We read with interest the manuscript (1) by Bruix et al. regarding a European Association for the Study of the Liver (EASL) position paper on the systemic treatment of hepatocellular carcinoma (HCC). Systemic treatment options for advanced HCC are remarkably increasing. Effective immune checkpoint inhibitors (ICIs) have recently emerged. The combination of atezolizumab with bevacizumab (IMbrave150) (2) and that of tremelimumab with durvalumab (HIMALAYA trial) (3) have achieved positive results in phase 3 trials in comparison to treatment with sorafenib. These two regimens are promising and are recommended for the first-line treatment according to the latest Barcelona Clinic Liver Cancer (BCLC) staging system (4). As the authors also point out, effective post-progression tyrosine kinase inhibitors (TKIs) have not been established yet.

IMbrave150 (2) demonstrated that atezolizumab plus bevacizumab (Atez/Bev), which is an anti-programmed cell death ligand 1 (PD-L1) inhibitor combined with a monoclonal antibody targeting vascular endothelial growth factor (VEGF), improved survival in previously untreated patients in comparison to sorafenib treatment. The hazard ratio (HR) for death with Atez/Bev was 0.58 [95% confidence interval (CI): 0.42–0.79]. The overall survival (OS) and progression-free survival (PFS) were well stratified, and the quality of life in Atez/Bev group remained better than that in the sorafenib group. The HIMALAYA trial (3) which was designed to compare a high priming dose of tremelimumab plus durvalumab (Dur/Tre) versus sorafenib, reported that the STRIDE regimen significantly extended OS in comparison to the sorafenib arm. The HR for death with Dur/Tre was 0.76 (95% CI: 0.61–0.96). The Dur/Tre regimen is the first approved combination therapy with anti PD-L1 and anti-cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody for advanced HCC. COSMIC-312 trial (5) evaluated the efficacy and safety of cabozantinib plus atezolizumab in patients with advanced HCC as first-line treatment in comparison to sorafenib. The COSMIC-312 (5) did not show improvement of the OS in patients who received cabozantinib plus atezolizumab. Checkmate 459 (6) investigated nivolumab monotherapy vs. sorafenib in treatment-naive patients. Nivolumab resulted in better OS; however, the result did not reach statistical significance. KEYNOTE-240 (7) assessed the efficacy and safety of pembrolizumab monotherapy in comparison to best supportive care in patients previously treated with sorafenib. Pembrolizumab resulted in improved OS and PFS; however, with the specified criteria, the results did not
**Table 1** Summary of global RCTs of ICI treatment

| Study          | Study arm          | Treatment arm | Treatment Sample size | PS 0/1/2 (%) | BCLC stage A/B/C (%) | Child-Pugh AS/A6/B7 (%) | Stratification factors                                                                 | Median OS (months) | Median PFS/TTP (months) | ORR (RECIST) | Grade ≥3 AEs (%) | irAEs requiring immunosuppressive therapy (%) | Subsequent treatment (%) |
|----------------|--------------------|---------------|-----------------------|--------------|----------------------|-------------------------|-------------------------------------------------------------------------------|-------------------|-----------------------|-------------|------------------|-----------------------------------------------|-------------------------|
| IMbrave150     | Atez/Bev; Sorafenib| First line    | 336; 165              | 62/38/0; 62/38/0 | 2/15/82; 4/16/81    | 72/28/0; 73/27/0         | Geographic region (Asia excluding Japan vs. the rest of the world); AFP (<400 vs. ≥400 ng/mL); MVI or EHS or both (yes or no); PS | NE; 13.2          | 6.8; 4.3              | 27.3         | 56.5            | 12.2; NE                                      | 36; 52                  |
| HIMALAYA       | Dur/Tre; Sorafenib | First line    | 393; 389              | 62.1/37.7/0.3; 62.0/37.8/0.3 | 0/19.6/80.4; 0/17.0/83.0 | 7.1/26.2/2.6           | MVI; Etiology of liver disease (viral vs. non-viral); PS                       | 16.43             | 3.78                  | 20.1; 5.1   | 50.1          | 20.1; 1.9                                    | 40.7; 45.0              |
| COSMIC-312     | CAB/Atez; Sorafenib| First line    | 432; 217              | 64/36/<1; 66/34/0 | 0/32/68; 0/35/65    | 100 (CP-A); 100 (CP-A)   | Etiology of liver disease (viral vs. non-viral); geographical region (Asia vs. other); MVI or EHS or both (yes or no) | 15.4              | 6.8; 4.2              | 11; 6         | 76; 57         | 7; NE                                          | 20; 37                  |
| Checkmate 459  | Nivolumab; Sorafenib| First line    | 371; 372              | 73/27/0; 70/30/0 | 4/14/82; 5/17/78    | 98 (CP-A); 96 (CP-A)     | Etiology of liver disease (viral vs. non-viral); geographical region (Asia vs. other); MVI or EHS (yes or no) | 16.4              | 3.7; 3.8              | 15; 7         | 22.3; 49.6     | 8 (hepatitis), 3 (rash); <1 (rash)            | 49; 53                  |
| KEYNOTE-240    | Pembrolizumab; BSC | Second line    | 278; 135              | 58.3/41.7/0; 52.6/47.4/0 | 0/20.1/79.9; 0/21.5/78.5 | 63.3/36.3/0.4; 63.7/34.8/1.5 | Geographic region (Asia without Japan vs. non-Asia with Japan); MVI (yes or no); AFP (<200 vs. ≥200 ng/mL) | 13.9              | 3.0; 2.8              | 18.3; 4.4    | 52.0; 46.3    | 8.2; 0.7                                       | 41.7; 47.4              |

RCT, randomized control trial; ICI, immune checkpoint inhibitor; Atez/Bev, atezolizumab plus bevacizumab; Dur/Tre, durvalumab plus tremelimumab; CAB/Atez, cabozantinib plus atezolizumab; BSC, best supportive care; PS, performance status; BCLC, Barcelona Clinic Liver Cancer; CP-A, Child-Pugh class A; AFP, α-fetoprotein; MVI, macroscopic vascular invasion; EHS, extrahepatic spread; OS, overall survival; PFS, progression-free survival; TTP, time to progression; NE, not evaluated; ORR, objective response rate; AEs, adverse events; irAEs, immune-related adverse events.
reach statistical significance. We described a summary of these recent global ICI trials in Table 1.

One problem is which treatment should be selected, Atez/Bev or Dur/Tre? The criteria for using these two regimens as the first-line treatment remain to be determined. One of the key points to be judged is whether or not anti-VEGF therapy is acceptable and tolerable. VEGF induces some adverse events (AEs), including hypertension, proteinuria, thromboembolic events, impaired wound healing, and hemorrhage, including bleeding from gastrointestinal sites. IMbrave150 reported that the most frequent bevacizumab-related AEs was hypertension (31.0%), followed by hemorrhage (25.2%) and proteinuria (21.3%). Screening for esophageal varices were conducted before enrollment and varices were treated as needed based on the local standard of care, because bleeding from the gastrointestinal tract is a well-known AEs related to bevacizumab and sometimes results in fatal events. We believe that proteinuria might be important AE, because post-progression TKI regimens such as sorafenib and lenvatinib also inhibit VEGF and dose reduction and/or interruption of these regimens might occur in patients who developed bevacizumab-related proteinuria. We reported that early bevacizumab interruption due to AEs is associated with shorter PFS and poor OS in patients receiving Atez/Bev (8). On the other hand, Dur/Tre might be preferred to patients who were unable to tolerate anti-VEGF therapy because this regimen did not include an anti-VEGF inhibitor. Another point is that Atez/Bev might be preferred for patients with a high tumor burden. In IMbrave150, patients who received Atez/Bev showed a PFS time of 6.8 months and response rate of 27.3%, while those who received Dur/Tre showed a PFS time of 3.8 months and a response rate of 20.1% in HIMALAYA trial. Patients with main portal vein tumor thrombosis (Vp4) were included in IMbrave150, but were excluded from HIMALAYA trial. The percentage of progressive disease was lower in patients who received Atez/Bev treatment in comparison to those who received Dur/Tre (19.6% vs. 39.9%). Therefore, Atez/Bev might be a better choice for patients with a high tumor burden such as 50% liver involvement and portal vein tumor thrombosis. Another point is that Atez/Bev might be preferred for patients with WNT/β-catenin mutation and with non-viral infection. Anti-VEGF therapy, including Atez/Bev and TKI regimens, improve the tumor microenvironment and lead to a response to some extent. However, Dur/Tre might be less effective for tumors with WNT/β-catenin mutation and non-viral-related HCC.

Although there is growing evidence to support that systemic therapy is effective and safe for patients with advanced HCC, which of these two regimens is better for first-line treatment remains unclear.

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Footnote

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