Reply

TO THE EDITOR:

We read with interest the recent contribution by Yang et al.[1]

Data on the use of immunotherapy in liver transplantation (LT) recipients have shown that immune checkpoint inhibitor (ICI)–based anticancer therapy in these patients does not necessarily cause graft rejection.[2] Therefore, in some cases, the possibility of rejection might be regarded as preferrable to the certainty of disease progression. To this regard, some cautionary remarks appear to be necessary.

1. Rejection rates in LT recipients upon treatment with ICI have not yet been accurately determined. In two recent reports, a 30% to 37.5% likelihood of rejection was described, with the time interval between ICI initiation and LT appearing to influence the risk of rejection.[3,4] However, rejection itself might be difficult to distinguish from other causes of liver dysfunction (eg, intrahepatic tumor progression). Furthermore, rejection rates might be underestimated as a result of publication bias.
2. If the risks of ICI use in LT recipients are scarcely known, to assess their efficacy is even more difficult. Tumor-specific immune responses might be compromised by immunosuppression, and data from non-LT populations should not be used as measures of the potential clinical benefit. Although objective responses from case series suggest efficacy, disease control and survival are difficult to estimate in the absence of a control population. It is therefore difficult to weigh the risk-benefit ratio of using ICI after LT. ICI should thus not be considered until other potentially effective alternatives have been administered.
3. To date, there is no reliable method to predict liver rejection upon treatment with ICI in LT recipients (just as there are no predictive markers of response or toxicity to ICI in hepatocellular carcinoma). Positive programmed cell death ligand 1 (PD-L1) staining in the graft was suggested as a potential predictor of rejection.[2] In one case, Yang et al.[1] based the initiation of ICI on negative PD-L1 expression in the graft biopsy. However, the purported correlation between PD-L1 staining and graft rejection is based on episodic reports and should not be relied on as predictive biomarker of rejection. We nevertheless suggest that biopsies are taken prior to ICI initiation in LT patients to further investigate the potential biomarkers of rejection. Pretreatment biopsies will also allow assessment of suspected organ rejection with respect to a baseline histology.
4. Finally, it should be remembered that every therapeutic decision must be based on the informed consent of the patients and their families. It is our duty to provide information to the best of our knowledge. In this case, this means acknowledging the highly experimental nature of the use of ICI in this setting, the uncertainty of the clinical benefit, and the impossibility of predicting a potentially fatal outcome.

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Received December 2, 2021; accepted December 14, 2021.

View this article online at wileyonlinelibrary.com.

DOI 10.1002/lt.26410

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