Author's response to reviews

Title: Cyclo-oxygenase-2 (Cox-2) expression and resistance to platinum versus platinum/paclitaxel containing chemotherapy in advanced ovarian cancer

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Reply to Referee 1 (Dr Joanna Stewart)

General:

According to the Referee's suggestion, we acknowledge that the statements in the Title and Discussion could appear too conclusive with respect to what results from the analysis. The Title has been modified, as well as the Abstract (page 2, lines 21-23), the Discussion (page 11, lines 3-6), and the Conclusions (page 12, lines 2-4).

Major compulsory revisions:

1. We really thank the Referee for the proper analysis of the design of the study which has to defined as a "retrospective" analysis of ovarian cancer patients undergoing chemotherapy. This issue has been acknowledged in the text (page 2, line 8, page 5, line 3).

2. As correctly pointed out by the Referee, the term "matching" has been erroneously used instead of "comparison" between the two treatment groups, as appeared from the analysis summarized in the old version of Table 2. The erroneous paragraph has been deleted. No patients selection was performed.

Analysis:

1. As suggested by the Referee, Table 2 has been modified removing the unnecessary p values relative to the comparison of the distribution of cases according to clinico-pathological characteristics in the two treatment groups. Clinico-pathological factors likely to affect response to treatment (such as residual tumor at surgery, and stage of disease), have been taken into account in the analysis of response (see the following point).

2. We also agree with the Referee that the small number of platinum/paclitaxel treated patients has to be taken into account as a limit to the power of the analysis. This has been acknowledged in the text (page 11, lines 3-6).

We agree with the Referee that the logistic regression analysis would have provided more useful information. We erroneously believed that logistic regression analysis could have been not so reliable given the relatively small sample series.

According to the Referee's suggestion, the logistic regression analysis including the variables likely to affect response (i.e. residual tumor after surgery, and stage of disease) as well as type of treatment, COX-2 status and their interaction, has been performed. The p value associated with this interaction appears to be...
As correctly pointed out by the Referee, with this sample size it cannot be conclusively stated that COX-2 status has a differential effect on response depending on treatment. This issue as well as the need to explore a larger data set has been emphasized in the text (page 9, lines 11-14; page 13, lines 2-4).

Minor essential revisions:

1. The heading on Table 2 has been corrected according to the Referee’s suggestions.

2. The label on the Y-axis has been corrected, as suggested by the Referee.

Reply to Referee 2 (Dr. Ralph S. Freedman)

1) As suggested by the Referee, we better specified in the text (page 5, lines 13-19) the definition of response according to WHO criteria.

Moreover, we agree with the Referee, that the application of the WHO criteria to the evaluation of response to treatment in ovarian cancer can be hampered by the difficulties in the assessment of measurable disease. For this reason, we analyzed a series of patients left with measurable disease at surgery, as confirmed by total body CT scan which was routinely performed together with the analysis of Ca125, to specifically measure response to treatment. This is now better specified in the text (page 5, lines 11,12).

2) We agree with the Referee that the use of the raw data would provide more information with respect to the use of cut-off values. Indeed, in cases considered COX-2 positive, the percentage of positive staining per total tumor area ranged from 15% to 45% (median value= 20%). We decided to use the cut-off value instead of the raw data in the analysis of association with clinico-pathological features for the following reasons: i) 32 cases were considered as COX-2 positive and the analysis of this data according to two treatment groups and to different response to treatment would lead to a “dilution” of the cases in very low sized sample series; in this case the use of raw data could make sometimes the analysis and the interpretation of the data more difficult; ii) moreover, the use of clear cut threshold levels may be sometimes practically useful to define low versus high risk patient categories. The issues pointed out by the Referee have been acknowledged in the text (page 8, lines 10-14).

We agree with the Referee that the significance of our findings is not certain given that the standard first-line treatment for ovarian cancer is a combination of platinum with a taxane. However, we think that our data could provide, if confirmed in a wider series, the rationale to ask for the immunohistochemical assessment of COX-2 status as predictor of Response to treatment, only in cases triaged to platinum-based therapy (including platinum/anthracycline or platinum/alkylants combinations, which are still a valid option in selected patients).

As suggested by the Referee this has been acknowledged in the revised version of the manuscript (page 12, lines 3-8).