Peer Review File

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Reviewer A

In this Editorial Commentary, Toyoaki Hida and colleagues discussed the development of Antibody-drug conjugate for EGFR-mutant EGFR tyrosine kinase inhibitor-resistant NSCLCs. This manuscript is novel and nicely discusses the importance and challenges of ADCs for EGFR-mutant EGFR tyrosine kinase inhibitor-resistant NSCLCs. However, I have some minor comments.
Thank you for valuable comments.

Comments 1: In many statements, references are missing for example-
"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."
"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 depends on other mechanisms than EGFR signaling, i.e., alternative pathway kinase activation (e.g., MET; HER2; HER3)."
Reply 1: I have added references to this part as well.
Changes in the text: see Page 1, line 19 referece 1.
see Page 2, line 14 referece 8.

Comments 2: Currently, various ADCs are under evaluation, MET-, HER2-, HER3-, or TROP-2-targeting ADCs presenting potential applicability in patients with non-small cell lung cancer (NSCLC). - Please specify this statement with some examples.
Reply 2: In this point, I have mentioned in the text.
Changes in the text: see Page 2, line 1~4
Patritumab deruxtecan is a HER3-directed ADC with a payload consisting of a topoisomerase I inhibitor. As EGFR-TKI treatment can increase cell surface HER3 expression in EGFR-mutant NSCLC, it is of interest to evaluate patritumab deruxtecan in EGFR-mutant NSCLC (6).

Comments 3: It is better to add the website and clinical trial name along with ID when discussing any clinical trials. For example- "Other newly developed ADCs include ABBV-400 targeting c-MET and topoisomerase with an ongoing phase 1 study (NCT05029882) (10)" "In a phase II 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- and50 c-Met-positive nonsquamous NSCLC (8).” “Currently, an ongoing phase 1 trial investigates AZD9592 as monotherapy or combination with other anticancer agents in patients with advanced solid tumors. (NCT05647122).”

Reply 3: In this point, I added the website and clinical trial name along with ID.

Changes in the text:

see Page 2, line 21: Study of Telisotuzumab Vedotin (ABBV-399) in participants with previously treated c-Met+ non-small cell lung cancer.
https://clinicaltrials.gov/study/NCT03539536.

see Page 2, line 26: A study evaluating the safety, pharmacokinetics (PK), and preliminary efficacy of ABBV-399 in participants with advanced solid tumors. https://clinicaltrials.gov/study/NCT02099058

see Page 2, line 33: 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

see Page 3, line 6: First in human study of AZD9592 in solid tumors (EGRET). https://clinicaltrials.gov/study/NCT05647122

see Page 4, line 2: Study of REGN5093-M114 (METxMET antibody-drug conjugate) in adult patients with mesenchymal epithelial transition factor (MET) overexpressing advanced cancer. https://www.clinicaltrials.gov/study/NCT04982224

Comments 4: Some statements are not clear, for example- “Future challenges involve drug sequencing, management of brain metastasis in patients with CNS involvement, ADC combination with other drugs, and reduced toxicity, particularly ILD.

Reply 4: I have deleted the sentence and inserted the following sentence.

Changes in the text: see Page 5, line 1~6

EGFR-TKI therapy significantly prolong progression-free survival 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 understanding of osimertinib resistance mechanisms, next-line novel therapeutic agents such as MET ADCs, HER3-directed ADC, and EGFR-MET bispecific antibody (26) are being developed showing promising efficacy.

Comments 5: The whole manuscript is a generalized view of ADCs; adding more discussion of EGFR-mutated NSCLC would make it more focused.

Reply 5: I have inserted the following sentence.

Changes in the text: see Page 5, line 1~6

EGFR-TKI therapy significantly prolong progression-free survival 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 understanding of osimertinib resistance mechanisms, next-line novel therapeutic agents such as MET ADCs, HER3-directed ADC, and EGFR-MET bispecific antibody (26) are being developed showing promising efficacy.

Reviewer B

Thank you for valuable comments.

Comments 1: The author report an interesting commentary on ADCs development for EGFR-mutant NSCLC after failure of anti-EGFR TKI. To improve the quality of this commentary, please clarify current major issues in previous clinical trials conducted in this field due to the challenge of patients' stratification (lack of standard threshold for MET amplification). This is to add in future challenges related to anti-MET therapies.

Reply 1: The problems with clinical trials in this area are discussed in the text.

Changes in the text: see Page 3, line 8~13

MET amplification is traditionally 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 for the detection of MET amplification. As with FISH, there is not a consensus of copy number to define amplification. Establishing a universal definition of MET amplification will be important in standardizing clinical trial eligibility.

Comments 2: L78 please specify ESMO meeting 2023

Reply 2: I have added references to this part as well.

Changes in the text: see Page 3, line 31

18. Cho BC, Kim SW, Ann MJ et al. Early safety, tolerability, and efficacy of REGN5093 in patients (pts) with MET-altered advanced non-small cell lung cancer (aNSCLC) from a first-in-human (FIH) study. Ann Oncol 2022; 33 :S1085 DOI: 10.1016/j.annonc.2022.07.1296

Comments 3: L102 a vital instead of an vital

Reply 3: I have corrected.

Changes in the text: see Page 4, line 24

a vital aspect

Comments 4: Please cite the study of Catherine A. Shu et al., Amivantamab and lazertinib in patients with EGFR-mutant non–small cell lung (NSCLC) after progression on osimertinib and platinum-based chemotherapy: Updated results from CHRYSALIS-2.. JCO 40, 9006-9006(2022).

Reply 4: I have included a reference.

Changes in the text: see Page 5, line 6

Ref. 26. Shu CA, Goto K, Ohe Y, et al: Amivantamab and lazertinib in patients with EGFR-mutant non–small cell lung (NSCLC) after progression on osimertinib and platinum-based chemotherapy: Updated results from CHRYSALIS-2. J Clin Oncol 2022; 40 (suppl 9006). doi.org/10.1200/JCO.2022.40.16_suppl.9006.