Reviewer’s report

Title: Rationale and design of LUX-Head & Neck 2: A randomised, double-blind, placebo-controlled, phase III trial of afatinib as an adjuvant therapy after chemoradiation in primary unresected, clinically intermediate- to high-risk head and neck cancer

Version: 2 Date: 24 July 2014

Reviewer: Sarah Damery

Reviewer’s report:

This is a well written protocol that outlines a study designed to assess the effectiveness of afatinib as adjuvant therapy following chemoradiotherapy for head and neck squamous cell carcinoma in patients with unfavourable risk of recurrence. I feel that the protocol would be improved if the authors were to address the following comments:

Major compulsory revisions:

1. Please define what is meant by T or N stage disease (mentioned first in abstract and then again elsewhere in the protocol)

2. The definition of intermediate to high risk of recurrence appears to vary throughout the protocol. For example, in the background section of the abstract, it is defined as advanced T or N stage disease, non-oropharynx primary sites, HPV-negative oropharyngeal cancer, or HPV positive oropharynx cancer with a > 10 pack year smoking history. In the methods part of the abstract, unfavourable risk is defined as non-oropharynx primary site or oropharynx cancer in tobacco-exposed patients. This seems to be a less specific definition. The definition given elsewhere in the protocol also emphasises slightly different criteria. As the definition of intermediate to high risk of recurrence is crucial in determining which patients will be eligible for recruitment to the trial, it is important that a definitive and consistent definition of intermediate to high risk is provided.

3. In the ‘afatinib’ paragraph of the background section, the final sentence compares median PFS of 11.1 months vs. 6.9 months in the LUX-Lung 3 study. Was this a statistically significant difference? What was the p value for this comparison of medians?

4. Whilst all recruited patients will begin on a 40mg daily dose of afatinib, some patients will have their doses increased to 50mg, whilst others will have theirs stepped down depending on the incidence and severity of adverse effects associated with the afatinib regime. Will these different dosage regimes be accounted for in any way within the analysis, or will the analysis assume that all participants received the same dose?
5. The methods section needs a formal sample size calculation rather than just a statement that there will be 669 patients randomised into the two arms in a 2:1 ratio. How was this sample size arrived at? I presume the study is powered to detect a significant difference between arms in terms of the primary endpoint (disease free survival) – what hypothesised difference in DFS between arms has the sample size been based on?

6. In the methods section (study design and treatments paragraph), what does ECOG performance status 0 vs. 1 mean?

7. How will randomisation be undertaken?

8. The protocol discusses evaluating the incidence and intensity of serious adverse events but does not mention how they will be reported. Will patients within the trial be expected to report SAEs as and when they occur? Will patients be regularly contacted or have to attend a follow-up clinic in which their SAEs will be discussed and evaluated?

9. Will there be a data monitoring committee associated with the trial to monitor patient safety and clinical efficacy throughout the course of the trial? Will there be any stopping rules for the trial in terms of the trial being closed down early if either afatinib shows no superiority over placebo or shows such a high degree of superiority that it would be unethical to continue within a trial in which a third of the patients are not receiving a proven efficacious treatment?

10. The authors need to mention that the trial will include biomarker assessment as one of the data collection streams at an early point of the methods when the trial is being summarised. As it is, the biomarker assessment paragraph towards the end of the methods section appears from nowhere with no prior mention within the protocol.

11. There is little detail given about the health related quality of life assessment beyond citing the specific tools that will be used to gather data. How often will these be administered? At baseline and end of the trial? At specific timepoints post-randomisation? How frequently? More detail is required on this part of the study, particularly as HRQoL is one of the stated secondary endpoints of the trial.

12. Will recruitment centre be taken into account within the analysis phase? The study is recruiting from a very large number of sites, and it might be expected that some recruitment centres may contribute very few patients to the overall cohort. Will any action be taken to evaluate the consistency with which the trial protocol has been followed in each of the participating centres?

13. There appears to be some inconsistency between the protocol text and Figure 1. The text (methods section) states that the trial will recruit 669 patients. Figure 1 cites an n of 660.

14. Following point 13, the wording of some of the text in the protocol and figure 1 causes confusion about the eligibility criteria for the trial. The text says that
patients who have not undergone tumour resection will be eligible. Figure 1 states that ‘Disease free (with or without tumour resection/neck dissection) after completed prior chemoradiotherapy’ will be recruited. This gives the impression that the trial will be open to patients who HAVE undergone tumour resection. This may be a question of unclear wording, so it would be useful if the eligibility criteria are spelt out in crystal clear fashion in the text and that this is consistent between the text protocol and the accompanying figures.

15. I note that the study began recruiting in 2011. Is there any particular reason that the authors have waited until the trial has been going for 3 years before deciding to publish the protocol?

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

**Quality of written English**: Acceptable

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

**Declaration of competing interests**: I declare that I have no competing interests.