Commentary

Atezolizumab plus bevacizumab and tremelimumab plus durvalumab: how should we choose these two immunotherapy regimens for advanced hepatocellular carcinoma?

Takeshi Hatanaka[1]^, Atsushi Naganuma[2]^, Yutaka Yata[3]^, Satoru Kakizaki[4]^

[1]Department of Gastroenterology, Gunma Saiseikai Maebashi Hospital, Maebashi, Japan; [2]Department of Gastroenterology, National Hospital Organization Takasaki General Medical Center, Takasaki, Japan; [3]Department of Gastroenterology, Hanwa Memorial Hospital, Osaka, Japan; [4]Department of Clinical Research, National Hospital Organization Takasaki General Medical Center, Takasaki, Japan

Correspondence to: Satoru Kakizaki, MD, PhD, AGAF. Department of Clinical Research, National Hospital Organization Takasaki General Medical Center, 36 Takamatsu-cho, Takasaki, Gunma 370-0829, Japan. Email: kakizaki@gunma-u.ac.jp.

Submitted Oct 25, 2022. Accepted for publication Nov 07, 2022.
doi: 10.21037/hbsn-22-510
View this article at: https://dx.doi.org/10.21037/hbsn-22-510

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-naïve 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

^ ORCID: Takeshi Hatanaka, 0000-0003-3656-285X; Atsushi Naganuma, 0000-0003-0663-0102; Yutaka Yata, 0000-0002-4592-3509; Satoru Kakizaki, 0000-0003-0224-7093.

Table 1 Summary of global RCTs of ICI treatment

Study	Study arm	Treatment line	Sample size	PS 0/1/2 (%)	BCLC stage A/B/C (%)	Child-Pugh A5/A6/B7 (%)	Stratification factors	Median OS (months)	Median PFS/TTP (months)	ORR (RECIST)	Grade ≥3 AEs (%)	irAEs requring 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; 11.9	56.5; 55.1	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	75.1/23.4/1.0; 71.2/26.2/2.6	MVI; Etiology of liver disease (viral *vs.* non-viral); PS	16.43; 13.77	3.78; 4.07	20.1; 5.1	50.1; 39.5	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; 15.5	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; 14.7	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; 10.6	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.

Acknowledgments

Finding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Hepatobiliary Surgery and Nutrition*. The article did not undergo external peer review.

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-22-510/coif). TH, AN and SK reported lecture fee from Chugai Pharmaceuticals and Eisai. The other author has no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Bruix J, Chan SL, Galle PR, et al. Systemic treatment of hepatocellular carcinoma: An EASL position paper. J Hepatol 2021;75:960-74.
2. Finn RS, Qin S, Ikeda M, et al. Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. N Engl J Med 2020;382:1894-905.
3. Abou-Alfa GK, Lau G, Kudo M, et al. Tremelimumab plus durvalumab in unresectable hepatocellular carcinoma. NEJM Evid 2022. doi: 10.1056/EVIDoa2100070.
4. Reig M, Forner A, Rimola J, et al. BCLC strategy for

prognosis prediction and treatment recommendation: The 2022 update. J Hepatol 2022;76:681-93.
5. Kelley RK, Rimassa L, Cheng AL, et al. Cabozantinib plus atezolizumab versus sorafenib for advanced hepatocellular carcinoma (COSMIC-312): a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol 2022;23:995-1008.
6. Yau T, Park JW, Finn RS, et al. Nivolumab versus sorafenib in advanced hepatocellular carcinoma (CheckMate 459): a randomised, multicentre, open-label, phase 3 trial. Lancet Oncol 2022;23:77-90.
7. Finn RS, Ryoo BY, Merle P, et al. Pembrolizumab as second-line therapy in patients with advanced hepatocellular carcinoma in KEYNOTE-240: a randomized, double-blind, phase III trial. J Clin Oncol 2020;38:193-202.
8. Hatanaka T, Hiraoka A, Tada T, et al. Association of early bevacizumab interruption with efficacy of atezolizumab plus bevacizumab for advanced hepatocellular carcinoma: A landmark analysis. Hepatol Res 2022;52:462-70.

Cite this article as: Hatanaka T, Naganuma A, Yata Y, Kakizaki S. Atezolizumab plus bevacizumab and tremelimumab plus durvalumab: how should we choose these two immunotherapy regimens for advanced hepatocellular carcinoma? HepatoBiliary Surg Nutr 2022;11(6):927-930. doi: 10.21037/hbsn-22-510

