Lung Cancer RESEARCH REVIEW™

Making Education Easy

Issue 20 – 2022

In this issue:

Abbreviations used in this issue

ALK = anaplastic lymphoma kinase
CT = computerised tomography
DFS = disease-free survival
EBUS = endobronchial ultrasound
ECOG PS = Eastern Cooperative Oncology Group performance status
EGFR = epidermal growth factor receptor
HR = hazard ratio
HRQOL = health-related quality of life
LDCT = low-dose computed tomography
MDT = multidisciplinary team
NSCLC = non-small cell lung cancer
ORR = objective response rate
OS = overall survival
PARP = poly(ADP-ribose) polymerase
PD-1 = programmed cell death receptor-1
PD-L1 = programmed cell death-ligand 1
PET = positron emission tomography
PET-CT = positron emission tomography-computed tomography
PFS = progression-free survival
TKI = tyrosine kinase inhibitor
TMB = tumour mutational burden

Welcome to the twentieth issue of Lung Cancer Research Review.

Selections include a comparison of atezolizumab and nivolumab using real-world data, a small phase 2 trial looking at combining the PARP inhibitor niraparib with pembrolizumab, and a study suggesting that smoking history can predict response to immune checkpoint inhibitors. Other research in this issue investigates how adjuvant osimertinib affects patient HRQOL, whether inclusion criteria for lung cancer screening should be extended to non-smokers, and the utility of a non-invasive genetic biomarker in the diagnosis of lung cancer.

We hope that you learn something new from reading this issue of **Lung Cancer Research Review** and hope to receive more of your comments and feedback.

Kind regards

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Comparative effectiveness of atezolizumab, nivolumab, and docetaxel in patients with previously treated non-small cell lung cancer

Authors: Ramagopalan S et al.

Summary: In this comparative effectiveness study, patients with advanced NSCLC resistant to platinum-based chemotherapy who initiated atezolizumab, docetaxel, or nivolumab were compared using nationally representative real-world data from more than 280 US cancer clinics. A total of 3,336 patients (mean age 67.1 years) were assessed in the main analysis, including 206 patients receiving atezolizumab, 500 receiving docetaxel, and 2,630 receiving nivolumab. The comparisons of interest were atezolizumab versus docetaxel and atezolizumab versus nivolumab. After adjustment for baseline characteristics, atezolizumab was associated with a significantly longer OS compared with docetaxel (HR 0.79; 95% CI: 0.64–0.97). There was no significant difference in OS between atezolizumab and nivolumab (HR 1.07; 95% CI: 0.89–1.28). The findings were consistent across all patient subgroups tested and robust to plausible deviations from random missingness for ECOG PS in real-world data.

Comment (AL): Although this is a retrospective series and fraught with all of the normal biases, it is likely that we will never get randomised prospective data that compares one checkpoint inhibitor with another. We are therefore limited to cross-trial comparisons in our decisions regarding which to use. In general there is a feeling that the efficacy is likely to be similar. In clinical practice, the substitution of one drug for another for cost and convenience reasons is not uncommon. It is worth noting that the sample size in this study is probably too small to detect a small difference in efficacy between atezolizumab and nivolumab and that the study is subject to confounding factors by its observational nature and some gaps in the information. Despite these weaknesses it is nice to have some data to back up our assumptions and give us some reassurance that the substitution of therapeutic agents is an appropriate practice.

Reference: JAMA Netw Open. 2021;4(11):e2134299
Abstract

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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.

JASPER: Phase 2 trial of first-line niraparib plus pembrolizumab in patients with advanced non-small cell lung cancer

Authors: Ramalingam SS et al.

Summary: In this phase 2 trial, the PARP inhibitor niraparib was evaluated in combination with the PD-1 inhibitor pembrolizumab in patients with metastatic and/or locally advanced NSCLC. Patients whose tumours had PD-L1 tumour proportion scores (TPS) ≥50% (cohort 1) or 1–49% (cohort 2) received first-line niraparib plus pembrolizumab. Thirty-eight patients were enrolled: 17 in cohort 1 and 21 in cohort 2. In cohort 1, the ORR was 56.3% (9/16 patients; 95% CI: 29.9–80.2); 2 of 16 patients had complete responses and 7 of 16 had partial responses (PRs). In cohort 2, ORR was 20.0% (95% CI: 5.7–43.7) with 4 of 20 PRs. In cohorts 1 and 2, the median duration of response was 19.7 months (95% CI: 4.2 to not estimable [NE]) and 9.4 months (95% CI: 4.2 to NE), the median PFS was 8.4 months (95% CI: 3.9–22.1) and 4.2 months (95% CI: 2.0–6.2), and the median OS was NE (95% CI: 6.0 to NE) and 7.7 months (95% CI, 4.0–12.5), respectively. The rates of grade ≥3 treatment-emergent adverse events were 88.2% and 85.7% in cohorts 1 and 2, respectively.

Comment (AL): Keynote 024 (Reck M, et al. NEJM 2016;375(19):1823–33) showed us that single-agent pembrolizumab is active and effective when the cancer has a PD-L1 >50%. The response rate in that group was 45%. This is a small phase 2 study looking at combining a PARP inhibitor with pembrolizumab. PARP inhibitors have not had much success in NSCLC previously; however, there is some good scientific basis for hoping they may add to the effectiveness of PD-1 inhibitors. The advantage of a single-agent PD-1 inhibitor is avoiding the toxicity of chemotherapy. We know that the addition of chemotherapy increases the response rate and so in certain patients with high-volume disease, that initial response is very important. If it could be achieved with the addition of an oral therapy instead, then it certainly would be an option that interests patients. This is a small study though and the response rate in the PDL-1 >50% group is a little higher than in Keynote 024 but at 56.3% it is not that impressive. The response rate and OS in the PD-1 <50% cohort is disappointing. I will be waiting for the phase 3 trial before considering this as an option in my practice.

Reference: Cancer. 2022;128(1):65–74
Abstract

Targeted therapy for advanced anaplastic lymphoma kinase (ALK)-rearranged non-small cell lung cancer

Authors: Cameron LB et al.

Summary: This Cochrane review of the literature evaluated the safety and efficacy of ALK inhibitors given as monotherapy to treat advanced ALK-rearranged NSCLC. Eleven studies (n=2,874) met the inclusion criteria: six studies compared an ALK inhibitor (crizotinib, ceritinib, and alectinib) with chemotherapy, and five studies compared a next-generation ALK inhibitor (alectinib, brigatinib, and lorlatinib) with crizotinib. The evidence for most outcomes was considered to be of moderate to high certainty. Although most studies were at low risk for selection, attrition, and reporting bias, no randomised controlled trials were blinded, resulting in a high risk of performance and detection bias for outcomes reliant on subjective measurement. The overall conclusion was that next-generation ALK inhibitors, including alectinib, brigatinib, and lorlatinib, are the preferred first systemic treatment for individuals with advanced ALK-rearranged NSCLC. Further trials are underway, including evaluation of first-line ensartinib. The next-generation inhibitors have not been compared with each other and which should be used first and what subsequent treatment sequence is optimal is not known.

Comment (AL): It is always reassuring to have a Cochrane systematic review of the evidence to back up our ideas about a subject. ALK rearranged lung adenocarcinoma does better with ALK-directed therapy than chemotherapy and later generation ALK-directed therapies are better than crizotinib. None of us know which later generation drug is best and sometimes it is also nice to have someone look at all the data available and confirm that we are not missing anything. There is no evidence to tell us whether brigatinib, lorlatinib, or alectinib should be first line. There are no ground-breaking revelations from this Cochrane review but it provides reassurance to us that gaps in our knowledge are not a personal fault but a hole in the international patchwork of knowledge. It also confirms a sensible option for future study albeit investigator led as no drug company is going to be rushing to show their drug is inferior.

Reference: Cochrane Database Syst Rev. 2022;1(1):CD013453
Abstract

Smoking history as a potential predictor of immune checkpoint inhibitor efficacy in metastatic non-small cell lung cancer

Authors: Wang X et al.

Summary: Patient smoking history, clinicopathological characteristics, TMB by clinical targeted next generation sequencing, and PD-L1 tumour proportion score (TPS) by immunohistochemistry were prospectively collected from 644 advanced NSCLC patients treated with immune checkpoint inhibitor (ICI) monotherapy. The association of smoking history with clinical outcomes of ICI monotherapy in metastatic NSCLC patients was evaluated after adjusting for other potential predictors. Of the 644 patients evaluated, 105 (16.3%) were never smokers, 375 (58.2%) were former smokers (median pack-years = 28), and 164 (25.4%) were current smokers (median pack-years = 40). Multivariable logistic and Cox proportional hazards regression analyses indicated that doubling of smoking pack-years is statistically significantly associated with improved clinical outcomes of patients treated with ICI monotherapy (ORR OR was 1.21; 95% CI: 1.09–1.36; p<0.001; PFS HR was 0.92; 95% CI: 0.88–0.95; p<0.001; and OS HR was 0.94; 95% CI: 0.90–0.99; p=0.01).

Comment (AL): It makes sense that there would be a correlation between smoking status and response to PD-L1. Essentially the carcinogenic substances in tobacco smoke are mutagenic. The more smoking, the more mutations, or the higher the TMB. Now while that is never going to be a perfect linear correlation it is pleasing to see this study showing that the correlation exists. In reality I am not sure that smoking status will ever directly inform decisions about the use of checkpoint inhibitors, and this doesn't really move forward our hunt for useful biomarkers. We may use it in place of TMB when next-generation sequencing is not immediately available,i.e., for most NZ patients, but really, we need to move towards making next-generation sequencing available as a priority. Surrogate markers like this may leave more questions than answers for the individual patient, especially if they have never been a smoker.

Reference: J Natl Cancer Inst. 2021;113(12):1761–1769
Abstract

Health-related quality of life outcomes in patients with resected epidermal growth factor receptor-mutated non-small cell lung cancer who received adjuvant osimertinib in the phase III ADAURA trial

Authors: Majem M et al.

Summary: These investigators report HRQOL outcomes from ADAURA, a phase 3 trial that demonstrated a statistically significant and clinically meaningful disease-free survival benefit in patients with completely resected stage IB-IIIA EGFR-mutated (EGFRm) NSCLC who received adjuvant treatment with osimertinib versus placebo, with/without prior adjuvant chemotherapy, for 3 years or until recurrence/discontinuation. Baseline physical/mental component summary (PCS/MCS) scores were comparable between osimertinib and placebo (range 46–47) and maintained to week 96, with no clinically meaningful differences between treatment arms; difference in adjusted least squares mean (95% CI): -1.18 (-2.02 to -0.34) and -1.34 (-2.40 to -0.28) for PCS and MCS, respectively. In addition, there were no differences between treatment arms for time to deterioration of PCS and MCS: HR 1.17 (95% CI: 0.82–1.67) and HR 0.98 (95% CI: 0.70–1.39), respectively.

Comment (AL): The initial efficacy results of the ADAURA trial were presented last year. There was a significant improvement in DFS when osimertinib was given for 3 years after surgery and adjuvant chemotherapy for early-stage EGFR mutant lung adenocarcinoma. Many places around the world have adopted the adjuvant osimertinib strategy although it remains controversial as there is not yet OS data. QOL information is critical, however, when deciding if a DFS benefit is enough to justify the treatment. There are always limitations to assessing QOL with questionnaires; however, it is patient reported data and therefore not as susceptible to physician bias as toxicity data. It is certainly reassuring if a patient wishes to take the adjuvant osimertinib approach based on the current data to know that although we cannot yet say it will offer prolonged survival, we can be reasonably confident it will not impact their QOL too much.

Reference: Clin Cancer Res. 2022 Jan 10 [Online ahead of print]
Abstract

Discussion of advance care planning on end-of-life decisions with lung cancer patients in Wuhan, China: attitude, timing and future directions

Authors: Hu L et al.

Summary: These researchers conducted questionnaire-based interviews with Chinese lung cancer patients to describe their knowledge of advanced care planning (ACP) end-of-life (EOL) care preferences, and the predictors of patients' preference for ACP, as well as who should mention ACP. Two hundred and fifty-eight lung cancer patients were recruited when first admitted to a hospital lung cancer clinic in China. Interviews revealed that 91.1% (n=235) favoured ACP on EOL issues and 60% (n=160) wanted to make EOL decisions on their own. Only 10% of patients were familiar with advance directions. Eighty-two (31.8%) patients were familiar with do not resuscitate/do not intubate (DNR/DNI) directions. In 92.2% of patients, ACP was not mentioned. Significant predictors of preference for autonomous ACP were: gender (male, OR 4.87; 95% CI: 2.16–5.83), tumour stage (stage III, OR 0.108; 95% CI: 0.06–0.51); stage IV, OR 1.780; 95% CI: 1.02–2.11), and number of children (every increase in the number of children, OR 0.267; 95% CI: 0.09–0.93). Female patients were 2.743-fold and patients currently receiving treatment 1.8-fold more willing to need ACP initiated by doctors.

Comment (PD): This study is relevant to those treating our patients of Chinese origin in lung cancer clinics. They interviewed more than 250 patients in a lung cancer clinic in Wuhan, China, and found an overwhelmingly positive response (>90%) to the concept of discussing advanced care planning and the majority wanting to make this decision on their own. However, there was poor awareness of ACP or DNR orders before the questionnaire and very few had had the issue brought up by their clinicians. Females, those with one child, and those with early cancer were identified as those who were less likely to raise the issue of ACP planning themselves. This study may challenge preconceptions about the preferences of this group of patients and it behoves us to address cultural engagement.

Reference: Intern Med J. 2021;51(12):2111–2118
Abstract

Effect of a postoperative home-based exercise and self-management programme on physical function in people with lung cancer (CAPACITY): protocol for a randomised controlled trial

Authors: Granger CL et al.

Summary: After the feasibility assessment stage (phase I) of CAPACITY confirmed the feasibility of a 12-week home-based exercise and self-management programme (the programme) delivered postoperatively, the efficacy stage (phase II) of CAPACITY will determine whether the programme, compared with usual care, is effective in improving physical function in patients after lung cancer surgery. Phase II of CAPACITY will be a prospective, randomised parallel-group superiority trial with assessors blinded to group allocation. A total of 112 patients scheduled for surgery for lung cancer will be recruited and randomised to usual care (no exercise programme) or usual care plus the 12-week programme. The primary endpoint will be physical function measured with the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ c30) questionnaire. Secondary endpoints will include: HRQOL; exercise capacity; muscle strength; physical activity levels, and patient-reported outcomes (PROs). HRQOL and PROs will be measured out to 12 months, and survival out to 5 years. Additionally, patient experience interviews will be conducted in a subgroup of intervention participants.

Comment (PD): After a positive feasibility study, the CAPACITY trial enters its second phase of a home-based and self-managed exercise and activity programme versus usual care (which is usually very little) for people who have had lung cancer surgery. Physical function and QOL outcomes will be measured. Other studies are addressing "prehabilitation", exercise programmes before surgery in order to improve fitness in the peri- and post-operative period. Physiotherapy resourcing will have to be improved significantly in order to deliver these potentially important interventions in future surgical care.

Reference: BMJ Open Respir Res. 2022;9(1):e001189
Abstract

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Association of computed tomographic screening promotion with lung cancer overdiagnosis among Asian women

Authors: Gao W et al.

Summary: To determine the association of lung cancer incidence with the promotion of screening in a largely non-smoking population, this population-based ecological cohort study of stage-specific lung cancer incidence used the Taiwan Cancer Registry to identify women diagnosed with lung cancer. In a population of approximately 12 million Taiwanese women, a total of 57,898 women were diagnosed with lung cancer. Following the introduction of LDCT screening, the incidence of early-stage (stages 0-I) lung cancer increased more than 6-fold, from 2.3 to 14.4 per 100,000 population (absolute difference, 12.1 [95% CI: 11.3–12.8]) from 2004 to 2018. However, there was no change in the incidence of late-stage (stages II-IV) lung cancer, from 18.7 to 19.3 per 100,000 (absolute difference, 0.6 [95% CI: -0.5 to 1.7]). The additional 12.1 per 100,000 early-stage cancers were not accompanied by a concomitant reduction in late-stage cancers, indicating that virtually all the additional cancers detected represent overdiagnosis.

Comment (PD): Most lung cancer screening risk protocols at present incorporate smoking history as a central criterion and non-smokers are usually excluded. However, 10–20% of lung cancers are in non-smokers (depending on the population) so will not be picked up using these protocols. This Taiwanese study followed a large cohort of women over a 14-year period diagnosed with lung cancer as a result of a low dose CT screening programme. There was a low smoking prevalence of <5% in Taiwanese women. Disappointingly, although more early-stage lung cancers were picked up there was no corresponding decrease in stage 4 lung cancer over this period, suggesting these excess tumours are over-diagnosed (i.e., they would not have become clinically relevant). Overdiagnosis is a potential problem in any lung cancer screening programme and this study would suggest extending inclusion criteria to non-smokers would not be cost effective, at least in the population studied.

Reference: JAMA Intern Med. 2022 Jan 18 [Online ahead of print]
Abstract

Hospital-based multidisciplinary lung cancer care in Australia: a survey of the landscape in 2021

Authors: Brims FJH et al.

Summary: Because there are no data on compliance with treatment guidelines and little is known about lung cancer MDT infrastructure around Australia, these researchers invited clinicians from institutions treating lung cancer to complete an online survey regarding the local infrastructure for lung cancer care and contemporary issues affecting lung cancer. Responses from 79 separate institutions were obtained, which represented 72% of all known institutions treating lung cancer in Australia. The majority (93.6%) held a regular MDT meeting although recommended core membership was only achieved for 42/73 (57.5%) sites. There was no thoracic surgery representation in 17/73 (23.3%) of MDTs and surgery was less represented in regional and low case volume centres. Specialist nurses were present in just 37/79 (46.8%) of all sites. Access to diagnostic and treatment facilities was limited for some institutions and IT infrastructure was variable. Most sites (69%) did not perform regular audits against guidelines.

Comment (PD): Variations in resources and personnel across Australia have been highlighted in this survey. Under half of surveyed centres had a lung cancer nurse specialist and just over half had core membership of thoracic MDT meeting fulfilled. There was inequity of access to investigations such as PET-CT and EBUS and to thoracic surgery identified in geographically remote areas and lower volume centres. The authors argue that a national lung cancer registry (along the lines of the UK LUCADA database) would help identify variations like this and enable national audit. Variations in lung cancer care have recently been identified in NZ in the Lung Cancer Quality Improvement Monitoring Report. A central lung cancer specific database would certainly have benefits here too. There would also be opportunities to benchmark our performance against Australia.

Reference: BMJ Open Respir Res. 2022;9(1):e001157
Abstract

A cost-effective and non-invasive pfeRNA-based test differentiates benign and suspicious pulmonary nodules from malignant ones

Authors: Liu W, et al.

Summary: In this retrospective three-stage study that included healthy patients, patients with benign pulmonary nodules, patients with suspicious nodules, and patients with malignant nodules, the investigators determined that plasma protein functional effector sncRNAs (pfeRNAs) serve as non-invasive biomarkers for determining both the existence and the nature of pulmonary nodules. Following the standards required for a clinical laboratory improvement amendments (CLIA)-compliant laboratory-developed test (LDT), the investigators identified a pfeRNA classifier containing eight pfeRNAs in 108 biospecimens from 60 patients by sncRNA deep sequencing, deduced prediction rules using a separate training cohort of 198 plasma specimens, and then applied the prediction rules to another 230 plasma specimens in an independent validation cohort. They found that the pfeRNA classifier could differentiate patients with or without pulmonary nodules with an average sensitivity and specificity of 96.2% and 97.35%. It could also differentiate malignant versus benign pulmonary nodules with an average sensitivity and specificity of 77.1% and 74.25%. The biomarkers were considered cost-effective, non-invasive, sensitive, and specific.

Comment (PD): At present we have no biomarkers in routine use in the diagnosis of lung cancer. The development of biomarkers is receiving much attention since they may be a way of making LDCT screening more cost effective if incorporated into the risk assessment algorithms. These may include volatile compounds detected in the breath or saliva or, as in this case, genetic markers in the plasma. This study looked at a group of non-coding RNA markers that are involved in transcriptional and translational processes. They not only could differentiate the presence or absence of nodules with high sensitivity and specificity (>95% each) but could also differentiate between benign and malignant nodules with moderate sensitivity and specificity (>70% each). Studies like this are early days of biomarker development and we can expect to see better sensitivity and specificity of candidate biomarkers as the research continues.

Reference: Noncoding RNA. 2021;7(4):80
Abstract

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Independent commentary by Dr Paul Dawkins

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