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Neoadjuvant atezolizumab plus bevacizumab prior liver transplantation for hepatocellular carcinoma

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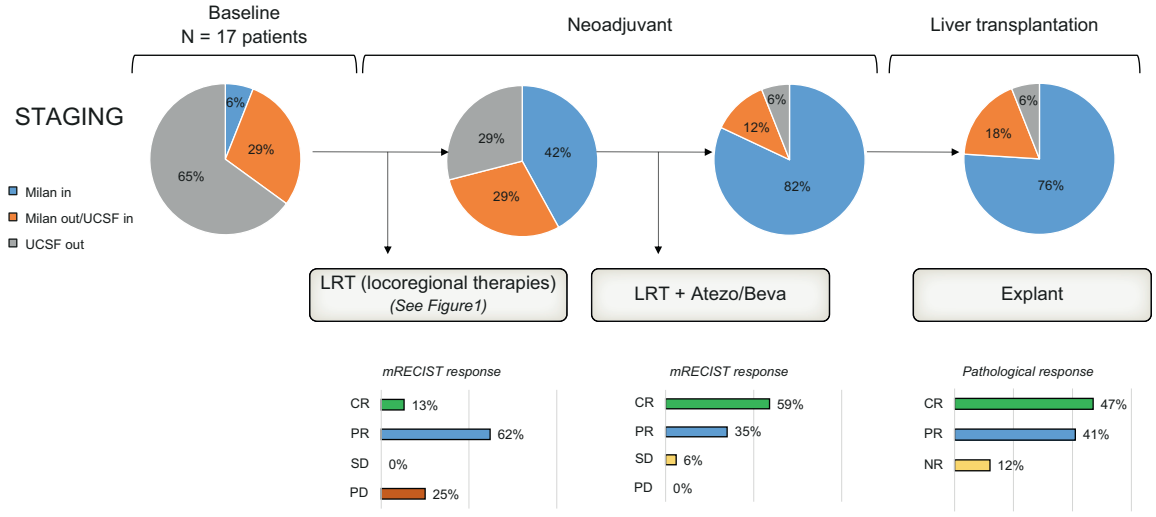
Graphical abstract



Highlights:

- A prospective assessment of 17 patients who underwent successful LT following neoadjuvant atezolizumab + bevacizumab was performed.
- A total of 82% of patients achieved downstaging to within Milan criteria, 94% achieved radiological objective response and 88% achieved pathological response.
- No drop-outs due to treatment-related adverse events or graft loss were recorded.
- Neoadjuvant atezolizumab+bevacizumab is a promising option in the pre-LT setting.

Impact and Implications:

Studies on the combination of atezolizumab and bevacizumab in the neoadjuvant setting prior to liver transplantation for hepatocellular carcinoma have been limited, despite its potential to enhance anti-tumor responses and downstaging, owing to concerns about its safety profile. Among 17 patients who underwent successful liver transplantation following neoadjuvant atezolizumab/bevacizumab, 82% achieved downstaging to within Milan criteria, 94% radiological objective response and 88% pathology response, without drop-outs due to treatment-related adverse events or graft loss. The neoadjuvant combination of atezolizumab plus bevacizumab prior to liver transplantation for hepatocellular carcinoma shows an encouraging safety profile and stands out as a promising pre-transplant optimization treatment, leading to improved oncological outcomes.

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Neoadjuvant atezolizumab plus bevacizumab prior liver transplantation for hepatocellular carcinoma☆

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Background & Aims: The combination of atezolizumab and bevacizumab offers a novel approach to immunomodulation, showing efficacy as a primary treatment in advanced hepatocellular carcinoma (HCC). Concerns about graft safety and rejection have limited its exploration in the neoadjuvant setting of liver transplantation (LT). In this study, we investigate the clinical efficacy and the safety profile of pre-transplant administration of atezolizumab and bevacizumab for HCC.

Methods: Herein, we performed a prospective assessment of 17 patients with HCC treated with neoadjuvant preoperative atezolizumab and bevacizumab prior to LT for HCC, obtained from December 2020 and December 2023 at seven Western transplant centers.

Results: Among the 17 patients with HCC included in the study, 16 (94.1%) had a tumor burden outside of Milan criteria. Neoadjuvant locoregional therapies along with the administration of atezolizumab plus bevacizumab (median: 5 months; discontinued at least 4 weeks prior to LT) led to an objective response rate of 94% (complete response: 59%), downstaging to within Milan criteria (82%) and a pathological response at explant examination of 88%. Grade 3-4 treatment-related adverse events accounted for 17.6% of cases and were manageable. During the 25-month median follow-up period, two cases of mild (rejection activity index ≤4), biopsy-proven rejection were reported but no instances of severe allograft rejection or graft loss were reported. The 1-year and 3-year post-LT survival rates were 94.2% and 88.2%, respectively.

Conclusions: This study highlights the favorable oncological and survival outcomes associated with atezolizumab and bevacizumab treatment in the pre-LT setting. This immune-based combination was safe in terms of treatment-related adverse events, and absence of severe post-transplant rejection or graft loss. These preliminary results could pave the way for expanding transplant eligibility criteria in patients at more advanced HCC stages.

Introduction

Hepatocellular carcinoma (HCC) remains a global health problem, with liver transplant (LT) being the established gold standard treatment for patients within the Milan criteria (MC).[1] Moderate expansion of these criteria leads to acceptable, competitive long-term outcomes, with bridging therapies used in patients on the waiting list to reduce patient dropout rates and decrease tumor burden.[2–6] This treatment period enables the identification of candidates with favorable tumor biology who may be suitable for transplant.

The advent of immunotherapies, particularly atezolizumab plus bevacizumab (atezo+beva), has revolutionized HCC therapy.[7,8] Combining locoregional therapy (LRT) with immunotherapy in the pre-LT setting has the potential to enhance immune responses as a result of the neo-antigen release, and might expand the range of bridging and downstaging options.

Reports on the efficacy and safety of this combination in transplant recipients – for whom immunotherapy has been discouraged due to the risk of severe rejection and graft loss – have been obtained from heterogenous cohorts, including a mix of single and combined regimens outside guidelines, leading to preliminary results.[9–12]

To address ongoing concerns, particularly regarding safety and efficacy, we present the largest experience with the neoadjuvant use of atezo+beva prior to LT for HCC, based on data from high-volume transplant centers.

Patients and methods

A prospectively maintained database of adult patients transplanted for HCC between 12/2020-12/2023 at seven international high-volume centers was analyzed. The study was approved by the institutional review boards of the participating

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Table 1. Characteristics of the HCC patients at diagnosis, at time of transplant and explant pathology.

Characteristics at diagnosis	All patients, N = 17
Age, median (IQR), years	61 (58–65)
Male sex – n (%)	14 (82.4%)
BMI, median (IQR), kg/m^2	24.9 (23.2–28.7)
Underlying liver disease – n (%)	
HCV	6 (35.3%)
HBV	4 (23.5%)
MASLD	3 (17.6%)
ALD	1 (5.9%)
Other	3 (17.6%)
MELD, median (IQR)	9 (7–10)
Child-Pugh class	
A	14 (82.4%)
B	3 (17.6%)
AFP at diagnosis, median (IQR), ng/ml	181.1 (5.70–1,775)
AFP at diagnosis – n (%)	
<400 ng/ml	8 (47.1%)
400–1,000 ng/ml	4 (23.5%)
>1,000 ng/ml	5 (29.4%)
Pre-ICI largest viable tumor diameter – n (%)	
<3 cm	2 (11.8%)
3–5 cm	7 (41.2%)
>5 cm	8 (47.1%)
Number of tumors, median (IQR)	3 (1–4)
Total tumor diameter, median (IQR), cm	8.4 (6.00–12.1)
Criteria for liver transplantation	
Milan in	1 (5.9%)
Milan out/up-to-Seven in/UCSF in	5 (29.4%)
UCSF out/up-to-Seven in	2 (11.8%)
UCSF out/up-to-Seven out	9 (52.9%)
Characteristics at the time of liver transplant	**All patients, N = 17**
AST, median (IQR), U/L	51 (32–106)
ALT, median (IQR), U/L	56 (39–111)
Total Bilirubin, median (IQR), mg/dl	1.24 (0.79–2.55)
Creatinine, median (IQR), mg/dl	0.87 (0.71–1.12)
INR, median (IQR)	1.12 (1.01–1.29)
Platelet median, (IQR) 10^9/L	129 (77–185)
Neutrophil to Lymphocyte ratio, median (IQR), ng/mL	2.16 (3.54–5.14)
AFP, median (IQR), ng/ml	3.15 (2.20–6.30)
Pre-LT downstaging strategy – n (%)	
Atezolizumab/Bevacizumab only	1 (5.9%)
Atezolizumab/Bevacizumab + LRT	16 (94.2%)
Sessions of pre-LT LRT per patient – n (%)	
0	1 (4.2%)
1	9 (37.5%)
2	8 (33.3%)
3	3 (12.5%)
≥4	3 (12.5%)
Type of first LRT – n (%)	
Y90	6 (35.3%)
TACE	4 (23.5%)
Ablation	2 (11.8%)
SBRT	1 (5.9%)
Other	3 (17.6%)
Pre-LT resection – n (%)	3 (17.6%)
Number of ICI cycles, median (IQR)	7 (5.0–18.0)
Duration of ICI, median (IQR), months	7 (4.0–13.0)
Washout period (last ICI prior to LT), median (IQR), days	78 (41–123)
Washout period (last ICI prior to LT) – n (%)	
30-60 days	4 (23.5%)
60-90 days	9 (52.9%)
>90 days	4 (23.5%)
Best mRECIST response to ICI – n (%)	
Stable	1 (5.9%)
Partial	5 (29.4%)
Complete	11 (64.7%)
Pre-LT largest viable tumor diameter – n (%)	
<3 cm	15 (88.2%)
3–5 cm	2 (11.8%)
>5 cm	0 (0.0%)
Pre-LT number of viable tumors, median (IQR)	1 (0–2)
Pre-LT maximum total viable tumor diameter, median (IQR), cm	0.5 (0.0–4.00)
Criteria for Liver Transplantation	
Milan in	14 (82.4%)
Milan out/up-to-Seven in/UCSF in	2 (11.8%)
UCSF out/up-to-Seven in	0 (0.0%)
UCSF out/up-to-Seven out	1 (5.9%)
MELD, median (IQR)	10 (8–13)
Explant pathology	**All patients, N = 17**
Criteria for liver transplantation	
Milan in	13 (76.5%)
Milan out/up-to-Seven in/UCSF in	1 (5.9%)
UCSF out/up-to-Seven in	0 (0.0%)
UCSF out/up-to-Seven out	3 (17.6%)
Number of viable tumors, median (IQR), cm	1 (0–3)
Maximum total viable tumor diameter, median (IQR), cm	1.4 (0–7.20)
Pathological response – n (%)	
Complete response	8 (47.1%)
Partial response	7 (41.2%)
Non-response	2 (11.8%)
Vascular invasion – n (%)	
Absent	13 (76.5%)
Microvascular	4 (23.5%)
Macrovascular	0 (0.0%)
Grade – n (%)	
Well differentiated	2 (11.8%)
Moderately differentiated	6 (35.3%)
Poorly differentiated	1 (5.9%)
NA (complete necrosis)	8 (47.1%)

Normally distributed continuous variables are reported as means and standard deviation, non-normally distributed variables as median and IQR, and categorical variables as numbers and percetages.

AFP, alpha-fetoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; HCC, hepatocellular carcinoma; ICI, immune checkpoint inhibitor; LRT, locoregional therapy; LT, liver transplant; MC, Milan criteria; MELD, model for end-stage liver disease; ORR, objective response rate; SBRT, stereotactic body radiotherapy; TACE, transarterial chemoembolization; UCSF, University of California San Francisco.

institutions, and each Institutional Medical Ethics Committee waived the requirement for individual informed consent. Patients receiving atezo+beva prior to transplant were included, whereas patients receiving other immunotherapies, or with extrahepatic disease or other tumors (cholangiocarcinoma or mixed) were excluded. The study endpoints were assessment of response, downstaging rate, overall survival, safety measured as treatment-related adverse events (TRAEs) in the neoadjuvant setting and rejection/graft loss after transplant.

Neoadjuvant therapies included LRT first, as per clinical practice guidelines,[1,13] followed by atezo+beva therapy given up to 4 weeks prior to LT. Atezo+beva was used as a downstaging or bridging therapy based on tumor characteristics and multidisciplinary clinical judgment, regardless of initial MC

Table 2. Safety assessment of neoadjuvant immunotherapy.

Adverse events	n (%)	
Pre-transplant adverse events from any cause	10 (58.8%)	
Grade 3 or 4 event	5 (29.4%)	
Grade 5	0 (0.0%)	
Adverse event leading to atezo+beva withdrawal	4 (23.5%)	
TRAEs leading to atezo+beva withdrawal	2 (11.8%)	
Pre-transplant ICI-related adverse events)	8 (47.1%)	
Systemic-treatment TRAEs – n (%)	**Any grade**	**Grade 3-4**
n = 11*	11 (64%)	3 (17.6%)
Hypertension	3 (27.3%)	0 (0.0%)
Thrombocytopenia	2 (18.2%)	2 (18.2%)
AST/ALT increase	3 (27.3%)	0 (0.0%)
Hyperthyroidism	1 (9.1%)	0 (0.0%)
Autoimmune esophagitis	1 (9.1%)	1 (9.1%)
Asthenia	1 (9.1%)	0 (0.0%)
Rejection <90 days	2 (11.8%)	
Mild (RAI 3-4)	2 (11.8%)	
Moderate (RAI 5-6)	0 (0.0%)	
Severe (RAI 7-9)	0 (0.0%)	
Postoperative complications, Clavien-Dindo		
Minor (Clavien I-II)	4 (23.5%)	
Severe (Clavien ≥III)	6 (35.3%)	
Graft losses		
1-year post-LT overall survival	16 (94.2%)	
3-years post-LT overall survival	15 (88.2%)	
RETREAT score, median (IQR)	3 (0–5)	
1-year disease free survival	16 (94.2%)	
3-year disease free survival	16 (94.2%)	

Normally distributed continuous variables are reported as means and standard deviation, non-normally distributed variables as medians and IQR, and categorical variables as numbers and percentages.
ICI, immune checkpoint inhibitor; RAI, rejection activity index; TRAEs, treatment-related adverse events.
*Please note that when referring to the total number of ICI-related adverse events, some patients might have experienced more than one adverse event during the course of treatment. All percentages are calculated over the grand total of ICI-related adverse events experienced (11).

status. It was primarily administered to patients who had exhausted LRT options, had high alpha-fetoprotein (AFP) levels (>400 ng/ml), or had tumors unsuitable for LRT. Atezo+beva were administered at a dose of 1,200 mg and 15 mg/kg every 3 weeks, respectively. Treatment response was evaluated by mRECIST (CT or MRI) every 3 months. Pathological response was defined as complete (100%) or partial (>70% HCC necrosis) at the explant analysis.

After successful HCC downstaging, patients were eligible for a model for end-stage liver disease exception and were listed for transplantation, following the required 6-month waiting period.

Standardized immunosuppressive protocols were used consistently throughout the study. Corticosteroids were used (initial dose of 500 mg during transplant, tapering over 2 weeks to 10 mg daily) in combination with mycophenolate mofetil (1 g every 12 h) and tacrolimus dose was adjusted to maintain a serum concentration of 8-12 ng/ml. One patient received induction (anti-IL2 receptor antibody) therapy prior to LT. Diagnosis of recurrence was based on imaging and/or pathology. Biopsies were performed to investigate all suspected cases of acute rejection, with allograft rejection graded histologically according to the Banff working group classification.

Statistical analysis

All statistical analyses were conducted using SPSS 28.0 (Chicago,IL,USA). Normally distributed continuous variables were reported as means ± SD, while non-normally distributed variables were reported as medians and IQR. Categorical variables were presented as numbers and percentages.

Results

During the 3-year period, 17 patients received neoadjuvant atezo+beva and were transplanted (15 deceased donors including 4 donation after circulatory death donors; 2 living donors). Median follow-up post-transplant was 25 months (IQR 11–32 months). Patient and baseline tumor characteristics are shown in Table 1. At diagnosis, the median patient age was 61 years, with tumors outside MC in 16 patients (94%) and AFP >1,000 ng/ml in 30% of cases.

Assessment of downstaging and response

Neoadjuvant LRT – either transarterial chemoembolization (47%) or Yttrium-90 radioembolization (35%) – were performed at baseline, with an objective response rate (ORR) of 75%

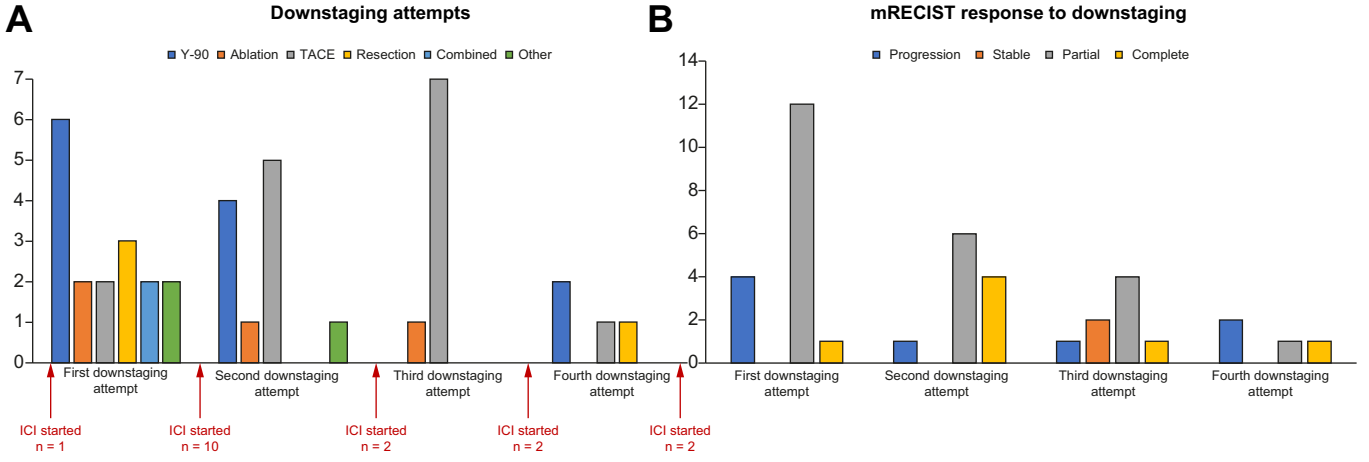

Fig 1. Downstaging attempts and response to such attempts. (A) Overall timeline of all downstaging attempts categorized according to the strategy employed (LRT and/or Resection) and time of ICI start in relation to the downstaging attempts. (B) Radiologic response according to mRECIST criteria to downstaging attempts. ICI, immune checkpoint inhibitor; LRT, locoregional therapy.

(complete response rate [CRR] of 13%) and downstaging to MC in 42% of cases (Table 1). Afterwards, atezo+beva was administered for a median of 5 months, leading to an ORR of 94% (CRR of 59%) and downstaging to within MC in 14 patients (82% of cases). Median AFP level at diagnosis was 181.1 ng/ml (IQR 5.70-1,775 ng/ml) and significantly decreased prior to LT to 3.15 ng/ml (IQR 2.20-6.30 ng/ml; p <0.001). Explant analysis confirmed a pathological response in 88% of cases, with 47% showing complete pathological response (cPR). The median viable tumor diameter was 1.4 cm (IQR 0-3 cm), and microvascular invasion was present in 23.5% of cases, with no evidence of macrovascular invasion. Pathological tumor staging revealed 13 patients (76.5%) with tumors within MC, three patients (17.6%) with more advanced stage than on the pre-LT imaging and one patient (5.9%) whose stage was consistent with pre-LT imaging findings (Table S1). The timeline of downstaging attempts categorized according to the strategy employed and the radiologic response are summarized in Fig. 1.

Safety assessment

The median exposure to atezo+beva was 5 months (7 cycles; IQR 5-18 cycles), and 88.2% of patients received more than four treatment cycles. All treatments were discontinued at least 4 weeks (washout period) prior to LT (41-123 days pre-LT), and the majority within 3 months before LT (10 patients, 58%). TRAEs occurred in eight patients (Grade 3-4: 17.6%), and led to discontinuation in two cases (11.8%) related to thrombocytopenia, after completing four and five cycles, respectively (Table 2). Overall, three patients required systemic corticosteroids for the medical management of Grade 3-4 TRAEs.

The median hospital stay for transplant was 14 days (IQR 10-25 days), with 0% perioperative mortality. Regarding perioperative rejection, assessed according to the rejection activity index, two cases (11.8%) of mild rejection (rejection activity index ≤4) occurred (Table 2), which were successfully treated with optimization of immunosuppressant regimens and corticosteroid pulses, and no cases of moderate/severe rejection were reported. Severe postoperative complications were recorded in six patients (35.3%) (Table 2). After a median of 25 months of follow-up, no major allograft rejections or losses were encountered. The 1-year and 3-year survival rates were 94.2% and 88.2% post-LT, respectively. Two deaths occurred, one related to lung/bone HCC recurrence at 8 months, and the other to postoperative comorbidities beyond 90 days, leading to multiorgan failure.

Discussion

In this multicenter study, we provide evidence supporting the use of atezo+beva in the neoadjuvant setting prior to LT for HCC. First, we establish the efficacy of combining LRT and immunotherapies in the pre-LT setting, whose rationale is based on the immune-related response to the release of neoantigens[8] and better progression-free survival in intermediate HCC.[8,13] In our study, LRT alone led to an ORR of 75%, and was further improved with the addition of immunotherapy, thus achieving 94% ORR (including 59% CR) and downstaging to Milan in 82% of cases. These results are competitive with the best outcomes reported so far in terms of downstaging (MERITS-LT consortium study[2] and XXL Italian study[4]).

Our good preoperative outcomes were followed by favorable pathological response, a feature associated with reduced recurrence rates and improved survival outcomes.[14,15] In a study of 3,439 LT recipients, 23% achieved cPR, resulting in markedly lower 5-year (5.2%) incidences of HCC recurrence, and superior survival rates compared to those without cPR.[14] In our cohort, 88% achieved pathological response with almost ~50% cPR. The 1-year and 3-year survival rates post-LT were 94.2% and 88.2%, respectively.

Secondly, we report an encouraging safety profile. After a median of 5 months of treatment, 17.6% grade 3-4 TRAEs occurred and these were manageable as previously reported.[7,8] Similarly, post-LT biopsy-proven rejections were mild, despite 60% of patients receiving their last dose within 3 months prior to transplant. Reported rates of graft rejection have ranged from 25% to 54%, often resulting in post-LT mortality.[8,10,12]

The safety profile observed in our cohort is consistent with, and may even surpass, recent findings from a systematic review and meta-analysis on pre-LT immune checkpoint inhibitors. This review of 91 patients reported a 26.4% rate of allograft rejection, with over 80% managed successfully with similar overall survival rates in patients with and without rejection. Our results confirm that pre-LT immune checkpoint inhibitors are associated with a reliable postoperative safety profile and could play a crucial role in expanding access to LT.[10] Similarly, the reported median washout period of 78 days is consistent with previous findings and further highlights that washout periods of less than 30 days could potentially lead to higher rejection rates.[10]

As a retrospective review of a prospectively maintained LT database, this study may be subject to selection bias, as the number of patients who received the atezo+Beva combination but dropped out is unknown. While it represents the largest cohort for pre-LT neoadjuvant atezo+beva, the small sample size and variability in locoregional treatments used prior to and alongside immunotherapy emphasize the pressing need for prospective clinical trials.

Our study frames a clinical scenario where atezo+beva can be safely applied by adopting a minimum pre-transplant washout period with good clinical outcomes and marginal impact on rejection. Thus, initial concerns about graft rejection have been alleviated, but clinical trials are needed to confirm these encouraging results in terms of safety and efficacy measurements.

Affiliations

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Abbreviations

AFP, alpha-fetoprotein; atezo+beva, atezolizumab plus bevacizumab; CRR, complete response rate; HCC, hepatocellular carcinoma; LT, liver transplant; MC, Milan criteria; ORR, objective response rate; TRAEs, treatment-related adverse events.

Financial support

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Conflict of interest

J.M.L received research support from Eisai Inc, Bayer HealthCare Pharmaceuticals, and Sagimet, and consulting fees from Eisai Inc, Merck, Genentech, Roche, AstraZeneca, Bayer HealthCare Pharmaceuticals, Moderna, Bristol-Myers Squibb, Exelixis and Glycotest. M.I. received consulting fees, travel grants or lectures honoraria from EISAI, IPSEN, MSD, Gilead, Astra-Zeneca, Roche, Roche Diagnostics. P.T received lecture honoraria from Astra-Zeneca, Bayer, Boston Scientific. All others no COI.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

P.T, R.M, J.M.L: Conceptualization, Methodology, Validation, Investigation, Writing – Original Draft, Writing – Review & Editing. P.T, J.M.L, V.M: Project Administration, Supervision. R.M: Software, Formal Analysis, Data Curation. M.Z: Software, Writing – Original Draft, Data Curation. S.B, V.M, N.S: Validation, Writing – Review & Editing, Methodology. N.M, V.B: Validation, Writing – Review & Editing, Supervision. S.G, M.I: Supervision, Writing – Review & Editing, Resources. C.M: Writing – Review & Editing, Resources, Data Curation. All authors critically reviewed and approved the final manuscript.

Data availability statement

Data supporting the findings of this study are available from the corresponding author upon reasonable request.

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Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhepr.2024.101246.

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