**Reviewer comment**

**Reviewer 1#: (Revision Required)**  
In this work, Manish Parihar et al. found sex-dependent lifespan extension of ApcMIn/+ FAP mice by chronic mTOR inhibition. However, the demonstration of experimental process and results is not clear enough. We suggest that the author improving more discussion and supporting materials.

A few additional comments:

-It is suggested to state the total number of ApcMin/+ MICE in groups, the number of control group, the number of male and female mice, and the number of mice used for specimen collection and survival analysis.

-Please use a single paragraph to state the statistical methods used.

-At the end of “Mouse husbandry and diets” ，we found“In our longevity studies, ”，The author seems to have left this paragraph unfinished.

-The dosage form of rapamycin is described in this paper. It is suggested that the dosage form of rapamycin should be described in detail (How much per day?How many times a day?Total duration of medication，only 16 weeks or lifelong).

-No data and graphs were found in the paper or in the graph to prove that "polyp reduction is almost the same in male and female patients receiving eRapa treatment". Please provide the P value.

-Anemia is a common clinical symptom of decreased peripheral erythrocyte volume, which is lower than the lower limit of the normal range.Hemoglobin (Hb) concentration is often substituted clinically.

Hematocrit can be seen in various types of anemia or blood dilution, which is helpful in the identification and classification of anemia.“Since ApcMin/+ mice primarily die from anemia, which chronic eRapa prevents in females(8), we next asked if a sex difference in hematocrit response by rapamycin could account for the difference in longevity effects.”

Whether additional elaboration is needed to clarify the association between hematocrit, anemia, and survival.

-Are there sex different effects of rapamycin on normal mice? The experiment involved two research factors ApcMin/+ and rapamycin, so the author need to add experiments or citations of normal mice + rapamycin.

-"Immunohistochemical results showed that the phosphorylation level of rpS6 in small intestinal polyps of control animals (Figure 3G) was significantly higher than that in eRapa group (Figure 3H)." The intestinal villi in the section of Figure 3H were orderly and intact, rather than polyp tissue.Previous experiments showed that rapamycin could reduce polyps rather than eliminate them. Should polyp sections in the eRapa group be selected here?

**Reviewer 2#: (Revision Required)**

Parihar et al. investigated the effect of rapamycin on lifespan extension in ApcMin/+ mice. They found that the rapamycin-containing diet extended the lifespans of ApcMin/+ mice, reduced polyp numbers and restored hematocrits in ApcMin/+ mice. They also found that the survival of males mice was greater than females mice. these findings link rapamycin-mediated intestinal polyposis prevention with mTORC1 inhibition in Paneth cells and concomitant reduced epithelial cell proliferation. The study is interesting, however, they did not provide the evidence to show the sex differences in response to chronic rapamycin in ApcMin/+ mice.