Lung Cancer RESEARCH REVIEW™

Making Education Easy

Issue 18 – 2021

In this issue:

Abbreviations used in this issue

ECOG = Eastern Cooperative Oncology Group
ECOG-PS = Eastern Cooperative Oncology Group performance status
EGFR = epidermal growth factor receptor
EGFR-TKI = epidermal growth factor receptor-tyrosine kinase inhibitor
NSCLC = non-small-cell lung cancer
OS = overall survival
PD-L1 = programmed death-ligand 1
PS = Performance status
PFS = progression-free survival
SABR = stereotactic ablative radiotherapy
SCLC = small-cell lung cancer
TKI = tyrosine kinase inhibitor

Welcome to this issue of Lung Cancer Research Review.

This issue features three papers that report on the status of lung cancer management in NZ, including ethnic disparities in EGFR-activating mutation rates and testing, age disparities in lung cancer survival, and how NZ compares with other OECD countries in terms of lung cancer survival.

Other selections investigate outcomes after immune checkpoint inhibitor treatments in NSCLC patients with leptomeningeal metastases, the real-world utility of next-generation sequencing, and performance status and pembrolizumab in the first-line treatment of advanced NSCLC.

We hope that you enjoy reading this issue of **Lung Cancer Research Review**. Your comments and suggestions are always appreciated.

Kind regards

Dr Paul Dawkins
pauldawkins@researchreview.co.nz

Dr Aileen Ludlow
aileenludlow@researchreview.co.nz

Sotorasib for lung cancers with KRAS p.G12C mutation

Authors: Skoulidis F et al.

Summary: This single-group phase 2 trial investigated the activity of sotorasib in 124 patients with *KRAS* p.G12C-mutated advanced NSCLC previously treated with standard therapies. An objective response was observed in 46 patients (37.1%; 95% CI: 28.6–46.2), which included 4 (3.2%) achieving a complete response and 42 (33.9%) achieving partial response. Median duration of response was 11.1 months (95% CI: 6.9–could not be evaluated). Disease control was achieved in 100 patients (80.6%; 95% CI: 72.6–87.2). Median PFS was 6.8 months (95% CI: 5.1–8.2) and median OS was 12.5 months (95% CI: 10.0–could not be evaluated). Treatment-related adverse events were observed in 88/126 patients (69.8%), with grade 3 events seen in 25 patients (19.8%) and a grade 4 event in one patient (0.8%).

Comment (AL): KRAS mutations have long been the bane of a lung oncologist's life. The poor outcomes for KRAS mutant lung cancer have previously evaded attempts at targeted intervention. It is very pleasing now to see drugs in development with such promising results. This trial is a single-arm phase 2, but in this population of pre-treated patients an objective response rate of 46% is very impressive. A median OS of 12.5 months is also very encouraging. It is wonderful to have the potential of a further option for therapy that has a decent chance of benefiting patients rather than the rather debateable benefit of third-line docetaxel. I look forward to the phase 3 data.

Reference: N Engl J Med. 2021;384(25):2371–2381
Abstract

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Perspectives on Precision Oncology

Dr Angela George is the Consulting Editor for the Perspectives on Precision Oncology series.

In her opening editorial Dr George remarks:

"We have entered an age of oncology where we can now use molecular information from patients and their tumours to match treatments in ways that would have been unthinkable only a decade ago. It is a world in which almost every tumour has the potential to have a molecularly matched drug – if the testing and appropriate drug are accessible."

This review is a unique NZ publication that aims to provide readers with topical and accessible information on the fast-developing and exciting field of precision or personalised cancer treatments. The review includes significant recent research in the field, focusing on tests, techniques and treatments that are relevant to the NZ setting.

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Population-based incidence rates and increased risk of EGFR mutated non-small cell lung cancer in Māori and Pacifica in New Zealand

Authors: Aye PS et al.

Summary: These researchers analysed data from 3,815 non-squamous NSCLC patients diagnosed in northern NZ obtained from a population-based cancer registry. About 45% (n=1,709) of the patients had EGFR mutation testing, with 22.5% being EGFR mutation-positive. The age-standardised rate (ASR) of EGFR mutation-positive NSCLC was 5.05 (95% CI: 4.71–5.39) per 100,000 person-years. ASRs for EGFR mutation-positive NSCLC were higher for females than males: standardised incidence ratio (SIR) 1.50 (1.31–1.73); and higher for Pacifica, Asians, and Māori than for NZ Europeans: SIRs 3.47 (2.48–4.85), 3.35 (2.62–4.28), and 2.02 (1.43–2.87), respectively.

Comment (AL): It is great to finally have the data to support our anecdotal knowledge that EGFR mutations are more common in Pacific and Māori populations. The timeframe that this study covers is mostly before the funding of EGFR-targeted agents in NZ, which happened in 2017. The rates of testing steadily increased over the study period but the percentage tested in this study remains disappointingly low. It is now a national standard to test all lung non-squamous NSCLCs for EGFR mutations. I would be interested to see the data surrounding that and how good our testing rates are. This study certainly supports the idea that we should be placing Māori and Pacific ethnicities in the basket of patients who have a higher chance of having a EGFR-activating mutation.

Comment (PD): This paper shows population incidence of EGFR mutations is higher in Pacifica, Asians, and Māori. However the denominator is the general population, not just patients with lung cancer. In the case of Māori, therefore, another explanation may be that the higher incidence of EGFR mutations could be because Māori are more likely to have lung cancer full stop. Their data show Māori are twice as likely to get EGFR-positive disease and 3.5-times as likely to get EGFR-negative disease, that is to say lung cancer is more common in this ethnic group per se. Testing rates were lower in Māori, possibly because of preconceptions about the incidence of EGFR-positive disease. Appropriate molecular testing is in the national lung cancer standards, but it is patchily applied. Whilst reflex EGFR testing is done in some regions, introducing this across the country would be the obvious solution for inequities in testing.

Reference: PLoS One. 2021;16(5):e0251357
Abstract

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Clinical outcomes of non-small cell lung cancer patients with leptomeningeal metastases after immune checkpoint inhibitor treatments

Authors: Zheng M-M et al.

Summary: These researchers screened 255 NSCLC patients diagnosed with leptomeningeal metastases (LM) at their institute as well as cases reported in the literature and identified 32 patients who had received immune checkpoint inhibitors after LM diagnosis. ICI regimens included nivolumab (n=21), pembrolizumab (n=9), and atezolizumab (n=2). Neurological symptom control was experienced by 62.5% of patients. Two patients had both intracranial and extracranial complete tumour response; one patient had both intracranial and extracranial partial response (PR), one patient had intracranial PR and a systemic PR, and one patient had central nervous system PR without extracranial response. Median PFS in the single-agent subgroup was 2.1 months (95% CI: 1.4–2.9) and median OS was 4.0 months (95% CI: 0.1–13.3). A better ECOG-PS score was associated with prolonged PFS (p=0.04).

Comment (AL): Leptomeningeal disease is always bad news. We know that chemotherapy has little utility in this circumstance and there remains uncertainty regarding the utility of immunotherapy in this setting. This retrospective data looks at a small number of patients with only 35 having received immunotherapy after diagnosis of leptomeningeal disease. 62% neurological symptom control seems encouraging but a PFS of 2.1 months and an OS of 4 months is still fairly poor. As the story often is with immunotherapy, a small number of patients do very well. Picking those patients seems to be the key. Having said all that, in a situation that is otherwise dire, the hope of a possible prolonged response means trying immunotherapy is a reasonable option.

Reference: Eur J Cancer. 2021;150:23–30
Abstract

Durvalumab for stage III EGFR-mutated NSCLC after definitive chemoradiotherapy

Authors: Aredo JV et al.

Summary: In this multicentre retrospective analysis of patients with unresectable stage 3 EGFR-mutated NSCLC who completed concurrent chemoradiotherapy (CRT), Kaplan-Meier analyses were used to evaluate PFS between patients who completed CRT with or without durvalumab. Thirteen of 25 patients initiated durvalumab a median of 20 days after CRT completion. Two patients completed 12 months of treatment, with five patients discontinuing durvalumab due to progression and five due to immune-related adverse events. Of 24 patients who completed CRT without durvalumab, 16 completed CRT alone and eight completed CRT with induction or consolidation EGFR-TKIs. Median PFS was 10.3 months in patients who received CRT plus durvalumab compared with 6.9 months with CRT alone (p=0.993). CRT plus EGFR-TKI was associated with a significantly longer median PFS (26.1 months) compared with CRT plus durvalumab or CRT alone (p=0.023).

Comment (AL): When patients with EGFR-mutant cancer have been left out of most of the immunotherapy trials due to previous poor performance of immunotherapy in this setting it becomes difficult to know what to do with the standard of care for these patients. Should we be offering durvalumab or not? This study has a very small number of patients. There is a numerical improvement in PFS but it is not statistically significant. There is also a comparison to using EGFR-TKIs in this setting. This is probably not a helpful comparison and PFS is not the right outcome. Does it improve survival? One message from this study (bearing in mind the small number of patients) is the high rate of discontinuations due to immunotherapy toxicity. I think the question of benefit to EGFR-mutant lung cancer outcomes from durvalumab in the stage 3 setting remains unanswered but I certainly think the potential toxicity gives reason to pause.

Reference: J Thorac Oncol. 2021;16(6):1030–1041
Abstract

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Metformin in combination with chemoradiotherapy in locally advanced non-small cell lung cancer: the OCOG-ALMERA randomized clinical trial

Authors: Tsakiridis T et al.

Summary: The Ontario Clinical Oncology Group Advanced Lung Cancer Treatment with Metformin and Chemoradiotherapy (OCOG-ALMERA) study was a multicentre, randomised, phase 2 trial that evaluated whether metformin, given concurrently with chemoradiotherapy and as consolidation treatment, could improve outcomes in patients with locally advanced NSCLC (LA-NSCLC). The trial was designed to enrol 96 patients with unresected LA-NSCLC who did not have diabetes but was stopped early due to slow accrual. A total of 54 patients were randomised: 26 to the experimental arm and 28 to the control arm. Treatment failure was observed in 18 patients (69.2%) receiving metformin within 1 year compared with 12 (42.9%) control patients (p=0.05). The 1-year PFS rate was 34.8% (95% CI: 16.6–53.7) in the metformin arm and 63.0% (95% CI: 42.1–78.1) in the control arm (HR 2.42; 95% CI: 1.14–5.10). Rates of OS were 47.4% (95% CI: 26.3–65.9) in the metformin arm and 85.2% (95% CI: 65.2–94.2) in the control arm (HR 3.80; 95% CI: 1.49–9.73). At least one grade 3 adverse event was reported by 53.8% of patients in the experimental arm versus 25.0% in the control arm.

Comment (AL): This trial was slow to accrue and did not meet its target. It therefore had a very small number of patients with which to draw conclusions. The results are quite striking though. Metformin did not only fail to improve outcomes for stage III patients but appears to be detrimental. The utility of several widely used medications repurposed for treating cancer is a popular question from patients. This study highlights the need for specific research into this area rather than the blind hope that if it is not helpful, it at least will not do any harm. In reality the outcomes from the trial are not very reliable with the small numbers recruited; however, I suspect it is enough to put anyone off from an attempt at a repeat.

Reference: JAMA Oncol. 2021 Jul 29 [Online ahead of print]
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.

Pembrolizumab for first-line treatment of advanced non-small-cell lung cancer: analysis of prognostic factors of outcomes

Authors: Tibaldi C et al.

Summary: This retrospective study evaluated the safety and efficacy of pembrolizumab as monotherapy for advanced NSCLC without activating mutations and with PD-L1 ≥50% and to investigate potential prognostic factors in daily clinical practice. In 14 patients with a median follow-up of 15.2 months, median PFS (mPFS) and OS (mOS) were 9.2 months (95% CI: 4.8–13.5) and 15.9 months (95% CI: not yet evaluable), respectively. Patients with an ECOG-PS of 2 had an mPFS of 2.8 months (95% CI: 2.1–3.4) and an mOS of 3.9 months (95% CI: 2.5–5.3). Patients with liver metastases at diagnosis had an mPFS of 3.2 months (95% CI: 0.6–5.8) and an mOS of 6.0 months (95% CI: 3.7–8.4). OS gender, ECOG-PS 2, and presence of liver metastases were independent prognostic factors.

Comment (AL): This retrospective review of Italian patients treated with pembrolizumab for NSCLC with PD-L1 ≥50% reinforces the idea that just because pembrolizumab is better tolerated than chemotherapy, does not mean it is a good treatment option for patients with a poor performance status. Liver metastases are also a poor prognostic factor and single-agent pembrolizumab does not seem as effective in that setting. All of these retrospective reviews add a little more to our knowledge when faced with decisions about the best first-line treatments for our patients in this rapidly expanding field.

Reference: Anticancer Agents Med Chem. 2021 Jul 26 [Online ahead of print]
Abstract

Real-world utility of next-generation sequencing for targeted gene analysis and its application to treatment in lung adenocarcinoma

Authors: Kim JH et al.

Summary: These researchers reviewed data from 391 patients with lung adenocarcinoma who had undergone next-generation sequencing (NGS) to evaluate the clinical utility of NGS for detection of genetic alterations and its implications for treatment of lung adenocarcinoma in real-world practice. At least one actionable mutation (AM) was identified in 294 patients (75.2%). The most commonly mutated gene was EGFR (n=130, 33.2%), involving EGFR exon 19 deletion (n=48, 12.3%), L858R (n=47, 12%), and others (n=35, 9%), followed by KRAS (n=48, 12.3%), ALK (n=40, 10.2%), RET (6%), MET (3%), ROS-1 (3%), and BRAF (2%) mutations. With a median follow-up duration of 16.8 months, median OS was 36.8 months in patients with stage IV disease. Patients treated with the corresponding targeted therapy for AMs based on NGS reports lived longer than those not treated with such therapy (p<0.001). Targeted therapy for AMs was a favourable factor for survival (AM without targeted therapy vs AM with targeted therapy: HR 2.58; 95% CI: 1.57–4.25; p<0.001).

Comment (PD): This Korean study used next-generation sequencing (NGS) for detection of actionable mutations in lung adenocarcinoma. One third had an EGFR mutation and other mutations with available treatments (ALK, ROS-1, RET) were common as well as others for which novel treatments are being developed. The authors found a link with an actionable mutation to OS. The advantage of NGS is that it enables quick and easy identification of multiple genetic alterations simultaneously, rather than using conventional sequential tests. As we move into the era of personalised and precision medicine, and as more targeted treatments become available and funded, the role of NGS will become increasingly important.

Reference: Cancer Med. 2021;10(10):3197–3204
Abstract

Age disparities in lung cancer survival in New Zealand: the role of patient and clinical factors

Authors: Pilleron S et al.

Summary: Using population-based cancer registry data linked to hospitalisation data, these authors describe the role of patient-related and clinical factors on the age pattern in lung cancer survival and excess mortality hazard by stage at diagnosis in NZ. Data from 22,487 new lung cancer cases aged 50–99 years were extracted from the national population-based cancer registry. The age difference in net survival was particularly marked for localised and regional lung cancers, with a sharp decline in survival from age 70 years. No identified factors influenced age disparities in patients with localised cancer. For other stages, however, there was a greater difference in survival between middle-age and older-age for females than for males. Ethnicity and deprivation had no effect on age disparities in lung cancer survival.

Comment (PD): This paper addresses the issue of why the improvement in lung cancer survival we have seen over the past few years has not been reflected to such an extent in the over 75s. The authors statistically modelled the effect of various factors to excess mortality hazard. They found that early-stage lung cancer had a particular age disparity for survival, probably because the younger are more likely to receive curative treatment. In later stage disease, females had greater age disparities for survival. Various reasons for this are postulated including the possible implication of sex hormones, higher receipt of treatment, or better response to treatment. Comorbidities and presentation through emergency departments only had a small effect on age disparity. Perhaps surprisingly ethnicity and socioeconomic status had no effect on age disparity, even though they are strongly linked to lung cancer survival per se.

Reference: Lung Cancer. 2021;157:92–99
Abstract

Stereotactic ablative radiotherapy in T1-2N0M0 small cell lung cancer: a systematic review and meta-analysis

Authors: Safavi AH et al.

Summary: These researchers performed a systematic review and meta-analysis of the literature on SABR for T1-2N0M0 SCLC to summarise outcomes including local control (LC), OS, recurrence rates, and toxicity. Seven (399 patients) of 11 studies identified in the systematic review were selected for the meta-analysis. Inoperability was noted as the indication for SABR in 94% of patients. Median follow-up was 19.5 months and median tumour size 24 mm. Rates of chemotherapy and prophylactic cranial irradiation use were 44.1% (95% CI: 27.0–61.9) and 13.8% (95% CI: 0.4–41.2), respectively. Local control was 97.3% (95% CI: 92.3–99.8) at 1 year and 95.7% (95% CI: 74.2–100.0) at 2 years. OS was 86.3% (95% CI: 74.4–94.9) at 1 year and 63.7% (95% CI: 45.7–79.9) at 2 years. Nodal and distant recurrence rates were 17.8% (95% CI: 7.5–31.2) and 26.9% (95% CI: 7.4–53.0), respectively. No grade 4 or 5 events were observed across the studies.

Comment (PD): Surgery is indicated for early-stage (node-negative) SCLC, but what about when the patient is not fit to undergo this? This meta-analysis (where inoperability was noted as the indication in the vast majority) showed good local control rates. Nearly half also received chemotherapy. OS was 97.3% at one year but dropped to 63.7% at two years. Toxicity rates were low. SABR should be considered an option in patients with early-stage SCLC unfit for surgery and with concerns of toxicity with concomitant chemoradiation.

Reference: Lung Cancer. 2021 Jul 21 [Online ahead of print]
Abstract

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International differences in lung cancer survival by sex, histological type, and stage at diagnosis: an ICBP SURVMARK-2 study

Authors: Araghi M et al.

Summary: The International Cancer Benchmarking Partnership (ICBP) SURVMARK-2 study analysed 236,114 NSCLC and 43,167 SCLC cases diagnosed in Australia, Canada, Denmark, Ireland, New Zealand, Norway, and the UK during 2010–2014. Irrespective of stage at diagnosis, 1-year and 3-year net survival (NS) was consistently higher for Canada and Norway and lower for the UK, NZ, and Ireland. Three-year NS for NSCLC ranged from 19.7% for the UK to 27.1% for Canada for men. It was consistently higher for women (25.3% in the UK; 35.0% in Canada), partly because men were diagnosed at more advanced stages. International differences in survival for NSCLC were largest for regional stage and smallest at the advanced stage. For SCLC, 3-year NS also showed a clear female advantage with the highest being for Canada (13.8% for women vs 9.1% for men) and Norway (12.8% for women vs 9.7% for men).

Comment (PD): Whilst a lot of attention is rightly paid to variations in lung cancer survival within NZ, international benchmarking is important for us to understand how we stand compared with our peers in equivalent OECD countries. This paper from the ICBP looks at 1- and 3-year net survival in seven countries including NZ. Not only is NZ placed near the bottom of the league (6th, with the UK slightly behind), but it has the worst improvement in lung cancer survival of the seven countries since the analysis between 1995 and 1999. Although stage at diagnosis was a factor, making a strong argument for screening, the differences in survival within stage suggest that access to and quality of treatment are relevant factors. Access to the latest technologies and treatments is a big issue for NZ to keep up with its neighbours. The superiority of Australia's outcomes are particularly telling.

Reference: Thorax. 2021 Jul 19 [Online ahead of print]
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. **FOR FULL BIO CLICK HERE.**