Reviewer's report

Title: Relationship between EGFR expression, copy number and mutation in lung adenocarcinomas

Version: 1 Date: 22 March 2010

Reviewer: Robert Clifford

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Summary

In their paper “Relationship between EGFR expression, copy number and mutation in lung adenocarcinomas”, Liang et al. demonstrate non-random associations between EGFR copy number (determined by fluorescence in situ hybridization), mutation (determined by a PCR-based assay) and protein expression (measure by immunohistochemical staining). They also show that the observed associations are dependent on the method by which copy number and protein expression are measured.

Major compulsory revisions

1) In their statistical analysis Liang and coworker do not make adjustment for multiple tests. In some cases, this changes the interpretation of the data. The data in Table 1 should be Bonferroni corrected for 5 tests (association with age, gender, smoking status, lymph node metastasis and tumor stage). After this correction, only the association between mutation and smoking status is statistically significant. The p-values in Table 3 should Bonferroni correct for 2 tests (association with mutation and FISH). After this correction, the association between third criteria and FISH approaches significance (p = .054)

2) One goal of the study is to provide insight into which molecular feature “is more suitable for selection of patients for EGFR-targeted therapies.” Previous studies have shown that tyrosine kinase inhibitor therapy is most effective against lung cancers with activating kinase mutations. The authors do demonstrate a correlation between EGFR copy number, mutation and protein expression. But since 50% of protein expression-positive tumors are negative for EGFR mutations (Table 3), as are 29% of FISH-positive tumors (Table 2), it seems that mutation detection is the most useful predictor of whether a cancer will respond to TGI therapy. The authors, however, recommend that all three assays be used to prior to treatment. What evidence supports the idea that copy number and protein expression information - alone or in combination with mutation status – are useful predictors of response to treatment? The paper would benefit greatly from a more comprehensive discussion of the benefits (or lack of benefits) of incorporating EGFR copy number and protein expression in the determining how to treat lung cancer.
3) Liang et al argue for the need to establish standard methods for assaying molecular features of tumor samples. The tissue fixation protocol, which impacts these assays, should be described in greater detail in section 2.2.

Minor essential revisions

1) The authors should provide a more thorough explanation of the Scorpion ARMS data shown in Figures 1C, 1F, 2C, 2F, and 2I. To readers unfamiliar with the assay, it is unclear what the curves in these panels represent and what the colors of the lines mean.

2) In section 3.2, the phrase “... also exists exon ...” should be changed to “... also had an exon ...”

Discretionary revisions

1) In section 3.3, the phrase “showed EGFR mutations” should be moved to the end of the sentences.

2) In section 3.5, “Application of the latter two criteria, statistically similar results were yielded” should be changed to “Similar results were obtained using either of the latter two criteria” to improve clarity.

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

Quality of written English: Needs some language corrections before being published

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:

I declare that I have no competing interests.