Author's response to reviews

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

Authors:

Wenfeng Kang (kangwe@umdnj.edu)
Robert S DiPaola (dipaolrs@umdnj.edu)
Alexei Vazquez (vazqueal@umdnj.edu)

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Author's response to reviews: see over
Response to reviewers

We thank both reviewers for their comments and suggestions. We believe this work has improved significantly after addressing them.

Reviewer 1

Major comments

1. The benefit of using the Bayesian methods is not clearly motivated, especially noting that the parameters of the prior distributions are “non-informative”. Is it for convenience or what does the analysis gain from using Bayesian methods?

   Response: The Bayesian method is appropriate because it can systematically deal with the posterior distribution of response rates, which is necessary when dealing with Phase II clinical trials of small sample sizes. As we explain in the text, it is used to determine whether trials testing the same combination but in different cancer types have similar response rates, beyond the uncertainty due to finite sample sizes. We don’t exclude there could be other ways to address this problem. However, the Bayesian method is correct.

2. I think the major difference between the proposed analysis and the meta-analyses techniques is being able to assess synergy and antagonism. The authors should describe this difference in their paper and describe synergy and antagonism in more detail and what they add to the analysis.

   Response: We agree with the reviewer, the inference of synergy/antagonism is the major addition. We have emphasized this in the new version by rephrasing the title, adding a note in the introduction about our contribution relative to previous meta-analyses. We have also expanded the description of synergy/antagonism in the Results section, writing part of what written in the Methods in simple words.

3. I am concerned about assuming the ORRs are the same if the test used to test equality suggests so. Why not just include a random term for each trial?

   Response: We prefer to pool together cancer types when there is no evidence that the response to a combination is resulting in statistically different response rates. We believe this is a valid approximation. It is just saying that the variations seeing between cancer types are explained by the sample sizes. We believe the addition of a random term for each trial can be subject to the same concern, why adding a random term when there is no evidence for it.

4. The authors need to improve the link of the methods and results.

   Response: We have expanded the description of the results to have a better accounting of the methods used. We still prefer to leave the mathematical aspects in the methods section to make the manuscript more accessible to a general reader.

5. Can a simulation study be performed to show the operating characteristics of the methods described in the paper? This would strengthen the case for the proposed
methods.

Response: We have added a simulation testing the performance of the method to infer synergy/antagonism for two-drug combinations. The simulations show that, except for a band around the null model line, the method correctly assigns synergy and antagonism (new Fig. 2a-c).

Other comments
1. Abstract, first sentence is confusing. The first part talks about limitation of early phase trials while the second part talks about availability of data phase II trials. I think the sentences should be rewritten to say there exists a large number of phase II clinical trials but they have limitations in helping making decision for phase III trials.

Response: Corrected.

2. Background, line 1. I think it should be “phase III trials success”. “s” is missing.

Response: Corrected.

3. Background, line 4. It should be “… result in almost 5,000 two-drug combinations …” or “… result in 4,950 combinations …”.

Response: Corrected.

4. Background, last paragraph, line 2. There is a typo; it should be “assess” not “asses”.

Response: Corrected.

5. Background, last paragraph, line 6. “a” is missing before “single drug”.

Response: Corrected.

6. Study design: how is adequate number of trials (1,000 and 163) determined?

Response: Due to the effort of collecting the clinical trials information we aimed 1,000 trials. The 163 were added to collect the latest trials since our first pilot study. This is clarified in the new Methods section.

7. Section “Observed ORR”, the sentence starting with “In 142 of these combinations the data …”. What test was used to test that the trials were statistically equivalent?

Response: The Bayesian method. This has been now specified.

8. Section “Observed ORR”, the sentence starting with “In the 24 other combinations the data …”. This sentence is not clear.

Response: Corrected.

9. Section “Null model for combinations of two non-interacting agents”, the authors propose estimating p1 and p2 substituted in p12=1-(1-p1)(1-p2) using trials that are tested as single agents. I think it is strange that sometimes the authors assume ORRs are the same even for different agents (and combinations) but exclude them in this instance.

Response: This have been corrected by adding the appropriate indexes representing each pair of drugs.
10. Section “Null model for combinations of two non-interacting agents”, last expression. May be I did not follow but I thought $100\% \text{mean}(p12)$ is not equivalent to $100\%[1-(1-\text{mean}(p1)) (1-\text{mean}(p2))]$.

*Response:* p1 and p2 are measured in independent trials and therefore their posterior means are independent.

11. Section “Null model for combinations of two non-interacting agents”. Is the $p12$ used to calculate synergy same as $p12$ used to calculate antagonism so that $p_{\text{antagonism}}=1 - p_{\text{synergy}}$?

*Response:* We have “same or larger” for synergy and “same or lower” number of responses for antagonism. The fact that same “same” belongs to both makes $p_{\text{antagonism}}$ different from $1-p_{\text{synergy}}$. This is different from the case of continuous random variables where the case “same” does not contribute, unless there some singularity around that value.

12. Section “Two-agents approximation to the ORR”, second last sentence. This sentence needs to be rewritten to make it clear; may be splitting it into two sentences. Also, $J012$ (the value of $J12$ under the independence) should be defined explicitly.

*Response:* $J_{012}$ has now been properly defined.

13. Section “Statistical equivalence of trials testing the same combination”, paragraph 1. The last sentence seems incomplete.

*Response:* Corrected.

14. Section “Statistical equivalence of trials testing the same combination”, last sentence. Should be “These biases” not “This biases”.

*Response:* Corrected.

15. Section “Optimal number of agents in combination”, paragraph 1. I could not link the results presented in Figure 1 and the methods described before. In the methods, trials with “similar” ORR are assumed to have the same ORR. I assumed this is regardless of the number of combinations and so I wonder how the median ORR by the number of agents was done. Also, the authors need to report it is the median of, I think, posterior means. How were the 95% confidence intervals obtained?

*Response:* We have added a better description of the data shown in Fig. 1.

16. Section “Optimal number of agents in combination”, paragraph 2. Second sentence after the second comma, I suggest the authors rewrite this part of the sentence to “our assessment observed that the ORR for trials using monoclonal antibodies is 8% higher than _____ (54% vs 46%, …”. The authors need to state the ORR is higher than ORR for what agents (or combinations).

*Response:* Corrected.

17. Section “Clinical synergy”, paragraph 1. The authors refer Table 2 and 3 while I think it should be “Tables 1 and 2” (Note it should be Tables not Table).

*Response:* Corrected.

18. Section “Clinical synergy”, paragraph 2. May be rather than alpha-interpheron, use
alpha-interferon to be consistent with the table or vice-versa.

Response: Corrected.
Reviewer 2

Major points:

- Introduction of the concepts: by just reading the main paper it is pretty hard to understand what the authors propose. Since this paper is more a methodology article the authors may want to describe their approaches better. Without reading additional file 2 that introduces the statistical details I wasn’t able to grasp the method behind it. Therefore, I suggest to put the most important parts of this file in the Methods section.

  Response: We have rewritten some sections of the manuscript to make some of the methods more clear. We still would like to leave the technical details of the Bayesian method to the Additional file. We prefer to focus more on the methods associated with the inference of drug interactions in the main manuscript, which the main point we would like to emphasize.

- Choice of data: It appears weird that the authors would randomly choose the first bets 1,000 entries in pubmed that have trial in the title. Why is this a reasonable way to test the methodology? Wouldn’t it be better to have a more comprehensive curated data set? Also, what is the source of the 163 ‘more recent’ trials and the rationale to mix it with the random set?

  Response: We agree it may sound strange. Given the effort to extract all the information from pubmed abstracts, we aimed to collect the 1,000 most recent trials. However, after completing our first pilot we decided to add the trials that were reported from our initial search, to better represent current trends. This information has been added to the Methods section.

Minor points:

- Overall the paper appears terse and hastily put together with the expectable typos (e.g. Tables 2 and 3 mentioned in the text, while there are only 2 tables) and mistakes (e.g. Figure 2 is nowhere mentioned in the text). While it was certainly the intent of the authors to keep the paper short they may want to take the effort to make it more readable by adding more explanations as well as smooth out their phrasing. The paper has a couple of sentences that are awkward or simply unreadable. The first sentence in paragraph 2 of the background section is such an example.

  Response: We have edited the manuscript extensively to correct these typos and make the reading smoother.

- In the tables as well as Figure 2, it may be helpful to highlight the rows and data points that refer to common practice combinations.

  Response: We have followed the suggestion in the Tables. There is not much space for it in the Figure, however.

- To increase readability it would be helpful to add the data point legends to the figure instead of describing them in the figure legends.

  Response: We have followed the suggestion for Figure 2, but not for Fig. 3 due to lack of space.