Reviewer's report

**Title:** Tumor response and survival in patients with advanced non-small-cell lung cancer: the predictive value of chemotherapy-induced changes in fibrinogen

**Version:** 4  **Date:** 23 March 2012

**Reviewer:** Benjamin Nisman

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The authors in this study investigated prognostic value of plasma fibrinogen levels in 160 pts with advanced NSCLC. They reported that pre-chemotherapy (basal) plasma fibrinogen (FG) level was an independent prognostic parameter for the overall survival. Furthermore, in patients with hyperfibrinogenemia the changes in fibrinogen levels during chemotherapy were significantly associated with tumor response. The manuscript of Zhao et al is a valuable contribution showing the prognostic relevance of clinical factors and FG in non-small cell lung cancer. The strength of their study is the posing of an important clinical question, the investigation of a homogeneous patient sample (all are advanced NSCLC patients), the inclusion of tumor and therapy related factors as well as the kinetics of FG. However, there are some shortcomings which should be addressed in a revised version of the manuscript.

1. What assay for quantification of FG was used? The values reported in this study are higher than in studies of Yamaguchi et al 1995 and Jones et al 2006. What a reference level for FG in healthy population? What is an intra-assay variability of the assay?

2. In some paragraphs the terms "prognosis" and "prediction" are used interchangeably. The authors report that FG levels markedly decreased after chemotherapy in some of patients with pre-chemotherapy hyperfibrinogenemia (98 pts) and in this population; there was a significant link between the decrease in fibrinogen level and partial response or stable disease. The authors conclude in the discussion, that their results support the idea that fibrinogen might be a useful biomarker for predicting the response of advanced NSCLC to chemotherapy. "Prediction" would mean that clinical or laboratory factors before start of the therapy already indicate the therapy response (like EGFR mutations for Gefitinib therapy). Such is not the case in this study. If FG changes correlate with therapy response, the information provided is at the same time and may be a surrogate for therapeutic efficacy, however, it has no predictive value. Actually, the authors correctly conclude in the abstract that plasma fibrinogen levels induced by chemotherapy might be a promising biomarker for evaluating the efficacy of chemotherapy in advanced NSCLC. Appropriate changes in the study aims and discussion should be made.

3. It also desirable to present the percentages of FG evaluations that were concordant with the results of all response groups (PR, SD and PD).

4. The word “correlation” is generally reserved for computing correlation
coefficients (between continuous variables (Age and FG) and in this cases r should be indicated. The word “association” is usually preferred between continuous and categorical variables (FG and Gender or ECOG score).

5. According to the reference range of clinical criterion in the hospital, hyperfibrinogenemia was defined as a plasma fibrinogen concentration of >4g/L, but in survival analysis the authors appear to be trying to find more optimal cut-off and used the median of pre-chemotherapy plasma fibrinogen >4.4g/L (optimization?). To confirm the prognostic significance and avoid bias it would also be desirable to consider FG as a continuous variable i.e. without dichotomization.

6. There is a feeling that the work described could be presented without any loss, and perhaps with greater impact being significantly shortened. Some material is presented in the text and tables e.g. Text/Table 2 (crosstable) or in the text and figures (Text/Figure 1 and Text/Figure 2), or in the text, tables and figures (!) (Text/Table 3 /Figure 3, Text/Table 4/ Figure 4). This should be avoided.

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

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

**Declaration of competing interests:**

'I declare that I have no competing interests