Himani Aggarwal
Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46225, USA
Email: aggarwal_himani@lilly.com

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Assoc. Prof. Monjur Ahmed
Editor-in-Chief, *World Journal of Gastrointestinal Oncology*
Division of Gastroenterology and Hepatology
Department of Internal Medicine
Thomas Jefferson University, Philadelphia, PA 19107, USA
E-mail: monjur.ahmed@jefferson.edu

Dear Assoc. Prof. Ahmed,

Re: Resubmission of manuscript number 51356

On behalf of my co-authors, I would like to thank you for your prompt review of our manuscript titled, *Primary tumor location and survival in colorectal cancer: a retrospective cohort study*.

In support of our resubmission, we have revised our manuscript and addressed the reviewers' comments in the following pages. All revisions to our manuscript have been highlighted using Track Changes in Microsoft Word.

We thank you in advance for reviewing our revised manuscript and our responses to the reviewers' comments. With these revisions, we hope that our manuscript is now acceptable for publication in the *World Journal of Gastrointestinal Oncology*.

Yours sincerely,

Himani Aggarwal

Reviewer 1

Reviewer comment: FIRE-3 which comprised of FOLFIRI-back bone regimen indicated tumor sidedness as a predictive role and also CALGB80405 did as well regardless the trial included mixed backbone regimen (FOLFIRI and FOLFOX). It feels too strong that current study concluded tumor location has no predictive role for treatment with cetuximab versus bevacizumab in combination with 5-fluorouracil-based chemotherapy. In current study, about 70% patients were not evaluated for expanded RAS mutations. KRAS exon3,4 and NRAS mutations may affect study results.

Response to reviewer: We thank the reviewer for raising this point, and acknowledge that specific KRAS and NRAS mutations may impact the predictive effect of primary tumor location on treatment with cetuximab versus bevacizumab in combination with 5-fluorouracil-based chemotherapy. Since most patients in our study were not evaluated for expanded RAS mutations, we agree that differences in the chemotherapy backbone alone may not explain the lack of predictive effect. We have added several new sentences to the Limitations section (page 22) of our manuscript to further discuss possible explanations for why a predictive effect for primary tumor location was not found in our study, including an acknowledgement of the limitation that a large proportion of patients were not tested for RAS and BRAF mutations. Additional text includes the following wording:

…ECOG PS was missing for over 50% of patients in this study. It is not known if the beneficial effect of a therapy is lost if the regimen is used for a patient with an ECOG PS of 2 or 3 compared with an ECOG PS of 0 or 1. This loss of efficacy may be more pronounced with the addition of a biologic therapy that can significantly add to the toxicity of the chemotherapy backbone. Furthermore, in this study, approximately 60% of patients were untested for NRAS mutations and 57% of patients were untested for the BRAF mutation. If BRAF or NRAS mutations were present in these patients they may have impacted the study results and explained, in part, why the predictive effect of primary tumor location on treatment with cetuximab versus bevacizumab in combination with 5-fluorouracil-based chemotherapy was not observed.

We have also modified our conclusions accordingly (see the Core Tip, page 6, and the concluding paragraph of the Discussion section, page 22).

Reviewer 2

Reviewer comment: The results presented in this real world database, although supporting the prognostic role of sidedness of colorectal cancer, contrasts to previously published post hoc analysis of randomized trials which suggest a predictive effect of sidedness of the use of EGFRi versus VEGF inhibition dependent upon tumor location. The possible reasons behind this variation are less clear. Although the chemotherapy backbone could certainly be considered a possible explanation, this wouldn't be supported by the post-hoc data of the randomized trial data as this effect was seen with both a FOLFIRI or FOLFOX backbone. One has to then question more the other inherent biases with collecting retrospective data but also the application of trial results into daily practice. For example, does one lose the beneficial effect of a therapy if the protocol is used in an ECOG PS 2 or 3 patient; this may be more exaggerated adding a biologic therapy which can significantly add to the toxicity of the chemotherapy backbone. In this real world data, there were also a significant amount of patients who were untested for NRAS or BRAF mutations. I agree that a further randomized prospective studies

should be considered to answer this questions, but realistically given the acceptance of the current post hoc randomized data are those studies feasible and will they be supported.

Response to reviewer: We agree with the reviewer that, although the chemotherapy backbone may account for some of the lack of predictive effect of primary tumor location, there are likely to be other contributing factors as well, for example patients' ECOG PS, and NRAS and BRAF mutation status. The first reviewer made a similar comment, and we have added several new sentences to the Discussion and Limitations section of our manuscript to explore further these possible explanations for why a predictive effect for primary tumor location was not found in our study, including the following change to the wording on page 21 of the Discussion section:

Overall, these findings suggest that the chemotherapy backbone, among other factors, may contribute to outcomes, either alone, by interacting with the biologic agent, or as a proxy for disease biology if the backbone choice is driven by clinical history: stage at initial diagnosis and features of prior adjuvant chemotherapy (use, regimen choice, disease response, and the time since completion of adjuvant therapy).

We also agree that randomized prospective studies are unlikely to be funded given the acceptance of the current post hoc randomized data. In our manuscript, we suggest that future research is needed to determine the underlying reason(s) for the differences between clinical trials and real-world study populations but do not specify the type of research studies.