Melanoma Research Review™

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Issue 42 - 2021

In this issue:

Abbreviations used in this issue:

AID = autoimmune disease; **ASS1** = argininosuccinate synthase 1; **cICB** = combination immune checkpoint blocker; **DC** = dendritic cell; **EV** = extracellular vesicle; **HDI** = high-dose interferon; **IBD** = inflammatory bowel disease; **ICB** = immune checkpoint blocker; **ICI** = immune checkpoint inhibition; **ipi** = ipilimumab; **irAE** = immune related adverse effect; **OS** = overall survival; **PBMC** = peripheral blood mononuclear cell; **PFS** = progression-free; **RFS** = relapse-free survival; **sICB** = single agent immune checkpoint blocker; **TCI**= topical calcineurin inhibitors; **TCS**= topical corticosteroids; **TIL** = tumour-infiltrating lymphocytes; **TME** = tumour microenvironment; **uPAR** = urokinase-type plasminogen activator receptor.

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Welcome to the 42nd issue of Melanoma Research Review.

The articles in this month's review include a number of follow up studies on previous trials such as examination of the influence of immune related adverse effects (irAEs) on their outcomes. The study from the Oxford group has gone one further by including studies on $CD8^+$ T cells in relation to whether irAEs develop or not. There are also real-life assessments from the Netherlands of potential dangers of pre-existing auto immune diseases in patients receiving immune checkpoint inhibitors. Several unusual studies are covered such as use of arginine depletion in treatment and study of extracellular vesicles as resistance factors. I trust you find them interesting.

Kind Regards,

Professor Peter Hersey

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Adjuvant pembrolizumab versus placebo in resected stage III melanoma (EORTC 1325-MG/KEYNOTE-054): Distant metastasis-free survival results from a double-blind, randomised, controlled, phase 3 trial

Authors: Eggermont AMM, et al

Summary: The 1325/KEYNOTE-054 trial randomly assigned patients with resected high-risk stage III melanoma to receive pembrolizumab (n=514) or placebo (n=505) every 3 weeks for up to 18 doses. The authors previously reported pembrolizumab improved recurrence-free survival (HR 0.57, p<0.0001) compared with placebo at 15-month median follow-up. In this article they provide the final results for the secondary efficacy endpoint, distant metastasis-free survival and an update of the recurrence-free survival results. At an overall median follow-up of 42.3 months 3.5-year distant metastasis-free survival was higher in the pembrolizumab group than in the placebo group in the intention-to-treat (ITT) population (65.3% in the pembrolizumab group vs 49.4% in the placebo group; HR 0·60; p<0.0001). In the 853 patients with PD-L1-positive tumours, 3.5-year distant metastasis-free survival was 66.7% in the pembrolizumab group and 51.6% in the placebo group (HR 0.61; p<0.0001). Furthermore, recurrence-free survival remained longer in the pembrolizumab group 59.8% than the placebo group 41.4% at this 3.5-year follow-up in the ITT population (HR 0.59) and in those with PD-L1-positive tumours 61.4% in the pembrolizumab group and 44.1% in the placebo group (HR 0.59).

Comment: The results of this trial in terms of recurrence-free survival have been presented previously in the NEJM and in the Journal of Clinical Oncology and have been widely adopted in treatment of stage III melanoma. This report presents the results of distant metastasis free survival which was the secondary endpoint in the study. The median follow up was 3.5 years and no further reports of metastasis free survival are planned. The results confirm that pembrolizumab was more effective than placebo and this applied irrespective of whether classification of stage III was by AJCC-7 or AJCC-8. As before benefit was seen across all subgroups including those with ulcerated melanoma and BRAF mutations. Some mention is made of risk benefit analysis that received commentary in previous editions of Melanoma Research Reviews but is mainly appropriate for patients with stage IIIA disease. A sentence on this is repeated here- "adjuvant therapy with anti-PD-1 in patients with AJCC-8 stage IIIA disease can only be discussed with patients with much prudence and in great detail because of the risk of chronic immune-related adverse events."

Reference: Lancet Oncol 2021 May;22(5):643-654

Abstract

Association between topical calcineurin inhibitor use and risk of cancer, including lymphoma, keratinocyte carcinoma, and melanoma: A systematic review and meta-analysis

Authors: Lam M, et al

Summary: The meta-analysis evaluated observational studies investigating the association between treatment with topical calcineurin inhibitors (TCIs) and the development of cancer with nonactive or active comparators. Eight unique cohort studies (408,366 treated participants, 1,764,313 nonactive comparator controls, and 1,067,280 controls using topical corticosteroids) and 3 unique case-control studies (3,898 cases and 14,026 cancer-free controls) were included. The authors concluded there was no association between TCI use and cancer overall compared with nonactive comparators (RR, 1.03). Lymphoma risk was elevated with TCI use with both nonactive (RR, 1.86) and topical corticosteroid comparators (RR, 1.35). They found no significant association between TCI use and increased skin cancer (melanoma and keratinocyte carcinoma).

Comment: Topical calcineurin inhibitors, tacrolimus ointment and pimecrolimus cream, are indicated as second-line treatment of atopic dermatitis when first-line topical corticosteroids (TCSs) are ineffective or contraindicated. Given the long potential latency for cancer development, postmarketing studies with long follow-up are necessary to determine whether there is an association between TCIs and cancer. A clinically important association would indicate the need for caution with TCI use, particularly for patients with chronic atopic dermatitis requiring long-term topical anti-inflammatory therapy. Conversely, if there is no clinically meaningful association, unwarranted worry stemming from regulatory safety warnings could lead to nonadherence and undertreatment of atopic dermatitis. Several mechanisms have been proposed for the development of malignant neoplasms after calcineurin inhibitor use. The immunosuppressive effects of calcineurin inhibitors leading to decreased surveillance of cancerous cells may contribute to tumour promotion. In addition, evidence for direct tumour induction by calcineurin inhibitors exists. Although biologically plausible, the overall risk of malignant neoplasms attributable to these topical anti-inflammatory agents is likely low.

In a very detailed literature survey no increased risk of skin cancers were detected. Only 2 cases of solid tumours were reported in 25,000 patients treated with pimecrolimus, and no lymphoma in almost 10,000 patients treated with tacrolimus in clinical trials. The rate of lymphoma in those prescribed TCIs reported in the US Food and Drug Administration's adverse event reporting system was lower than the rate seen in the general population. This study appears to put to rest any fears about the topical use of these agents as a risk factor for melanoma.

Reference: JAMA Dermatol 2021 May 1;157(5):549-558
Abstract

Checkpoint-blocker-induced autoimmunity is associated with favourable outcome in metastatic melanoma and distinct T-cell expression profiles

Authors: Ye W, et al

Summary: This retrospective study evaluated the relationship between immune checkpoint blocker (ICB) elicited irAEs and baseline parameters and clinical outcome. The researchers assessed impact of irAEs on survival across primary (n = 144) and secondary (n = 211) independent cohorts of patients with metastatic melanoma receiving single agent (pembrolizumab/nivolumab-sICB) or combination (nivolumab and ipilimumab-cICB) checkpoint blockade. They reported 58.3% of patients developed early irAEs and this was associated with longer progression-free (PFS) and overall survival (OS) across both cohorts (log-rank test, OS: $P < 0.0001$). Median survival for patients without irAEs was 16.6 months (95% CI: 10.9-33.4) versus not-reached ($P = 2.8 \times 10\text{-}6$). They noted pre-treatment monocyte and neutrophil counts, but not BMI, were also predictors of clinical outcome. Differential expression of numerous gene pathway members was observed in $CD8^+$ T cells according to irAE development, and patients not developing irAEs demonstrating upregulated CXCR1 pre- and post-treatment.

Comment: This is one of many studies that has examined whether irAEs are associated with outcomes during treatment with anti-PD-1 or a combination with ipilimumab anti-CTLA-4. This was a prospective study on 144 patients -81 who received anti-PD-1 and 63 who had the combination. This was a real-world setting rather than a trial. The irAEs were recorded in the first 12 weeks of treatment. Development of an early irAE prior to the 5th cycle of treatment was associated with significantly longer OS and PFS (OS $P < 0.0001$, PFS $P = 0.00024$). This observation remained significant for OS in both groups. Patients only developing mild grade 1/2 irAEs had a significant OS benefit and this was also the case for grade 3/4 irAEs. Non-cutaneous melanoma subtype, raised performance status, neutrophil count, monocyte count and baseline lactate dehydrogenase levels were negatively prognostic. Analysis of $CD8^+$ T cell expression revealed that development of irAEs in the anti-PD-1 alone treated patients was associated with pretreatment T cell activation. In baseline and treated samples raised expression of CXCR1 on $CD8^+$ T cells was found to be associated with absence of developing irAEs. Plasma IL-8, a key cytokine mediator of neutrophil chemotaxis and ligand of CXCR1, is strongly associated with negative clinical outcomes to ICB treatment.

They conclude "The clinical utility of these findings will require prospective trials, but our results suggest that patients with raised neutrophil counts have reduced risk of irAE development and poorer prognosis—arguing for treatment with cICB. Conversely, in patients without oncological responses to sICB who have not developed irAE, there might be argument that effective immune stimulation has not been elicited and switching to cICB could be helpful"

Reference: Br J Cancer 2021 May;124(10):1661-1669
Abstract

$uPAR^+$ extracellular vesicles: A robust biomarker of resistance to checkpoint inhibitor immunotherapy in metastatic melanoma patients

Authors: Porcelli L, et al

Summary: This study aimed to assess urokinase-type plasminogen activator receptor (uPAR) expression in the plasma-derived extracellular vesicles (EVs) of 71 patients with metastatic melanoma before initiating immunotherapy to determine its potential correlation with clinical outcomes. The authors reported responders had a significantly lower percentage of tumour-derived, dendritic cell (DC)-derived and $CD8^+$ T cell-derived $uPAR^+$ EVs at baseline than non-responders. Higher levels of melanoma-derived $uPAR^+$ EVs were strongly correlated with poorer PFS ($p<0.0001$) and OS ($p<0.0001$). In addition, they found a statistically significant correlation between lower levels of $uPAR^+$ EVs from both $CD8^+$ T cells and DCs and better survival.

Comment: A refresher from google: "The plasminogen system has been implicated in clot lysis, wound healing, tissue regeneration, cancer and many other processes that affect health and disease. The urokinase receptor uPAR was originally thought to assist the directional invasion of migrating cells, but it is now becoming increasingly evident that this proteinase receptor elicits a plethora of cellular responses that include cellular adhesion, differentiation, proliferation and migration in a non-proteolytic fashion."

This is another study attempting to define markers of resistance against treatment with anti-PD-1 by studies on blood. Plasma from 71 patients about to undergo anti-PD-1 treatment was ultracentrifuged and analysed for nano particles that contain EVs by commercially available equipment. The content and site of origin of the EVs in the sediment was characterised by antibody staining and flow cytometry. Their findings showed that even if overall basal levels of $uPAR^+$ EVs in responders and non-responders were similar, responders had significantly lower basal levels of $uPAR^+$ EVs from melanoma cells, $CD8^+$ T cells and DCs than non-responders. They speculate that the increase in the percentage of $uPAR^+$ EVs from DCs in non-responders reflects the reactivation of a signaling in such cells, which could contribute to the recirculation of DCs and their removal from the tumour microenvironment (TME). $CD8^+$ T cell-derived EVs that express uPAR were found in the TME but they were considered dysfunctional cells. uPAR overexpression within melanoma was considered to drive a glycolytic and invasive phenotype in melanoma cells that were resistant to anti-PD-1. Tumours which release $uPAR^+$ EVs were considered to dramatically alter the TME by causing glucose deprivation. This study appears innovative but very speculative. They suggest it may lead to novel anticancer approaches, however, do not indicate what this may be. The methods and analysis of results appeared very complex so that it seems unlikely to become a routine procedure and is hardly robust!

Reference: J Immunother Cancer 2021 May;9(5):e002372
Abstract

Safety and efficacy of checkpoint inhibition in patients with melanoma and preexisting autoimmune disease. A cohort study

Authors: van der Kooij MK, et al

Summary: Dutch registry data was used to evaluate the safety and efficacy of immune checkpoint inhibition (ICI) in patients with advanced melanoma with and without autoimmune disease (AID). The study cohort included 4,367 patients. Of these 415 (9.5%) had AID, categorised as rheumatologic AID (n = 227), endocrine AID (n = 143), inflammatory bowel disease (IBD) (n = 55), or "other" (n = 8). 228 patients (55%) were treated with ICI (vs. 2,546 [58%] without AID); 87 were treated with anti-cytotoxic T lymphocyte-associated protein 4 (CTLA-4), 187 with anti-PD-1, and 34 with the combination. The incidences of irAEs of grade 3 or higher in patients with AID were 30% with anti-CTLA-4, 17% with anti-PD-1, and 44% with combination therapy; for patients without AID, the incidences were 30% (n = 916), 13% (n = 1,540), and 48% (n = 388), respectively. It was noted patients with AID more often discontinued anti-PD-1 treatment because of toxicity than patients without AID (17% vs. 9%). Furthermore, patients with IBD were more prone to anti-PD-1-induced colitis (6/31 = 19%) than patients with other AIDs (3%) and patients without AID (2%). The objective response rate was similar in patients with versus without AID who were treated with anti-CTLA-4 (10% vs. 16%), anti-PD-1 (40% vs. 44%), or the combination (39% vs. 43%). Survival did not differ between patients with and those without AID (median, 13 months vs. 14 months).

Comment: This is a large real-world study by a group of experienced oncologists in the Netherlands. They point out that patients with AID are not represented in trial data and this was the first study to bridge this knowledge gap by presenting "real-world" data on the safety and efficacy of ICI on a national scale. In this population-based cohort, 9.5% of all patients with advanced melanoma had preexisting AID. This was higher than the estimated 7.6% to 9.4% described in non-oncologic studies in their national registry. They found that tumour response as well as incidence of irAEs following ICI treatment for advanced melanoma were similar in patients with and without pre-existing AID of rheumatologic or endocrine origin in daily clinical practice. Although it was found that AID does not appear to be a contraindication to ICI in melanoma it was emphasised that preexisting IBD did lead to earlier discontinuation of ICI due to the severity of the colitis. They were also unable to find evidence that prior treatment of the AID had an influence on outcome. This was noted as a prior study had reported reduced survival of patients treated with anti-TNF for their AID. It was also considered that their findings on safety of ICI in patients with advanced melanoma and AID might be translatable to patients with other solid tumours. They conclude that physicians should not withhold ICI in most common AIDs.

Reference: Ann Intern Med 2021 May;174(5):641-648
Abstract

Randomized phase II trial of lymphodepletion plus adoptive cell transfer of tumor-infiltrating lymphocytes, with or without dendritic cell vaccination, in patients with metastatic melanoma

Authors: Saberian C, et al

Summary: The investigators tested the combination of tumour-infiltrating lymphocytes (TIL) and dendritic cells (DCs) in patients with advanced stage IV melanoma. HLA-A0201 patients whose early TIL cultures demonstrated reactivity to melanoma antigen recognised by T cells 1 (MART-1) peptide were randomly assigned to receive TIL alone (n =10) or TIL+DC (n = 8) pulsed with MART-1 peptide. Infused MART-1 reactive $CD8^+$ TIL were tracked in the blood over time and results showed good persistence in both arms, with no difference in the persistence of MART-1 between the two arms. They noted objective response rate was 30% in the TIL arm and 50% in the TIL+DC arm. The treatments were well tolerated.

Comment: The trial design used in this study was based on prior mouse modeling demonstrating that DC co-vaccination with adoptive transfer of anti-tumour T cells provided superior tumour control and persistence of anti-tumour T cells. The tumour antigen in that study was gp100. In translating this to the clinic they did not observe a significantly improved persistence of the MART-1 recognising TIL that they infused. Several possible reasons for this were discussed e.g., the design of the clinical trial involved DC infusion 4 hours after TIL infusion, which is different to the mouse studies where DC were infused immediately after T cells. It is possible that within 2 hours after infusion a large proportion of the TIL localised to the lungs, spleen, and liver and were not available to be restimulated by the DC. Other key differences included the source of the DCs (bone marrow derived, or monocyte derived), the DC maturation method, and the number of target antigen-specific T cells in the infusion product (very variable in patients, and as low as 0.1%, but 100% in mouse model). They considered the most important difference was the status of differentiation of the antitumour T cells used, as mouse models use peripherally (spleen or lymph nodes) derived T cells which contain a large fraction of naïve T cells whereas human TIL are effector memory cells with high expression of checkpoint molecules from chronic stimulation. They also, in retrospect, considered that MART-1 may not have been the optimal antigen to use for a DC co-vaccine approach. The clinical response was numerically higher in TIL+DC arm (4/8, 50%) compared with TIL arm (3/10, 30%), but the study was not powered to detect statistical significance between the two arms.

They conclude the addition of a DC vaccine targeting a single tumour antigen to the TIL therapy regimen may not be warranted. Multiantigen DC co-vaccination approaches have shown early signs of efficacy and are worth pursuing.

Reference: J Immunother Cancer 2021 May;9(5):e002449
Abstract

Predicting anti-PD-1 responders in malignant melanoma from the frequency of S100A9+ monocytes in the blood

Authors: Rad Pour S, et al

Summary: To identify potential predictive markers for response to anti-PD-1 researchers conducted single-cell RNA sequencing analyses of peripheral blood mononuclear cells (PBMC) (n=8), as well as an in-depth immune monitoring study (n=20) by flow cytometry in patients with advanced melanoma undergoing treatment with nivolumab. Blood samples were collected before the start of treatment and at the time of the second dose. RNA sequencing showed that a higher frequency of monocytes and a lower ratio of $CD4^+$ T cells to monocyte were inversely associated with OS. Moreover, S100A9 expression in the monocytic subset was correlated inversely with OS. They confirmed the results in an independent patient cohort.

Comment: The basis for this study is the need for biomarkers to identify patients who are likely to respond to treatment with anti-PD-1. The literature on this subject is now very expansive and mostly focused on tumour related biomarkers such as PDL-1 expression, tumour mutational load, T cell infiltration and various tumour gene signatures. There remains a need however for tests based on peripheral blood that is relatively easy to access. This study has focused on monocytes which has been the subject of a number of prior publications such as the Nature article by Kreig et al. Those authors also used single cell analysis and found that patients with pretreatment high levels of activated classical monocytes had higher responses to anti-PD-1. The present study was only on 8 patients treated with nivolumab. 4 were considered responders and 4 as non-responders. Non-response was believed to be associated with monocytes that expressed S100 family proteins S100A8 and S100A9. The results were validated in 9 patients with short PFS compared to 11 patients with long PFS (> 6 months). The number of $CD4^+$ T cells were also associated with responses. This article is difficult to read but it seems that there is considerable interest in the S100 Ca^{2+} binding proteins as targets for drug development in cancers and inflammatory diseases. Given this, it is probably a case of watch this space.

Reference: J Immunother Cancer 2021 May;9(5):e002171
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.

Phase 1 trial of ADI-PEG20 plus cisplatin in patients with pretreated metastatic melanoma or other advanced solid malignancies

Authors: Yao S, et al

Summary: This single-centre, phase 1 trial assessed the safety and tolerability of arginine deiminase pegylated with 20,000-molecular-weight polyethylene glycol (ADI-PEG20). The study cohort included 99 patients with metastatic argininosuccinate synthetase 1 (ASS1) deficient malignancies. The authors reported no dose-limiting toxic effects or treatment-related mortality. Three percent of patients discontinued treatment because of toxicity. After treatment, 5% of patients had partial responses, and 41% had stable disease. The median PFS and OS durations were 3.62 and 8.06 months, respectively. Tumour responses were associated with anti-ADI-PEG20 antibody levels at weeks 8 and 16. They noted substantial arginine depletion and citrulline escalation persisted in most patients through weeks 24 and 8, respectively.

Comment: The basis for this study is explained in their opening paragraph - arginine is a semi-essential amino acid involved in the regulation of numerous cellular processes like cell signalling, proliferation (by modulating polyamine and nucleotide synthesis), vasodilatation (via nitric oxide) and hormone synthesis. Arginine also plays a crucial role in immune-system regulation. Most normal human cells synthesise arginine from citrulline via two key enzymes, ASS1 and argininosuccinate lyase. However, some cancer cells, such as those in melanoma are deficient in the necessary enzymatic pathways and must instead obtain arginine from the blood to grow and survive. Therefore, in patients with arginine-dependent tumours, depleting arginine from the blood can control tumour growth and even eliminate arginine-requiring cancers without damaging normal cells.

The treatment product was arginase deaminase that degrades dietary arginine combined with polyethylene glycol. The patients included 24 patients with cutaneous melanoma and 13 with uveal melanoma. Liver cancer and ovarian cancer were also included. Patients had failed line 1 and 2 treatments. ASS1 deficiency was also an entry criteria. Stable responses were seen in 6 patients in each melanoma group. Patients received at least 1 dose and arginine levels were reduced to below 10% of pretreatment levels. Efficacy is hard to assess from this article. They conclude "Our preliminary clinical findings demonstrate that further evaluation of treatment with ADI-PEG20 plus cisplatin and the use of an anti-ADI-PEG20 antibody as a potential marker for antitumour efficacy is warranted in patients with metastatic melanoma and many other ASS1-deficient malignancies."

Reference: Br J Cancer 2021 Apr;124(9):1533-1539
Abstract

Neoadjuvant ipilimumab plus nivolumab in synchronous clinical stage III melanoma

Authors: Versluis JM, et al

Summary: The study cohort comprised of seven patients with synchronous clinical stage III melanoma identified from neoadjuvant trials of ipilimumab plus nivolumab. The investigators found six patients had a concordant response in primary site melanoma lesions or in-transit metastasis and the lymph node metastases. One patient had concordant progression in both the primary and nodal tumour lesions and developed stage IV disease during neoadjuvant treatment and therefore no resection was performed.

Comment: As stated in the introduction of this paper, patients who present with synchronous lymph node metastases with primary melanoma have inferior survival compared to those with metachronous lymph node metastases or with lymph node metastases and unknown primary. Recent neoadjuvant trials have often excluded patients who present with synchronous non-nodal locoregional melanoma lesions, such as primary melanoma, locally recurrent melanoma or in-transit metastases or have required surgery to these melanoma lesions before neoadjuvant therapy. Although the patient numbers were small (7) concordant responses at these sites were found with 4 showing partial or complete responses at all sites and 2 patients showing progression at all sites. A 7th patient was unevaluable due to progression. This study again draws attention to the impressive results being achieved with neoadjuvant immunotherapy with anti-PD-1 and anti-CTLA-4. Their summary states " Considering the high response rates previously shown in lymph nodes of stage III melanoma, one may consider postponing the resection of the primary site melanoma lesion until lymph node dissection following neoadjuvant treatment. Future trials investigating neoadjuvant immunotherapy in stage III melanoma should not exclude patients with synchronous primary melanoma or in-transit metastases."

Reference: Eur J Cancer 2021 May;148:51-57
Abstract

Immune adverse events (irAEs) with adjuvant ipilimumab in melanoma, use of immunosuppressants and association with outcome: ECOG-ACRIN E1609 study analysis

Authors: Tarhini AA, et al

Summary: The E1609 trial enrolled patients with resected high-risk melanoma and evaluated adjuvant ipilimumab 3 mg/kg (ipi3) and 10 mg/kg (ipi10) versus interferon-α. The association of irAEs and of use of immunosuppressants with RFS and OS (n=1,034) was also investigated. The authors reported occurrence of grades 1-2 irAEs was associated with RFS (5 years: 52% vs 41% with no AE; p=0.006) and a trend toward improved OS (5 years: 75% compared with 67% with no AE; p=0.064). They noted the most significant associations were seen for grades 1-2 rash with RFS (p<0.001, HR=0.70) and OS (p=0.01, HR=0.71) and for grades 1-2 endocrine+rash with RFS (p<0.001, HR=0.66) and OS (p=0.008, HR=0.7). Overall, grades 1-2 irAEs had the best prognosis in terms of RFS and OS and those with grades 3-4 had less RFS benefits and no OS advantage over no irAE. The authors also found patients experiencing grades 3-4 irAE had significantly higher exposure to corticosteroids and immunosuppressants than those with grades 1-2 (92% vs 60%; p<0.001), but no significant associations were found between corticosteroid and immunosuppressant use and RFS or OS.

Comment: North American Intergroup trial E1609 tested ipi3 and ipi10 as adjuvant therapy compared with high-dose interferon-α (HDI) and demonstrated significant improvement in OS with ipi3 compared with HDI and less toxicity with ipi3 compared with ipi10. This follow-up study investigated the differential impact of varying irAE grades on patient outcome. Patients with grades 1–2 irAEs had the best prognosis in terms of RFS and OS and those with grades 3–4 had less RFS benefit and no OS advantage over no irAE. These observations questioned whether high-dose corticosteroids and other immunosuppressants that were primarily initiated during the ipilimumab induction phase in response to grades 3–4 toxicities had a negative impact on survival in this adjuvant setting. If so, then investigation of adaptive strategies to minimise the use of corticosteroids and other immunosuppressants appear warranted. In terms of individual toxicities, rash followed by endocrinopathy provided the most significant associations. The authors conclude by emphasising the need to identify predictors of risk that might alert clinicians to possible high grade irAEs e.g., certain MHC antigens identify patients who have a 10-fold risk of diabetes. Patients with other MHC antigens have a 3-fold risk of hepatitis. Reference is also made to previous studies showing that combinations of ipilimumab with GM-CSF appeared to have reduced irAEs. The results of this analysis still appear relevant to ongoing studies with regimes that include ipilimumab.

Reference: J Immunother Cancer 2021 May;9(5):e002535
Abstract

