Author's response to reviews

Title: Quality-of-life evaluation for advanced non-small-cell lung cancer: a comparison between vinorelbine plus gemcitabine followed by docetaxel versus paclitaxel plus carboplatin regimens in a randomized trial: Japan Multinational Trial Organization LC00-03 (BRI LC03-01)

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Author's response to reviews: see over
RE: Resubmission of our manuscript entitled “Quality-of-life evaluation for advanced non-small-cell lung cancer: a comparison between vinorelbine plus gemcitabine followed by docetaxel versus paclitaxel plus carboplatin regimens in a randomized trial: Japan Multinational Trial Organization LC00-03 (BRI LC03-01)”.

Dear. Editor of BMC Cancer

Thank you for reviewing our manuscript “Quality-of-life evaluation for advanced non-small-cell lung cancer: a comparison between vinorelbine plus gemcitabine followed by docetaxel versus paclitaxel plus carboplatin regimens in a randomized trial: Japan Multinational Trial Organization LC00-03 (BRI LC03-01)” (MS: 1114274519428562). As suggested, I am here by sending a revised manuscript that has been altered in response to your comments.

I wish to thank you for your feedback, which I believe has helped to improve our paper. I appreciate the opportunity to resubmit our paper, and I hope that you will now find our paper acceptable for publication.

Sincerely yours

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Specific changes made in response to comments by each reviewer are described below.

**Reviewer's report**

**Title:** Quality-of-life evaluation for advanced non-small-cell lung cancer: a comparison between vinorelbine plus gemcitabine followed by docetaxel versus paclitaxel plus carboplatin regimens in a randomized trial: Japan Multinational Trial Organization LC00-03 (BRI LC03-01)

**Version:** 1  **Date:** 7 September 2010

**Reviewer:** Prunella Blinman

**Reviewer's report:**

This paper reports a study of the quality of life of patients with non-small-cell lung cancer during a randomised trial. Whilst this is a relevant clinical question, my overall impression is the paper is too brief (1800 words), lacks sufficient methodological detail, and the discussion and conclusion do not flow from the results obtained from the study.

**Major Compulsory Revisions**

1. page 5-6, QOL assessment, Methods.

   Each QOL instrument was described. Please clarify:
   - how many times the patients completed the FACT-G
     
     **Response:** Four times. We added some sentences in the Methods section (lines 15-18 on Page 5).
   
   - were the QOL instruments completed in English or Japanese?
     
     **Response:** We added that it was the QOL instruments of Japanese version in the Methods section (lines 21on Page 5, lines 5 and 10 on Page 6).
   
   - have the FACT-Taxane & FACIT-Sp been validated in patients with lung cancer
     
     **Response:** The FACT-Taxane & FACIT-Sp have been validated in patients with lung cancer.
   
   - has FACT-Taxane been validated in regimens with vinorelbine?
     
     **Response:** The validity of FACT-Taxane was not confirmed for regimens with vinorelbine.
   
   - why was a minimum of 50% subscale completion chosen for the FACT-G (& not 80% as specified in the next sentence)
     
     **Response:** We deleted sentences to ‘A subscale score was computed when 50% or more of the items had been answered. The FACT-G score is considered valid only when more than 80% of the items are complete’ in the Methods section, because it
was a confusing sentence. We added some sentences to the Methods section (lines 20-22 on page 6).

Suggest a Figure showing schema of parent trial & current QOL study.

Response: We added a new figure (Fig1) for showing the trial profile.

2. page 6-7, Statistical considerations, Methods

Please explain:

Response: This study (BRI LC03-01) was conducted as one of the additional studies of JMTO LC00-03 trial.

- rationale for sample size of 200

Response: We added to rationale for sample size 200 the Methods section (lines 9-10 on page 7).

- why ‘only 190 patients were potential candidates for the QOL study’

Response: We deleted a sentence to ‘only 190 patients were potential candidates for the QOL study’ in the Methods section, because it was a confusing sentence.

- provide power estimation

Response: We cannot provide power estimation in this study, because we didn’t calculate our sample size based on statistical considerations.

- been asked to enter since January 2004’?

Response: We began the preparations for this study after a JMTO LC00-03 trial start. It took the time to get approval of this study than we planned.

- why the study was commenced mid-way through the trial

Response: The opinion that it wanted to evaluate QOL based on not only an objective endpoint to treatment but also a subjective evaluation of the patient came out after the start of the JMTO LC00-03 trial from the investigator. Therefore, this study was planned.

- what the FACIST scoring guidelines are

Response: “FACIST scoring guidelines” was a guideline that provided for the rule concerning the scoring and missing data handling by the organization which developed and administrated the questionnaire. We added FACIT website address (FACIT : http://www.facit.org) as a reference to the Methods section (lines 20 on page 6).

- what difference in QOL scores was considered to be clinically meaningful?

Response: We was not consider to be clinically meaningful, because we didn’t
calculate our sample size based on statistical basis

- how will the groups be compared eg comparisons of means, slopes etc
  Response: QOL assessments in a group-based analysis were performed by analyzing changes of the mean scores over the course of treatment with a general linear mixed-effects model. (See, Statistical Considerations)

- if subgroup analyses were post-hoc or pre-specified
  Response: Subgroup analyses were ‘post-hoc’.

3. page 7-8, Results
Please clarify:
- why only 84 patients (& not the planned 200) entered this study
  Response: We assumed sample size 200 patients. It was possible to actually participate in this study only by 14 institutions among 45 participated institutions of the JMTO LC00-03 trial. 109 subjects participated in the JMTO LC00-03 trial from 14 institutions during the enrolled period of this study. 81 patients were finally enrolled for the reason such as not obtaining informed consent.

- why patients were excluded if <80% of any QOL instrument was completed because this contradicts statement in methods, referred to in comment (2)
  Response: As per FACIST scoring guideline, the QOL score was not computable.

- whether the patients in this study were similar to those in the parent study
  Response: The patient’s characteristics were similar to those in the parent study.

4. Page 8, Results. Last sentence of results should state that there is no difference in QOL between the sexes, rather than they were similar.
  Response: As the reviewer notes, we corrected a sentence to ‘This indicates that the sexes showed no difference tendencies for change in FACT-Taxane score between the two treatment groups.’ in the Results section (lines 13 on page 9).

5. Page 9, Discussion. ‘The present BRI LC03-01 study QOL evaluation demonstrates that patients treated with the VGD regimen generally experienced an improvement in their QOL compared with patients in the PC group, but only in terms of the FACT-Taxane questionnaire’ is misleading & does not reflect the results ie only a difference in slope of FACT-T.
  Response: As the reviewer notes, we changed to a sentence ‘The present BRI LC03-01 study QOL evaluation demonstrates that patients treated with the VGD regimen generally experienced an improvement in their QOL compared with patients in the PC group, but only a difference in slope of FACT-Taxane questionnaire’ in the Discussion section (lines 24 on page 9 - lines 2 on page 10).

5. Page 9, Discussion. ‘In terms of general health, patients receiving the VGD regimen had better QOL than those receiving PC treatment, as assessed by the
FACT-L, FACT Taxane and FACIT-Sp scores’ does not follow from results ie mean scores were no different. Provide evidence to support or revise.

Response: The difference in slope of FACT-Taxane was only statistically significant in this study. However, the VGD group was almost a level-off regardless of the time passage while the score had fallen whenever time passed in the PC group in each questionnaire. It was possible to interpret it from Fig 2. We added to the description of evidence to support (lines 2-5 on page 10).

6. Page 9, Discussion. JMTO LC00-03, a randomized trial of the VGD and … and progression-free survival (median survival time, 5.5 versus 5.8 months)’- how does this relate to the results of the QOL study?

Response: Some previously studies have suggested that there is the relationship between long time survivor and QOL. However, there was no previous study to which the influence of QOL on progression-free survival was evaluated. The influence of QOL on progression-free survival was not evaluated from the result of the present study. We deleted the description of progression-free survival in the Discussion section.

7. Page 9, Discussion. ‘We can be reasonably confident … was clinically meaningful,…’ doesn’t follow from results. What QOL improved? Clinically meaningful change in scores not defined. Provide evidence to support or revise.

Response: As the reviewer notes, we not defined clinically meaningful change in scores. In this study, the QOL improvements were not found. The QOL scores of patients with non-small cell lung cancer usually decrease at time. However, the QOL score is maintained though treatment advances in the VGD group. The possibility that the influence on QOL according to treatment is a little is suggested compared with the PC group as for the VGD group (lines 17-21 on page 10).

8. Page 9, Discussion. ‘Furthermore, Fossella et al. investigated … as first-line chemotherapy’ not comparable to current study where vinorelbine & docetaxel were in the same regimen. Most importantly, the authors have not considered that vinorelbine can also cause peripheral neuropathy anywhere in the paper.

Response: Your concern is reasonable; we deleted this reference and a related description. We added to incidence of grade 3 and 4 peripheral neuropathy in the Discussion section (lines 14-17 on page 10).

9. Page 10, Discussion. There are definitely more than one limitation to this study, suggest expand this part of the study & explain how the limitations of the study may affect the results?

Response: As the reviewer notes, we added limitation of this study to the Discussion section (lines 1-11 on page 11).

10. Page 10, Discussion. Poor compliance with QOL …potentially producing biased results’. Not relevant to the results as the authors state that the study has good compliance, likely because only those patients who completed >=1 QOL assessment were included.

Response: As the reviewer notes, we added the rate of the QOL questionnaire
completed at the time of all among the patients who completed the study treatment in the Discussion section (lines 15-17 on page 11).

11. No discussion of strengths of study, & clinical & research implications.
   Response: We added strength of study, clinical and research implications in the Discussion section (lines 18-20 on page 11).

12. Page 10, Conclusion. Doesn’t all follow from results and discussion.
   Response: We revised our manuscript the interpretation of data according to the comment from you in the all Conclusion section (lines 22 on page 11 to lines 5 on page 12).

Minor Essential Revisions

1. Page 4, study population, methods- please insert where the study was performed. ? did all centres participating in the parent trial participate, or just some?
   Response: Your concern is reasonable; we added the number of participated institutions of this study to the Methods section (lines 23 on page 4)

2. Page 7, results- extra word QOL- ‘and four patients QOL filled in…’
   Response: I am afraid that it was our mistake. We corrected a sentence to ‘and four patients filled in…’ in the Result section.

3. page 7, results- suggest commence new paragraph @ ‘Table 1..’
   Response: As the reviewer notes, we made a new paragraph.

4. page 8, results- suggest new paragraph @ ‘Compliance…’
   Response: As the reviewer notes, we made a new paragraph.

5. Suggest use a Figure to explain the patient recruitment
   Response: As the reviewer notes, we added trial profile to the new Figure1.