Author's response to reviews

Title: In vitro study on the schedule-dependency of the interaction between pemetrexed, gemcitabine and irradiation in non-small cell lung cancer and head and neck cancer cells.

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Version: 4 Date: 2 August 2010

Author's response to reviews: see over
Dear Prof. Norton,

Please find enclosed the amended version of our manuscript entitled “In vitro study on the schedule-dependency of the interaction between pemetrexed, gemcitabine and irradiation in non-small cell lung cancer and head and neck cancer cells”. We are grateful that the referees appreciated and accepted the revisions we made. We tried to amend our manuscript in line with the reviewer’s remaining recommendations, in detail:

Comment of the editor:

Information pertaining to private companies, previously mentioned in the ‘Acknowledgements’ section, is now moved to the ‘Competing interest’ section of the manuscript.

“Pemetrexed and gemcitabine were kindly provided by Eli Lilly (Indianapolis, USA).”

Comments of the third referee (Wainer Zoli):

We were very pleased about the reviewer’s statement that “...the article has been revised sufficiently to render it acceptable for publication”. Of course we want to answer to his final remarks:

1. We strongly agree with the reviewer that including a larger panel of cell lines, with at least two cell lines from the same histotype, would undoubtedly be a more realistic representation of the heterogeneity seen in human cancers. As correctly pointed out by the referee, whereas previously published in vitro studies often included no more than two cell lines, most papers did study cell lines from the same histotype. In our future experiments, we will certainly consider this highly relevant remark. Meanwhile, we are thankful that, in light of the cited previous studies, our argumentation is acceptable to the reviewer.
2. As suggested by the reviewer, we now underline in our conclusions that the obtained results are preliminary and will be followed by more in depth mechanistic unravelling of the pemetrexed-gemcitabine-radiation combination.

"Preliminary results from our in vitro model suggest that the sequence 24h MTA $\rightarrow$ 1h dFdC $\rightarrow$ RT is the most rational design. Further in depth mechanistic unravelling of the pemetrexed-gemcitabine-radiation combination is certainly needed."

We agree that our revised manuscript has clearly benefited from the reviewers’ profound evaluation of the paper. We hope to have convinced you and the reviewers to accept our manuscript for publication in *BMC Cancer* in its present form.

Looking forward to a positive response,

Yours sincerely,

An Wouters