Lung Cancer RESEARCH REVIEW™

Making Education Easy

Issue 16 – 2021

In this issue:

Abbreviations used in this issue

CXR = chest x-ray
CT = computerised tomography
EGFR = epidermal growth factor receptor
EGFR-TKI = epidermal growth factor receptor-tyrosine kinase inhibitor
FDG-PET = fluorodeoxyglucose-positron emission tomography
HR = hazard ratio
NSCLC = non-small-cell lung cancer
OS = overall survival
PET = positron emission tomography
PET-CT = positron emission tomography-computed tomography
PFS = progression-free survival
QOL = quality of life
SCLC = small-cell lung cancer
TKI = tyrosine kinase inhibitor

KINDLY SUPPORTED BY

Asthma + Respiratory FOUNDATION NZ

TUAPAPA PŪKAHUKAHU LUNG FOUNDATION New Zealand

Welcome to this issue of Lung Cancer Research Review.

Notable inclusions in this issue are an evaluation of patient-reported outcomes with pembrolizumab from the KEYNOTE-189 trial, validation of a computerised deep-learning algorithm for predicting lung cancer, a report on osimertinib in the treatment of EGFR-mutated NSCLC with leptomeningeal metastases, and a NZ study that investigates the association of a mutational variant of the anticholinergic receptor CHRNA5 with nicotine addiction and the development of pulmonary disease. Also included in this issue is a meta-analysis that explores the intriguing hypothesis that citrus fruit intake may lower the risk of lung cancer.

We hope that you learn something new from this issue of **Lung Cancer Research Review** and look forward to receiving more of your feedback.

Kind regards

Dr Paul Dawkins
pauldawkins@researchreview.co.nz

Dr Aileen Ludlow
aileenludlow@researchreview.co.nz

Patient-reported outcomes following pembrolizumab or placebo plus pemetrexed and platinum in patients with previously untreated, metastatic, non-squamous non-small-cell lung cancer (KEYNOTE-189): a multicentre, double-blind, randomised, placebo-controlled, phase 3 trial

Authors: Garassino MC et al.

Summary: These investigators evaluated prespecified exploratory patient-reported outcomes (PROs) following the addition of pembrolizumab to chemotherapy as first-line treatment in patients with metastatic NSCLC in the KEYNOTE-189 trial. Patients were randomised (2:1) to receive IV pembrolizumab or saline placebo every 3 weeks for up to 2 years (35 cycles); all patients received four cycles of IV pemetrexed with carboplatin or cisplatin (investigator's choice) every 3 weeks for four cycles, followed by pemetrexed maintenance therapy every 3 weeks. Key PRO endpoints were change from baseline to week 12 (during chemotherapy) and week 21 (following chemotherapy) in QLQ-C30 global health status/quality of life (GHS/QOL) score, and time to deterioration in cough, chest pain, or dyspnoea. A total of 616 patients were enrolled and the median follow-up was 10.5 months. The results indicated that adding pembrolizumab to pemetrexed-platinum maintained GHS/QOL, with improved GHS/QOL scores at week 21 being noted in the pembrolizumab plus chemotherapy group compared with the placebo plus chemotherapy group.

Comment (AL): Traditionally, adverse events have been recorded in trial outcomes and the tolerability of a regimen has been judged mainly on that data. While that information is important, we as physicians are notoriously bad at assessing the effect of these adverse events on our patients' lives and grading them appropriately. No questionnaire is perfect or all-encompassing but patient-reported outcomes are an important part of ensuring new treatments are indeed as tolerable as we believe them to be. To see that there was no significant difference in QOL measures with the addition of pembrolizumab is reassuring. I only question the unfortunate trend for publishing the data separately and often much later than the efficacy results (in this case 2 years) when in reality the regimen will be widely used already and most practitioners will not read the publication believing it to be old news. I think there is still some improvement to be made in viewing this information as of equally critical nature to the efficacy results.

Reference: Lancet Oncol. 2020 Mar;21(3):387-397
Abstract

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**

Time spent reading this publication has been approved for CNE by The College of Nurses Aotearoa (NZ) for RNs and NPs. For more information on how to claim CNE hours please **CLICK HERE**.

Neoadjuvant chemotherapy and nivolumab in resectable non-small-cell lung cancer (NADIM): an open-label, multicentre, single-arm, phase 2 trial

Authors: Provencio M et al.

Summary: The aim of this open-label, multicentre, single-arm phase 2 trial was to assess the antitumour activity and safety of neoadjuvant chemoimmunotherapy for resectable stage IIIA NSCLC. Patients received neoadjuvant treatment with IV paclitaxel and carboplatin plus nivolumab on day 1 of each 21-day cycle, for three cycles before surgical resection, followed by adjuvant IV nivolumab monotherapy for 1 year. Forty-six patients received neoadjuvant treatment. Median duration of follow-up was 24 months and 35/41 patients who had tumour resection were progression free. PFS was 77.1% (95% CI: 59.9-87.7) at 24 months. Treatment-related adverse events (TRAEs) were observed in 43/46 (93%) patients. Although 14 (30%) patients had TRAEs grade 3 or worse, none of the adverse events were associated with surgery delays or deaths.

Comment (AL): Stage IIIA lung cancer, even after resection and adjuvant chemotherapy, has a dismal prognosis. Given the inherently systemic nature of lung cancer, a neo-adjuvant approach to add systemic therapy earlier in the treatment paradigm is very appealing. In theory there are several benefits including decreasing size, improving chance of R0 resection, and treating any unidentified micrometastases. This phase 2 single-arm trial certainly suggests favourable outcomes with a high 2-year PFS. Patients were given a year of nivolumab following their surgery, however, so the question remains whether this is true improvement in cure or whether it is delay of recurrence. Only time will tell us that answer and upcoming phase 3 trials will be important.

Reference: Lancet Oncol. 2020;21(11):1413–1422
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.

Brigatinib versus crizotinib in advanced ALK inhibitor-naïve ALK-positive non-small cell lung cancer: second interim analysis of the phase III ALTA-1L trial

Authors: Camidge DR et al.

Summary: These investigators report results of the second prespecified interim analysis (150 events) from the open-label, phase III ALTA-1L trial in which patients with ALK inhibitor-naïve advanced ALK-positive NSCLC were randomised (1:1) to receive brigatinib (n=137) or crizotinib (n=138). With a median follow-up of 24.9 months for brigatinib, brigatinib showed consistent superiority in blinded independent review committee-assessed PFS versus crizotinib (HR 0.49 [95% CI: 0.35–0.68]; p<0.0001; median 24.0 v 11.0 months). Investigator-assessed PFS HR was 0.43 (95% CI: 0.31–0.61; median 29.4 v 9.2 months). Brigatinib also delayed median time to worsening of global health status/QOL scores compared with crizotinib (HR 0.70 [95% CI: 0.49–1.00]; p=0.049). There were no new safety concerns.

Comment (AL): The treatment landscape for ALK-rearranged adenocarcinoma of the lung is unrecognisable compared to that of 10 years ago. It is now moving into the realms of a chronic disease of several years rather than an imminently terminal diagnosis of short prognosis. With the introduction of the new generations of ALK inhibitors the questions have moved into the more complicated arena of sequencing of therapy and specific indications for each drug. This is an ongoing debate internationally amongst lung cancer physicians. The comparison of alectinib, lorlatinib, and brigatinib with the obviously inferior crizotinib establishes them as the better options but does not help the decision between these agents as to superiority. It is a question, however, that we shall watch with interest in NZ as, with the funding of alectinib in the last 2 years, we are not expecting another choice any time in the near future.

Reference: J Clin Oncol. 2020;38(31):3592–3603
Abstract

Indirect comparison between immunotherapy alone and immunotherapy plus chemotherapy as first-line treatment for advanced non-small cell lung cancer: a systematic review

Authors: Li L et al.

Summary: The objective of this systematic review was to compare the efficacy of immunotherapy (IO) alone with that of immunotherapy plus chemotherapy (IC) as first-line treatment for advanced NSCLC. Articles were included in the review if they met the following criteria: (1) randomised controlled trials on NSCLC treatment, (2) all individuals in the studies were treatment naïve; and (3) research on IO monotherapy using programmed death-1 (PD-1)/programmed death ligand-1 (PD-L1) inhibitors or IC. Ten randomised controlled clinical trials (n=5,765) were included. As first-line treatment, IC tended to result in better PFS, OS, and ORR than did IO. Furthermore, IC resulted in significantly better PFS than IO when tumour PD-L1 expression was ≥50% (HR 1.81, 95% CI: 1.18–2.78) and resulted in a better OS and PFS when tumour PD-L1 expression was ≥1%. Although IO resulted in fewer adverse events (AEs) than did IC, the incidence of immune-related AEs was higher for IO than for IC.

Comment (AL): This is a question which often takes a lot of time in discussion with patients in clinic. Unfortunately, a clinical trial of immunotherapy alone verses combination immunotherapy/chemotherapy is unlikely ever to be conducted unless it is undertaken by a collaborative group. There are several problems with this systematic review: they did not have access to raw data and there was a lot of missing data about PD-L1 levels; there was heterogeneity among the trials regarding both immunotherapy and chemotherapy choices; there were only a small number of published trials at the time this was undertaken and so some more recent results are not included. Despite that, I suspect this type of evidence is what we will be forced to make these decisions on for the foreseeable future. We can be reassured that the combination gives a better response rate and PFS so if the patient is fit and well it is probably a good option. OS is not definitely superior in this study so if your patient is not well enough to consider combination then it is reassuring that single-agent immunotherapy can have good results.

Reference: BMJ Open. 2020;10(11):e034010
Abstract

Osimertinib improves overall survival in patients with EGFR-mutated NSCL with leptomeningeal metastases regardless of T790M mutational status

Authors: Lee J et al.

Summary: This retrospective study explored whether treatment with osimertinib leads to improved OS for patients with EGFR-mutated NSCLC with leptomeningeal metastases (LM) compared with those not treated with osimertinib. A total of 351 patients with LM were included in the analysis and the median OS was 8.1 months (95% CI: 7.2–9.0). T790M mutation was detected in 88/197 patients tested, and a total of 110 patients were treated with osimertinib after LM. There was no difference in OS according to T790M mutational status (10.1 months [95% CI: 4.31–15.82] versus 9.0 months [95% CI: 6.81–11.21], p=0.936). Nonetheless, patients treated with osimertinib had a superior OS of 17.0 months (95% CI: 15.13–18.94) compared with those not treated with osimertinib (5.5 months [95% CI: 4.34–6.63]), regardless of T790M mutational status (HR: 0.36 [95% CI: 0.28–0.47], p<0.001). This was also longer than the OS of 8.7 months (95% CI: 7.01-10.39) for those who were never treated with osimertinib but had first- or second-generation EGFR-TKIs.

Comment (AL): Leptomeningeal metastases are universally devastating for our patients with lung cancer. Chemotherapy does not penetrate the blood brain barrier well so has little hope of working, radiotherapy is very toxic and has little benefit, and 1st line EGFR-TKI inhibitors such as erlotinib and gefitinib are more successful but only for short months. Osimertinib is not funded in NZ and is very expensive. In standard practice we would only give it after failure of a 1st-generation TKI if there was a T790m resistance mutation present. Osimertinib has good penetrance through the blood brain barrier though and so, in leptomeningeal disease, this study suggests that that penetrance gives it superiority in treatment regardless of the mutation status. This does not change the fact that it costs a lot of money but it does provide a relatively effective, non-toxic option for treating leptomeningeal disease. If the patient was financially able, I would be comfortable using it regardless of T790m status.

Reference: J Thorac Oncol. 2020;15(11):1758–1766
Abstract

Association of survival with adjuvant chemotherapy among patients with early-stage non-small cell lung cancer with vs without high-risk clinicopathologic features

Authors: Pathak R et al.

Summary: This retrospective cohort study used patient data from the National Cancer Database to assess the association between adjuvant chemotherapy and survival in the presence and absence of high-risk pathologic features in treatment-naïve patients with a completely resected node-negative early-stage NSCLC. A total of 50,814 eligible patients were identified, including 4,220 (8.3%) who received adjuvant chemotherapy and 46,594 (91.7%) who did not receive adjuvant chemotherapy. Among patients with tumour size ≤3 cm, chemotherapy was not associated with improved survival (HR 1.10; 95% CI: 0.96–1.26; p=0.17). For patients with tumour size >3 cm to 4 cm, adjuvant chemotherapy was associated with a survival benefit among patients who underwent sublobar surgery (HR 0.72; 95% CI: 0.56–0.93; p=0.004). For tumour size >4 cm to 5 cm, a survival benefit was associated with adjuvant chemotherapy only in patients with at least one high-risk pathologic feature (HR 0.67; 95% CI: 0.56–0.80; p=0.02). For tumour size >5 cm, adjuvant chemotherapy was associated with a survival benefit irrespective of the presence of high-risk pathologic features (HR 0.75; 95% CI: 0.61–0.91; p=0.004).

Comment (PD): The decision whether to give adjuvant chemotherapy is a balance of benefit and risk that up to now has been based on post-operative staging and size criteria, but not related to pathological features such as visceral pleural invasion, lymphovascular invasion, and tumour grade. The advantage of this study is its size with over 50,000 patients studied. This has produced graded recommendations for four groups according to size and high-risk pathological features that will enable a more considered approach to recommending adjuvant chemotherapy. Potentially genomic features could be incorporated that would make the recommendations even more granular. The flip side of patient fitness to receive chemotherapy still requires a subjective approach that is more difficult to quantify.

Reference: JAMA Oncol. 2020;6(11):1–10
Abstract

Prognostic value of ^{18}F-FDG-PET parameters in patients with small cell lung cancer: a meta-analysis and review of current literature

Authors: Christensen TN et al.

Summary: The aim of this review and meta-analysis was to identify the most promising PET parameter for prognostication in patients with SCLC. Of the 38 studies included in the qualitative analysis, 19 studies were included in the meta-analysis. According to pooled results, a high baseline metabolic tumour volume (MTV) was prognostic for OS (HR 2.83; 95% CI: 2.00–4.01) and PFS (HR 3.11; 95% CI: 1.99–4.90). The prognostic value of the baseline maximum standardised uptake value (SUVmax) was less pronounced (OS: HR 1.50 [95% CI: 1.17–1.91]; PFS: HR 1.24 [95% CI: 0.94–1.63]).

Comment (PD): The use of radiological investigations for prognosis as well as diagnosis could assist decisions about treatment approach. This meta-analysis looked at PET-CT scans in the context of SCLC. SUVmax is what is usually quoted in PET-CT reports as a measure of tumour activity, but it is limited in that it gives the data from only one voxel so does not represent the whole tumour metabolic burden. The MTV (a surrogate for tumour burden) was found to be a much better predictive factor of OS and PFS. MTV may be particularly useful after receiving treatment in that it can distinguish between viable and non-viable tumour.

Reference: Diagnostics (Basel). 2021;11(2):174
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.

Citrus fruit intake and lung cancer risk: a meta-analysis of observational studies

Authors: Wang J et al.

Summary: These researchers performed a meta-analysis of epidemiological studies with case-control or cohort design to explore the hypothesis that citrus intake may reduce the risk of lung cancer. Twenty-one studies were included in the final review. According to pooled analyses, those with the highest citrus fruit intake compared with the lowest intake had a 9% reduction in lung cancer risk (OR 0.91; 95% CI: 0.84–0.98). Also identified was non-linear association between citrus intake and lung cancer risk in the dose-response analysis (p=0.0054) and that the risk reached the minimum (OR 0.91) at around 60 g/day of citrus intake. However, no obvious dose-response association was observed with citrus intakes >80 g/day.

Comment (PD): Prevention is better than cure and in the context of lung cancer clearly smoking cessation is key. But what about other correctable risk factors? Dietary factors are an easy hit, and it is intriguing in this meta-analysis that there is a signal across 21 studies meeting the inclusion criteria that low citrus fruit intake was associated with greater risk of getting lung cancer. However, there is a plateau effect such that high intake confers no extra benefit suggesting supplementation to an already good diet will probably offer no benefit. The major criticism of this paper is that this is an association, and it is likely that there are many confounding factors related to socioeconomic groupings not fully corrected in the component studies.

Reference: Pharmacol Res. 2021;166:105430
Abstract

Chr15q25 genetic variant (rs16969968) independently confers risk of lung cancer, COPD and smoking intensity in a prospective study of high-risk smokers

Authors: Hopkins RJ et al.

Summary: This cohort study examined the association between the cholinergic receptor nicotinic alpha 5 (CHRNA5) variant (rs16969968 AA genotype) and the development of lung cancer, relative to its association with COPD and smoking. In 9,270 subjects from the US National Lung Screening Trial (US NLST), a sub-study of high-risk smokers were followed for an average of 6.4 years. The AA high-risk genotype was found to be associated with poorer lung function (p=0.005), higher smoking intensity (p<0.001), presence of COPD (OR 1.28 [95% CI: 1.10–1.49]; p=0.0015), and the development of lung cancer (HR 1.41 [95% CI: 1.03–1.93]; p=0.03). In mediation analyses, the AA genotype was found to be independently associated with smoking intensity (OR 1.42 [95% CI: 1.25–1.60]; p<0.0001), COPD (OR 1.25 [95% CI 1.66–2.53]; p=0.0015), and development of lung cancer (OR 1.37 [95% CI: 1.03–1.82]; p=0.03).

Comment (PD): This NZ study looks at the association of risk of mutational variants of the anticholinergic receptor CHRNA5 not only to nicotine addiction but also to pulmonary disease, namely COPD and lung cancer. The dataset was a subset of the US NLST trial that comprised Caucasian smokers followed for a number of years. The homozygous AA genotype was associated with greater smoking intensity as you would expect from a gene known to be linked with nicotine addiction but was independently associated with poorer lung function and COPD diagnosis, and odds of developing lung cancer. It is great to see comic book terminology ("triple whammy") finding its way into the medical literature and there is not a better way to express the effect.

Reference: Thorax. 2021;76(3):272–280
Abstract

CLICK HERE to read previous issues of Lung Cancer Research Review

Deep learning using chest radiographs to identify high-risk smokers for lung cancer screening computed tomography: development and validation of a prediction model

Authors: Lu MT et al.

Summary: In the US, the Centers for Medicare & Medicaid Services (CMS) eligibility criteria for lung cancer screening with CT require detailed smoking information and miss many incident lung cancers. These researchers developed and validated a convolutional neural network (CXR-LC) that predicts long-term incident lung cancer using data commonly available in the electronic medical record (chest radiograph, age, sex, and whether currently smoking). The CXR-LC model was developed in the PLCO (Prostate, Lung, Colorectal, and Ovarian) Cancer Screening Trial (n=41,856) and validated in additional PLCO smokers (n=5,615, 12-year follow-up) and National Lung Screening Trial (NLST) heavy smokers (n=493, 6-year follow-up). For the validation data sets, the CXR-LC model was found to have better discrimination (area under the receiver-operating characteristic curve [AUC]) for incident lung cancer than CMS eligibility (PLCO AUC of 0.755 vs 0.634; p<0.001). The CXR-LC model's performance was similar to that of PLCOm2012, a state-of-the-art risk score with 11 inputs, in both the PLCO data set (CXR-LC AUC of 0.755 vs PLCOm2012 AUC of 0.751) and the NLST data set (0.659 vs 0.650). When compared in equal-sized screening populations, the CXR-LC was more sensitive than CMS eligibility in the PLCO data set (74.9% vs 63.8%; p=0.012) and missed 30.7% fewer incident lung cancers. On decision curve analysis, CXR-LC had higher net benefit than CMS eligibility and similar benefit to PLCOm2012.

Comment (PD): Following publication of the Nelson study, targeted population-based lung cancer screening is gaining traction worldwide but it requires sophisticated risk prediction tools in order to make it cost effective. Usual criteria for entry to a lung cancer screening programme would be age, sex, and smoking history, but this particular model for validation incorporated a computerised deep learning algorithm applied to chest x-rays (CXR-LC) that was used to predict lung cancer incidence over a 12-year period in three different datasets from lung cancer screening trials. The model was found to be as predictive as the state-of-the-art 11-input PLCOm2012 risk score and superior to the standard eligibility criteria used in the US. However, this validation needs to be applied beyond lung cancer screening trials to real-life clinical settings.

Reference: Ann Intern Med. 2020;173(9):704–713
Abstract