Melanoma Research Review™

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Issue 49 - 2022

In this issue:

Abbreviations used in this issue:

CR = complete response; **HR** = hazard ratio; **ICI** = immune checkpoint inhibition; **IDO** = indoleamine 2,3-dioxygenase; **irAE** = immune-related adverse event; **MHC** = major histocompatibility complex; **MUP** = melanoma of unknown primary; **MSS** = melanoma-specific survival; **OR** = objective response; **ORR** = objective response rate; **OS** = overall survival; **PFS** = progression-free survival; **PR** = partial response; **RFS** = relapse-free survival; **TERT** = telomerase reverse transcriptase; **TRAE** = treatment-related adverse event.

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Welcome to the 49th issue of Melanoma Research Review

Dear Readers,

Selections from the literature this month provide several important updates on trials previously discussed in this forum as well as results from relatively new trials. There are also quite new ideas in the extracts that will be interesting to follow.

Kind Regards,

Professor Peter Hersey
peter.hersey@researchreview.com.au

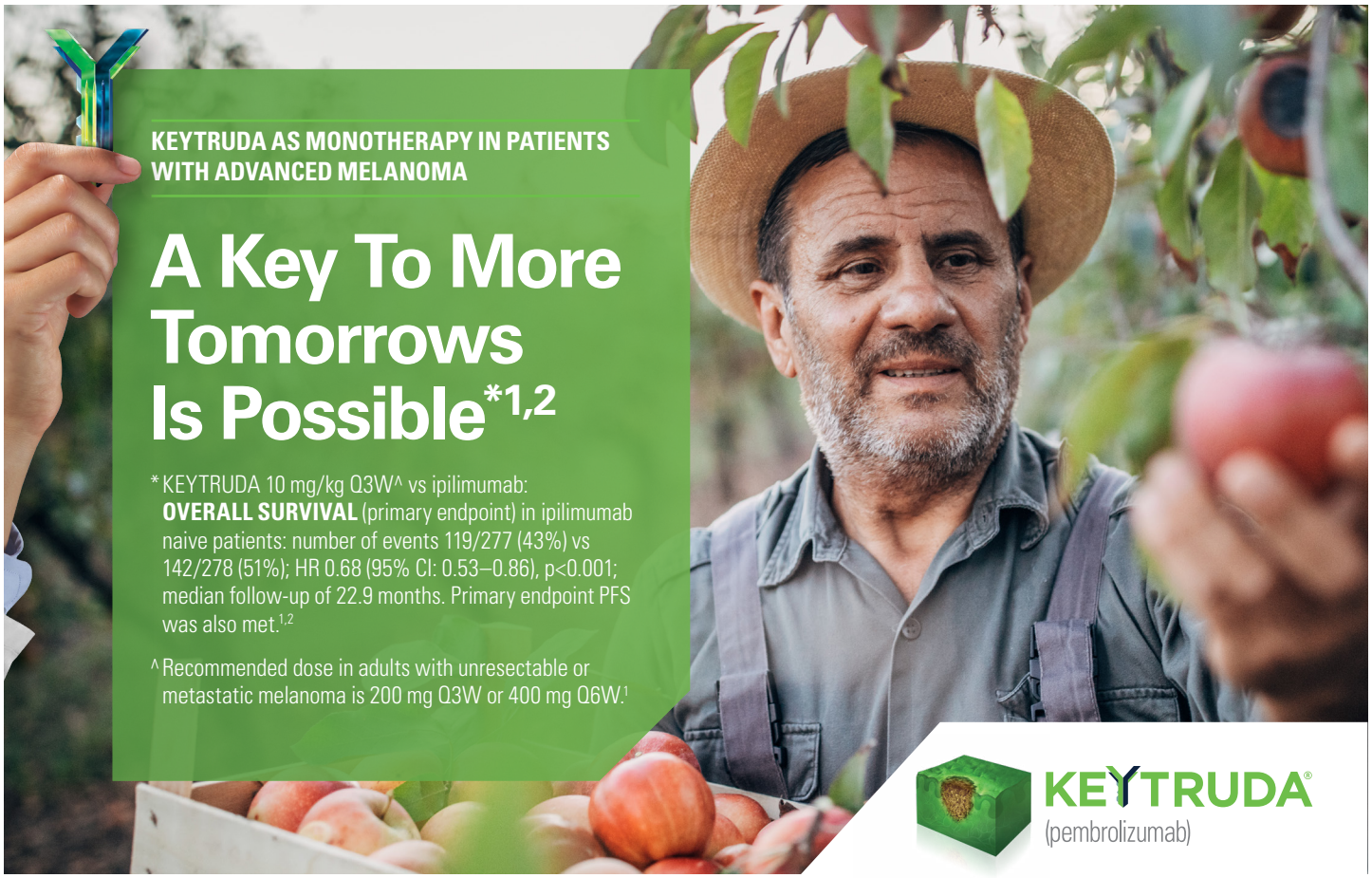
Long-term outcomes of patients with active melanoma brain metastases treated with combination nivolumab plus ipilimumab (CheckMate 204): Final results of an open-label, multicentre, phase 2 study

Authors: Tawbi HA, et al

Summary: This article reports on the final 3-year follow-up data from the CheckMate 204 trial. The study included adults with measurable melanoma brain metastases (0.5-3.0 cm in diameter). Asymptomatic patients (n = 101) had an ECOG performance status of 0 or 1 and no neurological symptoms or baseline corticosteroid use (median follow-up 34.3 months). Symptomatic patients (n = 18) had an ECOG performance status of 0-2 with stable neurological symptoms and could be receiving low-dose dexamethasone (median follow-up 7.5 months). Nivolumab plus ipilimumab was given every 3 weeks for four doses, followed by nivolumab every 2 weeks for up to 2 years, until disease progression or unacceptable toxicity. Investigator-assessed intracranial clinical benefit was observed in 58 (57.4%) of 101 patients in the asymptomatic cohort and three (16.7%) of 18 patients in the symptomatic cohort. Investigator-assessed objective response (OR) was observed in 54 (53.5%) patients in the asymptomatic cohort and three (16.7%) patients in the symptomatic cohort. In addition, 33 (33%) patients in the asymptomatic cohort and three (17%) patients in the symptomatic cohort had an investigator-assessed intracranial complete response (CR). For patients in the asymptomatic cohort, 36-month intracranial progression-free survival (PFS) was 54.1% and overall survival (OS) was 71.9%. For patients in the symptomatic cohort, 36-month intracranial PFS was 18.9% and OS was 36.6%. They noted the most common serious treatment-related adverse events (TRAEs) were colitis, diarrhoea, hypophysitis, and increased alanine aminotransferase. There was one treatment-related death (myocarditis in the asymptomatic cohort).

Comment: Challenges remain…. This is a follow up report on the phase 2 CheckMate 204 study of combination nivolumab plus ipilimumab in 101 patients with asymptomatic non-steroid treated melanoma brain metastases and 18 patients with neurologic symptoms. The results from this study, as well as those from smaller but comparable studies including those in Australia, indicate that responses in the brain are comparable to responses in extracranial sites and were durable with median PFS not being reached in the 3 year follow up period. Discussions of these results accompanying the report centred on the role of radiotherapy, risks of radiation necrosis with immune checkpoint inhibition (ICI) and the need for controlled studies on these questions

Reference: Lancet Oncol 2021 Dec;22(12):1692-1704
Abstract



KEYTRUDA AS MONOTHERAPY IN PATIENTS WITH ADVANCED MELANOMA

A Key To More Tomorrows Is Possible*[1,2]

* KEYTRUDA 10 mg/kg Q3W^ vs ipilimumab: **OVERALL SURVIVAL** (primary endpoint) in ipilimumab naive patients: number of events 119/277 (43%) vs 142/278 (51%); HR 0.68 (95% CI: 0.53–0.86), p<0.001; median follow-up of 22.9 months. Primary endpoint PFS was also met.[1,2]

^ Recommended dose in adults with unresectable or metastatic melanoma is 200 mg Q3W or 400 mg Q6W.[1]

KEYTRUDA® (pembrolizumab)

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

Crossover and rechallenge with pembrolizumab in recurrent patients from the EORTC 1325-MG/Keynote-054 phase III trial, pembrolizumab versus placebo after complete resection of high-risk stage III melanoma

Authors: Eggermont AM, et al

Summary: Patients with stage III cutaneous melanoma with complete resection of lymph nodes were randomised to receive pembrolizumab (n = 514) or placebo (n = 505) every 3 weeks, up to 1 year. On recurrence, patients could enter part 2 of the study: pembrolizumab every 3 weeks up to 2 years, for crossover (those who received placebo) or rechallenge (those who had recurrence ≥6 months after completing 1-year adjuvant pembrolizumab therapy). The authors reported in the placebo group, 298 patients had a disease recurrence, in which 155 (52%) crossed over. In the pembrolizumab group, 297 patients completed the 1-year treatment period; 47 had a recurrence ≥6 months later, in which 20 (43%) were rechallenged. In the crossover group, the median PFS was 8.5 months and the 3-year PFS rate was 32%. Among 80 patients with stage IV evaluable disease, 31 (39%) had an OR, 14 (18%) patients had CR and 17 (21%) patients had partial response (PR). The 2-year PFS rate from response was 69%. In the rechallenge group, the median PFS was 4.1 months. Among 9 patients with stage IV evaluable disease, 1 had an OR. Among the 175 patients, 51 (29%) had a grade I-IV immune-related adverse event (irAE) and 11 (6%) had a grade III-IV irAE.

Comment: A great study but does it say we can wait until patients relapse and get the same outcomes? The lead investigator Alex Eggermont, as an invited speaker, said that the Keynote-054 trial was the best trial he ever organised. One of the reasons for this was that a crossover was built into the study and this would allow an assessment as to whether early treatment after surgery was better than treatment at the time of relapse. In general, the response rates (39%) median PFS (8.5 mths), 3yr PFS (32%) and OS rates in the relapsed placebo group resemble closely the response to nivolumab in the BMS CheckMate-067 study at 3 years ORR 44%, median PFS 6.9 mths, PFS at 3yr 32% and OS at 2yrs 59%. Decision on whether timing of treatment is important requires longer follow up to compare survivals. Side effects in the relapsed group were also comparable with those in the CheckMate-067 trial - with endocrine side effects in 21%, hypothyroidism in 14%, diabetes in 2%, GI effects in 3%. How important will cost differences be? The authors are non-committal on relative costs, which no doubt will be the subject of ongoing debate.

Reference: Eur J Cancer 2021 Oct 18;158:156-168
Abstract

Association between sex and immune checkpoint inhibitor outcomes for patients with melanoma

Authors: Jang SR, et al

Summary: The investigators explored whether cancer immunotherapy effectiveness varies between female and male patients with advanced melanoma. The study cohort comprised of 1,369 adults (71.7% men, median age 75 years), with a diagnosis of stage III or stage IV melanoma and nivolumab plus ipilimumab combination therapy or anti-PD-1 therapy (pembrolizumab or nivolumab) as their last type of ICI. The investigators concluded the outcome of nivolumab plus ipilimumab combination therapy depended on sex (Wald $\chi 2 = 9.48$; $P = 0.009$ for interaction). The mortality hazard ratio (HR) for women with prior ipilimumab use receiving combination therapy was 2.06 times ($P = 0.003$) higher than their male counterparts. They noted no significant difference was observed between women and men receiving anti-PD-1 therapy with (HR, 0.97; $P = 0.85$) or without prior ipilimumab use (HR, 0.85; $P = 0.16$). For women with prior ipilimumab use, combination therapy was associated with 2.82 times higher mortality hazards than anti-PD-1 therapy. No statistically significant difference was seen in mortality risk between anti-PD-1 therapy and combination therapy for men.

Comment: Can difference in outcomes according to sex be exploited in treatment? A number of studies have shown that women have a much better survival from melanoma than men. It is therefore puzzling that men appear to respond much better to immunotherapy with ICI than women. This was shown in previous trial data but is now shown in retrospective analysis of US SEER Medicare linked database and closer to real life experience. This analysis showed that the difference was mainly in regimes including ipilimumab rather than just anti-PD-1. A number of explanations were canvassed. One is that melanoma in males tends to have a higher mutation burden which is a predictor of response to ICI. Another is that the strong immune response in women may have resulted in immunoselection of tumours with lower antigen expression. In discussion reference was made to studies in which women failing ICI responded better to chemotherapy given post ICI. They conclude:

'Although literature provides strong evidence that immunotherapy may not be as effective for female patients with melanoma as it is for their male counterparts owing to biological differences, we cannot completely rule out the possibility that the differences in outcomes may be due to differences in behavioral patterns (eg, smoking, outdoor activities, and health care resource use). It would be imperative to replicate this study with a larger patient population, including younger cohorts to examine whether genetic and hormonal factors play a role in ICI response'.

Reference: JAMA Netw Open 2021 Dec 1;4(12):e2136823
Abstract

Effect of immunotherapy time-of-day infusion on overall survival among patients with advanced melanoma in the USA (MEMOIR): A propensity score-matched analysis of a single-centre, longitudinal study

Authors: Qian DC, et al

Summary: Melanoma Outcomes Following Immunotherapy (MEMOIR) is a longitudinal study of all patients with melanoma who received ipilimumab, nivolumab, or pembrolizumab, or a combination of these at a single tertiary cancer centre in Atlanta, USA. The authors analysed a cohort of 299 patients from the MEMOIR database diagnosed with stage IV melanoma between 2012 and 2020; median follow-up was 27 months. 102 (34%) patients were female and 197 (66%) were male, with a median age of 61 years. The researchers reported every additional 20% of infusions of ICIs after 1630 hours (among all infusions received by a patient) conferred an OS HR of 1.31 (95% CI 1.00 to 1.71; p=0.046). A propensity score-matched analysis of patients who did (n = 73) and did not (n = 73) receive at least 20% of their infusions of ICIs after 1630 showed that having at least 20% of infusions in the evening was associated with shorter OS (median 4.8 years [95% CI 3.9 to not estimable] vs not reached; HR 2.04 [1.04 to 4.00; p=0.038]). They noted the most common adverse events were colitis (18%), hepatitis (9%), and hypophysitis (5%), and there were no treatment-related deaths.

Comment: Are diurnal rhythms important in outcomes in treatment with immune checkpoint inhibitors? Rather than summarising this study I found it more interesting to read several comments/criticisms of the findings, which are worth summarising. Dizman et al pointed out the socioeconomic and demographic characteristics of the patients were not mentioned (Dizman N et al, Lancet Oncol 2022 Feb;28(2):E56). This is particularly important, as both the primary predictor (ie, infusion time) and the clinical outcome (ie, overall survival) tested bear great potential to be affected by social factors. These factors include, but are not limited to, annual individual income, geographical residency, and distance to treating facility. Furthermore, employment status, medical insurance, primary language, access to transportation, marital status, and individual family responsibilities might be other effect modifiers or confounders in the study by Qian and colleagues. In clinical practice, infusion scheduling time is frequently chosen based on available time slots and the patient's personal schedule (including the need for continuing a full-time job), which would be affected by the factors mentioned above.

O'Brien et al had questions related to pharmacokinetics (O'Brien, et al. Lancet Oncol 2022 Feb;23(2):E55). Applying simple mathematics based on the linear clearance of nivolumab and an average half-life of 25 days, consider the following scenario. On the morning of day 2, a patient who received a dose of nivolumab the evening before (about 12 h earlier), has a plasma concentration that is about 99% of a patient who received a morning infusion. In other words, on 20 of the 21 days in the first cycle, patients who received their dose in the evening had morning plasma concentrations that were within 1% of those who received a morning infusion. This minor difference diminishes further with multiple doses as a steady state is achieved. Thus, changing the timing of infusion was unlikely to have represented a noteworthy intervention in this study. Furthermore, it seems implausible that a small difference in plasma concentration of drug could account for the large magnitude of effect observed. Therefore, it would seem more likely that confounding factors and biases inherent to all retrospective studies led to the results reported here. Indeed, repeating this study in other centres might yield conflicting results. The authors replied that there might be tissue distribution differences. Nevertheless, I suspect the article is not going to change infusion timing.

Reference: Lancet Oncol 2021 Dec;22(12):1777-1786
Abstract

A phase 1/2 trial of an immune-modulatory vaccine against IDO/PD-L1 in combination with nivolumab in metastatic melanoma

Authors: Kjeldsen JW, et al

Summary: The researchers tested a first-in-class immune-modulatory vaccine against indoleamine 2,3-dioxygenase (IDO) and PD-L1 combined with nivolumab in 30 anti-PD-1 therapy-naive patients with metastatic melanoma. After a median follow-up of 22.9 months, the median PFS was 26 months; median OS was not reached. The researchers found vaccine-specific responses were detected in the blood of >93% of patients during vaccination. Vaccine-reactive T cells comprised CD4+ and CD8+ T cells with activity against IDO- and PD-L1-expressing cancer and immune cells. Furthermore, they observed T cell influx of peripherally expanded T cells into tumour sites in responding patients, and general enrichment of IDO- and PD-L1-specific clones after treatment.

Comment: Are the Scandinavians pointing the way? It is always interesting to read studies out of the ordinary that have a fair amount of scientific backing and that involve human patients rather than just in animal models. The idea was to immunise patients against PD-L1 and IDO and examine whether this would increase the response rates and PFS in 30 patients given concurrent monotherapy with nivolumab. Targeting these immunosuppressive molecules avoided the difficulty of isolating neoantigens and other patient specific approaches. As you would expect in a Nature Immunology paper the studies appear to have been well conducted with evidence of successful vaccinations and induction of T cell responses in blood and at tumour sites. They compare their results with patients treated by nivolumab alone in the CheckMate-067 study (ORR of 43% and CR 13%). They finish their paper as follows:

'A larger randomized trial will be essential to validate these findings and determine the specific contribution of the vaccine to clinical responses and changes in the TME. In December 2020, the Food and Drug Administration granted breakthrough therapy designation for the IO102/IO103 vaccine combined with aPD1 therapy in metastatic melanoma based on data from the MM1636 trial.'

Reference: Nat Med 2021 Dec;27(12):2212-2223
Abstract

Ipilimumab alone or in combination with nivolumab in patients with advanced melanoma who have progressed or relapsed on PD-1 blockade: Clinical outcomes and translational biomarker analyses

Authors: Friedman CF, et al

Summary: This multicentre phase II trial randomised patients with advanced melanoma to receive nivolumab plus ipilimumab or ipilimumab alone every 3 weeks for up to four doses. Objective responses were seen in 5 of 9 patients in the ipilimumab arm and 2 of 10 patients in the ipilimumab plus nivolumab arm. It was noted disease control rates (66.7% vs 60.0%) and rates of grade 3-4 adverse events (56% vs 50%) were comparable between arms. In a pooled analysis, patients with clinical benefit (defined as RECIST response or progression-free for 6 months), showed increased circulating CD4+ T cells with higher polyfunctionality and interferon gamma production following treatment. In addition, patients with clinical benefit had enrichment of NRAS mutations and activation of transcriptional programs associated with innate and adaptive immunity.

Comment: Is ipilimumab alone better than in combination with nivolumab in PD-1 failures? The best treatment of patients failing anti-PD-1 treatments remains under investigation. This was a prospective randomised clinical trial with longitudinal biomarker sample collection to evaluate the clinical and biological activities of ipilimumab alone and in combination with nivolumab in patients with progression of disease on anti-PD-1 monotherapy. The trial was ended early due to poor accrual after 20 patients were enrolled out of a planned 24 in the first stage. A numerically higher ORR (objective response rate) was observed in the ipilimumab arm (56%) than the ipilimumab plus nivolumab arm (20%); however, the study was not designed to test between arms and is limited by the small sample size. In longitudinal peripheral immune profiling by CyTOF, there was increased fold change in CD4+ immune cell subsets, but not CD8+ T cells, associated with ORR to ipilimumab-based therapy, and these effects were more consistent and sustained in the ipilimumab monotherapy arm than in combination with nivolumab. Similar observations have been reported in peripheral blood analysis at baseline, where increased frequencies of CD45RA– T cells were associated with response to ipilimumab. These data suggest that successful eradication of metastatic tumours in patients that progress on PD-1 may require the concerted activation of both the CD4+ and CD8+ compartments of the adaptive immune response. It was also noted that all patients whose tumour harboured an NRAS mutation derived responses and that this has been demonstrated in previous retrospective analyses.

Reference: J Immunother Cancer 2022 Jan;10(1):e003853
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 phase III CheckMate 067 trial demonstrated durable clinical benefit with nivolumab plus ipilimumab (n = 314) and nivolumab alone (n = 316) versus ipilimumab (n = 315) in patients with previously untreated unresectable stage III or stage IV melanoma. This article reports on the 6.5-year efficacy and safety outcomes. Median OS 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. It was noted no new safety signals were observed.

Comment: Results that set the standard to beat. Long-term survival of patients with advanced melanoma treated with nivolumab plus ipilimumab and nivolumab alone versus ipilimumab has been demonstrated after 5-year follow-up in the phase III CheckMate 067 trial. The extent of the durability of this benefit is shown by this 6.5-year follow up. They summarise as follows:

'These 6.5-year data obtained with the combination of first-line nivolumab plus ipilimumab in patients with advanced melanoma in CheckMate 067 include the longest median OS reported to date in a phase III melanoma study, as well as a median MSS that had not been reached at 77 months. These trials have established the combination of nivolumab and ipilimumab as a standard care option for patients with metastatic melanoma.'

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

Improved prognosis and evidence of enhanced immunogenicity in tumor and circulation of high-risk melanoma patients with unknown primary

Authors: Tarhini AA, et al

Summary: The authors investigated the differences in prognosis and candidate immune biomarkers in patients with melanoma of unknown primary (MUP) compared with those with known primary melanoma enrolled in the E1609 adjuvant trial that tested ipilimumab at 3 and 10 mg/kg vs high-dose interferon-alfa (IFN). Of the total cohort of 1,699 patients 12.8% were MUP; including 11.7% on the ipilimumab arms and 14.7% on the IFN arm. Stratifying by stage, relapse-free survival (RFS) (p = 0.001) and OS (p = 0.009) showed outcomes significantly better for MUP. Furthermore, the primary tumour status remained prognostically significant after adjusting for treatment and stage. Including only ipilimumab-treated patients, RFS (p = 0.005) and OS (p = 0.023) were significantly better in favour of those with unknown primary. Gene expression profiling identified pathways and genes related to autoimmunity, inflammation, immune cell infiltration and immune activation that were significantly enriched in the MUP tumours compared with known primaries. They also reported enrichment with CD8+ and CD4+ T cells, B cells and NK cells as well as significantly higher major histocompatibility complex (MHC)-I and MHC-II scores in MUP compared with known primary.

Comment: Why doesn't the immune response wipe out melanoma before spread from the skin? This is one of several previous studies that suggest that melanoma in patients with unknown primaries are more immunogenic. The patients in this study were part of the large E1609 adjuvant study that also included high dose IFN. Their analysis was on the patients treated with ipilimumab; RFS and OS were significantly better in the unknown primary cases and this was associated with significantly higher MHC antigen expression on the melanoma and enhanced expression of immune-related genes. They conclude:

'Therefore, a completely regressed primary in MUP may represent a consequence of prior host immune recognition and development of melanoma immune resistance that benefits from immunotherapeutic interventions. We propose that future adjuvant trials consider stratifying for MUP and we support the AJCC efforts in further investigating the prognostic value of MUP and its contributions to the melanoma staging system.'

Reference: J Immunother Cancer 2022 Jan;10(1):e004310
Abstract

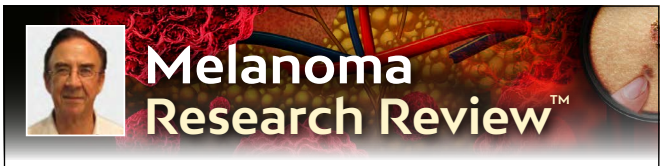
Relatlimab and nivolumab versus nivolumab in untreated advanced melanoma

Authors: Tawbi HA, et al

Summary: This phase 2-3, global, double-blind, randomised trial evaluated combination relatlimab and nivolumab versus nivolumab alone in patients with previously untreated metastatic or unresectable melanoma. The authors reported median PFS was 10.1 months with relatlimab-nivolumab as compared with 4.6 months with nivolumab (HR for progression or death, 0.75; P = 0.006). PFS at 12 months was 47.7% with relatlimab-nivolumab as compared with 36.0% with nivolumab. Grade 3 or 4 TRAEs occurred in 18.9% of patients in the relatlimab-nivolumab group and in 9.7% of patients in the nivolumab group.

Comment: Will agents targeting LAG3 extend the reach of ICI immunotherapy? Previous translational research identified a number of inhibitory receptors on T cells that limited their ability to kill melanoma cells that expressed ligands for the receptors. The development of blocking antibodies against these receptors has revolutionised immunotherapy of melanoma to the extent that blocking antibodies against PD-1 and CTLA4 are now the standard of care in treatment of AJCC stage III and IV melanoma. Blocking antibodies against other inhibitory receptors are now under investigation to see if combinations will further increase the effectiveness of immunotherapy. Preclinical studies suggested that antibodies against LAG3 might be effective when combined with antibodies against PD-1. These results have been very quickly tested in well designed clinical trials. The present report based on PFS provides an early indication of the effectiveness of this combination. We have to wait for longer follow up to see if the PFS translates to longer survivals. The current results also highlight that the incidence of serious side effects may be much less than seen with the anti-PD-1 anti CTLA4 combinations. The biology of T cells expressing LAG3 as well as its ligands and inhibitory mechanisms continues to be of great interest and no doubt will be the subject of many future reports.

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

TERT promoter mutations are associated with longer progression-free and overall survival in patients with BRAF-mutant melanoma receiving BRAF and MEK inhibitor therapy

Authors: Thielmann CM, et al

Summary: The authors explored whether BRAF-MEK inhibitor therapy response is associated with tumour TERT promoter mutation status in a clinical setting. The study cohort included 232 patients with metastatic or unresectable BRAF V600-mutated melanoma receiving combined BRAF/MEK inhibitor treatment. The cohort comprised of a single-centre retrospective discovery cohort (n = 120) and a prospectively collected multicentre validation cohort (n = 112). Most tumours harboured TERT promoter mutations (72%). The authors concluded a survival advantage was observed in both PFS and OS for patients with TERT promoter-mutant versus wild-type tumours in both the discovery cohort (mPFS of 9.6 months [n = 87] vs 5.0 months [n = 33]; HR = 0.56 and mOS of 33.6 months vs 15.0 months; HR = 0.47) as well as the validation cohort (mPFS of 7.3 months [n = 80] vs 5.8 months [n = 32]; HR = 0.67 and mOS of 51.1 months vs 15.0 months; HR = 0.33). In the pooled cohort of TERT promoter-mutant (n = 167) versus wild-type (n = 65) tumours, respectively, PFS was 8.9 versus 5.5 months, (HR = 0.62; P = 0.004), and OS was 33.6 versus 17.0 months, (HR = 0.51; P = 0.0001).

Comment: Identifying long term survivors from targeted treatment?
Telomerase reverse transcriptase (TERT) maintains telomeres at the ends of chromosomes in dividing cells and in cancer cells. Mutations in its promoter were found to be one of the earliest mutations in development of melanoma. Previous studies have shown that in melanoma with TERT promoter mutations TERT levels are maintained by the activation of the MAPK pathway and acts also to inhibit apoptosis. As a result of its MAPK dependence it was found that BRAFV600 mutated melanoma that had TERT promoter mutations were particularly sensitive to MAPK inhibitors. In the present study it was found that patients with mutations in both BRAF and TERT had more favourable outcomes when treated with BRAF/MEK inhibitors compared to that in patients that had melanoma with just BRAF mutations. This was significant for PFS and OS in univariate analysis. They conclude:

'Additional analyses of larger cohorts should be performed to confirm and expand our findings. If confirmed, TERT promoter mutation status may prove to be an important predictive marker not only in primary systemic therapy of advanced disease but also for sequential and adjuvant therapy regimens.'

Reference: Eur J Cancer 2022 Jan;161:99-107
Abstract

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