Peer Review File

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Reviewer A

Comment 1

"CAR-T is superior to conventional second line chemotherapy and autologous stem cell transplant (ASCT) in early treatment failure and is effective as third line therapy even after prior ASCT." --- Recommend having some citations here, e.g., international treatment guidelines. Also recommend being specific as to the type of CAR T, e.g., axi-cel or others (whenever applicable).

Reply 1: We have added text and references for Axi-cel and Liso-cel in 2nd line setting vs ASCT and separated second sentence with references for Axi-cel, Liso-cel, and Tisa-cel in 3rd line and beyond setting.

Lines 22-25

Comment 2

"Patients with r/r LBCL who are older or have significant comorbidities are increasingly being evaluated for CAR-T, but criteria for CAR-T fitness remain poorly defined." --- Recommend being clearer as to the prognosis (good or bad) of patients enrolled in the CAR T clinical trials (per pre-specified inclusion/exclusion criteria) for so far as well as the real-world treatment pattern (per clinicians' judgment for instance). The current description is a bit vague.

Reply 2

We have changed the wording and added the references from real world analysis of Axi-cel and Tisa-cel. Real world analysis is discussed in more detail later in commentary.

Line 27

Comment 3

Recommend specifying the treatment line of patients included in Kuhnl et al in the manuscript in an upfront manner.

Reply 3

Have added sentence that all patients had received two or more lines of therapy

Lines 31-32

Comment 4

“However, there was a significant drop out of unfit patients between CAR-T approval and CAR-T infusion, primarily due to clinical deterioration.” --- Any data to support this statement? Not that I think it’s an incorrect statement, but some evidence to support it would be helpful.

Reply 4

Changed wording of sentence to add percentage 34% (28 of 81)

Line 39

Comment 5

“Patients ≥ 65 years had higher rates of CRS and ICANS but better response rate.” --- Recommend adding quantitative data (in addition to qualitative statement).

Reply 5

Odds ratios added

Lines 46-47 and 59-60

Comment 6

“However, the recent development of CD3/CD20 bispecific antibodies may change the use of CAR-T in this patient population, as the risk of severe ICANS and CRS appears less with glofitamab and epcoritimab (15, 16).” --- This is the first and only time non-CAR T/chemo therapies were brought up. Would it worth either being restricted to CAR T/chemo therapies? Or expand glofi and epcor a bit more in other paragraphs (e.g., those related to discussion of fit or efficacy)?

Reply 6

We believe that bispecific vs CAR-T is a consideration that is being discussed more. We have added a sentence to clarify the difficulties of cross study comparisons.

Lines 117-118

Comment 7

“CAR-T is costly using the available commercial products and has not decreased despite the approval of competing products for LBCL.” --- Did you mean the “CAR T therapy price has not decreased …"? If so, it is advisable to be specific as to countries here (e.g., UK, US)? Also, any insights as to why the CAR T price has not decreased? Because of remaining superiority compared to competitors?

Reply 7

We have reworded this to state that CAR-T is high cost. The discussion of CAR-T cost compared to benefit is beyond the scope of this commentary, and we recognize that the cost varies depending on jurisdiction.

Lines 122-23

Comment 8

"... quality of life studies (QOL) have demonstrated that CAR-T responding recipients have a more rapid return to a normal QOL (17-19)" --- More rapid compare to what patients?

Reply 8

Have clarified that comparison is to ASCT based on Transform & Zuma-7 studies.

Lines 124-25

Comment 9

In general, recommend specifying the geographic location (e.g., UK, US) of studies cited in the manuscript.

Reply 9

We have stated in the text that the Kuhnl et al study is from UK. The references are available to guide the reader to geographic location of the other studies.

Line 30

Comment 10

In general, recommend being precise, providing qualitative and quantitative evidence (along with appropriate citations) throughout the manuscript.

Reply 10

We have added odds ratios as requested above and incorporated additional references as requested above.

Reviewer B

Comment 1

Chen and Maziarz present an expert commentary on an important controversy regarding the definition of "fitness" for CAR-T therapy in patients with large B-cell lymphoma. The authors are clearly very knowledgeable about this topic, but unfortunately the various arguments in the article are presented in a rather intricate manner.

Reply 1

We have used a standard commentary approach of reviewing the article then discussing it in context.

Comment 2

The style of the paper reflects that of a letter proposed to the British Journal of Hematology as a comment to the article published by Kuhnl et al. (2023;202:65-73), but of course this is not the case. Hence, while the paper by Chen and Maziarz relies on the assumption that the reader is familiar with the article by Kuhnl et al., this assumption cannot be made herein -at least in these terms-, and so a more complete description could be needed about the contents of Kuhnl et al.'s article. Alternatively, the style of this commentary might be revised entirely by making less reference to the article by Kuhnl et al.

Reply 2

We wonder if there is a misunderstanding, as our commentary was an invited commentary on the Kuhnl et al article. The first part of our commentary is reviewing the findings of the Kuhn et al article and then second part of our commentary is discussion of the issues it brings up in broader context.

Comment 3

3. Another point of controversy is that an explicit clarification might be needed about the regulatory context to which the authors intend to refer. In the current version, the regulatory context is primarily focused on the United Kingdom, but again it should be kept in mind that this is not the British Journal of Hematology. As proposed below, one solution might be to move the discussion of the regulatory aspects to the final part of the commentary, that is, after the discussion of the clinical aspects (along with the information on efficacy and adverse effects). An opposite solution might be to delete (or reword) lines 26-27 and add a short paragraph summarizing the main approval criteria for CAR-Ts in force in the UK, the US, and Europe. Presenting this regulatory information at the beginning of the commentary could be useful, later on, to better examine the information drawn from Reference 1 (regulatory context = United Kingdom), Reference 4 (regulatory context = United States), and Reference 5 (regulatory context = United States and Canada).

Reply 3

We have removed mention of regulatory approval and payer from our commentary. Instead, we have described the results of the various studies.

Comment 4

Lines 60-61 and lines 136-137: I suggest to avoid making direct reference in this manner to the article published by Kuhnl et al.

Reply 4

Lines 63 (prior 60-61) – have reworded sentence and removed reference to Kuhnl

Lines 136-37 – have reworded sentence