Reviewer's report

Title: The Clinical Efficacy of Afatinib 30 mg Daily As Starting Dose May Not Be Inferior to Afatinib 40 mg Daily in Patients with Stage IV Lung Adenocarcinoma Harboring Exon 19 or Exon 21 Mutation

Version: 0 Date: 11 May 2017

Reviewer: Barbara Wiśniowska

Reviewer's report:

The paper describes study aimed to evaluate efficacy and safety of two different doses of afatinib. This is very interesting research problem as the LUX-Lung trials showed decreased incidence of ADRs and similar PFS in patients that required dose reduction due to the occurrence of ADRs. If the efficacy of afatinib starting dose of 30 mg is proven to be similar to 40 mg, it will offer advantages of both safety and financial costs.

My main concerns are:

1. Very small group being evaluated, especially in subgroups and therefore substantial differences in groups’ characteristic, including chosen confounding factors; thus the statement on non-inferiority of afatinib 30 mg is not sufficiently supported by the presented results. It is a small observational study without confounding control while groups do differ significantly, thus in my opinion any meaningful conclusion is unjustified.

2. The character of the analysis is not clear. Patients treated from May 2014 till August 2016 were followed until December 2016, according to the text, but when the study was initiated? Was the data collected prospectively for all of the patients? This also brings another problem, if patients were qualified successively some of them were observed for a much shorter period than others, so how the survival analysis with the time scale of ca. 630 days was done? The drop in the number of cases on Figure 1 can be both due to patient death and termination of the individual observation time.

3. The Authors claim that: factors predictive for PFS and OS were identified (pp 8 line 58-63; pp 10 line 38-43; pp 12 line 49-52) and no difference in OS in 2 groups was found (pp 10 line 13) and OS was similar in 30 and 40 mg group (pp 11 line 52). At the same time (pp 12 line 38-39) - "in our study, OS is still undefined due to most patients are still alive until Dec 2016."
4. Pp 11 line 3-7: Grade 3 skin rash occurred in three patients (16%) using 40 mg daily of afatinib, while no patients using 30 mg daily had grade 3 skin rash - probably there is no statistically significant difference between the groups (3 and 0 cases of rash); data does not allow to draw some statistically significant conclusions. Thus it cannot be seen as a proof of lower skin rash risk in case of afatinib 30 mg.

5. There are statistically important differences between groups (30 and 40 mg) in age, sex, weight and height. The Authors state that male gender is a predictive factor of PFS, so the similar PFS value in 30 mg group can occur due to more female than male patients in this group. Also, while afatinib concentrations were not monitored and afatinib 30 mg group has lower BW and height, it is possible that effective concentrations do not differ between groups.

Other

6. Pp 12 line 10-17: "in a pooled analysis of the LUX-Lung 3 and LUX-Lung 6 trials, afatinib showed a statistically significant PFS benefit when compared with chemotherapy (HR [95% CI]: 0.42 [0.34 -0.53] [9]." I could not find this data and such statement in the referenced publication. Please clarify.

7. Pp 12 line 27-32: results were reported with the use of various time units (months and days). It would be easier to compare them if both are given in the same units.

8. "Lug-Lung series" - should it be LUX-Lung?

9. Keywords are missing.
Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

No

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?
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No

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