Reviewer's report

Title: A new anti-glioma therapy, AG119: Pre-clinical assessment in a mouse GL261 glioma model

Version: 3 Date: 27 April 2015

Reviewer: Paola Grandi

Reviewer's report:

AG119 is a small molecule discovered by the authors which possess anti-angiogenic and anti-microtubule activity. It was previously tested in xenograft models (in the flank) using U251 glioma and MB-435 breast cancer cells (both human). Here the authors showed that AG119 seems to be able to decrease tumor volume in mice bearing GL261 and to improve their survival compare to the untreated animals. However this drug has the same efficacy of anti-c-MET and anti-VEGF and failed to improve animal survival when compared to TMZ. Overall I find the results not justifying the conclusions and the utility of AG119 questionable.

Comments:

In order to compare the efficacy of AG119 with other standard therapies it is important to provide the information regarding those are drugs.

For example: how did they choose the concentration of the Abs? For example, Marchant and coll (PNAS, 2013, p 110(32): E2987–E2996) showed that antibodies against human c-Met (onartuzamab) had different effect at different concentrations: 1 and 3.75 mg/kg delayed tumor growth, whereas doses of #7.5 mg/kg drove tumor regression in animal model.

Please provide information and citations for anti-c-MET and anti-VEGF.

What's the vehicle in which AG119 is resuspended? Why the control animals did not receive the vehicle?

FIG1: Kaplan Meier: In the result section the authors said: “Percent survival of GL261 HGG-bearing mice treated with AG119 was significantly higher (p<0.05) compared to untreated tumors, as depicted in Fig. 1. TMZ, however was found to have a significant increased percent survival when compared to AG119 (p<0.01)” However in the figure legends they showed the statistical analysis for tumor volume.

Those data clearly showed that TMZ has a stronger therapeutic efficacy than AG119 and that AG119 has the same efficacy than anti-c-Met and anti-VEGF.

FIG 2:

Based on the Kaplan Meier plot, anti-VEGF, anti-c-Met and AG119 has the same therapeutic efficacy against GL261. All animals treated with these different
agents died by day 28. However the MRI imaging in fig.2 clearly showed strong tumor regression or absence of tumor (Fii) in animals treated with AG119. Why did the animal died?

Animals that received TMZ only partially respond to the treatment and show strong tumor growth. Why these MRI imaging do not correlate with the survival plot.

Is AG119 extremely toxic for these animals? According to their previous paper 3 HCL (now called AG119) is not toxic. How do they know if AG119 can cross the BBB? Clearly TMZ has a stronger therapeutic effect and AG119 does not improve life expectancy.

**Level of interest:** An article of limited interest

**Quality of written English:** Acceptable

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

**Declaration of competing interests:**

I have NO COI