

Reviewer #1:

**Scientific Quality:** Grade C (Good)

**Language Quality:** Grade B (Minor language polishing)

**Conclusion:** Major revision

**Specific Comments to Authors:** Retrospective data about liver transplant in India I wonder the effect of DAA on this practice Use of aletizumab before transplant is questionable How the details of manuscript predict burden of disease in 2040 is not clear.

Dear Reviewer,

On behalf of all the authors, I would like to thank you for your time to review our invited opinion piece article on HCC and liver transplantation. Your comments are very helpful and we have made the following changes.

1. Retrospective data about liver transplant: Dear reviewer, as this is an opinion piece about the current incidence and prevalence of HCC and the current trends and practices of LT for HCC, it is naturally based on retrospective data. The idea is to assimilate the existing literature about the recent future and conduct a survey to find out the present trends in HCC management with respect to LT. The overall goal is to establish how different set criteria (eg. Milan or UCSF) are used in India currently and the way going forward in the future.

2. The effect of DAA on this practice: Dear reviewer, thanks for your comment. We have added the relevant information under "Discussion" under the sub-heading "Selection Criteria for HCC" and the lines are highlighted in yellow and new references also have been added.

3. Use of atezolizumab before transplant: Thank you for your comment, the reviewer is absolutely correct in this respect. The use of immunotherapy prior to LT has always been controversial. Prior to atezolizumab/bevacizumab combination there was nivolumab, pembrolizumab and ipilimumab, with limited success. Since 2020, this Ate/Beva combination (PDL-1 inhibitor/VEGF inhibitor) demonstrated a significant survival benefit over the standard therapy, sorafenib, in the IMBrave 150 trial.

There is significant concern regarding the safety of using immunotherapy in patients with HCC who may later undergo liver transplant, especially given the risk of immune-related adverse events. The most frequently affected organs by immune-related adverse effects include the liver, colon, lung, skin and endocrine tissue. In the IMBrave 150 trial, grade 3 to 4 toxicities were reported in 38% of patients receiving combination therapy with atezolizumab and bevacizumab. The most frequent events were hypertension, fatigue and proteinuria. Bevacizumab has also demonstrated an increased risk of bleeding.

However, over the past 3 years, several case reports and small series have been reported with successful bridge to transplant using combination immunotherapy of Ate/Beva. **(see references at end)** Also, the most recent BCLC guidelines recommend Ate/Beva as first line for PVTT. **(see references at end)** In this respect, we have just taken an opinion regarding the use in India. We do not advocate for or against the use in our article. We have added a couple of lines in the article discussion to highlight the controversial nature of immunotherapy prior to LT (highlight in yellow under Discussion under "Downstaging for HCC" sub-heading).

4. How the details of manuscript predict burden of disease in 2040 is not clear: Thank you for your comment. The authors would like to point out that this is an invited opinion piece on the current trend of practices of HCC management with respect to LT in India. The purpose is not to predict the burden of HCC but simply to present the literature and the survey is to show us how we are

progressing towards the next 2 decades in the future. So, we have not made any attempt to predict or to give any recommendations, but just our opinion and the results of our survey in this article.

5. English Language Editing: Painstaking efforts have been made to improve the English language and Editage has helped us with this. They have provided an editing certificate which is being attached along with.

Once again, we thank you for your time and wish you a good day.

#### References:

- Giudicelli H, Roux C, Monsel A, Conti F, Scatton O, Allaire M. Successful advanced hepatocellular carcinoma downstaging with atezolizumab-Bevacizumab and radioembolization before liver transplantation. *Clin Res Hepatol Gastroenterol*. 2023 Aug;47(7):102167.
- Pramod Kumar, Krishna Pradeep, Ravindra Nidoni, et al. THE SUCCESSFUL DOWNSTAGING WITH ATEZOLIZUMAB/BEVACIZUMAB FOR LIVER TRANSPLANTATION IN HEPATOCELLULAR CARCINOMA WITH PORTAL VEIN THROMBOSIS. *JCEH* 2023 Jul. <https://doi.org/10.1016/j.jceh.2023.07.122>
- Chouik Y, Erard D, Demian H, Schulz T, Mazard T, Hartig-Lavie K, Antonini T, Mabrut JY, Mohkam K, Rode A, Merle P. Case Report: Successful liver transplantation after achieving complete clinical remission of advanced HCC with Atezolizumab plus Bevacizumab combination therapy. *Front Immunol*. 2023 Jun 12;14:1205997.
- M. Abdelrahim<sup>1</sup> , G. OKane<sup>2</sup> , A. Esmail<sup>1</sup> , et al. Atezolizumab and bevacizumab pre-liver transplantation for patients with hepatocellular carcinoma beyond Milan criteria. *Annals of Oncology* 2022 Apr. <https://doi.org/10.1016/j.annonc.2022.04.252>
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- Schwacha-Eipper B, Minciuna I, Banz V, Dufour JF. Immunotherapy as a Downstaging Therapy for Liver Transplantation. *Hepatology*. 2020 Oct;72(4):1488-1490.
- Ouranos K, Chatziioannou A, Goulis I, Sinakos E. Role of immunotherapy in downsizing hepatocellular carcinoma prior to liver transplantation. *World J Transplant*. 2022 Nov 18;12(11):331-346.
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