Antibody–Drug Conjugates: A New Addition to the Treatment Landscape of EGFR-Mutant Non–Small Cell Lung Cancer

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The emergence of treatment resistance to targeted agents is currently inevitable and inherently heterogeneous in cancer, presenting significant challenges for improving survival outcomes in patients. This is not an exception for cancers harboring *EGFR* mutations, one of the most prevalently observed oncogenic alterations in non–small cell lung cancer (NSCLC) targeted clinically. Currently, numerous efforts have attempted to delay or overcome acquired resistance to EGFR–tyrosine kinase inhibitors (TKI), changing the treatment landscape of *EGFR*-mutant NSCLC. Haikala and colleagues have developed a unique strategy using patritumab deruxtecan, an antibody–drug conjugate targeting human epidermal growth factor receptor 3 (HER3) linked to exatecan derivatives, for treating *EGFR*-mutant NSCLC. By incorporating EGFR TKIs to upregulate surface HER3 expression, the antitumor efficacy of patritumab deruxtecan was augmented in various preclinical models. In parallel, Jänne and colleagues reported the clinical activity of patrimumab deruxtecan in patients with *EGFR*-mutant NSCLC with prior EGFR TKI treatment. These two studies provide the grounds for hopeful anticipation for a novel strategy that concurrently targets compensatory feedback loops in addition to oncogenic signaling pathways.

See related article by Haikala et al., p. 130

The identification of activating mutations in the coding regions of the EGFR tyrosine kinase in patients with non–small cell lung cancer (NSCLC) and the subsequent development of targeted therapy with small-molecule EGFR–tyrosine kinase inhibitors (TKI) has substantially revolutionized the treatment landscape of NSCLC harboring oncogenic *EGFR* mutation (1). However, acquired resistance invariably occurs, and complex patterns of resistance are beginning to be observed (2). Elucidation of these heterogeneous resistance mechanisms is essential to guide future therapeutic approaches. For example, around 40% of patients developed resistance to the EGFR TKI osimertinib through activation of targetable oncogenes including additional *EGFR* mutations as well as alterations in mesenchymal–epithelial transition (MET), *ERBB2*, *BRAF*, and *PIK3CA*. Meanwhile, no clear resistance mechanism is identified in approximately 40% to 50% of patients treated with osimertinib, complicating treatment strategies after progression with EGFR TKIs. Nowadays, chemotherapy or investigational treatment strategies are the main treatment options for patients that have progressed on third generation EGFR TKIs (3).

Human epidermal growth factor receptor 3 (HER3) is a unique EGFR family member without autophosphorylation activity, rendering it as a nonprioritized target for drug development. Because HER3 is unable to form homodimers, its activation depends on heterodimerization with other receptors (4). The preferred dimerization partners for HER3 are EGFR and HER2, followed by lower affinity to HER4. HER3 can also bind non-EGFR family receptors, including c-MET, FGFR2, AXL, and IGF1R. HER3 activates oncogenic signaling pathways including PI3K/AKT, MAPK, JAK/STAT, and Src family of protein tyrosine kinase, resulting in cancer cell survival and treatment resistance. Recently, accumulating evidence has suggested the critical role of HER3 in resistance to EGFR TKIs (5). In addition, ubiquitous expression of HER3 makes itself as an attractive therapeutic target with broad applications. Because of minimal kinase activity of HER3, HER3-directed antibodies have been regarded as a suitable method to target HER3. Patritumab, seribantumab, and lumretuzumab are representative HER3-directed antibodies under preclinical and clinical development (6). Among these, patritumab (U3–1287) is a fully humanized antibody targeted toward the extracellular domain of HER3, which blocks HER3 ligand binding and heterodimerization with other partners. Patritumab as a single agent or combined with erlotinib has shown limited efficacy and failed to meet the primary endpoint in a phase 3 trial in *EGFR* wild-type NSCLC (NCT02134015). To enhance the therapeutic efficacy of patritumab, an antibody–drug conjugate (ADC) patritumab deruxtecan (HER3-Dxd, U3–1402) composed of patritumab linked to a topoisomerase I inhibitor (exatecan derivatives) via a cleavable tetrapeptide-based linker has been developed. Besides its predicted cytotoxic effects upon internalization, patritumab deruxtecan induced immunogenic cell death, boosted immune activation, enhanced antitumor immune responses, and synergized with PD-1 inhibitors in preclinical models. Accordingly, patrutumab deruxtecan as a single agent showed encouraging efficacy irrespective of resistance mechanisms in a phase I dose escalation/expansion study for patients with NSCLC that had progressed on EGFR TKIs (NCT3260491) presented by Jänne and colleagues (7).

In this issue, Haikala and colleagues have reported rationally designed strategies to enhance therapeutic efficacy of patritumab deruxtecan in *EGFR*-mutant NSCLC (8). They found a correlation between HER3 expression and the efficacy of patritumab deruxtecan as a single agent, as already demonstrated in colorectal cancer. One step further, they conceived strategies to upregulate HER3 expression to promote uptake of patritumab deruxtecan. Using current standard treatment options for *EGFR*-mutant NSCLC, they discovered that pretreatment with EGFR TKIs increased HER3 expression *in vitro* and

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in vivo, thus augmenting internalization of patritumab deruxtecan accompanied with DNA damage response. To further increase the clinical relevance, they proved enhanced efficacy of patritumab deruxtecan combined with osimertinib, the only approved third generation EGFR TKI, using various model systems. This unique interaction between inhibition of EGFR and HER3 is expected to broaden the treatment options for patients with *EGFR*-mutant NSCLC.

Currently, treatment strategies for emergent resistance to EGFR TKIs are rapidly evolving. For example, in the phase I TATTON study (NCT02143466), safety and efficacy of osimertinib combined with other agents including savolitinib (MET inhibitor), selumetinib (MEK inhibitor), or durvalumab (anti–PD-L1 antibody) were evaluated in patients with *EGFR*-mutant, *MET*-amplified advanced and/or metastatic NSCLC resistant to third generation EGFR TKIs. In this study, osimertinib combined with savolitinib showed encouraging efficacy in patients, justifying further clinical investigation of this combination in NSCLC with *MET*-amplification as a driver for resistance to EGFR TKIs. In addition, the phase I CHRYSALIS study (NCT02609776) investigated the safety and efficacy of the amivantamab (an EGFR-MET bispecific antibody) combined with lazertinib (a third generation EGFR TKI) in patients with osimertinib-relapsed NSCLC. This study reported that amivantamab combined with lazertinib showed a response rate of 36% in chemotherapy-naïve patients who progressed while on osimertinib. These representative studies commonly explored the combination of EGFR TKIs with other partners after progression on third generation EGFR TKIs. Previously, we witnessed rapid disease progression after EGFR TKI discontinuation in *EGFR*-mutant NSCLC (9), underscoring the importance of continuous inhibition of EGFR signaling pathways even after resistance to EGFR TKIs develops. Besides, continuous EGFR inhibition with TKIs can elicit effects that provide the biological underpinnings for combinations of genotype-directed or undirected treatment with EGFR TKIs as described by Haikala and colleagues (8). Specifically, EGFR TKIs can induce transcriptomic, translational, or posttranslational modifications to enhance the efficacy of other emerging agents such as HER3 ADCs. Collectively, emergent resistance to EGFR TKIs does not preclude continuous use of EGFR TKIs, but rather it suggests the need for additional combination partners to improve therapeutic efficacy and durable response.

While this study revealed EGFR TKIs as combination partners for patritumab deruxtecan for treating *EGFR*-mutant NSCLC with translational and clinical relevance, it also raised some points that need to be addressed in the future. Although it is evident that the ADC combined with EGFR TKI outperforms either single agent in terms of tumor control, optimal positioning of this combination should be determined. As in the case of trastuzumab deruxtecan, treatment emergent toxicities may interfere with the establishment of ADCs as a treatment option for first-line therapy. A prospective study currently in progress (NCT04676477) will provide answers for adequate use of patritumab deruxtecan as a new therapy combined with EGFR TKI. In addition, discovery of predictive biomarkers for patritumab deruxtecan combined with EGFR TKIs will be another important aspect of drug development to enrich patient populations deriving benefit from this combination. Previously, circulating heregulin ligand was identified as a predictive biomarker for patritumab efficacy in patients with NSCLC (10). A recent phase I study by Jänne and colleagues reported a trend toward enhanced efficacy of patritumab deruxtecan in patients with higher HER3 membrane expression (7). These studies may provide clues for proper biomarkers to predict treatment response of combination strategies. Finding appropriate combination partners for patritumab deruxtecan also represents an emerging avenue of important research. Although osimertinib is currently considered the standard treatment option for *EGFR*-mutant NSCLC, other third generation EGFR TKIs could be a more suitable mate based on their pharmacokinetic and pharmacodynamic profiles. Importantly, fourth generation allosteric EGFR TKIs targeting specifically C797S mutation, such as BBT-176, EAI045.3, and JBJ-04–125–02, are under active investigation. Whether combining fourth generation EGFR TKIs with patritumab deruxtecan would exhibit favorable tumor growth inhibition and delay emergence of treatment resistance needs to be further investigated. Additionally, exploring acquired resistance mechanisms of patritumab deruxtecan with or without EGFR TKIs will be needed for optimal patient care. Rigorous analysis with serially obtained clinical samples from patients under treatment or after progression would give insights toward determinants for treatment response and intrinsic and/or acquired resistance. Another area of clinical significance is whether patritumab deruxtecan and EGFR TKIs can be effective in patients with brain metastases, as the central nervous system is a common site of progression upon EGFR TKIs.

In summary, HER3 is a compelling therapeutic target involved in tumor initiation, progression, and treatment resistance. Recent efforts have revealed that exploiting the ADC patritumab deruxtecan combined with EGFR TKIs can be a more promising strategy to treat *EGFR*-mutant NSCLC with appreciable efficacy over either agent alone. Further efforts to confirm the efficacy and safety of patritumab deruxtecan with or without EGFR TKIs are expected to provide the rationale for incorporating this novel ADC as a new treatment option for patients with *EGFR*-mutant NSCLC.

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