

## PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	Pancreatic resection with perioperative drug repurposing of propranolol and etodolac – trial protocol of the phase II randomized placebo-controlled PROSPER-trial
<b>AUTHORS</b>	Hüttner, Felix; Rooman, Ilse; Bouche, Gauthier; Knebel, Phillip; Hüsing, Johannes; Mihaljevic, A; Thilo, Hackert; Strobel, Oliver; Buchler, Markus W.; Diener, M. K.

### VERSION 1 – REVIEW

<b>REVIEWER</b>	Damian Mole University of Edinburgh, UK.
<b>REVIEW RETURNED</b>	25-May-2020

<b>GENERAL COMMENTS</b>	<p>This is an interesting research question. The study design and attention to detail is of the highest quality. The protocol paper is exceptionally well written.</p> <p>The translational aspects of the study exploring the molecular mechanisms in blood and tissue samples will also likely be of significant interest.</p> <p>There are some specific changes to the text that will improve the paper:</p> <ol style="list-style-type: none"> <li>1. p2 line 6 - suggest 'death' singular rather than 'deaths'</li> <li>2. p2 line 33 omit the word 'correlating'</li> <li>3. p2 Abstract methods - Please clearly state the primary and secondary endpoints in the format: "The primary endpoint of this study is..... Secondary endpoints include....". This makes the paper much more likely to be included in any future systematic reviews and meta-analyses.</li> <li>4. p2 Abstract. Please state main inclusion and exclusion criteria explicitly.</li> <li>5. p3 line 17. Suggest alternative phrasing. Propranolol and etodolac are not really cancer-directed therapy. Can you use other language e.g. "window for therapies that influence tumour and inflammatory responses" or similar</li> <li>6. Introduction. Please acknowledge in a sentence or two the potential beneficial effects of catecholamines and prostaglandins in tumour and surgery responses in addition to potential negative effects.</li> <li>7. p4 line 9. Suggest change wording to "well-characterised drugs for a previously untested indication."</li> <li>8. p4 line 13. Etodolac is a NSAID that is a COX-1 *and* COX-2 inhibitor, albeit with a preference for COX-2. Please change wording to reflect this and add a reference if needed.</li> <li>9. p4 line 16. Suggest revising this sentence, including omitting the subordinate clause in this sentence and let it read: "...in the peri-</li> </ol>
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	operative setting of pancreatic cancer resection may result in attenuation of tumour-associated inflammation and stress responses." 10. p9. In the final draft, please ensure Table 2 does not break across pages.  I look forward to reading the final results of the study in due course.
<b>REVIEWER</b>	Dr Wasek Faisal Ballarat Regional Integrated Cancer Centre (BRICC), Ballarat Health Services, Ballarat, VIC, Australia
<b>REVIEW RETURNED</b>	31-May-2020
<b>GENERAL COMMENTS</b>	Although a drug(s) "re-purposing study" does not necessarily require pre-clinical data (given already established safety data), it would be nice to know if there is any pre-clinical/phase I data available relating to the drug combination of beta-blockers and COX-2 inhibitors, specifically in solid tumour population.

### VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Damian Mole

Institution and Country: University of Edinburgh, UK.

Please state any competing interests or state 'None declared': None declared.

This is an interesting research question. The study design and attention to detail is of the highest quality. The protocol paper is exceptionally well written.

The translational aspects of the study exploring the molecular mechanisms in blood and tissue samples will also likely be of significant interest.

**Thank you for your appreciation of our work.**

There are some specific changes to the text that will improve the paper:

1. p2 line 6 - suggest 'death' singular rather than 'deaths'

**Changed as suggested.**

2. p2 line 33 omit the word 'correlating'

**Changed as suggested**

3. p2 Abstract methods - Please clearly state the primary and secondary endpoints in the format: "The primary endpoint of this study is..... Secondary endpoints include.....". This makes the paper much more likely to be included in any future systematics reviews an meta-analyses.

**Since there is no formal hypothesis that will be tested and no sample size calculation, the term "primary endpoint" would not be appropriate in our opinion. Please see also our response to the first Editorial comment above. The methods section of the abstract has been changed to clearly state the main outcomes of the trial. However, we had to revise some other parts of the abstract subsequently to remain within the word limit.**

4. p2 Abstract. Please state main inclusion and exclusion criteria explicitly.

**The main inclusion criteria are now basically mentioned in the first sentence of the methods section of the abstract "adult patients with non-metastatic cancer of the pancreatic head undergoing elective pancreatoduodenectomy without contraindications to trial treatment". We think that stating the rather broad exclusion criteria in this place would go beyond the scope of an abstract. We already had to revise some other parts of the abstract subsequently to remain within the word limit.**

5. p3 line 17. Suggest alternative phrasing. Propanalol and edotolac are not really cancer-directed therapy. Can you use other language e.g. "window for therapies that influence tumour and inflammatory responses" or similar

**The phrase was rewritten in the sense of the reviewer's suggestion.**

6. Introduction. Please acknowledge in a sentence or two the potential beneficial effects of

catecholamines and prostaglandins in tumour and surgery responses in addition to potential negative effects.

Short sentences acknowledging the potential beneficial effects of catecholamines and prostaglandins in the perioperative setting have been introduced at the respective places in the introduction.

7. p4 line 9. Suggest change wording to "well-characterised drugs for a previously untested indication."

Changed as suggested.

8. p4 line 13. Etodolac is a NSAID that is a COX-1 \*and\* COX-2 inhibitor, albeit with a preference for COX-2. Please change wording to reflect this and add a reference if needed.

We added that etodolac is a semiselective COX-2 inhibitor. The reference (#17) after this sentence already provides some more information on the pharmacodynamics of etodolac.

9. p4 line 16. Suggest revising this sentence, including omitting the subordinate clause in this sentence and let it read: "...in the peri-operative setting of pancreatic cancer resection may result in attenuation of tumour-associated inflammation and stress responses."

Changed as suggested.

10. p9. In the final draft, please ensure Table 2 does not break across pages.

This was checked in our word file as well as in the created pdf in the submission system.

I look forward to reading the final results of the study in due course.

We hope that we can provide the results to you soon.

Reviewer: 2

Reviewer Name: Dr Wasek Faisal

Institution and Country: Ballarat Regional Integrated Cancer Centre (BRICC), Ballarat Health Services, Ballarat, VIC, Australia

Please state any competing interests or state 'None declared': None declared.

Although a drug(s) "re-purposing study" does not necessarily require pre-clinical data (given already established safety data), it would be nice to know if there is any pre-clinical/phase I data available relating to the drug combination of beta-blockers and COX-2 inhibitors, specifically in solid tumour population.

We thank the reviewer for this comment. Some information on pre-clinical studies and early-phase clinical trials in other solid tumor entities has been included in the introduction section of the manuscript.

### VERSION 2 – REVIEW

<b>REVIEWER</b>	Damian J Mole 1777 Chair of Surgery and MRC Senior Fellow Centre for Inflammation Research The University of Edinburgh Queen's Medical Research Institute 47 Little France Crescent Edinburgh EH16 4TJ United Kingdom
<b>REVIEW RETURNED</b>	28-Jul-2020

<b>GENERAL COMMENTS</b>	Thank you for submitting this revised and improved manuscript for this interesting study. Prior to acceptance, I would strongly recommend to the editor and authors that the terminology "primary outcome" is used to describe the primary outcome. This is good practice, but also important for search engines and subsequent citations etc. Furthermore, it is specifically included in the SPIRIT checklist (section 12) to which the authors have subscribed. The authors use the words "Main outcome of interest" in the abstract, and "primary objective" in the manuscript, p4. Which mean 'primary
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	outcome'. Please use the term "Primary outcome" for these concepts.
<b>REVIEWER</b>	Dr Wasek Faisal Ballarat Regional Integrated Cancer Centre (BRICC) Ballarat Health Services Ballarat, VIC, Australia
<b>REVIEW RETURNED</b>	02-Aug-2020
<b>GENERAL COMMENTS</b>	Thank you for submitting the revised manuscript. This now reads much more succinctly, and previously comments on the earlier version have been addressed adequately.

## VERSION 2 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Damian J Mole

Institution and Country: The University of Edinburgh, United Kingdom

Please state any competing interests or state 'None declared': No competing interests. DJM wishes to disclose directorship of Kynos Therapeutics Ltd, a private company developing medicines for systemic inflammation and cancer.

Thank you for submitting this revised and improved manuscript for this interesting study. Prior to acceptance, I would strongly recommend to the editor and authors that the terminology "primary outcome" is used to describe the primary outcome. This is good practice, but also important for search engines and subsequent citations etc. Furthermore, it is specifically included in the SPIRIT checklist (section 12) to which the authors have subscribed. The authors use the words "Main outcome of interest" in the abstract, and "primary objective" in the manuscript, p4. Which mean 'primary outcome'. Please use the term "Primary outcome" for these concepts.

As requested by the reviewer, we changed the term "main outcome of interest" to "primary outcome" throughout the manuscript. Nevertheless, we are of the opinion that the term "primary outcome" should be reserved for confirmatory trials that planned their sample size based on this "primary outcome", which is not the case in the current pilot trial. Therefore, we leave the final decision on whether using "main outcome" or "primary outcome" up to the editors.

Reviewer: 2

Reviewer Name: Dr Wasek Faisal

Institution and Country: Ballarat Regional Integrated Cancer Centre (BRICC), Ballarat Health Services, Ballarat, VIC, Australia

Please state any competing interests or state 'None declared': None declared.

Thank you for submitting the revised manuscript. This now reads much more succinctly, and previously comments on the earlier version have been addressed adequately.

We thank reviewer #2 for his positive appraisal of our work during the first revision.