Reviewer's report

Title: Novel c-Met inhibitor suppresses the growth of c-Met-addicted gastric cancer cells.

Version: 2 Date: 18 June 2015

Reviewer: Flavio Maina

Reviewer's report:

Major Compulsory Revisions.

The authors were inspired by the triazolopyrazine scaffold, which has been reported to exert effective and specific inhibition to the receptor tyrosine kinase Met, to synthetize and test the inhibitory properties of several compounds. This work has led to the discovery of two compounds, namely KRC-509 and KRC-715, capable to block Met activity at concentrations comparable with those of crizotinib used as a reference. The authors showed that these compounds are highly selective to Met over several other tyrosine kinases. Moreover, KRC-509 and KRC-715 suppress growth and impair phosphorylation of Met, Akt, and ERK in Met-overexpressing, but not in Met low-expressing, gastric cancer cells. Finally, in vivo studies showed that KRC-715 interferes with tumour growth, without showing major side effects within the short time of administration.

These findings contribute to highlight chemical features of compounds with inhibitory activity towards Met, a target that receives particular attention for its role in cancer. However, the manuscript requires major revisions before publications.

1) The authors used crizotinib as a reference Met inhibitor. It would be more relevant to compare the effects of identified compounds with PF04217903 for their structure similarities.

2) Concerning xenograft experiments, the authors should perform histological analysis during treatment to assess cell dead and proliferation index. Moreover, they should extend these studies by following tumour evolution overtime after KRC-715 treatment. This would clarify whether and to which extent cancer cells die, and establish a possible relapse kinetic mainly due to cytostatic versus cytotoxic effects exerted by KRC-715.

3) The author showed that KRC-715 does not cause loss of weight of mice during 10 days of treatments. Possible toxic effects should be analysed by following standard parameters and during a longer time of treatment. This is particularly important taking into account that mice die after administration of the other compound (KRC-509).

4) The quality of written English must be significantly improved, with extensive editing (besides several typing mistakes).

5) The discussion lacks of structure and in the present form the authors summarize the overall findings rather than discuss key points. For example: 1)
similarities versus differences in chemical, physical, and biological properties of KRC-509 and KRC-715 versus compounds like PF04217903; 2) advantages and limits compared to other Met inhibitors (particularly PF04217903).

Minor Essential Revisions.
1) I would include the kinase panel assay data in the manuscript rather than as a Supplementary Table.
2) Toxicity data reported in Supplementary Figure 3, together with additional studies I recommended above, should be included in Figure 5.

**Level of interest:** An article of importance in its field

**Quality of written English:** Not suitable for publication unless extensively edited

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests.