Editorial Commentary

Re-ORIENT-ing antitumor immunity in EGFR-mutant non-small cell lung cancer: are antiangiogenics the key?

Aaron J. Franke[1], Erin L. Schenk[2]^

[1]Division of Hematology-Oncology, Department of Medicine, University of Florida Health Cancer Center, Gainesville, Florida, USA; [2]Division of Medical Oncology, Department of Medicine, University of Colorado School of Medicine, Aurora, Colorado, USA

Correspondence to: Erin L. Schenk, MD, PhD. Division of Medical Oncology, Department of Medicine Anschutz Medical Center, Aurora, Colorado, USA. Email: erin.schenk@cuanschutz.edu.

Comment on: Lu S, Wu L, Jian H, *et al.* Sintilimab plus bevacizumab biosimilar IBI305 and chemotherapy for patients with EGFR-mutated non-squamous non-small-cell lung cancer who progressed on EGFR tyrosine-kinase inhibitor therapy (ORIENT-31): first interim results from a randomised, double-blind, multicentre, phase 3 trial. Lancet Oncol 2022;23:1167-79.

Keywords: EGFR mutation; immunotherapy; vascular endothelial growth factor (VEGF); non-small cell lung cancer (NSCLC)

Submitted Mar 31, 2023. Accepted for publication Apr 13, 2023. Published online Apr 25, 2023.
doi: 10.21037/cco-23-28
View this article at: https://dx.doi.org/10.21037/cco-23-28

For patients with advanced or metastatic non-small cell lung cancer (mNSCLC) harboring sensitizing mutations in the epidermal growth factor receptor (*EGFR*) tyrosine kinase domain (L858R and Ex19Del), targeted molecular therapy with *EGFR*-directed tyrosine kinase inhibitors (TKIs) have revolutionized the therapeutic landscape for this biomarker selected population (1).

Despite the remarkable success of EGFR TKIs generating sustained disease response, acquired resistance to targeted therapy and progressive disease is inevitable. The adoption of immune checkpoint inhibitors (ICI), specifically targeting the PD-1/PD-L1 axis, into the treatment paradigm of advanced non-small cell lung cancer (NSCLC) lacking an actionable oncogene (e.g., *EGFR*), has demonstrated the ability to induce durable clinical responses and improve survival outcomes for a select subset of patients (2). As such, numerous ongoing research efforts are exploring the role of incorporating anti-PD-(L)1 ICI into the treatment landscape of *EGFR*-mt NSCLC. However, initial attempts to incorporate ICI demonstrated that single agent immunotherapy is not an effective approach in the subsequent line or as a first line approach even with a concurrent high level of tumor PD-L1 expression (3,4). One potential strategy for post-TKI therapy emerged from IMpower150, a phase III trial testing atezolizumab immunotherapy in combinations including chemotherapy and bevacizumab. Exploratory analyses demonstrated patients with *EGFR*-mt NSCLC had improved progression free survival (PFS) with atezolizumab, bevacizumab, carboplatin, and paclitaxel (ABCP) compared to BCP (5). The prospective phase-III ORIENT-31 trial follows up on this observation.

The ORIENT-31 trial is a randomized, double-blind, phase III trial ongoing in multiple institutions across China. Patients with *EGFR*-mt NSCLC who had progressed after an *EGFR*-targeting TKI were eligible and were randomly assigned (1:1:1) to receive sintilimab (anti-PD-1), plus IBI305 (bevacizumab biosimilar), pemetrexed, and cisplatin (arm A), sintilimab plus pemetrexed and cisplatin (arm B), or pemetrexed and cisplatin alone (arm C). At the first planned interim analysis, a significant PFS benefit was reported in arm A with the quadruplet regimen (sintilimab/IBI305/cisplatin/pemetrexed) compared to chemotherapy alone [mPFS 6.9 *vs.* 4.3 months; hazard ratio (HR) 0.46; 95% confidence interval (CI): 0.34–0.64; P<0.0001] (6). Importantly, the survival benefit of quadruplet therapy was maintained across multiple key subgroups, including patients with brain metastases, which accounted for approximately half of subjects enrolled (7).

^ ORCID: 0000-0001-9418-9948.

While we await overall survival data in follow-up to these promising PFS results from the ORIENT-31 trial, several lines of evidence suggest a role for chemoimmunotherapy (chemo-ICI) with antiangiogenic therapy (VEGFi) in post-TKI *EGFR*-mt NSCLC.

Evidence of VEGFi combinations in *EGFR*-mt NSCLC

One potential complementary target of *EGFR* signaling blockade in NSCLC is inhibition of the vascular endothelial growth factor (VEGF) pathway (8). VEGF signaling plays an important role in neoangiogenesis and shares a common downstream pathway with EGF(r) (9,10). It has been suggested that *EGFR*-mt NSCLC are more VEGF-dependent than *EGFR* wild-type tumors, and at the time of acquired therapeutic resistance, this dual crosstalk between overlapping pathways may function exclusively of one another. Therefore, dual VEGF/EGFR blockade represents a rational combination strategy for *EGFR*-mt NSCLC treatment.

VEGFi + EGFR TKI

Results from several randomized controlled trials (RCTs) have demonstrated the combination of either of VEGFi with first-generation *EGFR*-TKIs significantly improved median PFS (mPFS) relative to TKI monotherapy (16–19 *vs.* 9–13 months) in treatment-naïve patients with advanced *EGFR*-mt NSCLC (8). However, in all three of these prospective RCTs, the addition of VEGFi failed to demonstrate an OS benefit but did highlight the increased toxicity in patients receiving dual VEGR/EGFR blockade. More importantly, these trials were conducted prior to first-line adoption of osimertinib, and only examined the potential benefit of adding VEGFi to early-generation TKIs, which are less favored approaches in the 1st line setting.

VEGFi + chemo-ICI

In addition to promoting tumor angiogenesis, accumulating preclinical and early clinical evidence of the immunomodulatory role of tumor-secreted angiogenic factors (e.g., VEGFA), particularly in *EGFR*-mt NSCLC, in promoting a pro-inflammatory milieu within the tumor microenvironment (TME), eliciting potent immunosuppression on both innate and adaptive anti-tumor immunity (11). This further understanding of the VEGF/TME interplay provides a strong biologic rationale for further prospective trials evaluating dual PD-(L)1/VEGF blockade (8). This synergistic combination approach may be of particular importance and represents a biologically pragmatic strategy to enhance tumor-specific T-cell activation and interferon gamma signaling to augment the TME, restore T-cell anergy to amplify the host anti-tumor response and ostensibly prevent or delay acquired ICI resistance (12).

IMpower-150 evaluated ABCP (atezolizumab, bevacizumab, carboplatin, and paclitaxel) compared to ACP or BCP, and included a pre-specified subgroup analysis of patients with *EGFR*-mt tumors (following PD on prior *EGFR*-TKI) (13). Initial results indicated in patients with sensitizing *EGFR*-mt tumors, the addition of ICI (ABCP quadruplet) resulted in an improvement in PFS and OS compared with BCP (HR 0.31; 95% CI: 0.11–0.83). However, with an additional 20 months of follow-up, the initial PFS and OS benefit was lost (HR 0.60; 95% CI: 0.31–1.14) (14). Note, the hazard ratio still seems to suggest a benefit to the quadruplet regimen, and although the upper 95% CI crosses unity, the small sample size limits the power for proper statistical analysis in these subgroups. The notable numerical benefit in median OS (mOS) with ABCP compared to BCP (29.4 *vs.* 18.1 months) may translate to clinically meaningful outcomes in a larger prospective and adequately powered trial.

Further supporting evidence of this combination come from an early report of a phase II trial of ivonescimab (first-in-class PD-1/VEGF bispecific antibody; Ak112), in combination with chemotherapy for patients with advanced NSCLC with PD on prior *EGFR*-TKI (cohort 2) (15). As of March 20, 2022, 19 patients in cohort 2 had been treated with the combination for up to 12 months. Encouraging findings were reported, with an ORR and DCR rate of 68.4% and 94.7% respectively, correlating with a mPFS of 8.2 months and 6-month PFS rate of 69.3%. More mature results from this cohort are awaited, as are findings from the ongoing phase-III RCT (NCT05184712) of ivonescimab + chemotherapy *vs.* chemotherapy in *EGFR*-mt mNSCLC after PD on prior EGFR-TKI.

Evidence showing lack of benefit with ICI + chemotherapy in EGFR-mt NSCLC

IMpower-130: an open label, randomized phase III trial was the first hint subsequent line ICI + chemotherapy would not generate meaningful patient outcomes in *EGFR*-mt

mNSCLC. IMpower-130 allowed these patients to enroll after progression on standard of care TKI. Subgroup analysis failed to demonstrated an improvement in PFS or OS with the addition of atezolizumab to initial chemotherapy (nab-paclitaxel and carboplatin) in the 44 patients with *EGFR*-mt NSCLC (16).

CheckMate-722: an open label, phase III RCT (NCT02864251) investigating the role of ICI in TKI-resistant *EGFR*-mt (non-T790m) mNSCLC. Following failure of either 1st- or 2nd-line TKI, patients were randomized to nivolumab plus chemotherapy followed by nivolumab/pemetrexed maintenance *vs.* chemotherapy alone. At ESMO Asia 2022, Mok *et al.* presented the results of 294 patients with a minimum follow-up of 18.2 months. Failing to meet the primary endpoint, Mok reported no observed mPFS benefit in the chemo-ICI *vs.* chemo alone arm (5.6 *vs.* 5.4 months; HR 0.75; 95% CI: 0.56–1.00, P=0.053) (17). Similarly, there was no significant difference in OS (19.4 *vs.* 15.9 months; HR 0.82; 95% CI: 0.61–1.10). There was a trend towards improved landmark PFS rates in the presented subgroup analysis, suggesting a potential benefit in patients harboring canonical sensitizing *EGFR*-mts and those who had only 1 prior line of TKI therapy. However, this interpretation requires further investigation as patient heterogeneity, small subgroup sample sizes, and the protocol adaptation required to offset slow accrual during the COVID-19 pandemic, limit the confidence in this observation.

KEYNOTE-789: further negative confirmatory data for chemo-ICI in this population comes from the phase III KEYNOTE-789 trial (NCT03515837). In this double-blind study, patients with *EGFR*-mt mNSCLC progressing on prior *EGFR*-TKI (including osimertinib) were randomized to chemo-ICI (pembrolizumab and Cis/carboplatin + pemetrexed) or platinum-doublet chemotherapy alone. Unlike the initial design of CheckMate-722, KEYNOTE-789 had an *a priori* enrollment protocol to include patients with *EGFR* T790M and acquired osimertinib resistance. In a recent press release, Merck announced the study failed to meet its dual primary endpoint (18). At the final analysis, there was reportedly a trend towards improved OS and PFS in patients receiving chemo-ICI, however, neither survival endpoint reached pre-specified statistical significance.

ORIENT-31 summary

ORIENT-31 offers the first prospective, phase-III data in *EGFR*-mt mNSCLC, showing a significant survival benefit of quadruplet therapy and a pathway forward towards incorporating immunotherapy into the *EGFR*-mt mNSCLC treatment paradigm. As we await more mature outcome data, several questions remain when considering using this regimen for patients post-TKI progression. The majority of patients enrolled in ORIENT-31 received a 1st or 2nd generation EGFR TKI as their single prior line of therapy, is this the population that derives the most benefit? Will patients post 1st-line 3rd generation TKI experience a similar degree of benefit? While expected levels of efficacy differ between the generations of EGFR TKIs, a further distinction is the landscape of resistance mechanisms that emerge. Resistance mechanisms at time of progression on 1st/2nd generation EGFR-TKIs are frequently EGFR-dependent while progression post-osimertinib is rarely due to additional *EGFR* mutations (19,20). While the impact of TKI resistance mechanisms on subsequent chemotherapy based regimens is unknown, this potential data set from the ORIENT-31 trial would be of great clinical interest.

While cross trial assessment is meant to be only hypothesis generating rather than clinically instructive, a comparison of quadruplet therapy for *EGFR*-mt patients in ORIENT-31 *vs.* IMpower150 reveals a shorter mPFS (6.2 *vs.* 10.2 months) and lower ORR (44% *vs.* 71%), which may be related to patient specific factors(20). The *EGFR*-mt population in ORIENT-31 was younger (median 57 *vs.* 64 years), included a higher proportion of never-smokers (70% *vs.* 59%), and enrolled participants with baseline CNS metastases (35%) (13). These critical differences likely account for the apparent discrepancies in anti-tumor efficacy (though mature survival results are awaited), but more importantly emphasize that ORIENT-31 enrolled a distinct population with higher risk disease compared to IMpower-150.

These observations may be important given the geographic variations in outcomes from prior studies (21). In the parallel phase-III FLAURA China trial (n=136), osimertinib resulted in significant outcome improvement verses the comparator arm, consistent with outcomes from the global FLAURA study. However, the mPFS and mOS for both *EGFR* TKI groups were numerically lower in FLAURA China (mPFS 17.8 *vs.* 9.8 months; mOS 33.1 *vs.* 25.7 months) compared to the global FLAURA population (mPFS 18.9 *vs.* 10.2 months; mOS 38.6 *vs.* 31.8 months) (21,22). While several confounding geographic and patient-dependent variability may have contributed to these differences, assessment of the subgroup baseline demographics shows subjects enrolled to FLAURA China had more advanced disease associated with a larger

tumor burden. This is highlighted by a disproportionately higher number of patients with WHO performance status 1 (85% *vs.* 59%), extra-thoracic visceral metastases (40% *vs.* 35%) and known/treated CNS metastases at study entry (28% *vs.* 21%) in the China versus global study population.

In summary, the ORIENT-31 trial quadruplet combination therapy including VEGFi plus chemotherapy and ICI represents a potential therapeutic option for *EGFR*-mt NSCLC patients after progression on TKI therapy. Follow-up survival data, translational studies, and incorporating biomarkers into subgroup analyses will be crucial to defining the role and context of this regimen for future patients post-TKI progression.

Acknowledgments

Funding: Dr. Schenk is supported by 2021 LUNGevity Career Development Award #25B1267, 2022 Hamoui Foundation/LUNGevity Clinic Research Award Program for RET-positive Lung Cancer, and NCI R01CA254730-01.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Chinese Clinical Oncology*. The article did not undergo external peer review.

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://cco.amegroups.com/article/view/10.21037/cco-23-28/coif). AJF reports serving on an advisory board for OncLive. ELS reports speaker fees from OncLive, Physicians' Education Resource, Takeda, Roche/Genetech, IDEO Oncology, Sanofi/Regeneron, MJH Life Sciences, consultant fees from Actinium, Bionest Partners, ExpertConnect, FCB Health, Guidepoint Network, the KOL Connection Ltd., Prescient Advisory, served on an advisory board for BioAtla, Regeneron, Janssen, and G1 therapeutics. ELS is also supported by 2021 LUNGevity Career Development Award #25B1267, 2022 Hamoui Foundation/LUNGevity Clinic Research Award Program for RET-positive Lung Cancer, and NCI R01CA254730-01. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Franke AJ, Schenk EL. Re-ORIENTing antitumor immunity in EGFR-mutant non-small cell lung cancer: are antiangiogenics the key? Chin Clin Oncol 2023;12(3):31. doi: 10.21037/cco-23-28