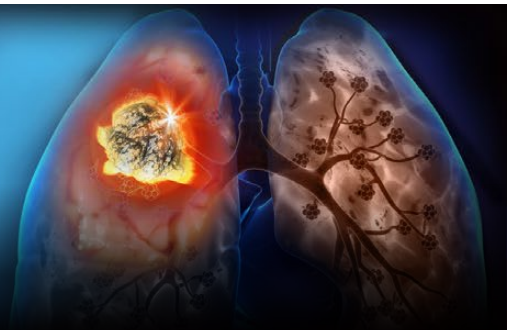
Lung Cancer Research Review™



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Issue 46 - 2020

In this issue:

Abbreviations used in this issue:

BSC = best supportive care; **CI** = confidence interval; **ctDNA** = circulating tumour DNA; **ECOG** = Eastern Co-operative Oncology Group; **EP** = etoposide and platinum; **HR** = hazard ratio; **NSCLC** = non-small-cell lung cancer; **ORR** = objective response rate; **OS** = overall survival; **PD-L1** = programmed death ligand 1; **PFS** = progression-free survival; **SCLC** = small-cell lung cancer.

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Welcome to issue 46 of Lung Cancer Research Review.

This issue begins with several immunotherapy studies, including the study of two different pembrolizumab combinations for non-small cell lung cancer (NSCLC), one combination for first-line small cell lung cancer (SCLC), and a study on the risk of progression following PD-L1 inhibition. We then move on to a study examining S-1 maintenance therapy for advanced squamous cell carcinoma and an insightful review on the treatment of NSCLC patients with brain metastases. The issue concludes with an examination of *MET* alterations and resistance in *ALK*-positive lung cancer, the use of denosumab for the treatment of NSCLC and the effect of aprepitant for cough suppression in advanced patients.

We hope you enjoy this issue, and we invite you to send any comments or feedback.

Kind Regards,

Dr Michael Slancar
michael.slancar@researchreview.com.au

Phase 1 trial of pembrolizumab administered concurrently with chemoradiotherapy for locally advanced non–small cell lung cancer

Authors: Jabbour SK, et al.

Summary: This prospective, nonrandomised controlled trial examined concurrent PD-1 inhibition and definitive chemoradiotherapy in 21 patients with locally advanced, unresectable, stage III NSCLC. Patients were treated with pembrolizumab combined with concurrent chemoradiotherapy (weekly carboplatin and paclitaxel with 60 Gy of radiation in 2 Gy per day). There were 5 dose cohorts including full-dose pembrolizumab (200 mg intravenously every 3 weeks) 2 to 6 weeks after chemoradiotherapy (Cohort 1), reduced-dose pembrolizumab (100 mg intravenously every 3 weeks) starting Day 29 of chemoradiotherapy (Cohort 2), full-dose pembrolizumab starting Day 29 of chemoradiotherapy (Cohort 3), reduced-dose pembrolizumab starting Day 1 of chemoradiotherapy (Cohort 4), and full-dose pembrolizumab starting Day 1 of chemoradiotherapy (Cohort 5). No dose-limiting toxic effects were observed in any cohort. There was 1 case of grade 5 pneumonitis in the safety expansion cohort with the Cohort 5 regimen. Grade ≥3 immune-related adverse events occurred in 4 patients. The median progression-free survival (PFS) was 18.7 months (95% CI, 11.8-29.4); 6-month PFS was 81.0% and 12-month PFS was 69.7%.

Comment: This is an interesting extension study looking at combination of chemotherapy, radiotherapy and immunotherapy in patients with locally advanced NSCLC. It is an early phase study looking mainly at safety and tolerability of this approach. Chemoradiation is a standard approach in this population. Immunotherapy after chemoradiation is already pushing the results in the right direction and this is just another step further to see if the combination of chemoradiation with immunotherapy will move us even higher in terms of outcomes. It appears that the treatment was safe and well tolerated, with expected incidence of adverse events in patients with immunotherapy added to the combination. The PFS was impressive, although not compared head to head with chemoradiation alone. This is a good indication of things to come in this field with an intuitive feeling that outcomes may be better using all modalities upfront. More studies will no doubt follow.

Reference: JAMA Oncol 2020;6(6):848-55.
Abstract

Efficacy and safety of pembrolizumab plus docetaxel vs docetaxel alone in patients with previously treated advanced non–small cell lung cancer

Authors: Arrieta O, et al.

Summary: The PROLUNG phase 2 randomised clinical trial investigated the combination of pembrolizumab plus docetaxel in patients with previously treated advanced NSCLC following platinum-based chemotherapy regardless of *EGFR* variants or PD-L1 status. Patients (n=78) were randomised to either pembrolizumab plus docetaxel or docetaxel alone. The primary endpoint was overall response rate (ORR). One third of patients had an *EGFR*/*ALK* alteration. Patients treated with pembrolizumab plus docetaxel had a significantly higher ORR compared to those treated with docetaxel alone (42.5% vs 15.8%; odds ratio, 3.94; 95% CI, 1.34-11.54; P=0.01). Median PFS was longer in the pembrolizumab plus docetaxel group (9.5 months) compared to the docetaxel alone group (3.9 months) with a HR of 0.24 (95% CI, 0.13-0.46; P<0.001). No new safety signals were identified; 23% of combination and 5% of monotherapy patients experienced grade 1 or 2 pneumonitis (P=0.02) and 28% and 3% of patients, respectively, experienced any-grade hypothyroidism (P=0.002).

Comment: Study from Mexico looking at scenarios relevant to situations where immunotherapy is not administered in the first line setting in advanced NSCLC. The question asked is whether in that setting the introduction of immunotherapy in second line treatment is going to enhance the response and thus be a valid manoeuvre in improving the outcomes. The comparator used is docetaxel in three weekly dosing schedules. Pembrolizumab was the immunotherapy of choice in this study. The conclusion is that adding immunotherapy to second line chemotherapy improves the ORR and PFS significantly after previous progression on platinum-based chemotherapy alone. The benefit also applies for patients with *EGFR* variations. We are fortunate in Australia as being able to use immunotherapy in the first-line setting, however, there may be circumstances where that does not happen for various reasons and this study confirms the validity of introduction of immunotherapy in second line with no apparent loss of efficacy.

Reference: JAMA Oncol 2020;6(6):856-64.
Abstract

Neoadjuvant atezolizumab and chemotherapy in patients with resectable non-small-cell lung cancer

Authors: Shu CA, et al.

Summary: This open-label, multicentre, single-arm, phase 2 trial examined the activity of atezolizumab with carboplatin and nab-paclitaxel given as neoadjuvant treatment prior to surgical resection. Patients (n=30) with stage IB–IIIA NSCLC, an ECOG status of 0–1, and a history of smoking received neoadjuvant treatment with intravenous atezolizumab, nab-paclitaxel and carboplatin. Patients without disease progression after two cycles proceeded to receive two further cycles, which were then followed by surgical resection. The primary endpoint was major pathological response, defined as the presence of 10% or less residual viable tumour at the time of surgery. In total, 29 patients were taken into the operating theatre, and 26 (87%) patients underwent successful R0 resection. Approximately 57% of patients (95% CI, 37-75) had a major pathological response. The most common treatment-related grade ≥3 adverse events were neutropenia (50%), increased alanine aminotransferase concentrations (7%), increased aspartate aminotransferase concentration (7%), and thrombocytopenia (7%). There were no treatment-related deaths.

Comment: Another study looking at a neoadjuvant approach in the setting of resectable NSCLC. The proposal is based on the fact that most patients in this cohort will receive chemotherapy in an adjuvant setting with relatively modest benefit. Based on neoadjuvant data in other malignancies, one could postulate, that the neoadjuvant approach could improve the statistics and deliver a meaningful improvement in this group of patients. There is also some well-established practical advantages of delivering chemotherapy upfront, decreasing the postoperative complications in that setting. A clean and well conducted phase 2 study utilising a combination of carboplatin, taxol and atezolizumab. Side effects and tolerance was predictable with no surprises. Most patients were suitable for resection after the treatment. Quite a large number of significant pathological responses with no detrimental effect on subsequent surgery have been observed. The authors conclude the promising hypothesis worth further evaluation and consideration of future incorporation into clinical practice.

Reference: Lancet Oncol 2020;21(6):786-95.
Abstract

Pembrolizumab or placebo plus etoposide and platinum as first-line therapy for extensive-stage small-cell lung cancer

Authors: Rudin CM, et al.

Summary: The randomised, double-blind, phase 3 KEYNOTE-604 study investigated pembrolizumab plus etoposide and platinum (EP) with placebo plus EP for patients with previously untreated extensive-stage SCLC. Patients (n=453) were randomised to pembrolizumab or saline placebo for up to 35 cycles plus 4 cycles of EP. The primary endpoints were PFS and overall survival (OS). Pembrolizumab plus EP significantly improved PFS compared to placebo plus EP (HR, 0.75; 95% CI, 0.61-0.91; P=0.0023), with 12-month rates of 13.6% for pembrolizumab plus EP and 3.1% for placebo plus EP. Although pembrolizumab plus EP prolonged OS compared to placebo plus EP, with 12-month estimates of 22.5% and 12.5% respectively, the significance threshold was not met (HR, 0.80; 95% CI, 0.64 to 0.98; P=0.0164). ORR was 70.6% in the pembrolizumab plus EP group and 61.8% in the placebo plus EP group. Grade 3-4 adverse events occurred in 76.7% of pembrolizumab plus EP-treated patients and in 74.9% of placebo plus EP patients.

Comment: This is a great study validating the use of immunotherapy in combination with chemotherapy in extensive stage small cell lung carcinoma. There is evidence of a positive immunotherapy effect in small cell lung cancer, but most of the studies so far have been done in a relapse setting as a second or further line of therapy. This excellent study is looking at first-line combination in this setting. The standard chemotherapy is used (platinum and etoposide) with pembrolizumab being the immunotherapy agent. The tolerance and toxicity are totally predictable from many other studies and reveals no unexpected problems. Quite a large cohort of patients randomised equally into two groups with immunotherapy or placebo on top of the standard chemotherapy. The conclusion brings confirmation of significant activity and superior outcome of the immunotherapy combination group with some prolonged responses not usually seen in this population and standard approaches. Very good study confirming the chemo-immunotherapy combination superiority over the previous best standard treatment in the setting of extensive small cell lung cancer. Another step forward.

Reference: J Clin Oncol 2020;JCO2000793.
Abstract

A randomized phase 3 study of maintenance therapy with S-1 plus best supportive care versus best supportive care after induction therapy with carboplatin plus S-1 for advanced or relapsed squamous cell carcinoma of the lung (WJOG7512L)

Authors: Tanaka K, et al.

Summary: This randomised, phase 3 study examined S-1 maintenance therapy following induction therapy with carboplatin plus S-1 in patients with advanced or relapsed squamous NSCLC. Patients (n=131) who did not progress after 4 cycles of induction therapy were randomised to either S-1 plus best supportive care (BSC) or BSC alone. The primary endpoint was PFS. Significantly fewer patients in the S-1 plus BSC group progressed compared to the BSC alone group (HR, 0.548; 95% CI, 0.374-0.802; P =0.0019). The most common toxicities during S-1 maintenance therapy were anorexia, anaemia, and fatigue.

Comment: Well conducted study from Japan, examining the role of S-1 maintenance after chemotherapy using platinum in patients with advanced or relapsed squamous cell carcinoma. Quite a good cohort of patients randomised to receive the combination of platinum with S-1 followed by best supportive care with or without S-1 maintenance afterwards. The tolerance of this regimen was acceptable with S-1 adding more anorexia, anaemia and fatigue of no high-grade toxicity rating however. The results were encouraging with significantly lower risk of disease progression in the group on S-1 maintenance versus best supportive care. The conclusion of the authors is the role of this approach in management of advanced lung squamous cell carcinoma, with a meaningful improvement and a tolerable toxicity profile. Certainly an interesting approach, however we may still wait for S-1 availability in Australia in this setting.

Reference: Cancer 2020;10.1002/cncr.32987.
Abstract

Systemic treatment of brain metastases in non-small-cell lung cancer

Authors: Page S, et al.

Summary: This review article on the significance of brain metastases in NSCLC highlights their prevalence, being found in up to 50% of NSCLC patients, and their association with significant morbidity. The authors also point out that most of the data related to local treatment of brain metastases is retrospective and that clinical trials examining systemic treatments often exclude patients with brain metastases. Some of the immunotherapy trials have included patients with brain metastases. Although there is no prospective data to guide the timing and use of local therapies with systemic treatments, retrospective data suggests that early local therapies may give better intracranial progression-free survival. The authors offer several conclusions from the available data and make suggestions for future clinical trials.

Comment: We would all agree that the treatment of brain metastases in the setting of NSCLC is challenging, often frustrating and demoralising. This paper is stimulating the discussion about the choice, timing and sequence of a successful approach to the management in this setting. It uses retrospective data to assess variable responses to chemotherapy and immunotherapy with some reports of success but not clear guidance or solid data. It brings to our attention some impressive results utilising targeted therapies for particular mutations, which is encouraging. It also confirms the impression of early deployment of localised treatments in terms of improved quality of life for these patients. I would agree that there is generally reluctance to include patients with central nervous system (CNS) metastases in clinical trials for usual concerns of diluting the data and the objectives of the studies carried out. This abstract is calling for reconsideration to include patients with CNS metastases into the studies, so we have more data and guidance as of choice of the agents, sequences and success in treatment of patients with CNS involvement in NSCLC.

Reference: Eur J Cancer 2020;132:187-98.
Abstract

Independent commentary by Dr Michael Slancar, who is a consultant medical oncologist affiliated with ICON Cancer Care in Southport, the Gold Coast. He started his training under the auspices of the European School of Oncology in Europe and completed his fellowship in Australia at Royal North Shore Hospital in Sydney prior to establishment of his practice on the Cold Coast in Queensland. He is an Associate Professor at Bond University. He is a long-term internationally recognised principal investigator in many clinical trials conducted via ICON Research Foundation. His particular interest is in breast cancer, gynaecological malignancies, prostate cancer and lung cancer.

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1L = first-line; ALK = anaplastic lymphoma kinase; CI = confidence interval; EGFR = epidermal growth factor receptor; HR = hazard ratio; I-O = immuno-oncology; mOS = median overall survival; NSCLC = non-small cell lung cancer; TGA = Therapeutic Goods Administration.

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References: 1. OPDIVO® (nivolumab) Approved Product Information (www.medicines.org.au/files/bqpopdiv.pdf). **2.** YERVOY® (ipilimumab) Approved Product Information (www.medicines.org.au/files/bqpyervo.pdf). **3.** Reck *et al.* Nivolumab + ipilimumab + 2 cycles of platinum doublet chemotherapy vs 4 cycles chemo as first-line treatment for stage IV/recurrent non-small cell lung cancer: Checkmate 9LA. Oral presentation at 2020 ASCO Congress. Virtual Scientific Program, May 29–31, 2020. Abstract 9501.

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BMS Medical Information: 1800 067 567. Bristol-Myers Squibb Australia Pty Ltd, ABN 33 004 333 322, 4 Nexus Court, Mulgrave, VIC 3170. 7356AU2005184-01. Date of preparation: July 2020. BRMSCH1597.

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Circulating tumor DNA analysis to assess risk of progression after long-term response to PD-(L)1 blockade in NSCLC

Authors: Hellmann MD, et al.

Summary: This study examined whether circulating tumor DNA (ctDNA) in long-term responders to PD-(L)1 blockade could be used to identify patients who will achieve ongoing benefit from those at risk of progression. Patients with NSCLC who had achieved long-term benefit from a PD-(L)1 inhibitor (n=31) had their ctDNA analysed in surveillance blood samples. At a median of 26.7 months after treatment initiation, 27 of the 31 patients had undetectable ctDNA and 93% of patients were progression-free. All 4 patients with detectable ctDNA eventually progressed (P<0.0001).

Comment: This is a relatively small study opening again the discussion of the role for one-time favourite topic of ctDNA in cancer management. We have all seen the hype and fall of this topic in the last few years. Generally speaking, there is no well-established role for ctDNA analysis at this point in time. This particular study is looking at long-term responders to PD-L1 blockade in NSCLC. We all have patients going well beyond expectation on immunotherapy at the same time as some others in the same setting doing poorly. It is interesting to have insight into this phenomenon and to understand whether we could predict the long-term survivors as well as prepare for failures as soon as ctDNA is detected. The authors of this study conducted ctDNA analysis in long-term responders to immunotherapy and attempted to correlate the detection of ctDNA to the risk of relapse. The conclusion is confirmatory in terms of strong correlation of presence of ctDNA to relapse or progression as well as the absence of ctDNA indicating the likelihood of sustained response. Despite the small numbers in this study, the findings are encouraging in terms of finding early predictors of failure in this setting potentially allowing us early intervention if this hypothesis is confirmed.

Reference: Clin Cancer Res. 2020;26(12):2849-58.
Abstract

MET alterations are a recurring and actionable resistance mechanism in ALK-positive lung cancer

Authors: Dagogo-Jack I, et al.

Summary: This analysis examined the frequency of *MET* genetic alterations in *ALK*-positive lung cancer patients. Next-generation sequencing was performed on 207 post-treatment tissue or plasma specimens from patients with *ALK*-positive lung cancer to detect *MET* genetic alterations. *MET* amplification was detected in 15% of tumor biopsies from patients who had relapsed on next-generation ALK inhibitors, including 12% and 22% of biopsies from patients progressing on second-generation inhibitors or lorlatinib, respectively. *MET* amplification was more likely to occur in patients treated with a second-generation ALK inhibitor in the first-line setting compared to patients who received next-generation ALK inhibitors after crizotinib (P=0.019). Two patients with *ALK*-positive lung cancer and acquired *MET* alterations achieved rapid responses to ALK/MET combination therapy.

Comment: This was an abstract looking at the very specific topic of *ALK*-positive lung cancers and development of resistance to ALK inhibitors. The hypothesis looked at *ALK*-positive NSCLC patients being treated with ALK inhibitors with subsequent resistance development and the molecular mechanism of this event in view of *MET* alterations which could be actionable. There have been some interesting lessons learned, for example, that the patients treated with second generation ALK inhibitors in the first-line setting were more likely to develop this particular alteration. The important practical suggestion then was the one involving MEK targeting together with ALK inhibition which re-sensitised the ALK inhibition activity. This did reverse the ALK inhibition resistance in these patients with subsequent potential for further responses. Very small numbers of patients involved, nevertheless a valuable abstract as our understanding of resistance responsible mutations grows and allow us to overcome it by novel strategies (sometimes…).

Reference: Clin Cancer Res 2020;26(11):2535-45.
Abstract

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A randomised open-label phase III trial evaluating the addition of denosumab to standard first-line treatment in advanced NSCLC – the ETOP and EORTC SPLENDOUR trial

Authors: Peters S, et al.

Summary: This randomised, open-label, phase 3 trial evaluated the addition of denosumab to standard first-line platinum-based doublet chemotherapy in stage IV NSCLC patients. Patients (n=514) were randomised to either chemotherapy plus denosumab or to chemotherapy alone. The trial closed prematurely due to decreasing accrual rate. Bone metastases was present in 53% of patients. The median OS was 8.7 months (95% CI, 7.6-11.0) in the control group compared to 8.2 months (95% CI, 7.5-10.4) in the chemotherapy plus denosumab group (HR, 0.96; 95%CI, 0.78-1.19; P=0.36). The HR in patients with bone metastases was 1.02 (95% CI, 0.77-1.35), and was 0.90 (95% CI, 0.66-1.23) in patient without bone metastases. Denosumab was well tolerated without unexpected safety concerns.

Comment: The evidence of subtle anti-neoplastic properties of zoledronic acid was well established many years ago while analysing use of bone modifying drugs in patients with bone metastases in breast and prostate cancers. Subsequently this phenomenon was confirmed in denosumab too. This study was looking at denosumab in relation to the suggestion of OS improvement observed retrospectively in lung cancer patients. To prove this hypothesis, patients with advanced NSCLC were treated with chemotherapy and denosumab or just chemotherapy alone. Quite an adequate size and clearly defined study with the objective to demonstrate OS advantage. There have been no problems with denosumab in combination with chemotherapy as we well know from other malignancies where this combination is routinely used. The conclusion of the authors was that unfortunately there was no statistical improvement in OS with denosumab regardless of the presence or absence of bone metastases. Negative study reminding us of the fact that we cannot extrapolate from potential benefits of certain approaches in different malignancies. Not all malignancies are created equal…

Reference: J Thorac Oncol 2020;S1556-0864(20)30481-0.
Abstract

Aprepitant for cough suppression in advanced lung cancer

Authors: Noronha V, et al.

Summary: This randomised trial examined cough improvement and quality of life in patients with advanced lung cancer treated with aprepitant. Patients (n=128) with cough lasting over 2 weeks despite a cough suppressant were randomised to aprepitant 125 mg orally on Day 1 and then 80 mg orally on Days 2 to 7 with physician's choice of antitussive, or to physician's choice of antitussive alone. The primary endpoint was subjective cough improvement on Day 9, measured by the Visual Analog Scale (VAS) and Manchester Cough in Lung Cancer Scale. The median baseline cough duration was 90 days. The mean VAS scores (in mm) at baseline and Day 9 were 68 and 39 in the aprepitant arm and 62 and 49 in the control arm, respectively (P<0.001). The mean Manchester Cough in Lung Cancer Scale scores at baseline and Day 9 were 33 and 23 in the aprepitant arm and 30 and 25 in the control arm, respectively (P<0.001). There was no significant difference between the groups in the overall quality of life, however there was a significant improvement in the cough-specific domain for aprepitant-treated patients compared to control (P=0.017). There was no increase in adverse events in the aprepitant group compared to the control group.

Comment: Interesting study looking at the control of a debilitating symptom of advanced lung cancer observed in our patients. Irritative cough related to the malignancy is a frequent symptom with relatively low success of control by standard measures. This study looked at the hypothesis of aprepitant (centrally acting neurokinin-1 inhibitor) to decrease the frequency of this symptom. The pilot study indicated significant decrease in cough frequency utilising this strategy. Simple and clear study of 1 to 1 randomisation of patients with cough for more than 2 weeks in duration were to receive either symptomatic control of physician's choice or aprepitant. The evaluation was performed using a couple of tools including a quality of life questionnaire as well as symptom specific evaluation (Manchester cough in lung cancer scale). Aprepitant significantly increased cough-specific quality of life scale in this study which is a valuable outcome offering our patients another option in controlling this symptom without any major side effects. Good lateral approach with positive result. Easy to implement in practice.

Reference: Chest 2020;157(6):1647-55.
Abstract

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