Author’s response to reviews

Title: BRAF mutant colorectal cancer: ErbB2 expression levels as predictive factor for the response to combined BRAFi/ErbB1 inhibitors

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Point by point response letter to Reviewer and Editor

Reviewer 1
Mohammad R. Akbari (Reviewer 1): - It has been well established that BRAF mutant CRC tumours will not respond to EGFR inhibitors and respond better to BRAF inhibitors alone or in combination with EGFR inhibitors. The authors reconfirmed somehow these known facts.

It is logical to expect that tumor cells with high levels of HER2 will response better to Afatinib which inhibit all ErbB proteins including HER2 and EGFR compared to drugs like panitumumab which specifically inhibit only EGFR and the authors here showed that with their cell line analysis.

It is recommended to add a table showing response to all different drugs and their combinations for all different cell lines together in one place at one view.

Authors’ reply: As suggested, we added a table (Table 3) summarizing response to all different drugs and their combination for all different cell lines together.
This is just a cell line analysis and before being able to recommend HER2 amplification analysis for choosing CRC patients for combined BRAF/HER2 inhibitors, we need to study this in a clinical trial, so, the authors should be very careful in concluding this based on their cell line analysis.

Authors’ reply: we thank the Reviewer for raising this issue. We revised the text adding a comment on this aspect (see page 8 of the revised manuscript, “Results” section)

There are several typos across the texts that need to be corrected.

Authors’ reply: we corrected the typos.

Reviewer 2
Pashtoon Murtaza Kasi, M.D., M.S. (Reviewer 2): Dear Authors,
I read your article with great interest.

BRAF-V600E mutant colorectal cancer constitute the worst kind of colorectal cancer. Outcomes are dismal and single agent RAF-inhibition efforts thus far have failed.

However, this article/research is grossly deficient if we don't take into account the recent developments in the field which the article does not mention or cite.

Authors’ reply: we thank the Reviewer for the interest in our work. We appreciated the suggestions and we have now implemented the Discussion sections by adding and commenting the developments in the field.

 Raf+EGFR inhibition has been studied preclinically as well as in trials. The so called VIP (Vemurafenib+Irinotecan+Panitumumab or Cetuximab) is now in guidelines as well for 2nd line BRAF.

Authors’ reply: we revised the discussion sections by adding and commenting these data and references (see pages 8-9 of the revised manuscript, “Discussion” section and pages 14-15 “References” section )

2. RAF+EGFR+MEK (the so called BEACON regimen just got published in NEJM). This is already in guidelines as well and should get FDA approval for 2nd line soon. ANCHOR trial evaluating it 1st line.

Authors’ reply: we revised the discussion sections by adding and commenting these data and references (see pages 8-9 of the revised manuscript, “Discussion” section and pages 14-15 “References” section )

2. Also with respect to HER2:
1. Anti-HER2 (lapatinib+trastuzumab) already in guidelines
2. Anti-HER2 dual combination (Trastuzumab+Pertuzumab) already in guidelines and published both in Lancet Oncology.

Authors’ reply: we revised the discussion sections by adding and commenting these data and references (see page 9 of the revised manuscript, “Discussion” section and page 15 “References” section )
A recent review in The Lancet on Colorectal Cancer highlights all these.
Without this, the approach and drugs and the implications are not up to date with the current evolving standard of care.
While the experiments/findings are of value, they won't impact practice if the research is not up to date with the field and current guidelines.

Authors’ reply: we thank again the Reviewer for considering of value our findings. We have added the reference and modified the discussion section to make the research up to date with the current literature and guidelines. (see pages 8-9 of the revised manuscript, “Discussion” section and pages 14-15 “References” section)