**Peer Review File**

**Article Information:** https://dx.doi.org/10.21037/tlcr-24-144

**Reviewer A**

The editorial commentary titled "REGN5093-M114: Can an ADC overcome the challenge of resistance to EGFR and MET TKIs in NSCLC?" provides an overview of current strategies in the setting of acquired resistance to EGFR-TKIs through MET dysregulation discussing the available data on the new antibody-drug conjugate REGN5093-M114.
The commentary is well-structured and relevant to current discussions in the field.

We thank the reviewer for making the time to review our editorial commentary and feedback.

Some minor points:
-In line 95 the text refers to a Table I which is not provided.
The reference to table 1 has been revised accordingly.

-The abbreviations in the text must be reviewed (e.g. PDX, FACS).
All the abbreviations have been revised as recommended.

-The sentence „REGN5093-M114 was the most effective treatment compared to osimertinib, REGN5093 (with or without osimertinib combination) for MET secondary alterations as well as other acquired alterations. “ (line 96-98) is to me not very clear and should be reformulated.
We agree with the reviewer, the sentence has been reformulated in order to improve its intelligibility: “Three patient-derived xenografts (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”.

**Reviewer B**

In their article the authors provide a clear overview of the use of REGN5093-M114, an antibody-drug conjugate, in overcoming resistance to EGFR and MET tyrosine kinase inhibitors in NSCLC. It effectively summarizes the preclinical findings and potential treatment implications for NSCLC patients with acquired resistance.
In my opinion, the structure of the manuscript is generally well-organized, with clear sections covering the introduction, preclinical findings, treatment implications, and potential mechanisms of action of REGN5093-M114 in NSCLC. However, there are a few points that need to be improved or elaborated in more detail, thus the following suggestions should be

considered:

We thank the reviewer for making the time to review our editorial commentary and feedback.

Major Points:

• In the introduction a short paragraph on the supposed mode of action (e.g. trigger for drug release) of REGN5093-M114 would be helpful for the reader.

We thank the reviewer and agree with this comment. A brief introduction to REGN5093-M114 has been added at the top of the comment "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 factor (MET) in patient-derived, MET-driven epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor (TKI)-resistant non-small cell lung cancer (NSCLC) models (1)."

A complete description of how the ADC works is also available in the manuscript "REGN5093 is a biparatopic antibody that recognizes two distinct epitopes of MET (METxMET). 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 METxMET-M114 (REGN5093-M114). This allows for selective cytotoxin delivery to MET overexpressing tumor cells. In MET overexpressing tumors, METxMET-M114 has demonstrated potent antitumor activity and a favorable preclinical safety profile (18)."

• Line 77-79: Give more detailed information about the in vivo data to which the authors refer, e.g. which mouse model was used, give information about the treatment setting

We added further details regarding the in vivo study accordingly.

• In general, more information about the treatment regimens (dosage, application) could be provided and compared to the currently available drug schemes.

The reviewer raised a good point, but for the moment the results are only preclinical. The REGN5093-M114 compound need to be tested in the clinic to be compared with currently available drug schemes. The ongoing phase I/II clinical trial NCT04982224 will determine these parameters but sole the protocol has been shared so far (ASCO 2022, https://ascopubs.org/doi/10.1200/JCO.2022.40.16_suppl.TPS8593). We discussed this point at the end of our commentary.

• Line 92-101: This paragraph needs to be re-structured and proper references should be added at the right place. It is difficult to distinguish which study is which, it seems that both are mixed within this paragraph?

We thank the reviewer for their advice, we have revised the paragraph in question to improve its clarity.

• I would include more of a personal opinion of the authors on the topic maybe also comparing REGN5093-M114 with already approved drugs and end the paper with a section on future

directions also discussing any limitations if available.
We thank the reviewer for the constructive suggestions that helped us to improve our commentary. A more personal perspective as well as potential limitations of the reviewed study have been included in the concluding section of the text.

Minor points:

• Line 84: Exchange „But“ with „However,“
• Line 95: the authors refer to a table (Table 1) which is not part of the manuscript. This needs to be changed.
The text has been amended accordingly.

**Reviewer C**

The authors provide a relevant editorial commentary on the article by Oh et al. 2023, Clin Cancer Res. "Preclinical Study of a Biparatopic METxMET Antibody-Drug Conjugate, REGN5093-M114, Overcomes MET-driven Acquired Resistance to EGFR TKIs in EGFR-mutant NSCLC".

I have a few points below that needs to be addressed before this commentary is acceptable for publication.

We thank the reviewer for making the time to review our editorial commentary and feedback.

- It seems that the authors have missed to cite the reviewed paper in the reference list.
The reviewer raised a crucial point! The reference of the reviewed paper has been added.

- On line 37-39 it is stated that MET amplification is reported in 5 - 20% of patients with NSCLC progressing on 1st, 2nd or 3rd-generation EGFR TKIs. The authors should clarify how much MET amplifications (or overall MET aberrations) contribute to resistance following 1st-line treatment with osimertinib since this is now the standard-of-care treatment in large parts of the world for EGFR-mutant NSCLC patients with advanced disease.
We thank the reviewer for the suggestion. We have added precision regarding the proportion of MET alteration following first-line osimertinib in NSCLC patients “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”.

- On line 95, the authors refer to a Table 1, but there is no Table 1 included in the commentary. Please include the Table or revise the sentence.
Thank you for pointing this out, the reference to table 1 has been revised since we decided just before the submission to remove this table.

**Reviewer D**

Overall is an interesting review, although more clarity in some paragraphs would be appreciated.

We thank the reviewer for making the time to review our editorial commentary and feedback.

Minor corrections:

- Line 74: "to the efficiency" -> "with the efficacy"
The text has been amended accordingly.
- Line 80: I would delete "predictive", as it is redundant with the verb "predict" used a few words later.
The text has been amended accordingly.
- Line 80: The whole paragraph is a bit confusing, it is hard to understand
The paragraph has been rewritten with the intention of simplifying the content.

- Line 92: Also a bit confusing, which is the goal of this study? The molecular alterations detected in patients who progressed to osimertinib and savolitinib is a different study? The phrase starting at line 96 might be clearer with another formulation.
This paragraph has been modified to improve its comprehensibility.

- In paragraph starting at line 102, I understand that Teliso-V is mentioned to highlight the activity of REGN5093 observed in tumors with T790M mutation, but this is not clear.
Thank you for raising this point, we modified the text to make this point more clear.

**Reviewer E**

The authors have submitted a commentary article to the published work on overcoming the EGFRmut TKI resistance in NSCLC through targeting MET with REGN5093. It is a biparatopic antibody that recognizes two distinct epitopes of MET. Authors describe the work by Oh and colleagues to which the reviewer does not have the access because it is not referenced. Therefore it is impossible to accurately review this work.
This crucial point has also been raised by reviewer C. We apologize for this.