Reviewer's report

**Title:** Evaluation of a novel rash scale and a serum proteomic predictor in a randomized phase II trial of sequential or concurrent cetuximab and pemetrexed in previously treated non-small cell lung cancer

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**Reviewer:** Balazs Halmos

**Reviewer's report:**

The manuscript of Maitland et al entitled “Evaluation of a novel rash scale and a serum proteomic predictor in a randomized phase II trial of sequential or concurrent cetuximab and pemetrexed in previously treated non-small cell lung cancer” reports on a valiant effort at developing predictive biomarkers of benefit from cetuximab therapy in the context of a randomized phase II study of cetuximab followed by pemetrexed at progression or concurrent cetuximab and pemetrexed. All of the patients two weeks of cetuximab therapy upfront without concurrent chemotherapy allowing the use of a skin rash scale rating scale to be used during this time to assess whether this would predict overall benefit from cetuximab. In addition, the commercially available Veristrat assay (which has been developed to classify lung cancer patients on EGFR TKI therapy into good and poor prognostic groups) was also used to see if this test would have similar predictive value in cetuximab treated patients as well. Overall, 43 patients had completed this study and outcome in the upfront cetuximab arm was extremely poor limiting the power of this study to arrive at relevant conclusions. While the novel skin rash scale the authors introduced did not seem to improve upon predictive power of the scale but the proteomic marker used classifying patients into poor and good prognosis groups as well as the absence of rash showed promise as to predicting non-small cell lung cancer outcomes in the context of cetuximab therapy.

The overall concept of the study certainly seems meritorious and the authors need to be commended for completing such an effort in a single institution given the difficulties conducting studies in such a setting. A number of shortcomings need to be noted, though when considering the data presented:

1. Their original statistical design called for 40 patients per arm and due to practice changes calling for study termination, this study needed to be terminated after a little more than half accrued, therefore their observations mostly seem to be in the thought-provoking range and there are concerns about false positive and negative observations. That being said, publication of the results appears to be of value and one suggestion might be just appropriately softening their statements as to the impact of their observations

2. The non-conventional imaging endpoints used for this study are not well explained and should be more clearly stated for the readership. Ideally, RECIST measurements and correlation of two imaging assessments should be added
3. There seemed to be 12 drop-outs, the authors should explain why they faced such a large drop-out rate.

4. The outcome of patients on the cetuximab arm overall seemed extremely poor with an overall survival of 3.5 months. One wonders how much this was the result of some introduced bias as a result of potentially too sick patients to join as better results would be expected even with best supportive care. The authors should comment on this more. Certainly one significant bias seems to be highlighted by the very large percentage of poor Veristrat group patients in arm A and indeed it needs to be highlighted that this bias makes it impossible to know whether the differences between the arms are treatment-related or related to accidentally biased assignment of patients to the two arms and this should be highlighted more in Discussion.

5. As standard premedications for pemetrexed include Decadron, one wonders whether this might have influenced rash rates on arm B and rash scaling on cycle 1, day 8. The authors should comment on this possibility.

6. As pemetrexed is felt to have poor activity in squamous cell patients, the authors should comment on impact of histology on outcome measures.

7. The authors find that the Veristrat good predictor class correlated with favorable changes in tumor size- was that noted for both treatment arm or arms combined?

8. The overall data for arm A clearly highlight that cetuximab has no discernible single agent activity in this setting (and would not have made it into phase 2 of a Simon two-phase design). If the authors agree with this statement, this should be stated more firmly in the Discussion. In essence, this aspect should also lead to some consideration for the actual need of developing biomarkers for cetuximab-based therapy and this should be more fairly stated in the Discussion on aspects of future development plans.

9. Many patients, especially on arm A were diagnosed with progressive disease/CNS metastases on brain MRI- were these symptom-directed MRIs. It seems that baseline brain MRIs were not needed. Would results be substantially different in arm A as to survival data if the early brain progressors were excluded?

10. Figure 4 is very difficult to understand and the authors should explain this figure better in the figure legend and make clearer statements as to what conclusions they reach by it.

**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