Melanoma Research Review™

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In this issue:

Abbreviations used in this issue:

BCC = basal cell carcinoma; **CLND** = completion lymph node dissection; **ICI** = immune checkpoint inhibitor; **irAE** = immune-related adverse event; **RFS** = recurrence-free survival; **SCC** = squamous cell carcinoma; **SLN** = sentinel lymph node; **SLNB** = sentinel lymph node biopsy; **WLE** = wide local excision.

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Welcome to the 41st issue of Melanoma Research Review.

A retrospective study in a real-world setting found ICI therapy for patients with advanced melanoma significantly improved survival in patients aged 65 years and older. Another study investigated response to ICI rechallenge after high-grade irAEs in patients with advanced melanoma. The authors concluded ICI rechallenge can be considered in this cohort as the risk-benefit profile appears favourable. A Dutch study used registry data to compare first-line anti-PD-1 monotherapy versus BRAF/MEK inhibitors in advanced BRAFV600-mutant melanoma patients. The results suggest anti-PD-1 monotherapy is the preferred first-line treatment in patients with relatively favourable patient and tumour characteristics. Also included in this issue is a small retrospective study of patients with metastatic melanoma over 75 years of age treated with BRAF inhibitor or BRAF/MEK inhibitor. The authors report response rate and median overall survival were comparable with those reported in clinical trials and combination therapy produced more and longer-lasting responses. The authors highlight the importance of personally tailored treatment in the management of this fragile group of patients.

Other interesting topics addressed in this issue include nomograms to predict recurrence in patients with thin melanomas and skin cancer and melanoma risk scores for population screening. Other articles explore nodal recurrence as a primary driver of early relapse for patients with SLN-positive melanoma and the impact of shave biopsy on diagnosis and management of cutaneous melanoma.

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,

Professor Michael Henderson

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First-line BRAF/MEK inhibitors versus anti-PD-1 monotherapy in BRAF V600-mutant advanced melanoma patients: A propensity-matched survival analysis

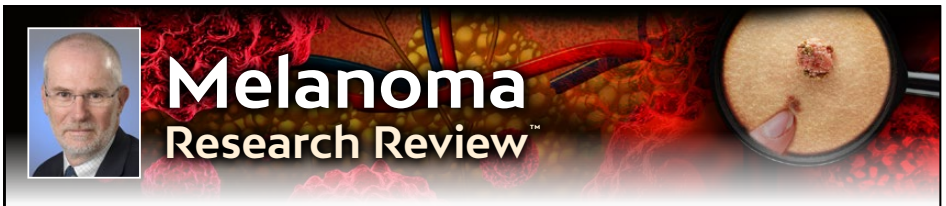
Authors: van Breeschoten J, et al

Summary: This Dutch study used registry data to compare first-line anti-PD-1 monotherapy (n = 254) versus BRAF/MEK inhibitors (n = 330) in advanced BRAFV600-mutant melanoma patients. In the matched cohort, patients receiving anti-PD-1 had a higher median and 2-year overall survival compared to patients treated with BRAF/MEK inhibitors; 42.3 months versus 19.8 months and 65.4% versus 41.7%, respectively.

Comment: For Stage 4 patients with V600 mutated melanoma the optimal primary treatment is currently unresolved although several trials will report in the next two years. This analysis of real-world data highlights some of the difficulties in making definitive recommendations. In this Dutch cohort, patients receiving anti-PD-1 monotherapy were more likely to have less symptoms and a lower burden of disease compared to patients receiving targeted therapy hence there was an issue with adequately matching patients in the two groups. Using overall survival as the endpoint they concluded that patients with a BRAF V600 mutation and significant symptoms requiring a quick response should receive targeted therapy otherwise single agent anti-PD-1 was preferred.

Reference: Br J Cancer. 2021 Mar;124(7):1222-123

Abstract



Independent commentary by Professor Michael Henderson.

Michael A Henderson is Professor of surgery in the University of Melbourne and surgeon in the multidisciplinary Melanoma and Skin Service at the Peter MacCallum Cancer Centre in Melbourne. He is a graduate of the University of Melbourne and after obtaining a Fellowship of the Royal Australasian College of Surgeons spent 2 1/2 years undertaking a fellowship in surgical oncology at the University of Texas MD Anderson Cancer Centre. His clinical practice is confined to surgical oncology. His major clinical interests are in the management of patients with melanoma and maintains an active clinical and translational research interest in melanoma. He led a major international multicentre study of adjuvant radiotherapy after link for melanoma and is currently the principal investigator of a multicentre international trial of margins of excision of intermediate and thick melanoma (MELMART).

Immune checkpoint inhibitors retain effectiveness in older patients with cutaneous metastatic melanoma

Authors: Howell AV, et al

Summary: The retrospective study in a real-world setting included a cohort of 541 patients aged ≥ 65 years with stage IV cutaneous melanoma treated with immune checkpoint inhibitors (ICIs) therapy. The authors reported median survival differed significantly between groups ($p < 0.0001$) and was longest in patients treated with PD-1 inhibitors (34.0 months), followed by CTLA-4 inhibitors (16.8 months), targeted therapy (9.7 months), chemotherapy (7.1 months), and no systemic therapy (3.6 months). It was noted ICI survival benefit persisted after adjusting for age, sex, comorbidities, M stage, the presence of brain metastases. They also reported hazard ratios comparing ICIs to no systemic therapy were 0.35 for PD-1 inhibitors and 0.48 for CTLA-4 inhibitors. There was no difference in ICI effectiveness by age group (65-74 vs ≥75).

Comment: Older patients are frequently underrepresented in trials of advanced disease. This is of potential significance as older patients may have impaired responses to immune checkpoint inhibitor therapy given their underlying age-related immune dysfunction. There has been some controversy in the literature particularly for patients > 75 years. Resolving this dilemma is of some significance and this large report based on SEER data clearly indicates similar effectiveness of both immune checkpoint and targeted therapy for patients 65-75 versus older. Furthermore, outcomes in older patients were similar to those seen in younger patients (< 65 years). As this was a retrospective study only the first therapy used was considered although the primary outcome measure was overall survival. There was no information on safety or tolerability of treatment.

Reference: J Geriatr Oncol. 2021 Apr;12(3):394-401
Abstract

Nodal recurrence is a primary driver of early relapse for patients with sentinel lymph node-positive melanoma in the modern therapeutic era

Authors: Mitra D, et al

Summary: This study aimed to identify patterns and predictors of early recurrence in a cohort of 215 patients with sentinel lymph node (SLN)-positive melanoma who did not have completion lymph node dissection (CLND). Adjuvant systemic therapy was administered to 47% of patients, with 93% of this subset receiving immunotherapy. Median follow-up from SLNB was 20 months, and 27% recurred during this time. The investigators found SLN basin was the most common site of recurrence (67% of recurrence), with isolated nodal recurrence being the most common first site of recurrent disease (39% of recurrence). Furthermore, lymphovascular invasion of the primary tumour, two or more involved nodes, and > 1 mm nodal deposit were independently associated with higher rates of nodal relapse.

Comment: Following publication of the MSLT-2 and DECOG studies, CLND for patients with a positive SLN has largely been abandoned in place of observation which although associated with a lower rate of lymph node basin control had no impact on survival compared with patients undergoing standard lymphadenectomy. This study explores the outcomes of patients with a positive SLNB and 27% recurred. The lymph node basin was the commonest first site of recurrence in 2/3 of cases. Multivariate analysis identified lymphatic-venous invasion, 2 or more nodes or node deposit greater than 1 mm in size as predictive of recurrence. The authors conclude that patients identified as likely to recur in the lymph node basin may benefit from additional regional treatment possibly radiotherapy.

Reference: Ann Surg Oncol. 2021 Apr 15. Online ahead of print.
Abstract

Development and validation of nomograms to predict local, regional, and distant recurrence in patients with thin (T1) melanomas

Authors: El Sharouni M, et al

Summary: The researchers developed and validated a model predicting recurrences in patients with thin melanomas using a Dutch population-based cohort (n = 25,930, development set) and a cohort from an Australian melanoma treatment centre (n = 2,968, validation set) with median follow-up 6.7 and 12.0 years, respectively. They generated multivariable Cox models for local, regional, and distant recurrence-free survival (RFS). Discrimination was assessed using Harrell's C-statistic for each outcome and the nomograms' C-statistics were compared with those of a model including T-stage and SLN status. The researchers found local, regional, and distant recurrences in 209 (0.8%), 503 (1.9%), and 203 (0.8%) Dutch patients, respectively, and 23 (0.8%), 61 (2.1%), and 75 (2.5%) Australian patients, respectively. The development model obtained C-statistics of 0.79 for local RFS, 0.77 for regional RFS, and 0.80 for distant RFS. External validation showed C-statistics of 0.80, 0.76 and 0.74, respectively. Using the nomogram, the C-statistic was increased by 9%-12% for the development cohort and by 11%-15% for the validation cohort, compared with a model including only T-stage and SLN status.

Comment: This paper reports the validation of another risk calculator from the Melanoma Institute of Australia (www.melanomarisk.org.au). It is worth reiterating that T1 primary tumours are the commonest melanomas but despite their excellent prognosis, the overwhelming number of these lesions means they account for the majority of deaths from melanoma. The nomogram provides estimates of local recurrence free survival, regional relapse free survival and distant relapse free survival based on scores allocated for sex, age, primary site, thickness, melanoma subtype, ulceration, mitosis, sentinel node status. As with any study there are methodological limitations to this report e.g., length of follow-up in a group of patients where the time to recurrence may be prolonged, but there is important information on the patterns of recurrence. Regional recurrence was the most common followed by distant and local and most distant recurrences occurred after three years. Given the increasing role of adjuvant therapy, identification of patients at significant risk is becoming increasingly a priority. This nomogram is certainly of assistance in helping patients to understand their risks and ongoing care.

Reference: J Clin Oncol. 2021 Apr 10;39(11):1243-1252
Abstract

Impact of shave biopsy on diagnosis and management of cutaneous melanoma: A systematic review and meta-analysis

Authors: Ahmadi O, et al

Summary: The authors conducted a systematic review to investigate the impact of shave biopsy on tumour staging, treatment recommendations, and prognosis. The meta-analysis, which included 13 articles with a total of 3,713 patients with melanoma diagnosed on shave biopsy revealed a positive deep margin in 42.9% biopsies. Following wide local excision (WLE), change in tumour stage was reported in 7.7% of patients. Additional treatment was recommended for 2.3% of patients in the form of either further WLE and/or SLN biopsy. There was no impact on local recurrence or survival among the studies analysed. The authors noted there was high heterogeneity across studies in all outcomes.

Comment: This meta-analysis, as have other reviews of biopsy techniques for melanoma, concluded that shave biopsy is an appropriate technique for diagnosis of melanoma. The authors report that in the literature over 40% of melanomas have a positive deep margin but the frequency of residual disease at the time of the definitive wide excision in the completely excised specimen is much lower and uncommonly leads to alterations in care. Currently the Australian guidelines recommend against partial biopsies i.e., shave and punch because of the risks of false negatives or underreporting. The technique is not simple and in general clinicians who perform the procedure infrequently should be cautious. The authors do not comment on the training/experience or specialty of the clinicians performing shave biopsy. Patients with a positive deep margin after shave biopsy should be strongly considered for a complete excision biopsy particularly if upstaging is likely to alter management e.g., wider margins of excision or need for a sentinel node biopsy.

Reference: Ann Surg Oncol. 2021 Mar 29;1-9
Abstract

Impact of a see-and-treat melanoma clinic on patient experience

Authors: Ip KH, et al

Summary: The prospective study examined patient's perception of a one-stop model for pigmented lesions, incorporating same-day excisional biopsy for lesions suspicious for melanoma. A total of 107/142 (75.4%) patients consented to participate in the study and completed a survey four weeks after their initial assessment. The authors concluded patients who underwent same-day biopsy reported higher satisfaction (4.9 vs. 4.5, p < .01) and perceived convenience (4.8 vs. 4.4, p < .01), compared to overall mean response. They noted of those who received same-day procedures no patient reported being given insufficient time to consider surgical treatment.

Comment: This is a small but prospective study of a one-stop specialist diagnostic clinic for pigmented lesions from New Zealand. Overall, there was a modest increase in customer satisfaction and convenience in the patients who underwent a same-day consultation and excision biopsy. Interestingly no patients felt they had not been given enough time. While these results are not surprising, the role of similar clinics in the wider health care system in the management of cutaneous malignancy is yet to be resolved. Many general practitioners certainly in Australia perform minor surgery in their offices and recent years have seen a proliferation of GP lead skin clinics. Public hospitals provide these types of services often in the setting of complex clinical or social scenarios. The future of these clinics will depend not just on patient preferences but also resource utilisation, health economic evaluation and patient outcomes.

Reference: J Dermatolog Treat. 2021 Apr 1;1-3
Abstract

Clinical utility of skin cancer and melanoma risk scores for population screening: TRoPICS study

Authors: Shetty A, et al

Summary: Participants (n = 507) in a volunteer-based screening clinic completed questionnaires to predict melanoma and keratinocyte cancers [basal cell carcinoma (BCC) and squamous cell carcinoma (SCC)] and were classified into one of five risk categories. Full skin examination was conducted by a dermatologist and suspicious lesions biopsied with all cancers histopathologically confirmed. The authors reported 22 BCCs, 19 SCCs and eight melanomas were diagnosed. The proportion of keratinocyte cancers diagnosed increased according to risk category from <1% in the lowest to 24% in the highest risk category (P < 0.001). They noted similar proportionate increases in BCC or SCC prevalence according to risk category. In contrast, a similar proportion of melanoma cases were detected in the low-risk and high-risk groups.

Comment: There is no randomised data to support population-based screening for melanoma although modelling of screening individuals at high risk appears to be cost effective (*J Clin Oncol 2017; 35: 63–71*). The current study of a relatively select group of attendees at the annual Hamilton Island yachting week used validated risk assessment tools for keratinocyte malignancy and melanoma to assess their effectiveness in identifying persons who might benefit from screening. While increasing risk of BCC/SCC was associated with increased frequency of these lesions, there was no relationship between risk of melanoma and the number identified in each of the five risk groups. There were only 8 melanomas in the nearly 800 persons screened which highlights the difficulty in assessing the role of population screening for melanoma but also highlights the difficulty in defining an appropriate risk group in the general population for screening if even one exists.

Reference: J Eur Acad Dermatol Venereol. 2021 May;35(5):1094-1098
Abstract

Response to immune checkpoint inhibitor rechallenge after high-grade immune related adverse events in patients with advanced melanoma

Authors: Shah P, et al

Summary: The study cohort comprised of 32 patients with stage IV or unresectable stage III melanoma with high-grade immune-related adverse events (irAEs) after first-line ICI systemic therapy and rechallenged with ICI therapy. The investigators found post rechallenge irAEs recurred in 71.9% (n = 23/32) of patients at a median of 5.1 weeks from rechallenge, with 46.9% (15/32) recurring as high-grade events. Clinical response was achieved in 46.9% (15/32) of patients, including 40.6% (13/32) with a complete response and 6.3% (2/32) with partial response. Median overall survival from first ICI initiation was 85.4 weeks and median progression-free survival was 42.9 weeks. The investigators noted patients with a shorter time to initial irAE and shorter time to post rechallenge irAE were at greater risk for disease progression (hazard ratio 7.8; P = 0.004; hazard ratio 7.45; P = 0.012). Furthermore, those with greater duration to rechallenge (>10 weeks) were at lower risk for disease progression (hazard ratio 0.15; P = 0.015).

Comment: Severe immune related toxicity complicates ICI therapy in approximately 1/3 of patients of whom 2/3 may cease ICI therapy. This is a small study which nevertheless claims to be the largest evaluation of ICI rechallenge after prior cessation for immune-related toxicity. There was a total of 32 patients and not surprisingly further immune related toxicity was common (71%) but apparently manageable mainly with steroids. The original toxicity was not always repeated. Patients who delayed reintroduction of ICI therapy (> 10 weeks) had reduced adverse events and better outcomes. This data is encouraging but still very limited given the very small number of patients treated.

Reference: Melanoma Res. 2021 Jun 1;31(3):242-248
Abstract

BRAF inhibitor treatment is feasible in the oldest-old advanced melanoma patients

Authors: Kohtamäki LM, et al

Summary: Patients with metastatic melanoma over 75 years of age were treated with BRAF inhibitor (n = 22) or BRAF inhibitor in combination with MEK inhibitor (n = 12). The researchers reported grade 1-2 adverse events occurred in 68% of the patients; 32% had grade 3 adverse effects. Dose reductions were made for 41% of patients and 29% terminated treatment due to toxicity. Overall, the response rate was 62%. Complete responses were achieved in 27% of the patients, and 35% had partial responses. The median progression-free survival was 8 months and the median overall survival was 15 months.

Comment: In the randomised studies of BRAF/MEK inhibition, the elderly (>75 years) are underrepresented and rarely reported as a subgroup of interest. This is a small retrospective study of elderly patients with an appropriate BRAF mutation who received combination BRAF/MEK inhibition. In summary the authors report similar survivals and rates of adverse events as seen in younger patients reported in the randomised studies. The authors reported use of a specialist geriatric clinic for the most vulnerable and judicious dosing with frequent reductions for adverse events. Despite this 44% of patients were hospitalised for adverse events. Quality of life data was not available. The authors highlight the importance of personally tailored treatment in the management of this fragile group of patients.

Reference: Melanoma Res. 2021 Jun 1;31(3):218-223
Abstract

