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Name of Journal: *World Journal of Clinical Oncology*

ESPS Manuscript NO: 27858

Manuscript Type: Original Article

Response letter to reviewers: Better to be alone than in bad company: the antagonistic effect of cisplatin and crizotinib combination therapy in non-small cell lung cancer (manuscript number: 27858)

Reviewer 1 (608185): This manuscript was interesting and worth publication. Prior to accept, it is necessary to perform minor language polishing.

We thank the reviewer for his kind comments on our manuscript. To address the language issue, the manuscript has been read and corrected by a native English speaker. These corrections have been made in the manuscript and have been highlighted in yellow.

Reviewer 2 (186496): The authors tested three different treatment schemes combining cisplatin and crizotinib in four NSCLC cell lines with a different cMET/EGFR genetic background. However, all treatment schemes showed an antagonistic effect in all cell lines, independent of the cMET status of these cell lines. These results are interesting and discourage further efforts to combine cMET inhibition with cisplatin chemotherapy in NSCLC. We have NO further comments.

We thank the reviewer for these kind comments. As stated in the response to the first reviewer, the manuscript has been corrected by a native English speaker.

Reviewer 3 (723142):

1. It is a reasonable idea to test target therapy and cytotoxic combination.

We thank the reviewer for this comment and we strongly agree. Combining a targeted therapy with cytotoxic drugs can result in a positive result as has been shown for the combination of bevacizumab with chemotherapy in NSCLC (see the recent publications of Matikas et al. in Cancer Chemotherapy and Pharmacology, 2016 and Cardona et al.

PlosOne 2016). However, the cited results on the combination of EGFR-targeted therapies with cytotoxic drugs report a number of failed clinical trials. These results warrant for preliminary *in vitro* research into these combinations before testing them in a clinical setting.

2. In clinical setting Crizotinib is effective in only Adenocarcinoma, so the Squamous cell lines EBC-1 and LUDLU are not expected to respond to Crizotinib

We thank the reviewer for this comment. However, a casereport has been published describing a patient with squamous non-small cell lung cancer, harboring cMET amplification but no ALK-translocation, that has responded very well to crizotinib (Schwab et al, Lung Cancer 2014).
A comparison can be made with EGFR, were activating mutations have a much lower frequency in Squamous cell lung cancer as compared to the adenocarcinomas, resulting in a negative cost-benefit balance for the screening of this population. However, squamous lung cancer patients harboring these mutations in EGFR also show a good response to EGFR-targeted therapies (see Xu J et al. Clinical Lung Cancer, 2016). It is therefore our opinion that the genetic background of the cell lines/ tumors determines the sensitivity to these targeted therapies, not the tumor histology. Although the histology can give a very useful indication for the frequency of these genetic aberrations, that can influence the screening of patients. This also explains our described results, showing a high sensitivity to crizotinib of the cMET amplified EBC-1 cell line, in contrast to the wild-type cMET LUDLU cell line.
Also, tumor histology is not fixed. This has been shown in patients that show acquired resistance to EGFR-TKIs through a histological transformation of adenocarcinoma to small cell lung cancer.

3. Even in Adenocarcinoma the clinical response is limited to ALK+ve tumours. What is ALK status of cell lines H1975 and HCC827?

We thank the reviewer for this notion and agree that crizotinib today is mainly used as an ALK inhibitor in the clinical setting. We acknowledge the importance of stating the ALK status of the cell lines and have added in the manuscript that all cell lines are wild-type for ALK (highlighted in yellow, line 108-109). However, crizotinib was originally being developed as a cMET inhibitor, and as such also shows strong activity (in cell lines, as well as in patients) that harbor cMET amplification (see casereport of Ou et al. 2011, Journal of Thoracic Oncology and the publication of Jenkins et al, 2015, Clinical Lung Cancer). A clinical trial is ongoing for crizotinib treatment of patients with cMET amplification (or ROS1 translocation), the METROS trial.

4. Language polishing

As stated in response to the first reviewer, the manuscript has been corrected by a native English speaker.

Reviewer 4 (02445408): This is an interesting work that will help to understand the molecular mechanism of resistance of EGFR inhibitors and the necessity of continuing search of new investigation for the treatment of such lethal disease that is NSCLC

We thank the reviewer for this kind comment.