Immuno-Oncology RESEARCH REVIEW™

Making Education Easy

Issue 6 – 2022

In this issue:

Abbreviations used in this issue

CRC = colorectal cancer
ECOG = Eastern Cooperative Oncology Group
EFS = event-free survival
HCC = hepatocellular carcinoma
HR = hazard ratio
ICI = immune checkpoint inhibitor
MSI = microsatellite instability
NSCLC = non-small-cell lung cancer
OS = overall survival
PD-1/PD-L1 = programmed cell death (ligand)-1
PFS = progression-free survival
RCC = renal cell carcinoma
RFS = relapse-free survival
SCC = squamous cell carcinoma
TPS = tumour proportion score

Welcome to the sixth issue of Immuno-Oncology Research Review.

This issue begins with a trial reporting that first-line treatment with sintilimab combined with cisplatin plus paclitaxel showed significant survival benefits in patients with advanced or metastatic oesophageal SCC. In other research, patients with stage IIB or IIC melanoma had less disease recurrence and were less likely to die when they received pembrolizumab as adjuvant therapy for ~1 year. After a few studies in patients with lung cancer, we turn our attention to advanced RCC and the long-term outcomes of the CheckMate-214 trial of nivolumab plus ipilimumab versus sunitinib. It is then the turn of two HCC studies: lenvatinib with/without ICIs in the real world, and long-term outcomes with pembrolizumab from KEYNOTE-224. Two other KEYNOTE trials of pembrolizumab conclude this issue, namely KEYNOTE-158 (MSI-high advanced endometrial cancer) and KEYNOTE-177 (MSI-high/mismatch repair-deficient metastatic CRC).

Thank you for your comments and feedback – please keep sending them.

Kind regards,

Dr Ahmed Kolkeila
ahmed@researchreviewmena.com

Sintilimab versus placebo in combination with chemotherapy as first line treatment for locally advanced or metastatic oesophageal squamous cell carcinoma (ORIENT-15)

Authors: Lu Z et al., on behalf of the ORIENT-15 study group

Summary: Adults with advanced or metastatic oesophageal SCC who had not received systemic treatment were randomised to receive sintilimab 3 mg/kg if bodyweight was <60kg or 200mg if bodyweight was ≥60kg (n=327) or placebo (n=332) combined with chemotherapy in this phase 3 trial; the initial chemotherapy regimen was cisplatin plus paclitaxel, but a subsequent trial amendment also permitted cisplatin plus 5-fluorouracil, which was ultimately used in 7% of the study participants. An interim analysis revealed that median OS was significantly longer in the sintilimab arm than in the placebo arm (16.7 vs. 12.5 months; HR 0.63 [95% CI 0.51, 0.78]), including the subgroup with a PD-L1 combined positive score of ≥10 (17.2 vs. 13.6 months; 0.64 [0.48, 0.85]), with similar results for median PFS (7.2 vs. 5.7 months; 0.56 [0.46, 0.68] and 8.3 vs. 6.4 months; 0.58 [0.45, 0.75], respectively). The treatment-related adverse event rate was 98% in both study arms, with rates of 60% and 55% for grade ≥3 events in the sintilimab and placebo arms, respectively.

Comment: A number of randomised first-line trials, including KEYNOTE-590 (pembrolizumab plus cisplatin/5-fluorouracil) and CheckMate-648 (nivolumab, ipilimumab, cisplatin/5-fluorouracil), have demonstrated efficacy for PD-1 inhibitors in combination with chemotherapy as first-line treatment for advanced/metastatic oesophageal SCC. In the ORIENT-15 trial, sintilimab (a fully recombinant IgG4 anti-PD-1 monoclonal antibody) was used in combination with cisplatin/paclitaxel or cisplatin/fluorouracil chemotherapy in a predominantly Chinese population. Cisplatin/paclitaxel is more commonly used in China, which accounts for more than half of the global number of patients with oesophageal SCC. The improvements in OS and PFS with sintilimab were found in all patients as well as in those with a PD-1 combined positive score of ≥10.

Reference: BMJ 2022;377:e068714

Abstract

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

Authors: Luke JJ 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. The first interim analysis at median follow-up of 14.3–14.4 months revealed that a lower proportion of pembrolizumab recipients experienced a first disease recurrence or death than placebo recipients (11% vs. 17%; HR 0.65 [95% CI 0.46, 0.92]), with similar findings at the second interim analysis at median follow-up of 20.9 months (15% vs. 24%; 0.61 [0.45, 0.82]); median recurrence-free survival had not been reached in either group at either timepoint. The grade 3–4 treatment-related adverse event rates in the respective pembrolizumab and placebo arms were 16% and 4% at the first interim analysis. There were no deaths related to study treatment.

Comment: Patients with stage IIB and IIC melanoma remain at high risk of disease recurrence. Whilst the KEYNOTE-054 (pembrolizumab) and CheckMate-238 (nivolumab) trials established improved RFS and distant metastases-free survival in stage III and resected stage IV disease with adjuvant PD-1 inhibitors, the KEYNOTE-716 trial is 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 risk of disease recurrence or death (12-month RFS 90.5% vs. 83.1%, HR 0.65) with fewer distant recurrences (4.7% vs. 7.8%). The safety profile of pembrolizumab appears consistent with previous trials, but it is worth noting that 19% of patients in the pembrolizumab arm received long-term hormonal therapy for management of endocrine toxicities (mainly hypothyroidism). Quality of life was maintained with adjuvant pembrolizumab treatment versus placebo. Trial follow-up remains short at this stage (<24 months), and any OS benefit will take time for the results to mature. In the absence of a 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.

Reference: Lancet 2022;399:1718–29
Abstract

Neoadjuvant nivolumab plus chemotherapy in resectable lung cancer

Authors: Forde PM et al., for the CheckMate 816 Investigators

Summary: Patients with stage IB–IIIA resectable NSCLC received platinum-based chemotherapy with or without nivolumab prior to resection in this open-label phase 3 trial; 83.2% and 75.4% of participants from the nivolumab and chemotherapy-only arms underwent surgery. Compared with chemotherapy alone, the addition of nivolumab was associated with a longer median EFS duration (31.6 vs. 20.8 months [p=0.005]) and a greater pathological complete response rate (24.0% vs. 2.2% [p<0.001]), with favourable results for these coprimary endpoints seen across most subgroups. A first prespecified interim analysis revealed a nonsignificantly decreased likelihood of death (HR 0.57 [99.67% CI 0.30, 1.07]). The grade 3–4 treatment-related adverse event rate was 33.5% in the nivolumab arm and 36.9% in the chemotherapy-alone arm.

Comment: In patients with resectable stage IB–IIIA NSCLC lacking driver mutations, the CheckMate-816 trial demonstrated an improved pathological complete response rate (24% vs. 2.2%) in the nivolumab plus platinum-based chemotherapy group (three cycles of platinum doublet) with more patients than those in the control group who underwent surgery (83% vs. 75%). An improved EFS was demonstrated despite a larger proportion of patients who underwent adjuvant chemotherapy (11.9% vs. 22.2%). No significant differences in rates of serious adverse events were demonstrated. Importantly, no significant delays to surgery or surgery-related adverse events were noted with the addition of nivolumab to platinum doublet chemotherapy. At present, neoadjuvant checkpoint inhibitors are not funded in the NZ setting for this indication.

Reference: N Engl J Med 2022;386:1973–85
Abstract

Uptake of adjuvant durvalumab after definitive concurrent chemoradiotherapy for stage III nonsmall-cell lung cancer

Authors: Bryant AK et al., on behalf of the Michigan Radiation Oncology Quality Consortium

Summary: These researchers reported on the uptake of adjuvant durvalumab among 421 real-world patients with stage III NSCLC treated with definitive concurrent chemoradiation. Adjuvant durvalumab was started in 76.5% of the patients, with an increase in the proportion initiating adjuvant durvalumab from 66% early during the 2018–2020 study period to 92% at the end of the study period, and substantial heterogeneity (53–90%) across the 22 treatment centres. A multivariable logistic regression analysis revealed that significant independent predictors of durvalumab initiation were more recent study month (odds ratio per month 1.05 [95% CI 1.02, 1.08]) and ECOG performance status score 0 vs. ≥2 (4.02 [1.67, 9.64]); females were nonsignificantly more likely to initiate durvalumab (1.66 [0.98, 2.82]).

Comment: A recent update of the PACIFIC trial (J Clin Oncol 2022;40:1301–11) demonstrated robust and sustained OS and durable PFS with durvalumab after chemoradiation in stage III NSCLC, with an estimated 43% of patients in the durvalumab arm remaining alive at 5 years and 33% of patients randomly assigned to durvalumab remaining alive and disease-free. We are now fortunate enough to have durvalumab available in NZ in an early access programme with funded access becoming available in August 2022 for patients with stage III NSCLC following chemoradiation. It is noteworthy that whilst uptake of durvalumab in a real-world setting was low to begin, this quickly increased to a significant majority of patients once it became readily available. This would be encouraging in the NZ setting to improve survival outcomes in our lung cancer patients.

Reference: Am J Clin Oncol 2022;45:142–5
Abstract

Independent commentary by Dr Alvin Tan

Alvin is a consultant medical oncologist at Waikato Hospital. He achieved his Bachelor of Medicine and Surgery at the University of Otago, Dunedin, and commenced his advanced Medical Oncology training at Auckland City Hospital where he developed particular interest in genitourinary cancers and participation in oncology clinical trials. He is the primary site investigator for a number of collaborative and industry-funded oncology trials being conducted at Waikato Hospital. He is a past participant of the Australia & Asia Pacific Clinical Oncology Research Development (ACORD) Workshop (2016), a graduate of the ESMO Leaders Generation Programme (2019) and now serves as a member of the ESMO Practising Oncologist Working Group Committee (2021). He is a member of the Waikato Cancer and Blood Research Governance Board, whose main goals are to promote a culture of innovation and quality assurance, supporting research as a core component of clinical practice and being an integral part of the Regional Cancer service.

First-line nivolumab plus ipilimumab versus chemotherapy in patients with unresectable malignant pleural mesothelioma

Authors: Peters S et al.

Summary: Adults with previously untreated, histologically confirmed, unresectable malignant pleural mesothelioma (ECOG performance status score ≤1) were evenly randomised to receive nivolumab 3 mg/kg every 2 weeks plus ipilimumab 1 mg/kg every 6 weeks for ≤2 years or six cycles of platinum plus pemetrexed chemotherapy in the CheckMate-743 trial; this article reported 3-year outcomes (median follow-up, 43.1 months). Compared with chemotherapy, nivolumab plus ipilimumab was associated with longer median OS (18.1 vs. 14.1 months; HR 0.73 [95% CI 0.61, 0.87]) with a higher 3-year OS rate (23% vs. 15%), as well as a higher 3-year PFS rate (14% vs. 1%); however, the objective response rate was not increased (40% vs. 44%). Among 3-year responders, response was ongoing in a greater proportion of the immunotherapy arm (28% vs. 0%). The improvement in survival with nivolumab plus ipilimumab versus chemotherapy was seen across subgroups, including histology, and there appeared to be a correlation between a high four-gene inflammatory signature score and improved survival with nivolumab plus ipilimumab. There were no new safety signals detected among immunotherapy recipients. The median OS among participants who discontinued immunotherapy due to treatment-related adverse events was 25.4 months, and responses were maintained for ≥3 years after discontinuation in 34% of responders.

Comment: At follow-up of at least 3 years, nivolumab plus ipilimumab continued to provide durable and long-term survival benefit versus chemotherapy despite patients being off treatment for more than 12 months. Overall, 23% of patients treated with nivolumab plus ipilimumab were alive at 3 years and 14% remained progression-free. This benefit was seen in both epithelioid and nonepithelioid subgroups, with no new safety issues. In the CONFIRM trial of nivolumab versus placebo in relapsed malignant mesothelioma, there appeared to be an improved survival benefit in patients with an epithelioid subtype, although patient numbers were much smaller in the nonepithelioid subtype (Lancet Oncol 2021;22:1530–40). Neither PD-L1 expression nor tumour mutational burden appears to be predictive of checkpoint inhibition response in malignant mesothelioma.

Reference: Ann Oncol 2022;33:488–99
Abstract

Efficacy and safety of maintenance immune checkpoint inhibitors with or without pemetrexed in advanced non-squamous non-small cell lung cancer

Authors: Gu X et al.

Summary: This retrospective study reported on 120 patients with nonsquamous NSCLC who received maintenance therapy after 4–6 cycles of ICI with (n=82) or without (n=38) pemetrexed as maintenance therapy. No significant difference was seen between ICI monotherapy versus ICI plus pemetrexed for median PFS1 (interval between initiation of treatment and systemic progression/death or last follow-up; 12.00 vs. 12.07 months [p=0.979]), although median PFS1 was shorter with ICI monotherapy for the subgroup with a PD-L1 TPS of <1% (9.50 vs. 14.20 months [p=0.039]) with no significant difference for participants with a PD-L1 TPS of ≥50% or between 1% and 49%. Results for median PFS2 (interval between maintenance treatment initiation and systemic progression/death or last follow-up) were similar to median PFS1. The two groups had similar 2-year survival rates. ICI plus pemetrexed recipients had a significantly higher incidence of fatigue.

Comment: First-line ICIs in combination with chemotherapy have significantly prolonged PFS and OS in patients with advanced nonsquamous NSCLC, and would now ideally be the standard first-line treatment in NSCLC patients without a driver gene mutation. The PARAMOUNT study showed that pemetrexed maintenance could reduce the risk of disease progression following initial platinum/pemetrexed chemotherapy in metastatic NSCLC. ICIs as monotherapy maintenance are common in a number of first-line NSCLC lung trials, in an effort to potentially reduce the toxicities of longer term chemotherapy whilst maintaining efficacy. This retrospective study was designed to compare the maintenance of ICI monotherapy or ICI plus pemetrexed chemotherapy, and the results demonstrated similar efficacy in patients with a PD-L1 TPS >1% and the overall incidence of fatigue was less. The CheckMate-9LA trial (two cycles of chemotherapy plus nivolumab/ipilimumab followed by nivolumab maintenance, although chemotherapy maintenance was allowed) also showed that a shorter course of chemotherapy was possible with durable responses and avoidance of adverse events caused by long-term chemotherapy. In clinical practice, it is therefore reasonable to cease maintenance chemotherapy in patients who develop troubling adverse effects that may impact their quality of life, without significant compromise to survival outcomes, particularly in those with a positive PD-L1 score.

Reference: BMC Cancer 2022;22:576
Abstract

Conditional survival and long-term efficacy with nivolumab plus ipilimumab versus sunitinib in patients with advanced renal cell carcinoma

Authors: Motzer RJ et al.

Summary: Patients with untreated advanced RCC were randomised to receive four cycles of nivolumab 3 mg/kg plus ipilimumab 1 mg/kg every 3 weeks, then four 6-week cycles of either nivolumab monotherapy or sunitinib 50 mg/day in the CheckMate-214 trial. After a median 67.7 months of follow-up, previously reported median OS, PFS and objective response rate benefits with nivolumab plus ipilimumab versus sunitinib were maintained (55.7 vs. 38.4 months, 12.3 vs. 12.3 months, and 39.3% vs. 32.4%, respectively, in an intent-to-treat analysis). Compared with sunitinib, nivolumab plus ipilimumab was associated with higher point estimates for 2-year conditional OS beyond the 3-year landmark (81% vs. 72%; intermediate- to poor-risk participants, 79% vs. 72%; favourable-risk participants, 85% vs. 72%), as were conditional PFS and response point estimates beyond 3 years. Conditional OS point estimates increased or remained steady with nivolumab plus ipilimumab at each subsequent year of survival in participants stratified according to tumour PD-L1 expression, grade ≥3 immune-mediated adverse event experience, BMI and age.

Comment: Although clinical response and survival estimates using standard prognostic models can help individualise therapy regimens (e.g. IMDC risk groups), prognoses may change over time, particularly among patients with a poor outlook according to baseline assessment. Conditional survival estimates survival probability for patients as the length of survival increases in response to treatment and can help provide long-term prognostic information as prespecified survival milestones are reached. In the CheckMate-214 trial, the survival benefits with nivolumab/ipilimumab were largely durable with extended follow-up, regardless of IMDC risk group in metastatic clear-cell RCC patients who respond to treatment, although these results are largely exploratory, given the *post hoc* trial design of this current analysis. It is worth noting that first-line sunitinib also demonstrated durable response and conditional survival estimates of over 70% at the 3-year landmark, although the conditional point estimates seemed to decline with subsequent years. It is encouraging to see that most patients who remain alive or continue to be in response at the 3-year landmark with nivolumab/ipilimumab or VEGF inhibitors will remain alive or in response at 5 years.

Reference: Cancer 2022;128:2085–97
Abstract

Lenvatinib with or without immune checkpoint inhibitors for patients with unresectable hepatocellular carcinoma in real-world clinical practice

Authors: Chen K et al.

Summary: This retrospective study assessed the efficacy and safety of lenvatinib with (n=65) or without (n=45) ICIs in patients with unresectable HCC. Compared with lenvatinib monotherapy, adding ICIs to lenvatinib resulted in significant increases in OS and PFS (respective HRs 0.47 [95% CI 0.26, 0.85] and 0.35 [0.20, 0.63]), as well as higher rates of objective response and disease control (41.5% vs. 20.0% [p=0.023] and 72.3% vs. 46.7% [p=0.009], respectively). There were no treatment-related deaths recorded, and grade ≥3 adverse events affecting ≥10% of participants in either treatment group were hypertension (20.0% and 17.8% of lenvatinib plus ICI and lenvatinib monotherapy recipients, respectively) and palmar-plantar erythrodysaesthesia (10.8% and 4.4%).

Reference: Cancer Immunol Immunother 2022;71:1063–74
Abstract

Updated efficacy and safety of KEYNOTE-224: a phase II study of pembrolizumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib

Authors: Kudo M et al., on behalf of the KEYNOTE-224 Investigators

Summary: This paper reported efficacy and safety findings from the KEYNOTE-224 trial ~2.5 years after antitumour activity and tolerability had initially been reported with ≤35 cycles of pembrolizumab 200mg every 3 weeks in 104 adults with HCC who had progressed on or were intolerant to sorafenib. After a median time from first dose to data cutoff of 45.1 months, the objective response rate was 18.3% with a median response duration of 21.0 months, the disease control rate was 61.5%, the median time to progression was 4.8 months, and the median PFS and OS durations were 4.9 months and 13.2 months, respectively. The treatment-related adverse event rate was 73.1%, with grade 3–4 and grade 5 event rates of 25.0% and 1.0%, respectively. Three participants developed grade 3 immune-mediated hepatitis with no virus-induced hepatitis flares.

Reference: Eur J Cancer 2022;167:1–12
Abstract

Comment: The REFLECT trial established an improvement in PFS with lenvatinib over sorafenib in the first-line treatment of advanced HCC, with a median PFS of 8.9 vs. 3.7 months, with an HR of 0.63, and a response rate of 24% vs. 9%. The first retrospective study above demonstrated the efficacy of lenvatinib in combination with ICIs in a real-world clinical setting in a Chinese population. The overall response rate was double that of lenvatinib monotherapy (41.5% vs. 20%) and the overall disease control rate was improved. The second paper was an update on the KEYNOTE-224 with the use of pembrolizumab in the second-line setting following first-line sorafenib, with demonstrable durable antitumour activity. The estimated 2-year OS rate was 31%. The safety profile was as expected, and no cases of hepatitis B or C flare were observed in patients who were carriers. Results from the LEAP-002 (randomised phase 3 trial of lenvatinib plus pembrolizumab in the first-line setting) are pending maturity.

Pembrolizumab in patients with microsatellite instability-high advanced endometrial cancer

Authors: O'Malley DM et al.

Summary: Efficacy and safety outcomes were reported for 90 KEYNOTE-158 trial participants with MSI-high or mismatch repair-deficient endometrial cancer. At data cutoff (Oct 5, 2020), 20% of the participants had completed 35 cycles of pembrolizumab and 58% had discontinued treatment. For participants who had received ≥1 dose of pembrolizumab and had ≥26 weeks of follow-up (efficacy population; n=79; median time from first dose to data cutoff, 42.6 months), the objective response rate (primary endpoint) was 48%, median response duration was not reached, median PFS duration was 13.1 months and median OS duration was not reached. Among all participants who received treatment, 76% experienced ≥1 treatment-related adverse event (12% grade 3–4; none fatal), and 28% experienced immune-mediated adverse events or infusion reactions (7% grade 3–4; none fatal).

Comment: Continuing the trend of checkpoint inhibition in deficient mismatch repair cancers, as a surrogate for MSI (see commentary for the KEYNOTE-177 trial in this issue), pembrolizumab was assessed in patients with progressive MSI-high advanced endometrial cancer in this phase 2 trial. This was used in the second or further line of systemic treatment and overall response rates were high (close to 50% objective response rates) and a median PFS of 13.1 months – significantly longer than standard second- or third-line chemotherapy or endocrine therapy options. There are as yet no randomised trials comparing the efficacy of first-line chemotherapy versus checkpoint inhibition in mismatch repair-deficient/MSI-high endometrial cancer, and checkpoint inhibition is not funded in the NZ setting for this indication.

Reference: J Clin Oncol 2022;40:752–61
Abstract

Pembrolizumab versus chemotherapy for microsatellite instability-high or mismatch repair-deficient metastatic colorectal cancer (KEYNOTE-177)

Authors: Diaz LA Jr et al., on behalf of the KEYNOTE-177 Investigators

Summary: The final analysis of the open-label, phase 3 KEYNOTE-177 trial was reported; KEYNOTE-177 randomised patients with stage IV MSI-high or mismatch repair-deficient CRC to receive front-line intravenous pembrolizumab 200mg every 3 weeks for ≤35 cycles (n=153) or investigator's choice of one of six standard chemotherapy regimens (mFOLFOX6 or FOLFIRI with or without bevacizumab or cetuximab; n=154). Consistent with the previously published primary and secondary interim analyses, pembrolizumab prolonged PFS versus chemotherapy, conferring a >40% reduction in the risk of disease progression or death at >3-year median follow-up (16.5 vs. 8.2 months; HR 0.59 [95% CI 0.45, 0.79]). Although the coprimary endpoint of OS favoured the pembrolizumab arm (not reached vs. 36.7 months; HR 0.74 [95% CI 0.53, 1.03]), the benefit did not demonstrate superiority at a threshold of p<0.025. Lower rates of grade ≥3 treatment-related adverse events (22% vs. 66%), serious adverse events (16% vs. 29%) and treatment-related deaths (0 vs. 1) were reported for the pembrolizumab versus chemotherapy group.

Comment: Although the update of the KEYNOTE-177 trial did not demonstrate a significant difference in OS, the HR favoured pembrolizumab with a median OS not reached and 36.7 months in the pembrolizumab and chemotherapy arms, respectively. It is worth noting that 60% of patients did crossover to a checkpoint inhibitor as a subsequent line of treatment in the chemotherapy group and may have contributed to the nonsignificant difference in OS. An earlier updated analysis had also demonstrated an improvement in patient reported outcomes with pembrolizumab with regards to physical, emotional and social functioning, but notable declines in physical, role and social functioning in the chemotherapy arm. This is clinically meaningful, as many patients are likely to remain active and function well whilst on first-line ICI therapy with durable responses.

Reference: Lancet Oncol 2022;23:659–70
Abstract