Reviewer's report

**Title:** Is overexpression of HER-2 a predictor of outcome in colorectal cancer?

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**Reviewer:** Arun Rishi

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The manuscript by Kavanagh et al investigates a hypothesis that HER-2 expression is a predictor in colorectal cancer. This hypothesis is constructed in part on the rationale that HER-2 expression is an indicator of poor response in breast cancers where it serves as an effective target for therapeutic intervention. The authors conduct this clinico-pathological study to determine HER-2 expression to test this hypothesis. Paraffin embedded specimens from 132 patients with colorectal malignancies were subjected to immunohistochemical (IHC) analyses for HER-2 presence. The data revealed a very small subset of specimens with HER-2 positivity. This HER-2 positivity did not correlate with gender, age, tumor grade and stage, time to recurrence and 5-year survival parameters. Authors further use FISH methodology to reveal that HER-2 overexpression was due in part to gene amplification. HER-2 expression and its therapeutic utility for colorectal cancers is somewhat controversial. Although, earlier studies have indicated overexpression of this receptor in colon cancers that was often localized at the plasma membrane or in the cytoplasm, its utility as a target for intervention remains unclear. The study utilizes antibodies that detect membranous receptor, and therefore unlikely to detect the cytoplasmic presence. Emerging evidence indicates nuclear presence of EGFRs that likely function independent of growth factor signaling. As far as the use of herceptin class of agents is concerned, this study would support that in the absence of the membranous HER-2 in a majority of colorectal cancers likely precludes utilization of herceptin class of agents in this malignancy. Overall, the manuscript is well written and the data presented in coherent fashion.

1. Last paragraph in the background section: Authors should consider modifying the last sentence as ..........gene amplification and establish whether overexpression of HER-2 is a predictor of outcome.

2. Materials & Methods: Immunohistochemistry: first sentence- Staining for HER-2/neu protein was performed on 5um (micro-meter) thick slides.

3. Figure 2 is FISH photograph. The FISH is usually conducted to detect the gene or the mRNA of a given protein in cells or tissues. The gene is nuclear encoded by chromosome while mRNA could be nuclear but predominantly cytoplasmic. Therefore, the indication in the legend to figure 2 that amplified Her-2 gene is detectable at the cell membrane by orange stain is incorrect. Please correct this discrepancy and if possible highlight in the figure with the arrows the presence of HER-2 gene/mRNA staining.
**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

**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.