Author’s response to reviews

Title: Association between the XRCC1 polymorphisms and clinical outcomes of advanced NSCLC treated with platinum-based chemotherapy: A meta-analysis based on the PRISMA statement

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Author’s response to reviews:

Dear Editors and Reviewers,

Thank you very much for your letter and for the comments concerning our manuscript entitled “Association between the XRCC1 polymorphisms and clinical outcomes of advanced NSCLC treated with platinum-based chemotherapy: A meta-analysis based on the PRISMA statement” (ID: BCAN-D-16-01768R1). We have studied comments carefully and have made correction which we hope meet with approval. The main corrections in the paper and the responds to the comments are as following:

Comments to the Author

Reviewer 1: The manuscript describes a meta-analysis about the predictive role of XRCC1 polymorphisms in lung cancer patients treated with platinum-based chemotherapy.

Although the performance of meta-analysis about the topic is interesting in itself, the authors should admit the limited clinical application of the data.

I suggest the following changes:

- please comment in the discussion about other potential predictive markers of sensitivity to platinum-based chemotherapy in lung cancer

Answer: We have comment in the discussion about other potential predictive markers of sensitivity to platinum-based chemotherapy in lung cancer. (Discussion section, line 26-50, page 14).
please discuss about the limited potential application of the data, given the results of clinical trials investigating the role of predictive markers and the detrimental effect of omit platinum (if clinically feasible) in the treatment of advanced lung cancer patients.

Answer: We have comment in the discussion about the limited potential application of the data, the role of predictive markers and the detrimental effect of omit platinum in the treatment of advanced lung cancer patients. (Discussion section, paragraph 1, page 12).

please review the language of the text

Answer: We have reviewed the language of the text to make sure that there aren’t any written errors or grammatical errors.

please check the references, for example page 7 line 8 and the lack of reference about clinical role of platinum in the introduction (the sentence is too generic anyway).

Answer: We have checked the references carefully, and found that there was a mistake with wrong reference number annotated and have made correction (Materials and methods section, line 15, page 6). Moreover, we have added reference about clinical role of platinum in the introduction. (Introduction section, line 16, page 4) And we have made a more detailed description. (Introduction section, line 16-23, page 4)

Reviewer 2:

1. There are 20 studies in Table 1 but only 19 in Figure 1. Please clarify it.

Answer: In total, 19 articles of eligible studies were included in this meta-analysis. As the study carried out by Liao et al. [Reference 20] included training set and validation set two subpopulations, each set was used as a separate study in the meta-analysis, so we show 20 studies in Table 1.

2. It is better to put Table 1 in some order with the 20 studies, maybe by Year or first author or genotype.

Answer: The 20 studies in Table 1 has been rearranged in order by Year (Table 1, page 8).
3. In the statistical analysis section, it states that "When heterogeneity was present, and the number of the studies included was large enough to perform the multivariable regression analysis, a meta regression analysis was employed to explore the sources of heterogeneity." Please show, in which model which parameters were included and comprehensively present the results (fixed, random effects, meta regression model, etc). Give the names of Stata procedures/functions used for each analysis. This should make the process of analysis easier to understand/reproduce.

Answer: In this meta-analysis, the fixed effects model was applied when the effects were assumed to be homogenous (Q test shown P value > 0.1), otherwise a random effects model was applied for meta-analysis. For example, in the “Objective response of XRCC1 194 polymorphism” part, we show “in the homozygous model, the Arg genotype was inverse associated with objective response in all patients (ArgArg vs TrpTrp: OR=0.636(95%CI: 0.442-0.914), p=0.190, PBe=0.368, PEgger=0.943, Fig. 2A).”(line 5-7, page 10), we adopted fixed effects model first, Stata command: metan “case NO. of ArgArg genotype with treatment response” “case NO. of ArgArg genotype with non-response” “case NO. of TrpTrp genotype with treatment response” “case NO. of TrpTrp genotype with non-response”, or label (namevar=study, yearvar=year). Because the result show p=0.190(> 0.1), fixed effects model is appropriate. If the result show p< 0.1, then random effects model would applied.

In Table 2, for those existed heterogeneity among studies (Ph value <0.05 and I2 value >50%), and number of studies included ≥10, we applied meta regression method to explore potential sources of heterogeneity, including year, sample size, ect. Data not showed.

4. In the sensitivity analysis section, what do you mean by "the results did not change"? Is there any detail of the result? Also, the 19 studies were published ranged from 2004 to 2014, did you perform a sensitivity analysis on time of published years?

Answer: In the sensitivity analysis section, "the results did not change" means in the meta-analysis part, if pooled OR value or pooled HR value >1, pooled OR value or pooled HR value still >1 in the sensitivity analysis; if pooled OR value or pooled HR value <1, pooled OR value or pooled HR value still <1 in the sensitivity analysis; if pooled OR value or pooled HR value range includes 1, pooled OR value or pooled HR value range still includes 1 in the sensitivity analysis. To do improvements to the English language, "the results did not change" was replaced by "the conclusion remain unchanged". (line 21,23, page 12)

In Table 2, we showed the results when the study of small sample (sample size≤100) was excluded. (page 10)
Additionally, we performed a sensitivity analysis on time of published years. We excluded the papers published before 2009, and performed meta-analysis. Detailed results were showed in Table 2.