Reviewer's report

Title: Enhancement of the Radiosensitizing Effect of Temozolomide: Targeting EGFR-associated Signaling in Malignant Glioma Cells

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Reviewer: Jann N Sarkaria

Reviewer's report:

The authors present an interesting study evaluating 4 different novel therapeutic agents in combination with radiation without and with Temozolomide. Overall, the studies are carefully done and results are convincing. However, there are numerous minor essential revisions, predominantly editorial issues that need to be addressed.

The title is somewhat misleading, since 2 of the 4 targets being evaluated are not specifically in the EGFR pathway. Inhibition of HDAC and HSP90 have pleiotropic effects that extend well beyond the EGFR pathway. Cell lines used are not EGFR over expressing, so the discussion within the results and discussion should acknowledge this limitation.

in the results and discussion section, the authors suggest a mechanistic link between the effects of HDAC or HSP90 inhibition on specific signaling molecules and phenotypic responses. For example, they attribute suppression of Eph2a, VEGF and MMP2 by HDAC inhibition to vasculogenic mimicry, invasion and migration. HDAC inhibition has numerous effects on many proteins, and the authors do not demonstrate a mechanistic link to these specific targets. Thus, they should reword the results and discussion sections carefully when describing the results for both HDAC and HSP90 inhibitors.

Figure 2 not clear if results represent triplicate samples from a single experiment or results from 3 independent experiments

Figure 3b - how many independent experiments were performed? PI103 certainly attenuated P-DNAPK, but not necessarily the other compounds. This result suggests that PI103 is directly inhibiting DNAPK, which could explain the Radiosensitizing effects seen with this drug. This should be made clear in the discussion.

Figure 1 and 2 - statistical analysis should be provided for comparisons of the clonogenic survival curves.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Needs some language corrections before being
published

**Statistical review:** No, the manuscript does not need to be seen by a statistician.