Melanoma Research Review™

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In this issue:

Abbreviations used in this issue:

BRAFi = BRAF-inhibitor; **CNS** = central nervous system; **DFS** = disease free survival; **ICI** = immune checkpoint inhibitor; **iNOS** = inducible nitric oxide synthase; **IT** = in-transit; **LN** = lymph node; **LR** = local recurrences; **MEKi** = MEK-inhibitor; **ORR** = overall response rate; **OS** = overall survival; **PFS** = progression-free survival; **SLNB** = sentinel lymph node biopsies; **SRT** = stereotactic radiotherapy; **TMB** = tumour mutational burden.

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Welcome to the 37th issue of Melanoma Research Review.

Dear readers of the Melanoma Research Review, the articles in this issue cover a wide range of topics including uveal and nonuveal melanoma, whether subungual melanoma differ from acral melanoma and the role of SLNB in local and in-transit recurrences. There are two community based studies, one of which studies cost effectiveness of the new systemic treatments. The retrospective study from France on prevention of brain metastases by anti-PD1 treatments is difficult to read but helps focus on this question and whether we already have enough information to select patients for prophylactic anti-PD1 to prevent brain metastases.

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 Peter Hersey

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Toxicity of combined targeted therapy and concurrent radiotherapy in metastatic melanoma patients: A single-center retrospective analysis

Authors: Ziegler JS, et al

Summary: The investigators assessed the safety of concurrent radiotherapy and combination targeted therapy with BRAF inhibitors (BRAFi) and MEK inhibitors (MEKi). The study cohort included 32 patients with 51 sessions of radiotherapy. Radiotherapy-associated toxicities were retrospectively collected and compared between targeted therapy during radiotherapy with and without interruption, and radiotherapy before the start of targeted therapy. Targeted therapy was interrupted during radiotherapy in 16, not interrupted in 14, and only started after radiotherapy in 21 sessions. Stereotactic radiotherapy (SRT) was applied in 28 sessions, conventionally fractionated radiotherapy in 23. The brain was the most common site of irradiation (n = 36). The investigators reported radiotherapy-associated toxicities occurred in 41.2% (n = 21) of sessions and did not differ significantly among the groups. Overall survival (OS) was 11.7 months and progression-free survival (PFS) was 8.4 months.

Comment: In the context of improving OS and overall responses, the combination of systemic therapies and localised therapeutic measures such as radiotherapy comes into focus for the management of mono- and oligometastatic disease. However, there are several reports that BRAFi may enhance radiotherapy-associated toxicity - mostly concerning skin reactions. Dermatitis has also been observed as a recall phenomenon at the start of BRAFi treatment several weeks after the end of radiotherapy. Radiosensitising effects of BRAF inhibition with vemurafenib in BRAFV600E mutated melanoma cells have been shown in vitro. An increase of chromosomal aberrations in peripheral blood lymphocytes of patients treated with BRAFi monotherapy have also been reported for vemurafenib, but not for dabrafenib.

The aim of this study was to provide real-life safety and clinical outcome data on concurrent radiotherapy and combination treatment with BRAFi and MEKi. It was hypothesised that the addition of a MEKi 'neutralises' the skin toxicities and radiosensitivity characterising BRAFi monotherapy. Additionally it was considered that the use of conformal radiotherapy such as SRT and radiosurgery would reduce the risk of toxicity. Their results showed that irrespective of whether targeted therapy was interrupted or not, no significant difference in overall radiotherapy-toxicity was seen. This was observed for any grade of toxicity as well as severe toxicity (grades 2 and 3). They conclude that a controlled, blinded, prospective clinical trial is warranted to confirm their findings and to make definite recommendations.

Reference: Melanoma Res 2020 Dec;30(6):552-561

Abstract

An observational study of drug utilization and associated outcomes among adult patients diagnosed with BRAF-mutant advanced melanoma treated with first-line anti-PD-1 monotherapies or BRAF/MEK inhibitors in a community-based oncology setting

Authors: Cowey CL, et al

Summary: The retrospective study included 224 patients with BRAF-mutant advanced melanoma who initiated first line anti-PD1 (36.2%) or BRAF/MEKi (63.8%). The authors found median OS and physician-assessed PFS were longer among anti-PD1 versus BRAF/MEKi patients (OS: not reached vs 13.9 months, log-rank P = .0169; PFS: 7.6 vs 6.5 months, log-rank P = .0144). In addition, receipt of anti-PD1 was associated with improved OS (HR = 0.602 versus BRAF/MEKi; P = .0287). Among patients without an event within 6 months of first line initiation, receipt of anti-PD1 was associated with a decreased risk of progression or death from 6 months onwards (HR = 0.228; P = .0002). This association was not observed among patients within 6 months of first line initiation (HR = 1.146).

Comment: This is a community based study by a US oncology network which documents the first line and subsequent line treatments for metastatic melanoma and survivals in the community setting. The improved survival with anti-PD1 compared to targeted treatments was very evident and targeted treatments appear to be increasingly relegated to the second line setting. There was no discussion of 3rd line treatments in this community setting. Disease progression was the reason for treatment discontinuation in both targeted and immune checkpoint inhibitor (ICI) treatments. Discontinuation for treatment toxicity was similar for both anti-PD1 (11.3%) and targeted treatments (14.2%). They conclude by saying that research is needed to explore factors associated with disease progression in the first 6 months of treatment with either anti-PD1 or targeted treatments.

Reference: Cancer Med 2020 Nov;9(21):7863-7878
Abstract

Increased serum CCL26 level is a potential biomarker for the effectiveness of anti-PD1 antibodies in patients with advanced melanoma

Authors: Fujimura T, et al

Summary: The researchers analysed increased serum levels of CCL11, CCL24, and CCL26 in 46 cases of advanced cutaneous melanoma treated with anti-PD1 antibodies. Serum levels on day 42 were compared to baseline. They concluded increased serum levels of CCL26 correlated significantly with the efficacy of anti-PD1 antibodies. However, no significant correlations were seen between increased serum levels of CCL11 and CCL24 and efficacy of anti-PD1 antibodies.

Comment: Baseline or ''early on treatment" biomarkers of response to anti-PD1 remains a subject of some interest to avoid unnecessary treatments and to avoid exposure to possible toxicity of anti-PD1. Many potential biomarkers have been described such as gene expression signatures in the tumour, presence of particular T cells or B cells in the tumour, mutation rates in the tumour, as well as particular leukocytes in the circulation such as monocytes or neutrophil / lymphocyte ratios. The present study was on proteins called eotaxins in the circulation, which are chemokines for eosinophils and referred to as CCL11, CCL24 and CCL26. They are produced by dermal fibroblasts, blood endothelial cells, dendritic cells, keratinocytes and macrophages. Blood samples were collected from 46 patients before and 42 days after treatment with nivolumab or pembrolizumab. Compared to baseline, serum levels of CCL26 but not CCL11 or CCL24 were strongly correlated with responses to treatment with 94.3% specificity and 72.7% sensitivity. There was no correlation between responses and eosinophil levels in the circulation. They conclude that the tests are simple and that results warrant further investigation. As they stand the false negative rate of 27.3 would limit its application. A positive result would, however, herald a response to anti-PD1?

Reference: Melanoma Res 2020 Dec;30(6):613-618
Abstract

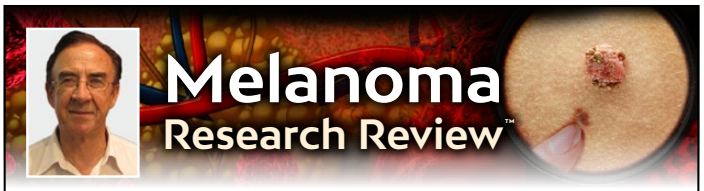
PD-1 inhibitors might limit the development of brain metastases in patients with advanced melanoma

Authors: Marcaillou M, et al

Summary: The retrospective study included a cohort of 293 patients with metastatic melanoma, without brain metastasis at diagnosis. Patients were separated into two groups according to the first line of treatment: ICI versus other and anti-PD1 versus other. At 12 months, the cumulative incidence of brain metastases was 13.78% in the ICI group and 27.26% in the other group (P = 0.004). The cumulative incidence was 9.49% in the anti-PD-1 group versus 30.11% in the other group (P < 0.0001). In multivariable analysis (n = 277), anti-PD1 reduced the risk of brain metastases by almost 70% (hazard ratio = 0.29, P < 0.0001).

Comment: Among common cancers, metastatic melanoma has the highest risk of spreading to the central nervous system (CNS) with CNS involvement being detected in up to 43% of metastatic melanoma patients in clinical studies, and in up to 75% of patients in autopsy series. Previous adjuvant studies including interferon and biochemotherapy reported a relapse rate of 15% in the brain (*Samlowski WE, et al Cancer Med. 2017 Nov; 6(11): 2576–2585*). Recent phase II clinical trials evaluated the combination of nivolumab and ipilimumab in treatment of brain metastases and found response rates of 45-57% and intracranial progression free survivals of more than 50% at 18 months. This has prompted a query as to whether treatment with anti-PD1 may prevent development of brain metastases. To obtain more evidence about this the authors have carried out retrospective analysis of patients with metastatic melanoma in 2 centres in France who were treated with ICIs (probably ipilimumab?) or with anti-PD1/PD-L1. The comparator was mostly targeted treatment with BRAFi and or MEKi and a small number of treatments with chemotherapy. Patients did not have brain metastases at the beginning of the study. After 1 year of follow up there appeared to be a much lower incidence of brain metastases in patients treated with anti-PD1. This adds some evidence towards the hypothesis but there were many variables that are difficult to control in such a study. Stronger evidence may result from relapse rates in the Merck Keynote-054 trial, which is comparing anti-PD1 with placebo in 1,019 patients. This study is now entering 4-5 years of follow up. Readers interested in prevention of brain metastases by anti-PD1 should read a recent paper by Haydu et al, in JCO 2020 which documents expected rates over time and which describes the importance of mitotic rate as a predictor of brain metastases

Reference: Melanoma Res 2020 Dec;30(6):580-589
Abstract



Independent commentary by Peter Hersey, FRACP, D Phil

Peter Hersey is an honorary Professor of Immuno Oncology in the University of Sydney and a faculty member of the Melanoma Institute Australia. He has conducted a number of phase I to III trials of immunotherapy in melanoma, including use of modified peptide antigens and dendritic cell vaccines. He has taken a leading role in studies investigating properties of melanoma cells that make them resistant to treatment and new treatment approaches to overcome these properties. He is generally recognized as a pioneer of immunotherapy for melanoma in Australia, and has participated in most of the key clinical trials on immunotherapy with immune checkpoint inhibitors. He continues translational research on melanoma in the Centenary Institute as joint holder of a NHMRC program grant on melanoma.

Frontline BRAF testing–guided treatment for advanced melanoma in the era of immunotherapies a cost-utility analysis based on long-term survival data

Authors: Wu B, et al

Summary: The authors compared cost-utility outcomes of 8 strategies containing different ICIs and BRAF and MEK inhibitors for newly diagnosed advanced melanoma with unknown BRAF pathogenic variant status. The key clinical data were derived from the CheckMate 067, KEYNOTE-006, COMBI-d, and COMBI-v trials, and the cost and health preference data were derived from the literature. The authors reported nivolumab plus ipilimumab without patient selection based on BRAF pathogenic variant testing yielded the most significant health outcome, and the nivolumab strategy was the cheapest option. The ordered incremental cost-utility ratios were $8593/QALY for pembrolizumab versus nivolumab and $125,593/QALY for nivolumab plus ipilimumab versus pembrolizumab.

Comment: Long-term survival of patients with metastatic melanoma is now relatively common after treatment with ICIs and BRAF and MEK inhibitors. In patients with previously untreated advanced melanoma, the CheckMate-067 trial showed the OS at 5 years was more than 50% in the nivolumab plus ipilimumab group and 44% in the nivolumab group, while the KEYNOTE-006 trial showed the median OS was 39% in the pembrolizumab group. In patients with previously untreated advanced melanoma with a BRAF V600E or V600K pathogenic variant, the COMBI-d and COMBI-v trials showed the OS rates of dabrafenib plus trametinib treatment were 34% at 5 years.

The question then is which of these treatments is most cost effective? The present analysis, from a US payer perspective, investigated the health and economic outcomes of 8 potential up-line novel treatment regimens for newly diagnosed advanced melanoma with unknown BRAF status by using the latest long-term survival data. Key findings were up-front use of nivolumab plus ipilimumab without BRAF pathogenic variant testing could maximise the health outcome, followed by BRAF-guided nivo/ipi-niv and pembrolizumab strategies. It was concluded that the up-front use of BRAF and MEK inhibitors for the subgroup with the BRAF pathogenic variant was not found to be cost-effective, which indicates that BRAF and MEK inhibitors are increasingly seen as playing an active role in the second-line setting.

Reference: JAMA Dermatol 2020 Jul 22;e202398
Abstract

Differential association of CD68+ and CD163+ macrophages with macrophage enzymes, whole tumour gene expression and overall survival in advanced melanoma

Authors: Tremble LF, et al

Summary: The investigators explored the association of macrophage infiltration with prognosis and functional changes in the tumour microenvironment in primary melanoma. Fifty-seven primary melanoma tumour blocks were analysed by immunohistochemical analysis of CD68, CD163, inducible nitric oxide synthase (iNOS) and arginase expression. RNA sequencing was performed on 20 of the tumours to determine the influence of macrophage infiltration on gene expression. They found CD68+ cells are a functionally active subset of macrophages that are associated with increased iNOS and arginase staining and altered gene expression. In contrast, while there is a greater accumulation of CD163+ macrophages in larger tumours, these cells are comparatively inactive, with no association with the level of iNOS or arginase staining, and no effect on gene expression within the tumour. They noted the infiltration of either subset of macrophages did not correlate to OS.

Comment: Macrophages are often a prominent component of the microenvironment of melanoma and have been implicated in progression of the tumour as well as resistance to treatment. Traditionally macrophages have been referred to as M1 expressing CD68+ macrophages that express iNOS and have interferon inducible cytotoxic roles. M2 macrophages express CD163 and CD214 and are suspected to have roles in melanoma progression. As discussed by the authors these markers may not be stable and possibly reflect different states of transition. They studied macrophages in 57 primary melanomas by immunohistochemistry and in 20 of the melanomas matched the marker studies with RNAseq expression data. They found that M1 and M2 macrophages were distinct subsets located at different sites in the melanoma. M2 but not M1 were related to Breslow thickness. There were more M1 in BRAF+ melanoma. iNOS expression was not confined to either M1 or M2 but was mostly in M1 cells. They were unable to correlate M2 macrophages with angiogenesis related genes like VEGF in the melanoma but CD68+ M1 macrophages appeared to be associated with more gene alterations than M2 macrophages. They conclude that treatments that focus on M1 macrophages may improve treatment outcomes.

Reference: Br J Cancer 2020 Nov;123(10):1553-1561
Abstract

Nivolumab and ipilimumab in metastatic uveal melanoma: Results from a single-arm phase II study

Authors: Pelster MS, et al

Summary: This phase II study treated patients with metastatic uveal melanoma (n = 35) with nivolumab and ipilimumab for four cycles, followed by nivolumab maintenance therapy for up to 2 years. Any number of prior treatments was permitted. The overall response rate (ORR) was 18%, including one confirmed complete response and five confirmed partial responses. The median PFS was 5.5 months, and the median OS was 19.1 months. Grade 3-4 treatment-related adverse event were observed in 40% of patients.

Comment: Uveal melanoma is the commonest primary intraocular tumour and is associated with mutations in GNAQ or GNA11 genes, which lead to activation of MAPK, PI3K and YAP pathways. Metastases occur in approximately 50% of patients and are usually associated with losses in chromosomes 1 and particularly 3 (which codes for BAP1) and gains in chromosomes 6 and 8. BRAF and NRAS mutations are uncommon so that treatments targeting these mutations are not available for patients with uveal melanoma. Various chemotherapy regimes have also been ineffective. There are no or few lymphatic vessels in the choroid and consequently spread is via the haematological route resulting frequently in liver metastases. Immunohistological studies have shown evidence of dendritic cells and T cells in metastases and hence are a target for immunotherapy. Previous trials have shown only minor responses to monotherapy with anti-PD1 or PD-L1 and the focus has been on combinations of anti-PD1 with ipilimumab. The study described here is consistent with or better than several other phase 2 studies of this combination. Although there was the usual toxicity associated with this treatment it is probably the treatment of choice until other treatment approaches are found to be more effective. Examples of other approaches are reviewed elsewhere (*Yang J, et al. Ther Adv Med Oncol, 2018*)

Reference: J Clin Oncol 2020 Oct 30;JCO2000605
Abstract

GNAQ and GNA11 mutant nonuveal melanoma: A subtype distinct from both cutaneous and uveal melanoma

Authors: Livingstone E, et al

Summary: The study objective was to characterise GNAQ and GNA11 mutant nonuveal melanoma in terms of genetics and clinical behaviour. Registry data was used to identify 18 patients with metastatic GNAQ/11 mutant nonuveal melanoma. The researchers found tumours had a lower tumour mutational burden and fewer ultraviolet signature mutations than cutaneous melanomas. In addition to GNAQ and GNA11 mutations (nine each), six splicing factor 3b subunit 1 (SF3B1), three eukaryotic translation initiation factor 1A X-linked (EIF1AX) and four BAP1 mutations were detected. In contrast to uveal melanoma, GNAQ/11 mutant nonuveal melanomas frequently metastasised lymphatically and concurrent EIF1AX, SF3B1 and BAP1 mutations showed no apparent association with patient prognosis. In addition they reported objective response to immunotherapy was poor with only one partial response observed in 10 treated patients (10%).

Comment: This article draws attention to the rarely occurring but prognostically relevant GNAQ/11 mutations in nonuveal melanoma. Ocular melanoma, which most commonly occurs as uveal melanoma, normally lacks BRAF, NRAS or c-KIT mutations, but frequently (80% of somatic mutations) presents with mutations in GNAQ or GNA11, which are involved in signalling via G-protein-coupled receptors. Additional mutations typically occur in SF3B1, EIF1AX or BAP1 and have been shown to be of prognostic. The Livingstone et al. study of tumour tissues from 18 patients with nonuveal melanoma included immunohistochemistry staining, targeted sequencing for known recurrent hotspot mutations and a 130-gene panel to determine tumour mutational burden (TMB). In addition to the GNAQ and GNA11 loci, six SF3B1, three EIF1AX and four BAP1 mutations were detected in this cohort. The data were correlated with the clinical outcome of these patients. The GNAQ/11 mutant nonuveal melanomas behaved in a clinically different manner regarding the site of first metastases and showed much more ultraviolet-derived mutations compared with uveal melanomas. The TMB was situated between uveal (low) and cutaneous melanoma (high). However, nonuveal melanomas had a poor response to immune checkpoint inhibitor treatments with anti-CTLA4 and anti-PD1, similar to that seen in uveal melanomas. It was concluded that the nonuveal melanoma were a distinct subtype of malignant melanoma that shares the clinical behaviour of cutaneous melanoma and the genetic alterations of uveal melanoma. The poor treatment responses render this subtype a candidate for further research on therapeutic targets.

Reference: Br J Dermatol 2020 Nov;183(5):928-939.
Abstract

The role of sentinel lymph node status performed in melanoma patients with local recurrence or in transit metastasis

Authors: Mattavelli I, et al

Summary: This study aimed to assess the role of sentinel lymph node biopsy (SLNB) in melanoma patients who developed first loco-regional recurrence. Melanoma patients (n = 72) who received SLNB for a first in-transit metastasis (IT) or local recurrence (LR) were identified from an Italian prospective database and clinicopathological characteristics analysed. Of the study cohort 43 patients (59.7%) received SLNB for LR and 29 (40.3%) for IT. The average interval between treatment of primitive melanoma and first recurrence diagnosis was 19 months. Sentinel node identification rate was 97.2%. Sentinel node positivity was detected in 37.1% of patients. It was noted the sentinel node positive rate in melanoma patients who had LR or IT was significantly higher than reported for primary tumours. Of patients with nodal involvement 17 had LR and 9 IT lesions. Disease free survival (DFS) was slightly higher in SN negative patients, however, the difference was not statistically significant. OS analysis showed similar values in the two groups.

Comment: The advent of effective adjuvant treatments for stage III melanoma have reinforced the need for SLNB for accurate staging of melanoma so that patients can be offered the best available adjuvant treatments. Such staging is usually carried out after removal of the primary melanoma but it is not uncommon for patients to present with or represent with IT metastases or with a local recurrence (<2 cm) at the site of the primary. The question then arises as to whether staging by SLNB still has value in identifying patients who will benefit from adjuvant treatments. This is particularly pertinent, as patients presenting in this way may have had thick primary melanoma or previous positive lymph nodes. The above study examined this question in 43 patients who had LR and 29 who had IT recurrences. The interval from treatment of the primary to the recurrence was 19 months. The SNLB rate was high at 37% and was followed by complete lymph node dissection in all cases. The rate in non-sentinel nodes was high at 16.2% in patients with LR and 13.7 % in IT. Importantly the DFS and OS were similar, irrespective of whether the SLNB was positive or not. Adjuvant treatments with ICI or targeted therapies were not available at the time of these studies and further study with new recent adjuvant treatments is needed.

Reference: Eur J Surg Oncol 2020 Nov 1;S0748-7983(20)30864-7
Abstract

Clinical and molecular features of subungual melanomas are site-specific and distinct from acral melanomas

Authors: Holman BN, et al

Summary: The authors compared the clinical and molecular features between 54 cases of subungual melanomas and 78 cases of nonsubungual acral melanoma. Compared to patients with acral melanoma, patients with subungual melanomas were younger at diagnosis, had a higher prevalence of primary melanomas on the hand, and had more frequent reports of previous trauma at the tumour site. Furthermore, subungual melanomas were deeper than acral melanomas at diagnosis, which correlated with an increased frequency of metastases. KIT and KRAS mutations were predominantly found in subungual melanomas, whereas BRAF and NRAS mutations occurred almost exclusively in acral melanoma. CDK4/CCND1 amplifications were more frequent in subungual melanomas and CDKN2A/B loss occurred mostly in acral melanoma, and in the PI3K/mTOR pathway, where RICTOR amplification and TSC1 K587R mutations were exclusively in subungual melanomas and PTEN loss and AKT1 mutations were exclusively in acral melanoma.

Comment: The authors state that 'The proximal nail fold is part of acral skin which eventually becomes the nail matrix. In the nail matrix, melanocytes are present but in fewer numbers than in normal skin, and in Caucasians, it is thought that these melanocytes do not produce melanin and are inactive'. Given this origin of the nail bed it is understandable why subungual melanoma have been grouped with acral melanoma. This article however, produces convincing evidence that subungual melanoma are a separate entity to acral melanoma. It occurred at an earlier age, predominantly on the hand, often with a history of trauma and had a high rate of metastases. Although there was a low frequency of BRAF and NRAS mutations in acral melanoma these mutations were uncommon in subungual melanoma, which instead had a much higher incidence of KIT mutations. Importantly they identified differences in cell cycle pathways between the 2 forms of melanoma with a higher incidence of CDK4/CCND1 (Cyclin D1) amplifications in subungual melanoma, which they reasoned may respond to targeted treatments against these pathways.

Reference: Melanoma Res 2020 Dec;30(6):562-573
Abstract

