Pentheroudakis G et al., have studied “Biomarkers of benefit from cetuximab-based therapy in metastatic colorectal cancer: interaction of EGFR ligand expression with RAS/RAF, PIK3CA genotypes”, a retrospective study among 226 colorectal cancer patients, who underwent cetuximab treatment (1st to 3rd line therapy). In this study authors have evaluated the efficacy of cetuximab treatment emphasizing the prognostic significance of biomarkers of EGFR dependent CRCs. Formalin fixed tumor biopsies were analyzed for mRNA expression of EGFR and its ligands (epiregulin-EREG and amphiregulin-AREG), transforming growth factor – alpha (TGFA) by real-time analysis and mutations were screened for KRAS, NRAS, BRAF, and PIK3CA. Authors observed BRAF and codon 12 KRAS mutations are associated with non-responsive CRCs to cetuximab treatment. It is observed that AREG and EREG are having prognostic significance in cetuximab treated patients. However, AREG retains significance only in KRAS wt patients but EREG levels are shown to be significantly correlated both in KRAS wt and mutants. This study has revealed the possible prognostic significance of AREG/EREG mRNA expression levels in KRAS wild type and mutant patients of cetuximab treatment.

Major Compulsory Revisions:

1. The present work is depicting the efficiency of AREG and EREG as prognostic markers in CRC patients treated with cetuximab. Authors have mentioned in the discussion about EREG mRNA expression as independent of KRAS mutation due to HER4 receptor. Authors have not shown the functional significance of EREG-HER4 interaction in KRAS mutants with high EREG mRNA expression levels of cetuximab treated CRC patients.

2. What could be the reason for lower EREG/AREG expression in KRAS mutant vs wild type tumors, especially with respect to status of HER4? Is it only a selection phenomenon? Authors should discuss this observation in discussion section.

3. The authors should discuss the wide literature available on similar studies and highlight the unique and important contribution of this work.

Minor Essential Revisions:

1. Cetuximab and panitumumab are already in clinical trials; previous work related to cetuximab role in EGFR mediated response in CRCs may be cited in
the introduction.

2. Method section should be better organized. It is not as per BMC Cancer journal format.

3. Authors mentioned in methods that they followed manual tumor macro dissection in tumors with less than 50% tumor cells. They may mention about the criteria of tumor macro dissection and why low cellularity tumor samples were included.

4. Typographical errors have to be taken care. Eg: On page 9, line #7 word ‘was’ is repeated.

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Needs some language corrections before being published

**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’