Author's response to reviews

Title: Optimal schedule of adjuvant chemotherapy with S-1 for stage III colon cancer: study protocol for a randomized controlled trial

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Author's response to reviews: see over
DEAR PROF. DOUG ALTMAN, CURT FURBERG, JEREMY GRIMSHAW, AND PETER ROTHWELL

WITH THIS COVER LETTER, WE WILL SUBMIT THE REVISED MANUSCRIPT OF A STUDY PROTOCOL ENTITLED "OPTIMAL SCHEDULE OF ADJUVANT CHEMOTHERAPY WITH S-1 FOR STAGE III COLON CANCER: STUDY PROTOCOL FOR A RANDOMIZED CONTROLLED TRIAL", BY YOSHIMURA ET AL, FOR PUBLICATION IN TRIALS. WE WOULD LIKE TO THANK REVIEWER, CHIRSTOPHER CARROLL, FOR THE CAREFUL AND CONSTRUCTIVE REVIEWS. BASED ON THE COMMENTS FROM THE REVIEWER, WE HAVE MADE CHANGES OF THE MANUSCRIPT, WHICH ARE DETAILED BELOW.

**REPLY TO THE INSTRUCTION BY EDITORS**

**Comment:** Title: please ensure the title conforms to journal style for study protocol articles. The title should follow the format _______________: study protocol for a randomized controlled trial.

**Answer:** We made a change in the title as “Optimal schedule of adjuvant chemotherapy with S-1 for stage III colon cancer: study protocol for a randomized controlled trial” as you instructed.

**REPLY TO THE EVALUATION BY REVIEWER, CHIRSTOPHER CARROLL**

1. **Comment**

Are sufficient details provided to allow replication of the work or comparison with related analyses: if not, what is missing?

Yes, on the whole.

p.11: Is there a threshold for "and adequate hematological, liver and renal functions"?

p.13: How is follow-up to be conducted? How is attrition to be minimised?

**Answer:** In this trial, we set the thresholds. The following criteria is added in the manuscript to clarify the thresholds for adequate hematological, liver and renal functions.

p.11: and adequate hematological, liver and renal functions as below.

i) White blood cell count of $\geq 3,500/\text{mm3}$ and $<12,000/\text{mm3}$.

ii) Neutrophil count of $\geq 3,500/\text{mm3}$.

iii) Hemoglobin of $\geq 9.0 \text{ g/dL}$.

iv) Platelets of $\geq 100,000/\text{mm3}$.

v) Total bilirubin of $\leq 2.0 \text{ mg/dL}$.
vi) AST of $\leq 100$ IU/L and ALT of $\leq 100$ IU/L.

vii) Creatinine level of $\leq 1.2$ mg/dL.

viii) Creatinine clearance of $\geq 60$ mL/min.

And, in this trial, we have a detailed follow-up plan to minimize attrition. The detailed follow-up plan is added in the manuscript as follow.

p.14: All the patients will be evaluated every 3 months for the first 3 years after surgery and every 6 months for the next 2 years. The evaluation included a physical examination, a complete blood count, blood chemical tests, and serum tumor markers. Computed tomography will be performed every 6 months.

2. Comment
Is the writing acceptable?
Yes, on the whole.

pp.12-13 is written in past tense, but should be future (this is a protocol), e.g. "treatment will be discontinued if ..."

Also, there is the odd typo, e.g. p.6: "a favorable results" - delete "a"; p.9: "participating institutions included" - should be "include"; p.11: "PATIENT REGISTARION"; p.16: "financial supports" - should be "support"

**Answer:** Corrected. Now pp.12-14 is written in future tense. All the odd typos, which the reviewer kindly indicated, were corrected.

3. Comments:
I would take issue with the statement in cover letter and manuscript that "Although S-1 has not been approved yet as a standard treatment in an adjuvant setting, it is likely to become an important treatment option in the near future." This overstates the case, I think. The authors provide no evidence to support this claim, only the success of the therapy in another population in a single trial; there is a difference between something being a "promising option" (as the authors also claim) and a likely "important treatment option in the near future".

**Answer:** We agree with the comment. We made changes of the manuscript as below.

p.5 (abstract): **Discussion:** Although S-1 has not been approved yet as a standard treatment of colon cancer in an adjuvant setting, it is a promising option.

p.15: Although S-1 has not been approved yet as a standard treatment in an adjuvant setting, it is a promising option.
4. Comments

p.6 "This study compared uracil and tegafur (UFT)/LV with 5-FU/LV as an adjuvant chemotherapy for patients with stage III colon cancer, and demonstrated that the 3-year disease-free survival (DFS) of all patients was 78.6%." Was this the FU result? If across both arms, what was it in each arm?

**Answer:** This results that we referred in the manuscript was 3-year disease-free survival (DFS) of all patients, that is, results of combined arm. We made a change of the manuscript to refer the result of each arm as below.

p.6: This study compared uracil and tegafur (UFT)/LV with 5-FU/LV as an adjuvant chemotherapy for patients with stage III colon cancer, and demonstrated that the 3-year disease-free survival (DFS) was 77.8% in UFT/LV arm and 79.3% in 5-FU/LV arm, respectively.

In the manuscript, we highlighted and undelined all changes made when revising the manuscript.

We appreciate the comments from the reviewer. Thank you for reviewing our manuscript. I believe that our paper will appeal to readers of your journal. I look forward to receiving a positive reply.

Respectfully yours,

Keisuke Uehara, Corresponding author