Lung Cancer RESEARCH REVIEW™

Making Education Easy

Issue 19 – 2021

In this issue:

Abbreviations used in this issue

ALK = anaplastic lymphoma kinase
CT = computerised tomography
DFS = disease-free survival
EBUS = endobronchial ultrasound
EBUS-EUS = endobronchial ultrasound + endoscopic ultrasound
EGFR = epidermal growth factor receptor
HER2 = human epidermal growth factor receptor 2 gene
HR = hazard ratio
MDM = multidisciplinary meeting
NSCLC = non-small cell lung cancer
OS = overall survival
PET = positron emission tomography
PFS = progression-free survival
RCT = randomised controlled trial
SABR = stereotactic ablative radiotherapy
TKI = tyrosine kinase inhibitor

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Welcome to this issue of Lung Cancer Research Review.

This issue features summaries of clinical trials that evaluate immunotherapy in the adjuvant and neoadjuvant settings, immunotherapy plus SABR in advanced NSCLC, and immunotherapy for squamous cell lung cancer. Other selections include an investigation of how smoking cessation after diagnosis of lung cancer affects the risk for disease progression and mortality, an analysis of whether new cancer therapies are having a tangible effect on real-world survival outcomes, and an observational study that assesses whether MDM case discussion improves palliative care referral rates in lung cancer.

We hope that this issue of Lung Cancer Research Review is an informative read. Please keep your comments and feedback coming.

Kind regards

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Trastuzumab deruxtecan in HER2-mutant non-small-cell lung cancer

Authors: Li BT et al.

Summary: This multicentre phase 2 study in which trastuzumab deruxtecan (6.4 mg per kg of body weight) was administered to patients who had metastatic HER2-mutant NSCLC that was refractory to standard treatment enrolled 91 patients and had a 13.1-month (0.7–29.1) duration of follow-up. Objective response (primary endpoint) was achieved in 55% of the patients (95% CI: 44–65) and the duration of response was 9.3 months (95% CI: 5.7–14.7). PFS was 8.2 months (95% CI: 6.0–11.9) and OS was 17.8 months (95% CI: 13.8–22.1). Grade 3 or higher drug-related adverse events occurred in 46% of patients, with neutropenia (19% of patients) being the most common event. Adjudicated drug-related interstitial lung disease, which occurred in 26% of patients, resulted in two deaths. Responses were observed across different HER2 mutation subtypes. Responses were also observed in patients with no detectable HER2 expression or HER2 amplification.

Comment (AL): The pool of targetable driver mutations in non-squamous NSCLC is ever increasing. HER2 mutations have long been identified as targets but attempts to target this with more longstanding HER2-directed agents such has trastuzumab have been unsuccessful. The use of an antibody-drug conjugate in this trial does seem to be more successful. HER2-mutant lung cancer has a baseline poor prognosis so to expect the dramatic and significant improvement in survival such as those seen with targeting EGFR and ALK mutations is probably unrealistic. A median PFS of 8 months in a second-line therapy is not to be dismissed. Having said that, a pulmonary toxicity rate of 26% with two fatal episodes is a little worrying. Further exploration is needed but this is not an easy non-toxic treatment.

Reference: N Engl J Med. 2021 Sep 18 [Online ahead of print]
Abstract

SAKK 16/14: durvalumab in addition to neoadjuvant chemotherapy in patients with stage IIIA(N2) non-small-cell lung cancer-a multicenter single-arm phase II trial

Authors: Rothschild SI et al.

Summary: The objective of this trial was to demonstrate that the addition of perioperative durvalumab to neoadjuvant chemotherapy in patients with resectable stage IIIA(N2) NSCLC is efficacious and feasible. Neoadjuvant treatment consisted of three cycles of cisplatin 100 mg/m^2 and docetaxel 85 mg/m^2 once every 3 weeks followed by two doses of durvalumab 750 mg once every 2 weeks. Durvalumab was continued for 1 year after surgery. Of the 68 patients enrolled, 67 were included in the full analysis. The addition of perioperative durvalumab to neoadjuvant chemotherapy resulted in an increase in the 1-year event-free survival (EFS; primary endpoint) to 73% compared with 48% in a patient population selected with identical inclusion and exclusion criteria but receiving chemotherapy only in previous trials. Median EFS and OS were not reached after 28.6 months of follow-up. Fifty-nine (88%) patients had an adverse event grade ≥3, which included two fatal adverse events that were considered not to be treatment-related.

Comment (AL): Here we have another early example of immunotherapy moving forward into the early-stage NSCLC space. Neoadjuvant therapy for lung cancer remains controversial and in NZ is only used in very specific circumstances. This trial has limited its inclusion to a very small group of resectable N2 disease, which is probably sensible. It is a group in which the ease of successful resection is always questioned by the MDM. The response rate is important and 58% is reasonable. A low progressive disease rate of 11% is reassuring. The chosen end point for this study is 1-year event-free survival. Given the durvalumab is given for 1 year after surgery, this seems a premature time to draw conclusions. Of course, in this phase 2 trial there is no control arm and that remains the problem with a lot of neoadjuvant data. The hope is that in the future we will see the same trial with chemo-rad and consolidation immunotherapy as the control arm.

Reference: J Clin Oncol. 2021;39(26):2872–2880
Abstract

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A randomized phase 2 trial of nivolumab and stereotactic ablative body radiotherapy (SABR) in advanced non-small cell lung cancer, progressing after first- or second-line chemotherapy (NIVORAD)

Authors: Mitchell P et al.

Summary: This paper reports results from the NIVORAD, which was a randomised study that determined the activity and safety of treating a site of disease with a single fraction of SABR during therapy with nivolumab in adult patients with metastatic NSCLC progressing after one or two lines of chemotherapy and a disease site suitable for SABR. Fifty of the planned 120 patients were recruited and randomised to receive nivolumab plus SABR (n=34) or nivolumab alone (n=16). Based on a follow-up of 25 months, the primary endpoint of PFS was similar among those assigned nivolumab plus SABR compared with nivolumab alone (HR 0.82; 95% CI: 0.44–1.54; p=0.6). Objective tumour response rate (8/34 [24%] vs 4/16 [25%]), OS (HR 0.94, p=0.9), and rates of grade 3–4 adverse events (24/30 [80%] vs 12/16 [75%]) were also similar in the two treatment groups There were no treatment-related deaths.

Comment (AL): This was a co-operative group trial which was recruited to here in NZ. The theory of providing increased tumour antigens with radiotherapy for immunotherapy to act upon has been tried in many settings. The slow accrual to this trial is disappointing as it really does not allow us to draw any conclusions. It does, however, add to the evidence that using SABR in the midst of immunotherapy is safe.

Reference: Int J Radiat Oncol Biol Phys 2021;111(35):S11
Abstract

Nivolumab plus ipilimumab vs nivolumab for previously treated patients with stage IV squamous cell lung cancer: the Lung-MAP S1400I phase 3 randomized clinical trial

Authors: Gettinger SN et al.

Summary: To determine whether the addition of ipilimumab to nivolumab improves survival in patients with advanced chemotherapy-pre-treated immunotherapy-naive squamous cell lung cancer, the Lung Cancer Master Protocol (Lung-MAP) S1400I open-label trial randomised patients to receive nivolumab alone or combined with ipilimumab. Duration of follow-up in surviving patients was 29.5 months. Of the 252 eligible patients, 125 received nivolumab/ipilimumab and 127 nivolumab. The study was closed for futility at a planned interim analysis. The primary endpoint of OS did not differ significantly between the treatment groups (HR 0.87; 95% CI: 0.66–1.16; p=0.34). Median survival was 10 months (95% CI: 8.0–14.4 months) in the nivolumab/ipilimumab group versus 11 months (95% CI: 8.6–13.7 months) in the nivolumab group. Grade 3 or higher treatment-related adverse events occurred in 49/124 patients (39.5%) who received nivolumab/ipilimumab versus 41/123 (33.3%) who received nivolumab alone. Toxicity resulted in discontinuation in 31/124 patients (25%) on nivolumab/ipilimumab versus 19/123 (15%) on nivolumab.

Comment (AL): With the success of the CheckMate 227 and CheckMate 9LA trials it is tempting to think that adding ipilimumab to nivolumab in the second-line setting would also be beneficial. This phase 3 trial shows us that in squamous cell carcinoma it does not add anything other than cost and toxicity. The cost of ipilimumab and nivolumab in NZ is so prohibitive that this treatment is never anyone's first choice; however, at least this study gives us the security of being able to advise a much more affordable option as the better choice of treatment.

Reference: JAMA Oncol. 2021;7(9):1368–1377
Abstract

Adjuvant atezolizumab after adjuvant chemotherapy in resected stage IB-IIIA non-small-cell lung cancer (IMpower010): a randomised, multicentre, open-label, phase 3 trial

Authors: Felip E et al.

Summary: IMpower010 was a multicentre, randomised, open-label, phase 3 study that evaluated adjuvant atezolizumab versus best supportive care after adjuvant platinum-based chemotherapy in adult patients with completely resected stage IB (tumours ≥4 cm) to IIIA NSCLC. A total of 1,005 patients were eligible for randomisation to atezolizumab (1,200 mg every 21 days; for 16 cycles or 1 year; n=507) or best supportive care (observation and regular scans for disease recurrence; n=498); 495 in each group received treatment. Duration of follow-up was 32.2 months (IQR: 27.4–38.3). Atezolizumab treatment improved DFS compared with best supportive care in patients in the stage II-IIIA population whose tumours expressed PD-L1 on ≥1% of tumour cells (HR 0·66; 95% CI: 0.50–0.88; p=0.0039) and the overall stage II-IIIA population (0.79; 0.64–0.96; p=0.020). In the ITT population, HR for DFS was 0.81 (0.67–0.99; p=0.040). No new safety signals were observed.

Comment (AL): Now we are starting to see immunotherapy moving up into the adjuvant space. Note, however, that adjuvant chemotherapy was given prior to the adjuvant immunotherapy. In this setting, the immunotherapy is an addition rather than an alternative to chemotherapy. That will be a disappointment to many patients. The full, potentially practice changing, results for adjuvant trials always take longer to reach their natural conclusion. This trial is an inkling of what is to come but in my view is too early to be practice changing. The question in the adjuvant setting is always; are you curing the disease or are you delaying the relapse? The results in this trial are too immature to tell us at this point. Otherwise, this trial follows the patterns we have come to expect. The higher the stage of disease the greater the effect of adjuvant therapy, the higher the PDL1 the higher the effect – not to say that there is no effect if the PDL1 is 0%.

Reference: Lancet. 2021;398(10308):1344–1357
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.

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.**

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Postdiagnosis smoking cessation and reduced risk for lung cancer progression and mortality: a prospective cohort study

Authors: Sheikh M et al.

Summary: In this prospective study, investigators evaluated whether quitting smoking after diagnosis of lung cancer affects the risk for disease progression and mortality. A total of 517 current smokers with early-stage (IA-IIIA) NSCLC were included in the study. During 7 years of follow-up, there were 327 (63.2%) deaths, 273 (52.8%) cancer-specific deaths, and 172 (33.7%) cases of tumour progression. OS was 21.6 months higher among patients who had quit smoking than those who continued smoking (6.6 vs 4.8 years; p=0.001). Patients who quit had a higher 5-year OS (60.6% vs 48.6%; p=0.001) and PFS (54.4% vs 43.8%; p=0.004) than those who continued smoking. Smoking cessation was associated with decreased risk for all-cause mortality (HR 0.67; 95% CI: 0.53–0.85), cancer-specific mortality (HR 0.75; 95% CI: 0.58–0.98), and disease progression (HR 0.70; 95% CI: 0.56–0.89).

Comment (PD): This paper addresses a common question: is there a benefit of stopping smoking after the diagnosis of lung cancer has been made? Intuitively we would say "yes, it is never too late to stop", but here is some evidence to support this stance. This prospective cohort study of stage 1 to 3A NSCLC found increased overall and progression free survival in self-reported quitters. Furthermore, adjustments for cumulative smoking history did not affect the finding that smoking cessation improved all-cause and lung cancer-specific mortality and disease progression.

Reference: Ann Intern Med. 2021;174(9):1232–1239
Abstract

Impacts of multidisciplinary meeting case discussion on palliative care referral and end-of-life care in lung cancer: a retrospective observational study

Authors: Sridharan K et al.

Summary: The primary question asked in this retrospective cross-sectional study involving 352 patients diagnosed with primary lung cancer was whether MDM discussion influenced palliative care referrals. Secondary questions were whether MDM discussion and early palliative care reduced aggressive treatment (including intensive care unit [ICU] admission and in-hospital death) during the last 30 days of life. MDM discussion was not found to independently affect palliative care referral. There was reduced likelihood of MDM presentation in patients with metastatic disease (p<0.0001) and in patients with poorer performance status (p=0.025) and a higher likelihood of palliative care referral in these patients (both p<0.001). MDM discussion reduced end-of-life ICU admission in patients with metastatic disease (p=0.04). A palliative care referral-to-death interval of ≥30 days was associated with reduced hospitalisation at the end of life (p<0.0001) and hospital deaths (p=0.001).

Comment (PD): Presentation of all lung cancer cases at the MDM is a standard of care. Therefore, we would hope that we see better referral processes in patients presented through MDMs. This study looked at referral to palliative care services and it found perhaps surprisingly that presentation through MDM did not improve palliative care referral rates in patients with metastatic disease. It did reduce ICU admission (seen as a futile event) suggesting MDM presentation did affect end-of-life management. The study did find that earlier referral to palliative care (irrespective of MDM presentation) led to reduced hospitalisation and death in hospital, suggesting better end-of-life pathways of care. Presence of palliative care physicians at the MDMs would probably decrease futile decisions at end of life, but this requires resourcing.

Reference: Intern Med J. 2021;51(9):1450–1456
Abstract

The value of innovation: association between improvements in survival of advanced and metastatic non-small cell lung cancer and targeted and immunotherapy

Authors: Ramagopalan S et al.

Summary: These researchers investigated the degree to which population-level improvements in survival of advanced and/or metastatic NSCLC (admNSCLC) patients were associated with changes in treatment patterns. They analysed 28,154 admNSCLC patients with non-oncogene positive tumours, 598 with ALK+ tumours, and 2,464 with EGFR+ tumours. The hazard of death in patients who had non-oncogene positive tumours diagnosed in 2015, 2016, 2017, 2018, and 2019 was found to be 12%, 11%, 17%, 20%, and 21% lower, respectively, than that for those diagnosed in 2012. Upon adjusting for receipt of first-line or second-line immunotherapy, the decrease in the hazard of death by calendar year was no longer observed. Similarly, decreases in the hazard of death were only observed in patients with ALK+ tumours diagnosed between 2017 and 2019 relative to 2012 but were no longer observed following adjustment for the use of first- and later-generation ALK inhibitors. The hazard of death in patients with EGFR+ tumours did not improve significantly over time.

Comment (PD): I am not sure how the title of this paper got past the journal copy editors, but the content is worth comment. This is based on the large US SEER dataset and the authors have attempted to correlate improvements in lung cancer outcomes in time with changes in treatment patterns over time. They looked at three cohorts of patients (no mutation, ALK mutation positive, and EGFR mutation positive). For the no mutation cohort, they found an improvement in risk of death over time that was cancelled out when taking into account receipt of immunotherapy treatment. Similarly, for the ALK positive cohort they found a decrease in risk of death over time that was cancelled out when taking into account receipt of ALK inhibitors. In the EGFR cohort, no improvement in risk of death over time was seen since EGFR inhibitors have been available for the duration of the study period. This is strong evidence that new therapies are having a tangible effect on real-world survival outcomes.

Reference: BMC Med. 2021;19(1):209
Abstract

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A comparison of outcomes and survival between Victoria and Denmark in lung cancer surgery: opportunities for international benchmarking

Authors: Stenger M et al.

Summary: Although Victoria (Australia) and Denmark have similar population sizes and high-quality healthcare systems, lung cancer surgery is performed in more than 20 Victorian hospitals compared with four in Denmark. Because such differences in centralisation may influence outcomes, these researchers engaged clinical quality registries to enable international benchmarking by exploring patterns of lung cancer surgery including mortality and survival. A total of 1,554 Victorian and 4,319 Danish patients were included in the analysis. Although resection rates were similar in Victoria (26.3%) and Denmark (28%), a higher proportion of Victorian patients underwent wedge resection (19.1% versus 8.8%). Stage concordance was 59.6% in Victoria and 54.9% in Denmark. The 30- and 90-day mortality in Victoria (1.3% and 2.6%) and Denmark (1.4% and 2.8%) were also similar, with no difference in OS (p=0.28) or risk-adjusted survival (HR 1.10; 95% CI: 0.89–1.37; p=0.38).

Comment (PD): Benchmarking of quality performance indicators across equivalent OECD countries is important since it can drive improvement by learning from other healthcare systems. The state of Victoria in Australia is similar in population size and healthcare budget to Denmark, but has a less centralised thoracic surgery system. This cross-registry comparison found that the two settings had similarly high resection rates, low post-operative mortality rate, and poor pre- and post-surgical stage concordance. The main difference found was over double the patients in Victoria had wedge resection as opposed to lobectomy. Whether this is a good thing (from preservation of lung function) or a bad thing (from increased risk of local recurrence) would require longer term and more detailed outcome analysis. There are attempts at harmonising approaches internationally through collaboration and comparative analysis (for instance through the International Cancer Benchmarking Project, ICBP). On a global scale we can lift standards by learning from each other.

Reference: ANZ J Surg. 2021 Oct 22 [online ahead of print]
Abstract

In patients with lung cancer is combined endobronchial ultrasound and endoscopic ultrasound superior to conventional mediastinoscopy in staging the mediastinum?

Authors: Gunawan A et al.

Summary: Mediastinal assessment is essential for management of lung cancer patients but controversy remains regarding the optimal method. This review of the literature was performed to address the question: "in patients with lung cancer, is combined EBUS + EUS superior to cervical mediastinoscopy (CM) in staging the mediastinum?". Of more than 110 relevant papers identified, one meta-analysis, two RCTs, and two cohort studies represented the best evidence to answer the clinical question. Notwithstanding studies directly comparing EBUS + EUS with CM being limited in number and quality, with the majority of studies focusing on comparing endosonographic techniques or a single technique with cervical mediastinoscopy, the authors concluded that a combined approach of endosongraphy (EBUS + EUS) in the first instance, followed by surgical staging of the mediastinum with CM, results in higher sensitivity of nodal disease and subsequent greater accuracy in upstaging and determining treatment plans with a concurrent improvement in complication rates and futile procedures.

Comment (PD): This systematic review paper provides evidence that using EBUS/EUS to stage the mediastinum, then conventional mediastinoscopy if the former is negative, results in fewer inappropriate thoracotomies and the associated complications and decreased quality of life, compared with conventional mediastinoscopy alone. What the paper does not address is how PET-CT scan and EBUS/EUS alone performs against conventional mediastinoscopy, since the latter investigation is associated with a general anaesthetic and possible surgical complications in itself, as well as introducing time delays in the diagnostic and staging pathway. This will be increasingly relevant as endoscopic ultrasound assisted biopsies become more sophisticated with better yields.

Reference: Ann Med Surg (Lond). 2021;71:102953
Abstract