of nivolumab and relatlimab in melanoma patients who had been heavily pre-treated.

Comment: Immune checkpoint inhibitor (ICI) therapy has revolutionised advanced melanoma management, initially targeting the CTLA4 receptor and subsequently the PD-1 receptor and PD-1 ligand. The RELATIVITY-047 trial showed similar benefit in targeting the LAG-3 receptor with relatlimab combined with a PD-1 inhibitor – nivolumab – compared to nivolumab alone in patients previously untreated with ICI's. This paper examines the benefit and safety of using combination LAG-3/PD-1 therapy in heavily pre-treated patients, both ICI's and targeted therapies. The ORR ranged from 9.2-12% and these responses appeared durable with continued benefit seen in the majority of responders at 6 months. The OS was between 14.7 and 17.1 months, illustrating the poor prognosis in this group of patients despite immunotherapy. The addition of LAG-3 inhibitors offers another treatment option and combination ICI treatment adds additional benefits as has been shown with combination CTLA4/PD-1 therapy versus single agent therapy.

Reference: J Clin Oncol. 2023;20;41(15):2724-2735.
Abstract

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

Authors: Galus Ł et al.

Summary: Researchers aimed to determine whether vitamin D3 impacts the effectiveness of anti-PD-1 treatment in cancer patients. Two hundred patients with advanced melanoma were included and each received anti-PD-1 immunotherapy as first-line treatment. Their serum vitamin D levels were then measured before treatment and every 12 weeks during treatment. After analysis, the response rate of those with low vitamin D levels and not supplemented was 36.2%, however those with normal baseline levels or a normal level obtained with supplementation was 56.0% (p=0.01). PFS for each group was 5.75 and 11.25 months (P=0.03), with a higher OS being identified for those with normal vitamin D levels (27 vs 31.5 months, respectively; P=0.39). Researchers state that maintaining vitamin D levels within the normal range for advanced melanoma patients, whilst receiving anti-PD-1 immunotherapy, is of great importance and should be a standard procedure to improve treatment outcomes.

Comment: Vitamin D has anti-proliferative effects and immunity enhancing benefits which result in clinical effects against viral infections and malignancies. Higher levels of vitamin D are also correlated with improved prognosis in many cancers including breast and colorectal cancers. The mechanisms by which this may occur are varied but include enhanced CD8 and CD4 lymphocyte activity and tumour penetration, reduced inflammation with potentially reduced immune-related adverse reactions as well as antiproliferative effects. In this Polish trial, the majority of patients were vitamin D deficient and all those with low levels were supplemented to achieve normal levels. Those who still had low levels as well as a retrospective group whose plasma had been frozen and had low levels, were compared against patients with normal levels (with or without supplementation). Normal vitamin D levels were associated with improved ORR and PFS. In Australia, approximately 30% of the population is vitamin D deficient and it is standard practice now to normalise this prior to immunotherapy.

Reference: Cancer. 2023;1;129(13):2047-2055.
Abstract

Clinical, histopathological and molecular features of dedifferentiated melanomas: An EORTC melanoma group retrospective analysis

Authors: Hench J et al.

Summary: The clinical, histopathological, and molecular features of dedifferentiated melanoma (DedM) was explored within this analysis. Seventy-eight DedM tissue samples from 61 patients were centrally reviewed. Majority of these patients (60/61) had a metastatic DedM that frequently showed an unclassified pleomorphic, spindle cell, or small round cell morphology. Twenty tissue samples (from 16 patients) were successfully assessed, where researchers found retained melanoma-like methylation signature in seven and non-melanoma-like methylation signature in 13 samples. Two patients in particular provided multiple samples, containing preserved cutaneous melanoma methylation signature, however other samples contained specimens that exhibited an epigenetic shift towards a mesenchymal/sarcoma-like profile. Copy number profiling was predominantly identical across all analysed specimens in these two patients, despite modification of their epigenome. This study highlights that DedM represents a real diagnostic change, and that DedM in melanoma is commonly associated with epigenetic modifications.

Comment: DedM refers to the phenomenon seen in some metastatic lesions where there is a change to a more sarcoma-like primitive neural crest phenotype with loss of melanoma-specific immunohistochemical markers such as S100, SOX10, Melan-A and HMB-45. This may occur as part in metastatic deposits de novo or as a form of resistance during or after targeted or immunotherapy. When patients develop a new mass, or a lesion suspected of being "melanoma of unknown primary", there can be diagnostic difficulty due to the lack of specific melanoma markers. Comparing metastatic DedM deposits with matched cutaneous melanoma the most common feature was a pleomorphic, spindle cell morphology similar to undifferentiated pleomorphic sarcoma. Despite the dedifferentiation, in this study there was a good response to systemic therapy – immunotherapy or targeted therapy - with 41% responding and 26% showing a long-term response. A history of cutaneous melanoma should be sought when undifferentiated sarcoma-like metastases are found to avoid missing the diagnosis.

Reference: Eur J Cancer. 2023;187:7-14.
Abstract

Discontinuation of anti-PD1 in advanced melanoma: an observational retrospective study from the Italian melanoma intergroup

Authors: Rubatto M et al.

Summary: This study evaluated the PFS of patients with metastatic melanoma who stopped anti-PD-1 treatment due to the absence of disease progression. The cohort comprised of 237 patients (mean age 68.9 years), where their risk of relapse was investigated after a median time of 33 months. 128 patients (54%) interrupted the anti-PD-1 for CR, 74 (31.2%) for AEs and 35 (14.8%) by their own choice. After a median follow-up of 21 months, PFS after treatment discontinuation was 85.7%, with 34 patients (14.3%) developing disease progression after a median duration of 12 months. 10/34 patients (29.4%) developed disease progression after discontinuation in CR, 17 (50%) after discontinuation of treatment limiting toxicity and 7 (20.6%) after discontinuation, by the patient's decision. 7.8% of patients who interrupted in CR (10/128), 23% of patients who interrupted because of treatment limiting toxicity (17/74) and 20% of patients who interrupted by their own choice (7/35), developed reoccurrence. Those who discontinued treatment due to CR had a negative association between recurrence and site of primary melanoma (P=<0.05, HR 15.57, 95% CI 2.64 to 91.73). Results suggest that long-lasting responses can be sustained after anti-PD-1 interruption.

Comment: Optimal duration of ICI therapy was established at 2 years in the KEYNOTE-06 study but there have been other studies suggesting 6 months of treatment may be sufficient. A reduction in the length of treatment would offer advantages as far as cost and immune-related AEs. Patients in this study were divided into three groups: those that stopped treatment due to a CR, those who stopped due to treatment limiting toxicity and those who elected to cease therapy against medical advice. After a 21 month follow up, 7.8% of patients who ceased due to CR developed progressive disease compared to 23% in the treatment toxicity group and 20% in the patient-request group. It appears that the likelihood of progression is higher in those receiving less than 6 months of treatment and for every month of treatment there was a 6.8% decreased relapse rate. Interestingly, mucosal melanoma recurrence rates were high, and the authors suggest keeping these patients on therapy for as long as possible.

Reference: Eur J Cancer. 2023;187:25-35.
Abstract

Health-related quality of life with nivolumab plus relatlimab versus nivolumab monotherapy in patients with previously untreated unresectable or metastatic melanoma: RELATIVITY-047 trial

Authors: Schadendorf D et al.

Summary: In this phase II/III RELATIVITY-047 trial, researchers provide updated health-related quality of life (HRQoL) results from melanoma patients receiving nivolumab plus relatilmab. Patients were randomised to received intravenous nivolumab plus relatilmab (480mg and 160mg, respectively) or nivolumab (480mg) every 4 weeks. Results were consistent to the initial analysis, with HRQoL remaining stable for both groups. HRQoL results were also consistent across instruments and scales/subscales. There was a low proportion of patients reporting that they were "quite a bit" or "very much" bothered with treatment related adverse reactions (trAEs). Researchers highlight that PFS has greater improvements with nivolumab plus relatimab compared to nivolumab alone, and that this treatment option could be beneficial for advanced melanoma patients.

Comment: Combination treatment with nivolumab and ipilimumab has been shown to be more effective than monotherapy with nivolumab but with an increase in trAE's. Treatment courses may last 2 years or more and so it is important to take into account patients' quality of life. The recent RELATIVITY-047 trial compared a LAG-3 inhibitor combined with the PD-1 inhibitor nivolumab versus single agent nivolumab. Reassuringly there was no significant decrease in quality of life between the two regimens and patients generally tolerated the therapy well despite increased trAE's in the combination treatment arm. The quality of life scores decreased after ceasing treatment surprisingly, which may reflect worsening disease control or perhaps the uncertainty of the future prognosis off treatment and corresponding mood changes?

Reference: Eur J Cancer. 2023;187:164-173.
Abstract

Activity and safety of first-line treatments for advanced melanoma: A network meta-analysis

Authors: Boutros A et al.

Summary: This study reviews the available first-line treatment options for advanced melanoma patients. Researchers indirectly compared ICI combinations ipilimumab/nivolumab and relatlimab/nivolumab as well as all other first-line treatment options, in terms of safety and activity. A total of 9,070 patients with metastatic melanoma were included, deriving from 18 randomised clinical trials. After analysis, researchers identified that there was no difference in PFS or ORR between ipilimumab/nivolumab and relatlimab/nivolumab (HR=0.99 [95% CI 0.75 to 1.31] and RR=0.99 [0.78 to 1.27], respectively). PD-(L)1/BRAF/MEK inhibitor triplet combinations displayed better results compared to ipilimumab/nivolumab based on PFS (HR=0.56 [0.37 to 0.84]) and ORR (RR=3.07 [1.61 to 5.85]). Patients receiving ipilimumab/nivolumab had the greatest risk of developing ≥ G3 trAEs, whereas those taking relatlimab/nivolumab had a deceased risk (RR=0.71 [0.30 to 1.67]). These results highlight that relatlimab/nivolumab has a better safety profile than ipilimumab/nivolumab, despite having similar PFS and ORRs.

Comment: There are now a range of treatment options available for advanced melanoma but few head-to-head comparisons. Combination ICI therapy with ipilimumab and nivolumab has been shown to have the best OS and now has data up to over 7 years showing prolonged benefit but this comes at the cost of the highest rate of trAEs. The RELATIVITY-047 study using the LAG-3 inhibitor relatlimab, combined with the PD-1 inhibitor nivolumab, showed a comparable PFS and ORR, but the survival data is still immature due to the lack of long-term patient experience. The risk ratio of grade 3 trAEs was 70% of that with ipilimumab/nivolumab. For patients with a greater tumour burden or symptomatic brain metastases, targeted therapy with a MEK/BRAF inhibitor combination achieves a more rapid effect but the OS is shorter than with ICI. The SECOMBIT trial used a short, targeted therapy followed by combination ICI therapy with comparable results to upfront immunotherapy. Overall, combination ICI therapy gives the best long-term survival and ipilimumab/nivolumab has the longest survival data but relatlimab/nivolumab has similar PFS with a lower rate of adverse reactions and in time may prove to be as beneficial as the older combination.

Reference: Eur J Cancer. 2023;188:64-79.
Abstract

Association of excision margin size with local recurrence and survival in patients with T1a melanoma at critical structures

Authors: Maurichi A et al.

Summary: Researchers aimed to determine whether a narrow (5mm) excision margin, in patients with T1a melanoma, is associated with local recurrence and melanoma-specific mortality. 1,179 patients were included (median age 50.0 years, 610 females [51.7%], 569 males [49.3%]). 626 (53.1%) of patients received a wide excision (434 [69.3%] with linear repair, 192 [30.7%] with flap or graft reconstruction) and 553 (46.9%) of patients received a narrow excision (491 [88.8%] with linear repair, 192 [30.7%] with flat or graft reconstruction). The 10-year melanoma-specific mortality rate for those in the wide group was 1.8% (95% CI 0.8 to 4.2) and 4.2% (2.2 to 7.9) for those in the narrow group. Ten-year local recurrence rates were 5.7% (3.9 to 8.3) in the wide group and 6.7% (4.7 to 9.5) in the narrow group. A Breslow thickness greater than 0.4mm and mitotic rate greater than 1/mm^2 were both associated with a worse melanoma-specific mortality rate. Local recurrence incidence was increased with acral lentiginous melanoma, lentigo maligna melanoma and increasing Breslow thickness. Findings may be beneficial for future melanoma treatment guidelines.

Comment: Currently, T1 melanoma is treated with wide excision to achieve a 10mm clinical margin, but this can be hard to perform in areas such as the face where cosmetic and/or functional concerns are important. T1a tumours - less than 0.8mm Breslow thickness and non-ulcerated - have a very good prognosis and the authors examined a cohort of 1,341 patients treated between 2001 and 2020 to determine whether those that declined the recommended wide margins had a worse outcome. After a 10-year follow up, there was no significant difference in melanoma specific mortality or local recurrence. Subgroup analysis showed that Breslow thickness greater than 0.4mm and mitotic rate greater than 1/mm^2 were associated with a worse prognosis. The rate of complex closures was higher in the wide margins group as might be expected and this might be expected to result in a greater risk of cosmetic and functional problems.

Reference: JAMA Dermatol. 2023;1;159(6):587-595.
Abstract

The MC1R r allele does not increase melanoma risk in MITF E318K carriers

Authors: Wallingford CK et al.

Summary: In this study, researchers evaluated whether melanocortin-1 receptor (MC1R) genotypes impact the risk of melanoma in microphthalmia-associated transcription factor (MITF) E318K+ vs E318K- individuals. 1,165 MITF E318K- cases and 322 E318K+ cases were included, to which their melanoma status and genotype data was collated from research cohorts (5 Australian, 2 European). For E318K- individuals, MC1R R and r alleles increased their melanoma risk, relative to wild type (wt), P<0.001. Each MC1R red colour hair (RHC) genotype (R/R, R/r, R/wt, r/r and r/wt) increased melanoma risk to wt/wt (P<0.001). For E318K+ individuals, R alleles increased their melanoma risk to the wt allele (OR=2.04, 95% CI 1.67 to 2.49, P=0.01), however their r allele risk was comparable to their wt allele (0.78, 0.54 to 1.14). E318K+ cases, who had the r/r genotype, had a decreased melanoma risk relative to wt/wt (0.52, 0.20 to 1.38) however those with R genotypes (R/R, R/r, R/wt) had a significantly higher risk compared to non-R genotypes (r/r, r/wt, wt/wt) (P<0.001). Results highlight, for E318K+ individuals, that the MC1R allele risk is comparable with wt and that this knowledge could aid in management.

Comment: Melanoma risk is known to be increased in families carrying familial melanoma genes, with the most common being the CDKN2A variant. There are also variants with a lower penetrance, such as MC1R and MITF, which interact to increase melanoma risk. MITF acts as a driver of melanoma progression and can regulate multiple biological processes in melanoma cells resulting in proliferation, differentiation, migration, and senescence. The action of MITF is modulated by upstream activators and suppressors. MC1R has RHC alleles described as strong or weak – R or r. This study looked at the effect of these RHC alleles on a functional variant of MC1R known to be associated with an increased incidence of melanoma. It appeared that only the strong RHC-R allele when combined with MC1R resulted in a greater risk. Genetic testing to identify a population suitable for melanoma screening in Australia is yet to be determined but these studies will help to narrow down the individuals most at risk.

Reference: Br J Dermatol. 2023;24;188(6):770-776.
Abstract

Independent commentary by Dr David Simpson

Dr Simpson is a skin cancer doctor on the Sunshine Coast in Queensland and a teaching assistant and senior lecturer on the University of Queensland MMED Skin Cancer program. He also acts as a tutor, examiner and Blog Author for the Skin Cancer College of Australasia.

Similar local recurrence and survival in patients with T1 radial growth phase melanoma on head and neck treated with 5 or 10 mm margins: A retrospective study

Authors: Maurichi A et al.

Summary: The outcomes of wide (10mm) vs narrow (5mm) excisions in radial growth phase T1 melanoma patients were compared. Patients derived from 6 European centres and were retrospectively examined. 317 (51.8%) patients received a wide excision (219 [69.3%] with primary wound closure, 97 [30.7%] with reconstruction) and 264 (89.8%) patients received a narrow excision (264 [89.8%], 30 [10.2%]) (P<0.001). Median follow up for wide excision patients was 88 months, and 187 months for narrow excision patients (IQR 43-133 and 79-206, respectively). The 10-year OS was 96.7% (95% CI 94.2 to 99.3) for wide and 98.2% (96.4 to 100) in narrow patients, and their 10-year local recurrence incidences were 6.4% (4.1 to 10.1) and 7.8% (5.3 to 11.6). The lentigo maligna melanoma subtype seemed to be linked to an increased risk of local recurrence for narrow patients compared to wide (15.0% vs. 7.5%, P=0.190). There was no association between narrow excision margins and a decreased OS (HR 0.97, P=0.996) or increased local recurrence (substitution HR 0.87, P=0.751) when compared to wider margins.

Comment: Current guidelines suggest wide local excision with 10mm margins for the treatment of T1 (Breslow thickness <1mm) melanomas, but wider excision margins may result in cosmetic and functional deformities which may be unacceptable to the patient. The majority of T1 melanomas are diagnosed when they are in the radial growth phase and in theory are yet to achieve the ability to metastasize despite small clusters of non-proliferating melanocytes being present in the papillary dermis. In the subsequent vertical growth phase, the melanoma cells expand into the dermis and may metastasize. Not all patients will consent to wide excisions, especially on the head and neck, and the authors were able to compare those who underwent surgery to achieve a 10mm histological margin with those with a target of 5mm histological margin. After a median follow up of 88 months there was no statistical difference in local recurrence, disease-free survival or OS between the groups which suggests that patients whose initial excisional biopsy shows a T1 tumour in radial growth phase can safely be treated with a more conservative wide local excision aiming for a histological margin of 5mm. In the lentigo maligna melanoma patients there was a non-significant increase in local recurrence, and it may still be wise to treat this group with wider margins.

Reference: J Eur Acad Dermatol Venereol. 2023;37(7):1318-1326.
Abstract

In vivo reflectance confocal microscopy can detect the invasive component of lentigo maligna melanoma: Prospective analysis and case–control study

Authors: Gouveia BM et al.

Summary: Researchers aimed to assess the accuracy of reflectance confocal microscopy (RCM) when detecting invasion on lentigo maligna or lentigo maligna melanoma lesions. 229 cases, that were evaluated by histopathology, were then assessed prospectively by an expert confocalist. 210 cases were lentigo maligna, and 19 were lentigo maligna melanoma, as determined by histopathology. The correct identification of an invasive component was obtained for 17 out of 19 lentigo maligna cases (89%), with 190 out of 210 lentigo maligna melanoma cases being correctly identified (90%), due to the absence of a dermal component. Epidermal and junctional disarray, large size of melanocytes and nests of melanocytes were independent predictors of lentigo maligna melanoma cases, for the matched-control patients (35 lentigo maligna melanoma patients, 58 lentigo maligna patients). These three features had a fair reproducibility between the two investigators (K=0.4) and showed a high predictive performance [AUC=74%] (95% CI 64 to 85), sensitivity [63%] (52 to 78) and specificity [79%] (74 to 88). Researchers state that these three characteristics can aid in the identification of invasive melanoma.

Comment: Lentigo maligna is commonly found on areas of skin with chronic sun exposure such as the head and neck and is often quite broad when diagnosed. In situ disease can be treated with smaller surgical margins or even with non-surgical methods such as imiquimod or radiotherapy, but it is vital to identify those lesions harbouring an area of invasion so that appropriate treatment is performed. Using reflectance confocal microscopy, the authors examined a large number of lesions suspected of being either lentigo maligna or lentigo maligna melanoma and found that three RCM features, not usually used as part of the RCM score, were highly predictive of areas of invasion – epidermal and junctional disarray, large melanocyte size and nests of melanocytes (more frequent and florid in areas of invasion). If RCM is available, it may be a useful tool for accurately identifying areas of possible invasion which can then be scored to direct the pathologist to those locations most likely to harbour invasive melanoma.

Reference: J Eur Acad Dermatol Venereol. 2023;37(7):1293-1301.

Abstract