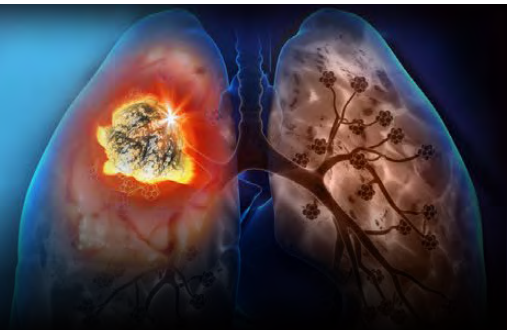
Lung Cancer Research Review™



Making Education Easy

Issue 59 - 2021

In this issue:

Abbreviations used in this issue:

AUC = area under the curve; **HR** = hazard ratio; **ICI** = immune checkpoint inhibitor; **NSCLC/SCLC** = (non-)small-cell lung cancer; **ORR** = objective response rate; **OS** = overall survival; **PD-1/PD-L1** = programmed cell death (ligand)-1; **PFS** = progression-free survival.

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Welcome to issue 59 of Lung Cancer Research Review.

This issue begins with an analysis of real-world patient data to assess the efficacy and safety of pembrolizumab in patients with metastatic NSCLC of Black ethnicity, who have been largely under-represented in the pivotal clinical trials of ICIs. In other included research, a machine learning-based clinical decision support algorithm was established for predicting response to anti-PD-1 therapy in NSCLC. It has also been reported that nab (nanoparticle albumin-bound)-paclitaxel was noninferior to docetaxel for OS in patients with previously treated advanced NSCLC and should therefore be considered a standard treatment option in this setting. This issue concludes with three trials of rovalpituzumab tesirine (an antibody-drug conjugate targeting DLL3) for the treatment of extensive-sage SCLC, all reporting disappointing results.

We hope you find this issue helpful in your everyday practice. Please keep sending us your comments and suggestions.

Kind Regards,

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Safety and efficacy of first-line pembrolizumab in Black patients with metastatic non-small cell lung cancer

Authors: Peravali M et al.

Summary: The records of 136 US patients with stage IV NSCLC treated with first-line pembrolizumab were retrospectively reviewed to assess efficacy and safety in minority racial groups; there were 74 White patients, 53 Black patients, two Asian patients and seven from other racial groups. Compared with White patients, Black patients were of lower median age (65 vs. 70 years [p<0.01]), but there was no significant difference for median PFS or OS (5.9 vs. 5.7 months [p=0.651] and 12.4 vs. 11.8 months [p=0.949], respectively), including for patients with tumour PD-L1 expression ≥50%, or for the incidence of immune-related adverse events (22.6% vs. 24.3% [p=0.83]).

Comment: Peravali et al. in a single-centre study showed that the proportion of immune-related adverse events was significantly higher in Caucasians versus African Americans (60.4% vs. 30.8%), especially in patients with low PD-L1 expression, lower lactate dehydrogenase level, older age and those who had more treatment cycles with ICIs (World J Clin Oncol 2021;12:103–14). The same authors found that in a retrospective analysis across three centres, there was no difference in safety or efficacy of first-line pembrolizumab in White and Black patients. This is very reassuring in day-to-day practice.

Reference: Oncologist 2021;26:694–700
Abstract

Radiomics predicts risk of cachexia in advanced NSCLC patients treated with immune checkpoint inhibitors

Authors: Mu W et al.

Summary: These researchers predicted cachexia risk using radiomics analysis of 18F-FDG-PET/CT images to assess subsequent associations with clinical outcomes for 210 patients with advanced NSCLC treated with ICIs. In training, test and external test cohorts, the radiomics signature was able to predict cachexia risk with AUC values of ≥0.74, and was also able to discriminate for durable clinical benefit from ICI therapy with AUCs of ≥0.66. Across the three cohorts, patients with higher radiomics-based cachexia probabilities had significantly shorter PFS and OS durations, particularly for potentially immunotherapy-sensitive patients with PD-L1-positive status (p<0.05).

Comment: This study is useful to identify patients who are at high risk of cachexia and require intensive monitoring while having treatment with ICIs. This may become a useful tool if proven in a multicentre study, as FDG-PET is routinely used in the staging of NSCLC.

Reference: Br J Cancer 2021;125:229–39
Abstract

Clinical decision support algorithm based on machine learning to assess the clinical response to anti-programmed death-1 therapy in patients with non-small-cell lung cancer

Authors: Ahn B-C et al.

Summary: These researchers established a machine learning-based clinical decision support algorithm for predicting response to anti-PD-1 therapy. Patient characteristics, mutations and laboratory findings from 142 patients with NSCLC treated with anti-PD-1 therapy were analysed for clinical outcomes, and 19 clinically meaningful features were used in supervised machine learning algorithms to predict anti-PD-1 responses; the optimal algorithm was selected and validated in an independent validation set of anti-PD-1 inhibitor recipients. In the discovery set, there were several independent predictors of anti-PD-1 response, including PD-L1 expression, tumour burden and neutrophil-to-lymphocyte ratio. Prediction performance was significantly better for machine learning platforms based on the LightGBM algorithm using 19 clinical features compared with individual clinical features and traditional multivariate logistic regression (AUC 0.788 vs. 0.759).

Comment: This is an attempt to organise the 19 known predictors of response to anti-PD-1 therapy in NSCLC. The individual predictors have failed to be suitable biomarkers for response, and hence logically combining predictors may assist in the clinical decision making. This algorithm will need to be validated in a larger cohort, but regardless, it is an approach that is worth exploring.

Reference: Eur J Cancer 2021;153:179–89
Abstract

Intracranial efficacy of selpercatinib in *RET* fusion-positive non-small cell lung cancers on the LIBRETTO-001 trial

Authors: Subbiah V et al.

Summary: Patients with advanced *RET*-altered solid tumours received 28-day cycles of oral selpercatinib 160mg twice daily in the phase 1/2 LIBRETTO-001 trial. This preplanned analysis reported on 80 heavily pretreated participants with *RET* fusion-positive NSCLC with baseline intracranial metastases; 56% had received ≥1 course of intracranial radiation (14% whole-brain radiotherapy and 45% stereotactic radiosurgery). Among participants with measurable intracranial disease at baseline (n=22), the intracranial ORR (primary endpoint) was 82%, including a complete response rate of 23%. Among all intracranial responders (n=38), the median duration of intracranial response had not been reached after median follow-up of 9.5 months, and 55% had ongoing intracranial responses at 12 months. After median follow-up of 11.0 months, the median intracranial PFS duration for all 80 participants was 13.7 months. There were no new safety signals detected.

Comment: This is an early-phase trial highlighting the efficacy of selpercatinib dosed orally (160mg twice every day) – a RET inhibitor, especially for intracranial efficacy. The drug showed efficacy in the heavily pretreated population. The drug will need to be evaluated in a bigger cohort of patients, especially the untreated population. This drug will be suited for a small subset of the population and looks promising. The drug warrants further evaluation and may provide a useful treatment.

Reference: Clin Cancer Res 2021;27:4160–7
Abstract

Nivolumab with carboplatin, paclitaxel, and bevacizumab for first-line treatment of advanced nonsquamous non-small-cell lung cancer

Authors: Sugawara S et al.

Summary: Treatment-naïve patients with stage IIIB/IV or recurrent nonsquamous NSCLC without sensitising *EGFR*, *ALK* or *ROS1* alterations were randomised to receive ≤6 cycles of combination carboplatin, paclitaxel and bevacizumab with either nivolumab (n=273) or placebo (n=275) every 3 weeks, followed by nivolumab or placebo with bevacizumab until disease progression or unacceptable toxicity, in this phase 3 study. The results of a preplanned interim analysis at median follow-up of 13.7 months were reported. Compared with the placebo group, the nivolumab group had longer median PFS (assessed by an independent radiology review committee; primary endpoint; 12.1 vs. 8.1 months; HR 0.56 [96.4% CI 0.43–0.71]), with the benefit seen across all PD-L1 expression levels including PD-L1-negative participants. The ORRs for the respective nivolumab and placebo arms were 61.5% and 50.5%. The incidences of grade 3–4 treatment-related adverse events in the two study arms were comparable, with treatment-related adverse events resulting in death occurring in five participants from the nivolumab arm and four from the placebo arm.

Comment: The results are consistent with the IMPower50 study where patients received ACP (atezolizumab, carboplatin, paclitaxel) or ABCP (ACP, bevacizumab) or BCP every 3 weeks for four or six cycles, followed by maintenance therapy with atezolizumab, bevacizumab or both. The median OS among the patients in the wild-type population was significantly longer in the ABCP group than in the BCP group (19.2 vs. 14.7 months). Among the wild-type population, the median PFS was longer in the ABCP group than in the BCP group (8.3 vs. 6.8 months [p<0.001]). The subgroup analysis showed that PFS among patients with *EGFR* mutations or *ALK* rearrangements increased with ABCP compared with that with BCP (9.7 vs. 6.1 months; HR 0.59 [95% CI 0.37–0.94]). The results of this study have shown that PFS in the wild-type NSCLC population was around 4 months, compared with the IMPower50 study of around 1.5 months. Nivolumab in combination with carboplatin, paclitaxel and bevacizumab every 3 weeks for up to six cycles can be considered standard of care, but needs validation outside the southeast Asian population.

Reference: Ann Oncol 2021;32:1137–47
Abstract

Tepotinib in patients with NSCLC harbouring *MET* exon 14 skipping

Authors: Sakai H et al.

Summary: Patients with advanced/metastatic NSCLC with *MET* exon 14 skipping mutation received open-label oral tepotinib 500mg once daily in the phase 2 VISION study; a subgroup safety analysis of 18 Japanese participants was reported, 15 of whom had ≥9 months of follow-up data and could be analysed for efficacy. The ORR by independent review was 60.0%, the median duration of response was not reached and median PFS duration was 11.0 months. The ORRs for participants with *MET* exon 14 skipping mutations identified by liquid (n=8) and tissue (n=12) biopsies were 87.5% and 50.0%, respectively. The participants' quality of life was maintained on tepotinib. The safety analysis revealed that the most frequent any-grade treatment-related adverse events were blood creatinine level increase (n=12) and peripheral oedema (n=9).

Comment: Tepotinib, an oral MET inhibitor, has shown efficacy data in a small number of Japanese patients harbouring the *MET* exon 14 skipping mutation. *MET* exon 14 skipping is reported in 3–4% of NSCLCs, and hence it is highly unlikely there will be large trials. The data are promising, and MET inhibitors may become a standard of care. At this point, this remains an area of interest and a potential future therapeutic area.

Reference: Jpn J Clin Oncol 2021;51:1261–8
Abstract

Tislelizumab plus chemotherapy as first-line treatment for locally advanced or metastatic nonsquamous NSCLC (RATIONALE 304)

Authors: Lu S et al.

Summary: Patients with histologically confirmed stage IIIB or IV nonsquamous NSCLC were randomised to receive tislelizumab plus carboplatin or cisplatin and pemetrexed every 3 weeks (n=222), or carboplatin or cisplatin and pemetrexed every 3 weeks during induction treatment, followed by intravenous maintenance pemetrexed every 3 weeks (n=110), in this open-label phase 3 trial. Median follow-up was 9.8 months. Compared with chemotherapy alone, the addition of tislelizumab was associated with longer median PFS (9.7 vs. 7.6 months; HR 0.645 [95% CI 0.462–0.902]) and more and longer responses. Both treatments resulted in common haematological adverse events, mostly grade 1–2. The most frequent grade ≥3 adverse events were associated with chemotherapy and included neutropenia (44.6% and 35.5% in the tislelizumab plus chemotherapy and chemotherapy alone arms, respectively) and leucopenia (21.6% and 14.5%).

Comment: Tislelizumab, an anti-PD-1 monoclonal antibody, was engineered to minimise binding to FcγR on macrophages to abrogate antibody-dependent phagocytosis, a mechanism of T-cell clearance and potential resistance to anti-PD-1 therapy. It needs to be seen how this drug combination fits into the treatment paradigm. This may be the dawn of second-generation anti-PD-1 drugs in anti-PD-1 treatment-resistant patients. The results are promising and may change practice.

Reference: J Thorac Oncol 2021;16:1512–22
Abstract

Phase 3 trial comparing nanoparticle albumin-bound paclitaxel with docetaxel for previously treated advanced NSCLC

Authors: Yoneshima Y et al.

Summary: Patients with advanced NSCLC previously treated with cytotoxic chemotherapy were randomised to receive 21-day cycles of nab-paclitaxel 100 mg/m^2 on days 1, 8 and 15 (n=252) or docetaxel 60 mg/m^2 on day 1 (n=251) in this open-label, phase 3 noninferiority trial. For the respective nab-paclitaxel and docetaxel arms, median OS durations (primary endpoint) were 16.2 and 13.6 months (HR 0.85 [95.2% CI 0.68–1.07]), median PFS durations were 4.2 and 3.4 months (0.76 [0.63–0.92]) and the ORRs were 29.9% and 15.4% (p=0.0002). Grade ≥3 adverse events included febrile neutropenia (2% and 22% in the nab-paclitaxel and docetaxel arms, respectively) and peripheral sensory neuropathy (10% and 1%).

Comment: This study is worth mentioning, as in the current era of target treatment and immune modulation, there is a small subset of patients who respond to chemotherapy. This study is a noninferiority trial; however, the median OS of 16.2 months and ORR of 29.9% are worth mentioning. This should be considered as a treatment option for patients with advanced NSCLC. There were no new adverse events or safety concerns regarding nab-paclitaxel.

Reference: J Thorac Oncol 2021;16:1523–32
Abstract

Efficacy and safety of rovalpituzumab tesirine compared with topotecan as second-line therapy in DLL3-high SCLC

Authors: Blackhall F et al.

Summary: The open-label phase 3 TAHOE study randomised patients with DLL3-high advanced or metastatic SCLC (7% with extensive disease at diagnosis) to second-line therapy with two 42-day cycles (with two additional cycles for participants who met protocol-defined criteria) of intravenous rovalpituzumab tesirine 0.3 mg/kg on day 1 (evaluable n=296) or a 21-day cycle of intravenous topotecan 1.5 mg/m^2 on days 1–5 (evaluable n=148). Compared with topotecan, rovalpituzumab tesirine was associated with a shorter median OS duration (6.3 vs. 8.6 months; HR 1.46 [95% CI 1.17–1.82]), and enrolment into the trial was discontinued. Safety for both drugs was consistent with previous reports.

Comment: This study is a negative study showing the inferiority of rovalpituzumab tesirine, an antibody-drug conjugate containing a DLL3-targeting antibody tethered to a cytotoxic agent pyrrolobenzodiazepine in the second-line setting of extensive SCLC, as compared with standard-of-care topotecan. This highlights the unmet needs and the challenges of treating patients with extensive SCLC.

Reference: J Thorac Oncol 2021;16:1547–58
Abstract

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

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

A phase 1–2 study of rovalpituzumab tesirine in combination with nivolumab plus or minus ipilimumab in patients with previously treated extensive-stage SCLC

Authors: Malhotra J et al.

Summary: Two cohorts of patients with previously treated (43% with ≥2 prior therapy lines) extensive-stage SCLC were enrolled into this open-label phase 1–2 study: cohort 1 (n=30) received two cycles of rovalpituzumab tesirine 0.3 mg/kg once every 6 weeks plus two 3-week cycles of nivolumab 360mg beginning on week 4; cohort 2 (n=12) received the same rovalpituzumab tesirine regimen plus four 3-week cycles of nivolumab 1 mg/kg and ipilimumab 1 mg/kg beginning week 4; both cohorts also received nivolumab 480mg every 4 weeks starting at week 10. All participants experienced ≥1 treatment-emergent adverse event, with 41 adverse events considered to be study drug-related. The most frequent treatment-emergent adverse event was pleural effusion (48%), and the most frequent grade ≥3 adverse event was anaemia (21%). There were three grade 5 study drug-related treatment-emergent adverse events, namely pneumonitis (n=2) and acute kidney injury (n=1), all in cohort 1. The respective ORRs in cohorts 1 and 2 were 27.6% and 36.4%, all partial responses.

Comment: This study is a negative study showing the intolerance of rovalpituzumab tesirine, an antibody-drug conjugate containing a DLL3-targeting antibody tethered to a cytotoxic agent pyrrolobenzodiazepine, in combination with nivolumab plus or minus ipilimumab in previously treated extensive-stage SCLC. The combination was not tolerated and not to be pursued in this setting.

Reference: J Thorac Oncol 2021;16:1559–69
Abstract

Rovalpituzumab tesirine as a maintenance therapy after first-line platinum-based chemotherapy in patients with extensive-stage-SCLC

Authors: Johnson ML et al.

Summary: Patients with extensive-stage SCLC (78% stage IV) who had not progressed after four cycles of platinum-based, front-line chemotherapy (n=748) were randomised 1:1 to receive rovalpituzumab tesirine 0.3 mg/kg or placebo every 6 weeks, omitted every third cycle, in the phase 3 MERU trial. A futility analysis in participants with DLL3-high tumours revealed no significant difference between rovalpituzumab tesirine versus placebo for median OS duration (8.5 vs. 9.8 months; HR 1.07 [95% CI 0.84–1.36]), although rovalpituzumab tesirine was associated with significantly longer investigator-assessed median PFS duration (4.0 vs. 1.4 months; HR 0.48 [p<0.001]). Any-grade adverse events affecting ≥20% of rovalpituzumab tesirine recipients were pleural effusion, decreased appetite, peripheral oedema, photosensitivity, fatigue, nausea and dyspnoea.

Comment: This study is a negative study with rovalpituzumab tesirine, an antibody-drug conjugate targeting DLL3, an atypical Notch ligand expressed in SCLC tumours, in the maintenance setting after platinum-based therapy for extensive SCLC. The rovalpituzumab tesirine showed new toxicities such as pleural, pericardial effusions as well as photosensitivity reactions and peripheral oedema. The drug rovalpituzumab tesirine has had three negative trials: in the second-line setting, in combination with immunotherapy and as maintenance therapy. This drug unfortunately has no clinical role in extensive-stage SCLC.

Reference: J Thorac Oncol 2021;16:1570–81
Abstract