Lung Cancer RESEARCH REVIEW™

Making Education Easy

Issue 17 – 2021

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Abbreviations used in this issue

AI = artificial intelligence
ALK = anaplastic lymphoma kinase
CXR = chest x-ray
CT = computerised tomography
ECOG = Eastern Cooperative Oncology Group
EGFR = epidermal growth factor receptor
EGFR-TKI = epidermal growth factor receptor-tyrosine kinase inhibitor
LDCT = low dose computerised tomography
MPE = malignant pleural effusion
NSCLC = non-small cell lung cancer
OS = overall survival
PDL1 = programmed death-ligand 1
PS = Performance Status
PFS = progression-free survival
TKI = tyrosine kinase inhibitor
TMB = tumour mutational burden

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Welcome to this issue of Lung Cancer Research Review.

Selections in this issue include predicting immunotherapy benefits using biomarkers, whether immunotherapy rescues a poor performance status, real-world survival outcomes with immunotherapy in large-cell neuroendocrine lung carcinoma, and updated survival and other outcomes data in SCLC from IMpower133. Other selections report on the impact of the COVID-19 pandemic on cancer diagnosis and service access in NZ and the performance of an AI algorithm for the automated detection of lung nodules and coronary artery calcium.

We hope that the research and expert insight in this issue of **Lung Cancer Research Review** helps to inform your clinical practice. Please keep your comments and suggestions coming!

Kind regards

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A gene mutation signature predicting immunotherapy benefits in patients with NSCLC

Authors: Pan D et al.

Summary: These researchers assessed whether mutations in select genes may be a better predictor of NSCLC response to immune checkpoint inhibitor (ICI) therapy than TMB-high (TMB-H). They compiled a list of candidate genes that may predict for benefits from ICI therapy using data from a cohort of 350 patients with NSCLC and then evaluated the effects of different mutation signatures in the candidate genes on ICI efficacy. They were also compared with TMB-H. The main finding was a genetic signature with mutations in at least two of 52 candidate genes was better than TMB-H in predicting clinical benefits with ICI therapy in patients with NSCLC. Specifically, the median duration of OS was 36 versus 8 months in those with two or more versus none of the 52 genes mutated.

Comment (AL): This is another new take on biomarkers for immunotherapy. Ultimately, no biomarker has proved reliable enough to either rule out or rule in the use of immunotherapy. The more widely used TMB and PDL1 levels correlate with outcomes but are not definitive. They are also plagued by the variability in testing methods. Different drug companies and different trials use different cut-off levels in different circumstances. The idea of a gene panel, which is more definitive and less of a spectrum open to interpretation is appealing. This study is retrospective and comes with all the biases associated with that. In clinical reality in NZ, testing is not available for these genes and will not be in the near future. I am also not convinced that we will be able to deny people immunotherapy based on these results either. I do believe that better biomarkers or predictive tools for immunotherapy would be very useful in clinical practice so I will watch this space.

Reference: J Thorac Oncol. 2021;16(3):419–427
Abstract

Independent commentary by Dr Aileen Ludlow

Aileen Ludlow is a medical oncologist at Auckland Public Hospital specialising in the management of Lung and GI cancer. She completed her oncology training in Christchurch before going on to do a research fellowship at the Royal Marsden Hospital in London. She is a principal and sub-investigator on several industry and collaborative group trials. She is also involved in medical oncology training, taking over as Director of Physician Education in Auckland and as a member of the NZ advanced training committee for medical oncology.

This Research Review has been endorsed by The Royal New Zealand College of General Practitioners (RNZCGP) and has been approved for up to 1 CME credit for the General Practice Educational Programme (GPEP) and Continuing Professional Development (CPD) purposes. You can record your CME credits in your **RNZCGP Dashboard**

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Association of performance status with survival in patients with advanced non-small cell lung cancer treated with pembrolizumab monotherapy

Authors: Sehgal K et al.

Summary: This cohort study conducted at a single academic cancer centre evaluated whether an ECOG PS score of ≥2 at the start of therapy is associated with PFS and OS in advanced NSCLC treated with pembrolizumab monotherapy. Compared with patients with PS scores of 0 or 1 (n=74), those with PS scores of ≥2 (n=29) had significantly lower disease control rates (38 [88.4%] vs 15 [53.6%]; p=0.002), shorter median PFS (7.9 [95% CI, 4.6–15.4] months vs 2.3 [95% CI, 1.8–4.8] months; p=0.004), and shorter median OS (23.2 [14.0 vs 35.7] months vs 4.1 [95% CI, 2.1–6.9] months; p<0.001). Multivariable adjustment for baseline characteristics confirmed ECOG PS of ≥2 as an independent risk factor for worse PFS (HR 2.02; 95% CI: 1.09–3.74; p=0.03) and worse OS (HR 2.87; 95% CI: 1.40–5.89; p=0.004).

Comment (AL): I think this study probably supports what we all already know. It was shown in melanoma first and now there are a few retrospective studies in lung cancer. Immunotherapy does not rescue a poor performance status and outcomes remain poor. It is very tempting to consider single agent immunotherapy for patients with a poor performance status because the toxicity is preferable to chemotherapy. As this study suggests, with 40% of patients receiving pembrolizumab at this centre having an ECOG PS of 2 or more, it is relatively common practice in the real world. From this study it is not clear whether the ECOG is cancer burden related or co-morbidity related; however, we need to be mindful of this data when our low ECOG PS patients are hoping immunotherapy will provide a miracle.

Reference: JAMA Netw Open. 2021;4(2): e2037120
Abstract

Real-world survival outcomes with immune checkpoint inhibitors in large-cell neuroendocrine tumors of lung

Authors: Dudnik E et al.

Summary: In this real-world cohort analysis, 25 consecutive patients with advanced large-cell neuroendocrine lung carcinoma (aLCNEC) were identified in the electronic databases of four participating cancer centres. Patients were divided into those who received immune checkpoint inhibitors (ICI) [group A; n=41] and those who did not receive ICI (group B; n=84). OS since advanced disease diagnosis (OS DX) and OS since ICI initiation (OS ICI) were determined. With median follow-up of 11.8 and 6.0 months, 66% and 76% of patients died in groups A and B, respectively. Median OS DX was 12.4 months (95% CI: 10.7–23.4) and 6.0 months (95% CI: 4.7–9.4) in groups A and B, respectively (p=0.02). For ICI administration, HR for OS DX was 0.59 (95% CI: 0.38–0.93, p=0.02-unadjusted), and 0.58 (95% CI: 0.34–0.98, p=0.04-adjusted for age, ECOG PS, presence of liver metastases, and chemotherapy administration). According to propensity score matching analysis (n=74; 37 patients in each group matched for age and ECOG PS), median OS DX was 12.5 months (95% CI: 10.6–25.2) and 8.4 months (95% CI: 5.4–16.9) in matched groups A and B, respectively (p=0.046). OS ICI for patients receiving ICI as monotherapy (n=36) was 11.0 months (95% CI: 6.1–19.4).

Comment (AL): It is always nice to have some data specifically regarding large-cell neuroendocrine tumours. They are always lumped in the trials alongside the "non-squamous" groups and the numbers are always tiny. It is impossible to extract data from the large phase 3 trials about whether new treatments are of benefit to this group. Retrospective data has its drawbacks but it is definitely helpful in this situation. The outcomes for the immunotherapy groups are encouraging and it certainly gives me some confidence that offering immunotherapy to this group is reasonable.

Reference: J Immunother Cancer. 2021;9(2):e001999
Abstract

Immune-related adverse events of a PD-L1 inhibitor plus chemotherapy versus a PD-L1 inhibitor alone in first-line treatment for advanced non-small cell lung cancer: a meta-analysis of randomized control trials

Authors: Wang M et al.

Summary: This meta-analysis assessed the rate of immune-related adverse events (irAEs) with a PDL1 inhibitor plus chemotherapy (I+C) versus a PDL1 inhibitor alone (I) and evaluated the indirect relative risk (RR) of I+C versus I. Overall, I+C had a lower rate of grade 3 or higher irAEs than I (7.1% vs 10.6%), although irAEs of any grade were similar. The rate of pneumonitis with I+C was lower than the rate with I for any grade (5.9% vs 7.1%) and for grade 3 or higher. For endocrine system irAEs, I+C was associated with a lower overall rate in comparison with I (16.1% vs 20.1%) whereas irAEs of the digestive system were similar with I+C and I. The rate of skin reactions, including rash, was lower with I+C compared with I (10.4% vs 12.9%).

Comment (AL): I think this is interesting to note. When trials that first combined chemotherapy and immunotherapy started, I think there was always a great concern that the toxicity might be prohibitive. In fact, the toxicity profiles from all the phase 3 trials show that the rates of toxicity do not vary that much between chemotherapy alone and combination therapy. This meta-analysis proves something that I think a lot of us have anecdotally observed – that the immune toxicity is reduced in the combination. Of course, the chemotherapy toxicity still exists, and this study does not address that. I think it gives us confidence that even if there is a low PDL1 level and the benefit to the patient of adding immunotherapy is less, the toxicity is not greatly increased so it is still worthwhile.

Reference: Cancer. 2021;127(5):777–786
Abstract

Updated overall survival and PD-L1 subgroup analysis of patients with extensive-stage small-cell lung cancer treated with atezolizumab, carboplatin, and etoposide (IMpower133)

Authors: Liu SV et al.

Summary: These authors report updated OS, disease progression patterns, safety, and exploratory biomarkers (PDL1 and TMB) from IMpower133, a randomized, double-blind, phase I/III study that demonstrated that the addition of atezolizumab to carboplatin plus etoposide (CP/ET) for first-line treatment of extensive-stage SCLC resulted in significant improvement in OS and PFS versus placebo plus CP/ET. At the updated analysis, median follow-up for OS was 22.9 months. Median OS was 12.3 and 10.3 months with atezolizumab plus CP/ET and placebo plus CP/ET, respectively (HR 0.76; 95% CI: 0.60–0.95; p=0.0154). At 18 months, 34.0% and 21.0% of patients were alive in the atezolizumab plus CP/ET and placebo plus CP/ET arms, respectively. Patients derived benefit from the addition of atezolizumab regardless of PDL1 immunohistochemistry or TMB status.

Comment (AL): This update of IMpower 133 continues to demonstrate consistent results with longer follow-up. It also supports the theory that PDL1 level or TMB are not relevant to the efficacy of the combination. This is an exploratory analysis that was mandated by the European regulators before they would consider licensing the combination for SCLC. The results are consistent with other studies showing that the PDL1 level or TMB are not good biomarkers for small cell carcinoma. I am disappointed by the small margin of benefit with combination chemo-immunotherapy in SCLC but at least it is a step forward in a disease that has been lacking any progress for many years. We have to hope that Pharmac is willing to consider a 13% increase in 18-month OS worthwhile and overlook the poor median OS benefit. It is abundantly clear that medians are not an appropriate way to evaluate immunotherapy.

Reference: J Clin Oncol. 2021;39(6):619–630
Abstract

The impact of the COVID-19 pandemic on cancer diagnosis and service access in New Zealand-a country pursuing COVID-19 elimination

Authors: Gurney JK et al.

Summary: These researchers sourced data (2018–2020) from national collections, including cancer registrations, inpatient hospitalisations, and outpatient events, to describe changes in cancer registrations, diagnosis, and treatment over the course of NZ's response to COVID-19. Descriptive analyses of count data were performed, stratified by ethnicity. Compared with 2018–2019, there was a 40% decline in cancer registrations during NZ's nationwide lockdown in March–April 2020, returning to pre-lockdown levels over subsequent months. There was a severe decline in endoscopies but volumes were back to pre-shutdown levels by August. Cancer surgery and medical oncology were only minimally affected; however, there has been an 8% year-to-date decline in radiation therapy attendances. Except for lung cancer, COVID-19 did not exacerbate existing inequities in service access between ethnic groups.

Comment (PD): Those of us working in cancer witnessed a lightening of workload during the 2020 COVID-19 lockdowns that was concerning. In lung cancer there was good statistical evidence that registrations decreased, particularly in the Māori population, with lower numbers of bronchoscopies and curative surgeries. Bronchoscopy is an aerosol-generating procedure so other diagnostic modalities, like CT-guided biopsy, could have been employed in its place. It is likely that people presenting with cough had more difficult access to CXRs and instead got a COVID-19 swab. Advice for people with pulmonary comorbidities to socially isolate because of the increased risk of complications in the event of COVID-19 may have disproportionately affected Māori. We are yet to see what effect the COVID-19 epidemic has had on lung cancer mortality outcomes.

Reference: Lancet Reg Health West Pac. 2021;10:100127
Abstract

Metformin use and lung cancer survival: a population-based study in Norway

Authors: Brancher S et al.

Summary: This study linked 22,324 lung cancer patients from the Cancer Registry of Norway with the Norwegian Prescription Database to evaluate associations between metformin use and survival. Pre-diagnostic metformin use was not associated with improved survival in any patient; however, it was associated with better lung cancer-specific survival (LCSS) in squamous cell carcinoma (SCC) patients (HR 0.79; 95%CI: 0.62–0.99) and in patients with regional stage SCC (HR 0.67; 95%CI: 0.47–0.95). Post-diagnostic metformin use was associated with improved LCSS in all patients (HR 0.83; 95%CI: 0.73–0.95), those with SCC (HR 0.75; 95%CI: 0.57–0.98), regional stage LC (HR 0.74; 95%CI: 0.59–0.94), and those with regional stage SCC (HR 0.57; 95%CI: 0.38–0.86). Similar results were observed for OS.

Comment (PD): The benefits of metformin in diabetic patients, particularly with cardiovascular disease, are well known. Less well known is the increasing evidence that metformin may confer survival benefits, in general and particularly in the context of cancer. This Scandinavian population study suggested an association between survival from lung cancer and metformin use. This applied to lung-cancer specific survival as well as OS. Although this does not necessarily mean cause and effect, it is intriguing evidence from an epidemiological study of the potential survival benefits of metformin in lung cancer.

Reference: Br J Cancer. 2021;124(5):1018–1025
Abstract

Independent commentary by Dr Paul Dawkins

Paul Dawkins is a Respiratory Physician at Middlemore Hospital and Honorary Senior Lecturer in Medicine at the University of Auckland. He is clinical lead for lung cancer at Middlemore, and chairs the National Lung Cancer Working Group and Northern Cancer Network lung tumour stream. He is principal and co-investigator for a number of commercial clinical trials in respiratory medicine. He is Director of Physician Education at Middlemore Hospital and is an examiner and training workshop facilitator for RACP. He trained as an undergraduate in Bristol (UK) and then undertook postgraduate training based in West Midlands (UK), including research for a higher degree at Brigham and Women's Hospital, Boston (USA). He worked for 6 years as a respiratory physician in Wolverhampton (UK) before leaving to work in New Zealand.

Association of the intensity of diagnostic evaluation with outcomes in incidentally detected lung nodules

Authors: Farjah F et al.

Summary: This comparative effectiveness research study assessed the association between the intensity of lung nodule diagnostic evaluations and outcomes, safety, and health expenditures. Data from 5,057 health plan enrolees with an incidental lung nodule was analysed: 1,925 (38%) received guideline-concordant, 1,863 (37%) less intensive, and 1,269 (25%) more intensive diagnostic evaluations. Compared with guideline-concordant evaluations, less intensive evaluations were associated with fewer procedure-related adverse events (risk difference [RD] -5.9%; 95% CI: -7.2% to -4.6%), lower mean radiation exposure (-9.5 milliSieverts [mSv]; 95% CI: -10.3 mSv to -8.7 mSv), and lower mean health expenditures (-$US10,916; 95% CI: -$US16,112 to -$US5,719); no difference in stage III or IV disease was found among patients diagnosed with lung cancer (RD 4.6%; 95% CI: -22% to +31%). More intensive evaluations were associated with more procedure-related adverse events (RD +8.1%; 95% CI: +5.6% to +11%), higher mean radiation exposure (+6.8 mSv; 95% CI: +5.8 mSv to +7.8 mSv), and higher mean health expenditures ($US20,132; 95% CI: +$US14,398 to +$US25,868); no difference in stage III or IV disease was observed (RD -0.5%; 95% CI: -28% to +27%).

Comment (PD): The increased use of CT scanning in clinical practice, and the commencement of population lung cancer screening in some countries, has resulted in more incidental nodules being picked up that require surveillance. Whilst this may be a good thing when early-stage lung cancers are picked up, there are potential patient harm events from procedure-related complications. This is not to mention the anxiety and psychological effects on patients from surveillance that is difficult to quantify. More sophisticated imaging protocols incorporating volume measurements may ameliorate this "collateral damage". This paper highlights the hazards of over-investigation of incidental lung nodules.

Reference: JAMA Intern Med. 2021;181(4):480–489
Abstract

Risk factors for and time to recurrence of symptomatic malignant pleural effusion in patients with metastatic non-small cell lung cancer with EGFR or ALK mutations

Authors: Schwalk AJ et al.

Summary: This retrospective cohort study of consecutive patients with metastatic NSCL and actionable mutations who underwent initial thoracentesis for MPE was undertaken to determine risk factors for and time to recurrence of symptomatic MPE in patients. A total of 396 patients were included in the study: 295 (74.5%) without and 101 (25.5%) with EGFR or ALK mutations. Most patients with actionable mutations (90%) were receiving targeted treatment within 30 days of initial thoracentesis. Patients with actionable mutations showed a significantly higher hazard of MPE recurrence on univariate but not multivariate analysis. Larger pleural effusion size on chest radiography ($p<0.001$), higher pleural fluid lactate dehydrogenase ($p<0.001$), and positive cytologic examination results ($p=0.008$) were associated with an increased hazard of recurrence.

Comment (PD): Papers like this that directly address issues of clinical practice are very helpful to physicians. There is sometimes a tendency to not treat malignant pleural effusions in patients with actionable mutations in the expectation that they will improve on the TKI treatment. This retrospective study challenges this dogma and provides evidence that malignant pleural effusions are just as likely to recur whether the patient has a mutation or not, suggesting that management of the effusions should be the same in both groups.

Reference: Chest. 2021;159(3):1256–1264
Abstract

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Automated detection of lung nodules and coronary artery calcium using artificial intelligence on low-dose CT scans for lung cancer screening: accuracy and prognostic value

Authors: Chamberlin J et al.

Summary: The main aim of this retrospective study was to investigate the performance of a fully automated AI convolutional neural network (CNN; a multi-layered machine-learning algorithm) in simultaneously detecting solid pulmonary nodules and quantifying coronary artery calcium volume (CACV) on routine LDCT scans of the chest when compared against expert radiologists. The AI CNN results were also evaluated for patient outcomes after at least a 12-month follow-up to evaluate for prognostic value. A total of 117 patients were included in the study. Agreement of the AI findings with experts was excellent (CACV ICC = 0.904, lung nodules Cohen's kappa = 0.846), with high sensitivity and specificity (CACV: sensitivity = 0.929 and specificity = 0.960; lung nodules: sensitivity = 1 and specificity = 0.708). The AI findings improved the prediction of major cardiopulmonary outcomes at 1-year follow-up, including major adverse cardiac events (MACE) and lung cancer (AUC_{MACE} = 0.911 and $AUC_{Lung\ Cancer}$ = 0.942).

Comment (PD): The addition of coronary artery calcium scoring (CACS) to LDCT screening for lung cancer is attractive in that it may improve cost effectiveness of lung cancer screening programmes by incorporating a second health economic benefit using the same technology. Use of AI to achieve this would decrease the manpower costs of radiologist time in performing these analyses. This study shows that there was excellent agreement between AI and expert radiologist findings of CACS on LDCT scans such as used in lung cancer screening programmes, suggesting this technology could be used in such a context. This is being explored in current lung cancer screening studies, such as the European 4-IN-THE-LUNG-RUN.

Reference: BMC Med. 2021;19(1):55
Abstract