Author's response to reviews

Title: Association between CHEK2 H371Y Mutation and Response to Neoadjuvant Chemotherapy in Women with Breast Cancer

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December 26, 2014

Re: ID 1308785163143994, “Association between CHEK2 H371Y Mutation and Response to Neoadjuvant Chemotherapy in Women with Breast Cancer”

Dear BMC Cancer Editors,

Thank you very much for reviewing this paper.

We have revised this paper according to the reviewer’s comments. The changes were highlighted with yellow.

How we have met the reviewer’s comments is listed on the separate letter.

Yours sincerely,

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Reply to Reviewer 1

major comment
the material on three year recurrence free survival is premature. should be removed. revisit cohort in three years and report on five year overall survival. Three year recurrence free survival is not a valid indicator of progression. compare the pcr rate to that of BRCA1 carriers in recent paper by Byrski et al. the difference is very large and might discuss possible reasons discuss the potential use of neoadjuvant therapy in chek2 carriers discuss the potential for genotyping cases at diagnosis for chek2 and other mutations.

R. Agree. Due to the relatively short follow-up, we use the 5-year distant disease-free survival rather than overall survival. Byrski et al. paper is cited and we add the discussion in the revised version. BRCA1 is critical for the DNA-repair and BRCA1 mutation carriers are extremely sensitive to cisplatin-based neoadjuvant chemotherapy. It would be interest to investigate whether CHEK2 H371Y mutation carriers are sensitive to cisplatin. (p12, 2nd paragraph of the revised version)

Reply to Reviewer 2

1) Although the author previously failed to identify to detect the 1100delC mutation in Chinese woman it would be worth to screen the much larger patient collective of this study for the presence of this mutation.

R. Since the primers used in this study covered the CHEK2 1100delC mutation, none CHEK2 1100delC was found in the current study. (p8, 2nd paragraph of the revised version)

2) There is a recent study from Kriege et al (Br J Cancer. 2014 Aug 26;111(5):1004-13) that investigated the sensitivity to adjuvant chemotherapy in CHEK2-mutated versus non-CHEK2 breast cancer patients under adjuvant chemotherapy. In this study the CHEK2 1100delC-associated breast cancers were associated with a higher contralateral breast cancer rate as well as worse survival measures beyond 6 years after diagnosis and no differential sensitivity to adjuvant chemotherapy. The author should include this study in the discussion.

R. Kriege et al study is cited. Kriege et al found that breast cancer patients with CHEK2 1100delC mutation had a worse survival beyond 6 years after diagnosis.
than did non-carriers. In our study we found CHEK2 H371Y mutation carriers had a slightly worse survival than non-carriers within 5-years after diagnosis, it would be interest to see the survival impact of the CHEK2 H371Y mutation in a long-term follow-up. (p11, 4th paragraph of the revised version)

A total of 39 woman were carrier of CHEK2 H371Y, and only 13 achieved a pCR. These were further stratified in different therapy group i.e. anthracycline-treated, anthracycline/taxane-treated, taxane-treated subgroup which resulted in very small sample sizes (18, 10, and 11). From my perspective the authors should state the statistical power and discuss the limitation of sample size in more detail.

R. Agree. The sample size of CHEK2 H371Y mutation carriers is small, particularly when the mutation carriers were stratified in several treatment groups; therefore, the results are premature and should be interpreted cautiously. (p12 and 13, the revised version)

4) The author report a better response to neo-adjuvant chemotherapy and higher pCR rates for CHEK2 H371Y carrier than non-carriers, but a worse RFS. How can this be explained especially since CHEK2 mutations have previously been associated with chemoresistance?

R. Only small subset of CHEK2 mutation carriers reached a pCR, the majority of mutation carriers did not reach a pCR and might have an aggressive phenotype. (p12, 1st paragraph of the revised version)

- Minor Essential Revisions

1) Line 149: It would be beneficial to the reader if the author briefly explain how pCR was evaluated rather than just referring to previous studies.

R. the pCR is already clearly defined and references are also cited. (p7, 2nd paragraph of the revised version)

2) The authors should briefly discuss recentlz published studies regarding CHEK2 mutation analysis, e.g. Rashid et al. BMC Cancer 2013, 13:312, Baloch et al. Mol Biol Rep. 2014.

R. Thanks for the reviewer’s suggestion. These papers may not be associated with the current study.

- Discretionary Revisions

3) Line184: Please also include absolute numbers in addition to percentages.

4) Line 209: Please add percentages.
5) Line 477: Space missing between CHEK2 and H371Y, also the author might include a space between figures and (%).

R. Changes are made.