Meta-analysis of the efficacy and safety of PD-1/PD-L1 inhibitors administered alone or in combination with anti-VEGF agents in advanced hepatocellular carcinoma

We read with great interest the article by Gerbes *et al*,[1] which indicated the prospects of immune-based therapies in hepatocellular carcinoma (HCC) and that by Zhu *et al*,[2] which proposed their new strategy for sensitising HCC to anti-programmed death-ligand 1 (PD-L1) blockade. As they suggest, immunotherapy for HCC has great potential, and combination therapy may further improve survival benefits.

Many patients with HCC have advanced stage disease (aHCC) at the time of diagnosis, and some of them even have progressive disease after first-line therapy. Recently, the clinical benefits of immunotherapy for HCC have emerged. Blocking the PD-1/PD-L1 signalling pathway with humanised monoclonal antibodies is effective in alleviating immune escape and enhancing T cell-mediated antitumour immunity. However, no more than 20% of patients with HCC robustly respond to anti-programmed cell death protein 1 (PD-1)/PD-L1 monotherapy.[3 4] The combination of anti-vascular endothelial growth factor (VEGF) agents with PD-1/PD-L1 blockade may synergistically reverse the immunosuppressive microenvironment.[5] Preclinical and preliminary clinical reports suggest that combined treatment shows improved efficacy over PD-1/PD-L1 blockade alone in aHCC.[6–8] Therefore, we conducted a meta-analysis to evaluate the efficacy and safety of PD-1/PD-L1 inhibitors as a monotherapy or in combination with anti-VEGF agents in aHCC.

We extensively searched PubMed, Embase and ClinicalTrials.gov to identify relevant studies published before 25 November 2019. Eligibility criteria were (a) population, patients with unresectable aHCC; (b) intervention, PD-1/PD-L1 inhibitors or combined anti-VEGF with anti-PD-1/PD-L1 agents; (c) response evaluation, radiological confirmation using Response EvaluationCriteria In Solid Tumors V.1.1; (d) outcomes, objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS), overall survival (OS) and treatment-related adverse events (TrAEs) and (e) study design, clinical trials. Random-effects or fixed-effects models were used to synthesise data.

A total of 1958 patients from 13 studies (including 4 articles and 9 latest conference abstracts) were included. The pooled estimates for ORR, DCR, PFS, OS, TrAEs and ≥grade 3 TrAEs reporting rates were summarised by single-arm analysis (table 1). The ORR, DCR and PFS of combined treatment cohorts were significantly improved compared with those of anti-PD-1/PD-L1 cohorts (ORR, p=0.016; DCR, p<0.001; PFS, p<0.001; Z-test; figure 1A–C). Two randomised controlled trial studies analysed the survival benefit of combined treatment as first-line therapy and indicated that atezolizumab plus bevacizumab significantly prolonged PFS (pooled HR: 0.58, 95% CI: 0.47 to 0.72; p<0.001) compared with atezolizumab or sorafenib alone in unresectable patients with aHCC.[9] We also found comparable incidence rates for TrAEs between the two cohorts (p=0.205) but an increased incidence of ≥grade 3 TrAEs in the combined treatment cohort (p=0.014; figure 1D–E).

Furthermore, among the five studies with available PD-L1 status data, 138/672 patients were positive for PD-L1 expression. Stratification according to PD-L1

Table 1 Main characteristics and pooled outcomes of included studies.

	PD-1/PD-L1 inhibitors group	PD-1/PD-L1 inhibitors+anti-VEGF agents group
Drug	Nivolumab (*NCT01658878, NCT02576509*), Pembrolizumab (*NCT02702414, NCT02658019, NCT02702401*), Camrelizumab (*NCT02989922*), Durvalumab (*NCT01693562*), Atezolizumab (*NCT02715531*)	Camrelizumab+apatinib (*NCT03463876*), Durvalumab+ramucirumab (*NCT02572687*), Pembrolizumab+lenvatinib (*NCT03006926*), Avelumab+axitinib (*NCT03289533*), Atezolizumab+bevacizumab (*NCT02715531, NCT03434379*)
Study design		
Non-RCT phase Ib, I/II and II, n (%)	6 (75)	4 (67)
RCT phase III, n (%)	2 (25)	2 (33)
Multicentre, n (%)	6 (75)	4 (67)
Number of patients, n	1360	598
Pooled ORR (95% CI), %	16.1 (14.2 to 18.1)*	25.6 (18.1 to 33.0)
Pooled DCR (95% CI), %	52.4 (45.6 to 59.2)	74.6 (67.6 to 81.6)
PFS time, median (95% CI), months	3.6 (2.7 to 4.5)	6.1 (5.3 to 6.9)*
OS time, median (95% CI), months	14.6 (13.3 to 16.0)*	10.7 (5.1 to 18.4)*†
TrAEs reporting rate (95% CI), %	74.4 (60.8 to 88.0)	84.3 (77.2 to 91.3)
≥grade 3 TrAEs reporting rate (95% CI), %	18.0 (12.9 to 23.1)	32.7 (22.2 to 43.2)
PD-L1 positive rate (95% CI), %	19.3 (16.3 to 22.4)*	42.3 (23.3 to 61.3)*†

*Fixed effects model was used.
†Only one study was pooled.
DCR, disease control rate; NR, not reached; ORR, objective response rate; OS, overall survival; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PFS, progression-free survival; RCT, randomised controlled trial; TrAEs, treatment-related adverse events; VEGF, vascular endothelial growth factor.

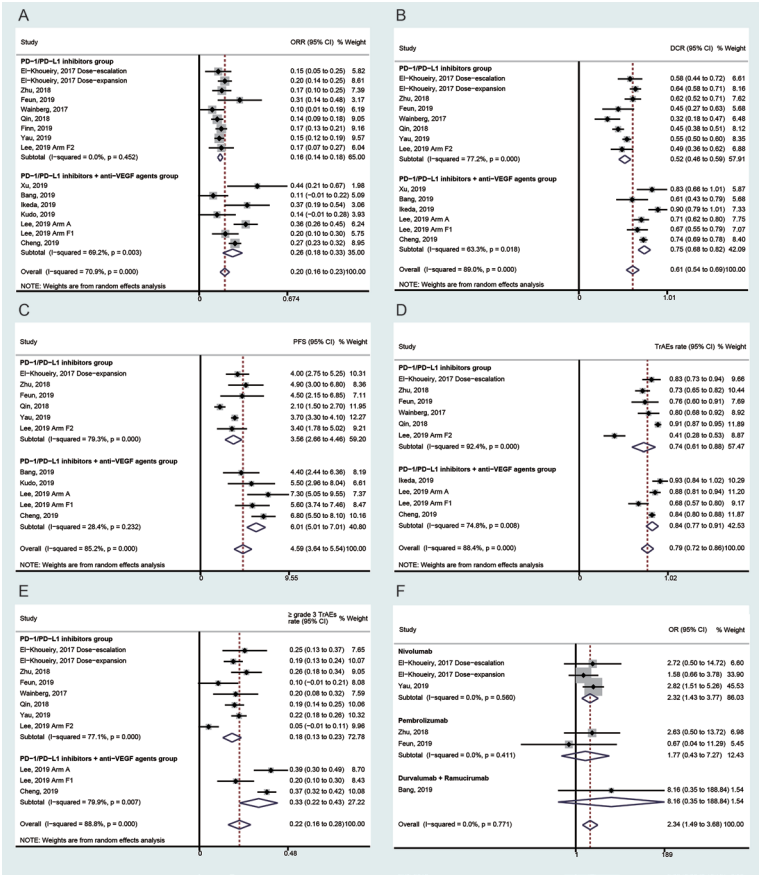

Figure 1 Forest plots for ORR (A), DCR (B), PFS time (C), TrAEs (D) and ≥grade 3 TrAEs reporting rates (E) in studies of PD-1/PD-L1 inhibitors and PD-1/PD-L1 inhibitors combined with anti-VEGF agents, and OR for the ORR (F) comparing PD-L1-positive patients vs PD-L1-negative patients grouped by drug. DCR, disease control rate; ORR, objective response rate; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PFS, progression-freesurvival; TrAEs,treatment-related adverse events; VEGF, vascularendothelial growth factor.

expression showed that the patients with PD-L1-positive HCC had a significantly increased ORR when treated with nivolumab (OR: 2.32, 95% CI: 1.43 to 3.77; p<0.05; figure 1F). Single-arm trials have a high risk of bias due to their nature and some results reported in conference abstracts might be updated as the follow-up time increases before peer review; therefore, they were not further assessed for bias.

Our research provides evidence that the combination of PD-1/PD-L1 inhibitors with anti-VEGF agents results in clinically significant improvements in certain outcomes in aHCC but still needs to be treated with caution because of a noticeably increased level of immune-related toxicity. More data from updated clinical trials are needed to confirm these observations, and long-term clinical outcomes are being evaluated. Given that tumoural PD-L1 expression only correlates with the objective response to nivolumab in patients with aHCC by our analysis, optimal predictive biomarkers of response still need to be identified.[10] In general, combining PD-1/PD-L1 inhibitors and anti-VEGF agents may be rationally recommended as an earlier line for patients with aHCC to maximise the survival benefit with controllable toxic effects.

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REFERENCES

1 Gerbes A, Zoulim F, Tilg H, *et al*. Gut roundtable meeting paper: selected recent advances in hepatocellular carcinoma. *Gut* 2018;67:380–8.
2 Zhu Y, Yang J, Xu D, *et al*. Disruption of tumour-associated macrophage trafficking by the osteopontin-induced colony-stimulating factor-1 signalling sensitises hepatocellular carcinoma to anti-PD-L1 blockade. *Gut* 2019;68:1653–66.
3 El-Khoueiry AB, Sangro B, Yau T, *et al*. Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial. *Lancet* 2017;389:2492–502.
4 Zhu AX, Finn RS, Edeline J, *et al*. Pembrolizumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib (KEYNOTE-224): a non-randomised, open-label phase 2 trial. *Lancet Oncol* 2018;19:940–52.
5 Ma L, Hernandez MO, Zhao Y, *et al*. Tumor cell biodiversity drives microenvironmental reprogramming in liver cancer. *Cancer Cell* 2019;36:418–30.
6 Lee M, Ryoo B-Y, Hsu C-H, *et al*. LBA39Randomised efficacy and safety results for atezolizumab (Atezo) + bevacizumab (Bev) in patients (PTS) with previously untreated, unresectable hepatocellular carcinoma (HCC). *Ann Oncol* 2019;30:mdz394.030.
7 Shigeta K, Datta M, Hato T, *et al*. Dual programmed death receptor-1 and vascular endothelial growth factor receptor-2 blockade promotes vascular normalization and enhances antitumor immune responses in hepatocellular carcinoma. *Hepatology* 2019. doi:10.1002/hep.30889. [Epub ahead of print: 05 Aug 2019].
8 De Toni EN. Immune checkpoint inhibitors: use them early, combined and instead of TACE? *Gut* 2020;69:1888–9.
9 Khunger M, Rakshit S, Pasupuleti V, *et al*. Incidence of pneumonitis with use of programmed death 1 and programmed death-ligand 1 inhibitors in non-small cell lung cancer: a systematic review and meta-analysis of trials. *Chest* 2017;152:271–81.
10 Lu S, Stein JE, Rimm DL, *et al*. Comparison of biomarker modalities for predicting response to PD-1/PD-L1 checkpoint blockade: a systematic review and meta-analysis. *JAMA Oncol* 2019. [Epub ahead of print: 18 Jul 2019].