Reviewer's report

Title: Immunophenotypic Identification of High-Risk Monoclonal Gammopathy of Undetermined Significance

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Reviewer: Andy C Rawstron

Reviewer's report:

Identifying the risk of disease progression in patients with MGUS is an important topic and this study helps to confirm previously published data indicating that plasma cell immunophenotype is a powerful prognostic factor.

Major Compulsory Revisions

1) I have no doubt that the phenotype is highly predictive of outcome based on the Salamanca data and our own findings. However a publication of this nature requires statistical justification for the authors’ assertion that they are identifying high-risk MGUS. Ideally the progression-free survival would be presented. It would also be helpful to know the time from diagnosis until progression in the two MGUS patients who developed myeloma, what criteria were used to define progression and whether they had treatment for ROTI.

2) The level of CD45 expression in normal and neoplastic plasma cells is an issue that continues to generate a lot of debate, and I think that some of this arises from the use of different clones and conjugates. It is therefore important that you state exactly which 2D1 conjugate or conjugates were used during the study and if possible provide the fluorochrome and specific combinations for all the antibodies used.

Discretionary Revisions

1) I would prefer if the data in Figure 5 were combined with Figure 4 and all the information was presented in the same format as Figure 4. Figure 6 is probably superfluous because there is sufficient information about this in the text.

2) Overall the flow cytometry looks good and a fine attention to detail is evident. However, I think you understate the importance of CD138 for gating plasma cells. The EMN group recently tested the different gating approaches using CD38/FSC/SSC, or CD38/CD45/FSC/SSC or CD38/CD138/FSC/SSC or CD38/CD138/CD45/FSC/SSC characteristics to identify plasma cells and it was clear that for reproducible detection of neoplastic plasma cells all three gating markers are required (http://www.haematologica.org/cgi/content/full/93/3/431). It is notable that in the Salamanca series, 18% of their MGUS cases have <5% CD19+ plasma cells, whereas in your series 19% of MGUS cases have <10% CD19+ plasma cells. This probably makes very little difference to the overall results for defining MGUS at risk of progression, although it may make it difficult
to reach a consensus about the exact cut-off to use. However, it can make a very big difference when it comes to residual disease monitoring. So this comment is not specifically about the data in the paper, but more a general comment about plasma cell analysis in different settings.

Minor Essential Revisions

1) Page 3 last sentence: “The majority of MGUS patients has a protracted disease course and succumbs due to unrelated conditions”. Should this be: “The majority of MGUS patients have a protracted disease course and die of an unrelated condition”?

2) Page 6, Clinical and laboratory characteristics section: “Statistically significant differences between the MGUS and PCM group were in the…”. Should this be: “Statistically significant differences between the MGUS and PCM group were observed in the…”?

**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