Author's response to reviews

Title: Phase II Study of the Combination Carboplatin plus Celecoxib in Heavily Pre-treated Recurrent Ovarian Cancer Patients

Authors:

Francesco Legge (francescolegge@libero.it)
Amelia Paglia (amelia.paglia@alice.it)
Marco D'asta (marcodasta@hotmail.com)
Gilda Fuoco (gildafuoco@gmail.com)
Giovanni Scambia (giovanni.scambia@rm.unicatt.it)
Gabriella Ferrandina (gabriella.ferrandina@libero.it)

Version: 4 Date: 17 February 2011

Author's response to reviews: see over
Campobasso, 17th February, 2011

Editorial Office, BMC Cancer

Dear Editor,

Please find enclosed the new electronic version of the manuscript “Phase II Study of the Combination Carboplatin plus Celecoxib in Heavily Pre-treated Recurrent Ovarian Cancer Patients” by Legge F. et al., which has been revised according to the pertinent Reviewers suggestions. Please find also attached the replies to the Reviewers. We hope that the manuscript is now suitable for publication as Research Article in BMC Cancer.

Best regards,
Gabriella Ferrandina.

Corresponding author:
Dr. Gabriella Ferrandina
Gynecologic Oncology Unit, Department of Oncology,
Catholic University
Largo A. Gemelli, 1
86100 Campobasso, Italy
Tel.:+39 0874 312343/549; Fax +39 0874 312324
Response to dr. Maurie Markman

1. We acknowledge the limits intrinsic to our study relative to the heterogeneity of the sample population. However, we do not agree with the Referee about the definition of our series as a “non-platinum-resistant” setting: indeed, about half of the enrolled cases experienced progression/recurrence of disease within 6 months from the completion of primary or secondary platinum based therapy. For sake of clarity the definitions of primary and secondary platinum resistance have been better elucidated in the Methods (page 6, lines 5-8) and Table 1. As better outlined at the end of the Introduction (page 4 lines 17-20), the aim of the study was to explore the feasibility in terms of efficacy and safety of this combination in a setting of heavily pre-treated recurrent ovarian cancer patients with very limited chances of alternative treatment options (as shown also by the post-study treatments now reported in the Results; page 13, lines 10-13). However, according to the pertinent Referee’s suggestion in order to permit a better interpretation of our results, the response rates according to the platinum-sensitivity, have been now reported in the Results (page 11, lines 7-12) and Discussion (page 15, lines 10-21).

2. The choice of conducting a phase II randomised study was since the beginning considered not sustainable given the lack of any report about the combination of carboplatin with celecoxib. The results in terms of efficacy and safety reported in our study may now justify further clinical trials, possibly randomised, aimed at investigating the platinum-celecoxib combination in specific clinical settings (e.g. platinum-resistant ovarian cancer patients), as correctly pointed out by the Referee. This has been better specified in the Discussion (page 15, lines 19-21) and Conclusions (page 19 lines 3-8).
Response to dr. David Tan

Major revisions

1. Since the patients eligible for the study were heavily pre-treated (i.e. 86.7% had received ≥ 2 prior chemotherapy regimens for recurrent disease), a 4 weekly carboplatin regimen was since the beginning chosen on purpose to reduce the potential toxicities and to favor quality of life issues (i.e. low frequency of hospital visits). According to the pertinent Referee’s suggestion, this issue has been better elucidated in the Discussion (page 17, lines 22-25).

2. Clinical benefit was defined as a complete/partial response or a disease stabilization for at least 3 months, according to RECIST criteria. This definition has been better presented in the Methods (page 7, lines 9-10).

3. We agree with the Referee on the importance of calculating the response rate according to the platinum-sensitivity: although taking into account the limits of a small and heterogeneous series, the response rates were not found significantly associated with the grade of platinum-sensitivity. As suggested by the Referee this important information has been now added in the Results (page 11, lines 7-12) and Discussion (page 15, lines 10-21). Moreover, we have specified in Table 1 the patients with primary refractoriness versus those with primary resistance: 1(25%) response was observed among 4 platinum-refractory patients versus 3(15.8%) responses among 19 platinum-resistant patients (p=n.s); given the small numbers of the latter subgrouping we have presented in the manuscript only the analysis of the response in platinum-resistance versus platinum-relatively sensitive patients.

4. We agree with the Referee that the interval time from the last platinum may influence the response to a platinum re-treatment. However, we also acknowledge that an improvement in response rate by an artificial prolongation of this interval with intervening non-platinum agents has been recently questioned [Pignata S, Oncol, 2007]. In our study the response rate calculated on an intent-to-treat basis, was not associated with the interval time from the last platinum, with 1 (33.3%) response retrieved among the 3 patients experiencing interval from the last platinum of 6-12 months compared to 12 (28.6%) responses among the 42 patients experiencing interval from the last platinum of >12 months (p value>0.9). Similarly
6 (23.1%) responses were retrieved among the 26 patients experiencing interval from the last platinum of 6-24 months compared to 7 (36.8%) responses among the 19 patients experiencing interval from the last platinum of >24 months (p value=0.34). For sake of clarity, according to the Referee’s suggestion this information has been synthesized in the Results (page 11, lines 11-12).

5. We agree with the referee that bearing a BRCA mutation may affect the sensitivity to platinum re-challenge, however we had only one patient with a proven BRCA-1 mutation in the study population: interestingly enough this patient experienced a partial response to the celexoxib-carboplatin combination. Given the singularity of this report we have not discussed this single case in the study.

6. This is another translational research interesting issue to be explained. Indeed, in a preliminary series we have assessed immunohistochemically the status of COX-2 in 10 primary ovarian cancer included in the study: COX-2 was found overexpressed in 4 cases with 1 one of these responding to the celecoxib-carboplatin combination (25%) with respect to 2 (33%) responses found among the 6 COX-2 negative cases (p=n.s.). However, we should acknowledge that COX-2 expression in a primary tumor may differ from that in a recurrent, heavily-treated tumor. Since obtaining a tumor biopsy from ovarian cancer patients previously submitted to multiple surgical and medical treatment required an invasive and risky surgical procedure, we renounced to this potentially important information. Moreover, as clarified in the Introduction, celecoxib seems to exert its antineoplastic activity in both COX-2 positive and COX-2 negative tumors, given its role in modulating angiogenesis and immunological response (page 3 lines 24-25; page 4, line 1). For these reasons we have omitted this information in the text.

Minor Revisions

1. As pointed out by the Referee, English grammatical errors have been corrected.
Response to Dr. Stephen Ackland

Major revisions

1. According to the pertinent Referee’s suggestion the definitions of primary and secondary platinum resistance as well as platinum refractoriness have been better elucidated in the Methods (page 6, lines 5-8): progression during first line platinum-based therapy has been defined as platinum refractoriness, primary and secondary platinum resistance have been defined as progression of disease within 6 months of completion of first line or salvage, respectively, platinum-based therapy. As a consequence 23 (51.1%) of the enrolled patients presented platinum primary (n= 13, 28.9%) or secondary (n=10, 22.2%) resistance. While the progression-free interval from first line platinum-based therapy is useful to define primary platinum resistance, the “interval from the last platinum” indicates only the time period from the end of the last platinum (first line or re-challenge) to the start of the experimental carboplatin-celecoxib regimen and can not be considered a measure of platinum-sensitivity (e.g it may be related to the administration of non-platinating regimens). Since the really important information for the purpose of the study is the proportion of patients with primary/secondary platinum resistance according to previously reported definitions, we have eliminated in Table 1 these confounding variables (however data about progression-free interval from first platinum-based therapy and the interval from the last platinum are maintained in the Results, page 10). For sake of clarity, in order to permit a better interpretation of our results according to this important criticism correctly raised by the Referee, the response rates according to the platinum-sensitivity, have been now reported in the Results (page 11, lines 7-12) and Discussion (page 15, lines 10-21).

2. Since the patients eligible for the study were heavily pre-treated (i.e. 86.7% had received ≥ 2 prior chemotherapy regimens for recurrent disease), a 4 weekly carboplatin regimen was since the beginning chosen on purpose to reduce the potential toxicities and to favor quality of life issues (i.e. low frequence of hospital visits). According to the pertinent Referee’s suggestion, this issue has been better elucidated in the Discussion (page 17, lines 22-25).

3. The measurement of potential changes of angiogenesis markers represented only a surrogate end-point of the study: as a consequence we preferred to simplify the information by selecting VEGF and endostatin as potential pro-angiogenic and anti-angiogenic,
respectively, targets of the study regimen, according to a prior study [Ferrandina G, Clin Cancer Res, 2006] (page 16, lines 19-21).

4. All enrolled patients had measurable disease to permit the assessment of progression of disease, as well as response, radiologically according to RECIST criteria. A separate assessment of serological response according to the Rustin’s criteria has been also separately reported.

5. As suggested by the Referee, in the Discussion (page 15, lines 19-21) and Conclusions (page 19, lines 3-8) the potential investigational developments to draw more definitive conclusions about the role of celecoxib in increasing platinum sensitivity have been indicated.

Minor comments

1. We agree with the referee that the potential individual differences in the pharmacokinetic of celecoxib and carboplatin may affect the efficacy and toxicity of the combination. However, no pharmacokinetic interaction has been reported up till now between the two drugs.

2. Actually patients taking chronically NSAIDs were excluded. This has been better specified in the Methods (page 5, lines 23-24).

3. Details about the serum separator tube have been added (page 8, line 13).

4. We enrolled about 1 patient/month and, as a consequence 4 years have been necessary to complete the study. However as correctly pointed out by the Referee, no relevant advances have been obtained meanwhile, especially in the setting of recurrent heavy treated ovarian cancer.

5. The details about the post-study treatments have been included in the results (page 13, lines 10-13): since most of the patients had been previously treated with the classical second-line drugs (i.e. topotecan, liposomal doxorubicin, paclitaxel), 47% of patients were submitted to palliative care support, 35% to oral/intravenous etoposide or cyclophosphamide, 18% to other second-line cytotoxic drugs such as weekly gemcitabine or taxanes.
6. PGE-M refers to 11α-hydroxy-9,15-dioxo-2,3,4,5-tetranor-prostane-1,20-dioic acid, which is the major metabolite of prostaglandin E2, measurable in the urine. This has been now specified in the Conclusion (page 19, lines 8-10).

7. Categories of platinum-sensitivity have been now defined in the Methods (page 6, line 5-8)

8. According to the Referee suggestions, the number of patients at risk for progression and death has been indicated below the X-axis of the PFS and OS curves in Figure 1.
Response to Dr. Sandro Pignata

Minor essential revisions

1. We agree with the Referee that the really important information for the purpose of the study is the proportion of patients with primary/secondary platinum resistance: as a consequence, we have eliminated in Table 1 other confounding variables (i.e. interval from the last platinum and PFS from first line therapy).

2. For sake of clarity, in order to permit a better interpretation of our results according to this important criticism correctly raised by the Referee, the response rates according to the platinum-sensitivity, have been now reported in the Results (page 11, lines 7-12) and Discussion (page 15, lines 10-21).
Response to Dr. Filippo Bellati

According to the Referee suggestion the interesting paper by Bellati et al. about immunological and clinical response with intraperitoneal anti-VEGF therapy has been cited (Reference 9).