Author’s response to reviews

Title: Efficacy and safety of weekly nab-paclitaxel plus gemcitabine in Chinese patients with metastatic adenocarcinoma of the pancreas: a phase II study

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Author’s response to reviews:

Thank you for your review and the opportunity to revise this manuscript to address the reviewer’s comments. We have made every effort to address each comment, and believe this manuscript has been greatly improved as a result of the revisions made. Please see below for a
Reviewer #2:

In this phase II bridging study Shen et al. evaluate the safety and efficacy of nab-paclitaxel/gemcitabine (Metastatic Pancreatic Adenocarcinoma Clinical Trial [MPACT] regimen) in Chinese patients with metastatic pancreatic cancer (MPC). Given known differences in cancer drug tolerability between Asian and European populations, this study has a high significance. In general the manuscript is well written, provides all details of the study’s design and obtained results. However, the authors should consider some comments and questions in order to improve the quality of the publication.

Comment 1: There is inconsistency throughout the whole manuscript in the total number of patients involved in Part 1 and Part 2 of the study. In some cases, the manuscript says it is 82 and in other cases 83 patients. The authors should correct this discrepancy.

The 82 patients mentioned in the Methods and Discussion sections refer to the planned Part 2 sample size. In Part 2, a planned sample size of 82 patients was estimated to provide 90% power at a 1-sided significance level of 0.05 (Methods, p 8). If more than 9 of these 82 patients responded to treatment, the null hypothesis would be rejected and the study would not progress to Part 3 (Methods, p 6; Discussion, p 14). Overall, 83 patients were included in safety and efficacy analyses from Part 2 of this study. Since we refer to statistical methodology in the Discussion section, however, for clarity we have now included ‘planned sample size’ after the ’82 patients’ (p 14).

Comment 2: As a result of the study, Shen et al. determined that the median duration of response (DOR) for Chinese patients with MPC is 8.9 months and progression-free survival (PFS) is 5.5 months. The authors should explain why the PFS is shorter than DOR.

DOR is evaluated only in patients with a complete or partial response, while PFS is assessed in all patients, including those who died. Therefore, given the different patient populations, it is not appropriate to make observations regarding differences in length of time between DOR and PFS.

Comment 3: In the Introduction section the authors refer to a recent phase I/II study of nab-paclitaxel/gemcitabine treatment in Chinese patients. It is important to explain why this other study used a dose and schedule of treatment different from the MPACT study and what was the difference. And since that phase I/II study already came up with the regimen of treatment,
comparable by intensity and safety with MPACT regimen, it should be more carefully explained what is the principal relevance of the current analysis.

This is an interesting point. Results from the MPACT trial were published the same year as the Zhang et al. study; therefore, one study could not inform the design of the other, and a treatment regimen for Chinese patients with metastatic pancreatic cancer was not yet established. The MPACT trial was a large (N = 861), global phase III study demonstrating favorable efficacy results with nab-paclitaxel/gemcitabine treatment. The Zhang et al. study, which was a phase I/II, independently conducted, single institution study in China, reported efficacy data comparable to MPACT; however, the nab-paclitaxel 125 mg/m2 dose used in MPACT was not tested. Given the positive efficacy data from both of these studies, an analysis of the MPACT regimen in Chinese patients was warranted.

Comment 4: The study assessment section could benefit from a more detailed explanation of how often the other metrics than computed tomography scan or magnetic resonance imaging were evaluated.

Additional information regarding assessment schedules has been added to the Methods section, p 8.

Comment 5: The sample size and statistical analysis section is only described for Part 2. How was Part 1 analyzed?

No formal statistical analyses were performed for Part 1.

Comment 6: Table 1 of the manuscript describes baseline characteristics of all patients enrolled in Part 2. What are the distribution and characteristics for patients enrolled in Part 1 of the study?

No formal analysis of Part 1 patients was performed. Therefore, we are unable to provide baseline characteristics for these patients.

Comment 7: The study design section explains that the number of patients needed for Part 1 of the study is 10. However, the efficacy results section mentions that 15 patients were evaluated in part 1 study. The authors should consider clarifying this discrepancy.

The number of patients for Part 1 exceeded 10 due to the rapid registration. Since the study was open label, initial data on the first patients enrolled suggested safety and tolerability results
similar to the global population. Therefore, any patients who had provided consent to participate in the study were allowed to enroll. Further, since patients in Part 1 could withdraw due to reasons unrelated to safety and tolerability, additional patients were enrolled to ensure a sufficient number of evaluable patients.

Comment 8: The treatment exposure section describes changes (dose reductions and delays) of treatment for some patients which occurred during the study. It would be important to discuss what the reasons of changing the regimen of treatment were and how these changes correlated with outcome results (including DOR, PFS, OS, etc.).

Additional data describing the primary reason for nab-paclitaxel and gemcitabine dose reductions have been added (Treatment Exposure section, p 10). We cannot, however, speculate on how these changes correlated with outcome results, as relevant analyses were not performed.

Best regards,

Lin Shen