Immuno-Oncology
RESEARCH REVIEW™

Making Education Easy

Issue 4 – 2022

In this issue:

Abbreviations used in this issue

DCR = disease control rate
DFS = disease-free survival
HER2 = human epidermal growth factor receptor-2
HR = hazard ratio
NSCLC = non-small-cell lung cancer
ORR = objective/overall response rate
OS = overall survival
PD-1/PD-L1 = programmed cell death (ligand)-1
PFS = progression-free survival
SCC = squamous cell carcinoma
VTE = venous thromboembolism

Welcome to issue 4 of Immuno-Oncology Research Review.

We begin this issue with the CONFIRM trial of nivolumab in patients with pleural or peritoneal malignant mesothelioma who had progressed on platinum-based chemotherapy, followed by research published in the Lancet reporting the results of the IMpower010 trial, which compared adjuvant atezolizumab with best supportive care following adjuvant platinum-based chemotherapy in patients who had undergone complete surgical resection of early-stage NSCLC. We also take a look at a couple of potential complications of immune checkpoint inhibitor therapy, namely VTE and sarcoidosis, and we conclude with the prespecified interim analysis of the phase 3 KEYNOTE-564 trial reporting that DFS was significantly better with pembrolizumab compared with placebo.

We hope you enjoy this update in immuno-oncology research. We always enjoy receiving your comments and feedback.

Kind regards,

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Nivolumab versus placebo in patients with relapsed malignant mesothelioma (CONFIRM)

Authors: Fennell DA et al., on behalf of the CONFIRM trial investigators

Summary: Adults with progressive pleural or peritoneal mesothelioma (Eastern Cooperative Oncology Group performance status 0–1) after first-line platinum-based chemotherapy were randomised to receive 30-min intravenous infusions of nivolumab 240mg (n=221) or placebo (n=111) every 2 weeks for 12 months or until disease progression, and were followed for a median of 11.6 months, in this phase 3 trial. Compared with placebo, nivolumab recipients had significantly longer median PFS (3.0 vs. 1.8 months; adjusted HR 0.67 [95% CI 0.53, 0.85]) and median OS (10.2 vs. 6.9 months; 0.69 [0.52, 0.91]). The most frequent grade ≥3 treatment-related adverse events were diarrhoea (3% and 2% in the nivolumab and placebo arms, respectively) and infusion-related reactions (3% and 0%), and serious adverse events occurred in 41% of nivolumab recipients and 44% of placebo recipients; there were no treatment-related deaths.

Comment: The CONFIRM trial is the first placebo-controlled phase 3 trial of a PD-1 inhibitor in relapsed mesothelioma, with an improvement in OS following standard first-line doublet platinum/pemetrexed. Significant benefit was seen for both PFS and OS, noting that PD-L1 expression did not appear to predict benefit. Benefit also appeared to be significant for epithelioid subtypes but not nonepithelioid (noting that 88% of patients in both arms had epithelioid histology); however, this needs to be cautiously considered due to the smaller number of patients in the nonepithelioid subtype (n=39). Median OS in the epithelioid subtype was 9.4 months with nivolumab and 6.6 months with placebo, and 12-month OS was 40% vs. 26.7%; HR 0.71 (p=0.021). Median OS in the nonepithelioid subtype was 5.9 vs. 6.7 months; HR 0.79 (p=0.572). There are as yet no randomised trial results that have demonstrated a survival difference between PD-1 inhibitors versus second-line chemotherapy in relapsed mesothelioma, so both of these approaches would be reasonable options in suitable patients with maintained performance status.

Reference: Lancet Oncol 2021;22:1530–40
Abstract

Adjuvant atezolizumab after adjuvant chemotherapy in resected stage IB–IIIA non-small-cell lung cancer (IMpower010)

Authors: Felip E et al., for the IMpower010 Investigators

Summary: Adults with completely resected stage IB–IIIA NSCLC were randomised to receive 16 cycles of adjuvant atezolizumab 1200mg every 21 days for 1 year (n=507) or best supportive care (n=498) following 1–4 cycles of adjuvant platinum-based chemotherapy in the open-label phase 3 IMpower010 trial; 495 participants from each group received treatment. Compared with best supportive care, atezolizumab was associated with improved DFS after median follow-up of 32.2 months in participants with stage II–IIIA disease (HR 0.79 [95% CI 0.64, 0.96]) including those with ≥1% PD-L1 expression on tumour cells (0.66 [0.50, 0.88]); a DFS benefit was also evident in the intent-to-treat population (0.81 [0.67, 0.99]). The incidence of grade 3–4 adverse events related to atezolizumab use was 11%, and the incidence of grade 5 adverse events was 1%.

Comment: IMpower010 is the first phase 3 trial of a checkpoint inhibitor to demonstrate DFS improvement in the adjuvant NSCLC setting. Whilst DFS was the primary endpoint in this trial and is clinically important for patients and clinicians, mature OS results will require more time to confirm if these DFS gains do translate to an OS benefit given the established role of checkpoint inhibitor therapy in advanced NSCLC in patients who do relapse. Whilst checkpoint inhibitor agents are generally well tolerated, a small but significant proportion do experience immune-related adverse events with long-term consequences (e.g. thyroid endocrinopathies that may require life-long supplement replacement). There is still a lack of an accurate biomarker that can predict which patients are most likely to relapse following surgery, who may benefit the most from adjuvant treatment.

Reference: Lancet 2021;398:1344–57
Abstract

Adjuvant pembrolizumab after nephrectomy in renal-cell carcinoma

Authors: Choueiri TK et al., for the KEYNOTE-564 Investigators

Summary: Patients with clear-cell renal-cell carcinoma at high risk for postnephrectomy recurrence, with or without metastasectomy, were randomised to receive ≤17 cycles of adjuvant intravenous pembrolizumab 200mg (n=496) or placebo (n=498) once every 3 weeks in the phase 3 KEYNOTE-564 trial; this paper reported the results of a prespecified interim analysis undertaken a median 24.1 months from randomisation to data cutoff. Compared with placebo, pembrolizumab recipients had a greater 24-month DFS rate (primary endpoint; 77.3% vs. 68.1%; HR for recurrence or death, 0.68 [95% CI 0.53, 0.87]) with a greater proportion alive at 24 months (96.6% vs. 93.5%; HR for death, 0.54 [0.30, 0.96]). The incidences of grade ≥3 adverse events in the respective pembrolizumab and placebo arms were 32.4% and 17.7%, and there were no deaths related to pembrolizumab therapy reported.

Comment: Randomised trials of adjuvant vascular endothelial growth factor inhibitors in resected renal-cell cancer have to date given inconsistent DFS results with no trend towards OS benefit. The KEYNOTE-564 trial is potentially practice changing, with a significant improvement in DFS in patients with high-risk resected renal cancer who were treated with adjuvant pembrolizumab. The trial did include patients with resected M1 disease, although this made up only a small proportion (4%) of the trial population. We do not as yet have mature OS results, and there could be a possibility of DFS improvement in the absence of an OS improvement eventually. Whilst generally well-tolerated, immune checkpoint inhibitors are associated with serious and potentially long-term immune-related toxicities (e.g. thyroid dysfunction requiring thyroid replacement), notwithstanding the significant costs of these medications. The ESMO guidelines (updated Sept 2021) have considered this as an option for patients with high-risk operable clear-cell renal-cell cancer after careful patient counselling regarding immature OS and potential long-term adverse events (level of evidence I, recommendation C). The results of other adjuvant checkpoint inhibitor trials in this setting would be useful to support this approach, particularly when more mature OS data become available.

Reference: N Engl J Med 2021;385:683–94
Abstract

Overall survival benefit with tebentafusp in metastatic uveal melanoma

Authors: Nathan P et al., for the IMCgp100-202 Investigators

Summary: This open-label, phase 3 trial randomly assigned untreated HLA-A*02:01-positive patients with metastatic uveal melanoma to receive tebentafusp (n=252) or the investigators' choice of therapy with single-agent pembrolizumab, ipilimumab or dacarbazine (n=126). In the intent-to-treat population, the 1-year OS rate was greater in the tebentafusp arm than in the control arm (73% vs. 59%; HR for death, 0.51 [95% CI 0.37, 0.71]), as was the 6-month PFS rate (31% vs. 19%; HR for disease progression or death, 0.73 [95% CI 0.58, 0.94]). The most common treatment-related adverse events in the tebentafusp group were cytokine-mediated events and skin-related events, including rash, pyrexia and pruritus.

Comment: Uveal melanomas account for 3–5% of all melanomas, and have a low prevalence of targetable *BRAF* mutations and limited sensitivity to monotherapy immune checkpoint inhibitors. As such, prognosis remains poor overall. Tebentafusp is a novel form of immunotherapy that uses an engineered high-affinity HLA-A*02:01 T-cell receptor and CD3-directed fusion protein to specifically target glycoproteins, which are present on melanoma target-cell surfaces. This binding helps to recruit and activate polyclonal T-cells to release cytokines and cytolytic mediators against the melanoma cell. The prevalence of the HLA-A*02:01 serotype is estimated to be ~45% of patients in the US and Europe, whom may benefit from tebentafusp. The ORR was 9% vs. 5%, and the median OS was 21.7 vs. 16 months, favouring the tebentafusp group. Whilst cytokine-mediated events such as rash (83%), fever (76%) and pruritus (69%) were common, these infrequently led to treatment discontinuation (2%). In comparison, a single-arm phase 2 trial (J Clin Oncol 2021;39:599–607) has demonstrated an ORR of 18%, median PFS of 5.5 months and median OS of 19.5 months with the combination of nivolumab and ipilimumab. It is uncertain how combination checkpoint inhibitors would compare with tebentafusp, and would be of interest in future trials.

Reference: N Engl J Med 2021;385:1196–206
Abstract

Final results from the PERUSE study of first-line pertuzumab plus trastuzumab plus a taxane for HER2-positive locally recurrent or metastatic breast cancer, with a multivariable approach to guide prognostication

Authors: Miles D et al., on behalf of the PERUSE investigators

Summary: Patients with inoperable HER2-positive locally recurrent/metastatic breast cancer for which no systemic therapy had previously been given except endocrine therapy (n=1436) received docetaxel, paclitaxel or nab-paclitaxel with trastuzumab and pertuzumab until disease progression or unacceptable toxicity in the PERUSE trial; 41% of the participants had initially received paclitaxel and 64% had hormone receptor-positive disease. Common grade ≥3 adverse events included neutropenia (10%, mostly docetaxel recipients) and diarrhoea (8%). After a median 5.7 years of follow-up, the median PFS duration was 20.7 months, with similar durations seen according to HR status or taxane exposure, and the median OS duration was 65.3 months, with similar durations seen according to receipt of a taxane backbone but longer durations reported for hormone receptor-positive versus -negative disease. Exploratory analyses revealed that median PFS and OS were shortest in participants pretreated with trastuzumab with visceral disease (13.1 months and 46.3 months, respectively).

Comment: The CLEOPATRA trial established the addition of pertuzumab to first-line trastuzumab and docetaxel as a new standard for metastatic HER2-positive breast cancer. Subsequent trials have evaluated alternative non-taxane based chemotherapy agents (e.g. vinorelbine, eribulin) and the PERUSE trial evaluated the safety and efficacy of three widely used taxanes in combination with dual HER2 blockade. It is encouraging to see consistent OS (median 64–71 months) and efficacy regardless of taxane choice, when compared with that of CLEOPATRA (median OS 57 months). Unlike in CLEOPATRA, maintenance endocrine therapy was allowed in PERUSE, which is relatively common in routine practice in those with hormone receptor-positive disease. As expected, docetaxel was associated with a higher incidence of grade ≥3 adverse events (neutropenia 15% vs. 5% and febrile neutropenia 11% vs. 1%) when compared with paclitaxel.

Reference: Ann Oncol 2021;32:1245–55
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.

PD-1 inhibitors versus chemotherapy as second-line treatment for advanced esophageal squamous cell carcinoma

Authors: Zhu X et al.

Summary: This meta-analysis of five randomised controlled trials on treatments for advanced oesophageal SCC sought to determine the role of PD-1 inhibitors as second-line therapy. Compared with chemotherapy recipients (n=983), PD-1 inhibitor recipients (n=987) had longer OS (HR 0.73 [95% CI 0.66, 0.81]) and a greater ORR (relative risk 1.89 [1.16, 3.05]), with particularly better OS in PD-L1-positive participants (HR 0.64 [0.53, 0.77]); however, neither PFS nor DCR were significantly improved with PD-1 inhibitor recipients as second-line therapy (HR 0.88 [0.68, 1.14] and relative risk 0.89 [0.59, 1.37], respectively). PD-1 inhibitors were also associated with significantly lower incidences of grade 3–5 treatment-related adverse events.

Comment: Whilst OS was improved, PFS and DCR were not improved with second-line PD-1 inhibitors in advanced oesophageal SCC in this meta-analysis. This may be due to the longer period of time before treatment effects of immunotherapy become apparent, but in those who do benefit, responses could be more durable when compared with chemotherapy. It was worth noting that PD-1 inhibitors did not significantly prolong OS in patients with a negative PD-L1 status. So, whilst a positive and higher level of expression of PD-1 may predict for a better response and survival, a negative PD-1 status is more likely to dissuade initial commencement of a checkpoint inhibitor in this second-line setting. Cost and access remain a significant barrier to PD-1 inhibition, although the favourable safety profile and tolerance make it an attractive alternative to chemotherapy in patients with oesophageal SCC, particularly in those with positive PD-1 expression.

Reference: BMC Cancer 2021;21:1195
Abstract

Immune checkpoint inhibitors for cancer and venous thromboembolic events

Authors: Gong J et al.

Summary: The risk of VTE during immune checkpoint inhibitor use was assessed in this retrospective study of 2854 patients treated with these agents at a single centre. From immune checkpoint inhibitor initiation, the respective 6-month and 1-year VTE rates were 7.4% and 13.8%. The VTE risk was increased significantly over the 2-year period after starting treatment compared with a 2-year control period prior to immune checkpoint inhibitor initiation (HR 4.98 [95% CI 3.65, 8.59]), with increased risks of both deep vein thrombosis and pulmonary embolism (5.70 [3.79, 8.59] and 4.75 [3.20, 7.10]). The risk of developing a VTE was lower in older patients and those with a history of melanoma, but increased in those with a higher Khorana risk score and a history of hypertension or VTE.

Comment: There are several postulated mechanisms of action for the observed increased risk of thromboembolism with checkpoint inhibitor use, including off-target autoimmunity, induced systemic inflammation on the haemostatic system and longer duration of survival in advanced-stage disease, which itself becomes a risk factor for thrombotic events due to the improved survival time. Similar to this study, an Austrian retrospective study of 672 patients commenced on immune checkpoint inhibitors demonstrated a cumulative incidence of VTE of 12.9% and arterial thromboembolism of 1.8%, which were associated with increased mortality (Blood 2021;137:1669–78). In randomised controlled trials, rates of pulmonary embolism range from 2% to 3% (KEYNOTE-042 and KEYNOTE-057) Clinicians should be aware of this increased risk of thromboembolism, particularly as the use of checkpoint inhibitors increases over multiple tumour subtypes. Future prospective studies may help to identify risk factors and biomarkers to risk stratify patients on checkpoint inhibitor therapy who may benefit from thromboprophylaxis.

Reference: Eur J Cancer 2021;158:99–110
Abstract

Immune checkpoint inhibitor–associated sarcoidosis: a usually benign disease that does not require immunotherapy discontinuation

Authors: Chanson N et al., on behalf of the ICIR

Summary: These researchers reported on 32 patients from the ImmunoCancer International Registry who developed sarcoidosis while receiving immune checkpoint inhibitors for cancer (for myeloma in 24). Eighteen of the patients had received anti-PD-1monotherapy, one had received ipilimumab monotherapy and the remaining 13 had received combination ipilimumab plus nivolumab. Sarcoidosis was diagnosed 2–29 months (median 3) after immune checkpoint inhibitor initiation, with more rapid onset of symptoms seen in combined immune checkpoint inhibitor recipients. Sarcoidosis symptoms (mostly cutaneous, respiratory and general) were present in 59% of the patients, involved organs included the mediastinal lymph nodes (n=32), lungs (n=11), skin (n=10) and eyes (n=5), and all patients had bilateral hilar lymphadenopathy on pulmonary CT scans, but no severe manifestations were reported. Nine patients were treated with oral glucocorticoids, and three with hydroxychloroquine. Twenty-five of the patients withheld their immune checkpoint inhibitor therapy, with 18 definitively discontinuing therapy. Among the seven patients who continued treatment, one experienced a flare. One patient who restarted immune checkpoint inhibitor therapy experienced sarcoidosis recurrence, whereas six restarted without harm.

Comment: Immune checkpoint inhibitors may potentially affect any tissue, and may present as sarcoidosis-like reaction, with mediastinal adenopathy, dermatological nodules or plaques. Without a tissue biopsy, it may be difficult to differentiate a sarcoidosis-like reaction with mediastinal adenopathy on chest imaging from an immune-related adverse event causing reactive lymphadenopathy. A biopsy would also be useful to exclude infection or progressive malignancy as an underlying cause. In patients who do develop immune-mediated sarcoidosis and are symptomatic, this does appear to respond well to corticosteroid treatment. Patients may not necessarily need to discontinue checkpoint inhibitor therapy as there is also clinical association between the development of an immune-related adverse event and beneficial antitumour response.

Reference: Eur J Cancer 2021;158:208–16
Abstract

Combination immunotherapy with nivolumab and ipilimumab in patients with rare gynecological malignancies

Authors: Klein O et al.

Summary: Patients with advanced rare gynaecological cancers received four induction doses of nivolumab 3 mg/kg and ipilimumab 1 mg/kg every 3 weeks followed by nivolumab monotherapy 3 mg/kg every 2 weeks for 2 years or until disease progression in the phase 2 CA209-538 trial. In the respective intent-to-treat (n=43) and radiologically evaluable (n=33) populations, the ORRs were 28% and 36%, with seven additional participants achieving stable disease for DCRs (primary endpoint) of 58% and 44%, respectively; durable responses were recorded across tumour histologies. The response rate was greater in participants who had a baseline PD-L1 expression of ≥1% on tumour cells, but was independent of tumour mutational burden. The overall and grade 3–4 immune-related adverse event incidences were 72% and 16%, respectively.

Comment: With the exception of microsatellite unstable (MSI-high) endometrial cancer, anti-PD-1/PD-L1 inhibitors have shown only limited activity in patients with common gynaecological malignancies such as high-grade serous ovarian or endometrioid endometrial cancers. Combination PD-1/PD-L1 and CTLA-4 (cytotoxic T-lymphocyte-associated protein-4) inhibition in this phase 2 trial demonstrated some encouraging ORRs and DCRs over a number of rarer gynaecological cancers: uterine serous carcinoma (ORR 13%, DCR 25%), uterine/ovarian carcinosarcoma (ORR 33%, DCR 55%), uterine leiomyosarcoma (ORR 60%, DCR 80%), ovarian clear cell (ORR 33%, DCR 33%), low-grade serous ovarian (ORR 25%, DCR 25%) and vaginal/vulva SCC (ORR 20%, DCR 40%). A number of these rarer gynaecological malignancies, such as uterine leiomyosarcoma or carcinosarcoma, have only modest and short responses to standard chemotherapy. From a biomarker standpoint, it appears that PD-L1 expression may enrich for likely responders, but tumour mutational burden does not.

Reference: J Immunother Cancer 2021;9:e003156
Abstract

Pembrolizumab for persistent, recurrent, or metastatic cervical cancer

Authors: Colombo N et al., for the KEYNOTE-826 Investigators

Summary: Patients with persistent, recurrent or metastatic cervical cancer were evenly randomised to receive ≤35 cycles of pembrolizumab 200mg or placebo every 3 weeks along with platinum-based chemotherapy and, at investigators' discretion, bevacizumab in this phase 3 trial; this paper reported results from a prespecified first interim analysis. Median PFS was significantly longer in the pembrolizumab arm than the placebo arm in: i) participants with a PD-L1 combined positive score of ≥1 (n=548; 10.4 vs. 8.2 months; HR for progression or death, 0.62 [95% CI 0.50, 0.77]); ii) the intent-to-treat population (n=617; 10.4 vs. 8.2 months; 0.65 [0.53, 0.79]); and iii) participants with a PD-L1 combined positive score of ≥10 (n=317; 10.4 vs. 8.1 months; 0.58 [0.44, 0.77]); in these respective (sub) populations, pembrolizumab recipients had significantly greater 24-month OS rates (53.0% vs. 41.7%; HR for death, 0.64 [0.50, 0.81], 50.4% vs. 40.4%; 0.67 [0.54, 0.84], and 54.4% vs. 44.6%; 0.61 [0.44, 0.84], respectively). The most common grade 3–5 adverse events were anaemia (30.3% and 26.9% in the respective pembrolizumab and placebo arms) and neutropenia (12.4% and 9.7%).

Comment: The GOG 240 trial demonstrated that chemotherapy plus bevacizumab is a first-line treatment option in advanced cervical cancer, with an observed prolonged OS (by 3.7 months) over chemotherapy alone. In this KEYNOTE 826 trial, there was increased tumour response and control and improved survival with the addition of pembrolizumab to doublet chemotherapy with or without bevacizumab. The improvement in PFS and OS was observed regardless of bevacizumab use and appears independent of PD-L1 status, and thus this combined chemotherapy plus checkpoint inhibitor approach could be considered in first-line treatment. What is uncertain and will be worth waiting for will be trial results utilising maintenance checkpoint inhibitors following definitive chemoradiation in high-risk localised cervical cancer (this approach having been validated in the PACIFIC trial for NSCLC).

Reference: N Engl J Med 2021;385:1856–67
Abstract