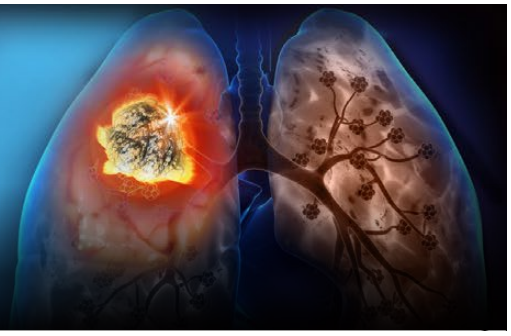
Lung Cancer Research Review™



Making Education Easy

Issue 65 - 2022

In this issue:

Abbreviations used in this issue:

CR/PR = complete/partial response; **DCR** = disease control rate; **EGFR** = epidermal growth factor receptor; **HR** = hazard ratio; **ICI** = immune checkpoint inhibitor; **NSCLC** = non-small-cell lung cancer; **ORR** = objective response rate; **OS** = overall survival; **PFS** = progression-free survival; **TKI** = tyrosine kinase inhibitor.

Welcome to issue 65 of Lung Cancer Research Review.

This month's issue includes three trials of third-generation EGFR TKIs in *EGFR* T790M-mutant NSCLC that has progressed on EGFR TKI therapy, beginning with a phase 1 dose escalation and dose expansion trial of the agent D-0316 in locally advanced or metastatic disease that had progressed after first- or second-generation EGFR TKI therapy. The second is a phase 2 trial of abivertinib and the third is a phase 1–2 trial of lazertinib. The remaining papers cover a wide array of different research topics, including a phase 2 trial of tepotinib for patients with *MET*ex14 skipping NSCLC, a subanalysis of Asian participants from the CheckMate 9LA trial (nivolumab plus ipilimumab combined with two cycles of chemotherapy in advanced NSCLC) and, to conclude, the viability of continuing lorlatinib after disease progression in patients with *ALK*-positive NSCLC.

We hope you find the selected research to be helpful in your everyday practice. Please feel free to send us your comments and feedback.

Kind Regards,

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Phase I trial of a third generation *EGFR* mutant-selective inhibitor (D-0316) in patients with advanced non-small cell lung cancer

Authors: Jian H et al.

Summary: In this open-label phase 1 trial from China, 17 patients with advanced NSCLC received dose-escalated oral D-0316 (third-generation EGFR TKI) 25–150 mg/day, and 67 patients received 50mg or 100mg in a dose-expansion phase. The tolerability of D-0316 was good at 25–150mg, with the maximum tolerated dose not reached. Most treatment-related adverse events were grade 1–2, and the most common were decreased platelet count, corrected QT-interval prolongation, anaemia, rash, low white blood cell count, hypertriglyceridaemia, high cholesterol level, headache, pruritus, cough and increased aminotransferase levels. For the respective 50 and 100 mg/day dosages, the overall response rates were 33.3% and 45.5%, the DCRs were 86.7% and 93.9%, and the median PFS durations were 8.3 and 9.6 months. The recommended phase 2 dose was 100mg.

Comment: These data are early and for a new drug in the ongoing field of EGFR TKIs. The data need further validation. The adverse events are as expected from previous studies of similar EGFR TKIs.

Reference: Oncologist 2022;27:163–e213
Abstract

Tyrosine kinase inhibitor activity in patients with NSCLC harboring uncommon *EGFR* mutations

Authors: Popat S et al.

Summary: The medical records of 246 consecutive patients (84% of Asian ethnicity) with uncommon *EGFR* mutations treated with erlotinib, gefitinib, afatinib or osimertinib as first-line (92%) or second-line therapy were examined in the international, retrospective UpSwinG study; 54%, 43% and 3% of the patients received afatinib, first-generation TKIs and osimertinib, respectively. On EGFR TKI therapy, the median time to treatment failure was 9.9 months, the median OS duration was 24.4 months and the ORR was 43%. For 20 patients who had received first-line chemotherapy, the median time to treatment failure was 6.6 months and the ORR was 41%. Patients with major uncommon or compound mutations had the best outcomes. Across mutation categories, the median times to treatment failure with afatinib and first-generation EGFR TKIs were 11.3 months and 8.8 months, respectively. Most mutation categories were associated with median OS durations of >2 years.

Comment: The data have clinical validation as we are all experienced with uncommon *EGFR* mutations. The data are reassuring and will be useful when discussing the uncommon mutations and in implications for patient care.

Reference: Oncologist 2022;27:255–65
Abstract

Immune biomarkers and response to checkpoint inhibition of *BRAF*^{V600} and *BRAF* non-V600 altered lung cancers

Authors: Murciano-Goroff YR et al.

Summary: These US researchers analysed data on 5945 patients with lung cancers that had undergone next-generation sequencing between 2015 and 2018, with follow-up through to 2020. They identified 127 patients with metastatic *BRAF*-altered lung cancers, including 29 and 59 tumours with class I and II/III alterations, respectively, and 39 with variants of unknown significance. Class II/III tumours exhibited greater mutational burden than class I-altered tumours (8.8 vs. 4.9 mutations per megabase [p<0.001]), with the difference lessened on stratification by smoking status. ICI therapy, for a median of 1.9 months, led to overall response rates of 9% and 26% in class I-altered and class II/III tumours, respectively (p=0.25). In patients with class I–III tumours, ICI ever-recipients had a greater likelihood of death over 36 months than those who had never received ICIs (HR 1.82 [CI 1.17–6.11]). Two patients with class I mutations, two with class II/III alterations and five with variants of unknown significance received ICIs for >2 years.

Comment: The data imply minimal immunogenicity of the *BRAF*-altered cancers. This information is more important when discussing various molecular subtypes of *BRAF*-altered lung cancers. There may be a subset of *BRAF*-altered cancers that respond better to ICIs.

Reference: Br J Cancer 2022;126:889–98
Abstract

Tepotinib efficacy and safety in patients with *MET* exon 14 skipping NSCLC

Authors: Le X et al.

Summary: Patients with *MET*ex14 skipping NSCLC received tepotinib 500mg (450mg active moiety) in the open-label phase 2 VISION study, with assessments of efficacy (evaluable n=152) and safety (evaluable n=255) in predefined subgroups according to age, prior therapy and brain metastasis. The overall ORR was 44.7%, with rates of 48.8% and 39.7% for participants aged <75 and ≥75 years, respectively. For treatment-naïve and previously treated participants, the ORRs were 44.9% and 44.6%, respectively, and the median durations of response were 10.8 and 11.1 months, respectively. Thirteen of the 15 participants analysed by Response Assessment in Neuro-Oncology Brain Metastases criteria achieved intracranial disease control; five of seven participants with measurable brain metastases had intracranial PRs. The grade ≥3 treatment-related adverse event rate was 25.1% with an associated discontinuation rate of 10.6%; adverse event rates were broadly consistent regardless of prior therapy.

Comment: The data are from a phase 2 study of tepotinib in patients with *MET*ex14 skipping NSCLC. The data are promising for intracranial response. There is a 25% chance of ≥3 adverse events, and about 10% discontinuation makes a management issue for clinicians. Adverse event management will be key for long-term management of patients with this drug. The data will need to be evaluated in a bigger cohort.

Reference: Clin Cancer Res 2022;28:1117–26
Abstract

A novel third-generation EGFR tyrosine kinase inhibitor abivertinib for EGFR T790M-mutant non-small cell lung cancer

Authors: Zhou Q et al.

Summary: Adults with *EGFR* T790M-positive NSCLC received abivertinib 50–350mg twice per day in phase 1 of this open-label study from China. Based on pharmacokinetics, efficacy and safety data, a recommended phase 2 dose of 300mg twice daily was established and administered to 227 participants for a median of 24.6 weeks. Among participants evaluable for response (n=209), the confirmed ORR was 52.2%, the DCR was 88.0%, the median duration of response was 8.5 months, and the median PFS and OS durations were 7.5 months and 24.9 months, respectively. All 227 participants experienced ≥1 adverse event, of which 96.9% were deemed to be treatment-related. The serious treatment-related adverse event rate was 13.7%; none of the ten deaths were considered to be treatment-related.

Comment: This is another novel third-generation TKI similar to the other group (D-0316) by Jian et al. The data are encouraging and in line with the other drugs in the development phase. This needs further ongoing validation and ongoing trials.

Reference: Clin Cancer Res 2022;28:1127–35
Abstract

Phase II study of carboplatin-paclitaxel alone or with bevacizumab in advanced sarcomatoid carcinoma of the lung

Authors: Oizumi S et al., on behalf of North East Japan Study Group, Hokkaido Lung Cancer Clinical Study Group

Summary: Sixteen chemotherapy-naïve patients with histologically confirmed pulmonary sarcomatoid carcinomas received carboplatin plus paclitaxel with or without bevacizumab followed by bevacizumab maintenance in the HOT1201/NEJ024 trial from Japan; slow participant accrual led to early trial closure. The overall response rate (primary endpoint) was 25.0%, all from the bevacizumab group (two with pleomorphic carcinoma and two with carcinosarcoma), and the DCR was 56.3%. Median PFS duration was 2.6 months (1.2 and 4.2 months in the non-bevacizumab and bevacizumab groups, respectively), and median survival duration was 8.8 months (7.9 and 11.2 months in the non-bevacizumab and bevacizumab groups, respectively). Haematological and nonhaematological adverse events were generally frequent and reversible, but there was one report of grade 4 ileus and one of grade 3 nasal bleeding among the bevacizumab recipients.

Comment: Pulmonary sarcomatoid carcinoma is a diagnostically challenging group of tumours. It's a rare histological subtype of NSCLC. This is known to be rare and aggressive, with no successful treatment to date. This study provides clinical efficacy data in this rare malignancy, as a randomised trial in this setting seems very unlikely.

Reference: Int J Clin Oncol 2022;27:676–83
Abstract

First-line nivolumab plus ipilimumab combined with two cycles of chemotherapy in advanced non-small cell lung cancer

Authors: John T et al.

Summary: This subanalysis of the CheckMate 9LA trial focussed on its Asian participants from Japan and China. CheckMate 9LA randomised adults with treatment-naive, histologically confirmed stage IV or recurrent NSCLC, Eastern Cooperative Oncology Group performance status 0–1 and no sensitising *EGFR* or *ALK* mutation to receive two cycles of chemotherapy with or four cycles without the addition of nivolumab 360mg every 3 weeks and ipilimumab 1 mg/kg every 6 weeks. Compared with Asian chemotherapy only recipients (n=30), Asian immunochemotherapy recipients (n=28) had longer median OS after a minimum 12.7 months of follow-up (not reached vs. 12.7 months; HR 0.33 [95% CI 0.14–0.80]), longer median PFS (8.4 vs. 5.4 months; 0.47 [0.24–0.92]) and a greater ORR (57% vs. 23%), with similar grade 3–4 treatment-related adverse event rates (57% vs. 60%).

Comment: These data are based on an open-label trial (Paz-Ares L et al. Lancet Oncol 2021;22:198–211), in which 719 patients from sites in 19 countries were randomly assigned between August 2017 and January 2019 to receive nivolumab/ipilimumab with two cycles of histology-based platinum doublet chemotherapy (n=361) or four cycles of chemotherapy alone (control group; n=358). Overall, approximately 40% of patients had tumour PD-L1 expression ≤1%. Treatment consisted of nivolumab at 360mg every 3 weeks plus ipilimumab at 1 mg/kg every 6 weeks combined with chemotherapy every 3 weeks for two cycles, or chemotherapy alone every 3 weeks for four cycles. **Overall survival:** in longer-term follow-up, with a median duration of 13.2 months (IQR 6.4–17.0 months), median OS was 15.6 months (95% CI 13.9–20.0) in the nivolumab/ipilimumab group versus 10.9 months (9.5–12.6) in the control group (HR 0.66 [0.55–0.80]). OS benefit in the nivolumab/ipilimumab group was observed across all PD-L1 expression levels, and similar benefit was observed among patients with nonsquamous histology and those with squamous histology. With longer-term follow up, median PFS was 6.7 vs. 5.0 months (HR 0.68 [95% CI 0.57–0.82]). Objective responses were observed in 38.2% vs. 24.9% of patients (CRs in 2% vs. 1%), and the median duration of response was 11.3 vs. 5.6 months. **Adverse events:** grade 3–4 treatment-related adverse events occurred in 47% vs. 38% of patients, with the most common in the nivolumab/ipilimumab group being neutropenia (7% vs. 9% in the control group), anaemia (6% vs. 14%), increased lipase level (6% vs. 1%) and diarrhoea (4% vs. 1%). This substudy in the Asian population showed similar results and is reassuring to exclude any racial and ethnic response to the treatment. The adverse events were similar given the small sample size of the Asian population.

Reference: Int J Clin Oncol 2022;27:695–706
Abstract

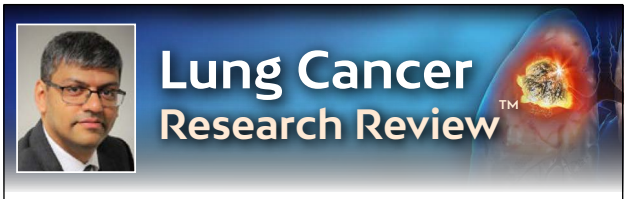
Camrelizumab plus carboplatin and paclitaxel as first-line treatment for advanced squamous NSCLC (CameL-Sq)

Authors: Ren S et al., on behalf of the CameL-sq Study Group

Summary: Patients with stage IIIB–IV squamous NSCLC were randomised to receive 4–6 cycles of carboplatin plus paclitaxel with camrelizumab (n=193) or placebo (n=196) every 3 weeks, followed by maintenance camrelizumab or placebo, in the phase 3 CameL-sq trial from China. Compared with the placebo arm, the addition of camrelizumab to chemotherapy was associated with significantly longer median PFS (8.5 vs. 4.9 months [p<0.0001]) and median OS (not reached vs. 14.5 months [p<0.0001]). There were no unexpected treatment immune-related adverse events. A biomarker analysis revealed significant independent associations between peripheral blood ctDNA (circulating tumour DNA) clearance after two cycles and increased PFS and OS durations in camrelizumab plus chemotherapy recipients.

Comment: The data are comparable with other combination chemoimmunotherapy approaches. In the phase 2 KEYNOTE-021 trial (Peng L et al. Front Oncol 2021;11:657545), data from cohort G showed that first-line pembrolizumab combined with chemotherapy provided a higher ORR (58% vs. 33%) and longer PFS (median, 24.5 vs. 9.9 months), and long-term follow-up (median 49.4 months) revealed a longer OS (median, 34.5 vs. 21.1 months; HR 0.71 [95% CI 0.45–1.12]) versus chemotherapy alone in patients with advanced *EGFR*/*ALK* wild-type nonsquamous NSCLC. The biomarker analysis revealed that ctDNA clearance makes this study unique and is a predictive marker for response.

Reference: J Thorac Oncol 2022;17:544–57
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.

A phase 1/2 study of lazertinib 240 mg in patients with advanced *EGFR* T790M-positive NSCLC after previous EGFR tyrosine kinase inhibitors

Authors: Cho BC et al.

Summary: Adults with *EGFR* mutation-positive NSCLC who had progressed after EGFR TKI therapy (n=78) received oral lazertinib 240 mg/day until disease progression in this phase 1–2 study from South Korea. Among participants with T790M-positive tumours at baseline (n=76), the ORR was 55.3% (one CR and 41 PRs), median PFS duration was 11.1 months and median OS duration was not reached. Among participants with measurable intracranial lesions (n=7), the intracranial ORR was 85.7% (one CR and five PRs). Treatment-emergent adverse events were mostly mild or moderate, with the most common being rash (37.2%), pruritus (34.6%) and paraesthesia (33.3%). Three participants experienced serious drug-related adverse events, namely gastritis, pneumonia and pneumonitis. *EGFR* T790M loss was the main mechanism of resistance.

Comment: This study is an ongoing quest for third-generation TKIs. The drugs in these categories continue to have good intracranial responses. The drug needs ongoing trial and validation.

Reference: J Thorac Oncol 2022;17:558–67
Abstract

Continuation of lorlatinib in *ALK*-positive NSCLC beyond progressive disease

Authors: Ou S-HI et al.

Summary: The clinical benefit of continuing lorlatinib >3 weeks after progressive disease was evaluated in this retrospective analysis of an ongoing phase 2 trial, which included patients who had previously received crizotinib (group A; n=28) and those who had received ≥1 prior second-generation ALK TKI (group B; n=74). The respective median durations of treatment for participants who continued and did not continue lorlatinib beyond progressive disease were 32.4 and 12.5 months in group A, and 16.4 and 7.7 months in group B. Compared with participants who did not continue lorlatinib beyond progressive disease, those who did had longer median OS (not reached vs. 24.4 months in group A and 26.5 vs. 14.7 months in group B) as well as median postprogression OS (not reached vs. 8.0 months in group A and 14.6 vs. 5.3 months in group B).

Comment: This provides clinical data in a subsection of patients and will be clinically useful in a subset of patients. The evidence in this population is limited, and these data will be useful in a carefully selected population.

Reference: J Thorac Oncol 2022;17:568–77
Abstract