Melanoma Research Review™

Making Education Easy

Issue 52 - 2022

In this issue:

Abbreviations used in this issue:

AR = adrenergic receptors; **AUC** = area under curve; **D** = dabrafenib; **FATE** = favourable antitumour effect; **HCQ** = hydroxychloroquine; **ICI** - immune checkpoint inhibitor; **ipi** = ipilimumab; **LN** = lymph node; **MM** = malignant melanoma; **nivo** = nivolumab; **NK** = natural killer; **ORR** = objective response rate; **OS** = overall survival; **pCR** = pathologic complete response; **PD** = progressive disease; **pembro** = pembrolizumab; **PFS** = progression-free survival; **RFS** = recurrence-free survival; **scRNAseq** = single-cell RNA sequencing; **SDDI** = sequential digital dermoscopy imaging; **TBP** = total body photography; **TLND** = therapeutic lymph node dissection; **T** = trametinib.

Welcome to the 52nd issue of Melanoma Research Review

Dear Readers,

The melanoma studies reviewed this month cover several that examine whether responses to immune checkpoint inhibitors can be detected at earlier times during treatment. There are also two studies examining whether inhibition of autophagy with hydroxychloroquine may have a role in treating heavily pretreated patients. Good trials keep on giving information such as the suggestion that beta blockers may have a role in immunotherapy. The study on small melanoma seems a must read for those diagnosing melanoma.

I trust you enjoy reading this month's selections

Kind Regards,

Professor Peter Hersey
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Adaptive dosing of nivolumab + ipilimumab immunotherapy based upon early, interim radiographic assessment in advanced melanoma (the ADAPT-IT study)

Authors: Postow MA, et al

Summary: In this multicentre, single-arm, phase II trial 60 patients with advanced melanoma received two doses of 1mg/kg nivolumab (nivo) + 3mg/kg ipilimumab (ipi) followed by a CT scan at week 6. Patients without new lesions or index lesion tumour growth of >4% had protocol-defined early favourable antitumour effect (FATE) and ceased nivo + ipi, transitioning to nivo monotherapy. Patients without FATE at week 6 received the standard third and fourth doses of nivo + ipi followed by nivo monotherapy. The authors reported 68% of patients had FATE at week 6 and met criteria for stopping nivo + ipi. Best overall response rates by RECIST at week 12 or any time afterward were 48% and 58%, respectively. With a median follow-up of 25 months, the estimated 18-month progression-free survival (PFS) and overall survival (OS) are 52% and 80%, respectively. They noted 57% of patients had grade 3-5 treatment-related toxicity.

Comment: Examining whether doses of combined ipi + nivo reduces toxicity. This study was prompted by the high toxicity of nivo plus ipi and the hypothesis that responses to the combination depended only on the first 2 doses. This was supported also by results from neoadjuvant studies where high response rates were seen after just 2 doses of ipi plus nivo. They comment in the discussion that no patients who developed multiple lesions in the first 6 weeks responded and that this information could be used in planning future trials. Unfortunately, the toxicity rate was not reduced in patients getting just 2 doses suggesting that toxicity was also driven by the first 2 doses. They conclude a CT scan after two doses of nivo + ipi may help guide future treatment plans, but the impact of treatment modification on response durability and longer-term OS requires additional follow-up. Larger, randomised studies are also needed to confirm these findings.

Reference: J Clin Oncol. 2022 Apr 1;40(10):1059-1067
Abstract

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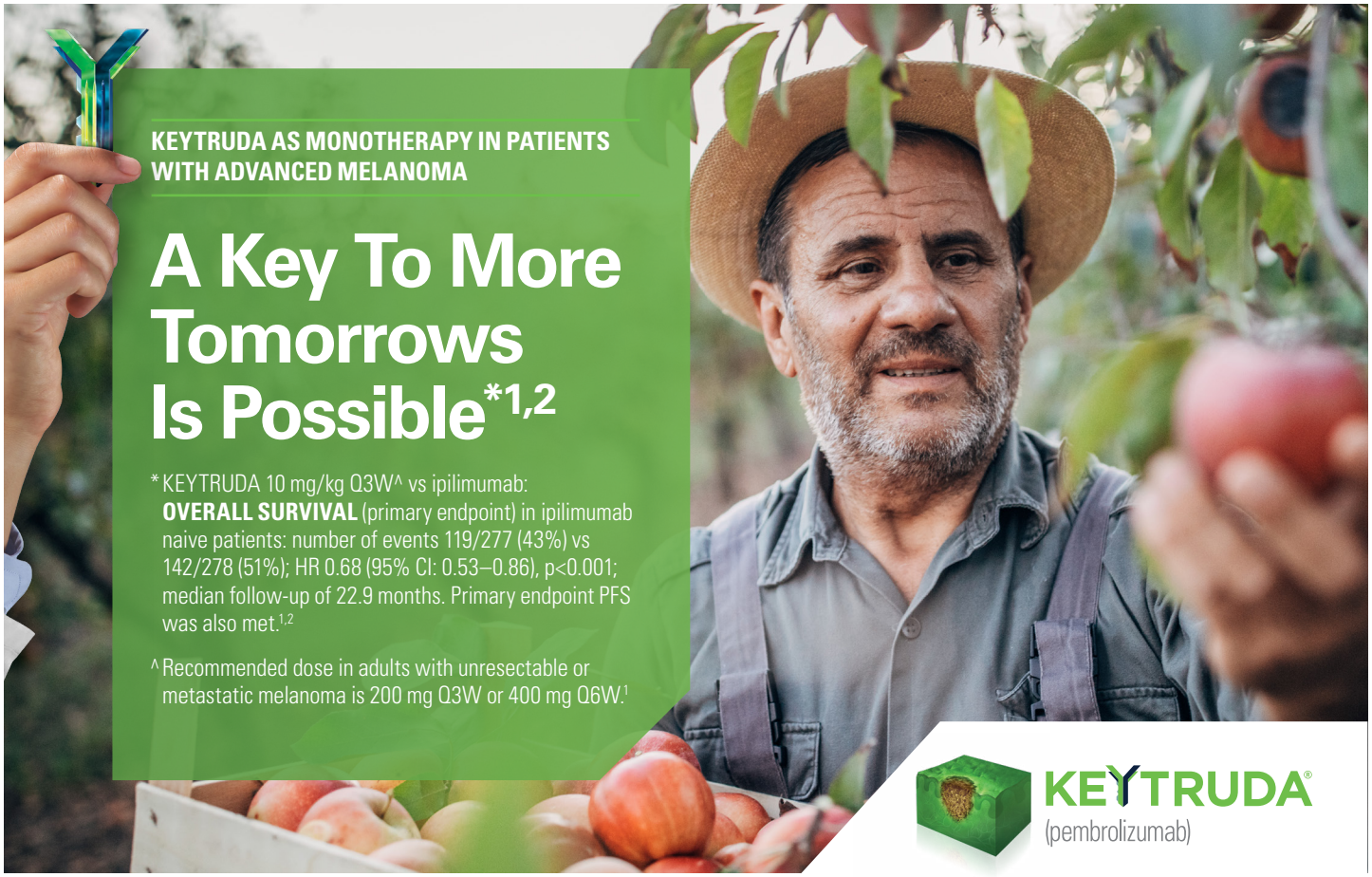

7-year follow-up data for the KEYNOTE-006 trial was presented at the 18th International Congress of the Society for Melanoma Research, 2021[3]

CLICK FOR STUDY DESIGN and 7-year follow-up data

PBS Information can be viewed at www.pbs.gov.au Please review the Product Information before prescribing, available HERE or by visiting www.msdinfo.com.au/keytrudapi.

KEYNOTE-006 ADVERSE EVENTS AT MEDIAN FOLLOW-UP OF 57.7 MONTHS:

- Treatment-related AEs (investigator assessed) that occurred in ≥10% of patients in the KEYTRUDA arm based on Grade 1–2 events included diarrhoea (17%), nausea (13%), asthenia (12%), fatigue (25%), arthralgia (13%), pruritus (20%), rash (17%), and vitiligo (13%).[4]
- Any-grade serious treatment-related AEs occurred in 14% of patients in the combined KEYTRUDA groups and in 18% of patients in the ipilimumab group. The most common were: colitis (2% vs 6%, respectively), diarrhoea (1% vs 4%), autoimmune hepatitis (1% vs <1%), and pneumonitis (1% vs <1%).[4]
- Treatment-related AEs led to the discontinuation of 10% of patients in the combined KEYTRUDA groups vs 9% for ipilimumab.[4]
- 13 (3%) patients in the combined KEYTRUDA groups and three (1%) in the ipilimumab group had died from AEs; one death (sepsis) in the KEYTRUDA group was treatment-related.[4]

SELECTED SAFETY INFORMATION:

Precautions:

- Immune-mediated adverse reactions, including severe and fatal cases, have occurred in patients receiving KEYTRUDA. These have included, but not limited to: pneumonitis, colitis, hepatitis, nephritis, endocrinopathies, uveitis, myositis, Guillain-Barre syndrome, myasthenic syndrome/myasthenia gravis (including exacerbation), myelitis, vasculitis, pancreatitis, sarcoidosis, encephalitis, myocarditis, pericarditis and pericardial effusion, peripheral neuropathy, sclerosing cholangitis, solid organ transplant rejection, severe skin reactions, and severe infusion reactions (hypersensitivity, anaphylaxis).[1]
- Immune-related adverse reactions have occurred after discontinuation of treatment with KEYTRUDA. Immune-mediated adverse reactions affecting more than one body system can occur simultaneously.[1]
- Monitor thyroid and liver function.[1]

Adverse events:

- The safety of KEYTRUDA was evaluated in 2799 patients with unresectable or metastatic melanoma or metastatic NSCLC in controlled and uncontrolled studies. The most common treatment-related serious adverse events were: pneumonitis, colitis, diarrhoea, and pyrexia. The most common treatment-related adverse reactions (reported in >10% of patients) were: fatigue, pruritus, rash, diarrhoea, and nausea.[1]

References: 1. KEYTRUDA Product Information, http://msdinfo.com.au/keytrudapi. **2.** Schachter J *et al.* Pembrolizumab versus ipilimumab for advanced melanoma: final overall survival results of a multicentre, randomised, open-label phase 3 study (KEYNOTE-006). *Lancet* 2017; 390(10105): 1853–62. **3.** Roberts C *et al.* 7-Year Follow-Up of KEYNOTE-006: Pembrolizumab Versus Ipilimumab in Advanced Melanoma. Poster presented at the 18th International Congress of the Society for Melanoma Research (SMR); 28–31 October 2021; Virtual. **4.** Robert C *et al.* Pembrolizumab versus ipilimumab in advanced melanoma (KEYNOTE-006): post-hoc 5-year results from an open-label, multicentre, randomised, controlled, phase 3 study. *Lancet Oncol* 2019; 20(9): 1239–51.

MSD

Circulating immune bioenergetic, metabolic, and genetic signatures predict melanoma patients' response to anti–PD-1 immune checkpoint blockade

Authors: Triozzi PL, et al

Summary: The investigators compared bioenergetics of circulating immune cells and metabolomic profiles of plasma obtained at baseline from patients with melanoma treated with anti-PD-1 therapy. In addition, single-cell RNA sequencing (scRNAseq) was performed to investigate transcriptional changes. They found pretreatment PBMC from responders had a higher reserve respiratory capacity and higher basal glycolytic activity compared with nonresponders. Differential levels of specific lipid, amino acid, and glycolytic pathway metabolites were observed by response. Moreover, scRNAseq analysis revealed upregulation of T-cell genes regulating glycolysis. The investigators noted that SLC2A14 (Glut-14; a glucose transporter) was the most significant gene upregulated in responder patients' T-cell population. Flow cytometry analysis confirmed significantly elevated cell surface expression of the Glut-14 in $CD3^+$, $CD8^+$ and $CD4^+$ circulating populations in responder patients, and LDHC was also upregulated in the responder population.

Comment: A focus on metabolic activity of T cells to predict responses to ICI in melanoma patients. This is one of many studies that are trying to identify predictors of response to treatment with immune checkpoint inhibitors (ICIs). It is novel in that it looks at changes in circulating lymphocytes rather than tumour infiltrating lymphocytes (TILs) and examines their metabolic activity as the readout. The study included 20 patients who responded to ICI and 20 who did not respond. Importantly, responders and nonresponders had similar frequencies of circulating immune cell populations on transcriptome and flow cytometric analyses but had higher levels of glycolytic activity and glucose transporters. They suggest that the metabolic differences observed are not due to changes in the proportion of circulating immune cell types but rather to changes in their metabolism. It is a high quality study including single-cell RNA sequencing and plasma biochemical analyses. It is not clear, however, how these studies could be included in routine treatment programs.

Reference: Clin Cancer Res 2022 Mar 15;28(6):1192-1202
Abstract

Early readout on overall survival of patients with melanoma treated with immunotherapy using a novel imaging analysis

Authors: Dercle L, et al

Summary: This prognostic study used radiomics and machine learning to retrospectively analyse CT images obtained at baseline and first follow-up and their associated clinical metadata. The researchers analysed data from the KEYNOTE-002 trial (testing pembrolizumab [pembro], 2 mg/kg or 10 mg/kg every 2 or every 3 weeks) and the KEYNOTE-006 trial (testing ipi 3 mg/kg every 3 weeks and pembro 10 mg/kg every 2 or 3 weeks). The study cohort included 575 patients with a diagnosis of advanced melanoma who were randomly assigned to training and validation sets. They assessed the performance of the signature CT imaging features for estimating OS at 6 months post pembro treatment using an area under the time-dependent receiver operating characteristics curve (AUC). A random forest model combined 25 imaging features extracted from tumours segmented on CT images to identify the combination (signature) that best estimated OS. The signature combined 4 imaging features, 2 related to tumour size and 2 reflecting changes in tumour imaging phenotype. In the validation set (287 patients), the signature reached an AUC for estimation of OS status of 0.92 (95% CI, 0.89-0.95). The standard method, Response Evaluation Criteria in Solid Tumors (RECIST) 1.1, achieved an AUC of 0.80 (95% CI, 0.75-0.84) and classified tumour outcomes as partial or complete response (93 of 287 [32.4%]), stable disease (90 of 287 [31.3%]), or progressive disease (104 of 287 [36.2%]).

Comment: Modifying CT scans to detect responders to ICI immunotherapy at an early stage. The ability to identify responders to ICI treatment at an early stage in treatment has been the subject of many studies. RECIST 1.1 is based on tumour size but the present study suggests that phenotypic changes also added to accuracy of survival estimates. The studies were on CT images collected from patients in the KEYNOTE 002 and 006 trials and were arranged in test and evaluation cohorts. The evaluation of results was highly technical, but the authors believed the 4 features could be automated and expressed as a standard CT assessment. The criteria were based on responses at 3 months, but they believe that the 4 criteria used for responses were evident at much earlier periods. Given that CT scans remain the main assessment of responses further evaluation of this modified version will be of interest.

Reference: JAMA Oncol 2022 Mar 1;8(3):385-392
Abstract

Representativeness of the index lymph node for total nodal basin in pathologic response assessment after neoadjuvant checkpoint inhibitor therapy in patients with stage III melanoma

Authors: Reijers ILM, et al

Summary: The researchers assessed the concordance of response between the index lymph node (LN) and the total LN bed. The retrospective multicentre trial Included 82 patients with stage III melanoma treated with 6 weeks neoadjuvant ipi plus nivo followed by therapeutic lymph node dissection (TLND). The researchers found the pathologic response in the index LN was concordant with the entire TLND specimen response in 81 of 82 patients (99%) and in 79 of 82 patients (96%) concordant when comparing the index LN response with the response in every individual lymph node. In the single patient with a discordant response, the index LN response (20% viable tumour, partial pathologic response) underestimated the entire TLND specimen response (5% viable, near-complete pathologic response). Two other patients each had 1 small nonindex node that contained 80% viable tumour (pathologic nonresponse) whereas all other lymph nodes (including the index LN) showed a partial pathologic response.

Comment: An innovative study with important implications for surgical management. As discussed in previous articles the introduction of neoadjuvant checkpoint inhibition in stage III melanoma promises to be a major change in surgical management of melanoma. The results from this retrospective pathologic analysis of LNs removed during complete LN dissection from 82 patients treated in an international consortium suggest that total LN dissection may not be needed if there is a pCR or near pCR in LNs identified as an index LN. The discussion points out some limitations such as use of the largest LN as the index LN in the pathologic specimens which may not be the same as the largest LN in patient pretreatment assessments. Because of this they consider that prospective assessment was needed. This was already in progress in a study referred to as the PRADO extension cohort of OpACIN-neo. They also pointed to 2 patients with limited regression in a single nonindex LN despite partial responses in index and other LNs. This they considered may indicate a non-responsive clone of melanoma and such patients may undergo relapse if total LN dissections were omitted. Watch this space for follow up studies!

Reference: JAMA Surg 2022 Apr 1;157(4):335-342
Abstract

Characterization of the treatment-naive immune microenvironment in melanoma with BRAF mutations

Authors: Wang M, et al

Summary: The researchers explored the immune microenvironment in patients with BRAF-mutant and BRAF wild-type melanoma using single-cell RNA sequencing, bulk RNA sequencing, flow cytometry and immunohistochemistry. In single-cell data, BRAF-mutant melanoma displayed a significantly reduced infiltration of $CD8^+$ T cells and macrophages but also increased B cells, natural killer (NK) cells and NKT cells. They noted, BRAF-mutant tumours had more $CD4^+$ T cells than BRAF wild-type samples in both primary and metastatic cohorts. In the metastatic cohort, BRAF-mutant melanoma demonstrated more B cells but less $CD8^+$ T cell infiltration when compared with BRAF wild-type samples. They confirmed that BRAF-mutant melanoma metastases were enriched for $CD4^+$ T cells and B cells and had a co-existing decrease in $CD8^+$ T cells. In addition, they found B cells were associated with a trend for improved survival (p=0.078) in the BRAF-mutant samples and Th2 cells were associated with prolonged survival in the BRAF wild-type samples.

Comment: BRAFV600 mutated melanoma have different T cell populations in their microenvironment. This is a well conducted study on data from a range of melanoma cohorts that identifies differences in the immune cells associated with BRAFV600 mutated melanoma versus BRAF wildtype melanoma. Although a largely descriptive study it includes a thorough review of previous studies and raises questions of interest for future studies. These include why $CD8^+$ T cells are less around BRAFV600 melanoma and what is the role of $CD4^+$ and particularly B cells in the improved responses of BRAFV600 melanoma to treatment with anti-PD-1 and CTLA4 combinations.

Reference: J Immunother Cancer 2022 Apr;10(4):e004095
Abstract

BAMM (BRAF Autophagy and MEK inhibition in Melanoma): A phase I/II trial of dabrafenib, trametinib, and hydroxychloroquine in advanced BRAFV600-mutant melanoma

Authors: Mehnert JM, et al

Summary: The trial, conducted in four centres, used hydroxychloroquine (HCQ) to inhibit autophagy in combination with dabrafenib (D) 150mg twice daily and trametinib (T) 2mg every day in 34 patients with advanced BRAFV600-mutant melanoma. Patient demographics were: elevated LDH: 47%; stage IV M1c/M1d: 52%; prior immunotherapy: 50%. The primary objectives were the recommended phase II dose (RP2D) and the one-year PFS rate of >53%. In phase I, there was no dose-limiting toxicity. The authors reported HCQ 600mg orally twice daily with D+T was the recommended phase II dose. The one-year PFS rate was 48.2%, median PFS was 11.2 months, and response rate (RR) was 85%. The complete RR was 41% and median OS was 26.5 months. In a patient with elevated LDH (n=16), the RR was 88% and median PFS and OS were 7.3 and 22 months, respectively.

Comment: Testing whether inhibition of autophagy increases response to BRAF/MEK inhibitors in heavily pretreated melanoma patients. This is a report on a phase 1 study by an experienced group of oncologists and includes RNAseq analysis of pretreatment biopsies. Autophagy is considered a pro-tumorigenic process by providing nutrients for cell survival. It also reduces inflammasome mediated cell death. BRAF/MEK inhibition can activate autophagy by activating ER stress. Given this background it was logical to examine whether an inhibitor of autophagy may help overcome resistance to treatment with BRAF/MEK inhibitors. Patients entered into the study were generally second line with adverse features such as high LDH and large tumour size. Nevertheless, when compared to other studies in this adverse prognostic group there were enough findings to suggest that a larger randomised trial in patients with high LDH was justified comparing D+T alone to D+T with HCQ.

Reference: Clin Cancer Res 2022 Mar 15;28(6):1098-1106
Abstract

A lead-in safety study followed by a phase 2 clinical trial of dabrafenib, trametinib and hydroxychloroquine in advanced BRAFV600 mutant melanoma patients previously treated with BRAF-/MEK-inhibitors and immune checkpoint inhibitors

Authors: Awada G, et al

Summary: The researchers investigated combination BRAF-/MEK-inhibition with D and T plus HCQ in patients with advanced BRAFV600 mutant melanoma who previously progressed on prior treatment with BRAF-/MEK-inhibitors and ICIs. Following a safety lead-in phase, patients were randomised to upfront treatment with D, T plus HCQ (experimental arm, n=10), or D + T, with the possibility to add-on HCQ at the time of PD (control arm, n=4). The researchers reported objective response rate (ORR) was 20.0% and the disease control rate was 50.0% in the experimental arm, whereas no responses were observed before or after adding HCQ in the control arm. Based on an early negative evaluation of the risk/benefit ratio for adding HCQ to D and T when 'rechallenging' BRAFV600 mutant melanoma patients, recruitment to the trial was closed prematurely. They noted there were no new safety signals observed for dabrafenib and trametinib, while HCQ was suspected of causing an anxiety/psychotic disorder in one patient.

Comment: Further attempts to treat heavily pretreated patients by inhibition of autophagy. The objective of this randomised phase 2 trial (COMBI-R 2) was to explore the efficacy and safety of the combination of D, T and the autophagy inhibitor HCQ in patients with advanced BRAFV600 mutant melanoma who had been previously treated with BRAF-/MEK-inhibitors and ICIs and who developed PD on these treatments. In discussion they explain that the study was aborted as the ORR in 10 patients was 20.0% (90% CI, 3–50%, per intention-to-treat analysis) which was lower than that reported in a similar population of patients where rechallenge with D and T alone had an ORR of 32%. They concluded the addition of HCQ did not seem to efficiently reverse resistance to BRAF-/MEK-inhibitors. Nevertheless, they are investigating this drug combination in a less heavily pretreated population and are considering selection of patients on the basis of expression of autophagy markers (e.g., microtubule associated protein 1 light chain 3 beta) on baseline or on-treatment tumour samples. Patients without this characteristic could be offered other treatments.

Reference: Melanoma Res 2022 Jun 1;32(3):183-191
Abstract

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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.

Efficacy and safety of angiogenesis inhibitors in melanoma: A meta-analysis of seven randomized controlled trials

Authors: Fu XL, et al

Summary: The meta-analysis included randomised controlled trials that investigated the efficacy and safety of angiogenesis inhibitor therapy in patients with melanoma (n=3,185). The authors conclude there was no significant difference in OS (HR, 0.99; 95% CI, 0.90-1.09) or PFS (HR, 0.91; 95% CI, 0.83-1.00) between the treatment groups. In addition, no significant effect of angiogenesis inhibitor therapy was identified on disease control (OR, 1.23; 95% CI, 0.97-1.55) or objective response (OR, 1.27; 95% CI, 0.99-1.62). The authors noted angiogenesis inhibitor therapy increased risks of hypertension, neurological symptoms, and diarrhoea.

Comment: Limited role of angiogenesis inhibitors in treatment of melanoma. This meta-analysis of 7 randomised trials conducted in the USA and Europe involving 3,185 patients came to several definite conclusions. First, there was no significant difference in OS or PFS between treatment groups. Second, from a safety perspective, angiogenesis inhibitors led to more hypertension, neurological symptoms, and diarrhoea. They discuss possible reasons for treatment failure such as induction of hypoxia which triggers HIF-1a pathway activation and vascular regeneration as well as cancer stem cell proliferation. A possible limitation of the review was the absence of trials including immunotherapy with ICIs but presumably those available did not meet the rigid selection criteria for the meta-analysis.

Reference: Melanoma Res 2022 Jun 1;32(3):159-165
Abstract

Prognostic and predictive value of β-blockers in the EORTC 1325/ KEYNOTE-054 phase III trial of pembrolizumab versus placebo in resected high-risk stage III melanoma

Authors: Kennedy OJ, et al

Summary: The KEYNOTE-054 trial randomised patients with resected stage IIIA, IIIB or IIIC melanoma and regional lymphadenectomy to receive 200mg of adjuvant pembro (n=514) or placebo (n=505) every three weeks for one year or until recurrence or unacceptable toxicity. At a median follow-up of 3 years, pembro prolonged recurrence-free survival (RFS) compared to placebo (HR 0.56). Ninety-nine (10%) of 1,019 patients used β-blockers at baseline. The authors found β-blockers had no independent prognostic effect on RFS (HR 0.96). The HRs of RFS associated with β-blocker use were 0.67 in the pembro arm and 1.15 in the placebo arm. The HR of RFS associated with pembro compared to placebo was 0.34 among β-blocker users and 0.59 among those not using β-blockers.

Comment: Do beta blockers have a role in immunotherapy of melanoma? One of the ways that the nervous system regulates immune responses is via β-adrenergic receptors (AR) on immune cells. As reviewed their activation on lymphocytes leads to immune suppression. AR are also expressed on melanoma cells particularly in metastatic melanoma and previous studies showed that their activation resulted in release of VEGF, IL-6 and IL-8. Given this background the authors examined whether β-blockers influenced survival in the randomised clinical trial (KEYNOTE-054) testing whether adjuvant pembro improved survival in patients with resected stage III melanoma. There were 1,019 patients in the study; 10% who were on beta blockers. The results showed that the β-blockers had no effects on OS but strong trends were shown for increased survival benefit in patients also getting anti-PD-1. In discussion, distinctions were also made between β-blockers versus selective blockers with better results associated with pan blockers. Their discussion provides references to a number of other studies that support the case for further investigation of β-blockers in immunotherapy studies.

Reference: Eur J Cancer 2022 Apr;165:97-112
Abstract

Dermoscopic features and screening strategies for the detection of small-diameter melanomas

Authors: Regio Pereira A, et al

Summary: The retrospective study explored the clinical, histopathological and dermoscopic features of tiny malignant melanomas (MMs), and the impact of imaging tools, including total body photography (TBP) and sequential digital dermoscopy imaging (SDDI) in their detection. Of the 312 MMs included, 86 (27.6%) were classified as tiny MMs (diameter of ≤ 5 mm on dermoscopy), and 44.2% of these were invasive. Tiny MMs were more frequently excised for being new and/or changing compared with nontiny MMs (77.9% vs. 50.9%; P < 0.001). The investigators found half of the tiny MMs would have been missed by the dermoscopic seven-point checklist (48.2%) or the three-point checklist (49.4%), while Menzies' method and the revised pattern analysis correctly identified respectively 65.9% and 63.5% of the tiny MMs. They noted the most frequent positive features for tiny MMs were asymmetry in structure or colour (77.6%), brown dots (65.9%), irregular dots and globules (76.5%) and atypical pigment network (44.7%). Dermoscopic features predictive of invasion in tiny MMs were atypical vascular pattern (OR=26.5, P< 0.01), shiny white lines (OR=12.4, P=0.04) and grey/blue structures (OR=3.7, P=0.01).

Comment: Small melanoma can be difficult to diagnose. This study reports that diagnosis of small diameter melanoma is relatively common (27.6%) and apparently presents some difficulties in histopathological diagnosis as referred to in discussion particularly in borderline lesions. They emphasise that small diameter did not mean in situ as 44.2% were already invasive upon diagnosis and frequently showed a vertical growth phase. The take home message appears to be that dermoscopy alone is likely to only detect about 20% of small melanoma and TBP and SDDI and careful history taking is needed for diagnosis. The article seems to be a must read for those involved in diagnosis of skin lesions.

Reference: Clin Exp Dermatol. 2022 May;47(5):932-941
Abstract