Editorial Commentary

REGN5093-M114: can an antibody-drug conjugate overcome the challenge of resistance to epidermal growth factor receptor and mesenchymal epithelial transition tyrosine kinase inhibitors in non-small cell lung cancer?

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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.

Keywords: Epidermal growth factor receptor (EGFR); non-small cell lung cancer (NSCLC); resistance; mesenchymal epithelial transition (MET); REGN5093-M114

Submitted Feb 13, 2024. Accepted for publication Jun 26, 2024. Published online Jul 26, 2024.
doi: 10.21037/tlcr-24-144
View this article at: https://dx.doi.org/10.21037/tlcr-24-144

Recently, Oh and colleagues have investigated the *in vitro* and *in vivo* activity of REGN5093-M114, a novel biparatopic antibody-drug conjugate (ADC) targeting two epitopes of mesenchymal epithelial transition (MET) factor in patient-derived, MET-driven epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor (TKI)-resistant non-small cell lung cancer (NSCLC) models (1).

Among the various oncogenic drivers in NSCLC, targeting the EGFR with TKI has significantly improved patient outcomes (2,3). However, administering these treatments can lead to the acquisition of resistance through *EGFR* mutations, which counteract the therapeutic effect of TKI for many patients. Although osimertinib, a third-generation EGFR TKI, is effective against the EGFR T790M mutation, responsible of resistance to anti-EGFR TKI of first and second generation, emergence of resistance mutations such as C797S, L718Q or L792H remain an issue for the management of patients (4). Another major resistance mechanism to EGFR TKI therapy is the dysregulation of the tyrosine kinase receptor MET, which is also a driver of oncogenesis in NSCLC. *MET* oncogenic activation is enhanced by several mechanisms, including exon 14 skipping, activating mutations in the kinase domain, gene amplification, gene rearrangement, and protein overexpression (5).

MET copy number gains occur through polysomy or focal amplification. Polysomy is defined as the inappropriate replication of chromosome 7, which contains *MET*. In amplification *MET* undergoes regional or focal copy number gain in the 7q31 region without any other alteration. Amplification is more likely to result in oncogenic MET addiction than polysomy (6,7). *MET* amplification can occur as a *de novo* driver alteration in approximately 1% to 5% of NSCLC (8) or as a mechanism of acquired resistance after treatment with TKI. Indeed, *MET* amplification has been reported in about 5% to 20% of patients with NSCLC progressing after treatment by first, second and third-generations of EGFR TKI (7,9,10). In particular, approximately 15% to 25% of patients undergoing osimertinib treatment, which is the current preferred first-line option, develop *MET* amplification or other MET-based acquired resistance mechanisms (11,12).

One strategy envisaged to overcome MET-driven EGFR TKI resistance in patients is to use MET plus EGFR TKI

combination. Although promising, this strategy seems to be beneficial for a small subset of patients. Recently the INSIGHT phase II study has evaluated the combination of the MET TKI tepotinib plus the EGFR TKI gefitinib *vs*. chemotherapy in patients with MET-altered EGFR-mutant NSCLC. Although the combination of therapies significantly improved progression-free survival (PFS) and overall survival (OS) for a subgroup of patients with *MET* amplification, it did not significantly improve survival outcomes in the overall population (13).

Another therapeutic strategy being investigated is antibody targeting MET and its ligand hepatocyte growth factor (HGF). The first clinical trials evaluating specific anti-MET antibodies such as onartuzumab or emibetuzumab have shown disappointing results (14,15). However, novel bispecific antibodies designed to target two different antigens have demonstrated their potential. Amivantamab, a bispecific antibody targeting both EGFR and MET, is the first bispecific antibody to receive Food and Drug Administration approval after demonstrating clinically relevant efficacy in patients with *EGFR* exon 20 insertion NSCLC (16). ADC are antibodies that are covalently bound through a linker to cytotoxic agents, called payloads, which can be delivered to tumor cells expressing specific antigens on their surface. REGN5093 is a biparatopic antibody that recognizes two distinct epitopes of MET (MET×MET). It has demonstrated promising therapeutic effects by promoting lysosomal trafficking and MET degradation through the inhibition of MET recycling in MET-dependent tumor models (17). This compound has been conjugated with a novel maytansinoid M114 payload, a potent inhibitor of microtubule assembly, to generate the ADC MET×MET-M114 (REGN5093-M114). This allows for selective cytotoxin delivery to MET overexpressing tumor cells. In MET overexpressing tumors, MET×MET-M114 has demonstrated potent antitumor activity and a favorable preclinical safety profile (18).

The effectiveness of REGN5093-M114 was assessed by Oh and colleagues in commercial NSCLC cell lines, in patient-derived cell (PDC) lines, and in patient-derived organoids (PDOs) established from patients acquiring *MET* amplification after failure to different generation of EGFR TKI therapy. The results showed that REGN5093-M114 reduced cell viability and was more effective in high *MET* amplificated cells [gene copy number (GCN) ≥15]. Although REGN5093-M114 demonstrated antiproliferative effects as a single agent, it does not exhibit a synergistic effect when combined with osimertinib. After demonstrating its potent antitumoral activity in *MET*-amplified EGFR-TKI-resistant NSCLC cells, the authors showed that REGN5093-M114 was also effective in MET overexpressed NSCLC cells. Using fluorescence activated cell sorting (FACS) analysis, they observed that MET surface expression was associated with the efficacy of REGN5093-M114. This was explained by a higher binding of the ADC in cells with high MET surface expression. Moreover, REGN5093-M114 decreased cell viability in cells with MET overexpression and without *MET* amplification. Finally, REGN5093-M114 was evaluated *in vivo* in nude mice bearing patient-derived xenografts (PDX) harboring EGFR-TKI-induced *MET* amplification. Consistent with the *in vitro* results, REGN5093-M114 induced tumor regression at a dose of 10 mg/kg.

The study aimed to determine the best cut-off values to predict response to REGN4093-M114 treatment. The authors analyzed area under the curve (AUC) score for different parameters including *MET* copy number, expression mean fluorescence intensity (MFI), and percentage of cells with surface MET expression in responder or non-responder cells. The performance was higher for both MFI and MET surface expression parameters rather than for *MET* amplification alone. However, the combination of MET expression and amplification status showed the highest predictive value than each parameter alone. Finally, the authors determined that the optimal threshold value for predicting REGN5093-M114 efficacy was 136.5 MFI MET surface expression. Since there is no consensus on the cut-off value to determine *MET* copy number alterations (7), the use of MET surface expression as a predictive biomarker is of great interest. Interestingly, authors have analyzed the EGFR cell surface expression to evaluate the possibility of a crosstalk between EGFR and MET. However, the efficacy of REGN5093-M114 was not correlated with EGFR expression.

Ultimately, this study evaluated the activity of REGN5093-M114 in acquired resistance to combined EGFR and MET TKIs. Various molecular alterations were identified in patients who progressed upon osimertinib combined to the MET TKI savolitinib. Three PDX harboring distinct alterations were selected to assess the efficiency of REGN5093-M114, osimertinib and REGN5093 with or without osimertinib combination. Among the treatments evaluated, REGN5093-M114 demonstrated the greatest efficacy in the treatment of MET secondary alterations as well as other acquired alterations. In light of the previous

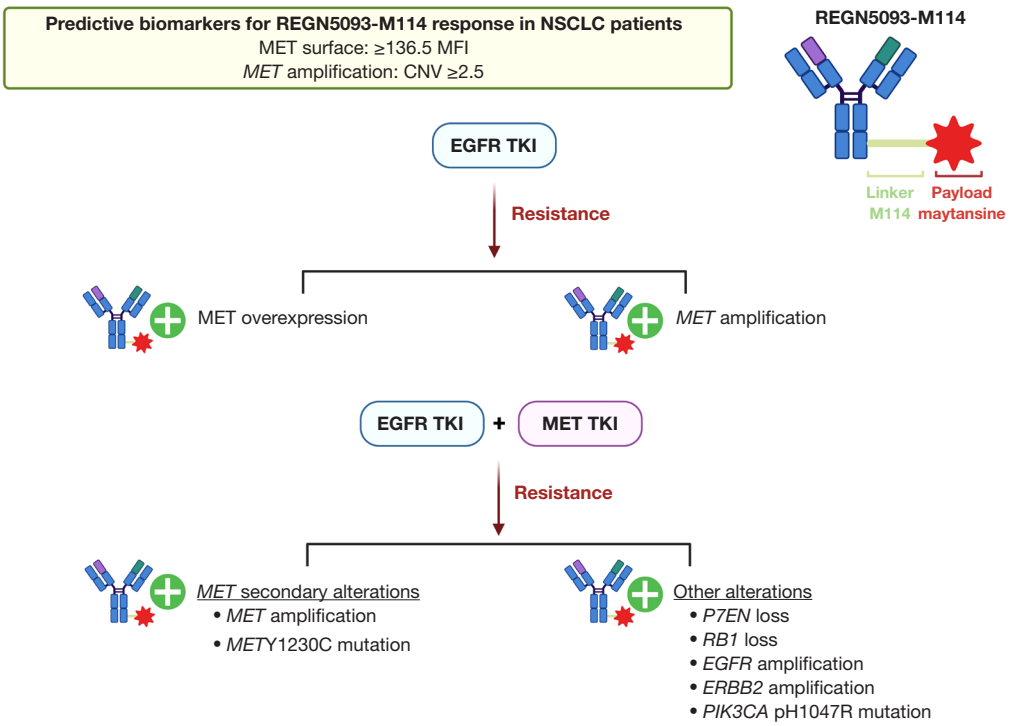

Figure 1 Potential targets for REGN5093-M114 in the management of patients with NSCLC. REGN5093-M114 is an ADC that targets two distinct epitopes of MET factor. It is conjugated with a novel maytansine derivative (M24) using the M114 protease-cleavable linker, with an average drug: antibody ratio of approximately 3.2. The administration of EGFR-TKI with or without MET TKI combination can lead to several resistance mechanisms. REGN5093-M114 may be effective against the listed alterations and counter resistance to EGFR and MET TKI. NSCLC, non-small cell lung cancer; MET, mesenchymal epithelial transition; MFI, mean fluorescence intensity; CNV, copy number variation; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; ADC, antibody-drug conjugate.

study demonstrating the efficacy of the combination of osimertinib and cabozantinib in tumors harboring *MET* Y1230C mutations (19), the authors sought to investigate this combination in a PDX model bearing the same *MET* mutation. The combination of osimertinib and cabozantinib induced tumor growth suppression, while REGN5093-M114 demonstrated potent efficiency by inducing tumor regression.

A previous study evaluated the efficacy of another ADC targeting MET, telisotuzumab vedotin (Teliso-V), in NSCLC patients with MET overexpression. Teliso-V demonstrated encouraging antitumor activity in *EGFR* mutated patients with MET overexpression (20). However, it had limited activity in patients with the *EGFR* T790M mutation, highlighting the unmet need for these patients. In this preclinical study, REGN5093-M114 exhibited broad antitumor activity against several distinct molecular alterations that were acquired either after EGFR TKI therapy, with or without the combination of MET TKI therapy (*Figure 1*). In addition, the added value of this study lies in its ability to provide a predictive biomarker to assess the efficacy of the ADC, which represents a significant contribution to the field of personalized medicine. These findings are highly promising in terms of addressing the current therapeutic gap. However, further validation is required in a clinical setting with a large panel of patients exhibiting diverse alterations. Furthermore, the potential emergence of new REGN5093-M114 resistance alterations cannot be excluded. Currently, a phase I/II study of REGN5093-M114 in patients with MET overexpressing advanced NSCLC (NCT04982224) is ongoing to confirm the potential role of this ADC in the management of NSCLC patients. The objective of this study is to evaluate the safety, tolerability, pharmacokinetics, maximum tolerated dose and/or recommended dose. The pharmacokinetics analysis of REGN5093-M114 will assess

the total antibody and payload concentration. Overall, this study offers new hope for overcoming the failure of MET and EGFR targeting in TKIs-resistant NSCLC patients by proposing a potent ADC for which predictive biomarkers are available.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Translational Lung Cancer Research*. The article has undergone external peer review.

Peer Review File: Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-144/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-144/coif). A.H. received consulting fees from Amgen and Janssen; received payment for lectures from Amgen, AstraZeneca, Janssen and Pierre Fabre; and received support for attending meetings from AstraZeneca. The other authors have no 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: Dardare J, Witz A, Harlé A. REGN5093-M114: can an antibody-drug conjugate overcome the challenge of resistance to epidermal growth factor receptor and mesenchymal epithelial transition tyrosine kinase inhibitors in non-small cell lung cancer? Transl Lung Cancer Res 2024;13(8):2082-2086. doi: 10.21037/tlcr-24-144