Melanoma Research Review™

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In this issue:

Abbreviations used in this issue:

DMFS = distant metastasis-free survival; **MSS** = melanoma-specific survival; **OS** = overall survival; **PFS** = progression-free survival; **RFS** = recurrence-free survival; **SEER** = Surveillance, Epidemiology, and End Result.

Welcome to the 56th issue of Melanoma Research Review

This issue of Research Review includes the 2022 update on the European guidelines for the treatment of melanoma. The guidelines were written to assist clinicians and aim to address the advances in the medical treatment of melanoma which justify a newer multidisciplinary therapeutic strategy. Another article reviews the current evidence for neoadjuvant systemic therapy in stage III melanoma from the International Neoadjuvant Melanoma Consortium. The consortium aims to provide definitive proof of the safety and efficacy of neoadjuvant systemic therapy in melanoma to allow more personalised, biomarker-driven approaches to subsequent treatment and surveillance. Other interesting research covered in this issue includes a large, whole-genome sequencing study of melanoma that provides etiological and biological insights into melanoma subtypes and an epidemiologic analysis of melanoma overdiagnosis in the United States from 1975-2017.

Updates on long term outcomes of two immunotherapy studies are also included in this issue. The 5-year analysis of adjuvant therapy with pembrolizumab resulted in a sustained improvement in the long-term recurrence- and distant metastasis-free survival compared with placebo in patients with resected stage III melanoma. The concluding article reports on extended follow up of CheckMate 067 at 6.5 years. The results showed durable, improved clinical outcomes with nivolumab plus ipilimumab or nivolumab versus ipilimumab in patients with advanced melanoma and, in descriptive analyses, with the combination over nivolumab monotherapy.

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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European consensus-based interdisciplinary guideline for melanoma. Part 2: Treatment - Update 2022

Authors: Garbe C, et al

Summary: The guidelines were written in order to assist clinicians in treating patients with melanoma. In particular, the guidelines aimed to address the advances in the medical treatment of patients with cutaneous melanoma, which justify a newer multidisciplinary therapeutic strategy. Contributors included different specialties involved in the management of melanoma patients including dermatology, medical oncology, surgical oncology, radiotherapy and pathology. The guidelines were prepared under the auspices of the European Dermatology Forum (EDF), the European Association of Dermato-Oncology (EADO), and the European Organization for Research and Treatment of Cancer (EORTC). Recommendations were based on the level of best quality available evidence and graded according to the Oxford classification.

Comment: This large paper (28 pages) from the major European cancer organisations is a consensus based review of the current state of management for melanoma as of November 2021 (part one reviewed diagnosis). The recommendations based on the best available evidence are classified as strong 'shall", medium "should" and indeterminate or inconsistent "can/may" after discussion and represent the consensus of the majority of the participants. The guidelines are not limited to cutaneous melanomas and include the latest information on mucosal and uveal melanoma as well as a number of areas where clearly the authors felt further information was required e.g., acral lentiginous melanoma. The guidelines are well written and are in line with standard of care in Australian melanoma units. For instance, the authors note the early data for neoadjuvant systemic therapy for patients with palpable lymphadenopathy but in the absence of definitive data the recommended management is lymphadenectomy followed by adjuvant systemic therapy. The sections on systemic therapy are well referenced and provide nuanced justification for the recommendations. While these recommendations may be of limited interest to melanoma specialists, they are probably the most up-to-date guidelines available. The Australian guidelines which are currently under review remain the gold standard in view of the use of formal evaluation methodology (PICO) of the data.

Reference: Eur J Cancer 2022 Jul;170:256-284
Abstract

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Melanoma risk during immunomodulating treatment

Authors: Zheng YJ, et al

Summary: This literature review summarises the effects of commonly used immunomodulating agents on melanoma development, recurrence and progression. The authors outline the mechanism of action of each drug and discuss the available evidence on its influence on melanoma. They recommend in patients with a history of invasive melanoma avoiding: cyclosporine, sirolimus, natalizumab, IL-6 inhibitors, cyclophosphamide, methotrexate and the TNF-alpha inhibitors infliximab and etanercept. If there are no viable alternative agents, they recommend patients see a dermatologist every 6 months for a thorough skin examination.

Comment: This paper is a review of immunosuppressive agents associated with an increased risk of melanoma, now an area of active interest given the widespread use of these drugs in patients with a variety of illnesses and the increasing reliance on immunotherapy in the management of patients with advanced melanoma. The data is complicated by ascertainment bias, diagnosis and treatment details e.g., length and dose, so reviews such as this do have limitations, but this is an extensive review. Epidemiological evidence suggests that cyclosporine, natalizumab and sirolimus are associated with an increased risk. The data for other agents is far less certain but agents where the possibility of harm exist based on limited data include IL-6 inhibitors, cyclophosphamide, methotrexate and the TNF-alpha inhibitors infliximab and etanercept. Agents such as glucosteroids, everolimus, mycophenolate and azathioprine do not appear to be associated with an increased risk of melanoma.

Reference: Melanoma Res 2022 Dec 1;32(6):411-418
Abstract

Relatlimab and nivolumab versus nivolumab in untreated advanced melanoma

Authors: Tawbi HA, et al

Summary: The phase 2-3, global, double-blind, randomised trial evaluated relatlimab and nivolumab as a fixed-dose combination compared with nivolumab alone in patients with previously untreated metastatic or unresectable melanoma. The authors reported the median progression-free survival (PFS) was 10.1 months (95%CI, 6.4 to 15.7) with relatlimab-nivolumab as compared with 4.6 months (95% CI, 3.4 to 5.6) with nivolumab (HR for progression or death, 0.75 [95% CI, 0.62 to 0.92]; P=0.006 by the log-rank test). PFS at 12 months was 47.7% (95% CI, 41.8 to 53.2) with relatlimab-nivolumab as compared with 36.0% (95% CI, 30.5 to 41.6) with nivolumab. They noted grade 3 or 4 treatment-related adverse events occurred in 18.9% of patients in the relatlimab-nivolumab group and in 9.7% of patients in the nivolumab group.

Comment: This is the first report describing experience with the novel immune checkpoint inhibitor relatlinib. Single agent nivolumab was compared with combination nivolumab and relatlinib. The primary end point, PFS, strongly favoured the combination (median 10 and 4 months). Grade 3/4 toxicity was higher in the combination arm (19% and 10%) but quality of life was similar in both arms. Outcomes and toxicity of single agent nivolumab was similar to previous reports but the combination was less toxic than the combination of ipilimumab and nivolumab as reported in CheckMate 067. The effects of the combination persisted in all previously specified subgroups examined. These are early results (median follow-up 13 months) and at this stage neither response rate nor overall survival have been reported. Of note patients with >1% tumour LAG-3 expression had superior PFS (median 12 v 5 months). The combination of LAG-3 and PD-1 inhibition are similar to results from the combination of ipilimumab and nivolumab (CheckMate 067, median PFS 12 months) but with reduced toxicity indicating the potential for this combination.

Reference: N Engl J Med 2022 Jan 6;386(1):24-34
Abstract

An epidemiologic analysis of melanoma overdiagnosis in the United States, 1975-2017

Authors: Kurtansky NR, et al

Summary: The investigators used Surveillance, Epidemiology, and End Result (SEER) Program data from 1975 to 2017 to examine epidemiologic trends of melanoma incidence and mortality in white Americans. During the 43-year period they found incidence and mortality showed discordant temporal changes across population subgroups, with trends most suggestive of overdiagnosis alone in females aged 55-74. They noted encouraging trends included long-term declines in mortality in younger individuals and recent stabilisation of invasive incidence in individuals aged 15-44 years and males aged 45-54 years. However, melanoma in situ incidence continued to increase throughout the population.

Comment: In 2019 Welch and colleagues (NEJM) in an opinion piece highlighted the role of over diagnosis in the increasing incidence of melanoma in the USA. The current report explores incidence and mortality rates over 43 years. In summary this group found evidence of over diagnosis in all age groups, but they argue the situation is complex for example with changes in personal UV exposure, increasing uptake of skin examination over the time period etc. Using the SEER database, they identified middle-aged and younger females as being the most at risk for over diagnosis as identified by significant discordance between incidence and mortality rates. The most striking finding was the increasing incidence in melanoma in situ which the authors conclude can only be partially explained by changes in diagnostic criteria. The original report by Welch and colleagues incited considerable debate and this report, whilst it has its limitations and given the complexity of the situation, supports their hypothesis.

Reference: J Invest Dermatol 2022 Jul;142(7):1804-1811.e6
Abstract

Comparative genomics provides etiological and biological insights into melanoma subtypes

Authors: Newell F, et al

Summary: This whole-genome sequencing study of melanoma profiled 570 tumours as well as methylation and RNAseq for subsets of tumours. The authors reported uveal melanoma is genomically distinct from other melanoma subtypes, harbouring the lowest tumour mutation burden and with significantly mutated genes in the G-protein signaling pathway. Although most cutaneous, acral and mucosal melanomas share alterations in components of the MAPK, PI3K, p53, p16 and telomere pathways, the mechanism by which these pathways are activated or inactivated varies between melanoma subtypes. The authors also identified potential novel germline predisposition genes for some of the less common melanoma subtypes.

Comment: This report from Australian colleagues is the largest study of the genomic landscape of melanoma and unlike many of the previous reports employed whole genome sequencing rather than whole exon sequencing. Not surprisingly uveal melanoma is shown to be genomically distinct from other subtypes including cutaneous, acral and mucosal melanoma which share significant alterations in the MAPK, PI3K, TP53, p16, and telomere pathways, although how these pathways behave differs between these 3 tumour types. The relationship between the major subtypes with tumour mutational burden and the presence of a UV signature is described. This is a detailed and complex report which highlights important genomic similarities between the 3 major subtypes indicating potential common therapies.

Reference: Cancer Discov 2022 Sep 13; Online ahead of print
Abstract

Five-year analysis of adjuvant pembrolizumab or placebo in stage III melanoma

Authors: Eggermont AMM, et al

Summary: The trial randomly assigned 1,019 patients to receive 200mg pembrolizumab or placebo for approximately 1 year and had previously reported data with a 15-, 36-, and 42-month median follow-up. This article reports data at a median follow-up of 4.9 years. The authors showed in the overall intention-to-treat population, pembrolizumab was still associated with longer recurrence-free survival (RFS) than placebo (5-year rate of RFS, 55.4% [95% CI, 50.8 to 59.8] versus 38.3% [95% CI, 33.9 to 42.7]; HR for recurrence or death, 0.61 [95% CI, 0.51 to 0.72]) and a longer distant metastasis-free survival (DMFS) (5-year rate of DMFS, 60.6% [95% CI, 56.0 to 64.9] versus 44.5% [95% CI, 39.9 to 48.9]; HR for distant metastasis or death, 0.62 [95% CI, 0.52 to 0.75]). It was noted similar findings were obtained in the subgroup of 853 patients with PD-L1–positive tumours.

Comment: This trial initially reported 15 months (and subsequently at 3.5 years) of follow up is now updated with nearly 5 years median follow up to confirm the long term stability of improved RFS and DMFS with adjuvant nivolumab. Entry into this trial required a completion lymphadenectomy and included patients with minimal lymph node involvement (minimum 1mm). Crossover to pembrolizumab was possible in the placebo arm on recurrence or rechallenge in the treatment arm (>18 months). Both the primary and secondary end points, RFS and DFMS confirmed stability of treatment. Outcomes after recurrence were poor with median time to second recurrence or death of 9 months (estimated five-year survival 20%). Very few adverse events were reported during the extended follow up (9 and 1 cases).

Reference: NEJM Evid 2022 September 10;1 (11). Online ahead of print
Abstract

Assessing the potential for patient-led surveillance after treatment of localized melanoma (MEL-SELF): A pilot randomized clinical trial

Authors: Ackermann DM, et al

Summary: The study objective was to determine whether patient-led surveillance in patients with prior localised primary cutaneous melanoma is as safe, feasible, and acceptable as clinician-led surveillance. Participants were randomised to 6 months of patient-led surveillance, (usual care plus reminders to perform skin self-examination, patient-performed dermoscopy, teledermatologist assessment, and fast-tracked unscheduled clinic visits) or clinician-led surveillance (usual care). Of 326 patients who were eligible, 100 (31%) patients were randomised to patient-led (n=49) or clinician-led (n=51) surveillance. Data were available on patient-reported outcomes for 66 participants and on clinical outcomes for 100 participants. Compared with clinician-led surveillance, patient-led surveillance was associated with increased skin self-examination frequency (OR, 3.5) and thoroughness (OR, 2.2), had no detectable adverse effect on psychological outcomes (fear of cancer recurrence subscale score; mean difference, -1.3), and increased clinic visits (RR, 1.5), skin lesion excisions (RR, 1.1), and subsequent melanoma diagnoses and subsequent melanoma diagnoses (risk difference, 10%). New primary melanomas and 1 local recurrence were diagnosed in 8 (16%) of the participants in the intervention group, including 5 (10%) ahead of routinely scheduled visits; and in 3 (6%) of the participants in the control group, with none (0%) ahead of routinely scheduled visits (risk difference, 10%).

Comment: There is little evidence on how to base follow-up regimes after a diagnosis of melanoma, but what is clear in Australia is the magnitude of the burden surveillance places on the health system. This report is essentially a pilot study investigating patient-led surveillance. Patients were provided with a dermatoscope device to place on their phone and were encouraged to provide pictures for review by a team of dermatologists as well as having the opportunity for rapid access for concerning lesions. Surprisingly only one third of patients approached for this study participated and only 50% of these successfully completed the whole program. Nevertheless, clinic attendances increased. Numbers are small but most patients in the intervention arm who had a melanoma diagnosed presented through the rapid access mechanism (5/8). This is an interesting study and highlights the possibilities for a combination of patient self-awareness and technology as one solution to the problem of surveillance.

Reference: JAMA Dermatol 2022 Jan 1;158(1):33-42
Abstract

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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 lymphadenectomy for melanoma and is currently the principal investigator of a multicentre international trial of margins of excision of intermediate and thick melanoma (MELMART).

Neoadjuvant systemic therapy (NAST) in patients with melanoma: Surgical considerations by the international neoadjuvant melanoma consortium (INMC)

Authors: van Akkooi ACJ, et al

Summary: This consortium summarises the past decade of developments in melanoma treatment and the current evidence for neoadjuvant systemic therapy in stage III melanoma. They aim to provide definitive proof of the safety and efficacy of neoadjuvant systemic therapy in melanoma to allow more personalised, biomarker-driven approaches to subsequent treatment and surveillance.

Comment: This report is a very detailed review of the current status of neoadjuvant systemic therapy in patients with stage III disease from the International Neoadjuvant Melanoma Consortium, an international group of predominantly surgeons. This paper reviews the major topics including definition of inoperability, extent of surgery, pathology evaluation including the extent of any response and probably the major concerning, identification and management of progression during pre-operative therapy. Finally, the role of biomarkers is considered leading to perhaps the most desirable outcome, treatment tailored to the individual patient. This is a valuable resource.

Reference: Ann Surg Oncol 2022 Jun;29(6):3694-3708
Abstract

Long-term outcomes with nivolumab plus ipilimumab or nivolumab alone versus ipilimumab in patients with advanced melanoma

Authors: Wolchok JD, et al

Summary: The article reports on the 6.5-year efficacy and safety outcomes of the phase III CheckMate 067 trial. Patients with previously untreated unresectable stage III or stage IV melanoma were randomly assigned to receive nivolumab 1mg/kg plus ipilimumab 3mg/kg once every 3 weeks (four doses) followed by nivolumab 3mg/kg once every 2 weeks (n=314), nivolumab 3mg/kg once every 2 weeks (n=316), or ipilimumab 3mg/kg once every 3 weeks (four doses; n=315). The authors reported median overall survival (OS) (minimum follow-up, 6.5 years) was 72.1, 36.9, and 19.9 months in the combination, nivolumab, and ipilimumab groups, respectively. Median melanoma-specific survival (MSS) was not reached, 58.7, and 21.9 months, respectively; 6.5-year OS rates were 57%, 43%, and 25% in patients with BRAF-mutant tumours and 46%, 42%, and 22% in those with BRAF-wild-type tumours, respectively. In patients who discontinued treatment, the median treatment-free interval was 27.6, 2.3, and 1.9 months, respectively. They noted no new safety signals were observed since the 5-year analysis.

Comment: This paper reports extended follow up of CheckMate 067 at 6.5 years. The headline feature of this report is the mature survival data which has not been previously reported which indicates clear superiority of combination ipilimumab and nivolumab over single agent therapy. The survival curves have plateaued and there has been no change in survival between the 5 and 6.5 year analyses. The response is durable and the majority of patients at this stage are off treatment. The study confirms the long-term benefit of single agent nivolumab although it was not powered to compare ipilimumab and nivolumab with nivolumab alone (although the survival curves demonstrate a small but persistent advantage for combination therapy over single agent nivolumab). For nivolumab containing regimes BRAF status had no effect on outcomes. Finally, there have been no changes in safety profiles since the initial reports.

Reference: J Clin Oncol 2022 Jan 10;40(2):127-137
Abstract

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