Editorial Commentary

Antibody-drug conjugate development: opening windows for *EGFR*-mutant EGFR tyrosine kinase inhibitor-resistant non-small cell lung cancers?

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Comment on: Oh SY, Lee YW, Lee EJ, *et al*. Preclinical Study of a Biparatopic METxMET Antibody-Drug Conjugate, REGN5093-M114, Overcomes MET-driven Acquired Resistance to EGFR TKIs in EGFR-mutant NSCLC. Clin Cancer Res 2023;29:221-32.

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Antibody-drug conjugates (ADCs) are innovative therapeutic agents made up of a monoclonal antibody (Ab) connecting a cytotoxic agent through a linker. Such drugs exhibit highly specific targeting abilities, could effectively attack targeted cells, and potentially reduce toxicity in contrast with other nontargeted cells. ADCs exert their activity as follows. The first step is tumor penetration, followed by target coupling, then ADC-antigen complex internalization via antigen-dependent endocytosis and endo- or lysosomal trafficking (1). The drug release occurs in the endosomes or lysosomes (1). For individual ADC, the drug-to-antibody ratio (DAR) aims to reflect drug potency and higher cytotoxicity (2). ADCs with higher DAR exhibit more strong *in vitro* action. However, *in vivo* experiments displayed faster liver plasma clearance, potentially related to the overall compound volume, making ADCs easily subject to clearance by the liver (3). Cleavable linkers allow for extracellular drug release within the tumor tissue due to the redox tumor microenvironment (TME) with high protease concentrations and low pH (4). Along with passive drug diffusion through the cell membrane after internalization and processing, drug emission in the TME leads to the bystander effect, a cytotoxic action influenced on neighborhood cells irrespective of targeted antigen expression (5).

Currently, various ADCs are under evaluation, MET-, HER2-, HER3-, or TROP2-targeting ADCs presenting potential applicability in non-small cell lung cancer (NSCLC). Patritumab deruxtecan is a HER3-targeted ADC with a payload composing of a topoisomerase I inhibitor. As EGFR-tyrosine kinase inhibitor (TKI) treatment can increase cell surface HER3 expression in EGFR-mutant NSCLC, it is interesting to study patritumab deruxtecan in EGFR-mutant NSCLC (6). Osimertinib, a third-generation TKI, is used in first-line therapy for progressed *EGFR*-mutated NSCLC and in the adjuvant use for stage IB–IIIA operated *EGFR*-mutated NSCLC. However, osimertinib resistance is an inevitable challenge. The second-line therapy for osimertinib resistance has not yet been established. After disease progression on Osimertinib, patients are often treated with platinum-based chemotherapy with or without an immune checkpoint inhibitor and antiangiogenic therapy (7). Osimertinib resistance patterns, including EGFR-dependent (on-target) and independent (off-target) resistance mechanisms, have thus been studied. Concerning EGFR-independent resistance, tumor growth partly relies on other mechanisms than EGFR signaling, i.e., alternative pathway kinase activation (e.g., MET, HER2, HER3) (8).

MET amplification could happen as a resistance mechanism in *EGFR*-mutant osimertinib-resistant NSCLCs (8). ADCs could provide a potential solution

to this obstacle. Telisotuzumab vedotin (Teliso-V) is a MET-targeted ADC made up of ABT-700, an anti-c-Met monoclonal antibody, and monomethyl auristatin E (a powerful microtubule inhibitor) as an anticancer drug. Teliso-V exhibited antitumor effect in solid tumors with *MET* gene alterations and has thus been studied in clinical studies in patients with acquired EGFR-TKI resistance. In a phase II study [Study of Telisotuzumab Vedotin (ABBV-399) in participants with previously treated c-Met$^+$ Non-Small Cell Lung Cancer. https://clinicaltrials.gov/study/NCT03539536], the Teliso-V monotherapy objective response rate (ORR) was 52.2% in the non-squamous *EGFR* negative group with c-Met high, and 13.3% in patients with *EGFR*- and c-Met-positive nonsquamous NSCLC (9). Combined Teliso-V and EGFR-TKIs also undergo testing in a phase I/Ib study [A study evaluating the safety, pharmacokinetics (PK), and preliminary efficacy of ABBV-399 in participants with advanced solid tumors. https://clinicaltrials.gov/study/NCT02099058], involving patients with acquired c-Met overexpression upon first-line osimertinib treatment. In the interim analysis, combined Teliso-V and osimertinib displayed an ORR of 58% in patients previously treated with first-line osimertinib (10). Other newly developed ADCs include ABBV-400 targeting c-MET and topoisomerase with an ongoing phase 1 study [Study to assess adverse events and change in disease activity in adult participants with advanced solid tumors receiving intravenous (IV) ABBV-400. https://www.clinicaltrials.gov/study/NCT05029882] (11). AZD9592 is a bispecific ADC designed to deliver a topoisomerase 1 inhibitor, targeting *EGFR* and c-MET with a monovalent bispecific IgG platform. It displays an increased affinity toward c-MET to reduce EGFR-related toxicities. In patient-derived xenograft experiments, 73% (16/22) of *EGFR*-mutant NSCLC models exhibited tumor growth inhibition, defined as ≥30% reduction in tumor volume from the baseline after a single 8-mg/kg AZD9592 dose (12). Currently, an ongoing phase 1 trial investigates AZD9592 as monotherapy or combination with other chemotherapeutic drugs in patients with advanced solid tumors [First in human study of AZD9592 in solid tumors (EGRET). https://clinicaltrials.gov/study/NCT05647122]. MET amplification is conventionally diagnosed through fluorescence-in-situ hybridization (FISH) using two main methods (gene copy number with multiple cutoffs, or a ratio of MET per cell to chromosome 7 centromere). Next-generation sequencing can also be used to detect MET amplification. As with FISH, there is not an agreement of copy number to define amplification. Establishing a universal definition of MET amplification will be important in standardizing clinical trial eligibility.

In *Clinical Cancer Research*, Oh *et al.* studied the preclinical activity of REGN5093-M114, a novel MET-targeting ADC in MET-driven patient-derived models (13). Previously, DaSilva and colleagues (14) created a biparatopic METxMET antibody (REGN5093), in which each arm of the antibody recognized a distinct MET epitope, then developed REGN5093-M114 by conjugating a novel maytansinoid M114 drug to REGN5093. Biparatopic Abs reportedly binds tumor cells with increased saturation compared with canonical monospecific Abs and induces receptor crosslinking, leading to cell-intrinsic effects including receptor internalization and downregulation, decreased receptor signaling, and growth inhibition (15). METxMET-M114 applies a protease-cleavable linker, potentially resulting in reduced susceptibility to ADC resistance mechanisms such as reduced lysosomal proteolysis (16). A further design consideration was using a cytotoxic drug with poor cell permeability (17), leading to ADCs with likely insignificant bystander-killing activity. As MET is expressed in several healthy tissues, lacking bystander killing could be favorable from a tolerability aspect. The authors demonstrated potent activity of a biparatopic MET ADC, REGN5093-M114 both *in vitro* and *in vivo*, in patient-derived, *EGFR*-mutated NSCLCs with acquired *MET* amplification after progression on prior EGFR-TKI. Preliminary first-in-human results for REGN5093 were presented at the European Society for Medical Oncology (ESMO) meeting (18). Among 36 patients with *MET*-altered advanced NSCLC, 6 displayed a partial response, of which 5 occurred in patients with prior anti-PD-1 treatment (18). Adverse ≥ grade 3 events occurred in 25% (n=11) of the cases, with pneumonia and pulmonary embolism occurring in 2 patients. No dose-limiting toxicities or treatment-related deaths were reported. A separate phase 1/2 trial is ongoing with 18 patients having been enrolled across five dose levels as of June 26, 2023 (19) [Study of REGN5093-M114 (METxMET ADC) in adult patients with mesenchymal epithelial transition factor (MET) overexpressing advanced cancer. https://www.clinicaltrials.gov/study/NCT04982224].

Although ADCs represent a promising solution, several aspects should be considered. Although the latest ADCs display improved safety profiles, they could still trigger severe adverse (e.g., lung, liver, nerve, eye) events (20). Such toxicities are primarily due to off-target effects outcoming of premature ADC drug release in the circulation or TME

or ADC binding to target antigen-expressing noncancerous cells (21). Toxicity properties could also vary among different ADCs, even with similar drugs and linkers. In particular, interstitial lung disease (ILD) incidence in patients with lung cancer was observed at variable rates among ADC clinical studies (22). Although ADC-related ILD pathogenesis is not enough determined, multiple and potentially duplicate mechanisms are considered (23), including bystander effects and antibody-dependent cellular cytotoxicity. A higher-level bystander effect would be caused by a higher DAR and for ADCs with cleavable linkers, while TME properties would regulate linker cleavage and drug release (24). METxMET-M114 had a drug with poor cell permeability (17), resulting in an ADC with likely insignificant bystander-killing activity. As ADCs exhibit an increased ILD toxicity risk, ILD risk could be present if patients were to return to an EGFR-TKI afterward. This is a crucial consideration as new EGFR-TKIs are being created (e.g., BLU-945) to address *EGFR* C797X resistance, and questions arise regarding sequencing between drugs (25). The central nervous system (CNS) response rate is also a vital aspect. *EGFR*-mutated NSCLCs induced brain metastasis in approximately 50–60% of the patients, finding out agents with CNS activity is thus important. A phase 2 patritumab deruxtecan (HER3-DXd) study revealed a 33.3% CNS ORR (10/30, nine complete responses, and one partial response) in patients with brain metastasis (6), suggesting activity. However, further research efforts should be made, in particular, given the high incidence of CNS metastasis in *EGFR*-mutated patients.

EGFR-TKI therapy significantly prolong progression-free and overall survival in EGFR-mutant NSCLC, however, progression after EGFR inhibition invariably occurs, indicating the need for new therapeutic strategies beyond EGFR-TKI. Along with the growing knowledge of osimertinib resistance mechanisms, next-line innovative therapeutic agents such as MET ADCs, HER3-directed ADC, and EGFR-MET bispecific antibody (26) are being developed showing promising efficacy.

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