Reviewer's report

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

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Reviewer: Inti Zlobec

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The manuscript by Kavanagh et al takes an interesting look at the prognostic value of Her2 expression in colorectal cancer. Using both immunohistochemistry and FISH analysis, they determine that only a relatively small subgroup of patients over-express the marker and that these patients are those with predominantly poorly differentiated and Dukes’ C tumours. No prognostic significance was observed here. The manuscript may be improved by considering the following points:

Minor Essential Revisions

(1) The authors report the inter-observer variability of Her2/neu immunohistochemistry (presumably the value of 0.97 is for “agreement” rather than “variability” as stated in the results section). How was this agreement assessed? Using kappa, or weighted kappa values? Since the inter-observer agreement of biomarkers is generally under-reported in the literature and the authors do well to report these findings, it would be beneficial to see the values/concordance for the two observers in a table.

(2) The title suggests that Her2 was analyzed in the context of response to targeted-treatment (i.e., is a predictor of outcome) and therefore is at risk of misinterpretation. Having “prognosis” in the title may be a more appropriate representation of the findings.

(3) The authors emphasize, and correctly so, that the scoring method used in this study for Her2/neu immunohistochemistry is an internationally validated evaluation system. However, the assumption that the same scoring method which was devised for breast cancer should be applied, and is optimal, for colorectal cancer should be examined more closely. The absence of “significant” findings in this study may be a result of the evaluation system. I find that the authors are in a position to explore this further. I suggest that immunohistochemical analysis of Her2/neu be re-assessed using the percentage of positive tumor cells, independently of staining intensity, that an appropriate cut-off score be selected for positivity and then that associations with clinico-pathological features and prognosis be analyzed once more. This addition and comparison of scoring systems would, in my opinion, significantly add to the importance of this contribution.

Level of interest: An article of importance in its field
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