Author's response to reviews

Title: Sorafenib modulates the radiosensitivity of hepatocellular carcinoma cells in vitro in a schedule-dependent manner

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Author's response to reviews: see over
Subject: revision of MS: 1647313141732992 - Sorafenib modulates the radiosensitivity of hepatocellular carcinoma cells in vitro in a schedule-dependent manner by Qiaoqiao Li, Yonghong Hu, Mian Xi, Liru He, Lei Zhao and Mengzhong Liu

Dear Dr Belka,

Thank you for the thorough reviews by the editor and the reviewers. We have addressed each issue and believe that our revisions have improved the manuscript. We have detailed each of the issues raised by the reviewers and editor and have provided a point by point response detailed below.

Referee 1:
“Nicely done manuscript
The Radiation Therapy Oncology Group www.rtog.org) will be evaluating the combination of sorafenib and stereotactic body radiotherapy in a randomized phase II trial
Level of interest: An article of importance in its field
Quality of written English: Acceptable
Statistical review: No, the manuscript does not need to be seen by a Statistician”

Au: We agree with reviewer 1. However, we have revised the manuscript to address the concerns raised by reviewer #2.

Referee 2:
This is an interesting manuscript in which authors present a series of experiments that at least provide a partial explanation for the already known impact of schedule in the combination of sorafenib and radiation therapy in animal models. There is no major drawback. However some inconsistencies should be fixed, and they are most probably the consequence of a poor English edition
Major compulsory revision
1. English has to be checked throughout the manuscript.

Au: We have hired a scientific writer who is a member of American Medical Writers Association and have accepted her editorial suggestions. She is acknowledged in the Acknowledgment section, as per journal guidelines.
R2:
Introduction
2. The 3-5% 5-year survival rate and 80% of advanced cases at diagnosis are outdated.
AU: We have revised the 5 year survival rate to those recently presented at http://www.cancer.org/Cancer/LiverCancer/DetailedGuide/liver-cancer-survival-rates, which was updated on Jun 12, 2012. Our percentage of advanced cases is similar to the cited report.

R2: 3. Sorafenib prolongs in nearly 3 months the median survival of HCC patients
Au: We agree that sorafenib prolongs median survival by not quite 3 months. To clarify, we have revised the sentence to be “prolonging the median survival of patients with inoperable hepatocellular carcinoma by less than 3 months” as the use of the word “nearly” appeared to sound too much like marketing for sorafenib.

Material and methods
Reviewer 2: 4. It is not clear throughout the study whether post-irradiation sorafenib means that cells are incubated immediately after irradiation for a 24-hour period or that 24 hours after irradiation cells are incubated for ? time.
Au: We clarified the length of incubation after irradiation and addition of sorafenib in the methods and the figure legends.

Reviewer 2 5. Dose of radiation is 4 and 8 Gy in some experiments and 6 Gy in others. The reason for these variations should be explained.
Au: We have clarified the issue in the following 2 sentences in the methods section, “Subsequent experiments utilized a radiation dose of 6 Gy because the percentage of cells remaining after 8 Gy (SMMC-7721: 0.9-4%; BEL-7402: 2-5%) was too low for analysis. SMMC-7721 and BEL-7402 cells in subsequent experiments received one of the four treatments: (a) none (control), (b) 6 Gy radiation, (c) 15 μM sorafenib 30 min before 6 Gy radiation, or (d) 6 Gy radiation followed 24 h later with 15 μM sorafenib.”

Editorial requests:
We have added a Competing interests section and an Authors' contributions section. As requested, we have paid for and acknowledged the medical editor in the Acknowledgments section.

We have noted the revisions in the manuscript in green in track changes.

Thank you for the thoughtful reviews and we have addressed each of the issues in the manuscript. The revisions have improved the manuscript and we are looking forward to hopefully your approval for its publication. Please don't hesitate to contact me if you have any problems or questions regarding our revised manuscript.
With best wishes,

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