Skin Cancer Research Review™

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Issue 9 - 2021

In this issue:

Abbreviations used in this issue:

BCC = basal cell carcinoma; **CI** = confidence interval; **CTLA** = cytotoxic T-lymphocyte-associated protein; **EGFR** = epidermal growth factor receptor; **LDH** = lactate dehydrogenase; **OR** = odds ratio; **OS** = overall survival; **PFS** = progression-free survival; **SCC** = squamous cell carcinoma.

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Welcome to issue 9 of Skin Cancer Research Review.

Triplet therapy with encorafenib, binimetinib and pembrolizumab was shown to be feasible and safe, with clinically meaningful disease control in patients with advanced *BRAF*^{V600}-mutant melanoma in the IMMU-TARGET trial. In a multinational, retrospective trial we discover that combined immune checkpoint inhibitor (ipilimumab/nivolumab) therapy prolongs median overall survival with sustainable intra- and extra-cranial responses in patients with melanoma brain metastases and appears superior to combination targeted therapy. Other topics covered in this issue include 5-year outcomes with cobimetinib plus vemurafenib in *BRAF*^{V600}-mutant melanoma, watchful waiting and basal cell carcinoma behaviour, and Mohs cryosection concordance between surgeon and dermatopathologist.

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

Kind Regards,

Dr David Simpson

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Encorafenib, binimetinib plus pembrolizumab triplet therapy in patients with advanced *BRAF*^{V600} mutant melanoma: Safety and tolerability results from the phase I IMMU-TARGET trial

Authors: Zimmer L

Summary: The authors report on the dose-finding phase I safety results from an open-label, phase I/II study of pembrolizumab, encorafenib and binimetinib triplet therapy in advanced B-Raf proto-oncogene serine/threonine kinase (*BRAF*) ^{V600}-mutant melanoma in 15 patients. The study was terminated after the phase I part, with the combination being examined in a placebo-controlled, double-blinded phase III trial. Dose limiting toxicities at pembrolizumab 200 mg every three weeks, encorafenib 450 mg once daily and binimetinib 45 mg twice daily included creatine phosphokinase (CPK) elevation plus cytokine release syndrome and gamma glutamyl transferase (GGT) increase, each in 1 patient. Overall, 13 patients experienced a treatment-related adverse event (TRAE) with 8 patients experiencing a grade ≥3 TRAE (aspartate aminotransferases, GGT and CPK elevations). After triplet therapy for a median of 24 weeks, among 14 patients evaluable for efficacy, the overall response rate was 64% (95% CI 35-87). Twelve-month progression-free survival (PFS) was 41% (95% CI 13-68).

Comment: Sustained, significant survival benefits have been shown with both targeted therapies targeting BRAF and MAPK pathways and for immune checkpoint inhibitors (ICIs). This trial looked at dosing regimens and adverse reactions using triplet therapy – BRAF, MAPK pathway inhibitors and PD-1 inhibition. The main adverse reactions were elevation of liver function tests, and the combination was generally well tolerated using standard approved doses. Whilst meaningful responses were achieved in PFS, the benefit of triple therapy compared to either PD-1 immunotherapy alone or PD-1 plus CTLA inhibition are yet to be proven and further studies are planned.

Reference: Eur J Cancer. 2021;158:72-84
Abstract

Independent commentary by Dr David Simpson

Dr David Simpson is a skin cancer doctor on the Sunshine Coast in Queensland. He has a masters degree in Skin Cancer Medicine from the University of Queensland and is a teaching assistant on the MMed program.

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Real-life data for first-line combination immune-checkpoint inhibition and targeted therapy in patients with melanoma brain metastases

Authors: Hilbers M-L et al.

Summary: This multinational, retrospective analysis assessed efficacy and outcomes of combined ICI ipilimumab/nivolumab (n = 53) or targeted BRAF/MEK inhibitor therapy (TT; n = 63) as first-line treatment in patients with melanoma brain metastases within 3 months after diagnosis. In ICI recipients, the disease control rate was 60.3% and the intracranial response rate was 43.8% at 3 months with durable responses at 6 (46.5%) and 12 months (53.1%). The extracranial response rate was 44.7% at 3 months and 50% at 12 months. Median PFS was 9.6 months and median OS was 44.8 months. Among those receiving TT, the disease control rate was 60.4%. Intracranial response rate was 50% at 3 months but declined at 6 months (20.9%). Extracranial response rate was 69.2% at 3 months and 17.6% at 12 months. Median PFS was 5.8 months and median OS 14.2 months. In *BRAF*^{V600} patients, 26.7% received combination ICI and 73.3% TT with median OS (p = 0.0053) and median PFS (p = 0.03) favouring ICI.

Comment: ICI and targeted therapy have revolutionised the management of metastatic melanoma. Brain metastases carry a poor prognosis, but valuable response rates have been demonstrated with these new treatments. This study examined real-life treatment of patients presenting with melanoma brain metastases. Overall, combination immune checkpoint therapy – using ipilimumab and nivolumab – resulted in superior PFS and OS whilst targeted therapy led to superior short-term results but these were not sustained beyond 12 months. Clinicians appeared to manage patients with "dismal" disease characteristics such as symptomatic melanoma brain metastases and elevated LDH with targeted therapy, possibly due to its rapid action in reducing disease burden, but the duration of benefit was limited. Subsequent immunotherapy following targeted therapy was inferior to results achieved using immunotherapy as initial therapy. More research is required to establish the optimal sequence of therapies.

Reference Eur J Cancer. 2021;156:149-163
Abstract

5-Year Outcomes with cobimetinib plus vemurafenib in *BRAF*^{V600} mutation-positive advanced melanoma: Extended follow-up of the coBRIM study

Authors: Ascierto PA et al.

Summary: This report provides long-term follow-up data from the randomised phase III coBRIM study which demonstrated improved PFS and OS with cobimetinib plus vemurafenib versus placebo plus vemurafenib in 495 patients with previously untreated BRAF^{V600} mutation-positive advanced melanoma. Over a follow-up of 21.2 months for cobimetinib plus vemurafenib and 16.6 months for placebo plus vemurafenib, median OS was 22.5 months (95% CI 20.3-28.8) with cobimetinib plus vemurafenib and 17.4 months (95% CI 15.0-19.8) with placebo plus vemurafenib; 5-year OS rates were 31% and 26%. Median PFS was 12.6 months (95% CI 9.5-14.8) and 7.2 months (95% CI 5.6-7.5); 5-year PFS rates were 14% and 10%. The longest OS and PFS occurred in patients with normal baseline LDH levels and low tumour burden, and in patients achieving complete response.

Comment: Targeted therapy adding a MEK inhibitor to BRAF inhibitor has been shown to be successful in improving PFS and OS in advanced melanoma. The benefits appear to plateau after approximately 3 years and persist at 5 years suggesting evidence of durable survival benefits. Overall, around 30% of patients achieved a long-term response but there were marked differences between those with a greater tumour burden at entry as well as those with an elevated baseline LDH level. LDH is a marker of both metastasis and tumour activity and has been consistently shown to indicate a worse prognosis. For patients with a normal baseline LDH the OS at 5 years was 43% compared to 16% for those with an elevated LDH, but in the group with a normal LDH and minimal metastatic disease the OS was 68%, which compares favourably with immunotherapy.

Reference: Clin Cancer Res. 2021;Jun 22 [Epub ahead of print]
Abstract

A phase I, single-center, open-label study of RM-1929 photoimmunotherapy in Japanese patients with recurrent head and neck squamous cell carcinoma

Authors: Tahara M et al.

Summary: This Japanese study assessed an anti-EGFR antibody cetuximab conjugated with a light-activatable dye (RM-1929 photoimmunotherapy), in 3 patients with recurrent head and neck squamous cell carcinoma (rHNSCC; submental; right superficial cervical node; oropharynx; external auditory canal) who had failed ≥3 prior lines of therapy including radiation, chemotherapy, cetuximab, and immunotherapy. TEAEs (n = 17) occurred in all patients but none were dose-limiting and all were mild-to-moderate in severity except for grade 3 application-site pain in one patient; 13 TEAEs were possibly or probably related to study treatment (application-site pain and localised oedema). Objective partial responses occurred in two patients, a third patient experienced disease progression. RM-1929 levels and pharmacokinetic parameters were similar in all patients and no patients developed anti-drug antibodies.

Comment: Cetuximab, a monoclonal antibody targeting EGFR, is used in tumours over-expressing EGFR including colorectal cancer and locally advanced/recurrent SCC. This study investigated a novel treatment in which cetuximab was combined with a light-sensitive dye and infused intravenously in a small group of patients with locally advanced head and neck SCC. After 24 hours, the tumours were illuminated with a red-light source that activated the dye and disrupted the cell membrane integrity of the tumour cells with subsequent necrosis. In this treatment, cetuximab utilised its affinity for EGFR to selectively bind the dye to the tumour and spare normal cells. Only one treatment was carried out, but partial responses were seen in two out of three patients although recurrences were seen at the margin of the treatment area and the authors suggested that a course of sequential treatments might be optimal.

Reference: Int J Clin Oncol. 2021;26(10):1812-1821
Abstract

Evaluation of watchful waiting and tumor behavior in patients with basal cell carcinoma: An observational cohort study of 280 basal cell carcinomas in 89 patients

Authors: van Winden MEC et al.

Summary: This single-centre, observational study evaluated 89 patients (median age 83 years) who chose watchful waiting for 280 basal cell carcinomas (BCC). The most common (83% of patients) reason for watchful waiting was patient-related factors or preferences (i.e., prioritisation of comorbidities, severe frailty, or limited life expectancy), followed by tumour-related factors (55%). Over a median 9 months of follow-up, a minority of tumours (47%) increased in size. Tumour diameter increased by an estimated 4.46 mm over 1 year for BCCs containing at least an infiltrative/micronodular component and by 1.06 mm for remaining BCCs. Tumour growth was associated with BCC subtype (OR 3.35; 95% CI 1.47-7.96), but not with initial tumour size or location. The most common reasons for initiating treatment were tumour burden or potential tumour burden, resolved reasons for watchful waiting, and re-evaluation of patient-related factors.

Comment: There are often situations where either the patient, clinician or relatives wonder whether treating a less aggressive skin cancer is appropriate given the patients overall health or life expectancy. Reading this paper from the Netherlands was interesting and very applicable to real-life practice. Most of those patients who chose "watchful waiting" because of limited life expectancy were still alive at the end of the study. I often say to the more negative-minded patients that they might live longer than they think and then have to cope with a more advanced tumour. As one might expect, the low-grade and small tumours behaved in a much more indolent fashion and several lesions completely regressed following biopsy. 38% of patients went on to have treatment, although only a small percentage required more complex surgery than had been anticipated. In my practice I tend to advise surgery or radiotherapy for aggressive or advanced tumours unless a patient has a definite life-limiting comorbidity; it seems preferable to having to live with a bleeding, offensive tumour.

Reference JAMA Dermatol. 2021;157(10):1174-1181
Abstract

Interventions for basal cell carcinoma: Abridged Cochrane systematic review and GRADE assessments

Authors: Thomson J et al.

Summary: This updated Cochrane systematic review including 52 randomised controlled trials (n = 6990; median age 65 years) examined the effects of interventions for primary BCC in immunocompetent adults. 92% of studies included only histologically low-risk BCC (nodular and superficial subtypes). Certainty of evidence was predominantly low or moderate. Over a mean study duration of 13 months, surgical interventions have the lowest recurrence rates; there may be fewer recurrences with Mohs micrographic surgery over surgical excision for primary facial BCC (low-certainty evidence). Surgical interventions have lower recurrence rates and are the gold standard for high-risk BCC. Nonsurgical treatments in low-risk BCC are less effective than surgical treatments, but cosmetic outcomes are probably superior and recurrence rates are acceptable. Of nonsurgical treatments, topical imiquimod has the best efficacy for low-risk BCC.

Comment: A wide range of treatment options are available for BCC treatment ranging from Mohs surgery to cryotherapy. In this updated review, surgery was found to be the optimal therapy with regards to recurrence rate and Mohs was only slightly more efficacious than standard excision. Radiotherapy resulted in more recurrences and inferior cosmesis when compared to standard excision and of the other non-surgical treatments, imiquimod was the most effective and seemed to provide good cosmesis. The studies used were all selected for high quality but didn't mirror routine daily practice; imiquimod was compared with photodynamic therapy in mostly nodular tumours and only one study used aminolevulinic acid (ALA) with a fractionated protocol. Fractionated ALA photodynamic therapy has been shown to be more effective than standard protocols when treating thin nodular and superficial BCC's. Imiquimod can produce strong local reactions as well as systemic adverse effects and scarring can be unsatisfactory, but this was not apparent from this review. Dosing regimens for superficial radiotherapy used in Australia often lead to good cosmesis and reported efficacy is comparable to surgery, but this was not apparent in the review.

Reference: Br J Dermatol. 2021;185(3):499-511
Abstract

Accuracy of dermoscopic criteria for the differential diagnosis between irritated seborrheic keratosis and squamous cell carcinoma

Authors: Papageorgiou C et al.

Summary: This study examined the dermoscopic criteria that could serve as predictors for the differential diagnosis between irritated seborrheic keratosis (ISK; n = 61) and SCC (n = 104) based on evaluation by three independent investigators. Positive dermoscopic predictors of SCC on multivariate analysis were white circles surrounding follicles (OR 23.45; 95% CI 2.29-246.1), dotted vessels (OR 10.4; 95% CI 2.97-36.43), white structureless areas (OR 6.78; 95% CI 1.45-31.45). Additional univariate predictors included branched linear vessels (OR 5.30; 95% CI 1.51-18.58), a diffuse irregular (OR 2.55; 95% CI; 0.99-6.54) or peripheral (OR 2.80; 95% CI 1.10-7.12) vessel arrangement, and a central scale arrangement (OR 3.35; 95% CI 1.39-8.08). Dermoscopic predictors that negatively predicted SCC and made ISK more likely were hairpin vessels (OR 0.38: 95% CI 0.15-0.98), a diffuse regular vessel arrangement (OR 0.36), and white halos surrounding vessels covering >10% (OR 0.29) or >50% (OR 0.12) of the lesion.

Comment: ISKs can be challenging to distinguish from SCC since they share features and ISKs often fail to show classic seborrhoeic dermoscopic signs. The strongest clues for SCC were found to be white circles surrounding follicles, dotted vessels, white structureless areas, diffuse irregular vessel arrangement and linear branched vessels. Features that made SCC less likely were hairpin vessels, diffuse regular arrangement of vessels and white halos surrounding vessels in more than 10% of the lesion. Central scale and white scale rather than yellow scale may also help distinguish SCC from ISK.

Reference: J Am Acad Dermatol. 2021;85(5):1143-1150
Abstract

Tumor primary site as a prognostic factor for Merkel cell carcinoma disease-specific death

Authors: Cullison CR et al.

Summary: This retrospective (1973-2016) analysis of the US Survival, Epidemiology, and End Results (SEER) database examined the incidence by tumour primary site of death due to Merkel cell carcinoma (MCC). Of 9407 MCC patients, 6305 (67.0%) had localised disease, 2397 (25.5%) had regional metastasis, and 705 (7.5%) had distant metastasis. Tumour primary site predicted Merkel cell carcinoma-specific mortality (CMMI); tumours of the scalp/neck had the highest CMMI among localised MCC (26.0%), while tumours of the lip had the highest CMMI in MCC with regional (56.7%) and distant metastasis (82.1%).

Comment: MCC is an aggressive neuroendocrine tumour with an increasing incidence. It metastasises early and has a high mortality rate necessitating early diagnosis and often a combination of radiotherapy and surgery. The initial site of the primary tumour appears to be linked to prognosis with head and neck and truncal sites resulting in a worse prognosis. In patients with distant or regional metastases the primary site is less of a factor, although lip tumours still seem to confer a worse prognosis and eyelid tumours a more favourable one.

Reference: J Am Acad Dermatol. 2021;85(5):1259-1266
Abstract

Concordance between a Mohs surgeon and a dermatopathologist in evaluating Mohs cryosections

Authors: Atilla S et al.

Summary: This retrospective (2013-20) analysis of frozen sections from 237 cases of Mohs micrographic surgery for high-risk non-melanoma skin cancers that had been intraoperatively evaluated by a pathologist, was conducted by a certified Mohs surgeon in a blinded manner. Tumours were marked on copy maps and compared to the original maps to assess concordance; non-concordant cases were re-evaluated together by the Mohs surgeon and the dermatopathologist. There was concordance of 97.9% and inter-rater agreement of 0.96 between the Mohs surgeon and the dermatopathologist for evaluation of the Mohs slides.

Comment: In Turkey, skin cancers are usually excised by plastic surgeons, but Mohs surgery has been used in the reporting institution since 2013. Due to local laws the slides must be reported on by a dermatopathologist rather than the Mohs surgeon which adds to the cost and limits the availability of the service. Slides taken during Mohs surgery dating back over 7 years were used retrospectively to compare the accuracy and concordance of both the Mohs surgeon and dermatopathologist and there was a discrepancy in only 5 of 237 cases. Factors which affected an accurate Mohs diagnosis included inflammation and scarring due to a previous punch biopsy, difficulties taking thin enough slices in areas with a lot of subcutaneous fat tissue and very small areas of residual tumour. Overall, the concordance rate was 97.9%, which is comparable to previous studies in the USA and should provide reassurance that Mohs surgery is a reliable option even when instituted in a new centre.

Reference: J Eur Acad Dermatol Venereol. 2021;35(11):2219-2224
Abstract

