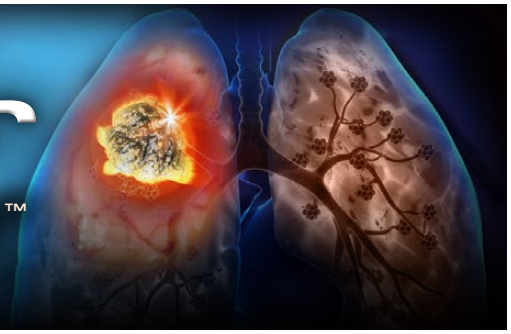
Lung Cancer Research Review™



Making Education Easy

Issue 25 - 2018

In this issue:

Abbreviations used in this issue:

AE = adverse event; **ALK** = anaplastic lymphoma kinase; **AUC** = area under the plasma drug concentration-time curve; **EGFR** = epidermal growth factor receptor; **HR** = hazard ratio; **IV** = intravenous; **NSCLC** = non-small cell lung cancer; **ORR** = objective response rate; **OS** = overall survival; **PD-1** = programmed cell death-1; **PD-L1** = programmed death-ligand 1; **PFS** = progression-free survival; **SCLC** = small cell lung cancer.

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Welcome to issue 25 of Lung Cancer Research Review.

Guest commentary is provided for this issue by Dr Ross Jennens, a consultant medical oncologist in the Brain and Spine, and Lung services at the Peter MacCallum Cancer Centre.

Age-specific rates of invasive lung cancer have generally declined over the last 20 years in the USA among men and women aged between 30 and 54 years in all races and ethnic groups, according to research reported in this issue of *Lung Cancer*. However, it goes on to report that the declines have been more marked in men, leading to a reversal in the historical patterns of higher incidence rates of lung cancer among men than among women in non-Hispanic whites and Hispanics born since 1965. The study researchers were unable to explain this finding of a gender crossover, which they do not believe is due to sex differences in smoking behaviour. They call for more research, to identify reasons for the higher rates of lung cancer among young women.

I hope you find these papers useful to you in your practice and I look forward to your comments and feedback.

Kind Regards,

Dr Ross Jennens

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Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer

Authors: Gandhi L et al.

Summary: This phase III trial recruited 616 patients with metastatic nonsquamous NSCLC without sensitising *EGFR* or *ALK* mutations who had not previously been treated for metastatic disease. They were randomised to receive pemetrexed and a platinum-based drug plus either 200 mg of pembrolizumab or placebo every 3 weeks for 4 cycles, followed by pembrolizumab or placebo for up to a total of 35 cycles plus pemetrexed maintenance therapy. Crossover to pembrolizumab monotherapy was permitted for patients in the placebo-combination group who had verified disease progression. After a median 10.5 months of follow-up, the estimated OS rates at 12 months were 69.2% in the pembrolizumab-combination group and 49.4% in the placebo-combination group (HR for death, 0.49; 95% CI, 0.38 to 0.64; p<0.001). Improvement in OS was seen across all PD-L1 categories that were evaluated. Median PFS was 8.8 months in the pembrolizumab-combination group and 4.9 months in the placebo-combination group (HR for disease progression or death, 0.52; 95% CI, 0.43 to 0.64; p<0.001). Similar proportions of patients in each treatment group experienced AEs of grade ≥3 (67.2% of the pembrolizumab-combination group vs 65.8% of the placebo-combination group).

Comment: This recently presented and published article, with its accompanying editorial in the *NEJM*, "A new standard of care for advanced lung cancer" penned by Dr. Joan Schiller, demonstrates a remarkable OS HR of 0.49 for all-comers with non-squamous metastatic NSCLC undergoing first line chemotherapy combined with pembrolizumab compared with chemotherapy alone. The chemotherapy was platinum/pemetrexed, with 72% of patients receiving carboplatin. Patients with higher PD-L1 expression (tumour proportion score >50%) had an even better HR of 0.42 for OS, however, even patients with PD-L1 <1% had an improved HR of 0.59 (95% CI, 0.38 to 0.92). AEs were as expected for PD-1 inhibitor therapy, although of note, 1.5% of patients in the pembro arm had grade ≥3 nephritis compared to 0% in the chemo-alone arm. This study raises the question of optimal therapy for patients with PD-L1 expression >50%, as we already know pembro alone is more efficacious (and less toxic) than platinum doublet chemotherapy. What is unknown is the additional benefit from combination pembro/chemo compared with pembro alone. Whilst this study indicates a new standard of care for patients with PD-L1 expression <50% (and even <1%), the cost of pembro is a significant factor for these patients. Similar results were also recently presented at ASCO for first-line metastatic squamous cell lung cancer from the Keynote-407 study of platinum/paclitaxel with or without pembro.

Reference: N Engl J Med. 2018;378:2078-92

Abstract

Neoadjuvant PD-1 blockade in resectable lung cancer

Authors: Forde PM et al.

Summary: In this pilot study, 22 patients aged ≥18 years with untreated, surgically resectable early-stage (I, II, or IIIA) NSCLC received 2 doses of IV nivolumab 3 mg/kg every 2 weeks, followed by surgery approximately 4 weeks after the first dose. Neoadjuvant nivolumab had an acceptable side effect profile and did not lead to any delays in surgery. Of the 21 tumours that were removed, 20 were completely resected. Nine patients (45%) achieved a major pathological response; these occurred in both PD-L1-positive and PD-L1-negative tumours. Pathological response was significantly correlated with the pretreatment tumour mutational burden. Blood samples from 9 patients revealed systemic increases from baseline in the number of T cell clones in both the tumour and peripheral blood after nivolumab treatment. Nivolumab induced a rapid peripheral expansion of mutation-associated, neoantigen-specific T cell clones that were also found in the tumour at the time of resection; some of these clones were not detected in the peripheral blood before treatment.

Comment: This study shows a remarkable, rapid effect of PD-1 inhibitor therapy as neoadjuvant treatment for lung cancer. Only two doses of nivolumab were administered, 2 weeks apart, resulting in a major pathological response in 45% of patients. Both PD-L1-positive and PD-L1-negative tumours responded, however, tumour mutational burden was associated with response. While we await outcomes from BR31 and other trials exploring adjuvant PD-(L)1 inhibitor therapy, there may theoretically be an advantage from administering immunotherapy while the primary tumour is *in situ*. This study demonstrates that such an approach is safe and feasible and did not delay surgery.

Reference: N Engl J Med. 2018;378:1976-86
Abstract

RESEARCH REVIEW — The Australian Perspective Since 2007

Higher lung cancer incidence in young women than young men in the United States

Authors: Jemal A et al.

Summary: This investigation into invasive lung cancer diagnoses among Americans aged 30–54 years between 1995 and 2014 reveals that over the past 20 years, the age-specific incidence of lung cancer has generally decreased among both men and women in this age group in all races and ethnic groups, but the decline has been steeper for men. Among non-Hispanic whites born since 1965, the female-to-male incidence rate ratios increased, exceeding 1.0 in those aged between 30 and 49 years. For example, the female-to-male incidence rate ratio among whites 40–44 years of age increased from 0.88 during 1995–1999 to 1.17 during 2010–2014. Sex-specific incidence rates converged among non-Hispanic blacks, Hispanics, and non-Hispanic Asians and Pacific Islanders but crossed over from a higher incidence among men to a higher incidence among women only among Hispanics. The prevalence of cigarette smoking among women born since 1965 has approached, but generally not exceeded, the prevalence among men.

Comment: We all unfortunately have young women in our practices, often non- or light smokers, many of whom sadly die in their 40s or 50s from metastatic lung cancer. We are rarely able to offer these women an explanation for why they have developed lung cancer. Anecdotally, the incidence seems to be increasing. Here, we have epidemiological evidence from the US that this is indeed the case, and cannot be explained by smoking. This study does not explore whether specific subtypes of lung cancer, such as *EGFR* mutation-positive, are increasing in incidence. What factors are contributing to this, and why are women at higher risk? Whilst inhaled fumes from cooking at high temperatures and radon emitted from brickwork or concrete are potential causes, the question of other environmental factors such as air-borne pollutants from combustion of fossil fuels needs consideration.

Reference: N Engl J Med. 2018;378:1999-2009
Abstract

Final overall survival analysis from a study comparing first-line crizotinib with chemotherapy: Results from PROFILE 1014

Authors: Solomon BJ

Summary: This phase III multinational trial randomised 343 patients with *ALK*-positive advanced nonsquamous NSCLC to receive oral crizotinib 250 mg twice daily (n=172) or IV pemetrexed 500 mg/m^2 plus cisplatin 75 mg/m^2 or carboplatin (AUC of 5–6 mg/mL/min) every 3 weeks for a maximum of 6 cycles (n=171). Crossover to crizotinib was permitted after disease progression. The median follow-up for OS was approximately 46 months in both groups. A total of 144 patients (84.2%) in the chemotherapy arm received crizotinib in subsequent lines. The hazard ratio for OS was 0.760 (95% CI, 0.548 to 1.053; p=0.0978). Median OS was not reached (NR) with crizotinib (95% CI, 45.8 months to NR) and 47.5 months with chemotherapy (95% CI, 32.2 months to NR). The probability of survival at 4 years was 56.6% with crizotinib and 49.1% with chemotherapy. After adjustment for crossover to crizotinib, the crizotinib group had an OS benefit (HR 0.346; 95% bootstrap CI, 0.081 to 0.718). The longest OS was observed in crizotinib-treated patients who received a subsequent ALK tyrosine kinase inhibitor. There were no new safety signals.

Comment: Prof. Solomon should be congratulated for his efforts in keeping Australia at the forefront of lung cancer research. Whilst targeted ALK inhibitor therapy has been standard first-line care for *ALK* gene rearranged lung cancer for a number of years, it is important to analyse mature data for a disease where the median survival has still not been reached for the crizotinib arm, even with a median follow-up duration of 46 months. This is a very impressive median survival compared with 10 years ago, when median survival was quoted in the order of 9–12 months for all-comers with metastatic NSCLC. Outcomes were better for first-line crizotinib, despite the crossover. Because of the prolonged survival of many patients on this study, they have been fortunate enough to gain access to the newer generations of ALK inhibitors, which can provide benefit for overcoming resistance mutations. This study noted that OS was particularly prolonged in patients who received subsequent lines of ALK inhibitor therapy.

Reference: J Clin Oncol. 2018 May 16. [Epub ahead of print]
Abstract

Exploratory analysis of brigatinib activity in patients with anaplastic lymphoma kinase-positive non-small-cell lung cancer and brain metastases in two clinical trials

Authors: Camidge DR et al.

Summary: Outcomes are reported from a phase I/II trial, in which 79 patients with *ALK*-positive NSCLC and baseline brain metastases received brigatinib (90–240 mg total daily), and from the subsequent phase II (ALTA) trial, in which 222 patients were randomised to either receive brigatinib 90 mg once daily (arm A; n=112), or brigatinib 180 mg once daily with a 7-day lead-in at 90 mg (n=110). Most patients with *ALK*-positive NSCLC had baseline brain metastases (63% of patients in phI/II; 71% of ALTA arm A and 66% of ALTA arm B), many of whom had no prior brain radiotherapy (46%, phI/II; 40%, ALTA arm A; 41%, ALTA arm B). All patients, except 4 in phI/II, had prior crizotinib therapy. Among patients with measurable (≥10 mm) brain metastases, confirmed intracranial ORR was 53% in phI/II, 46% in ALTA arm A, and 67% in arm B. The confirmed intracranial ORRs were similar in the subset of responders without prior brain radiation (phI/II) or with any active brain metastases (ALTA). Among patients with any baseline brain metastases, median intracranial PFS was 14.6 months in the phI/II cohort, 15.6 months for ALTA arm A and 18.4 months for ALTA arm B.

Comment: The explosion of agents for *ALK* gene rearranged NSCLC has provided excellent outcomes for patients fortunate enough to be able to access them, but also caused headaches in oncologists treating lung cancer who are trying to keep up with them! Even more complex are the potential resistance mutations that can develop and which agents, and in which order, are best able to overcome these. Presently, none of the international bodies recommend *ALK* resistance mutation testing and basing subsequent lines of therapy on such results outside a research setting. Brigatinib provides another CNS penetrant option, along with alectinib and lorlatinib (and, to a lesser degree, ceritinib). This study demonstrated an ORR of 53% of brain metastases to brigatinib. CNS failure is unfortunately common with crizotinib, and changing to a CNS penetrant option can defer the need for cerebral radiotherapy.

Reference: J Clin Oncol. 2018 May 16. [Epub ahead of print]
Abstract

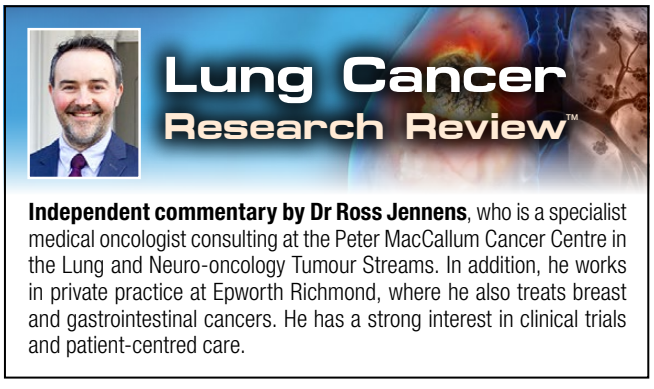
Safety of programmed death-1 pathway inhibitors among patients with non-small-cell lung cancer and preexisting autoimmune disorders

Authors: Leonardi GC et al.

Summary: This retrospective analysis examined clinicopathological data from 56 patients with NSCLC and a history of autoimmune disease (including, but not limited to: rheumatological, neurological, endocrine, gastrointestinal, and dermatological conditions) treated with a PD-(L)1 inhibitor as monotherapy. When they commenced therapy, 18% of patients had active autoimmune disease symptoms and 20% were receiving immunomodulatory agents for their autoimmune disease. Over half (55%) of the patients developed an autoimmune disease flare and/or an immune-related AE. Thirteen patients (23%) experienced an exacerbation of their autoimmune disease; 4 of them required systemic corticosteroids. Immune-related AEs occurred in 21 patients (38%): the majority (74%) were categorised as grade 1 or 2; the remaining 26% were grade 3 or 4; 8 patients required corticosteroids to manage the immune-related AEs. PD-(L)1 therapy was permanently discontinued in 8 patients (14%) because of immune-related AEs. The overall response rate to immunotherapy was 22%.

Comment: Optimal management of patients in the real world is often fraught with difficulty, due to the highly selected cohort of patients who are eligible for the clinical trials upon which we base our treatment decisions. Exclusion of patients with autoimmune disorders occurs in most PD-(L)1 inhibitor trials, leaving many oncologists to either not risk offering a patient with incurable lung cancer a highly effective therapy, or taking a risk based on little evidence and hoping a potentially fatal flare won't occur. This article is reassuring, in that despite a relatively small cohort of 56 patients with autoimmune disease, only a quarter had exacerbation of their autoimmune disease. Fewer than 10% had grade 3 or 4 immune-related AEs. These data provide some perspective, so oncologists can discuss the risks and benefits of immunotherapy with greater accuracy for this group of patients.

Reference: J Clin Oncol. 2018 May 10. [Epub ahead of print]
Abstract



Independent commentary by Dr Ross Jennens, who is a specialist medical oncologist consulting at the Peter MacCallum Cancer Centre in the Lung and Neuro-oncology Tumour Streams. In addition, he works in private practice at Epworth Richmond, where he also treats breast and gastrointestinal cancers. He has a strong interest in clinical trials and patient-centred care.

RESEARCH REVIEW — The Australian Perspective Since 2007

Five-year follow-up of nivolumab in previously treated advanced non-small-cell lung cancer: Results from the CA209-003 study

Authors: Gettinger S et al.

Summary: Five-year follow-up data are reported from an early phase I study in which 129 patients with pretreated, advanced NSCLC were treated with nivolumab 1, 3, or 10 mg/kg every 2 weeks in 8-week cycles for up to 96 weeks. The estimated 5-year OS rate was 16% for all treated patients; 5-year OS rates were similar for squamous (16%) and nonsquamous (15%) NSCLC. Of the 16 patients who survived to 5 years, most (88%) were known current or former smokers. At 5 years, of 10 survivors with quantifiable PD-L1 expression, 70% had ≥1% PD-L1 expression at baseline. Twelve survivors (75%) achieved a partial response to nivolumab at 5 years; stable disease and progressive disease was recorded in 2 patients each. Nine 5-year survivors completed the maximum 96 weeks of nivolumab; 4 discontinued because of AEs and 3 because of disease progression. After the database was locked in November 2016, 12 of the 5-year survivors received no subsequent therapy and had no evidence of progressive disease at last follow-up.

Comment: The two questions I am inevitably asked by patients responding to immunotherapy are: 1) How long do I need to stay on it? and 2) What happens if I stop it? Most of the PD-(L)1 inhibitor trials treated for 2 years and we do not know if providing immunotherapy for a longer duration provides any benefit. However, it is understandably difficult for a patient who has had an impressive response to stop a therapy, particularly if they are not experiencing any toxicity. Nonetheless, the cost of treatment to the PBS and the community (approximately $130,000 annually for an 80 kg patient on nivolumab), plus day therapy costs, plus time off work, etc., surely requires justification for treating beyond 2 years. This article doesn't answer the question of optimal duration, however, it does show that 16% of pre-treated patients are alive at 5 years with less than 2 years of nivolumab, and 75% of those patients had no subsequent therapy. It also demonstrates that PD-L1-negative patients can respond and survive 5 years.

Reference: J Clin Oncol. 2018;36(17):1675-84
Abstract

Early mortality in patients undergoing adjuvant chemotherapy for non-small cell lung cancer

Authors: Morgensztern D et al.

Summary: These researchers queried data from the National Cancer Database for patients aged ≥18 years diagnosed with stage IB–IIA NSCLC between 2004 and 2012 and treated with multi-agent adjuvant chemotherapy starting within 120 days from the surgical resection with negative surgical margins. The analysis focused on the percentage of deaths within the first 6 months of starting chemotherapy (n=19,398). The median age was 65 years. Cumulative mortality rates at 1, 2, 3, 4, 5 and 6 months after commencing chemotherapy were 0.7%, 1.3%, 1.9%, 2.6%, 3.2% and 4.1%, respectively. Six-month mortality rates for each age group (≤50 years, 51–60, 61–70, 71–80, and >80) were 2.6%, 3.1%, 4.1%, 5.3% and 7.6%, respectively (p<0.001). In a multivariate analysis, factors that independently predicted a higher likelihood of mortality at 6 months included age 71–80 years versus ≤50 years (OR 1.72; 95% CI, 1.16 to 2.55; p=0.007), age >80 years versus ≤50 years (OR 2.43; 95% CI, 1.40 to 4.20; p=0.002), male sex (OR 1.42; 95% CI, 1.21 to 1.67; p<0.001), Charlson-Deyo comorbidity score of 2 versus 0 (OR 1.52; 95% CI, 1.22 to 1.89; p<0.001), pneumonectomy (OR 1.38; 95% CI, 1.11 to 1.73; p=0.004), postoperative stay lasting >6 days after surgery (OR 1.21; 95% CI, 1.03 to 1.41; p=0.02) and readmission within 30 days from surgery (OR 1.48; 95% CI, 1.15 to 1.90; p=0.02).

Comment: The decision whether to proceed with adjuvant chemotherapy for NSCLC always involves a complex discussion between oncologist and patient. I recall an editorial in the early-2000s, when the first positive trials of adjuvant chemotherapy were reported, stating that if a patient isn't suitable for cisplatin, they probably aren't suitable for adjuvant chemotherapy. I have always considered that a good yardstick. This article reports a disturbingly high 6-month mortality of 7.6% for patients aged over 80 treated with adjuvant chemotherapy following lung resection. We must exercise caution when treating in the adjuvant setting, to ensure that we do more good than harm. No matter how fit someone in their 80s seems before chemo, they are rarely that fit afterwards.

Reference: J Thorac Oncol. 2018;13(4):543-9
Abstract

Safety of combined PD-1 pathway inhibition and intracranial radiation therapy in non-small cell lung cancer

Authors: Hubbeling HG et al.

Summary: These researchers examined data from a cohort of patients with advanced NSCLC with brain metastases who received cranial radiotherapy and were treated with (n=50) or without (n=113) PD-(L)1 inhibitors. Radiation regimes consisted of stereotactic radiosurgery (n=94), partial brain irradiation (n=28), and/or whole-brain radiotherapy (n=101). Half of the patients received >1 course of radiation. Rates of all-grade AEs and grade ≥3 AEs did not differ significantly between the PD-(L)1-naïve and PD-(L)1-treated cohorts across different types of cranial radiotherapy (grade ≥3 AEs in 8% of the PD-(L)1-naïve vs 9% of PD-(L)1-treated patients for stereotactic radiosurgery [p=1.00] and in 8% of the PD(L)1-naïve vs 10% of PD-(L)1-treated patients for whole-brain radiotherapy [p=0.71]). Moreover, AE rates did not differ according to the timing of PD-(L)1 administration with respect to radiotherapy.

Comment: This study provides some retrospective data showing that patients receiving cerebral radiotherapy, whether stereotactic or whole brain, had no difference in radiotherapy toxicity regardless of whether they were receiving a PD-(L)1 inhibitor or not. Timing of immunotherapy treatment also had no impact. This is reassuring evidence that we can continue immunotherapy during cranial irradiation.

Reference: J Thorac Oncol. 2018;13(4):550-8
Abstract

The addition of chemotherapy to radiation therapy improves survival in elderly patients with stage III non-small cell lung cancer

Authors: Miller ED et al.

Summary: A search of the National Cancer Database identified 23,229 elderly patients (≥70 years) diagnosed with stage III NSCLC between 2003 and 2014 who were treated with either definitive radiation (≥59.4 Gy; n=5,023) or definitive chemoradiation (n=18,206). Chemoradiation was concurrent (radiation and chemotherapy started within 30 days of each other) or sequential (radiation started >30 days after chemotherapy). In Cox proportional hazards regression analysis, OS was significantly improved after chemoradiation compared with after radiation, both before propensity score matching (HR 0.66; 95% CI, 0.64 to 0.68; p<0.001) and after propensity score matching (HR 0.67; 95% CI, 0.64 to 0.70; p<0.001). Sequential chemoradiation was superior to concurrent chemoradiation, reducing the risk of death by 9% (HR 0.91; 95% CI, 0.85 to 0.96; p=0.002).

Comment: Chemoradiotherapy is considered the standard of care for inoperable stage III NSCLC. However, elderly patients are often underrepresented in clinical trials. This database registry trial confirms that chemoradiotherapy is superior to radiotherapy alone in patients aged over 70 years, with a hazard ratio of around 0.67 for survival. Interestingly, patients who received sequential chemotherapy followed by radiotherapy did slightly better (HR 0.91) compared with concurrent chemoradiotherapy. Is this due to increased toxicity from concurrent therapy in a less robust patient group, or to biases inherent in non-randomised retrospective observational studies?

Reference: J Thorac Oncol. 2018;13(3):426-35
Abstract

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