Author's response to reviews

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

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Version: 3 Date: 3 November 2014

Author's response to reviews: see over
Dear Editor,

Thank you for communicating the reviews of our manuscript entitled “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” (MS: 8835894601295634). We have addressed all of the reviewer comments as discussed in detail below and highlighted in the revised manuscript. In addition, we have made a number of minor updates owing to recent relevant publications since submission of this manuscript; these are also listed below for your information.

Reviewer #1

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

   T and N stages refer to the TNM staging system for cancers, with T referring to the size of the primary tumour (including invasion into adjacent tissues and structures) and N referring to lymph node involvement. A more descriptive explanation of these terms, plus an appropriate reference, has been included in the abstract (page 2) and main text (pages 4, 11 and 12).

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.

   Unfavourable (i.e., intermediate-to-high) risk of recurrence in all patients with HNSCC includes those with advanced stage disease, non-oropharynx primary sites, HPV-negative oropharyngeal cancer, or HPV-positive oropharynx cancer with a >10 pack year smoking history, as stated in the Background section of the Abstract. In the LUX-H&N 2 study, HPV status will not be determined for patient eligibility and thus was not included in the definition of unfavourable risk for these patients. As such, only
primary tumour site (i.e., non-oropharynx vs oropharynx) and smoking history (>10 pack-year) were considered in determining risk of recurrence in this study, which has been further explained in the following sections:

Abstract (page 2): “As HPV status will not be determined for eligibility, unfavourable risk is defined as non-oropharynx primary site or oropharynx cancer in patients with a >10 pack-year smoking history.”

Methods (page 12): “As HPV status will not be determined for eligibility in this study, unfavourable risk is defined as non-oropharynx primary site or oropharynx cancer in heavy smokers (>10 pack years).”

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?

   The p-value for this comparison has been added to page 9, as follows:

   “Approval was based on findings from the pivotal phase III LUX-Lung 3 study, which demonstrated a median PFS of 11.1 months in patients treated with afatinib versus 6.9 months in patients treated with chemotherapy (p<0.001) in the first-line EGFR mutation-positive setting [35].”

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?

   Efficacy analyses will be conducted in the intent-to-treat population (i.e., all patients randomised to either afatinib 40 mg or placebo), thus changes in afatinib dosage will not be considered when performing these analyses. However, dosage changes will be reported with regards to safety, including extent of afatinib exposure, any dose reductions (including time on the reduced dose), and any adverse events that led to dose reductions.
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?

A description of sample size determination has been included on pages 14-15, as follows:

“This trial is powered to detect a prolonged median DFS of 6.2 months with afatinib over an assumed DFS of 15.8 months in the placebo arm [8]. A total of 669 patients randomised 2:1 to afatinib and placebo is required to detect a difference in DFS (with a hazard ratio of 0.72) at a power of 90%, with a one-sided type-I error of $\alpha=0.025$.”

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

We apologize if this information was unclear – we have revised the statement to provide more explanation (page 11) as follows. ECOG has been previously defined on page 7.

“Stratification will be based on patients’ nodal status (N0–N2a vs. N2b–N3, based on the TNM Staging Classification for Head and Neck Cancers) and ECOG performance status (0 vs. 1) at screening.”

7. How will randomisation be undertaken?

The following additional information has been added to page 11:

“Randomisation will be conducted centrally with a validated random number-generating system at Boehringer Ingelheim, verified by a trial-independent statistician, and implemented via an interactive internet and voice-response system. Access to the randomisation code will be supervised by the clinical trial support group; those directly involved in the conduct and analysis of the trial will not have access to the randomisation schedule prior to database lock.”

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?

The following additional information has been added to pages 13-14:

“All AEs, serious and non-serious, occurring during the course of the trial (i.e., from randomisation until 28 days after end of treatment), regardless of relatedness to study medication, will be collected, documented and reported by the investigator. Serious and non-serious AEs occurring later than 28 days after the last administration of study medication will only be reported if they are considered relevant by the investigator. All AEs, including those persisting after end of study medication, must be followed until they have resolved or have been sufficiently characterised.”

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?

The following additional information has been added to page 12:

“An independent data monitoring committee will oversee the trial and will advise on the further conduct of the trial based on ongoing evaluation of efficacy and safety data.”

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.

A statement on voluntary biomarker assessments has been added to the ‘Objectives’ section at the beginning of the Methods (page 11):

“Secondary endpoints include the DFS rate at 2 years, OS, health-related quality of life (HRQoL) and safety. Voluntary biomarker assessments were also conducted.”

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.

The following additional information has been added to page 14:

“Questionnaires will be completed at randomisation and at each tumour assessment time point until disease progression. Questionnaires will be filled in by the patients at the clinic, prior to clinical assessment and treatment, and before provision of any new information about their disease status.”

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?

Protocol violation rules have been set up for the trial, and continuous medical review will be performed throughout the trial conduct. Although recruitment centre effect will not be included in our primary analysis comparisons between treatment arms, centre-level summary data (e.g., protocol violations, occurrence of adverse events, tumor recurrence etc.) will be examined to assess consistency across 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.

We apologize for this error in Figure 1. The number of patients to be recruited in Figure 1 has now been amended to 669 patients.

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.
We apologize for the potential confusion regarding patient eligibility criteria. We have amended the following sections to improve clarity:

Abstract (page 2):
“Patients with primary unresected LA HNSCC, in good clinical condition with unfavourable risk of recurrence, and no evidence of disease after chemoradiotherapy will be randomised 2:1 to oral once-daily afatinib (40 mg starting dose) or placebo.”

Background (page 10):
“LUX-Head & Neck 2 (NCT01345669) investigates the efficacy and tolerability of afatinib compared with placebo when given as adjuvant therapy after chemoradiotherapy, in patients with primary unresected HNSCC prior to chemoradiotherapy and no evidence of disease (with or without salvage tumour resection/neck dissection) post-chemoradiotherapy.”

Figure 1:
“Randomised, double-blind, placebo-controlled, phase III trial
Primary unresected, stage III-IVB HNSCC prior to chemoradiotherapy
Disease-free (with or without tumour resection/neck dissection) after completed prior chemoradiotherapy”

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?

A manuscript of the study protocol was originally written in 2012–2013 and submitted for publication in 2013 to another journal. However, due to significant delays within the previous journal editorial office, the manuscript was never sent out for peer review. Thus, we chose to retract the manuscript from the previous journal and re-style the article for submission to Trials.

Reviewer #2

1. It would be useful to provide current recruitment numbers to date.

The authors prefer not to include this information at this stage.
Editorial request:

1. Please move your key words below the Abstract.

   The key words are now positioned below the Abstract (page 3).

Minor updates by the authors:

1. Afatinib approval status in NSCLC has been updated, including relevant references, as follows (page 8):

   “Afatinib is approved in the major ICH (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use) regions of the US, EU and Japan for the treatment of patients with non-small cell lung cancer (NSCLC) harbouring distinct types of EGFR activating mutations [35-37].”

2. The overall survival benefit recently reported for afatinib over chemotherapy in patients with NSCLC harbouring the EGFR Del19 mutation in the LUX-Lung 3 and 6 trials, including the appropriate reference, has been added as follows (page 9):

   “In more recent analyses, an OS benefit with afatinib versus chemotherapy was also observed in patients with NSCLC harbouring the EGFR Del19 mutation [39].”

3. The proof of concept phase II study of afatinib versus cetuximab in patients with R/M HNSCC who failed platinum-based chemotherapy has now been published – this citation has been updated within the manuscript:


2. Updated information for the LUX-Head & Neck 1 (NCT01345682) study, including the appropriate references, has been added as follows (pages 15-16):

   “This is one of two phase III studies of afatinib in HNSCC; LUX-Head & Neck 1 (NCT01345682) is assessing afatinib versus methotrexate in patients with R/M HNSCC who have progressed on platinum-based therapy [50]. The primary endpoint for this trial
has been completed and results from the study were presented at the European Society for Medical Oncology 2014 congress [51].”

3. Updated participating countries list in the text, as follows (page 16), as well as in Figure 2:

“The trial was initiated in October 2011 and is currently recruiting patients in Argentina, Australia, Austria, Belgium, Brazil, Canada, Chile, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, India, Israel, Italy, Japan, Mexico, Portugal, Russia, Spain, Switzerland, Sweden, The Netherlands, the UK and the US (Figure 2). Other participating countries are the Czech Republic, Denmark, Egypt, Hungary, India, Poland and Ukraine.

Thank you very much for considering publication of our Study Protocol in Trials.

Sincerely,

Barbara Burtness, MD