**Author's response to reviews**

**Title:** Radiotherapy plus nimotuzumab or placebo in the treatment of high grade glioma patients: results from a randomized, double blind trial.

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Answers to reviewers

Dear editor:

We are grateful to the referee for the judicious comments on our manuscript, which led us to improve the paper accordingly. Below we reply point by point to questions and comments explaining the modifications we have introduced in the paper. The additions and modifications are highlighted in the text. Please, do not hesitate to contact us if you have further doubts or comments:

Authors do not say if it is a phase II randomized or a phase III study. They do not describe the sample size calculation method.
The trial was classified as Phase II and the sample size calculation method was added to Material and Methods.

The groups are not well balanced for two important prognostic variables as KPS (KPS \leq 70 39\% in control arm vs. 15\% in study arm) or debulking surgery (Total 5\% in control arm vs. 17\% in study arm). This can strongly influence in the results.
As stated in the results, no statistically significant differences were detected between the 2 groups regarding the most important prognostic characteristics: histology, age, surgical intervention and KPS. However, since a larger number of patients with poorer KPS and lack of debulking surgery were randomized to the control arm, a sentence was added to the discussion, declaring that the results should be interpreted with caution.

The recruitment was very long (5 years).
The referee is right: the enrollment was very prolonged. This was not a multinational trial and the slow recruitment was attributed to the low prevalence of the disease in Cuba mainly the anaplastic astrocytoma histology.

They should say why the number of patients between arms is quite different (39 vs. 31) when the randomization was 1:1

There was a mistake regarding the number of patients per arm: 38 patients received irradiation plus a placebo while 32 subjects were treated with radiotherapy and nimotuzumab. The referred numbers were corrected in the text.
A total of 73 patients were included in the study: 43 patients diagnosed with Anaplastic Astrocytoma (AA) and 30 patients diagnosed with glioblastoma multiforme (GBM). Three patients from the nimotuzumab arm (10, 54 and 61) abandoned the study from inclusion and did not receive any therapy. Information was available from 70 subjects: 41 AA and 29 GBM patients. In the AA group, 41 patients were analyzed per intention to treat: 23 received placebo and 18 received nimotuzumab. In the GBM group, 29 patients were analyzed, 15 of these received placebo and 14 received nimotuzumab. This explanation was added to material and methods.

Results shown important differences when the authors analyze AA and GBM separately. Results are better for AA than GBM and authors should
reflect this in the discussion and added figures of OS by histology and analyze if OS is statistically significant in GBM.

Survival figures by histology were added. The p values according the Weibull regression survival model were also added. Indeed, the survival differences were significant for the GBM histology and not for the AA patients, according the Weibull parametric model.

Authors should say how many patients were evaluable for response by each arm.

The number of patients evaluable for response was included in the results.

I suggest added a table of toxicities.

A table summarizing the most frequent unrelated and related toxicities was added.

Authors should include statistically significant differences in the abstract.

As recommended, it was highlighted in the abstract that nimotuzumab provided significant survival benefit.

Part of the background may be translated to discussion, especially previous experiences of German, Stupp and Hegi trials.

Part of the introduction was transferred to the Discussion as suggested.