**Reviewer’s report**

**Title:** Computational analysis of receptor tyrosine kinase inhibitors and cancer metabolism: Implications for treatment and discovery of potential therapeutic signatures

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**Reviewer:** Benoit Beganton

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In this manuscript titled « Computational analysis of receptor tyrosine kinase inhibitors and cancer metabolism: Implications for treatment and discovery of potential therapeutic signatures », Li and al use the recently published MCPM model to identify metabolite signature according to TKI treatment. The gene expression profile of 479 cancer cell lines treated with 8 drugs were used as input data, and the simulated values were analyzed to calculate the correlation with the corresponding IC50 values.

Cancer metabolism is an expending field and in silico analysis contribute to a better understanding of metabolism alteration during carcinogenesis and cancer development or treatment. The published MCPM model is a large scale model, and its strength has already been demonstrated. Here, authors are interested in metabolism alteration of cancer cell lines following TKI treatments. A similar approach has been performed to publish the MCPM model and thus decrease the originality of this article. However research to more characterize the connexion between cell signaling and metabolism is lagging behind and this article gives interesting clues to address cancer metabolism, and thus may be of interest for BMC Cancer readers. Despite these strengths, however, key points still need to be addressed / clarified before it is suitable for publication.

1. A figure describing the workflow to identify the metabolic impact and signature would be helpful for the readers to clearly understand the analysis performed.

2. The authors selected 8 drugs, but they should explain the rational of this selection.

3. This article aims to « focus on the possible impact of RTK inhibitors on the cancer metabolism », as it can be « antagonistic or agonistic during or after treatment ». To specifically address this question, authors should mention the main applications of these drugs (e.g : erlotinib used to treat lung cancer, etc), it would give a more clinical aspect to this article. This could be added to the Table 1.

4. In line with the previous comment, in the sections dealing about breast, liver/pancreas, and CNS cancer, the metabolic effect of the drug(s) generally used to treat these types of cancers should be more precisely discussed. Indeed, this is the direct application of this work and it is surprisingly less developed, it would reinforce the clinical perspective of the analysis conducted here. In addition, erlotinib is essentially used to treat lung cancer, and this type of cancer is particularly difficult to manage considering the high rate of new
cases and mortality. It would be interesting to characterize the metabolic pathways affected by this drug in the lung cancer cell lines of the CCLE.

5. In the section dealing about breast cancer, and also elsewhere, authors talk about « high impact on metabolism pathway » or « high affected metabolic components ». From this point of view it is hard to assess whether this impact corresponds to an increase of the metabolism pathway or whether a decrease of the metabolism pathway. This point should be clarified to more precisely understand the effect of the mentioned drugs on the corresponding metabolic pathway.

6. In the section dealing about CNS, authors say that « L2HGDH gene may be an indication of treatment outcome ». This is confusing since a genetic alteration or a gene expression deregulation may be informative on treatment outcome, not the gene by itself.

7. Background section, mTOR should not be listed as a tyrosine kinase receptor.

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?
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