Format for ANSWERING REVIEWERS

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 19941-edited).

Title: Targeted therapies for pancreatic adenocarcinoma: where do we stand, how far can we go?

Author: Dimitra Grapsa, Muhammad Wasif Saif, Konstantinos Syrigos

Name of Journal: *World Journal of Gastrointestinal Oncology*

ESPS Manuscript No: 19941

The manuscript has been improved according to the suggestions of reviewers:

1)" Please highlight the changes made to the manuscript according to the peer-reviewers' comments".

RESPONSE:

All changes made to the revised manuscript are highlighted in red in the text.

2)**Running title: ?**

RESPONSE: Running title was provided.
Running title: "Targeted therapies for pancreatic cancer"

Please also note that the reference format was revised as suggested by the editor.

COMMENTS FROM REVIEWER 1

1)"Please discuss common drugs such as aspirin and NSAIDs can be targeted therapeutic agents. X Liao et al (N Engl J Med 2012) showed that aspirin works for a specific tumor molecular subtype. The finding was confirmed by E Domingo et al (J Clin Oncol 2013). Those studies took a molecular pathological epidemiology approach, which has a big potential and promise using big data science (S Ogino et al. Oncogene 2014).

RESPONSE:

The issue raised by the reviewer was further discussed in the revised manuscript as follows:

"*Interestingly, in accordance with increasing data suggesting potential preventive and therapeutic effects of aspirin and non-steroidal inflammatory drugs in gastrointestinal cancers, particularly colorectal cancer*[37,38], *aspirin is being explored as a targeted therapeutic agent for pancreatic cancer as well*[39,40]. *As shown in recent preclinical studies, aspirin, either alone or in combination with the antidiabetic drug metformin, may inhibit pancreatic cancer cell growth, counteract desmoplasia and cancer stem cell features and enhance the therapeutic efficacy of cytotoxic agents-such as gemcitabine- in pancreatic cancer by sensitizing pancreatic cancer cells to chemotherapy-mediated cytotoxicity*[41-43]". (Lines 140-150*)

COMMENTS FROM REVIEWER 2

1)"One addition I would suggest is the mention of a few representative negative clinical trials of once promising targeted agents, as well as of some selected ongoing trials, either at the adjuvant or at the metastatic setting".

RESPONSE:

The issues raised by the reviewer were further discussed in the revised manuscript as follows:

"*The EGFR and VEGF monoclonal antibodies cetuximab and bevacizumab, respectively, and the multikinase inhibitor sorafenib are representative examples of once-promising targeted agents who failed to produce a statistically significant improvement of survival when used in combination with gemcitabine versus gemcitabine alone in phase III randomized trials*[53-55]*.*". (Lines 170-175 *)

"*Hopefully, the results of ongoing clinical trials on current and emerging targeted therapeutics, including, among others, the anti-EGFR and anti-HER2/neu monoclonal antibodies nimotuzumab (NCT02395016) and trastuzumab (NCT01204372), respectively, the hedgehog inhibitors vismodegib (NCT01195415) and LDE225 (NCT01485744) and agents targeting the Notch pathway, such as the gamma-secretase inhibitor MK-0752 (NCT01098344), may help bridge the gap between preclinical and clinical outcomes.*". (Lines 214-221*)

Please also note the following minor modifications:

-Ten additional references were inserted (Ref. 37-43, 53-55)

-The order of references was accordingly modified.

*of the revised manuscript.

As you notice we responded to all editorial and reviewers' comments. We hope that these revisions address your concerns.

Kind regards,

Konstantinos Syrigos