Melanoma Research Review™

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In this issue:

Abbreviations used in this issue:

AJCC = American Joint Committee on Cancer;
ctDNA = circulating tumour DNA; **ICI** = immune checkpoint inhibitor;
irAE = immune-related adverse event; **LDH** = lactate dehydrogenase;
M = metastatic; **MM** = mucosal melanoma; **NM** = nodular melanomas;
OS = overall survival; **PFS** = progression-free survival;
PREM = patient-reported experience measure;
PROM= patient-reported outcome measure;
SDDI = sequential digital dermoscopy imaging;
SEER = Surveillance, Epidemiology, and End Results;
SSM = superficial spreading melanomas; **TBP** = total-body photography.

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Welcome to the 40th issue of Melanoma Research Review.

This month's scan of the literature has provided some interesting thoughts. One is whether the much touted AJCC 8th classification is of any use in treatment of metastatic disease with ICIs. There is also a question as to whether it should include histologic subtypes. In particular whether nodular melanoma should be used in staging. There is also an important follow up on diagnosis of melanoma particularly in patients who have already had one melanoma. Some critics might advocate reading this study together with recent articles in the NEJM questioning whether the increase is real or just better diagnosis. This is an old debate in Australia that was initiated following Professor Bill McCarthy's media campaigns in the 1980s. There is also another study alerting clinicians to a higher incidence of irAEs than appreciated in ICI treated patients that is relevant to their use as adjuvants in low-risk disease.

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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Validation of the American Joint Committee on Cancer Eighth Edition Staging of Patients With Metastatic Cutaneous Melanoma Treated With Immune Checkpoint Inhibitors

Authors: Waninger JJ, et al

Summary: The investigators evaluated the outcomes of patients with metastatic cutaneous melanoma receiving immune checkpoint inhibitors (ICIs) based on the metastatic (M) stage category from the American Joint Committee on Cancer (AJCC) eighth edition. Patient data were collected using electronic medical records with median follow-up time of 35.5 months. The discovery cohort included 357 patients and findings were externally validated in a multicentre nationwide cohort. All patients were treated with dual-agent concurrent ipilimumab and nivolumab followed by maintenance nivolumab or single-agent ipilimumab, nivolumab, or pembrolizumab therapy. The investigators reported in the discovery cohort the M category in the AJCC eighth edition showed limited prognostic stratification. It was noted the presence of liver metastases and elevated levels of serum lactate dehydrogenase (LDH) offered superior prognostic separation compared with the M category (liver metastases: HR 2.22; P < .001; elevated serum LDH: HR 1.73; P = .007). They externally validated an updated staging system based on these factors in a cohort of 652 patients with patients without liver metastases or elevated LDH levels having the longest survival (median overall survival (OS), 30.7 months).

Comment: The AJCC revised the AJCC melanoma staging manual in 2017, releasing an eighth edition. Prior to the eighth edition, the M stage included three categories based on the anatomic site of disease involvement, as follows: M1a (nonregional lymph nodes and/or skin or soft tissue lesions), M1b (lung involvement), and M1c (other visceral sites of disease). In the eighth edition, the M staging system was updated to include the addition of LDH subcategories for each stratum and the addition of a new M1d designation for patients with central nervous system metastases. Given that LDH may modify immune responses and that liver metastases may respond poorly to ICIs the authors examined whether the AJCC staging was still relevant in treatment of metastatic melanoma. To do this patient OS and progression-free survival (PFS) was stratified by M category at the time of ICI initiation. The model showed poor prognostic separation in that only patients designated as having stage M1a disease at the start of ICI had superior outcomes compared with patients with M1c or M1d disease but not those designated as having M1b disease. Both liver metastases and elevated LDH levels were independent predictors of a bad prognosis. They conclude that their findings suggest that the AJCC eighth edition staging of metastatic cutaneous melanoma (M1a-d) requires revisions in the era of ICI therapy and future updates to staging systems are needed for the optimal stratification of patients into clinically relevant prognostic groups.

Reference: JAMA Netw Open. 2021 Mar 1;4(3):e210980
Abstract

Combining BRAF/MEK inhibitors with immunotherapy in the treatment of metastatic melanoma

Authors: Ziogas DC, et al

Summary: The review outlines retrospective information up to the late-stage randomised evidence on combination ICIs and molecularly targeted agents for the treatment of metastatic melanoma. The authors note many clinical trials are currently underway exploring optimal timing, new immune biomarkers, and eligible patient subsets for these regimens. Currently treatment in the first-line setting for *BRAF*-mutant melanoma is still guided by the patients' characteristics and the biological aspects of melanoma.

Comment: This is a rather rambling review of many trials that are underway to assess whether combinations of targeted treatments with ICIs will improve outcomes for patients with *BRAF*-mutated melanoma. The rationale being that combining the two approaches will achieve the high response rates of targeted treatment with the longer survivals seen with ICIs. Several trials examined whether combined or sequential approaches would be best. Relevant combination trials were the Keynote -022 trial (reviewed in Melanoma Research Review issue 38), Triology IMspire150 and COMBI-1 and DREAMseq. These were the large phase III trials but many phase I and phase II trials are also mentioned.

They conclude by saying that the decision for first-line treatment of *BRAF*-mutant metastatic melanoma is still guided by clinical parameters such as increased LDH, high tumour load, brain involvement, and rapidly progressing disease. For patients with less extensive *BRAF*-mutant melanoma and more favourable characteristics, double checkpoint inhibition should be considered as the leading option, particularly if the patient's performance status and melanoma progression permit. According to the SECOMBIT trial, targeted therapy seems to be a mandatory component of the first-line approach or as an induction regimen that may give a PFS advantage in *BRAF*-mutated patients compared to immunotherapy. The review is a good summary of this very active research area that will continue for some time.

Reference: Am J Clin Dermatol. 2021 Mar 25. Online ahead of print.
Abstract

Randomized phase II study of bevacizumab in combination with carboplatin plus paclitaxel in patients with previously untreated advanced mucosal melanoma

Authors: Yan X, et al

Summary: This open-label, phase II study assessed the efficacy and safety of bevacizumab in combination with carboplatin plus paclitaxel in patients with previously untreated advanced mucosal melanoma (MM). The study cohort of 114 patients were randomised 2:1 to receive carboplatin plus paclitaxel once every 4 weeks in combination with or without bevacizumab once every 2 weeks. The median PFS was significantly longer in the bevacizumab arm (4.8 months) than in the carboplatin plus paclitaxel alone arm (3.0 months; HR 0.461; P < .001). Objective response rates were 19.7% and 13.2%, respectively (P = .384). The median OS was also significantly longer in the bevacizumab arm than in the carboplatin plus paclitaxel alone arm (13.6 vs 9.0 months; HR 0.611; P = .017). There were no new safety signals.

Comment: The treatment landscape for metastatic cutaneous melanoma has rapidly evolved in the past 10 years mainly because of targeted therapies and immunotherapies. However, the development of systemic therapies for MM has been much slower due in part to small numbers of patients. This is not the case in China where 20-25% of melanoma are of mucosal origin. The present randomised study on 114 patients predated the studies on checkpoint inhibitors and was based on favourable results in the so called BEAM trial in cutaneous melanoma comparing carboplatin and paclitaxel with the same combination with bevacizumab. In the current study there was an increase in response rates from 13.2% to 19.7% and of PFS from 3.0 to 4.3 months and extension of OS from 9 to 13.6 months. Large studies with ICI are not common but PFS was 3.9 months and response rates of 23% were reported in Shoushtari et al (*Cancer 2016;122:3354–3362*). Several studies have found higher response rates with anti-PD-1 alone compared to ipilimumab; 35% vs 8.2% (*Cancer Immunol Immunother 2019 Jul;68(7):1171-1178).* The present study provides evidence that combinations with bevacizumab may be of benefit in MM with ICI.

Reference: J Clin Oncol. 2021 Mar 10;39(8):881-889
Abstract

Chronic immune-related adverse events following adjuvant anti–PD-1 therapy for high-risk resected melanoma

Authors: Patrinely Jr JR, et al

Summary: This retrospective study was conducted across 8 centres in the United States and Australia. The study cohort comprised of 387 patients with stage III to IV melanomas treated with anti-PD-1 in the adjuvant setting. The authors reported 69.0% of patients had any acute immune-related adverse event (irAE), defined as those arising during treatment with anti-PD-1, including 19.5% with grades 3 through 5 events. Chronic irAEs, defined as those that persisted beyond 12 weeks of anti-PD-1 discontinuation, developed in 43.2% patients, of which most (96.4%) were mild (grade 1 or 2) and most persisted until last available follow-up (85.6%). They also noted endocrinopathies (83.0%), arthritis (48.9%), xerostomia (52.9%), neurotoxicities (73.3%), and ocular events (62.5%) were particularly likely to become chronic. In contrast, irAEs affecting visceral organs had much lower rates of becoming chronic.

Comment: Anti–PD-1 agents cause acute and chronic irAEs. Most present within the first 12 weeks of therapy and resolve with use of glucocorticoids. However, delayed, chronic, or even fatal events may also occur with long-term or permanent ramifications. The authors have studied patients treated with adjuvant anti–PD-1 for melanoma to obtain more accurate characterisation of persistent irAEs. The results are somewhat surprising in that 44.2% had grade 2 or higher acute toxicities - 1 with myocarditis and 1 with Guillain-Barré–like syndrome. A relatively high proportion of acute irAEs developed into chronic events defined as lasting longer than 3 months. Most were only grade 1 or 2.

After a median follow up of 287 days most of the chronic side effects persisted except for colitis, neurotoxicities and nephritis. They conclude that chronic irAEs, while usually low grade, occur more frequently than previously reported and particularly affect nonvisceral organs. They note that the adjuvant patient population may have been cured by surgery alone and have longer or normal life expectancies than patients with metastatic disease. Hence persistent, life-altering, or life-threatening irAEs should be integrated into patient counselling and treatment decision-making.

Reference: JAMA Oncol. 2021 Mar 25. Online ahead of print
Abstract

Efficiency of detecting new primary melanoma among individuals treated in a high-risk clinic for skin surveillance

Authors: Guitera P, et al

Summary: The researchers examined a structured surveillance program in patients (n=593) with very high risk of melanoma from 3 dermatology clinics and 1 primary care skin cancer clinic in New South Wales, Australia. The surveillance program involved full-body examinations every 6 months aided by total-body photography (TBP) and sequential digital dermoscopy imaging (SDDI). For equivocal lesions, the clinician performed SDDI at 3 or 6 months. Median follow-up was 2.9 years. There were 1,513 lesions excised during follow-up, including 171 primary melanomas. They observed the overall benign to malignant excision ratio, including keratinocyte carcinomas, was 0.8:1.0; the benign melanocytic to melanoma excision ratio was 2.4:1.0; and the melanoma in situ to invasive melanoma ratio was 2.2:1.0. The risk of developing a new melanoma was 9.0% annually in the first 2 years and increased with time, particularly for those with multiple primary melanomas. The thicker melanomas were mostly desmoplastic or nodular, self-detected, or clinician detected without the aid of TBP. They concluded new melanomas were most likely to be detected by a clinician with the aid of TBP (31.6%) followed by digital dermoscopy monitoring (29.2%).

Comment: The authors refer to previous studies showing that people who develop an in situ or invasive primary melanoma are at much greater risk of developing subsequent melanoma compared with the general population especially for those with additional risk factors, such as multiple primary melanomas, dysplastic nevi, family history, or a melanoma-predisposing gene variant. Australian clinical practice guidelines recommend that individuals at very high risk of melanoma be checked regularly by a clinician, with full skin examinations every 6 months supported by dermoscopy and using the aids of SDDI and TBP. In practice however, several factors may limit the application of the guidelines. To further evaluate the guidelines a cohort study was conducted in different settings including primary care. It was found that favourable long term early detection and excision results were sustained over a 10 year period by a range of clinicians such as dermatologists, dedicated residents and primary skin care doctors. In this expanded cohort, the mean excision rate was 0.9 per person-year of follow-up in the first 2 years and 1.2 per person-year in years 2 to 4. However, this rate also corresponded with an overall 1.6 times as high melanoma incidence rate in years 2 to 4 vs the first 2 years. They conclude "The structured surveillance program for individuals at high risk of new primary melanoma may be implemented on a larger scale, including primary care skin cancer clinics, given the study findings suggesting consistent and sustainable benefits." Given recent articles in the NEJM that the increased incidence of melanoma was largely due to increased diagnosis this aspect was dealt with very briefly. Reference to these discussions is in *N Engl J Med. 2021 Apr 8;384(14).*

Reference: JAMA Dermatol. 2021 Mar 17. Online ahead of print
Abstract

Multiple primary melanoma incidence trends over five decades: A nationwide population-based study

Authors: Helgadottir H, et al

Summary: This Swedish nationwide population-based study included patients diagnosed with a first primary cutaneous melanoma followed for up to 10 years for a diagnosis of subsequent primary melanoma. Of the study cohort of 54,884 patients 2,469 were diagnosed, within 10 years, with subsequent melanomas. The authors concluded, over the 5 decades, there was a statistically significant steady increase in the frequency, incidence rates and standardised incidence ratios for second primary melanoma. They noted in the 1960s cohort less than 1% had second primary melanoma and this rose to 6.4% in the women and 7.9% in the men in the 2000s cohort. The rise was independent of age, sex, invasiveness, or site of the melanoma. In patients diagnosed with a second melanoma, the frequency of those having more than 2 melanomas increased statistically significantly and was 0.0% in the 1960s and rose to 18.0% in the 2000s ($P < .001$).

Comment: Patients with melanoma are at increased risk of additional primaries; however, there have been large variations in the reported incidence with frequencies ranging from 1% to 13%. In this study the authors used a comprehensive Swedish Cancer Registry to address the question of how the incidence of second primaries has evolved in the decades since 1960. This included an analysis of whether primaries occurred at similar or distant sites. In women, the head and neck area was the only site with a statistically significantly higher rate of second melanomas occurring in the same site. In the men, the trunk was the only site that consistently had a statistically significantly higher rate of second melanomas occurring in the same site. As the standardised incidence ratio increased over time, the incidence of second primaries appeared to be even steeper than the melanoma incidence in the population. Hence, alongside the well-documented rise in the melanoma incidence, there has been a steeper increase in patients developing subsequent primaries. Further, the frequency, incidence, and standardised incidence ratio values for the second primary melanoma in the 2000s cohort is higher than what has been reported in previous studies involving patients diagnosed at earlier periods in, for example, Sweden, the Netherlands, Australia, or the United States. They conclude "Melanoma patients need to be informed about their risk of developing additional melanoma and thoroughly advised to avoid sunburns and tanning and, moreover, to seek medical help for suspicious lesions."

Reference: J Natl Cancer Inst. 2021 Mar 1;113(3):318-328
Abstract

Five-year survival in patients with nodular and superficial spreading melanomas in the US population

Authors: Allais BS, et al

Summary: The population-based cross-sectional analysis compared the 5-year relative survival of patients with nodular melanomas (NM) and superficial spreading melanomas (SSM) using data from the United Sates Surveillance, Epidemiology, and End Results (SEER) program. For patients diagnosed between 2004 and 2009, 5-year relative survival was lower in NM compared with SSM (53.7% vs 87.3%; Z score, -41.35; $P < .001$). Furthermore, for patients diagnosed between 2010 and 2015, 5-year relative survival was lower in NM compared with SSM (61.5% vs 89.7%; Z score, -2.7078; $P < .01$). Subgroup analyses showed inferior survival in NM in T1b, and survival differences remained significant after excluding patients with nodal or distant metastases.

Comment: This is an important paper which makes a strong case for inclusion of histologic subtypes in patient assessment. The impact of histologic subtype on melanoma prognosis and treatment has been relatively limited given that staging according to the AJCC does not incorporate histologic subtype. This finding is largely due to the assumption that increased risk with nodular histology is confounded by increases in thickness and ulceration. The present study has used data from the NCI population based SEER program to show that when known prognostic factors of the primary such as thickness, ulceration and mitotic rate are taken into account the NM subtype have a significantly worse 5 year survival in T1b, T2a and T2b melanoma. NM was also an independent predictor of positive SLNB. They further noted that the number of deaths in patients with thin melanoma exceeds numerically deaths in patients with thick melanoma. They also note "In SSM and NM, molecular studies have found differences in expression between these 2 subtypes. Jaeger et al identified 67 genes differentially expressed in SSM and NM. Increased expression of genes involved in tissue invasion, proliferation, and adhesion were more often found in nodular melanomas. Further research into the inherent biological differences between these two subtypes could assist in the development of novel approaches to therapy."

They conclude "Consideration should be given to incorporate these factors into the AJCC staging system, particularly so that patients diagnosed with thin NM can be more accurately staged. Research into the genomic differences in NM should also be sought to develop specific treatment regimens and improve survival. We believe the power in this analysis is that the nodular subtype was shown to have a statistically significant independent effect on overall survival across 2 independent data sets over a 10-year period."

Reference: Am Acad Dermatol. 2021 Apr;84(4):1015-1022
Abstract

Circulating tumour DNA in patients with advanced melanoma treated with dabrafenib or dabrafenib plus trametinib: A clinical validation study

Authors: Syeda MM, et al

Summary: The study objective was to evaluate whether cell-free circulating tumour DNA (ctDNA) baseline concentrations could predict survival outcomes in patients enrolled in the COMBI-d and COMBI-MB clinical trials. COMBI-d was a phase 3 study of dabrafenib plus trametinib versus dabrafenib plus placebo in previously untreated patients with BRAFV600 mutation-positive unresectable or metastatic melanoma. COMBI-MB was a phase 2 study evaluating dabrafenib plus trametinib in patients with BRAFV600 mutation-positive metastatic melanoma and brain metastases. Biomarker analysis was a prespecified exploratory endpoint in both trials. In COMBI-d pretreatment plasma samples were available from 345 of 423 patients and on-treatment (week 4) plasma samples were available from 224 of 423 patients. In COMBI-MB pretreatment and on-treatment samples were available from 38 of 76 patients with intracranial and extracranial metastatic melanoma. ctDNA was detected in pretreatment samples from 320 (93%) of 345 patients (COMBI-d) and 34 (89%) of 38 patients (COMBI-MB). The authors reported in COMBI-d elevated baseline BRAFV600 mutation-positive ctDNA concentration was associated with worse overall survival outcome (HR 1.13, $p<0.0001$ by univariate analysis), independent of treatment group and baseline LDH concentrations (1.08, $p=0.0020$). A ctDNA cutoff point of 64 copies per mL of plasma stratified patients enrolled in COMBI-d as high risk or low risk with respect to survival outcomes (HR 1.74, $p<0.0001$ for PFS; 2.23, $p<0.0001$ for OS) and was validated in the COMBI-MB cohort (3.20, $p=0.0047$ for PFS; 2.94, $p=0.016$ for OS). In COMBI-d, undetectable ctDNA at week 4 was significantly associated with extended PFS and OS, particularly in patients with elevated LDH concentrations (HR 1.99, $p=0.027$ for PFS; 2.38, $p=0.0089$ for OS).

Comment: Cell-free circulating tumour DNA (ctDNA) has emerged as a promising biomarker in many types of cancers. In melanoma patients with metastatic melanoma ctDNA in pretreatment blood samples was shown to have prognostic significance. The present studies, funded by Novartis, used a sensitive quantitative droplet digital PCR assay to determine whether measurements in plasma samples taken at 4 weeks during treatment with dabrafenib plus trametinib could predict treatment response against melanoma. The results showed a highly significant increase in PFS in patients having zero ctDNA at 4 weeks. These results were also validated in a second trial that included patients with brain metastases. Some of these patients had no evidence of extracranial metastases and it was noted that ctDNA was not detectable in these patients. The authors also point out that samples taken at 4 weeks may not be predictive of relapse at later times. A question remains as to how useful the ctDNA test would be in practice as a clinician may have to decide whether the test was reliable enough to base treatment decisions on them. As discussed by the authors a large prospective randomised study is needed that would also include measures of sensitivity of treatment response. If patients remained positive for ctDNA at 4 weeks would clinicians then stop treatment or change treatments? This would seem unlikely on current evidence and imaging would appear to remain the main outcome measure for some time.

Reference: Lancet Oncol. 2021 Mar;22(3):370-380
Abstract

Clinical, environmental and histological distribution of *BRAF*, *NRAS* and *TERT* promoter mutations among patients with cutaneous melanoma: A retrospective study of 563 patients

Authors: Manrique-Silva E, et al

Summary: The retrospective study investigating somatic mutations in *BRAF, NRAS* and *TERT* promoter in 563 patients with melanoma. The researchers observed co-occurrence of *TERT* promoter mutations with *BRAF* and *NRAS* mutations in 26.3% and 6.9% of melanomas, respectively. They found an independent association between *BRAF* mutations and a decreased presence of cutaneous lentigines at the melanoma site, and an increased association with the presence of any *MC1R* polymorphism. In addition, there was an independent association between *TERT* promoter mutations and increased tumour mitotic rate. Co-occurrence of *BRAF* and *TERT* promoter mutations was independently associated with occurrence of primary tumours at usually sun-exposed sites, lack of histological chronic sun damage in surrounding unaffected skin at the melanoma site, and increased tumour mitotic rate. Co-occurrence of *NRAS* and *TERT* promoter mutations was independently associated with increased tumour mitotic rate. They also noted the presence of *TERT* promoter together with *BRAF* or *NRAS* mutations was associated with statistically significantly worse survival.

Comment: The evolution of melanoma is known to involve mutations of *TERT* at an early stage which is added to by other mutations that activate the *MAPK* pathway and inactivate the P53 pathway. The present authors have examined whether clinical and pathologic features are associated with particular mutations or combinations of them. They note that young individuals tend to present with melanoma mainly on intermittently exposed skin such as the trunk, arms and legs, and have adjacent melanocytic naevi. In contrast, melanoma in older patients occur frequently at chronically sun-exposed sites like the neck and head. They examined the observed clinical and histopathological heterogeneity of melanoma in relation to frequently mutated loci in *BRAF*, *NRAS* and *TERT* promoter in 563 patients and compared them to triple negative melanoma. They found the *TERT BRAF* combination compared to *BRAF* mutations alone was detected at sun exposed sites and with solar elastosis. They conclude "Frequent co-occurrence of the *TERT* promoter with *BRAF* and, particularly, with *NRAS* alterations correlates with poor prognosis and melanoma survival implying a functional link between *BRAF* signalling and telomerase reactivation in melanomas. The synergistic effect from combined *TERT* promoter and *BRAF* and *NRAS* mutations could have an implication for patients treated with *MAPK* inhibitors." These results appear to extend previous studies by others such as those by Hunter Shain and Boris Bastian who implicated *TERT* promoter mutations as an early initiation event in development of melanoma. Whether they relate to resistance to *MEK* inhibition is an interesting question.

Reference: Dermatol. 2021 Mar;184(3):504-513
Abstract

Implementation of patient-reported outcome measures and patient-reported experience measures in melanoma clinical quality registries: A systematic review

Authors: Blood Z, et al

Summary: The authors conducted a systemic review of patient-reported outcome measures (PROMs) and patient-reported experience measures (PREMs) in clinical quality registries, for people with cutaneous melanoma. They identified 14 studies including four registries. These used seven measures of PROMs and one of PREMs. The authors reported PROMs/PREMs in registries improve transparency of care; facilitate clinical auditing for quality assessment; enable cost-effectiveness analyses and create large-scale research platforms. They also highlighted challenges including resource burden for data entry and potential collection bias toward younger, more affluent respondents.

Comment: PROMs are described as 'measurements of any aspect of a patient's health status that come directly from the patient'. PREMs focus on patients' satisfaction with care and cover topics such as dignity and respect; consistency and coordination of care; adequate involvement in, and explanation of care; trust and communication with nurses and doctors; and satisfactory discharge information. They considered these measures were increasingly being used for broader purposes, such as inclusion in routine healthcare or clinical quality registries for quality assurance and benchmarking. Nevertheless, in their very comprehensive review of the literature, there was little evidence of how PROM and PREM data were currently being used in daily clinical practice. This was considered largely due to local (non-registry) datasets being more likely to be used in clinical care, and not identified by systematic review. They conclude that developing future registries within electronic health records could overcome these problems and provide greater integration with existing online health systems. Cost and sample bias were considered possible limitations that would limit generalisability. Importantly, routine assessment and identification of patients who have poor PROMs and PREMs could provide clinical interventions that may improve overall melanoma care. (This is not the most concise article you will ever read).

Reference: BMJ Open. 2021 Feb 11;11(2):e040751
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.

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