Peer Review File
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**Reviewer A**

*This is a well-written review article with several helpful summative insights into the testing process for DLBCL.*

We thank the review for this very positive review.

*1) It would be helpful to the readers, to summarize and name the various trials that were conducted in the context of COO including naming the trials; some readers might have instant recall depending on the names of these trials e.g. ROBUST, REMoDL, PHOENIX, ECOG-ACRIN E1412 for front line induction and PRELUDE, REMARC, PILLAR etc for maintenance. Several of these trials had disappointing results vis a vis use of targeted agents for the ABC subtype. This point needs to be further emphasized and clarified as to why we still need to test for COO based on the IHC algorithms.*

Reply 1: We thank the reviewer for this helpful comment and agree that it might be helpful to some readers to list the clinical trials by name. The maintenance trials listed here were all negative trials that did not stratify patients by molecular classification and therefore we felt that they fell outside the scope of this review. We do discuss studies that examined the efficacy of non-cytotoxic therapies in later lines of treatment for studies that stratified patients by COO or other molecular differences.

Changes in the text: In order to address this, we added table 2 to summarize the front-line clinical trials and called them out by name in the text of the review.

*2) It is worth noting that at least one of the two classifications i.e. WHO 5th edition does not consider MYC and BCL6 rearrangements to be double-hit and reserves this terminology for only those high-grade lymphomas that harbor both MYC and BCL2 rearrangements. This is due to the heterogeneous nature of DLBCL cases with MYC and BCL6 rearrangements (Cucco F, Barrans S, Sha C, Clipson A, Crouch S, Dobson R, et al. Distinct genetic changes reveal evolutionary history and heterogeneous molecular grade of DLBCL with MYC/BCL2 double-hit. Leukemia 2020;34:1329–41.)*

Reply 2: We thank the reviewer for this helpful critique. We agree that this distinction should be highlighted.

Changes in the text: We have modified the text of the review to include this citation and reflect this caveat to the “double hit” classification.

*3) Traditionally, some institutions have also used the MIB 1 proliferation index and CD5 expression to determine prognosis. A brief discussion with regard to these and their diminished utility would be helpful.*

Reply 3: We agree that discussion of these historically used immunohistochemical tests and their current role would enhance this review article.

Changes in the text: We have added a section ("**Other IHC based testing in DLBCL"** discussing other immunohistochemical stains that focuses on CD5 and Ki-67 expression and their prognostic role for patients with DLBCL.

**Reviewer B**

*Schneider et al, in this comprehensive review, describe advancements in pathologic testing of DLBCL. Review is comprehensive, well written. Following minor edits:*

We thank the reviewer for these positive comments and the very positive review.

*1) Consider a figure summarizing molecular classification of DLBCL, for readers to have an outline of information provided in the manuscript.*

Reply 1: We agree that a summarizing figure will be helpful to allow readers to have an overview of the major points made in the review.

Changes in the text: We have added a figure (Figure 1) to the manuscript summarizing and highlighting some of the key tools used for the molecular characterization of DLBCL.

*2) Since this article describes pathologic testing, I recommend adding a paragraph on role of circulating tumor DNA in prognostication of DLBCL.*

Reply 2: We thank the reviewer for this helpful comment. We agree that it would enrich the review article to give a brief overview of the role of ctDNA testing in DLBCL.

Changes in the text: We have added a short section ("The utility of circulating tumor DNA in DLBCL") describing the potential future role for ctDNA testing in DLBCL.

*3) Could authors comment whether these new classifications have a role in designing "basket trials", offering treatment tailored to specific genetic signatures.*

Reply 3: We agree with this important point. Following the submission of our review article, one such basket trial was published with very exciting results. Trials like these will be invaluable in advancing the ideas presented in our review and using molecular testing to benefit patients with lymphoma.

Changes to the text: Since our initial submission, one such basket trial was published with very encouraging results (Zhang et al. *Cancer Cell* 2023). We explain this trial in the discussion section of the text and it serves as an example of the power basket trials can have in this space.