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Letter to the Editor

Surrogate Indicators of Overall Survival in Advanced Hepatocellular Carcinoma

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To the Editor,

For more than a decade, the targeted drug sorafenib[1, 2] has been the dominant first-line treatment for patients with advanced hepatocellular carcinoma (HCC). However, due to the low overall response rate and high drug resistance rate, many new targeted drugs have been developed, including sunitinib, brivanib, linifanib, nintedanib, dovitinib, sorafenib plus erlotinib, lenvatinib, and donafenib. On the other hand, with the increasing use of immune checkpoint inhibitors in solid tumors, several trials investigated the efficacy and safety of immune checkpoint inhibitors in advanced HCC. Among these trials, only lenvatinib and donafenib as monotherapy were non-inferior to sorafenib in overall survival in untreated advanced HCC. Most of other trials did not meet their primary end point of overall survival. However, the efficacy of the combination therapy with PD-1 or PD-L1 inhibitor plus bevacizumab (VEGF inhibitor) is amazing.[3, 4]

An expert panel convened by the American Association for the Study of Liver Diseases recommended time to progression as the primary endpoint in randomized phase 2 trials and overall survival as the main endpoint to measure effectiveness in phase 3 trials.[5, 6] In real world clinical practice, subsequent antitumor therapies after tumor progression and/or therapies for concurrent liver disease can confound the assessment of clinical benefit. In the recent issue of Journal of Hepatology, on behalf of EASL, Bruix and coworkers updated the recommendations of systemic treatment of HCC.7 This review proposed that "overall survival is the sole robust endpoint to assess the benefit from any intervention in advanced HCC" and "all proposed surrogates lack adequate validation". Here, we tried to reveal the relationship among objective response rate (ORR), median overall survival (OS) time and median progression-free survival (PFS) time by presenting them in a same curve graph. The potential relationship between PFS and OS is revealed by representing the hazard ratio (with 95% confidence interval) of PFS and OS with a forest plot.

We systematically searched PubMed and EMBASE databases and analyzed phase 3 clinical trials with large sample size. A total of 11 trials about first-line systemic therapies for advanced HCC published from 2008 to 2021 were included into analysis. All these 11 trials included a group of patients treated with sorafenib. In addition, 7 trials about second-line systemic therapies published from 2015 to 2021 were also included into analysis. The control group received placebo treatment in all these 7 trials. All these 18 trials reported ORR, median PFS and OS time. The ORR according to RECIST 1.1 in the sorafenib group ranged from 0.7% to 11.9% (median 6.1%). Among patients with sorafenib therapy, the median PFS and OS time was 3.75 (range 2.8 to 5.5) and 10.4 (range 6.5 to 14.7) months, re-

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spectively. The mean ORR of sorafenib was also calculated. The denominator equals the sum of the sample sizes for each sorafenib group. Percentage was obtained by the sum number of cases with complete or partial response in each trial divided by the denominator. The mean ORR of sorafenib was 6.0%. Actually, atezolizumab plus bevacizumab was associated with the highest ORR (27.3%) while donafenib with the lowest (4.6%). In addition, the median OS time of each trial tended to increase gradually with the increase of ORR and median PFS time (Fig. 1a). However, this trend was not significant in second-line treatment (Fig. 1b). And then, we describe the association between PFS and OS with forest plot (Fig. 1c). We found (1) PD-1 (sintilimab) or PD-L1 (atezolizumab) inhibitor plus bevacizumab was associated with the best survival benefit for patients with advanced HCC;[3, 4] (2) the significant benefit of PFS may not translate into significant benefit of OS (linifanib, lenvatinib, ramucirumab in REACH trial, S-1); (3) similar PFS generally does not translate into OS benefits (sunitinib, brivanib, sorafenib plus erlotinib), except in the ZGDH3 trial (donafenib); (4) a benefit in PFS could predict a benefit in OS when the hazard ratio for PFS is lower than 0.6 in most trials, except ZGDH3[8] (hazard ratio 0.91) and KEYNOTE 240 trial (hazard ratio 0.72).[9]

Tumor progression is the leading cause of death in patients with HCC. Increased ORR and PFS may increase OS in first-line setting, but not in second-line therapy. In addition, the optimum cut-off value of hazard ratio for PFS in predicting benefit in OS is still pending.

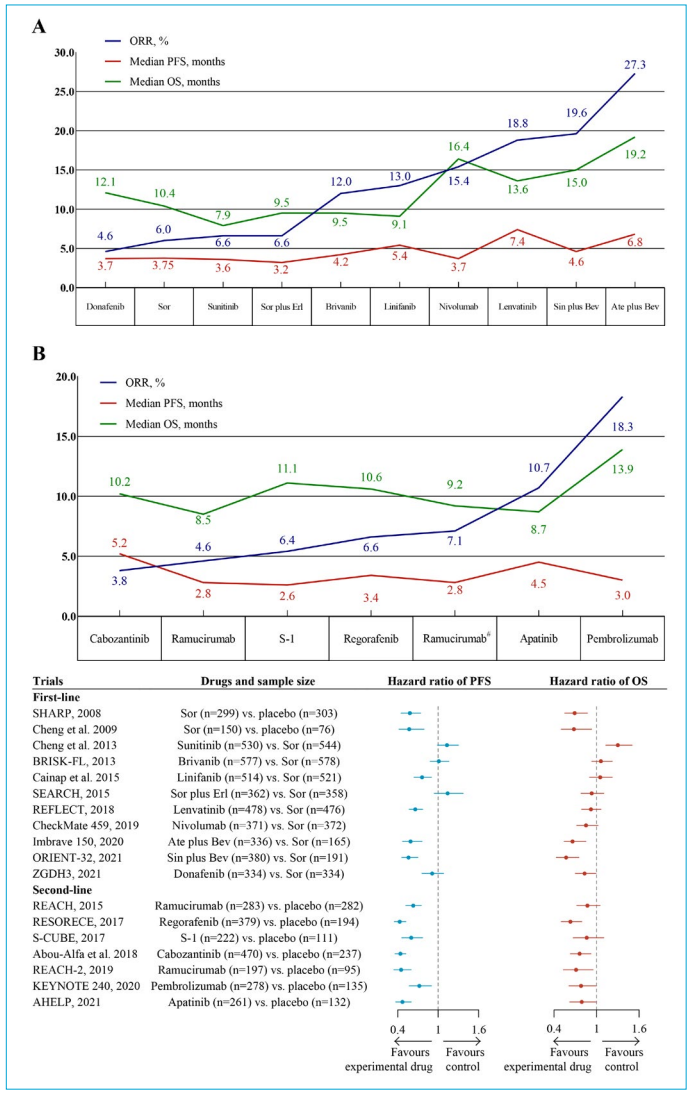

Figure 1. Analysis of survival data. **(a)** Survival trends among ORR, median PFS and OS time in first-line or **(b)** second-line therapy; **(c)** forest plot of PFS and OS.

Ate: atezolizumab; Bev: bevacizumab; Erl: erlotinib; OS: overall survival; ORR: objective response rate; PFS: progression-free survival; Sin: sintilimab; Sor: sorafenib. #For unselected patients.

Disclosures

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

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