Reviewer's report

Title: Dimethylaminoparthenolide and gemcitabine: a survival study using a genetically engineered mouse model of pancreatic cancer

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Reviewer: Francisco X. Real

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Yip-Schneider et al. analyze the effect of gemcitabine, alone or in combination with DMAPT, on tumor development and on several aspects of tumor biology using the KRas-driven genetic mouse model of pancreatic cancer. The work is based on the notion that DMAPT effects NF-kB activation and this may in turn modulate tumor growth. The work is largely descriptive and provides some interesting data. However, there are many issues that need to be clarified. The abstract reflects the contents of the paper and the ms. is well-written and clear.

Specific comments - Major revisions

1. The number of mice used in each group is too small in some experiments, therefore hampering the complete assessment of the treatment effects. (Compulsory)

2. It is striking that rather important effects of Gemcitabine (alone or in combination) on tumor incidence and size as shown in Table 1 result in minimal improvement on survival (Figure 1). Specifically, what is the cause of death of treated mice that do not develop any tumors? (Compulsory response)

3. Why did the authors not use the combination treatment in the non-invasive imaging experiments shown in Figure 2?

4. It is not always clear when the pancreata were sampled and what was the source of the used samples. For example, in Figure 3, does "normal pancreas" refer to tissue from normal wild type mice or is it "histologically normal pancreas" from KRas-mutant mice? All this as well as the age of the mice should be clarified. (Compulsory response)

5. The authors emphasize that PanIN-3 as well as tumors are reduced in Gem/DMAPT-treated mice. This is not surprising at all since it is thought that PanIN-3 are precursors of PDAC. The number of mice included in the studies shown in Figure 4 is too small. Indeed, it is interesting that PanIN-1 and PanIN-2 are not clearly reduced and this aspect should be studied in more detail because it has been proposed that these lesions are also precursors of PanIN-3 and PDAC. The number of mice should be increased and perhaps this question should be addressed in the KRas-mutant-only genetic background (without p53 mutation/inactivation). Indeed, there is some debate as to the linear relationship of the different types of precursor lesions and the authors' work might contribute to clarify this (Gastroenterology 2008; 135:724-8). (Compulsory response)
6. Ki67 staining and % of expressing cells should be performed not only in tumors but also in precursor lesions since this would be more informative. (Compulsory experiments)

7. NF-kB activation should be used as a biomarker of DMAPT effect in the treated and untreated mice; this would provide more mechanistic hints into the action of this compound. (Compulsory experiments)

8. It is hard to interpret the data in Figure 7. First, the timing of analysis is not indicated (I could not find it in the paper). In addition, sequential serum/plasma samples should be assessed since the differences reported may not be related to the effect of the treatment but simply to the differences in tumor growth (and be unrelated to the treatment itself, reflecting tumor burden or other aspects of tumor growth). (Compulsory experiments)

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

No conflict of interest