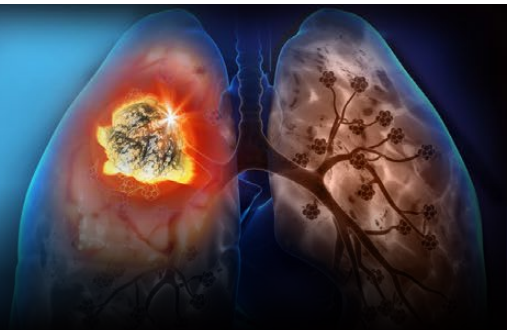
Lung Cancer Research Review™



Making Education Easy

Issue 53 - 2021

In this issue:

Abbreviations used in this issue:

ECOG = Eastern Cooperative Oncology Group; **HR** = hazard ratio; **NSCLC/SCLC** = (non-)small-cell lung cancer; **OS** = overall survival; **PD-1/PD-L1** = programmed cell death (ligand)-1; **PFS** = progression-free survival; **TKI** = tyrosine kinase inhibitor.

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Welcome to issue 53 of Lung Cancer Research Review.

This issue begins with research reporting that patients with advanced NSCLC treated with palliative pembrolizumab monotherapy have a worse prognosis if their ECOG performance status score is ≥2. There is also a report of real-world outcomes for patients with large-cell neuroendocrine lung tumours treated with immune checkpoint inhibitors. Other research selected for this issue includes a phase 3 trial that found that nivolumab plus ipilimumab with two cycles of chemotherapy provided patients with advanced NSCLC with longer OS, with a favourable risk-benefit profile, compared with four cycles of chemotherapy alone. We conclude this issue with research reporting the impact polypharmacy has on outcomes for older patients with advanced lung cancer treated with EGFR-TKIs.

We hope you enjoy the selected research, and we welcome your comments and feedback.

Kind Regards,

Dr Divyanshu Dua

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Association of performance status with survival in patients with advanced non-small cell lung cancer treated with pembrolizumab monotherapy

Authors: Sehgal K et al.

Summary: Associations of ECOG performance status score ≥2 at the start of therapy with PFS and OS were explored in 74 consecutive patients with advanced NSCLC treated with pembrolizumab monotherapy; 29 had an ECOG performance status score of ≥2, and only age differed at baseline between these patients and those with lower scores. Median follow-up was 19.5 months. Compared with patients with ECOG performance status scores of 0 or 1, those with scores of ≥2 had a significantly lower disease control rate (53.6% vs. 88.4% [p=0.002]), shorter median PFS duration (2.3 vs. 7.9 months [p=0.004]) and shorter median OS duration (4.1 vs. 23.2 months [p<0.001]). Among patients eligible for possible subsequent cancer-directed therapy beyond pembrolizumab monotherapy, a significantly lower proportion of those with ECOG performance status scores of ≥2 vs. 0–1 were less likely to receive it (8.3% vs. 45.2% [p=0.003]). An ECOG performance status score of ≥2 was an independent risk factor for worse PFS and OS (respective adjusted HRs 2.02 [95% CI 1.09–3.74] and 2.87 [1.40–5.89]).

Comment: This study is not surprising; however, it provides useful real-world data in terms of performance status and prognosis. The patients with a performance status of 2 or greater had a poor prognosis. This will help clinicians discuss immunotherapy in borderline and frail patients. It will be useful to further subtype if borderline functional patients may derive benefit.

Reference: JAMA Netw Open 2021;4:e2037120

Abstract

Real-world survival outcomes with immune checkpoint inhibitors in large-cell neuroendocrine tumors of lung

Authors: Dudnik E et al, the Israel Lung Cancer Group

Summary: These researchers reported on 125 consecutive patients with advanced large-cell neuroendocrine lung carcinoma treated at one of four cancer centres with (n=41; median follow-up 11.8 months) or without immune checkpoint inhibitors (n=84; median follow-up 6.0 months). For immune checkpoint inhibitor recipients and nonrecipients, the respective proportions who died were 66% and 76%. Immune checkpoint inhibitor recipients had a longer median OS duration since advanced disease diagnosis than immune checkpoint inhibitor nonrecipients (12.4 vs. 6.0 months; adjusted HR 0.58 [95% CI 0.34–0.98]). In an analysis of 37 immune checkpoint inhibitor recipients and 37 nonrecipients propensity score matched for age and ECOG performance status, median OS since advanced disease duration remained significantly longer for the immune checkpoint inhibitor group (12.5 vs. 8.4 months [p=0.046]). For 36 patients receiving immune checkpoint inhibitor monotherapy, the OS duration since starting such treatment was 11.0 months.

Comment: This is a small retrospective series of patients with neuroendocrine lung carcinoma. The use of immune checkpoint inhibitors is unknown in this population. The data will not change clinical practice; however, they do form a basis for a larger prospective trial of immune checkpoint inhibitors. There is an ongoing need for better treatments for advanced neuroendocrine carcinoma of the lung.

Reference: J Immunother Cancer 2021;9:e001999

Abstract

First-line nivolumab plus ipilimumab combined with two cycles of chemotherapy in patients with non-small-cell lung cancer (CheckMate 9LA)

Authors: Paz-Ares L et al.

Summary: Adults with treatment-naïve, confirmed stage IV or recurrent NSCLC (ECOG performance status of 0–1) were randomised to histology-based, platinum doublet chemotherapy with (n=361) or without (n=358) intravenous nivolumab 360mg every 3 weeks and intravenous ipilimumab 1 mg/kg every 6 weeks in this open-label phase 3 trial; chemotherapy was administered every 3 weeks for two cycles when combined with immunotherapy and for four cycles when given without immunotherapy. A preplanned interim analysis at median follow-up of 9.7 months revealed that the immunotherapy arm had longer median OS duration than the chemotherapy only arm (14.1 vs. 10.7 months), a difference that remained significant after a median of 3.5 months additional follow-up (15.6 vs. 10.9 months; HR 0.66 [95% CI 0.55–0.80]). Common grade 3–4 treatment-related adverse events were neutropenia (7% and 9% of immunotherapy plus chemotherapy and chemotherapy only recipients, respectively), anaemia (6% and 14%), diarrhoea (4% and 1%), increased lipase level (6% and 1%) and asthenia (1% and 2%), the any-grade serious treatment-related adverse event rates were 30% and 18%, and the treatment-related mortality rate was 2% in both groups.

Comment: This study is use of a limited number of chemotherapy cycles (two) along with nivolumab and ipilimumab. The data suggest an OS of median 14.1 months (95% CI 13.2–16.2) vs. 10.7 months (9.5–12.4); HR 0.69 [96.71% CI 0.55–0.87]; p=0.00065). Nivolumab plus ipilimumab has demonstrated superior survival compared with chemotherapy in the CheckMate-227 trial, irrespective of PD-L1 expression. Among 1739 patients with chemotherapy-naïve NSCLC across the spectrum of tumour PD-L1 expression, the median duration of OS was 17.1 months with nivolumab plus ipilimumab versus 13.9 months with chemotherapy (HR 0.73 [95% CI 0.64–0.84]). The benefit was significant in the high PD-L1 population. The adverse events reported in the CheckMate 9LA clinical trial are similar to previously known adverse events. In terms of using this combination, the subset population will need to be defined. It is another option available for treating physicians in the first-line setting. The patient selection will be key in identifying the right treatment for stage IV NSCLC in the first-line setting.

Reference: Lancet Oncol 2021;22:198–211
Abstract

Five-year outcomes from the randomized, phase III trials CheckMate 017 and 057: nivolumab versus docetaxel in previously treated non-small-cell lung cancer

Authors: Borghaei H et al.

Summary: The CheckMate 017 and CheckMate 057 trials randomised patients with advanced NSCLC (ECOG performance status score ≤1) who had progressed during or after first-line platinum-based chemotherapy to receive nivolumab 3 mg/kg once every 2 weeks or docetaxel 75 mg/m^2 once every 3 weeks until progression or unacceptable toxicity. This analysis of data pooled from both trials (n=854) reported 5-year efficacy and safety outcomes. Compared with docetaxel, nivolumab recipients had higher 5-year pooled OS and PFS rates (13.4% vs. 2.6% and 8.0% vs. 0%). The respective probabilities of survival among nivolumab recipients without disease progression at 2 years and at 3 years were 82.0% and 93.0%, and their likelihoods of remaining progression-free at 5 years were 59.6% and 78.3%. The treatment-related adverse event rate for nivolumab recipients at 3–5 years of follow-up was 25.8%, with seven participants experiencing new events; there was one grade 3 and no grade 4 treatment-related adverse events.

Comment: This study is more a tool for discussing particularly the long-term immune checkpoint inhibitors in lung cancer patients. The benefit against standard second chemotherapy with docetaxel was maintained. The patients with a response at a 2-year or a 3-year mark will have approximately 82–93% probability of being alive at 5 years. There were no new adverse outcomes, which is very reassuring. Immune checkpoint inhibitors remain the standard of care in the second-line setting.

Reference: J Clin Oncol 2021;39:723–33
Abstract

Updated overall survival and PD-L1 subgroup analysis of patients with extensive-stage small-cell lung cancer treated with atezolizumab, carboplatin, and etoposide (IMpower133)

Authors: Liu SV et al.

Summary: An updated interim analysis was reported for the phase 3 IMpower133 trial, which randomised patients with extensive-stage SCLC to receive four 21-day cycles of carboplatin and etoposide with either atezolizumab 1200mg (n=201) or placebo (n=202) on day 1, and then maintenance atezolizumab or placebo until unacceptable toxicity, disease progression or loss of clinical benefit. After median follow-up for OS of 22.9 months, there had been 302 deaths recorded. Compared with placebo, the atezolizumab-containing arm had longer median OS duration (12.3 vs. 10.3 months; HR 0.76 [95% CI 0.60–0.95]), with 34.0% vs. 21.0% of participants still alive at 18 months. The addition of atezolizumab provided a survival benefit irrespective of PD-L1 immunohistochemistry and blood-based tumour mutational burden status.

Comment: This is another ongoing validation of immune checkpoint inhibitors in extensive-stage SCLC. The 18-month data show that about 34% of the patients were alive in the atezolizumab plus chemotherapy arm. The benefit was demonstrated regardless of PD-L1 immunohistochemistry or blood-based tumour mutational burden status.

Reference: J Clin Oncol 2021;39:619–30
Abstract

Immune-related adverse events of a PD-L1 inhibitor plus chemotherapy versus a PD-L1 inhibitor alone in first-line treatment for advanced non-small cell lung cancer

Authors: Wang M et al.

Summary: This meta-analysis of randomised controlled trials evaluated immune-related adverse event rates with PD-(L)1 inhibitor plus chemotherapy versus PD-(L)1 inhibitor monotherapy regimens for the first-line treatment of advanced NSCLC. Compared with immunotherapy alone, immunotherapy with PD-(L)1 inhibitors combined with chemotherapy was associated with a lower rate of grade ≥3 immune-related adverse events (7.1% vs 10.6%; indirect relative risk 0.516 [95% CI 0.291–0.916]) but not any-grade immune-related adverse events; specifically, chemotherapy plus anti-PD-(L)1 therapy was associated with lower rates of pneumonitis (5.9% vs 7.1%; 0.217 [0.080–0.588]), events affecting the endocrine system (16.1% vs. 20.1%; 0.260 [0.120–0.564]) and skin reactions (10.4% vs. 12.9%; 0.474 [0.299–0.751]) including grade ≥3 reactions excluding rash (1.1% vs. 2.0%; 0.158 [0.032–0.765]), but not events of the digestive system or other immune-related adverse events.

Comment: This is a meta-analysis of previously published trials of combination chemo and immunotherapy. It is very encouraging to note that combination chemoimmunotherapy does not make the adverse events such as pneumonitis, endocrine side effects and skin reactions worse in any way. These adverse events are reduced. This will help clinicians to use the combination with more reassurance. The real-world utility for these data will be useful.

Reference: Cancer 2021;127:777–86
Abstract

A randomised phase 2b study comparing the efficacy and safety of belotecan vs. topotecan as monotherapy for sensitive-relapsed small-cell lung cancer

Authors: Kang J-H et al.

Summary: Patients with sensitive-relapsed SCLC (n=164) were randomised in a 1:1 ratio to receive six 3-week cycles of five consecutive daily intravenous infusions of topotecan 1.5 mg/m^2 or belotecan 0.5 mg/m^2. For the primary endpoint of objective response rate, there was no significant difference between the belotecan versus topotecan arm (33% vs. 21% [p=0.09]) or PFS, but belotecan recipients had a greater disease control rate (85% vs. 70% [p=0.030] and longer median OS duration (13.2 vs. 8.2 months; HR 0.69 [95% CI 0.48–0.99]), especially in participants aged <65 years, those with more advanced disease and those with an ECOG performance status score of 1 or 2. A significantly greater proportion of belotecan recipients also completed all treatment cycles compared with topotecan recipients (53% vs. 35% [p=0.022]).

Comment: The early data for the use of the camptothecin analogue belotecan are promising, but need validation in a large randomised study. The drug will be suited for a subset of patients with no imminent change in day-to-day clinical practice.

Reference: Br J Cancer 2021;124:713–20
Abstract

Phase I study of the efficacy and safety of ramucirumab in combination with osimertinib in advanced T790M-positive *EGFR*-mutant non-small cell lung cancer

Authors: Yu HA et al.

Summary: This open-label phase 1 study enrolled 25 patients with *EGFR* T790M-positive NSCLC who had progressed following EGFR-TKI therapy but had not previously received any third-generation EGFR-TKIs. The patients were treated with osimertinib as-needed with dose de-escalation, followed by an expansion cohort; daily oral osimertinib and intravenous ramucirumab were given every 2 weeks until progression or discontinuation. There were no dose-limiting toxicities. Over median follow-up of 25.0 months, grade ≥3 treatment-related adverse events included hypertension (8%) and decreased platelet count (16%); one participant experienced grade 5 subdural haemorrhage. Safety outcomes were similar between ten patients with CNS metastases and 15 without CNS metastases. Five patients were still on treatment at the time of this analysis. The objective response rate was 76% (60% and 87% with and without CNS metastases, respectively) with a median response duration of 13.4 months, and median PFS duration was 11.0 months (10.9 and 14.7 months with and without CNS metastases). Exploratory biomarker analyses indicated that on-treatment loss of EGFR exon 19 deletion or L858R mutations, but not on-treatment loss of T790M, at baseline correlated with longer PFS. C797S, MET amplification and EGFR amplification emerged after progression.

Comment: This is an early-phase study for the EGFR-TKI osimertinib plus the VEGFR2-directed antibody ramucirumab in patients with T790M-positive *EGFR*-mutant NSCLC. It is encouraging and needs evaluation in a larger prospective study.

Reference: Clin Cancer Res 2021;27:992–1002
Abstract

Variation in oral microbiome is associated with future risk of lung cancer among never-smokers

Authors: Hosgood HD et al.

Summary: The association between oral microbiota diversity and lung cancer risk among never-smokers was explored in lifetime never-smokers from the Shanghai Women's Health Study and the Shanghai Men's Health Study. Patients diagnosed with incident lung cancer (n=114) were each matched to a control. The risk of incident lung cancer was increased in individuals with lower versus higher microbiota alpha diversity but the risk was not affected by beta diversity. Compared with low abundances, high abundances of the Spirochaetia and Bacteroidetes phyla were associated with decreased lung cancer risk (respective odds ratios 0.42 [95% CI 0.21–0.85] and 0.31 [0.15–0.64]), while high abundances of the Bacilli class and the Lactobacillales order were associated with an increased risk of lung cancer (2.40 [1.18–4.87] and 3.26 [1.58–6.70]); the risk was also increased when there was a medium abundance of the Lactobacillales order (2.15 [1.03–4.47]).

Comment: This study looked at the microbiome and its impact on lung cancer. The results are encouraging; however, widespread clinical utility still needs to be defined.

Reference: Thorax 2021;76:256–63
Abstract

Polypharmacy among older advanced lung cancer patients taking EGFR tyrosine kinase inhibitors

Authors: Hakozaki T et al.

Summary: In this research, the records of 334 patients with advanced NSCLC treated with EGFR-TKIs were retrospectively reviewed to assess the impact of polypharmacy (≥5 concomitant medications) and potentially inappropriate medication use on survival; the prevalences of polypharmacy and potentially inappropriate medication use were 38.4% and 31.9%, respectively. The respective median OS durations for patients with and without polypharmacy recorded in their records were 19.4 and 27.3 months, with a significant correlation detected between polypharmacy and OS on multivariate analysis. Patients with polypharmacy recorded also had a higher frequency of unplanned hospitalisations during EGFR-TKI treatment than their counterparts without polypharmacy recorded (49.4% vs. 29.4%; odds ratio 2.34).

Comment: The results are not surprising with polypharmacy leading to poor outcomes. Polypharmacy should be identified early, and as demonstrated, leads to worse outcomes. The data are validated universally and are not limited to the lung cancer space.

Reference: J Geriatr Oncol 2021;12:64–71
Abstract

Independent commentary by Dr Divyanshu Dua

Dr Divyanshu 'Divy' Dua graduated from the Manipal Academy of Higher Education, India, followed by a fellowship at the Royal Australasian College of Physicians.

He trained in internal medicine and medical oncology in Australia, followed by a clinical fellowship in drug development, early-phase trials and thoracic malignancies at Guys Hospital in London as well as the Sarah Cannon Research Institute. He has worked as a consultant medical oncologist in Australia across various sites.

His main tumour stream interests include thoracic malignancies (lung, mesothelioma and thymoma), malignant melanoma, breast, genitourinary, sarcomas and central nervous system tumours. He is keenly involved in geriatric (older persons') oncology.

Divy has published several articles in peer-reviewed international journals. He is actively involved in teaching and research. His past academic affiliations include the University of Adelaide, Flinders University, Kings College, London, Monash Rural School of Medicine and currently the Australian National University.