Reviewers report

Title: Ki-67 is a valuable prognostic predictor of lymphoma but its utility varies in lymphoma subtypes: evidence from a systematic meta-analysis

Version: 1 Date: 30 December 2013

Reviewer: Andrea Janikova

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REVIEW TO THE ARTICLE:
Ki-67 is a valuable prognostic predictor of lymphoma but its utility varies in lymphoma subtypes: evidence from a systematic meta-analysis

In summary, the paper of Xin He and coworkers is not very original, because the proliferative index Ki67 has been used for a very long time in routine clinical practice and its value is generally known and accepted. On the other hand, the global meta-analysis could be useful and interesting for clinicians as well as for pathologists.

Generally I recommend this article for publication, but it will be necessary to revise some points of this article before acceptance:

Major comments:

1) I am not sure, if cut-off positivity was somehow taken account in this analysis. I strongly recommend to emphasize or better comment following facts:

- different cut-off values for Ki-67 index were identified in many retrospective studies, ranging from 10 to 50% (also even if immunohistohemistry used),
- the application of the Ki-67 index in experimental as well as in routine management is limited by relatively high inter-observer variability.

2) Conclusion concerning mantle cell lymphoma and loss of prognostic significance of Ki-67 in rituximab treated patients (based totally on 2 studies only!) is a little bit strange and must be precisely commented. For example, the most recent analysis of Salek and colleagues (Leuk Lymph 2013) which included 144 rituximab-treated patients, revealed that patients with the proliferation rate 30% (Ki-67) and more have significantly higher relative risk of death and shorter overall survival (median OS 22.6 vs 76.4 months, p<0.001).

3) It is necessary to be aware of limitation of rituximab influence itself on prognosis, because significant global changes in treatment strategy (not only rituximab addition) were made since year 2000, which are mirrored in general improvement of overall survival in MCL and DLBCL patients. This fact can also influence the relationship rituximab and Ki-67. Please, comment and explain more in detail the treatment regimens at least main subgroups like high-dose chemotherapy, antracyclins, or more intensive treatment like MaxiCHOP given with or without rituximab subgroups. The same is valid for DLBCL. Please, the
sentence…” Ki-67 expression has prognostic value in DLBCL only following rituximab treatment, while in MCL…”, I think that this interpretation must be corrected…

4) It is necessary to mention, that known negative prognostic factor naturally influence the choice of therapy in these patients, and so, the positive impact of adjusted treatment strategy can paradoxically decrease prognostic significance of such index.

5) Please, comment and interprete your results very carefully also in abstract!

6) Also, in the abstract please specify, which clinical—pathological fetaures of lymphoma have no correlation with Ki-67.

Minor comments:
1) Some english sentences seem to be a little strange, please review english
2) Please, give better titles, comments and footnotes of Figures and Tables