Editorial Commentary

Finding the right HARMONi-A

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Epidermal growth factor receptor (EGFR)-directed tyrosine kinase inhibitors (TKIs) have significantly advanced the treatment of metastatic *EGFR*-mutant non-small cell lung cancer (NSCLC), improving objective response rate (ORR), progression-free survival (PFS), and ultimately, overall survival (OS). However, resistance to TKIs inevitably develops, making metastatic *EGFR*-mutant NSCLC an incurable disease in most cases.

The emergence of immune checkpoint inhibitors (ICIs), particularly anti-programmed death 1 (anti-PD-1) and anti-programmed death-ligand 1 (anti-PD-L1) monoclonal antibodies, has revolutionized cancer therapy, moving these agents from the metastatic setting to the forefront of perioperative treatment. ICIs harness the adaptive immune system to potentially eradicate cancer, even in advanced disease. Yet, in *EGFR*-mutant NSCLC, ICIs have been largely ineffective due to several factors, including low tumor mutational burden, an immunosuppressive tumor microenvironment, limited cytotoxic T-cell infiltration, and low PD-L1 expression. For instance, Lisberg *et al.* found no response to ICIs in 10 metastatic *EGFR*-mutant NSCLC, despite seven of them having high PD-L1 expression [tumor proportion score (TPS) ≥50%] (1). Recent trials combining ICIs with chemotherapy also failed to improve PFS or OS in this population (2,3).

Conversely, the interplay between the EGFR and vascular endothelial growth factor (VEGF) pathways is critical. EGFR activation drives hypoxia-independent HIF1α activation, leading to constitutive VEGF-A (VEGFA) expression. Resistance to EGFR inhibition is associated with increased VEGFA levels and activation of the VEGF receptor (VEGFR) pathway. VEGFA also suppresses adaptive immunity by impairing lymphocyte trafficking, inhibiting dendritic cell maturation, and recruiting immunosuppressive cells such as myeloid-derived suppressor cells (MDSCs) and regulatory T cells (Tregs) (4,5). Multiple studies have shown that dual inhibition of EGFR and VEGF/VEGFR enhances ORR and PFS in NSCLC (6,7).

A subanalysis of the IMpower150 trial demonstrated improved PFS in *EGFR*-mutant patients who received chemotherapy, atezolizumab (an ICI), and bevacizumab (an anti-VEGFA antibody) after TKI failure, suggesting that VEGF blockade may potentiate ICI efficacy in this setting (8,9). A recent network meta-analysis by Zhao *et al.*, which included 17 single-arm and 15 randomized trials, confirmed that the combination of chemotherapy, ICI, and anti-angiogenics yielded the best PFS outcomes in metastatic *EGFR*-mutant NSCLC compared to other regimens (10).

Ivonescimab, a novel bispecific antibody targeting PD-1 and VEGFA, has shown promising results in metastatic *EGFR*-mutant NSCLC post-TKI failure. Its cooperative binding mechanism significantly enhances affinity for PD-1 when ligated to VEGF, creating a synergistic effect (11,12).

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The HARMONi-A trial, published in *JAMA*, compared ivonescimab plus chemotherapy (carboplatin and pemetrexed) to placebo plus chemotherapy in patients with advanced *EGFR*-mutant NSCLC (unresectable stage IIIB–IIIC or stage IV) who had progressed on TKIs (13). This well-designed, double-blind phase III trial evaluated PFS as the primary endpoint, assessed by blinded independent central review (BICR), and was conducted entirely in China. Notably, 20% of patients had brain metastases, and 85% had received third-generation TKIs. After a median follow-up of 7.9 months, the study demonstrated a significant reduction in the risk of disease progression [hazard ratio (HR) =0.46; P<0.001], with twice as many patients in the ivonescimab arm remaining progression-free at nine months (37.9% *vs.* 18.3%). Ivonescimab also showed activity in the central nervous system, likely due to the anti-edema effects of VEGF blockade. Interestingly, the incidence of immune-related adverse events (irAEs) and serious adverse events (SAEs) related to VEGF inhibition was lower than in previous trials combining ICIs, VEGF blockade, and chemotherapy (13).

The recently published phase 3 trial MARIPOSA-2 has established a new standard of care for *EGFR*-mutant NSCLC patients who progress after osimertinib. The study demonstrated the superiority of the combination of chemotherapy (carboplatin and pemetrexed) plus amivantamab, with or without lazertinib, over chemotherapy alone. Amivantamab, in combination with chemotherapy (with or without lazertinib), significantly extended PFS compared to chemotherapy alone (HR =0.48 and =0.44, respectively) and 6-month PFS rates (51% and 59%). The results of the HARMONi-A trial, which demonstrated a HR of 0.46 and a 6-month PFS rate of 55.4%, are comparable to those of MARIPOSA-2 (14).

The crucial question remains: does the simultaneous blockade of PD-1 and VEGF create an actual synergistic effect, or are we witnessing a merely additive impact of VEGF inhibition, which has improved PFS in previous studies without extending OS? Ivonescimab's promising results in other settings—such as PD-L1 high-expressing NSCLC and the perioperative setting, as reported at the World Conference on Lung Cancer (WCLC) 2024—suggest this drug class could significantly alter the treatment landscape for *EGFR*-mutant NSCLC (15,16).

Ivonescimab may harmonize therapeutic pathways for patients progressing on third-generation EGFR-TKI therapy, offering much-needed effective and tolerable treatment options, but, unfortunately, it has not yet provided us the so-desired final opus, the cure of patients.

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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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