

## 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>	Efficacy of oral administration of cystine and theanine in colorectal cancer patients undergoing capecitabine-based adjuvant chemotherapy after surgery: study protocol for a multi-institutional, randomized, double-blinded, placebo-controlled, phase II trial
<b>AUTHORS</b>	Hamaguchi, Reo; Tsuchiya, Takashi; Miyata, Go; Sato, Toshihiko; Takahashi, Kenichi; Ariyoshi, Keisuke; Oyamada, Shunsuke; Iwase, Satoru

### VERSION 1 – REVIEW

<b>REVIEWER</b>	Yazhou He West China School of Medicine, West China Hospital, Sichuan University, China.
<b>REVIEW RETURNED</b>	01-Mar-2018

<b>GENERAL COMMENTS</b>	<p>Hamaguchi et al. designed this trial to investigate efficacy and safety of cystine and theanine in reducing adverse event after capecitabine chemotherapy. This is a topic of merits. I have following comments:</p> <ol style="list-style-type: none"><li>1. Throughout the manuscript, authors should state somewhere about the treatment involving radiotherapy for rectal cancer patients.</li><li>2. The authors stated on page 7 that studies on the efficacy of adjuvant chemotherapy using UFT/LV versus capecitabine have not been performed yet. I have some doubts about that. In adjuvant setting for stage III colon cancer, the non-inferiority of capecitabine has been identified by Twelves et al, N Eng J Med.</li><li>3. Although only patients with a PS score less or equal to 1 are included. I would still be interested to see if the authors considered the performance status as a stratification factor? Since this factor could influence the tolerance on chemotherapy.</li><li>4. Could the authors explain why they adopted a one-sided test at an alpha of 5%, but planned to estimate a 90% CI? Currently, a rule of thumb could be a two-sided test with an alpha level of 0.05 and a 95% CI.</li></ol> <p>Minor issues: Page 7, line 41 it should be "have" instead of "has"</p>
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<b>REVIEWER</b>	Paul S Rooney department of surgery, royal liverpool hospital, prescot street, liverpool L, L78XP, UK
<b>REVIEW RETURNED</b>	09-Mar-2018

<b>GENERAL COMMENTS</b>	well written an interesting solution to a difficult problem will enable a larger study to take place if findings are positive the study is credible
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**VERSION 1 – AUTHOR RESPONSE**

Reviewer: 1

Reviewer Name: Yazhou He

Institution and Country: West China School of Medicine, West China Hospital, Sichuan University, China.

Please state any competing interests: None

Please leave your comments for the authors below

Hamaguchi et al. designed this trial to investigate efficacy and safety of cystine and theanine in reducing adverse event after capecitabine chemotherapy. This is a topic of merits. I have following comments:

1. Throughout the manuscript, authors should state somewhere about the treatment involving radiotherapy for rectal cancer patients.

Response:

We agree that a description regarding radiotherapy for rectal cancer patients should be added to the manuscript. We have hence inserted the following sentence to the Introduction section of the revised manuscript (page 6, lines 10–12).

“For rectal cancer patients, a combination of radiotherapy with chemotherapy before surgery may be a treatment option.”

2. The authors stated on page 7 that studies on the efficacy of adjuvant chemotherapy using UFT/LV versus capecitabine have not been performed yet. I have some doubts about that. In adjuvant setting for stage III colon cancer, the non-inferiority of capecitabine has been identified by Twelves et al, N Eng J Med.

Response:

As pointed out by the reviewer, our description “the studies on the efficacy of adjuvant chemotherapy using UFT/LV versus capecitabine have not been performed yet” is incorrect, and we thank the reviewer for pointing this out. We have hence deleted this sentence and added the following description to the revised manuscript (page 7, lines 11–13).

“Furthermore, the noninferiority of adjuvant capecitabine compared with 5-FU/LV treatment regarding disease-free survival was reported in a randomized phase III trial [5].”

We also included the following additional reference, as appropriate:

Reference no. 5: Twelves C, Wong A, Nowacki MP, et al. Capecitabine as adjuvant treatment for stage III colon cancer. N Engl J Med 2005;352:2696-704.

3. Although only patients with a PS score less or equal to 1 are included. I would still be interested to see if the authors considered the performance status as a stratification factor? Since this factor could influence the tolerance on chemotherapy.

Response:

We agree that the performance status can be a stratification factor. However, we expected the number of patients with PS1 who would be enrolled in this trial would be very small compared with

patients with PS0. We included both patients with PS0 and PS1 in this trial without setting PS as a stratification factor, to recruit a sufficient number of patients for the study.

4. Could the authors explain why they adopted a one-sided test at an alpha of 5%, but planned to estimate a 90% CI? Currently, a rule of thumb could be a two-sided test with an alpha level of 0.05 and a 95% CI.

Response:

We appreciate the reviewer's constructive comments. Firstly, because we were not interested in cystine and theanine treatment being significantly inferior to placebo, we adopted a one-sided test. Secondly, this trial was a phase II trial and we considered that feasibility should be given priority. Therefore, we adopted a one-sided alpha level of 0.05 to control the sample size to be a practical size. From the above, we adopted a one-sided test (one-sided alpha level of 0.05) and a 90% CI (two-sided alpha level of 0.10).

Minor issues:

Page 7, line 41 it should be "have" instead of "has"

Response:

We thank the reviewer for pointing out our mistake. However, in accordance with comment 2, we have deleted this sentence from the manuscript.

Reviewer: 2

Reviewer Name: Paul S Rooney

Institution and Country: Department of surgery, royal liverpool hospital, prescot street, liverpool L, L78XP, UK

Please state any competing interests: none declared

Please leave your comments for the authors below

well written an interesting solution to a difficult problem  
will enable a larger study to take place if findings are positive  
the study is credible

Response:

We appreciate the reviewer's positive comments.

FORMATTING AMENDMENTS (if any)

Required amendments will be listed here; please include these changes in your revised version:

1.Box not embedded

- Kindly embed your "Box 1" file. Tables and Boxes should be placed in the main text where the table or box is first cited. Tables or boxes must be cited in the main text in numerical order. Please note that tables and boxes embedded as Excel files within the manuscript are NOT accepted. Do not upload your table and box separately.

- Please make sure that your Tables and Boxes are on editable format.

Response:

We have embedded Box 1 and Table 1 and 2 appropriately in the revised manuscript, and have confirmed that they are in an editable format.

We also updated and made minor corrections to the authors' institutions.

### VERSION 2 – REVIEW

<b>REVIEWER</b>	Yazhou He West China School of Medicine/West China hospital
<b>REVIEW RETURNED</b>	13-May-2018
<b>GENERAL COMMENTS</b>	All the comments have been addressed.