Author's response to reviews

Title: Inference of synergy/antagonism between anticancer drugs from the pooled analysis of clinical trials

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Inference of synergy/antagonism between anticancer drugs from the pooled analysis of clinical trials
Wenfeng Kang, Robert S DiPaola and Alexei Vazquez

Senior Editor,
BMC Medical Research Methodology

Section Editor's Comment: "Please consider the revision to some of the longer sentences, recommended by one reviewer." We would be grateful if you could address the comments in a revised manuscript and provide a cover letter giving a point-by-point response to the concerns.

Dear Editor,

Thank you very much for handling our submission. We are very glad to hear that both reviewers consider our work worth of publication after minor revisions. Please, find below a point-by-point response to the reviewers comments and suggestions.

Sincerely yours,
Alexei Vazquez
Corresponding author
Reviewer 1

1. Section **Background**, Paragraph 2. Would the researchers on this topic be familiar with the term “objective response rate”? And is it the same as the “overall response rate” defined in the section Study design? If so, the definition given in the section study design should move to the background.

**Response:** We replace “objective response rate” by “overall response rate” in the second paragraph of the background section, since the latter is the quantity utilized in our study. Furthermore, following the reviewer suggestion, we brought the definition of overall response rate to the background section, to make it accessible to readers that are not familiar with the term.

2. Section **Study design**. The authors do not say whether the results from initial assessment are different from results of 1,163 trials. They need write something on this.

**Response:** The results from the initial assessment were basically the same as those reported using the final set of trials. We have noted that in the **Study design** section.

3. Section Study design, the sentence starting with “Our scope with that latter search ….” I think starting the sentence with “The reason for the latter search ….” would make it clearer.

**Response:** We agree and thank the reviewer for the suggestion.

4. Section **Observed ORR**. Sentence starting with “In 142 of these combinations …”. It is not clear from the sentence whether data are pooled for the same combinations only (but possibly tested in different cancer types) or for any combinations with similar results. Generally, make it clearer when you are grouping based on treatment combinations and when based on cancer types.

**Response:** We agree and we have modified the text to make clear that we pool by the combination tested:

“When pooling the clinical trials by the combination tested, in 142 of these combinations the data indicates that all trials are statistically equivalent as determined by the Bayesian method. In these cases we pooled together the data from clinical trials testing the same combination even though some were conducted in different cancer subtypes.”

5. Section **Observed ORR**. Give explanation for the excluded trials (not just how they were excluded).

**Response:** We have added the following text to explain the reason for exclusion:

“These trials were removed because the reported ORR were inconsistent with the report by trials testing the same combination in the same cancer type.”

6. Section **Observed ORR**, last sentence. The authors should consider deleting the words “In the latter case” and start
the sentence “The expected probability of response rates for equivalent trials is computed ………”.

Response: We agree and thank the reviewer for the suggestion.

7. Section *Null Model for combinations of two non-interacting agents*, sentence starting with “Using the latter probabilities …”. I prefer starting the sentence with “Using the probabilities $p_1$ and $p_2$ …”

Response: We agree and thank the reviewer for the suggestion.

8. Section *Null Model for combinations of two non-interacting agents*, sentence starting with “Using the latter number of responses …”. I prefer starting the sentence with “Using the generated number of responses …”

Response: We agree and thank the reviewer for the suggestion.

9. Section *Null Model for combinations of two non-interacting agents*, last paragraph. The authors need to give the conclusion from the results in Figures 2a-c in this paragraph (Not only later in the conclusion).

Response: We prefer to discuss the results reported in the figures in the *Results* section. Therefore, we have removed the reference to Fig. 2a-c from this sentence in the *Methods* section. The text in the *Methods* section now reads:

“The manifestation of synergy/antagonism was determined by comparing the expected ORR as obtained from the null model ORR$_1$=100%$q_{12}$ with the ORR as observed ORR$_0$=100%$p_{12}$. Specifically, the probability for synergy $p_{\text{synergy},12}$ and antagonism $p_{\text{synergy},12}$ were quantified as the fraction of times that, for the corresponding (ORR$_0$,ORR$_1$) pair, $p_{\text{synergy},12}$≥0.05 if ORR$_0$>ORR$_1$ or $p_{\text{antagonism},12}$≥0.05 if ORR$_0$<ORR$_1$.”

10. Section *Two-agents approximations*, the first three sentences. The authors need to rearrange these sentences for a better flow. I suggest that the authors should first state what $N_a$, $S_{ci}$, $S_{cj}$, $h_i$ and $J_{ij}$ represent, then define $p_c$ followed by ORR$_c$. Also, an intuitive explanation for $p_c$ would also make following the paper easier.

Response: We have modified this section following the reviewer suggestion. The different parameters are now defined before the equation for $p_c$ is introduced. We have also added a derivation of the equation of $p_c$ for the case of non-interacting agents, which provides an intuitive motivation for our equation for $p_c$. The modified section now reads:

“In the 2-agent approximation model the ORR for each agent combination $c$ is derived from parameters quantifying the response to a single agent and the interaction between two agents. These combinations are constructed out of $N_a$ agents. The combinations are specified using the agent to combination matrix $s_{ci}$, where $s_{ci}$=1 if agent $i$ is part of the combination $c$ and $s_{ci}$=0 otherwise. The parameter $h_i$ is defined as the response rate to agent $i$ when tested as a single agent. The parameters $J_{ij}$ are introduced to quantify corrections due to agent
interactions. The probability $p_c$ to respond to a combination $c$ is written as
\[ p_c = \sum_{i=1}^{N_c} s_i h_i + \sum_{i=1}^{N_c-1} \sum_{j=i+1}^{N_c} s_i s_j h_i h_j \]
and the associated overall response rate is $\text{ORR}_c = 100\% \times p_c$. To understand the equation for $p_c$, it is better to focus on the case when the drugs do not interact. In this case
\[ p_c = 1 - \prod_{i=1}^{N_c} (1 - h_i)^{x_{si}} = \sum_{i=1}^{N_c} s_i h_i - \sum_{i=1}^{N_c-1} \sum_{j=i+1}^{N_c} s_i s_j h_i h_j . \]
Therefore, in the absence of interactions the equation of $p_c$ can be written as we postulated above with $J_{ij}^0 = -h_i h_j$. The difference between an observed $J_{ij}$ and the non-interacting value $J_{ij}^0$ is used to quantify synergy (when positive) and antagonism (when negative).

11. Section **Two-agents approximations**. The sentence starting with "The variables $X_m$ were estimated solving ..." should start with "The variables $X_m$ were estimated **by** solving ...".

Response: We agree and thank the reviewer for the suggestion.

12. Section **Statistical equivalence of trials testing the same combination**, Paragraph 2, Sentence 2. Consider inserting a comma after the "... dataset studied".

Response: We agree and thank the reviewer for the suggestion.

13. Section **Trends as a function of the number of agents combined**, Sentence 5. I think " ... with increasing the number ..." should be " ... with the increasing number ...".

Response: In this case we consider that the wording “... with increasing the number …” is more appropriate and have not make any modification.

14. Section **Trends as a function of the number of agents combined**. Consider changing the order of Figures so that the figure referenced in this section is Figure 2.

Response: As the reviewer noticed Fig. 2 was referenced first in the previous manuscript. However, following the modification in comment 9, we have removed the reference to Fig. 2 from the **Methods** section. With this changes the order does not require any modifications.

15. Section **Clinical synergy**, Sentence 5. I suggest the authors replace “latter” with “probability that a patient responds to at least one drug in the combination”.

Response: We agree and thank the reviewer for the suggestion.

16. Section **Clinical synergy**, Paragraph 3. Shouldn’t the table referenced be Table 1?

Response: We agree and thank the reviewer for the note.

17. Section **Clinical synergy**, Paragraph 3. The authors should also report whether some standard combinations turned antagonistic.
Response: We have added a column to Table 3 to report combinations that are standard of care. There was only one antagonistic drug combinations currently used as standard of care. This observation was also added to the main text:

“In contrast, only one antagonistic drug combinations is currently used as standard of care for the corresponding cancer subtypes.”

18. Section *Quantifying agent interactions using a 2-agent approximation*, last sentence. I think it should be ORRs not ORR.

Response: We agree and thank the reviewer for the suggestion.

19. Section *Conclusions*, Paragraph 2, last sentence. “is” is missing between “what” and “expected”.

Response: We agree and thank the reviewer for the suggestion.

20. Figures 1 and 2. I think Figure 2 should be made Figure 1 and Figure 1 should be made Figure 2 because in the current version of the manuscript Figure 2 is encountered first.

Response: As the reviewer noticed Fig. 2 was referenced first in the previous manuscript. However, following the modification in comment 9, we have removed the reference to Fig. 2 from the *Methods* section. With this change the order does not require any modifications.
Reviewer 2

I only have some minor comments that the authors should consider: Throughout the manuscript I noticed a couple of awkward formulations, run-on sentences and grammatical mistakes. For example, in the study design section, the second to last sentence is one of those long run-on sentences that needs rephrasing. Another example of an awkward formulation is the last sentence on the first conclusion page that reads funny. In essence I'd like to ask the authors to go through their manuscript and 'dismantle' such language problems.

Response: We agree and thank the reviewer for the suggestion. The sentence in the Study design section has been split into two sentences:

“Recognizing the limitations of comparing response rates for each cancer type across separate trials, we chose the overall response rate as the main outcome measure. This choice was based on the assumption that most phase II trials used standard RECIST response criteria, and were powered for a clinically relevant response rate that could lead to a "go no-go" decision for a phase III study.”

We have also split the sentence in the Conclusions section:

“To evaluate the impact of targeted therapies, we focused on monoclonal antibodies. We recognize that there are many different and emerging targeted therapies such as kinase inhibitors. However, monoclonal antibodies were the only class present in a sufficient number to conduct the analysis.”

We have also revised the manuscript to correct these language problems.