

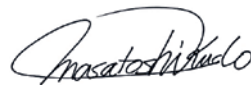
Selection of Systemic Treatment Regimen for Unresectable Hepatocellular Carcinoma: Does Etiology Matter?

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Introduction

Six systemic regimens with 7 agents are currently available for systemic therapy of hepatocellular carcinoma (HCC), but there is a lack of solid data supporting the need to select agents based on etiology. Although response to immune checkpoint inhibitors has been reported to be impaired with underlying non-alcoholic fatty liver disease (NAFLD), atezolizumab plus bevacizumab combination therapy must be chosen as the first-line treatment according to the recommendations in several

guidelines. However, in such situations it is recommended to assess the treatment effect early in the treatment course, with the possibility of impaired response to immunotherapy.

Etiology of HCC

HCC is a malignant tumor that primarily occurs with underlying hepatitis or cirrhosis caused by viruses such as hepatitis B virus (HBV) and hepatitis C virus (HCV). Other risk factors of HCC include non-viral cirrhosis, male sex, old age, drinking, smoking, obesity, fatty liver, and diabetes. Recent advances in antiviral therapy and consequent good control of HBV and HCV have resulted in a decrease in cases of HCC of viral etiology. On the other hand, the proportion with underlying NAFLD is on the rise [1], indicating that surveillance methods or related procedures need to be reviewed. NAFLD is becoming a common cause of HCC in recent years, especially in Western countries as compared with Asian countries, where hepatitis B-related HCC is more common. Although the incidence rate of HCC in NAFLD patients is not very high – 0.44 (range, 0.29–0.66) cases per 1,000 person-years – the reported global prevalence of NAFLD

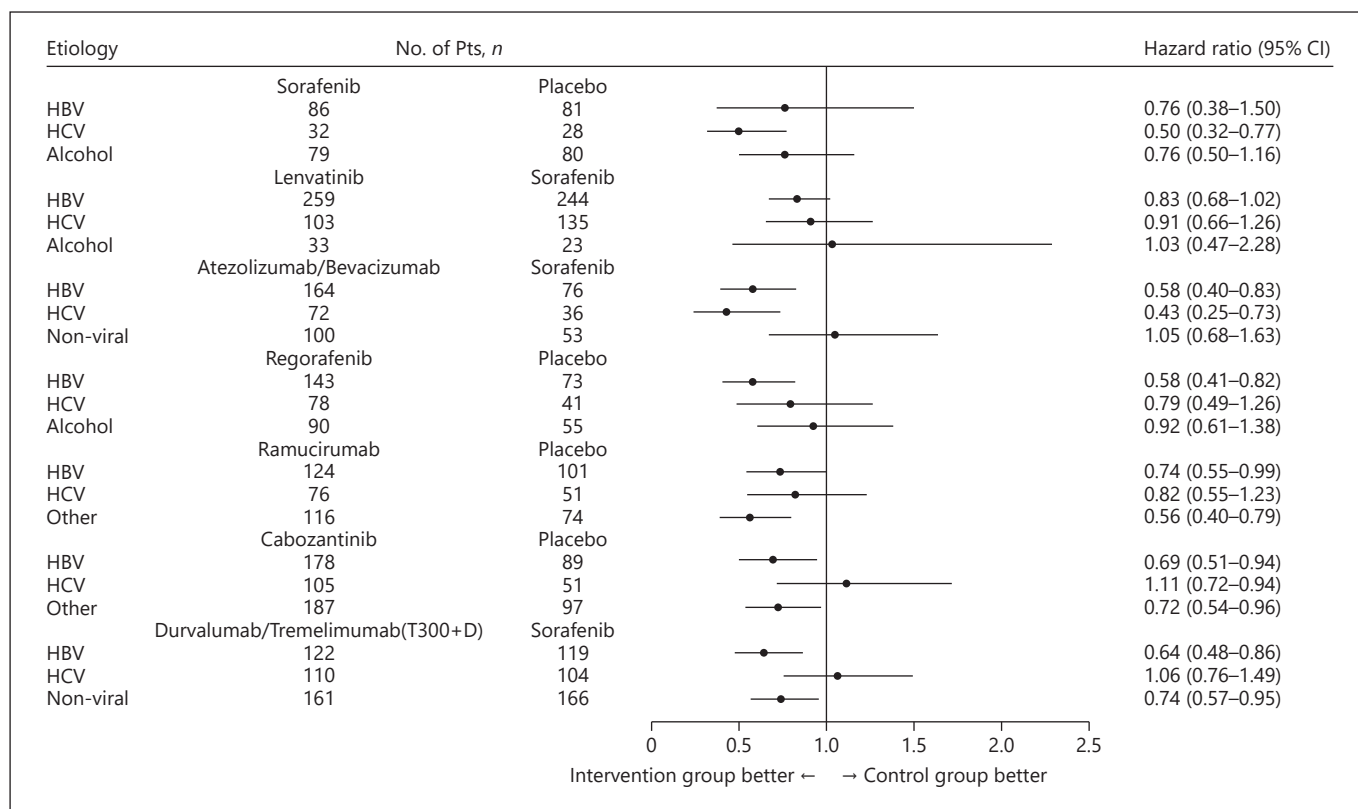


Fig. 1. Comparison of overall survival by etiology (hazard ratio) [3–8, 14]. HBV, hepatitis B virus; HCV, hepatitis C virus.

is 25.24% (95% confidence interval [CI], 22.10–28.65), so it is considered an important etiology of HCC [2].

In real-world practice, it is sometimes difficult to specify the etiology of HCC in an individual patient. For example, HCC cases with viral hepatitis are sometimes associated with heavy alcohol consumption or metabolic diseases. In this Editorial, however, data from several clinical trials were analyzed, where investigators estimated the most likely etiology of HCC in individual enrolled patients.

In most trials, subgroup analysis was performed only by HBV, HCV, and non-viral etiology. Non-viral etiology includes various liver diseases, including alcoholic liver disease, NAFLD, autoimmune hepatitis, or others.

Systemic Therapy of HCC

In 2007, sorafenib became the first agent approved for treatment of HCC, and now, 6 systemic regimens with 7 agents are available. More precisely, atezolizumab plus

bevacizumab combination therapy [3], lenvatinib [4], and sorafenib [5] have been approved as first-line treatment, and regorafenib [6], ramucirumab [7], and cabozantinib [8] have been approved as second-line treatment and beyond. Among them, atezolizumab plus bevacizumab combination therapy is recommended as first-line therapy in clinical practice guidelines for HCC published by EASL, AASLD, ESMO, ASCO, NCCN, and JSH [9]: lenvatinib or sorafenib will be selected as a first-line therapy when atezolizumab plus bevacizumab combination therapy is not suitable, for example, in patients with autoimmune disease [9]. These recommendations are based on a comprehensive review of results from various developments and clinical studies. In the actual clinical setting, individual physicians decide which agents to use for second and later lines of therapy because the only evidence available is for regorafenib, ramucirumab, and cabozantinib in patients who had prior sorafenib treatment.

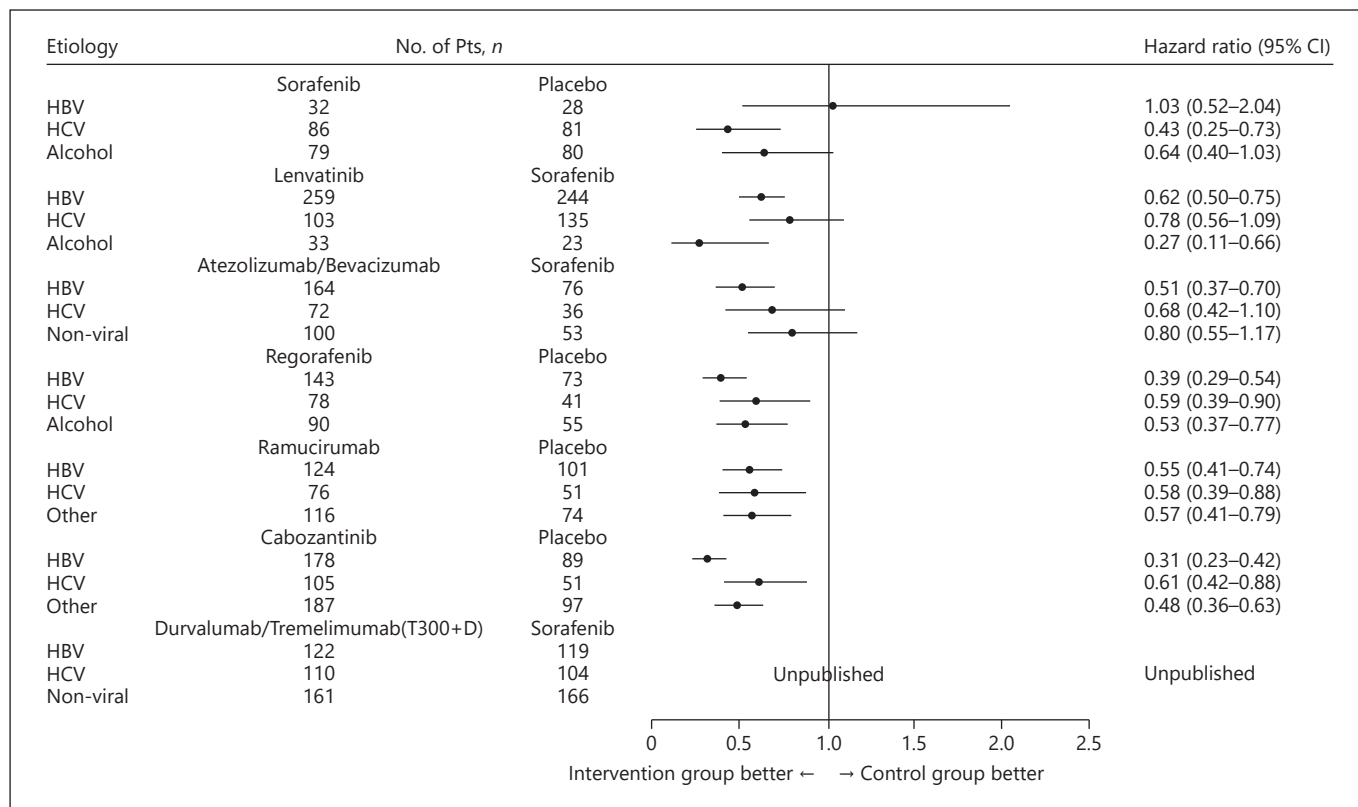


Fig. 2. Comparison of progression-free survival by etiology (hazard ratio) [3–8, 14]. HBV, hepatitis B virus; HCV, hepatitis C virus.

Treatment Effects of Individual Agents by Etiology

The treatment effects of individual agents by etiology have been reported from subgroup analyses in key clinical trials (Fig. 1–3). When interpreting subgroup analysis results, their low level of evidence must be fully considered.

Sorafenib

Sorafenib, which was tested in a phase 3 placebo-controlled study (the SHARP trial), was the first agent that showed prolonged survival in HCC patients [5]. The hazard ratio (HR) for overall survival (OS) was 0.76 (95% CI, 0.38–1.50) in patients with HBV etiology, and 0.50 (95% CI, 0.32–0.77) in those with HCV etiology [10]. The HRs for progression-free survival (PFS) were 1.03 (95% CI, 0.52–2.04) in patients with HBV etiology and 0.43 (95% CI, 0.25–0.73) in those with HCV etiology (Fig. 1–3). The Asia-Pacific study, another pivotal study, showed the HR for OS was 0.74 (95% CI, 0.51–1.06, not significant) in patients with HBV etiology and 0.57 (95% CI, 0.29–1.33) in patients with other etiolo-

gies [11]. Analysis of previous phase 3 studies showed that sorafenib was most effective in HCC with underlying hepatitis C [12].

Lenvatinib

The noninferiority of first-line lenvatinib versus sorafenib in OS, the primary endpoint, was demonstrated in a phase 3 REFLECT trial [4]. The HR for OS over sorafenib was 0.92 (95% CI, 0.79–1.06). Subgroup analyses showed that the HRs for OS were 0.83 (95% CI, 0.66–1.02) in patients with HBV etiology, 0.91 (95% CI, 0.66–1.26) in those with HCV etiology, and 1.03 (95% CI, 0.47–2.28) in those with alcohol-related etiology. The HRs of PFS were 0.62 (95% CI, 0.50–0.75) in patients with HBV etiology, 0.78 (95% CI, 0.56–1.09) in those with HCV etiology, and 0.27 (95% CI, 0.11–0.66) in those with alcohol-related etiology [4] (Fig. 1–3). Analysis of a Chinese subgroup showed extremely favorable prognosis, indicating that lenvatinib may be most effective in patients with hepatitis B [13].

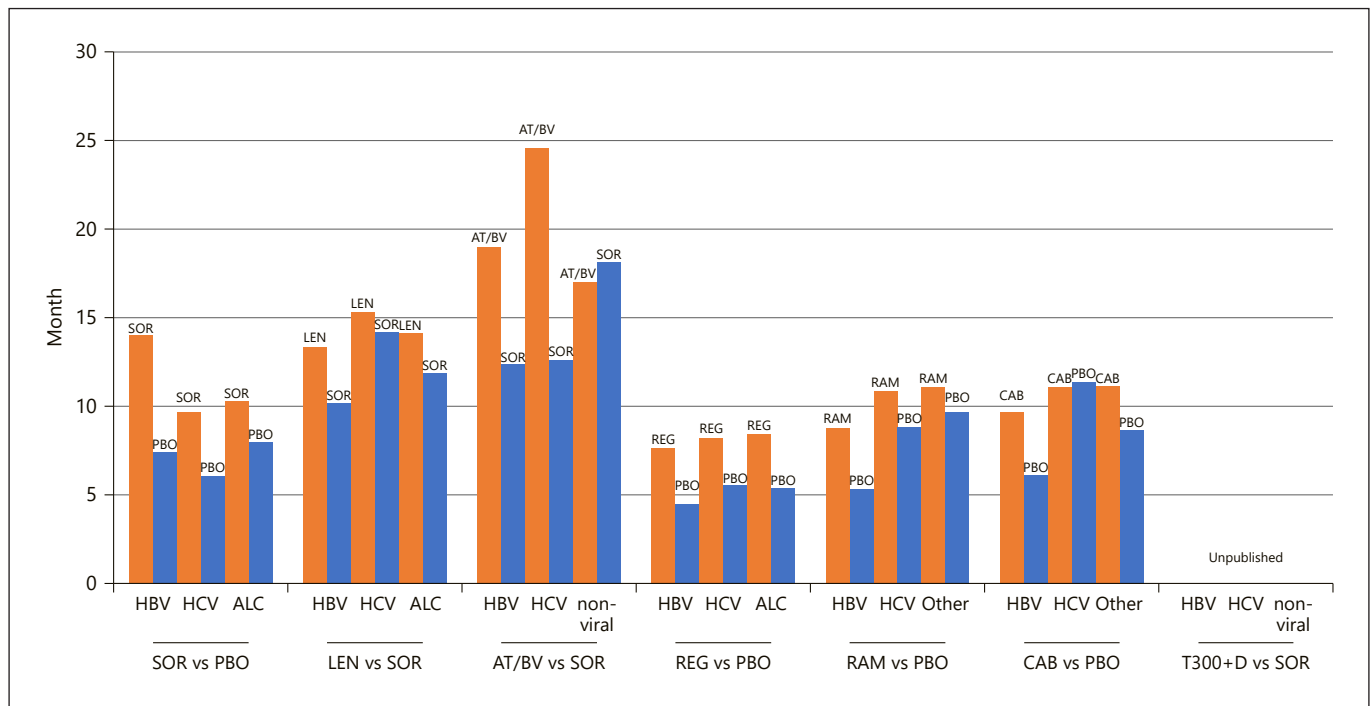


Fig. 3. Median overall survival by etiology [3–8, 14]. HBV, hepatitis B virus; HCV, hepatitis C virus; ALC, alcohol; SOR, sorafenib; LEN, lenvatinib; AT/BV, atezolizumab/bevacizumab; REG, regorafenib; RAM, ramucirumab; CAB, cabozantinib; T300+D, tremelimumab 300 mg 1 dose + durvalumab 1,500 mg Q4W.

Atezolizumab Plus Bevacizumab

First-line atezolizumab plus bevacizumab was shown to be superior to sorafenib in a phase 3 IMbrave 150 trial [3]. The HR for OS over sorafenib was 0.58 (95% CI, 0.42–0.79). Subgroup analyses showed that HRs for OS were 0.58 (95% CI, 0.40–0.83) in patients with HBV etiology, 0.43 (95% CI, 0.25–0.73) in those with HCV etiology, and 1.05 (95% CI, 0.68–1.63) in those with non-viral etiology. The HRs for PFS were 0.51 (95% CI, 0.37–0.70) in patients with HBV etiology, 0.68 (95% CI, 0.42–1.10) in those with HCV etiology, and 0.80 (95% CI, 0.55–1.17) in those with non-viral etiology [3] (Fig. 1–3).

Durvalumab Plus Tremelimumab

First-line durvalumab plus tremelimumab was shown to be superior to sorafenib in a phase 3 HIMALAYA trial. The HR for OS over sorafenib was 0.78 (95% CI, 0.65–0.92). Subgroup analyses of HR for OS were 0.64 (95% CI, 0.48–0.86) in patients with HBV etiology, 1.06 (95% CI, 0.76–1.49) in those with HCV etiology, and 0.74 (95% CI, 0.57–0.95) in those with non-viral etiology [14] (Fig. 1, 2).

Regorafenib

A placebo-controlled phase 3 study (the RESORCE trial) was conducted to test second-line regorafenib in non-responders to sorafenib [6]. Regorafenib improved OS, the primary endpoint, significantly over placebo with an HR of 0.63 (95% CI, 0.50–0.79). Subgroup analysis showed the HRs for OS were 0.58 (95% CI, 0.41–0.82) in patients with HBV etiology and 0.79 (95% CI, 0.49–1.26) in those with HCV etiology. The HRs for PFS were 0.39 in patients with HBV etiology and 0.59 in those with HCV etiology [6, 15] (Fig. 1–3).

Ramucirumab

Second-line ramucirumab for sorafenib non-responders and sorafenib-intolerant patients was tested in a phase 3 placebo-controlled REACH-2 trial [7]. The HR for OS over placebo was 0.710 (95% CI, 0.531–0.949). The HRs for OS were 0.74 (95% CI, 0.55–0.99) in patients with HBV etiology, 0.82 (95% CI, 0.55–1.23) in those with HCV etiology, and 0.56 (95% CI, 0.40–0.79) in those with other etiologies [7]. The HR for PFS was 0.549 (95% CI, 0.41–0.74) in patients with HBV etiology, 0.58 (95% CI,

0.39–0.88) in those with HCV etiology and 0.57 (95% CI, 0.41–0.79) in those with other etiologies (Fig. 1–3).

Cabozantinib

Second- and third-line cabozantinib for sorafenib non-responders and sorafenib-intolerant patients was tested in a phase 3 CELESTIAL trial. The HR for OS over placebo was 0.76 (95% CI, 0.63–0.92). The HRs for OS were 0.69 (95% CI, 0.51–0.94) in patients with HBV etiology, 1.11 (95% CI, 0.72–0.94) in those with HCV etiology, and 0.72 (95% CI, 0.54–0.96) in those with other etiologies: the HRs for PFS were 0.31 (95% CI, 0.23–0.42) in patients with HBV etiology, 0.61 (95% CI, 0.42–0.88) in those with HCV etiology, and 0.48 (95% CI, 0.36–0.63) in those with other etiologies [8, 16] (Fig. 1–3).

Efficacy by Etiology in 7 Regimens

Efficacy by etiology was described above for each of 7 regimens. Taken together, there are no marked differences in treatment effect between etiologies (Fig. 3). Some subgroups had a low HR suggesting a benefit of certain regimens, but it must be noted that the sample sizes were small, and the corresponding CIs were wide. The level of evidence of studies that used etiology as a stratification factor is considered to be high, but nevertheless, the results by etiology were from subgroup analyses, so it is recommended that these data be used for reference only.

Treatment Effects of Immune Checkpoint Inhibitors by Etiology

Pfister et al. [17] showed a poor treatment effect of an immune checkpoint inhibitor in the mouse model of HCC with nonalcoholic steatohepatitis (NASH) etiology, and then conducted a meta-analysis of randomized phase 3 clinical trials (CheckMate459, KEYNOTE-240, and IMbrave150). Immunotherapy improved survival in the overall population (HR 0.77, 95% CI, 0.63–0.94). Further, subgroup analysis showed that survival was significantly improved in patients with HCC of viral etiology (HR 0.64, 95% CI, 0.48–0.84), while the improvement tended to be slightly less in HCC of non-viral etiologies (HR 0.92, 95% CI, 0.77–1.11), suggesting that immunotherapy may be less effective in patients with HCC of non-viral etiologies (e.g., NASH). This study by Pfister et al. [17] had a considerable impact on daily clinical practice because it was published at the same time atezolizumab plus bevacizumab combination therapy was approved and gradually came to be used as a first-line treatment. The notion was

spreading, albeit not widely, that it was better to avoid immunotherapy for HCC of non-viral etiologies, especially for NASH related HCC. However, these data should not be blindly accepted and should be considered more comprehensively.

First, Pfister et al. [17] included all of non-viral etiology such as NASH, alcohol intake, autoimmune hepatitis, and primary biliary cholangitis in non-viral etiologies, so their meta-analysis results for non-viral etiologies should not be related to unfavorable outcomes of immunotherapy in the mouse model of NASH-induced HCC. Indeed, anti-PD-L1 antibody (durvalumab) plus anti-CTLA-4 antibody (tremelimumab), an immunotherapy-immunotherapy combination, significantly improved survival over sorafenib. Also, analysis by etiology showed the most favorable outcome was found in patients with non-viral etiology (Fig. 1) [14], a finding completely different from what had been believed.

Second, 2 of the 3 studies included in the meta-analysis tested single-agent treatment with anti-PD-1 antibody (nivolumab in CheckMate459 [18] and pembrolizumab in KEYNOTE-240 [19]), while the remaining IMbrave150 trial tested a combination immunotherapy of anti-PD-L1 plus anti VEGF-A antibodies (atezolizumab plus bevacizumab) [3]. Various findings to date have indicated that the efficacy of immune checkpoint inhibitor monotherapy is limited to certain populations, for example, those with an immune hot tumor from a perspective of the tumor immune microenvironment [20]. Meanwhile, anti-VEGF antibodies have two notable actions, that is, an anti-angiogenic action that directly attacks tumors and the improvement of immune microenvironment from suppressive to responsive. Thus, combination therapy with anti-VEGF antibody must be distinguished from immune checkpoint inhibitor monotherapy. More precisely, bevacizumab, with its anti-VEGF activity, can enhance the effect of immune checkpoint inhibitors at almost all 7 steps in the cancer immunity cycle even in HCC with underlying NASH. Particularly, because bevacizumab attacks tumors to promote tumor antigen release and also upregulates ICAM1 and VCAM1 in addition to CXCL9, and thereby facilitates intratumor infiltration of CD8⁺ T cells [21], atezolizumab plus bevacizumab combination therapy is likely to be effective even in HCC with underlying NASH.

Third, stratification factors used were different in these trials. The use of different stratification factors naturally causes biases in subjects, and thus, the results must be interpreted with caution. The CheckMate459 trial used the following stratification factors: (1) HCV versus

non-HCV (non-HCV included HBV infection and non-viral etiologies); (2) the presence or absence of macrovascular invasion or extrahepatic spread; and (3) geographic region (Asia vs. non-Asia). The KEYNOTE-240 trial used the following stratification factors: (1) geographic region (Asia excluding Japan versus non-Asia including Japan); (2) the presence or absence of macrovascular invasion; (3) and α -fetoprotein level (<200 vs. ≥ 200 ng/mL). The IMbrave150 trial used the following stratification factors: (1) geographic region (Asia excluding Japan vs. other countries); (2) the presence or absence of macrovascular invasion or extrahepatic spread; (3) baseline AFP level (<400 vs. ≥ 400 ng/mL); and (4) Eastern Cooperative Oncology Group performance status (0 vs. 1). The HIMALAYA trial used the following stratification factors: (1) macrovascular invasion (yes vs. no); (2) etiology of liver disease (HBV vs HCV vs. others); and (3) ECOG performance status (0 vs. 1).

When looking at the IMbrave150 results in detail, the OS benefit with atezolizumab plus bevacizumab was closer to that with sorafenib in the subgroup with non-viral etiology than in the subgroups with HBV and HCV etiologies (HR 1.05, 95% CI, 0.68–1.63). However, the actual median OS with atezolizumab plus bevacizumab was comparable between the subgroup with non-viral etiology (17.0 months) and the one with HBV etiology (19.0 months). Instead, OS of sorafenib was extremely longer in the subgroup with non-viral etiology (18.1 months) than in those with HBV (12.4 months) and HCV (12.6 months) etiologies, and this was the reason for the subgroup analysis results. Thus, the prognosis of atezolizumab plus bevacizumab was by no means unfavorable. Given that the etiology (viral vs. non-viral) was not a stratification factor in IMbrave150 trial, as described earlier, these data should be taken as reference only. In fact, in the actual clinical setting, atezolizumab plus bevacizumab is effective in many cases of HCC with underlying NASH, and thus, this regimen is regarded as a first choice for first-line treatment.

Should Disease Etiologies Be Considered when Selecting Systemic Treatment Regimen?

There is a lack of adequate data supporting the selection of particular systemic treatment regimens for HCC based on etiology. Thus, as recommended by the clinical practice guidelines for HCC issued by EASL, AASLD, ESMO, ASCO, NCCN, and JSH, it is reasonable for atezolizumab plus bevacizumab to be the first choice of first-line treat-

ment. However, it must be kept in mind that the effect of atezolizumab plus bevacizumab may be slightly impaired in HCC of non-viral etiology (e.g., NASH or NAFLD) as shown by Pfister, et al. [17]. For such cases, the response of treatment must be assessed early in the treatment course and a treatment switch (e.g., to lenvatinib) must be implemented if rapid tumor growth (e.g., hyperprogression) is observed. Agents for second and later lines of treatment are mostly decided based on clinical judgement because the evidence available is not yet enough. The lack of adequate evidence is also true for the selection of systemic therapy by etiology for second-line treatment and beyond, as well as for first-line atezolizumab plus bevacizumab. Thus, patients' condition (liver functional reserve, ECOG PS, activities of daily living, etc.) must be the upmost priority when selecting agents for treatment.

Taken together, the evidence available at present indicates that there is no need to select treatment agents based on etiology. However, when treating HCC patients with underlying NAFLD, the possibility of poor response to immunotherapy, especially single-agent immunotherapy, should be cautious, and it should be kept in mind to perform frequent follow-up imaging from the beginning of treatment, so that the treatment can be switched as soon as it is found to be ineffective. Although conducting clinical studies to investigate the efficacy and safety of treatment by etiology is difficult in practice, it is important to accumulate clinical data, especially those for atezolizumab plus bevacizumab and durvalumab plus tremelimumab, in order to reach firm conclusions on treatment efficacy in HCC with underlying NASH. There are probably no marked differences in the effect of combination immunotherapy among etiologies.

Conflict of Interest Statement

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Author Contributions

Masatoshi Kudo conceived, wrote, and approved the final manuscript.

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