Peer Review File

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Reviewer A

1.Given that the sample size is small, and the sample was restricted be patients of one institution only, I suggest the authors to make their conclusion with cautions. For me, it is a little over-stated to say the treatment is "safe and efficacious".

Response: We agree with the reviewer that the study is limited by a small sample size, although we did include patients from two institutions (University of Alabama, Birmingham and Kansas University Medical Center).

Changes made in text: Page 4, Line 68-69: Wording "safe and efficacious" has been changed to "offers a modest survival benefit with a tolerable safety profile"

2. Introduction. In addition to the short PFS of first-line regimens, I would like to suggest the authors to comment on their safety and survival, to strengthening the importance of second-line treatment. I also suggest the authors to provide more details of the NAPOLI-1 trial, since this is the only one available study. Comments on this study, including strengths and limitations, would make the necessity of the current study clear. The current study has a strength, that is, this is a real-world study. So the authors may consider to emphasize the lacking of real-world evidence as limitation of previous studies.

Response: We have modified the introduction to include the points suggested by the reviewer. The following statements have been added to the manuscript:

"Despite the use of newer combination chemotherapeutic agents, overall survival (OS) with first-line treatment remains less than one year on an average. In phase 3 randomized controlled trials, FOLFIRINOX was shown to significantly increase OS from 6.8 months to 11.1 months while Gem-Abraxane demonstrated an OS of 8.5 vs 6.7 months (P<0.001) when compared to gemcitabine monotherapy, albeit at the cost of increased risk of myelosuppression and neuropathy with both regimens. Similarly, progression-free survival (PFS) for the recommended first-line regimens such as gemcitabine, Gem-Abraxane, and FOLFIRINOX are only 3.4, 5.5, and 6.4 months, respectively. As such, most patients require second-line chemotherapy, but options remain scarce. A promising second-line combination of nano-liposomal irinotecan (nal-IRI) with 5-fluorouracil/leucovorin (5-FU/LV) emerged from the NAPOLI-1 trial, the largest global phase 3 trial to date, testing a second line regimen for patients with metastatic pancreatic cancer. Patients were randomly assigned to 3 arms: nal-IRI+5-FU/LV vs nal-IRI alone vs 5-FU/LV alone. The study reported improved OS (6.1 vs 4.2 months, p = 0.012) and PFS (3.1 vs 1.5 months, p = 0.0001) with nal-IRI + 5-FU/LV when compared to 5-FU/LV alone.

Despite the 2015 FDA approval of this combination, there is limited post-approval real- world data regarding its efficacy, safety and optimal sequencing. NAPOLI-1 trial only enrolled patients who failed prior gemcitabine-based therapy, leaving questions about response in patients with prior irinotecan-based therapy unanswered. Therefore, the purpose of this retrospective analysis is to expand on the currently available literature by sharing our institutional experiences regarding the effectiveness and safety of this combination as an advanced line of therapy in patients with advanced PAC irrespective of prior exposures, outside of the controlled environment of a clinical trial."

Changes made in text: Page 5, Lines 99-105, 110-115 &Page 6, Lines 120-127

3. Statistics. I do not think the paper needs so many figures (1-6), because the survival time did not differ significantly between all subgroups. Describing these results in table and the main text is enough.

Response: We reduced the number of figures to just 2 in the main text and added the rest of the figures to the supplementary file

4. Discussion. Please consider the small sample as a limitation of this study. Further, the study has 8

covariates, but the total sample is 58 only. In general, such sample does not allow for the proposed multiple Cox regression. There may be false-negative findings due to lack of statistical power.
Response:
We agree with the reviewers that the study is limited by the statistical power due to low sample size. We mentioned this in discussion section last paragraph (Page 17, Lines 365-366). As we noted, this study is intended to assess the safety and efficacy in post-approval real world clinical setting. Twelve covariates were evaluated during statistical analysis and highly relevant 8 covariates were mentioned in the manuscript as the analysis with both 12 vs 8 covariates did not yield any significant difference.

Reviewer B

1.There are many censored cases in the K-M curves of PFS, and the results are immature. I think there is a discrepancy between OS and PFS.
Response: The censored cases are due to patients being alive at the given median follow up. Per the reviewer's concern, the data was re-analyzed, and the results did not change.

2. It seems that PFS and DCR tend to be better in the patients without prior irinotecan, just because no statistically significant difference is shown.
Response: That is correct and intuitively, patients who never exposed to irinotecan have the potential to respond better with liposomal irinotecan. Statistical significance was not attained due to low sample size.
Changes made in text: We have mentioned this in the results section (Page 10, Lines 227-28, 236-238) and discussion section (Page 13, 287-88).

2. There is no difference in the OS analyses in Fig.1 and Fig.2, so it would be useful if there was data about the treatment after nal-IRI+5FU.
Response: Post nal-IRI+5FU, 22 percent went on to clinical trials, 24 percent received FOLFOX and the rest went to hospice
Changes made to text: This information has been included in the results section (Page 11, Lines 246-48)

3. Please indicate the range of doses of nal-IRI+5FU.
Response: The median dose is 70mg/m2 and the range is 50-70mg/m2; 15 (26%) patients received starting dose at 50mg/m2
Changes to text: Included in Results section (Page 10, Lines 205-208)