Immuno-Oncology RESEARCH REVIEW™

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Issue 8 – 2022

In this issue:

Abbreviations used in this issue

CR/PR = complete/partial response
CRC = colorectal cancer
DFS = disease-free survival
HR = hazard ratio
ICI = immune checkpoint inhibitor/inhibition
MCC = Merkel cell carcinoma
MSI = microsatellite instability
ORR = objective/overall response rate
OS = overall survival
PD-1/PD-L1 = programmed cell death (ligand)-1
PFS = progression-free survival
QOL = quality of life
RCC = renal cell carcinoma
SBRT = stereotactic body radiotherapy
SCC = squamous cell carcinoma
SCLC = small-cell lung cancer

Welcome to issue 8 of Immuno-Oncology Research Review.

We begin this issue with the results of a phase 3 placebo-controlled randomised trial of the PD-1 inhibitor serplulimab plus chemotherapy as first-line treatment in patients with extensive-stage SCLC. From the N Engl J Med, we have a pilot study of neoadjuvant cemiplimab for patients with resectable stage II, III or IV (M0) cutaneous SCC. We have included reports from two trials of good activity with PD-1 inhibitors as monotherapy or in combination with ipilimumab in MSI-high/mismatch repair-deficient CRC and non-CRCs. The issue concludes with two studies reporting on the risk of major adverse CV events associated with ICI use.

We appreciate your comments and feedback, as they help us identify research to review that will be of greatest relevance to you, so please keep sending them.

Kind regards,

Dr Ahmed Kolkeila
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Effect of first-line serplulimab vs placebo added to chemotherapy on survival in patients with extensive-stage small cell lung cancer

Authors: Cheng Y et al. for the ASTRUM-005 Study Group

Summary: The phase 3 ASTRUM-005 trial randomised patients (17.8% female) with systemic therapy-naïve extensive-stage SCLC to receive intravenous serplulimab 4.5 mg/kg (n=389) or placebo (n=196) every 3 weeks, along with intravenous carboplatin and etoposide every 3 weeks for ≤12 weeks; 42.1% of participants completed the trial and 79.5% discontinued study treatment. There was a median 12.3 months of follow-up at data cutoff for this interim analysis, at which time serplulimab was associated with a longer median OS duration (primary endpoint) compared with placebo (15.4 vs. 10.9 months; HR 0.63 [95% CI 0.49, 0.82]) as well as a longer median PFS duration (5.7 vs. 4.3 months; 0.48 [0.38, 0.59]). The incidence of grade ≥3 treatment-related adverse events in the respective serplulimab and placebo arms were 33.2% and 27.6%.

Comment: The ASTRUM-005 trial results of improved survival in extensive-stage SCLC confirm the efficacy of a further anti-PD-1 ICI in combination with platinum-based chemotherapy in the first-line setting. Previously reported randomised phase 3 trials (Impower-133, CASPIAN, KEYNOTE-604) have also demonstrated survival gains with the addition of atezolizumab, durvalumab or pembrolizumab to platinum chemotherapy, respectively, in the first-line setting (noting that KEYNOTE-604 demonstrated a significant benefit with pembrolizumab in regard to PFS but only a trend towards a OS benefit). Despite these modest gains, OS outcomes in extensive-stage SCLC remain poor, with only a smaller proportion of patients achieving durable tumour control: 2-year OS of 22% vs. 14% in the CASPIAN trial, and 18-month OS of 34% vs. 21% in the Impower-133 trial. There does not appear to be significant survival benefit with the addition of a CTLA-4 inhibitor as demonstrated in a subset of patients in the CASPIAN trial. Based on the negative results from CheckMate-451 with maintenance nivolumab versus placebo following induction chemotherapy in patients who achieve stable or responsive disease, it appears preferable to commence ICI plus platinum chemotherapy at the start of first-line therapy.

Reference: JAMA 2022;328:1223–32
Abstract

Independent commentary by Dr Alvin Tan

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Dr Alvin Tan is a consultant medical oncologist at Waikato Hospital, and also practices in private at SalutisCare. He completed his Bachelor of Medicine and Surgery at the University of Otago, Dunedin. He is the primary site investigator for a number of clinical trials being conducted at Waikato Hospital. He is a past participant of the 2016 Australia & Asia Pacific Clinical Oncology Research Development (ACORD) Workshop. He is a graduate of the 2019 ESMO Leaders Generation Programme Asia and currently serves as a member on the ESMO Practising Oncologist Working Group Committee (2021). He is the current Head of Department for Medical Oncology at Waikato Hospital and the current Deputy Chair of the Aotearoa New Zealand Advanced Training Subcommittee for Medical Oncology for the Royal Australasian College of Physicians.

Combined nivolumab and ipilimumab with or without stereotactic body radiation therapy for advanced Merkel cell carcinoma

Authors: Kim S et al.

Summary: Adults with advanced MCC (Merkel cell carcinoma) were randomised to receive combination intravenous nivolumab 240mg every 2 weeks plus ipilimumab 1 mg/kg every 6 weeks with (n=25) or without (n=25) SBRT 24Gy delivered in three fractions at week 2 in this open-label-phase 2 trial; one participant assigned to the SBRT arm did not receive this due to excess toxicity concerns, and two were not evaluable for the primary endpoint analysis. After a median 14.6 months of follow-up, the ORR (primary endpoint) for evaluable ICI-naive participants (n=22) was 100%, including CRs in 41%, whereas for those with prior ICI exposure (n=26), the ORR was 31%, including CRs in 15%. The ORR did not differ significantly for the non-SBRT versus SBRT arm (72% vs. 52% [p=0.26]). The incidences of grade 3–4 treatment-related adverse events in the respective non-SBRT and SBRT arms were 40% and 32%.

Comment: Monotherapy with PD-1 or PD-L1 inhibitors in advanced MCC is associated with a high ORR and potential for durable control. In the JAVELIN Merkel 200 trial utilising avelumab, the 2-year OS in cohort A patients (n=88 patients, at least one prior line of systemic treatment) was 33%. The ORR was 33% (CR of 11%). In cohort B patients (n=29, no prior systemic treatment), the ORR was 62% with durable response for at least 6 months seen in 83% of patients who responded to treatment. In the CITN-09/KEYNOTE-017 trial, pembrolizumab monotherapy in patients with advanced MCC naïve to systemic treatment was associated with an ORR of 56% (with CR in 24%). The 2-year OS was 68.7%. Whilst the above nivolumab-ipilimumab phase 2 trial did not have a comparator monotherapy arm, the observed ORR of 100% in treatment-naïve patients with a 41% CR rate is noteworthy. The addition of ipilimumab with an ORR of 31% in refractory disease following first-line ICI appears to be a reasonable option in advanced MCC. Median follow-up in this trial remains relatively short at 14.6 months at present, and it would be interesting to note if durable responses and control are seen in the treatment-naïve group as well as the refractory patients who responded to salvage ipilimumab.

Reference: Lancet 2022;400:1008–19
Abstract

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Adjuvant atezolizumab versus placebo for patients with renal cell carcinoma at increased risk of recurrence following resection (IMmotion010)

Authors: Pal SK et al.

Summary: In the phase 3 IMmotion010 trial, patients with RCC with a clear-cell or sarcomatoid component who were at increased risk of recurrence were randomised to receive intravenous atezolizumab 1200mg (n=390) or placebo (n=388) every 3 weeks for 16 cycles or 1 year. At data cutoff for the primary analysis, with a median 44.7 months of follow-up, there was no significant difference between the atezolizumab versus placebo arm for median DFS duration (primary endpoint; 57.2 vs. 49.5 months [p=0.50]). The most frequently recorded grade 3–4 adverse events were hypertension (2% and 4% for the atezolizumab and placebo arms, respectively), hyperglycaemia (3% and 2%) and diarrhoea (1% and 2%), and the respective incidences of serious adverse events were 18% and 12%; no treatment-related deaths were recorded.

Comment: Similar to the CheckMate-914 trial, the IMmotion010 trial did not demonstrate any improvement in DFS with adjuvant atezolizumab (versus placebo) in patients with resected high-risk RCC. The CheckMate-914 trial assessed adjuvant nivolumab-ipilimumab (versus placebo) in resected high-risk RCC, although it was worth noting that 43% of patients discontinued combination treatment, the majority due to side effects in the CheckMate trial. In contrast to these two trials, the 30-month update of the KEYNOTE-564 trial demonstrated continued recurrence-free survival gains of 75.2% vs. 65.5% (local recurrence rates of 3.8% vs. 7.6%, and distant metastasis-free survival of 77.3% vs. 68.8%) in patients treated with adjuvant pembrolizumab (versus placebo) in high-risk resected RCC. This trial did include 4% of patients with resected stage IV disease, and whilst making up a small percentage of the total trial population, there appeared to be a strong trend of benefit in this subgroup. Due to overall low event rates and potential censoring bias, we continue to monitor and await mature OS results from the KEYNOTE-564 trial. Given the two recent negative trials and the absence of significant OS as yet with adjuvant pembrolizumab, adjuvant ICI in resected high-risk disease may not be ready for primetime at this stage.

Reference: Lancet 2022;400:1103–16
Abstract

Pembrolizumab versus placebo as adjuvant therapy in resected stage IIB or IIC melanoma (KEYNOTE-716)

Authors: Long GV et al., on behalf of the KEYNOTE-716 Investigators

Summary: The phase 3 KEYNOTE-716 trial randomised patients aged ≥12 years with newly diagnosed, completely resected stage IIB or IIC melanoma to receive intravenous pembrolizumab 200mg or 2 mg/kg in paediatric patients (n=487) or placebo (n=489) every 3 weeks for 17 cycles or until disease recurrence or unacceptable toxicity; distant metastasis-free survival results were reported in this analysis, for which the median follow-up duration was 27.4 months. Compared with placebo, pembrolizumab was associated with significantly improved distant metastasis-free survival (HR 0.64 [95% CI 0.47, 0.88]), even though the median duration had not been reached in either arm, as well as a lower risk of recurrence (HR 0.64 [0.50, 0.84]). The most common grade ≥3 adverse events were hypertension (3% and 4% in the pembrolizumab and placebo arms, respectively), diarrhoea (2% and <1%), rash (1% and <1%), autoimmune hepatitis (1% and <1%) and increased lipase level (1% and 2%), and the respective incidences of serious treatment-related adverse events were 10% and 2%; there were no treatment-related deaths recorded.

Comment: As previously reported, the KEYNOTE-054 (pembrolizumab) and CheckMate-238 (nivolumab) trials established improved relapse-free survival and distant metastasis-free survival in stage III and resected stage IV disease with adjuvant PD-1 inhibitors. The KEYNOTE-716 trial was the first to assess the efficacy of adjuvant PD-1 inhibition in high-risk stage II melanoma. In the KEYNOTE-716 trial, 12 months of adjuvant pembrolizumab was associated with a significant reduction in the risk of disease recurrence or death (12-month relapse-free survival 90.5% vs. 83.1%; HR 0.65) with fewer distant recurrences (4.7% vs. 7.8%; HR 0.64). Trial follow-up remains short at this stage (<24 months), and any OS benefit will take time for the results to mature. It is worth noting that 19% of patients in the pembrolizumab arm received long-term hormonal therapy for the management of endocrine toxicities (mainly hypothyroidism). In the absence of proven OS benefit, a balanced discussion is needed with regards to reducing the risk of melanoma recurrence and offsetting the financial costs and potential long-term immune-mediated side effects of treatment. In the similar phase 2 IMMUNED trial (Lancet 2022;400:1117–29), the combination of adjuvant nivolumab and ipilimumab demonstrated improved recurrence-free survival and OS in resected stage IV melanoma; however, there was a significant increase in grade 3–4 treatment-related adverse events (71%) in this trial, which needs to be considered when counselling for its use in the adjuvant setting over ICI monotherapy or close surveillance with salvage ICI therapy options.

Reference: Lancet Oncol 2022;23:1378–88
Abstract

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Neoadjuvant cemiplimab for stage II to IV cutaneous squamous-cell carcinoma

Authors: Gross ND et al.

Summary: Seventy-nine patients with resectable stage II–IV (M0) cutaneous SCC, mostly located on the head and neck, received ≤4 doses of open-label cemiplimab 350mg every 3 weeks followed by curative-intent surgery in this phase 2 trial. The pathological CR rate was 51% and the pathological major response rate was 51% on independent review, with similar results by investigator assessment. The ORR on imaging was 68%. The incidence of any-grade adverse events was 87% with a grade ≥3 incidence of 18%.

Comment: The evidence for systemic chemotherapy for advanced cutaneous SCC remains limited, with cisplatin-based combinations appearing to be the most active regimens. Whilst cutaneous SCC appears to be chemoresponsive, duration of response generally remains short. Advanced cutaneous SCC occurs commonly in elderly patients who may have underlying comorbidities, which could preclude cisplatin chemotherapy use, and surgical resection of advanced disease may be associated with significant morbidity. A number of phase 1 and 2 trials (Migden et al., KEYNOTE-629) demonstrated ORRs of 30–50% in both the first- and second-line settings in patients with unresectable cutaneous SCC treated with ICIs. In the neoadjuvant trial above, the pathological CR plus major response rate of 63.3% exceeded trial assumptions of a pathological CR rate of 25%. We will need longer term follow-up of these patients who achieved pathological CR or major response with regards to DFS, but a neoadjuvant approach could spare potentially elderly patients from the morbidity of extensive surgery. From the KEYNOTE-629 trial, it appears that PD-L1 expression predicts for a better and more durable response to ICIs, and it is worth noting that PD-L1 expression levels appear to be increased in metastatic cutaneous SCC (upwards of 50% in a number of retrospective series).

Reference: N Engl J Med 2022;387:1557–68
Abstract

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First-line avelumab for patients with PD-L1-positive metastatic or locally advanced urothelial cancer who are unfit for cisplatin

Authors: Iacovelli R et al.

Summary: Patients with metastatic urothelial cancer (73.2% with bladder cancer as the primary tumour; 23.5% with liver metastases) ineligible for cisplatin-based chemotherapy and with PD-L1 expression ≥5% (n=71) were treated with avelumab as first-line therapy in this trial. The median OS duration was 10.0 months with 43% of participants alive at 1 year, and the respective CR and PR rates were 8.5% and 15.5%. The incidences of any- and high-grade adverse events were 49.3% and 8.5%, respectively; the only high-grade treatment-related adverse event was a grade 3 infusion reaction. There were no deaths attributed to the study treatment.

Comment: In patients who are unfit or ineligible for cisplatin chemotherapy, response rates to several different ICIs range from 20% to 40% in the first-line setting (KEYNOTE-052 – pembrolizumab; IMvigor 210 – atezolizumab), with higher response rates seen in patients with greater PD-L1 expression. The ARIES trial confirmed the efficacy of a further ICI in the first-line setting for advanced urothelial cancer in patients who are ineligible for platinum-based chemotherapy, noting a 1-year survival of 43%. In patients who are eligible for platinum chemotherapy, the JAVELIN Bladder trial demonstrated improved OS with maintenance avelumab (versus surveillance) following 4–6 cycles of induction platinum chemotherapy with 1-year survival 71% vs. 58% (HR 0.69). However, further trials utilising ICIs in combination with induction chemotherapy did not demonstrate any significant survival benefit with upfront combination treatment.

Reference: Ann Oncol 2022;33:1179–85
Abstract

Pembrolizumab in microsatellite instability high or mismatch repair deficient cancers

Authors: Maio M et al.

Summary: This updated analysis from the phase 2 KEYNOTE-158 study reported safety and efficacy outcomes after a median 37.5 months of follow-up for the study cohort of 351 participants with previously treated advanced MSI-high/mismatch repair-deficient non-CRCs (mostly endometrial [22.5%], gastric [14.5%] and small intestine [7.4%]) who had received pembrolizumab 200mg every 3 weeks for 35 cycles or until disease progression or unacceptable toxicity. For 321 efficacy-evaluable participants, the ORR was 30.8% with a median response duration of 47.5 months, and the respective median PFS and OS durations were 3.5 months and 20.1 months. The incidence of treatment-related adverse events was 64.7%, with a grade 3–4 incidence of 11.1% and a grade 5 incidence of 0.9% (myocarditis, pneumonia and Guillain-Barré syndrome).

Reference: Ann Oncol 2022;33:929–38
Abstract

Nivolumab plus low-dose ipilimumab in previously treated patients with microsatellite instability-high/mismatch repair-deficient metastatic colorectal cancer

Authors: André T et al.

Summary: Four-year follow-up from the CheckMate-142 trial was reported for the cohort of 119 participants with pretreated MSI-high/mismatch repair-deficient metastatic CRC who received nivolumab 3 mg/kg plus ipilimumab 3 mg/kg every 2 weeks until disease progression. After an additional 3 years of follow-up since the 1-year follow-up, the ORR had increased from 55% to 65% and the CR rate had increased from 3% to 13%. The disease control rate was 81% including 52% with a PR. Median response, PFS and OS durations were not reached. The safety profile was consistent with previous reports.

Reference: Ann Oncol 2022;33:1052–60
Abstract

Comment: Both trials above utilising a PD-1 inhibitor as monotherapy or in combination with ipilimumab have demonstrated good activity in patients with MSI-high/mismatch repair-deficient CRC and non-CRCs who have had prior lines of systemic therapy. It is worth noting that 13% of the patients did discontinue treatment in the CheckMate-142 trial; however, the rate of grade 3–4 treatment-related adverse events was not unexpected at 32% and is comparable with similar trials utilising this combination. In the first-line setting of MSI-high/mismatch repair-deficient colon cancer, KEYNOTE-177 has demonstrated improved PFS and a trend towards OS (median not reached vs. 36.7 months) in patients treated with pembrolizumab versus chemotherapy. The high crossover rate (60%) of patients in this trial is likely to have contributed to the nonsignificance in OS. Given the activity of ICIs in first-line treatment in MSI-high/mismatch repair-deficient colon cancer, and the efficacy of ICIs in second-line treatment for both colon and non-colon cancers, it may be reasonable to consider ICI use in the first-line setting for MSI-high/mismatch repair-deficient non-CRCs.

Persistent immune-related adverse events after cessation of checkpoint inhibitor therapy: prevalence and impact on patients' health-related quality of life

Authors: Schulz TU et al.

Summary: This cross-sectional study compared persistent immune-related adverse events and their impact on participants' lives for 200 patients with cancer ≥12 weeks after ICI cessation with those for 2705 patients with autoimmune diseases. The respective incidences of long-term and chronic immune-related adverse events in an outpatient ICI cohort of 147 patients (as an approximation of outpatients from German skin cancer centres) were 51.9% and 35.5%, including arthralgia (16.7% and 16.1%), myalgia (13.0% and 14.0%), hypothyroidism (11.1% and 10.8%), xerostomia (7.4% and 8.6%), vitiligo (13.0% and 7.5%) and hypophysitis (9.3% and 7.5%). Compared with ICI recipients without long-term or chronic immune-related adverse events, those with such events reportedly had clinically significantly worse health-related QOL. Clinically significant reductions in health-related QOL scores due to chronic immune-related adverse events were confirmed by multiple linear regression analyses. ICI patients with chronic immune-related adverse events had similar health-related QOL, burden of autoimmune symptoms and burden of respective therapies as patients with nonexacerbated autoimmune diseases. Patients with chronic immune-related adverse events reported feeling significantly less informed regarding adverse effects than those without chronic immune-related adverse events.

Comment: As ICIs become an integral backbone of systemic treatment for multiple malignancies, their increasing use and associated immune-related side effects (acute and long-term) will need to be considered in daily clinical practice. This is important when considering survivorship issues, particularly when treatment may be used in the adjuvant setting, with patients having long been discharged from the oncology clinic following completion of their adjuvant therapy. Long-term endocrine replacement (e.g. thyroxine) is reported in up to 10–15% of patients who are treated with an ICI. QOL measures have also demonstrated poorer outcomes in patients who do eventually develop long-term effects from their ICI. This should form part of our discussion and counselling of patients, particularly in the (neo)adjuvant setting for early-stage cancers that may have good long-term prognosis.

Reference: Eur J Cancer 2022;176:88–99
Abstract

Nivolumab plus ipilimumab plus cabozantinib triplet combination for patients with previously untreated advanced renal cell carcinoma

Authors: Apolo AB et al.

Summary: This was an exploratory analysis of the prematurely terminated CheckMate-9ER phase 3 randomised trial, in which 50 patients with advanced RCC received four cycles of nivolumab 3 mg/kg and ipilimumab 1 mg/kg every 3 weeks along with cabozantinib 40mg once daily, then nivolumab 240mg every 2 weeks plus cabozantinib 40mg once daily. After a median 39.1 months of follow-up, the respective median PFS durations by blinded independent central review and investigator assessment were 9.9 and 13.9 months, and the respective ORRs were 44.0% (8.0% CRs) and 48.0% (all PRs); median OS duration was 37.0 months. The incidence of grade 3–4 treatment-related adverse events was 84.0% (with no grade 5 events), mostly hepatotoxicity and aminotransferase level elevations; the incidence of grade 3–4 hepatic immune-mediated adverse events was 40.0%.

Comment: In the CheckMate-9ER trial, the triplet combination of nivolumab, ipilimumab and cabozantinib demonstrated an ORR of 44%, although hepatitis immune-mediated adverse events occurred in 40% of patients (mainly asymptomatic). It's worth noting that the ORR with nivolumab and cabozantinib in the final analysis of the CheckMate-9ER trial was 55%; however, as accrual to the triplet arm was discontinued early, further comparisons between these two arms cannot be made. The results from the COSMIC 313 trial were recently presented at ESMO 2022, which demonstrated improved PFS (HR 0.73) and ORR (40.3% vs. 36%) with the triplet combination of nivolumab, ipilimumab and cabozantinib versus nivolumab, ipilimumab and placebo in patients with intermediate-high risk disease. In subgroup analysis, the reported PFS benefit appears to be limited to patients with intermediate risk disease (HR 0.63), which made up 75% of the study population. OS is yet to be reported. Treatment was discontinued in 12% vs. 5% of patients. Although the triplet combination arm of CheckMate-9ER was discontinued early, there did not appear to be significant improvements in response rates over that of the nivolumab-cabozantinib combination. In the absence of an OS difference and the increased rates of toxicity with triplet therapy, a doublet combination of an ICI and VEGF inhibitor or dual ICI-ICI remains the standard options in the first-line setting for intermediate to high-risk disease in advanced clear-cell RCC.

Reference: Eur J Cancer 2022;177:63–71
Abstract

Incidence of cardiovascular events in patients treated with immune checkpoint inhibitors

Authors: Laenens D et al.

Summary: These researchers reported the incidence of and risk factors for major adverse CV events for a real-life cohort of 672 patients who received ICIs for cancer, with incidence rates in these patients compared with other patients with cancer not treated with ICIs and population controls. During a median 13 months of follow-up, the major adverse CV events incidence was 10.3%, with the risk significantly increased in patients with a history of heart failure and valvular heart disease (respective HRs 2.27 [95% CI 1.03, 5.04] and 3.01 [1.05, 8.66]). ICI recipients were also found to have higher cumulative incidence rates then patients with cancer not treated with ICIs and the population controls, which was driven by a higher risk of heart failure events.

Reference: J Clin Oncol 2022;40:3430–8
Abstract

Major adverse cardiac events with immune checkpoint inhibitors

Authors: Naqash AR et al.

Summary: Major adverse CV events and their associations with noncardiac immune-related adverse events were assessed for a retrospective cohort of 6925 ICI recipients entered in investigational clinical trials sponsored by the US National Cancer Institute – Cancer Therapy Evaluation Program; 48% of the participants had received single-agent anti-PD-(L)1 therapy. The incidence of ICI-related major adverse CV events was 0.6%, 77.5% of which were grade ≥3, with myocarditis accounting for 45%. Concurrent multisystem involvement with other noncardiac immune-related adverse events was recorded for 65% of the participants. There was ≥1 associated noncardiac immune-related adverse event in 83% of those who developed myocarditis. Compared with anti-PD-(L)1 plus anti-CTLA-4 combinations, anti-PD-(L)1 plus targeted therapy combinations were associated with a trend for a greater incidence of major adverse CV events (2.1% vs. 0.9% [p=0.08]), and compared with anti-PD-(L)1 monotherapy, anti-PD-(L)1-based combination therapies were associated with a trend for a greater incidence of myocarditis (0.36% v. 0.15% [p=0.08]). The myocarditis-related mortality rate was 22.5%, with all four affected patients having concurrent myositis.

Reference: J Clin Oncol 2022;40:3439–52
Abstract

Comment: Whilst ICIs are usually well tolerated, serious immune-related side effects are reported in about 15% of patients across multiple randomised trials. Participants in clinical trials are generally healthier with better performance status, and patients with pre-existing autoimmune disease are commonly excluded. However, the use of ICIs is commonly used in daily clinical practice, even in patients with autoimmune diseases, although careful monitoring is required. One of the rarer but now well recognised effects of ICIs is that of cardiotoxicity, and this is well illustrated in the two trials with patient populations taken from the real world. Whilst real-world patients are likely to have a higher prevalence of underlying CV disease, which increases the risk of cardiotoxicity, the cumulative incidence rates of CV events were significantly higher in the ICI groups compared with cancer patients not exposed to ICIs or population controls. Myocarditis with ICIs typically can occur early and needs to be considered in the differential in patients presenting with cardiac symptoms who are being treated with ICIs, and most cases have included prompt treatment with high-dose steroids.

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