Author's response to reviews

Title: Randomized phase 3 open-label trial of first-line treatment with gemcitabine in association with docetaxel or paclitaxel in women with metastatic breast cancer: a comparison of different schedules and treatments

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Author's response to reviews: see over
Florence, 14 Feb. 2013

Dr Thomas Ruhstaller

BMC Cancer

Dear Dr Ruhstaller

We thank you and the peer-reviewers for an accurate and useful revision and for the valuable feedback of our manuscript "RANDOMISED PHASE 3 OPEN-LABEL TRIAL OF FIRST-LINE TREATMENT WITH GEMCITABINE IN ASSOCIATION WITH DOCETAXEL OR PACLITAXEL IN WOMEN WITH METASTATIC BREAST CANCER: A COMPARISON OF DIFFERENT SCHEDULES AND TREATMENTS" (MS: 1616910620855100).

We have revised the previously submitted version taking into account reviewers’ feedback. Changes made to the previous version are highlighted in red within the manuscript body.

Moreover, we are including after this letter detailed answers to reviewers’ feedback. Reviewers’ comments are reported in bold italicized text while answers are in normal text (newly added text is reported in red). We strongly hope the revised manuscript is now suitable for publication in the BMC Cancer.

We look forward to your final decision.

The authors
Editor’s comment:
This is an interesting manuscript. The two reviewers find some important issues which have to be solved to improve the manuscript. However, the main issue is about the independence of the results of this study.
We thank the editor for the positive opinion towards the manuscript, and we are glad to answer his questions to solve the issue about independence of the results of the study.

Five authors are or were employees of Eli Lilly.
Eli Lilly & Co endorses ICMJE (International Committee of Medical Journal Editors) authorship criteria and all the authors that are or were employees met all the tree authorship criteria. Details about contribution of each author are listed in the “authors’ contribution” section.

The manuscript was written by a medical writer not presented in the list of authors and not as usually by the first author.
Seeking the support of professional medical writers is a common practice and Eli Lilly & Co recognizes this support giving credits in the acknowledgement section of manuscripts when appropriate. Medical writers are recognized professionals specialized in different areas, including scientific communication. Through their competency, accurate papers which meet publication guidelines and standards can be submitted to journals and delivered to audiences in an effective manner. The manuscript was extensively and substantially revised by principal investigators (S. De Placido, F. Cognetti) and by the first author (L. Del Mastro). Moreover, provided that professional medical writers do not fulfill all the ICMJE authorship criteria endorsed by the company, it would not be appropriate to include them in the authors byline.

Several questions have to be answered before accepting this manuscript:
Who is the owner of the database?
The database is owned by Eli Lilly & Co, who fully sponsored this study as declared in the manuscript

Who did the data cleaning? was that an from the company independent organisation?
Data cleaning was performed by AAI Pharma (Madrid), an independent organization contracted by Eli Lilly to complete this process.

Who did the final analysis? Was the statistical analysis done by an employee of Eli Lilly?
Statistical analysis was performed by the IRCCS AOU San Martino - IST - National Institute for Cancer Research, UO Epidemiologia Clinica, Genoa, Italy under the leading of Dr P. Bruzzi and D.F. Merlo. The statistical analysis was coordinated by G. Kazeem (former contractor employee of Eli Lilly UK), P. Bruzzi and D.F. Merlo. Other company employees who participated in the data analysis were M. Ceccarelli and P. Marchi. Data interpretation was mainly performed by P. Bruzzi, DF Merlo, L. Del Mastro, M. De Laurentiis, A. Fabi

Who has paid the medical writer?
Medical writing support was provided by Dr L. Cantini and payed by Eli Lilly & Co.
Who did the monitoring of the participating centers?
Monitoring of the participating centers was done by the following CROs (Contract Research Organizations):
- Farma Resa S.r.l (Cantù, Italy): From the beginning of the study until May 2009
- ICON: From May 2009 to the end of the study.

Reviewer’s #1 report:

1. Major Compulsory Revisions
In the “Background Section” you have cited papers reporting the superiority of the doublets Paclitaxel/Gemcitabine and Docetaxel/Capecitabine and the better tolerability of the doublet Docetaxel/Gemcitabine. These were the data available at the time of the study development. Meanwhile several papers and reviews (i.e. Nielsen JCO 2011; Qi Breast 2012) have reported results showing less or no advantage in adding gemcitabine to taxane and discussed that in general the taxane doublets are not more effective than single-agent therapy in unselected patients. I would suggest to enter a comment about this in your discussion and in the conclusion.
We thank the reviewer for this suggestion. We believed worth to include comments about recent results that were not available at the time the present study was developed. We included in the discussion section the following paragraph:

A recent paper [Nielsen] reported that the addition of Gemcitabine to docetaxel failed to prove any clinically meaningful benefit, given that no significant changes in OS were detected as compared to the taxane group. Although our study was not designed to compare double agents vs single agent therapy, it is worth to note that the study from Nielsen and co-worker was not powered to detect a benefit in survival. On the other hand, the combination Gemcitabine-Docetaxel showed increased TTP as compared to docetaxel only. With more caution, Qi et al in the recently published metanalysis aiming to compare double agents vs single agent therapy in MBC setting, report that the role of combination therapy in MBC setting is still unclear, although combination chemotherapy offers significant improvement in ORR and PFS.

2. Minor Essential Revisions
Did you used RECIST1.0 or 1.1? Please specify
The RECIST version has been clarified within body manuscript and tables. The study protocol endorsed the RECIST 1.0 version.

3. Discretionary Revisions
Figure 1: change legend to: CONSORT diagram summarizing patients eligible for the study

Reviewer’s # 2 report:
It's an interesting and well written paper
We thank the reviewer for the overall positive opinion on our manuscript

METHODS
1) Minor Essential Revisions:
Paragraph “outcome measures”: please precise the version of RECIST 1.0 versus 1.1?
As indicated in the answer to the comment of reviewer #1, the RECIST version has been clarified within body manuscript and tables. The study protocol endorsed the RECIST 1.0 version.

2) Minor Essential Revisions:
The definition of “stable disease” is not clear in your description: any patient without progression after 9 weeks?
We thank the reviewer for the comment. Stable disease has now been defined in accordance with the definition reported in the study protocol. The manuscript has been modified as follow:

A maximum of 6 cycles was scheduled in case of stable disease (SD, defined as neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progression taking as reference the smallest sum of the longest diameters since the treatment started), to be continued up to 10 cycles for observed partial or complete response, respectively.

RESULTS
3) Minor Essential Revisions:
Could you please describe the recruitment period of the study and the median follow up?
The recruitment period has been included in the “Results” section, “patient disposition and treatment compliance” subsection. Unfortunately, the median type of follow-up is not available. The manuscript has been modified as follow:

Overall, 241 patients were enrolled between September 2005 and August 2010, and were randomised as follow: […]

4) Minor Essential Revisions:
Patient disposition and treatment compliance, last paragraph: “Treatment-related discontinuations occurred in 6.7%, 6.2%, 10.3% and 13.6% of patients in Arms A, B, C and D…”, but in the figure 1 only one third of the patients completed the study: is one of the conclusions of the study that the feasibility of these regimen is limited?
As the reviewer correctly pointed out, the figure one shows that only one third of the patients completed the study. As depicted by the same figure, half of the patients discontinued the study for lack of efficacy. Thus, based on these results, we cannot conclude that feasibility of this regimen is limited.
On the other hand, as we believe that reporting only the percentages of treatment-related discontinuations may be misleading, we added the following wording to the text:
The median number of administered chemotherapy cycles was 6 in all arms. Treatment-related discontinuations occurred in 6.7%, 6.2%, 10.3% and 13.6% of patients in Arms A, B, C and D, respectively, while almost 50% of discontinuations were due to lack of efficacy (see also Figure 1 for details).

DISCUSSION

5) Minor Essential Revisions:
In your study and in your abstract and paper conclusions, you mix paclitaxel weekly with docetaxel weekly. The superiority of weekly paclitaxel over 3-weekly paclitaxel was shown in neoadjuvant, adjuvant and metastatic setting. This was not the case for docetaxel. Therefore it could be useful to stress in your conclusions the existence of these trials and the fact that the good results of the weekly taxanes is probably driven by paclitaxel.

To address the reviewer’s comments, the conclusion section now include also the following text highlighted in red:

Moreover, the results of this study confirm data from various studies supporting weekly taxane dosing as an active regimen in MBC, even in heavily pretreated, refractory disease and in elderly patients or those with poor performance status [9]. It is reasonable hypothesize that results obtained with the weekly schedule might be driven by paclitaxel. In fact, it has been previously reported that weekly administration of paclitaxel has superior efficacy over the three weekly schedule coupled with different toxicity profile [6,10] while weekly docetaxel schedule proved to be at least as efficacious as tree weekly schedule [6,11]. However, a recent review has concluded that use of paclitaxel in advanced BC given in a weekly regimen gives overall survival advantages compared with the standard every three weeks regimen [12].

6)Minor Essential Revisions:
The study arms were different in term of taxane (paclitaxel vs docetaxel) and schedule (weekly vs 3-weekly) but also in term of dose intensity of gemcitabine: Arm A=1000 ArmB=1250 ArmC and D=800 used for different durations (A and B vs C and D). The potential impact of gemcitabine dose intensity is not discussed in the conclusions.

We thank the reviewer for the comments. The different dosages of study drug and combined taxane were choosen based of the following rationale:

- **Arm A**: Data from Spielman et al [1] Docetaxel 75mg/m² in combination with Gemcitabine show that the dose 75 mg/m² of Docetaxel administered intravenously on day 1 with Gemcitabine 1000 mg/m² administered intravenously on day 1 and day 8 is safe and effective.

- **Arm B**: In a large randomized phase III trial [2], Gemcitabine 1250 mg/m² administered intravenously on day 1 and 8, in combination with Paclitaxel 175 mg/m² administered intravenously on Day 1, was demonstrated to be superior to single agent Paclitaxel 175 mg/m² administered intravenously on Day 1 in term of time to progressive disease and overall survival.
• **Arm C:** Data valuating the weekly combination [3,4] Gemcitabine 800 mg/m², 30 min i.v infusion on day 1, 8,15 every 28 days and Docetaxel 30 mg/m², 30-60 min i.v. infusion on day 1,8,15 has proven to be effective and have a tolerable toxicity profile also in patients with advanced age or poor performance status

• **Arm D:** Although effective the weekly combinations of Paclitaxel (80-100 mg/m² day 1,8,15 every 28 days) and Gemcitabine (1000 mg/m² day 1,8,15 every 28 days)[5,6,7], in order to get a better hematological profile, we selected the lower doses for the two drugs: Gemcitabine 800 mg/m² day 1,8,15 every 28 days, Paclitaxel 80 mg/m² day 1,8,15 every 28 days.

Thus, all the dosage were chosen based on the information available at the time the study was designed to maximize the effect of the combination. The discussion has been then modified as follow:

*This study was designed to address important information on these issues choosing dosages of combined drugs based on the information available at the time the study was designed in order to maximise the effect of each drug combination (except for the weekly combination of Paclitaxel and Gemcitabine, for which a lower dose was choosen in favour of a better haematological profile). Though, the slow accrual rate in the trial prevented the completion of the planned patients’ enrolment within a reasonable time.*


