Lung Cancer RESEARCH REVIEW™

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Issue 21 – 2022

In this issue:

Abbreviations used in this issue

CT = computerised tomography
EGFR = epidermal growth factor receptor
EGFR-TKI = epidermal growth factor receptor-tyrosine kinase inhibitor
HER2 = Human epidermal growth factor receptor 2
HR = hazard ratio
ICI = immune checkpoint inhibitor
NSCLC = non-small cell lung cancer
ORR = objective response rate
OS = overall survival
PD-L1 = programmed death-ligand 1
PFS = progression-free survival
PPI = proton-pump inhibitor
TKI = tyrosine kinase inhibitor

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Welcome to this issue of Lung Cancer Research Review.

This issue features a comparison of neoadjuvant nivolumab plus chemotherapy with chemotherapy alone for treatment of resectable lung cancer, an evaluation of the antibody-drug conjugate trastuzumab deruxtecan in metastatic HER2-mutant NSCLC, and an analysis that uses real-world data to help define the optimal duration of immunotherapy for NSCLC.

Concomitant PPI use is the subject of two other selections; specifically, its effect on the efficacy of EGFR-TKIs and ICIs. Also featured in this issue is research on the efficacy of the COVID-19 vaccine in patients with thoracic cancer and whether low-dose aspirin affects the incidence of lung cancer.

We hope that you enjoy this issue of Lung Cancer Research Review. Your feedback is important so please your comments and suggestions coming!

Kind regards

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Neoadjuvant nivolumab plus chemotherapy in resectable lung cancer

Authors: Forde PM et al.

Summary: In this open-label phase 3 trial, patients with stage IB to IIIA resectable NSCLC were randomly allocated to receive nivolumab plus platinum-based chemotherapy or platinum-based chemotherapy alone, followed by resection. Median event-free survival was 31.6 months (95% CI: 30.2 to not reached) with nivolumab plus chemotherapy versus 20.8 months (95% CI: 14.0–26.7) with chemotherapy alone (HR for disease progression, disease recurrence, or death 0.63; 97.38% CI: 0.43–0.91; p=0.005). Pathological complete response rate was 24.0% (95% CI: 18.0–31.0) in the nivolumab plus chemotherapy group versus 2.2% (95% CI: 0.6–5.6) in the chemotherapy alone group (OR 13.94; 99% CI: 3.49–55.75; p<0.001). Grade 3 or 4 treatment-related adverse events were observed in 33.5% of the patients in the nivolumab-plus-chemotherapy group versus 36.9% of those in the chemotherapy-alone group.

Comment (AL): Neoadjuvant therapy is a popular subject for research at the moment. Neoadjuvant chemotherapy alone has never really made it into standard care as there has not been a demonstrable benefit in survival versus adjuvant. With the addition of nivolumab, the complete response rate is certainly impressive. I do not buy the idea that this is a surrogate for survival, however. There certainly is an improvement in event-free survival. We know that immunotherapy improves survival in stage 4 disease and we know that it improves 3-year survival in stage 3 disease. I hope that adjuvant immunotherapy is successful when we get mature survival data. Will moving it into the neoadjuvant space in resectable disease make a difference? Time will tell but not with this trial.

Reference: N Engl J Med. 2022 Apr 11 [Online ahead of print]
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.

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

Authors: Li BT et al.

Summary: These investigators conducted an international, multicentre, phase 2 study in which trastuzumab deruxtecan was administered to patients with refractory metastatic HER2-mutant NSCLC. Median duration of follow-up was 13.1 months (range: 0.7–29.1). Centrally-confirmed objective response occurred in 55% of patients (95% CI: 44–65). Median duration of response was 9.3 months (95% CI: 5.7–14.7). Median PFS was 8.2 months (95% CI: 6.0–11.9) and median 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 the most common event being neutropenia (19% of patients). Adjudicated drug-related interstitial lung disease occurred in 26% of patients and resulted in death in two patients.

Comment (AL): HER2-mutant lung cancer is another mutation present in a small proportion of lung cancers, which should be targetable. Generally, this tends to be a mutation rather than amplification and attempts to use HER2 monoclonal antibodies like trastuzumab alone have been disappointing. Trastuzumab deruxtecan is an antibody-drug conjugate, which shows significant promise in the trial. A 26% pneumonitis rate with two deaths is quite significant though and how toxic this turns out to be in larger groups of patients will be important.

Reference: N Engl J Med. 2022;386(3):241–251
Abstract

Long-term outcomes in patients with advanced and/or metastatic non-small cell lung cancer who completed 2 years of immune checkpoint inhibitors or achieved a durable response after discontinuation without disease progression: Multicenter, real-world data (KCSG LU20-11)

Authors: Kim H et al.

Summary: To help inform the optimal treatment duration for ICIs, this multicentre, retrospective study assessed clinical outcomes in patients with NSCLC who completed 2 years of ICI therapy or were treated for more than 6 months and then discontinued ICIs without disease progression. The investigators reviewed a total of 96 patients who completed 2 years of ICI therapy. Median durations of treatment and follow-up were 24.0 and 33.9 months, respectively. Overall response rate (ORR) was 85.4%. Median PFS and OS periods were not reached. Following completion, PFS and OS rates were 81.1% and 96.4%, respectively, at 12 months. Forty-three patients were identified who discontinued ICIs without disease progression. Of these patients, 26 (60.5%) discontinued treatment because of adverse events. Median durations of treatment and follow-up were 10.5 and 21.2 months, respectively. ORR was 90.7%. Median PFS and OS periods were not reached. After discontinuation, PFS and OS rates were 71.0% and 90.0%, respectively, at 12 months.

Comment (AL): Defining the optimal duration of immunotherapy is important. Having real-world data to support stopping after 2 years is certainly helpful in what could otherwise be endless therapy. The PFS rates 1 year after stopping are high and support the idea that it is safe to stop. It is also really encouraging that even if a patient has to stop early for side effects, the PFS is very good. These statistics can be used to reassure both patients and us that stopping for toxicity is not the end of the road, and 2 years really is enough. The question is, do we need 2 years or could it be shorter?

Reference: Cancer. 2022;128(4):778–787
Abstract

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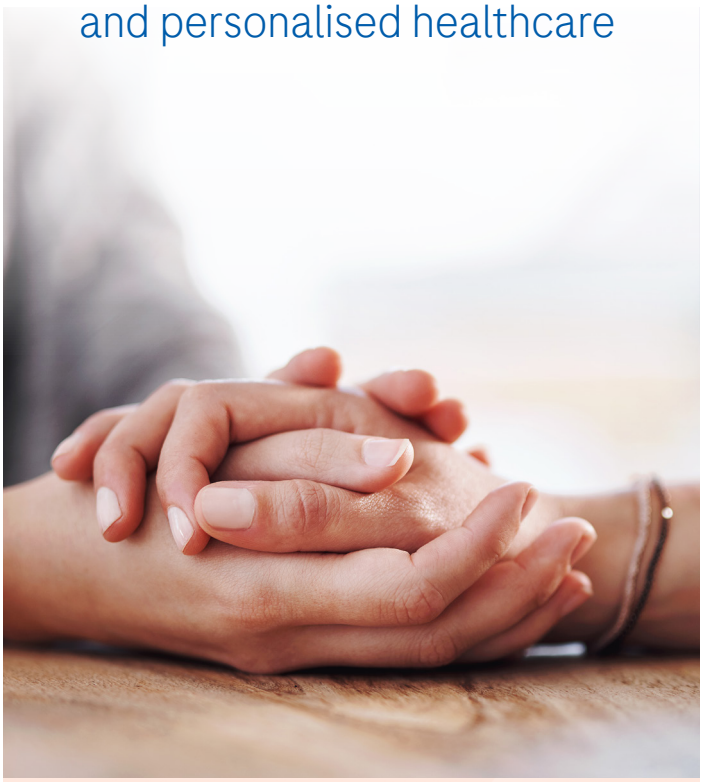

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Efficacy of first-line atezolizumab combination therapy in patients with non-small cell lung cancer receiving proton pump inhibitors: post hoc analysis of IMpower150

Authors: Hopkins AM et al.

Summary: These researchers conducted a post hoc, Cox proportional hazard analysis of the IMpower150 phase III trial to assess the association between PPI use and OS and PFS in chemotherapy-naive, metastatic, non-squamous NSCLC patients randomly allocated to receive atezolizumab plus carboplatin plus paclitaxel (ACP), bevacizumab plus carboplatin plus paclitaxel (BCP), or atezolizumab plus BCP (ABCP). PPI use was defined as any PPI administration between 30 days prior and 30 days after treatment initiation. Of 1,202 participants, 441 (37%) received a PPI. PPI use was found to be independently associated with worse OS (n=748; HR 1.53; 95% CI: 1.21–1.95; p<0.001) and PFS (1.34; 95% CI: 1.12–1.61; p=0.002) in the pooled atezolizumab arms (ACP plus ABCP). This association was not apparent for BCP (n=368; OS 1.01; 95% CI: 0.73–1.39; p=0.969 and PFS 0.97; 95% CI: 0.76–1.25; p=0.827). The observed OS treatment effect (HR; 95% CI) of the atezolizumab (ACP plus ABCP) arms versus BCP was 1.03 (0.77–1.36) for PPI users compared with 0.68 (0.54–0.86) for non-users (p[interaction]=0.028). A similar association was noted for ABCP versus BCP (PPI users 0.96 [0.68–1.35]; PPI non-users 0.66 [0.50–0.87]; p[interaction]=0.095).

Reference: Br J Cancer. 2022;126(1):42–47
Abstract

Proton pump inhibitors reduce the survival of advanced lung cancer patients with therapy of gefitinib or erlotinib

Authors: Lee C-H et al.

Summary: These researchers investigated the effects of concurrent use of either PPIs or histamine-2 receptor antagonists (H2RA) with first-line gefitinib or erlotinib therapy by surveying nationwide population-based databases and identifying newly diagnosed patients with advanced lung adenocarcinoma who received first-line gefitinib or erlotinib. PPIs or H2RAs users were defined if the period overlapped with TKIs by ≥20%. A total of 4,340 gefitinib and 1,635 erlotinib users were assessed. The PPI group had the shortest median OS and time to next treatment (TTNT) compared with the H2RA and non-user groups (in the gefitinib cohort: OS was 14.35 vs 17.67 vs 21.87 months; p<0.0001 and TTNT was 8.47 vs 10.78 vs 10.33 months; p<0.0001; in the erlotinib cohort: OS was 16.97 vs 20.07 vs 23.92 months; p<0.0001 and TTNT was 9.06 vs 11.85 vs 10.90 months; p=0.0808). Compared with the non-user group, the adjusted HR of the PPI group in the gefitinib cohort was 1.58 on OS (95% CI: 1.42–1.76) and 1.37 on TTNT (95% CI: 1.24–1.52); in the erlotinib cohort the adjusted HR was 1.54 on OS (95% CI: 1.30–1.82) and 1.19 on TTNT (95% CI 1.01–1.39).

Reference: Sci Rep. 2022;12(1):7002
Abstract

Comment (AL): I wanted to comment on both of these studies together. The information that PPIs decrease the bioavailability of EGFR-TKIs has been known for a long time. Seeing that translate into poorer survival with concomitant administration is not surprising. Seeing the numbers possibly helps to give us all a reminder that this is a clinically-significant interaction though. The idea that PPIs also decrease the efficacy of immunotherapy is interesting. There is a lot of evidence that differences in the gut microbiome can alter the efficacy of immunotherapy. We also know that PPIs can change the gut microbiome. This retrospective data certainly seems to suggest that PPIs will decrease the efficacy of ICIs. This is a hot topic at the moment and each of us should be doing a personal review of our PPI prescribing habits. Retrospective data like this with multiple confounding factors always has its drawbacks, but it is enough to promote caution.

Comment (PD): Our lung cancer patients are often comorbid, and it is important to consider drug interactions when using our treatments. A PPI like omeprazole, lansoprazole, or pantoprazole is very commonly prescribed for dyspeptic symptoms, or for gastric protection if on oral steroids, and we may forget to think about its potential interactions with other drugs. The study by Lee et al. shows a clear association of worse outcomes on two commonly prescribed TKIs for EGFR-positive lung cancer with a co-prescribed PPI, for OS and time to next treatment. Electronic prescribing with automatic interaction warnings would mitigate this issue.

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First-line nivolumab plus ipilimumab in advanced NSCLC: 4-year outcomes from the randomized, open-label, phase 3 CheckMate 227 Part 1 trial

Authors: Paz-Ares LG et al.

Summary: These authors report results from the CheckMate 227 trial with a minimum 4 years' follow-up. Adult patients with previously untreated stage IV or recurrent NSCLC were randomised (1:1:1) to receive nivolumab plus ipilimumab, nivolumab, or chemotherapy (PD-L1 ≥1%); or to receive nivolumab plus ipilimumab, nivolumab plus chemotherapy, or chemotherapy (PD-L1 <1%). After 54.8 months' median follow-up, the duration of OS remained longer with nivolumab plus ipilimumab versus chemotherapy in patients with PD-L1 ≥1% (HR 0.76; 95% CI: 0.65–0.90) and PD-L1 <1% (0.64; 0.51–0.81). The 4-year OS rate with nivolumab plus ipilimumab versus chemotherapy was 29% versus 18% (PD-L1 ≥1%) and 24% versus 10% (PD-L1 <1%). No new safety signals were reported. Immune-mediated adverse events (except endocrine events) occurred within 6 months from onset of treatment and resolved within 3 months, mainly with systemic corticosteroids. In a post hoc analysis, patients who discontinued nivolumab plus ipilimumab due to treatment-related adverse events had long-term OS benefits, as seen in all randomised patients.

Comment (AL): This trial is one of the few looking at the utility of combined checkpoint inhibition in NSCLC. It presents an alternative for patients who wish to avoid chemotherapy entirely. The outcomes are similar to those of the Keynote 189 trial. It seems likely that different patients benefit from the different approaches; however, currently we do not know how to differentiate those groups. In theory, patients who wish to avoid chemotherapy could take this option. In reality, the cost of nivolumab and ipilimumab in NZ is prohibitive to all but a very select few.

Reference: J Thorac Oncol. 2022;17(2):289–308
Abstract

Efficacy of severe acute respiratory syndrome coronavirus-2 vaccine in patients with thoracic cancer: a prospective study supporting a third dose in patients with minimal serologic response after two vaccine doses

Authors: Gounant V et al.

Summary: The main aim of this prospective vaccine monitoring study was to assess humoral responses to the SARS-CoV-2 vaccine in patients with thoracic cancer. SARS-CoV-2-spike antibodies were measured before the first injection of the BNT162b2 mRNA vaccine, at week 4, and 2 to 16 weeks after the second vaccine dose administration. In 283 patients who received two vaccine doses at 28-day intervals, eight patients (2.6%) contracted proven symptomatic SARS-CoV-2 infection after a 6.7-month median follow-up. Of 269 serologic testing results available beyond day 14 after the second vaccine dose administration, 17 patients (6.3%) were still negative (≤50 arbitrary units/mL), whereas 34 (11%) had IgG levels ≤300 arbitrary units/mL. In multivariate analysis, only age ($p<0.01$) and long-term corticosteroid treatment ($p=0.01$) were significantly associated with a lack of immunisation. Of 30 patients who received a third vaccine dose, only three patients showed persistently negative serology thereafter while the others exhibited clear seroconversion.

Comment (PD): Do lung cancer patients mount adequate antibody responses to the COVID-19 vaccine? The big vaccine trials could not answer this question since malignancy was invariably an exclusion criterion. This study looked at IgG responses in lung cancer patients after the first and second doses of the Pfizer vaccine. Two weeks after the second vaccine 11% of patients had inadequate levels. A third primary dose given from 28 days after the second shot led to adequate antibody levels in just less than 90% of patients (but only about 10% of the initial patients had this). The message would appear to be to recommend serology after two doses and then give a third primary dose if antibody levels are suboptimal; or to give a third primary dose anyway like we do in the immunocompromised patients. This study predated the Omicron variant (and any other new variants that may come along), against which current vaccines seem less protective, further supporting serological testing or repeated dosing in this group of patients, especially if they are elderly or on long term corticosteroids.

Reference: J Thorac Oncol 2022;17(2):239–251
Abstract

Segmentectomy versus lobectomy in small-sized peripheral non-small-cell lung cancer (JCOG0802/WJOG4607L): a multicentre, open-label, phase 3, randomised, controlled, non-inferiority trial

Authors: Saji H et al.

Summary: These researchers conducted this randomised, controlled, non-inferiority trial at 70 institutions to investigate if segmentectomy was non-inferior to lobectomy in patients with clinical stage IA NSCLC (tumour diameter ≤2 cm; consolidation-to-tumour ratio >0.5). A total of 1,106 patients (intention-to-treat population) were enrolled to receive lobectomy (n=554) or segmentectomy (n=552). In the segmentectomy group, 22 patients were switched to lobectomies and one patient received wide wedge resection. At a median follow-up of 7.3 years (range 0.0–10.9), the 5-year OS was 94.3% (95% CI: 92.1–96.0) for segmentectomy and 91.1% for lobectomy (95% CI: 88.4–93.2); superiority and non-inferiority in OS were confirmed using a stratified Cox regression model (HR 0.663; 95% CI: 0.474–0.927; one-sided p<0.0001 for non-inferiority; p=0.0082 for superiority). The occurrence of ≥1 postoperative complication of grade 2 or worse was similar in both groups: 142 (26%) patients who received lobectomy versus 148 (27%) who received segmentectomy.

Comment (PD): Landmark papers like this one challenge our preconceptions and change our practice. It has up to now been accepted that lobectomy is superior to segmentectomy for early-stage lung cancer because of the presumed high risk of recurrence after segmentectomy. In this study of surgical treatment of very early-stage NSCLC (stage 1A), even though the risk of local recurrence was twice as high in the segmentectomy group, there was actually higher OS in the segmentectomy group and no difference in 5-year relapse-free survival. Lung preserving surgery is especially important if there is pre-existent lung disease. It will be interesting to see if segmentectomy becomes the surgical treatment of choice for stage 1A lung cancer.

Reference: Lancet. 2022;399(10335):1607–1617
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.**

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Association of computed tomography screening with lung cancer stage shift and survival in the United States: quasi-experimental study

Authors: Potter AL et al.

Summary: These researchers analysed data from the US National Cancer Database and Surveillance Epidemiology End Results database to determine the effect of the introduction of low-dose CT screening in 2013 on lung cancer stage shift, survival, and disparities in the stage of lung cancer diagnosed in patients aged 45–80 years diagnosed as having NSCLC between 2010 and 2018. In patients aged 55–80 years (i.e. those potentially eligible for screening), the proportion diagnosed with stage I NSCLC did not significantly increase from 2010 to 2013 (from 27.8% to 29.4%) and then increased at 3.9% (95% CI: 3.0–4.8%) per year from 2014 to 2018 (from 30.2–35.5%). The increase in the odds per year of a patient having one lung cancer stage lower at diagnosis from 2014 to 2018 was 6.2% (multivariable adjusted OR 1.062; 95% CI: 1.048–1.077; p<0.001) higher than the increase in the odds per year from 2010 to 2013. Similarly, the median all-cause survival of patients aged 55–80 years did not significantly increase from 2010 to 2013 (from 15.8 to 18.1 months), and then increased at 11.9% (8.9% to 15.0%) per year from 2014 to 2018 (from 19.7 to 28.2 months). The hazard of death decreased significantly faster after 2014 compared with before 2014 (p<0.001).

Comment (PD): This study looks at the modelled impact of the introduction of low-dose CT screening for lung cancer from 2013 onwards, after publication of the NSLT landmark trial in 2011 confirming its efficacy in lung cancer detection and for mortality. There are clear associations of improvements in stage shift and survival comparing data before and after 2013. As we know availability of this screening mode is not universal in the US and it is not surprising that equity gaps have opened up, with worse outcomes for non-white people and those in lower socioeconomic groups. This is a lesson for us in New Zealand as we explore population-based lung cancer screening to ensure that it reaches those in the greatest need and does not further widen disparities in health outcomes.

Reference: BMJ. 2022;376:e069008
Abstract

Low-dose aspirin and incidence of lung carcinoma in patients with chronic obstructive pulmonary disease in Hong Kong: a cohort study

Authors: Yu S-Y et al.

Summary: In this retrospective cohort study, the investigators used a territory-wide clinical electronic medical records system to research the association between low-dose aspirin use (≤160 mg) and incidence of lung carcinoma and the corresponding risk of bleeding in COPD patients defined as aspirin non-users (35,049) and aspirin users (7,679 patients). Of all eligible patients, 1,779 (4.2%; 1,526 non-users and 253 users) were diagnosed with lung carcinoma over a median follow-up period of 2.6 years. Aspirin use was associated with a 25% lower risk of lung carcinoma (p<0.001) and 26% decrease in lung carcinoma-related mortality (p<0.001). Subgroup analysis showed that aspirin was beneficial for patients aged above or below 75 years. It was also beneficial in male, non-diabetic, and non-hypertensive populations. Aspirin use was not associated with an increased risk of upper gastrointestinal bleeding but was associated with an increased risk of haemoptysis (p<0.001).

Comment (PD): This retrospective epidemiological study shows an intriguing association between low-dose aspirin use and lower lung cancer incidence and mortality, specifically in those with COPD. The magnitude is reduction by a quarter in each. We all know association is not the same as cause and effect and the authors are open about this. For instance there may be a group of people who are more likely to avoid the doctor, fail to get on to aspirin, and have their lung cancer diagnosed late with the associated increased mortality. However the authors tried to adjust for confounders such as this in their statistical approach. The question of whether this is a genuine cancer mitigating effect of aspirin, and whether it is generalisable outside of a Hong Kong or Chinese population, is ripe for a clinical trial.

Reference: PLoS Med. 2022;19(1):e1003880
Abstract

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