Reviewer 00109509

The authors review the available literature regarding the use of erlotinib after treatment with gefitinib in advanced non-small cell lung cancer. In general, the manuscript is of interest, although some aspects should be improved.

- In particular, extensive language correction is required.
  Authors reply: This has been done as suggested

- Moreover, the mechanism of action of tyrosine kinase inhibitors should be better described.
  Authors reply: This has been done as suggested

- Finally, at the end of the manuscript, in the summary, the authors should speculate on the fact that several of the studies described in the manuscript were carried out in small groups of patients.
  Authors reply: We have carried out a pooled analysis of all available studies so that the limitations imposed by the small number of patients in individual publications is to some extent removed. Results of the pooled analysis have been included in the abstract of the revised manuscript as well as summarized in a separate paragraph and incorporated in a new table (table 4).

Specific comments

1. Abstract: language correction required : line 7: missing words: good response predictors?
Authors reply: The sentence has been modified as suggested to make it easily understandable for the reader

2. Page 3: mechanism of action paragraph line 2: different domains can be identified in the EGFR, not subunits
Authors reply: This has been changed as suggested

3. Page 3: mechanism of action paragraph line 8: carcinogenesis is not the correct term: change into “activation of cell survival pathways”
Authors reply: This has been changed as suggested

4. Page 3: improve the description of the mechanism of action of gefitinib by adding the concept that it is an ATP mimetic
Authors reply: The suggested description has been incorporated in the revised manuscript

5. Title to table 1 should be more precise
Authors reply: This has been made more precise as suggested

6. The word “viz” has been inserted in different parts of the text. Please check language.
Authors reply: The language usage has been appropriately modified

Reviewer 02494535

The authors revise the data available on the administration of erlotinib following gefitinib in NSCLC. This issue is now of very little clinical relevance and interest because research is focusing on novel EGFR-TKI that selectively block T790M mutant tumors. Some data with T790M inhibitors are available. Furthermore, this type of review has already been carried out previously. Most of oncologists would use EGFR-TKI beyond PD at progression on gefitinib or switch to chemo or clinical trial. With regard to switch to chemo, this work does not discuss the importance of intervening chemotherapy in determining response to E after G (repopulation of sensitive cells)
Authors reply: This manuscript was an invited concise review on the data available regarding use of erlotinib in patients with prior history of gefitinib usage. Although we agree with the comments of the reviewer, the ones listed are beyond the purview of the current manuscript since it does not focus on novel targeted therapies for patients who have progressed following initial therapy with EGFR TKIs (including development of T790M resistance) nor use of chemotherapeutic agents in this setting. This manuscript is of relevance to developing countries and resource constrained settings wherein EGFR mutation testing may not be readily available and treating oncologists may find it helpful to read the literature as to whether erlotinib treatment in patients with prior history of gefitinib treatment is justifiable or not.

Reviewer 00607648

1. Reference 1 attempted erlotinib because of industry emphasis on the 2 TKIs not being the same. This putative difference may account for some of the later responses to E.
Authors reply: Withdrawal of approval to gefitinib following the results of the ISEL trial occurred in the US. However, gefitinib continued to be available and used in other parts of the world. The current review lists reports from all parts of the world. The emphasis here is not related to reason that prompted the treating physicians to consider use of erlotinib following gefitinib use but the results of such an intervention.

2. It appears that, the longer the interval between ceasing a TKI and restarting the same or other TKI, the better. If such data are available, it could be of interest to see if a longer interval was associated with a greater likelihood of a secondary response to either TKI.
Authors reply: This data is not uniformly available in the publications included in this review and hence, even though we would have liked to incorporate it, it is not feasible.

3. References are needed for the contradictory factor of EGFR as related to TKI response.
Authors reply: The paragraph has been rephrased since the message intended to be conveyed to the reader is that the predictive value of EGFR mutations for clinical benefit with erlotinib is not as strong in this setting (erlotinib following gefitinib therapy) as it is for first line therapy with EGFR TKIs in EGFR mutation positive patients. We apologize for the grammatical error in the manuscript that mentioned the role of EGFR mutations to be contradictory.

4. It should be noted that some recommend continued administration of TKI past DP because of possible "flare" upon its cessation. This would decrease the number of cases suitable for TKI readministration.
Authors reply: We agree that there is a school of thought and even some evidence to support this. However, the cases and studies included in this review are those in which the second TKI (erlotinib) was used after the first TKI (gefitinib) had been discontinued.

5. It is of notable that E changing to G has not been attempted to my knowledge.
Authors reply: We agree. That is why the title of this focussed review is use of erlotinib following prior therapy with gefitinib and not re-use of another EGFR TKIs following prior therapy with one EGFR TKI

6. When giving references it is best not to use first authors, just reference numbers because the use of names can be distracting.
Authors reply: This has been changed as suggested