24 Oct 2018,

Dear Editor and Reviewers,

I would like to thank the editorial office for their consideration of our manuscript to *Word Journal of Gastrointestinal Oncology*. Also I would like to thank the reviewers, for taking their time and giving valuable feedbacks on our manuscript.

I adopted the comments of the reviewers and revised the manuscript accordingly. Also, I suggested opinions on some of the reviewers` comments. Please refer to the table below for summarized changes and answers. Also, every changes in revised manuscript are marked in yellow.

Thanks again to the reviewers and editorial office of the *Word Journal of Gastrointestinal Oncology* for kindly reviewing our manuscript. Please contact us if there are any additional requirements.

Sincerely,

Seungmin Bang, MD, PhD

Comment	Answer
Reviewer #1 (03805515)	
Congratulations on the work done. This study lays out the initial platform for larger comprehensive randomised trials to evaluate the efficacy and safety of modified FOLFIRINOX as a second-line treatment for gemcitabine refractory unresectable pancreatic cancer. Trial end points are well defined and analysed. I would like to raise the concern regarding the quality of life assessment using EORTC questioner. Was the questioner used a translated version with validation ? was it self administered or interviewer administered. If the English version was used please mention and include it on the discussion.	Thank you for your kind review and comments. In our trial, official Korean translated version of the questionnaire from EORTC was used, and it was self-administered by patients on the day of visit. We clarified this in the manuscript. **Line 9-12 of the 'Data assessment' paragraph of the materials and methods section (page 9):** "The Korean version of the questionnaire, officially translated and distributed by EORTC, was used. All patients filled-out and submitted the questionnaire by themselves on the day of visit."
Reviewer #2 (01191922)	
The authors should be congratulated on their nice work, which showed that modified FOLFIRINOX had acceptable toxicity and promising efficacy for gemcitabine-refractory unresectable pancreatic cancer. However, I have several comments about this manuscript. More baseline characteristics including tumor size and other tumor markers (CEA and CA125) should be listed in the Tables. One limitation of this work is the lack of a control group, such as patients received best supportive care. Although the sample size is small, this work would be better if the authors conduct some subgroup analyses. For example, studies have shown patients with liver metastasis had poorer survival than those with lung metastasis.	Thank you for your kind review and comments. 1) We appreciate your sincere comment on our baseline characteristics table and thoroughly reviewed about it. In our trial, almost 80% of the patients had metastatic disease at the baseline. These patients had variable numbers and sizes of the metastatic lesions. Quarter of the patients did not have primary site tumor because they had recurrence after pancreatic resection. Therefore, it is hard to determine and present the data of tumor size. Additionally, according to the trial protocol, we did not collect data of tumor markers other than CA 19-9. Because other tumor markers, such as CEA or CA125, are not clinically useful than CA 19-9 for pancreatic cancer to

	date. With all due respect to your comment, but we are unable to add other characteristics in the Table 1. We think, in our data, the number of metastatic site better represents disease burden than the tumor size of specific site. 2) We conducted several subgroup analyses for OS and PFS according to age (<65 vs ≥65), gender, ECOG (0 vs ≥1), CA 19-9 (normal vs elevated), presence of metastasis (LAPC vs MPC), number of metastatic site (single vs multiple). However, none of these analyses showed significant difference. Relatively small sample size for subgroup analysis might be the major reason. Regarding to subgroup analysis according to specific metastatic site (e.g. liver vs lung metastasis), only 18 patients had single site metastasis. Therefore, the number was too small to compare survival between patients with specific metastatic site.
Reviewer #3 (02544757)	
In the current article, Chung and Kang et al reported results of a multicenter phase II trial evaluating the efficacy and safety of uniquely modified FOLFIRINOX with reduced irinotecan and oxaliplatin in locally advanced and metastatic pancreatic cancer patients who failed gemcitabine (GEM)-based regimen. This trial demonstrated the adequate objective response rate, disease control rate, and the optimal global health status score except higher grade 3 to 4 of neutropenia.	Thank you for your kind review and comments. 1) All patients had cytologically or histologically confirmed adenocarcinoma according to the inclusion criteria. We added a sentence about this in the result section. **Line 2-4 of the 'Baseline characteristics of patients' paragraph of the results section (page 10):** "All patients had cytologically or histologically confirmed adenocarcinoma according to the inclusion criteria."

The authors also summarized the current clinical trials of second-line treatment for gemcitabine pre-treated unresectable pancreatic cancer. The optimal results of current multi-center clinical trials indicated that reduced dose of FOLFIRINOX can be a treatment option for un-operable pancreatic cancer patients who failed gemcitabine-based regimen. There are minor issues should be addressed: 1. In the results section, the pathologic characteristics of enrolled patients are not clear? 2. In the results section, if author could provide an example of patients who achieved CR or PR after receiving reduced dose of FOLFIRINOX, it will be helpful for readers. 3. In the discussion section, as authors mentioned that "NAPOLI-1 trial, the preferred second-line therapy for MPC in current guidelines showed the more non-hematologic adverse events (AEs) but less neutropenia when compared with the current results", the authors may revise the sentences in the conclusion section, at least, state that in addition to nal-IRI plus 5-FU, the modified FOLFIRINOX with reduced irinotecan and oxaliplatin plus prophylactic GCSF may be considered a treatment option for patients with GEM-refractory unresectable PC.	2) We added a brief example of patient who experienced radiologic CR in the results section. **Line 4-9 of the 'tumor responses and survival' paragraph of the results section (page 11): "**A sixty-year-old female patient, who progressed to multiple liver metastasis after gemcitabine monotherapy, achieved radiologic CR after 12 cycle of FOLFIRINOX with RIO. After twelfth cycle, the patient had not experienced disease recurrence on serial radiologic studies without chemotherapy for a year, until peritoneal seeding and liver metastasis were confirmed" . 3) We revised the sentences in the conclusion section. **Line 2-4 of the last paragraph of the discussion section (page 16):** "In addition to nal-IRI plus 5-FU regimen, FOLFIRINOX with RIO may be considered as a treatment option in patients with GEM-refractory unresectable PC." We also mentioned about considering routine use of G-CSF in the last sentence of same paragraph.