In their manuscript "Dual regulation of cell death by Akt kinase inhibitor MK-2206 in colorectal cancer", Agarwal et al. characterize the anti-tumoral mechanisms of the novel Akt kinase inhibitor MK-2206 in vitro and in vivo using IGF1R-dependent CRC cells.

First, effects of MK-2206 on apoptosis of CRC cells are shown by Western Blot and MTT assay. Western Blot analysis revealed a decrease in AKT and BAD phosphorylation as well as a decrease in Survivin.

Second, in vivo experiments in heterotopic, subcutaneous xenografts show a significant reduction in tumor growth after MK-2206 treatment. Also here, MK-2206-induced Akt inhibition can be seen. Furthermore, MK-2206 treatment results in increased expression of AIF and loss of pEzrin.

The authors conclude that MK-2206 mediates cell death by two separate mechanisms: Loss of Akt phosphorylation, resulting in induction and translocation of AIF from mitochondria to nuceus and, second, loss of pEzrin, mediating cell death by lott of XIAP.

As the authors correctly state, identification new molecular targeted therapeutic regimens are an important field of research in individualized cancer therapy. The present manuscript here presents relevant and novel results in a specific research field. However, minor essential revisions should be performed before publication:

1. There is a lot of discussion in the results part (e.g. discussion of BAD function page 12, discussion of the role of XIAP and survivin on page 12, discussion of AIF/Akt and Ezrin/Akt interaction on page 14 and 15, respectively.) Please rewrite the results/discussion part.

2. Figure 2E (of which results are reported on page 12) is missing.

3. For the in vitro tests, the dose of 350 nM and 500nM was used. Please show specificity of obtained results by testing MK-2206 in this dose on e.g. IGF1R-independent colon cancer cells and non-colon cancer cells / non-malignant cells

4. Please comment on the correlation of the in vivo MK-2206 dose (120mg/kg)
compared to in vitro testing cells.

**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