Peer Review File

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Reviewers' comments:

- Excellent review in TTFields. I would say the title might have to be changed to include the general review in othe tumor types in addition to PDAC. Perhaps “A Narrative Review of Therapuetic Evolution” for example. The review is well written.

Re: We appreciate the reviewer’s comments. In response to their suggestions, we have updated the title as follows:

Title: Emerging Potential of Tumor Treating Fields as a Treatment Modality for Pancreatic Cancer: A Narrative Review of Theurapuetic Evolution

- Abstract line 44- this should say locally advanced unresectable pancreatic cancer.

Re: Thank you for the suggestion. We have updated line 44 in the abstract as 'locally advanced unresectable pancreatic cancer' as recommended by the reviewer.

- Line 53, please take out in-“worldwide and fourth”.

Re: We appreciate the reviewer's feedback. As per their suggestion, we have removed 'in' before 'worldwide' in line 53.

- Line 56, I would say pancreatic cancer/malignancy but not neoplasm, some benign dysplatic lesions are described as neoplasms.

Re: We thank the reviewer for their helpful suggestion. In response, we have revised line 56 to use 'pancreatic malignancy' instead of 'pancreatic neoplasm' to avoid any potential confusion with benign dysplastic lesions.

- Line 64-Not so much clinically silent but the symptoms can be vague early.

Re: Thank you very much for this recommendation. We have updated the sentence as follows:

Due to its symptoms can be vague at early stage, most cases of PDAC are diagnosed at the locally advanced or metastatic stage, which makes them unsuitable for primary surgery.

- Line 65-surgery is front line if the disease is localized and resectable.

Re: We have revised line 65 to clarify that surgery is the frontline treatment when the disease is localized and resectable. Thank you for highlighting this important point.

- Line 65- the use of periopertive chemotherapy has improved recurrence, that percentage is higher now.

Re: We thank the reviewer for this comment. We have revised the sentence to clarify that the use of perioperative chemotherapy has led to a higher percentage of improved recurrence outcomes.

- Line 81-what are the dates, what were the terms used in the search, what were the inclusion and exclusion criteria used, etc…..

We appreciate the reviewer's comment. We have included these to the Table 1 as follows.

Table 1. The search strategy summary

Items	Specification
Date of Search	5.1.2023
Databases and other sources searched	PubMed, Google Scholar, Clinicaltrials.gov
Search terms used	Tumor Treating Fields (TTFields), pancreatic cancer, pancreas cancer, pancreatic ductal adenocarcinoma (PDAC)
Timeframe	01.01.2000- 05.01.2023
Inclusion and exclusion criteria	Studies that were not written in English and those lacking available full text were excluded from our analysis.
Selection process	All authors participated in the selection process together, reaching a consensus based on the potential benefits to clinical practice.

Any additional considerations, if applicable	N/A

- Page 5, line 37, I would the state results clearer, was their improvement in the TTF+TMZ arm? And also when compared to historical control?

Re: We thank the reviewer for this comment. The interim analysis demonstrated superior outcomes in the TTFields plus TMZ arm compared to the TMZ alone arm, with a median PFS of 7.1 months versus 4.0 months (p = 0.001) and a median OS of 19.6 months versus 16.6 months (p = 0.034).

The primary endpoints were PFS and OS, with a preplanned interim analysis evaluating the outcomes for the first 315 patients with at least 18 months of follow-up. The interim analysis demonstrated superior outcomes in the TTFields plus TMZ arm compared to the TMZ alone arm, with a median PFS of 7.1 months versus 4.0 months (p = 0.001) and a median OS of 19.6 months versus 16.6 months (p = 0.034) which resulting in Food and Drug Administration (FDA) approval for TTFields in primary GBM.

- Page 5, line 57---I would indicate no side effects with “TTFields alone”, for clarity.

Re: Thank you for your suggestion. We have clarified the statement on page 5, line 57 to indicate 'no side effects with TTFields alone' for improved clarity.

- Page 6, line 201—The trial’s name is the PANOVA2.

Re: We appreciate the reviewer's comment. We have updated page 6, line 201 to correctly mention the trial's name as 'PANOVA-2.'

- Line 216-below the arrays? You mean skin under the arrays---I would clarify.

Re: Thank you for your valuable feedback. We have revised line 216 to clarify that we are referring to the skin under the arrays as 'skin under the arrays.'

- Line 243-what did the other arm receive-gem plus nab-Paclitaxel, I would clarify the randomization.

Re: We thank the reviewer for the comment. We have revised the sentence as follows:

This trial is a prospective, randomized, open-label, pivotal study where the patients were randomized in two groups to receive combination therapy of TTFields with gemcitabine and nab-paclitaxel or TTFilelds and gemcitabine as a front-line treatment for locally advanced PDAC.

- Line 250-how is this fright line trial in China different from the PANOVA3 trial in locally advanced pancreatic cancer. (285)

Re: We thank the reviewer for this great question. The PANOVA3 trial is a prospective, randomized, open-label, pivotal study in which patients were randomized into two groups. One group receives combination therapy of TTFields with gemcitabine and nab-paclitaxel as a front-line treatment for locally advanced PDAC, while the other group receives TTFields with gemcitabine alone. However, the trial from China compares TTFields combined with gemcitabine and nab-paclitaxel against gemcitabine and nab-paclitaxel alone.

The first clinical trial mentioned is a Phase III randomized open label study from Fudan University, Shanghai, China (NCT05653453, P100-LAPC1), which aims to evaluate the safety and effectiveness of a combination of TTFields, gemcitabine, and nab-paclitaxel for the treatment of locally advanced PDAC in the first line treatment. This trial involves a comparison between TTFields combined with gemcitabine and nab-paclitaxel and gemcitabine plus nab-paclitaxel alone and will help determine whether this combination therapy can improve patient outcomes compared to standard treatments.

- Line 304-the results of the Lunar trial was presented at Annual ASCO 2023, I would indicate the results.

Re: We appreciate the reviewer's feedback. In response to their comment, we have added the results of LUNAR trial.

After an interim analysis involving 210 patients showed no increased systemic toxicity, the recent results of the LUNAR trial were presented at ASCO 2023. In the analysis, which included 267 patients, the median OS increased with the addition of TTFields to SOC (ICI or Docetaxel) (13.2 months compared to 9.9 months, $p = 0.035$). Additionally, a more substantial increase was observed in patients receiving combination therapy compared to those receiving ICI alone (18.5 months and 10.8 months, $p = 0.03$). The trial offers valuable insights into the effectiveness of adding TTFields to standard therapies in stage IV NSCLC patients, particularly in combination with ICI.

- Line 319-Ttfields is also attractive given non-invasiveness and potential efficacy in PDAC.

Re: Thanks for the reviewer for the valuable feedback. We have added a statement to line 319 to highlight TTFields' non-invasiveness and potential efficacy in PDAC.

The therapeutic ratio of TTFields for PDAC may be especially attractive because of its favorable safety profile, given non-invasiveness and potential efficacy.