PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Re-purposing the FDA Approved Anthelmintic Pyrvinium Pamoate for Pancreatic Cancer Treatment: Study Protocol for a Phase I Clinical Trial in early-stage pancreatic ductal adenocarcinoma
AUTHORS	Ponzini, Francesca M.; Schultz, Christopher W.; Leiby, Benjamin E.; Cannaday, Shawnna; Yeo, T; Posey, James; Bowne, Wilbur B.; Yeo, Charles; Brody, Jonathan R.; Lavu, Harish; Nevler, Avinoam

VERSION 1 – REVIEW

REVIEWER	Deng, Kai Sichuan University West China Hospital, Department of Gastroenterology and Hepatology
REVIEW RETURNED	20-May-2023

GENERAL COMMENTS	This study is an exploratory phase I research on the application of Pyrvinium Pamoate in pancreatic cancer. The study administered different high doses of the drug to patients for a short period of time, and indirectly reflected the safety and efficacy of Pyrvinium Pamoate in treating pancreatic cancer by monitoring peripheral blood indicators. However, there are certain issues in this study, such as the lack of specific grading criteria for defining the dose-limiting toxicity (DLT), making it difficult to quantify the execution process. Additionally, the monitored indicators only reflect short-term changes in peripheral blood, which are insufficient to macroscopically reflect the true effects of Pyrvinium Pamoate in the treatment of pancreatic cancer.

REVIEWER	Basha, Riyaz University of North Texas, Pediatrics and Women's Health
REVIEW RETURNED	31-Jul-2023

GENERAL COMMENTS	It is limited study and planned very well. Hope it will yield optimal results. All the best.

VERSION 1 – AUTHOR RESPONSE

Reviewer#1 This study is an exploratory phase I research on the application of Pyrvinium Pamoate in pancreatic cancer. The study administered different high doses of the drug to patients for a
short period of time, and indirectly reflected the safety and efficacy of Pyrvinium Pamoate in treating pancreatic cancer by monitoring peripheral blood indicators. However, there are certain issues in this study, such as the lack of specific grading criteria for defining the dose-limiting toxicity (DLT), making it difficult to quantify the execution process. Additionally, the monitored indicators only

reflect short-term changes in peripheral blood, which are insufficient to macroscopically reflect the true effects of Pyrvinium Pamoate in the treatment of pancreatic cancer.

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Thank you for your thoughtful comments. While we defined dose limiting toxicity (DLT) as "any grade 3 or higher adverse events due to the drug itself or delay of surgery" (page #12). We noticed that we have not clarified the grading system of the adverse events. Therefore we have added the following statement: "Adverse events reporting will conform to the "Classification and grading of AEs are reported using the Common Terminology Criteria for Adverse Events" (CTCAE)." . Furthermore, we agree with your observation that this study, as a surgical window of opportunity, is limited in its ability to assess oncological outcomes or macroscopic therapy effects. We have referred to this in our methods and discussion. However, our secondary molecular endpoints includes both blood and tissue samples for PK/PD analysis AND also tissue samples for target gene expression measurement, in order to assess drug effects beyond transient changes in peripheral blood.

Reviewer#2

It is limited study and planned very well. Hope it will yield optimal results. All the best.

We thank the reviewer for the kind comments.