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Editors-In-Chief
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Dear Editors,

On behalf of all coauthors, it is a pleasure to submit to ***World Journal of Gastrointestinal Oncology*** the revised version of our manuscript entitled "**FOLFOXIRI versus FOLFIRINOX as first-line chemotherapy in patients with advanced pancreatic cancer: a population-based cohort study**" (Manuscript NO.: 51067).

We would like to thank you and the reviewers for your interest in this manuscript and your relevant comments. We appreciate the opportunity you gave us to revise our manuscript.

A revised version of the manuscript with tracked-in-red changes in the body of the text addressing all the reviewers' comments was performed and included in this revision letter. Herein we present a point-to-point reply to these comments.

Reviewer 1

This paper submitted by Vienot et al, investigated the potential clinical interest of FOLFOXIRI in treating patients with advanced PDAC. The topic was interesting and the paper was well written. However, there were some minor language mistakes. Please check and correct all the mistakes.

Reply: We thank the reviewer 1 for in-depth reading of this manuscript and for his vigilance.

We considered its comment and English wording was reviewed by a native speaker of English. Thereby, polishing and correction of language mistakes were performed throughout the

manuscript. All changes have been highlighted in the attached revised version of the manuscript. Please find tracked-in-red changes in the body of the text.

Reviewer 2

Dear author, The manuscript entitled "FOLFOXIRI versus FOLFIRINOX as first-line chemotherapy in patients with advanced pancreatic cancer: a population –based cohort study" is well written.

Reviewer 2, comment 1: What is the important limitation of the study? The author should clearly state in the last paragraph of the discussion.

Reply: We thank the reviewer 2 for this important comment and the limitations of our study were further developed in the revised manuscript as detailed below:

The main limitation is the retrospective nature of the data collection. Indeed, our study consists of an exploratory evaluation of FOLFOXIRI in first-line chemotherapy. Thereby the study design included the retrospective analysis of two cohorts of patients treated either by FOLFOXIRI or the standard FOLFIRINOX, as well as the development of a propensity score-matched analysis. This methodology was set up to detect a potential signal of efficacy for FOLFOXIRI supporting the initiation of a prospective randomized clinical trial. We provided precision in the revised manuscript in discussion section, page 15: "Due to the design of this exploratory study, patients were included in an observational cohort and treatment regimens have not been randomized."

The data from our cohort were collected retrospectively and present thus different biases integrated in analyses interpretation. These points are explicitly discussed in more detail in the discussion section related to our study limits, page 15: "In addition to its retrospective nature, some limitations of the present study warrant discussion. Patients were treated in two centers, but these were all high-volume units with similar clinical practices. […] CT-scan assessment of the tumor response according to RECIST criteria was not performed centrally. This bias could explain a trend to a better tumor response in the FOLFIRINOX group. Additional variables, particularly febrile neutropenia, biological or HRQoL data, could not be evaluated in our study due to the retrospective design of the data collection, with a high rate of missing patients' information."

Moreover, we implemented another limitation in the discussion section of the revised manuscript, page 15: "Of note, patients with a different tumor extension were involved, either locally advanced or metastatic stages. Thus, sensitivity analyses were performed exclusively in the metastatic population."

Reviewer 2, comment 2: The number of the population in this study had enough power to analyze the difference between two groups or not?

Reply: We thank the reviewer 2 for this relevant comment. As mentioned above (refer to the comment #1), the study design was a population-based cohort study in order to investigate the interest of FOLFOXIRI as backbone chemotherapy for further research. The comparison between FOLFOXIRI regimen and the reference treatment (FOLFIRINOX) was only in an exploratory purpose. We provided this precision in the revised manuscript:

- at the end of the introduction section, page 7: "In this exploratory population-based cohort study, we aimed to compare clinical outcomes, in terms of safety and efficacy, between FOLFOXIRI and FOLFIRINOX regimens, in patients with advanced PDAC in routine clinical practice."
- in the discussion section, page 15: "Due to the design of this exploratory study, patients were included in an observational cohort and treatment regimens have not been randomized."

Our findings show a lack of efficacy signal and also an alert on toxicity with FOLFOXIRI schedule. Thereby we highlighted that FOLFOXIRI cannot be considered as backbone chemotherapy in first-line treatment in pancreatic cancer. By contrast, our results suggest that FOLFIRINOX provide a better efficacy/toxicity ratio, sustaining the conclusion that FOLFOXIRI should not be tester as a backbone chemotherapy in further clinical trials.

Then, our results ruled out the potential interest to increase the number of patients included in such investigations to assess the potential superiority of FOLFOXIRI.

A propensity score method and a specific sensitivity analysis was undertaken to sustain our results. As explained in the submitted manuscript in discussion section (page 15): "Most importantly, we used a rigorous methodological framework and applied a propensity score approach to take into account the potential heterogeneity in baseline characteristics between

the two populations." We applied also sensitivity analyses, especially in the metastatic population, as underlined in discussion section (page 15): "The obtained reproducibility with the performed a sensibility analysis in the metastatic cohort strengthened the observed results." These methodological approaches strengthened our results to the detriment of FOLFOXIRI chemotherapy.

Moreover, this sample size of our study is in accordance with others studies evaluating chemotherapy in the first-line treatment in pancreatic cancer. Indeed, as specified in the introduction section, page 6: "The FOLFIRINOX polychemotherapy became a reference regimen in this setting, based on the results of PRODIGE 4/ACCORD 11 phase III trial.", with 171 patients in each arm[1]. The previous observational studies, comparing FOLFIRINOX to modified FOLFIRINOX, are realized with an lower number of patients: 88 versus 42 patients in the Kang *et al.* cohort[2]; 60 versus 44 patients in the Fonseca de Jesus *et al*. cohort[3]; and 32 versus 18 patients in the Cavanna *et al.* cohort[4]. In our study, as detailed in the results section (page 10): "A total of 289 patients with advanced PDAC treated in L1 were included in this study. Of those, 124 patients received FOLFIRINOX regimen and 165 patients received FOLFOXIRI chemotherapy." Therefore, we consider our population as a well-phenotyped and "a large prospective population-based cohort of patients with advanced PDAC", as indicated in the discussion section (page 15).

References:

1. Conroy T, Desseigne F, Ychou M, et al. FOLFIRINOX versus Gemcitabine for Metastatic Pancreatic Cancer. *New England Journal of Medicine*. 2011;364(19):1817-1825. doi:10.1056/NEJMoa1011923

2. Kang H, Jo JH, Lee HS, et al. Comparison of efficacy and safety between standard-dose and modified-dose FOLFIRINOX as a first-line treatment of pancreatic cancer. *World J Gastrointest Oncol*. 2018;10(11):421-430. doi:10.4251/wjgo.v10.i11.421

3. de Jesus VHF, Camandaroba MPG, Donadio MDS, et al. Retrospective comparison of the efficacy and the toxicity of standard and modified FOLFIRINOX regimens in patients with metastatic pancreatic adenocarcinoma. *J Gastrointest Oncol*. 2018;9(4):694-707. doi:10.21037/jgo.2018.04.02

4. Cavanna L, Stroppa EM, Citterio C, et al. Modified FOLFIRINOX for unresectable locally advanced/metastatic pancreatic cancer. A real-world comparison of an attenuated with a full dose in a single center experience. *Onco Targets Ther*. 2019;12:3077-3085. doi:10.2147/OTT.S200754

Reviewer 2, comment 3: What is the author's suggestion for the future study? For example, do we need the further well-designed RCT study between two regimens in advanced pancreatic cancer?

Reply: We agree with the reviewer 2 and we added clarifications of the absence of interest of FOLFOXIRI as backbone chemotherapy for further research in the Conclusion section.

As highlighted in the Core tip section (page5), "These findings suggest any therapeutic benefit of FOLFOXIRI compared to FOLFIRINOX in first-line chemotherapy."

This precision and additional information are explicitly detailed in the conclusion section (page 18): "These results show that an additional evaluation is not required in future clinical trials. FOLFIRINOX chemotherapy remains the standard care in L1 in metastatic PDAC."

We believe that these revisions contribute to support our conclusions regarding the FOLFOXIRI schedule in pancreatic cancers and will prevent the initiation of clinical trials using FOLFOXIRI as an experimental arm in this disease. An exploratory finding that does not warranting evaluation in further dedicated studies.

We hope that these revisions, which substantially enhanced the quality of the manuscript and the robustness of our results, improve the paper such that you and the reviewers now deem it suitable for publication in ***World Journal of Gastrointestinal Oncology***.

As anticipated in the original submission, we confirm that the manuscript reports a previously unpublished work: preliminary results were presented as a poster at the ESMO (European Society for Medical Oncology) Congress 2019. The paper is not under consideration for publication elsewhere.

We remain at your disposal for any question and look forward to hearing from you at your earliest convenience.

Best regards,

Angélique Vienot