Immuno-Oncology RESEARCH REVIEW™

Making Education Easy

Issue 2 – 2020

In this issue:

Abbreviations used in this issue
CR = complete response
CRC = colorectal cancer
CTLA-4 = cytotoxic T-lymphocyte-associated protein 4
HR = hazard ratio
LDH = lactate dehydrogenase
NSCLC = non-small-cell lung cancer
ORR = objective response rate
OS = overall survival
PD1/PD-L1 = programmed cell death (ligand)-1
PFS = progression-free survival
QOL = quality of life

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

This issue begins with research reporting on the IMspire150 trial, which found that adding atezolizumab to targeted treatment with vemurafenib and cobimetinib was a safe and tolerable approach that significantly increased PFS in patients with *BRAF* V600 mutation-positive advanced melanoma. This is followed by a paper from Japan reporting on patients with stage III or IV unresectable acral melanoma who were managed with anti-PD1 therapy. Researchers from China have found that pretreatment neutrophil-to-lymphocyte ratio, LDH level and prognostic nutrition index score may hold potential for predicting clinical outcomes and immune-related adverse events in patients receiving PD1 inhibitors for advanced NSCLC. A paper reporting recurrence rates of the same immune-related adverse events that led to immune checkpoint inhibitor discontinuation, after rechallenge with the same immune checkpoint inhibitor concludes this issue.

We hope the research selected is informative and useful in your everyday practice. Your comments and suggestions are always appreciated.

Kind regards,

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Atezolizumab, vemurafenib, and cobimetinib as first-line treatment for unresectable advanced *BRAF* V600 mutation-positive melanoma (IMspire150)

Authors: Gutzmer R et al.

Summary: Patients with unresectable stage IIIc–IV *BRAF* V600 mutation-positive melanoma were randomised to receive 28-day cycles of vemurafenib and cobimetinib with (n=256) or without (n=258) atezolizumab from the second cycle in this phase 3 trial. Median follow-up was 18.9 months. Compared with vemurafenib and cobimetinib alone, the addition of atezolizumab was associated with significant prolongation of median investigator-assessed PFS (primary outcome; 15.1 vs. 10.6 months; HR 0.78 [95% CI 0.63, 0.97]). Common treatment-related adverse events in the respective atezolizumab and control arms were increased blood creatinine phosphokinase level (51.3% and 44.8%), diarrhoea (42.2% and 46.6%), rash (40.9% and 40.9%), arthralgia (39.1% and 28.1%), pyrexia (38.7% and 26.0%), increased ALT level (33.9% and 22.8%) and increased lipase level (32.2% and 27.4%), and the respective adverse event-related discontinuation rates were 13% and 16%.

Comment: NZ sites participated in this first-line study of combination BRAF- and PD-L1-directed therapies, importantly providing access to BRAF and MEK inhibitors, which are not funded for advanced melanoma patients in NZ. Similar studies of combination therapy have had difficulties with toxicity, and an advantage of this trial design was the staggered start to therapy, with atezolizumab introduced from cycle 2. The reported side-effect profile seems to be acceptable. The added benefit of atezolizumab is probably as expected: more prolonged disease control with an unknown effect on OS as yet. This trial hasn't addressed the question of whether sequential treatment with BRAF/MEK inhibitors followed by a PD1/PD-L1 inhibitor (or *vice versa*) is an equally effective strategy for disease management and at this point, sequential therapy remains the standard of care.

Reference: Lancet 2020;395:1835–44
Abstract

Anti-PD1 checkpoint inhibitor therapy in acral melanoma

Authors: Nakamura Y et al.

Summary: This retrospective study from 21 Japanese institutions evaluated patients with unresectable stage III or stage IV acral melanoma (nail apparatus, n=70; palm and sole, n=123) treated with anti-PD1 therapy (first-line in 74.1%). The ORR for all patients was 16.6% with respective complete and partial response rates of 3.1% and 13.5%, and the median OS duration was 18.1 months. Normal LDH levels showed a significantly stronger association with better OS than abnormal levels (median OS 24.9 vs. 10.7 months [p<0.001]). The ORR was significantly lower in the nail apparatus group than the palm and sole group (8.6% vs. 21.1% [p=0.026]), and their median OS duration was significantly shorter (12.8 vs. 22.3 months [p=0.03]).

Comment: This is a retrospective analysis, but it includes a large number of patients with a rare subtype of melanoma and is clinically meaningful because of the relative lack of immune checkpoint inhibitor efficacy. The results are relevant to the NZ population, in which we typically find acral melanomas in Pacific, Asian and other darker-skinned individuals. The prognosis for patients with nail apparatus melanomas is particularly poor; early diagnosis (although difficult) and local control remain important management principles.

Reference: Ann Oncol 2020;31:1198–206
Abstract

Nivolumab versus everolimus in patients with advanced renal cell carcinoma

Authors: Motzer RJ et al.

Summary: The CheckMate 025 trial randomised patients with clear cell advanced renal cell carcinoma who had previously received 1–2 antiangiogenic regimens to receive nivolumab 3 mg/kg every 2 weeks (evaluable n=406) or everolimus 10mg once a day (evaluable n=397) until disease progression or unacceptable toxicity; this report presented updated results. After ≥64 months of follow-up (median 72), median OS duration remained superior with nivolumab compared with everolimus (25.8 vs. 19.7 months; HR 0.73 [95% CI 0.62, 0.85]), with greater 5-year OS (26% vs. 18%), and both the ORR (23% vs. 4% [p<0.001]) and PFS (HR 0.84 [0.72, 0.99]) being favourable in the nivolumab arm. The most common any-grade treatment-related adverse events in the nivolumab arm were fatigue (34.7%) and pruritus (15.5%), and in the everolimus arm, they were fatigue (34.5%) and stomatitis (29.5%). There was also an improvement in health-related QOL among nivolumab recipients, but this either remained unchanged or deteriorated in the everolimus arm.

Comment: This publication is of interest because of its duration of follow-up and a relatively large number of patients in a population that can be challenging to enrol in clinical trials (due to performance status and an uncommon cancer type). Furthermore, the longer-term efficacy of second-line checkpoint inhibitor therapy, compared with the previous standard of care, the mTOR (mammalian target of rapamycin) inhibitor everolimus, is meaningful with improved OS and QOL. Everolimus toxicity is chronic and significant and it is not surprising that nivolumab was better tolerated. PD1 inhibitors are not currently funded for renal cell carcinoma in NZ, but international practice guidelines for kidney cancer now recommend nivolumab as a preferred second-line therapy over everolimus.

Reference: Cancer 2020;126:4156–67
Abstract

Independent commentary by Dr Rosalie Stephens MBChB; FRACP; MD (Res)

Rosalie Stephens is a medical oncologist at Auckland Hospital and Harbour Cancer Centre, specialising in the treatment of patients with melanoma and gynaecological cancers. Rosalie graduated from the University of Auckland School of Medicine in 2004 and completed specialist training in oncology in 2010. Between 2010 and 2013 she completed a fellowship at the Royal Marsden Hospital in London, and undertook clinical and translational research in melanoma, kidney, breast and gynaecological cancers. She is published widely in peer-reviewed journals in these areas, and she contributes to patient and public education. Rosalie completed a postgraduate degree (MD Res) through the University of London focussing on tumour biology and evolution. Rosalie is a trustee of Melanoma NZ and a member of the NZ Gynaecological Cancer Group. Melanoma is an active research focus, aiming to improve patient outcomes by access to new, improved therapies.

Peripheral blood markers predictive of outcome and immune-related adverse events in advanced non-small cell lung cancer treated with PD-1 inhibitors

Authors: Peng L et al.

Summary: Associations between inflammation-related peripheral blood markers and immune-related adverse events and outcomes were explored for a retrospective cohort of 102 patients receiving PD1 inhibitors for advanced NSCLC. Outcomes were significantly better for patients with a neutrophil-to-lymphocyte ratio of <5 vs. ≥5, an LDH level <240 vs. ≥240 U/L or a PNI (Prognostic Nutrition Index) score ≥45 vs. <45, with all three parameters significantly associated with better PFS (respective p values 0.049, 0.046 and 0.014) and longer OS (0.007, 0.031 and <0.001). Patients in whom all three parameters were favourable had better PFS and OS than those in whom only ≤2 were favourable. Both PNI score and neutrophil-to-lymphocyte ratio were associated with immune-related adverse event onset.

Comment: Patient selection for immune checkpoint inhibitor therapy remains elusive and although the use of inexpensive, accessible clinical markers to predict treatment benefit is appealing, this retrospective study has not really advanced the cause. Not unexpectedly, markers of tumour burden, inflammation and nutritional status appear to relate to outcome but may be prognostic rather than predictive. The association between immune-related adverse events and treatment outcome is of interest, and in other tumour types has produced conflicting results, discussed again in the following publication. Baseline patient and disease characteristics that would guide treatment selection would be hugely helpful in the NZ context of restricted drug funding, but currently it is almost impossible to justify the withholding of immune checkpoint inhibitors in certain tumour types.

Reference: Cancer Immunol Immunother 2020;69:1813–22
Abstract

Outcomes associated with immune-related adverse events in metastatic non-small cell lung cancer treated with nivolumab

Authors: Naqash AR et al.

Summary: Associations between immune-related adverse events and NSCLC outcomes after treatment with nivolumab were explored in a pooled analysis of a global cohort of 531 patients with metastatic disease who had failed platinum-based chemotherapy. Compared with patients without immune-related adverse events, the 33% of the cohort who experienced such events had longer median PFS (6.1 vs. 3.1 months; adjusted HR 0.69 [95% CI 0.55, 0.87]) and OS (14.9 vs. 7.4 months; 0.62 [0.55, 1.03]). Median PFS and OS durations were significantly shorter for patients who permanently discontinued immune checkpoint inhibitor therapy due to an index immune-related adverse event compared with those who did not permanently discontinue their immune checkpoint inhibitor therapy (2.3 vs. 6.6 months; HR 1.74 [95% CI 1.06, 2.80] and 3.6 vs. 17.6 months; 2.61 [1.61, 4.21], respectively).

Comment: This analysis addresses a question often posed by oncologists and their patients: does toxicity from checkpoint inhibition predict for a better outcome? The answer is probably more nuanced than the conclusions of this particular study, which found that the development of an immune-related adverse event did correlate with longer PFS in patients treated for lung cancer, but if permanent discontinuation was required because of that toxicity, patients fared considerably worse in terms of their OS. In other tumour types, permanent discontinuation for toxicity does not necessarily impact on overall outcome, and specific immune-related side effects are more predictive for benefit, such as the development of vitiligo in melanoma patients treated with checkpoint inhibitors. Counselling patients on this issue is accordingly increasingly complex.

Reference: Cancer Immunol Immunother 2020;69:1177–87
Abstract

Survivorship in immune therapy: assessing toxicities, body composition and health-related quality of life among long-term survivors treated with antibodies to programmed death-1 receptor and its ligand

Authors: Patrinely JR Jr. et al.

Summary: This study assessed toxicity, health outcomes and health-related QOL in 217 patients with >2 years survival after treatment with anti-PD1/PD-L1 therapy. Median OS was not reached and 15.2% of patients died during follow-up, primarily from disease progression. At the last follow-up, most patients' ECOG performance status scores were 0 (38%) or 1 (41%). Blood pressures, glucose levels and body mass index values did not change significantly from baseline to 2 years after treatment initiation. Adiposity, skeletal muscle mass and skeletal muscle gauge increased. Immune-related adverse events (up until last follow-up) included hypothyroidism (10.6%), arthritis (3.2%), adrenal insufficiency (3.2%) and neuropathy (2.8%). A new diagnosis of type 2 diabetes or hypertension was made for 6.5% and 6.0% of the patients, respectively. Patient-reported outcomes compared favourably with those for cancer and general populations.

Comment: It is really encouraging that we are starting to see reports of QOL for patients treated with immune checkpoint inhibitors, which in some tumour types can involve a long or indefinite duration of treatment. Most of the patients in this analysis were treated for melanoma, and survivors reported good QOL and psychosocial wellbeing despite chronic immune-related toxicity, defined as those present after cessation of therapy, being quite common. Our real-world experience suggests that side effects such as arthralgias, rash and endocrine abnormalities can be burdensome, but perhaps this is mitigated by the lack of cancer-related symptoms and psychosocial distress of an advanced cancer diagnosis. It will be important to follow this up with further quantitative and qualitative research, as the pool of patients treated with PD1 and CTLA-4 inhibitors increases, in order to inform decisions about duration of treatment, and we may find differing results between cancer types and by age.

Reference: Eur J Cancer 2020;135:211–20
Abstract

Patients with sarcomatoid renal cell carcinoma – re-defining the first-line of treatment

Authors: Iacovelli R et al.

Summary: This was a meta-analysis of four randomised clinical trials of patients with sarcomatoid renal cell carcinoma treated with immune checkpoint inhibitors (n=226) or sunitinib as a control (n=241). Compared with sunitinib, immune checkpoint inhibitor-based combinations were associated with: i) significantly better PFS and OS (respective HRs 0.56 and 0.56 [p≤0.001]); ii) a better ORR (>50% vs. 20%; relative risk 2.15 [p<0.00001]); and iii) a greater likelihood of obtaining CR (relative risk 8.15 [p=0.0002]; incidence 11%).

Comment: The results of this meta-analysis are impressive in this poor-risk group of patients with kidney cancer; an improved ORR was observed in immunotherapy-containing combinations of first-line treatment compared with sunitinib, which appears to translate to a survival advantage, although the prognosis for patients with sarcomatoid renal cell carcinoma is still worse than non-sarcomatoid clear cell renal cell carcinoma. This publication is further evidence of the depth to which immune checkpoint inhibitor therapy has changed the outlook for patients with kidney cancer, historically a disease that has been challenging to treat systemically.

Reference: Eur J Cancer 2020;136:195–203
Abstract

Neoadjuvant nivolumab for patients with resectable Merkel cell carcinoma in the CheckMate 358 trial

Authors: Topalian SL et al.

Summary: Thirty-nine patients with resectable Merkel cell carcinoma received intravenous nivolumab 240mg on days 1 and 15, with surgery planned on day 29, in the phase 1/2 CheckMate 358 study; three participants did not proceed to surgery due to tumour progression or adverse events. The respective any-grade and grades 3–4 treatment-related adverse event rates were 46.2% and 7.7%; there were no unanticipated toxicities. Among the participants who proceeded to surgery, the pathological CR rate was 47.2%. Among radiographically evaluable participants who underwent surgery (n=33), tumour reductions of ≥30% were evident in 54.5%. Responses were independent of tumour MCPyV, PD-L1 or tumour mutational burden status. The median recurrence-free survival and OS durations had not been reached at median follow-up of 20.3 months. Significant correlations were seen between recurrence-free survival and both pathological CR and radiographical response at the time of surgery. No participants who achieved a pathological CR experienced tumour relapse during observation.

Comment: This was an early-phase study of a limited number of patients but is worth highlighting for its neoadjuvant treatment setting, with only a short course (two doses or 1 month) of nivolumab given preoperatively. Although Merkel cell carcinoma is frequently resectable and if not, highly sensitive to radiotherapy, local treatment such as surgery can be morbid and there is a high risk of systemic relapse. Chemotherapy does not usually result in enduring control. The follow-up of these patients remains short but the early results are very promising. A high proportion of patients (>90%) underwent surgery, and it does not appear that the toxicity of preoperative nivolumab compromised the operability for these patients. Merkel cell carcinoma is uncommon but not infrequently seen in NZ, where it is typically associated with an older age and ultraviolet radiation exposure rather than being virus-driven. It is encouraging to think that this strategy could be extrapolated to patients with high-grade neuroendocrine cancers of other organ types, providing the disease control achieved in this study proves enduring with longer follow-up.

Reference: J Clin Oncol 2020;38:2476–87
Abstract

Effect of combined immune checkpoint inhibition vs best supportive care alone in patients with advanced colorectal cancer

Authors: Chen EX et al.

Summary: The Canadian Cancer Trials Group CO.26 phase 2 study randomised 179 evaluable patients with metastatic refractory CRC to combined PD-L1 and CTLA-4 inhibition with tremelimumab plus durvalumab or best supportive care. Over median follow-up of 15.2 months, median OS duration was longer for durvalumab plus tremelimumab than for best supportive care (6.6 vs. 4.1 months; HR 0.72 [90% CI 0.54, 0.97; 2-sided p<0.10]), with no significant difference for PFS duration (1.8 vs. 1.9 months; HR 1.01 [0.76, 1.34]). A greater proportion of durvalumab plus tremelimumab recipients experienced grade ≥3 adverse events compared with supportive care recipients (64% vs. 20%). Circulating cell-free DNA analysis (n=168) indicated that in participants who were microsatellite stable, OS was improved with durvalumab plus tremelimumab (HR 0.66 [90% CI 0.49, 0.89]). The 21% of microsatellite stable participants with plasma tumour mutation burden of ≥28 variants per megabase experienced the greatest OS benefit (HR 0.34 [90% CI 0.18, 0.63]).

Comment: This collaborative group study was chosen for the fact that it met its primary endpoint of improved OS for patients with heavily treated, advanced CRC treated with combination PD1 and CTLA-4 inhibitors compared with supportive care alone, but the clinical significance of this result is questionable with short PFS and poor OS times in both groups. The price to pay for approximately 2–3 months of longer survival was high, with >60% of patients treated with combination immunotherapy experiencing a grade ≥3 adverse event. The researchers achieved a high rate of sample collection for circulating tumour DNA, which is an achievement across many treatment centres in Canada. The authors concluded that further study is warranted, but perhaps even this is too optimistic without further definition of the optimal patient population.

Reference: JAMA Oncol 2020;6:831–8
Abstract

Immune checkpoint inhibitor rechallenge after immune-related adverse events in patients with cancer

Authors: Dolladille C et al.

Summary: This observational, cross-sectional, pharmacovigilance study of a cohort of 24,079 immune-related adverse event cases associated with ≥1 immune checkpoint inhibitor reported recurrences of the same immune-related adverse event that had initially prompted immune checkpoint inhibitor therapy discontinuation following rechallenge. Informative rechallenges accounted for 452 of 6123 immune-related adverse events associated with immune checkpoint inhibitor rechallenge. The recurrence rate for these informative rechallenges was 28.8%, with colitis (odds ratio 1.77 [95% CI 1.14, 2.75]), hepatitis (3.38 [1.31, 8.74]) and pneumonitis (2.26 [1.18, 4.32]) associated with higher recurrence rates, and adrenal events (0.33 [0.13, 0.86]) associated with a lower recurrence rate, compared with other immune-related adverse events.

Comment: This is a really important issue for clinical practice in NZ as we expand the use of immune checkpoint inhibitor treatment into many tumour types. The authors of this study attempted to analyse the issue on a global and large scale, and found a similar rate of recurrent immune-related adverse events on rechallenge to our anecdotal experience and to that reported in institutional series. The latter have also observed that the individual is not only at risk of the same toxicity recurring, but is also at higher risk for an inflammatory syndrome of another organ system. It is not new information that endocrine toxicities follow a different pattern, as it would seem that organs such as the adrenal glands, thyroid and pancreas are at risk of tissue destruction from the first immune-related insult and typically don't recover, therefore it is difficult to worsen their function on rechallenge. Risk assessment for rechallenge remains individual, based on the severity of the immune-related side effect, the physiological and functional reserve of the patient and their disease status, which influences the need for ongoing therapy.

Reference: JAMA Oncol 2020;6:865–71
Abstract