Review

# Comparative safety and efficacy of molecular-targeted drugs, immune checkpoint inhibitors, hepatic arterial infusion chemotherapy and their combinations in advanced hepatocellular carcinoma: findings from advances in landmark trials

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## 1. Abstract

**Background**: Several recent phase 3 trials have reported manageable safety profiles and promising anti-tumor activities of molecular-targeted drugs (MTDs; sorafenib, lenvatinib), immune checkpoint inhibitors (ICIs; nivolumab, pembrolizumab, atezolizumab), hepatic arterial infusion chemotherapy (HAIC) and their combinations in advanced hepatocellular carcinoma (AHCC); however, head-to-head comparisons among these regimens are lacking. **Methods**: We aimed to comprehensively review and compare the efficacy and safety of different MTDs, ICIs, HAIC and their combinations in AHCC. Adverse events (AEs), disease control rates (DCRs), objective response rates (ORRs), overall survival (OS) and progression-free survival (PFS) were assessed. **Results**: The pooled incidence rates of grade 1–5/3–5 AEs were 98.0%/48.6%, 98.3%/57.4%, 91.4%/22.0%, 96.4%/54.6%, 98.2%/61.1%, 86.3%/34.1%, 88.9%/9.4%, and 95.2%/53.2% for sorafenib, lenvatinib, nivolumab, pembrolizumab, atezolizumab plus bevacizumab, HAIC-cisplatin plus sorafenib, HAIC-oxaliplatin, and HAIC-oxaliplatin plus sorafenib, respectively, which suggested that nivolumab exhibited optimal safety regarding grade 1–5 AEs, whereas HAIC-oxaliplatin monotherapy ranked lowest regarding grade 3–5 AEs. According to RE-CIST1.1, lenvatinib (72.8%), atezolizumab plus bevacizumab (73.6%), HAIC-oxaliplatin (78.8%) and HAIC-oxaliplatin plus sorafenib (75.2%) showed higher DCRs than sorafenib (57.3%), nivolumab (33.9%), and pem-

brolizumab (62.3%), whereas only HAIC-oxaliplatin-based treatments demonstrated a higher ORR than the others. Pooled OS and PFS analysis favored the combination regimens other than sorafenib along. **Conclusions**: Here, we present preliminary evidence for the comparative safety and efficacy of existing MTDs, ICIs, HAIC and their combinations in AHCC, which indicated that HAIC-oxaliplatin monotherapy has acceptable toxicity and efficacy and could be the cornerstone for future combination of systemic treatments in AHCC. Our findings might provide insight into the future design of multidisciplinary treatments in AHCC.

## 2. Background

Hepatocellular carcinoma (HCC) is one of the most common digestive system cancers and the fifth leading cause of cancer-related death in the United States in 2019. HCC is also one of the few neoplasms that has had a steadily increasing incidence and mortality in recent years [1, 2]. With decades of development, there are increasing selections for treating advanced HCC (AHCC; **Supplementary Fig. 1**) [3]. Recently, the first phase 3 trial in AHCC, the landmark KEYNOTE-240 study (NCT02702401), has supported favorable disease control and toxicity profiles for pembrolizumab in AHCC patients [4]. However, no consensus has been reached beyond the first-line setting because of the insignificant outcomes and extremely poor prognosis.

In China, most HCC is etiologically associated with hepatitis B virus infection. This virus-associated cancer represents the archetypal "inflamed tumor", which exhibits different expression levels of programmed death-ligand 1 (PD-L1) and indicates different prognostic outcomes [5, 6]. These biological profiles make immunotherapy a promising treatment option for HCC patients. In 2017, another landmark CheckMate-040 study (NCT01658878) first reported potential antitumor activities and manageable safety profiles of nivolumab in a previous phase I/II study of treated AHCC [7]. Whereas, the follow-up phase III study, CheckMate-459 (NCT02576509) failed to reach significant outcomes in 2019 [8]. Apart from immunotherapy, there are still several promising treatment strategies for AHCC that also provide solid evidence. In 2018, a phase III study reported that lenvatinib, a molecular-targeted drug, was noninferior to sorafenib which has been a stand-alone first-line treatment over the past 10 years in treating AHCC patients, and this study enriched the first-line treatment choices for treating AHCC [9–11]. In 2020, IMbrave-150 (NCT03434379), a potent combination of atezolizumab and bevacizumab which firstly used anti-PD-L1 and vascular endothelial growth factor (VEGF) inhibitor together, demonstrated superior survival benefits compared to sorafenib monotherapy for patients with AHCC [12]. Moreover, a novel interventional therapy, hepatic arterial infusion chemotherapy (HAIC), shows potent antitumor efficacy when combined with sorafenib or as a single therapy. In the sorafenib plus low-dose cisplatin and fluorouracil hepatic arterial infusion chemotherapy versus sorafenib alone in patients with advanced hepatocellular carcinoma study (SILIUS; NCT01214343), sorafenib plus low-dose cisplatin and fluorouracil HAIC (HAIC-cisplatin) had a durable disease control ability compared to sorafenib alone [13]. Another two HAIC phase III studies from China that used different regimens, including oxaliplatin, fluorouracil, and leucovorin (HAIC-oxaliplatin) alone (NCT03164382) or combined with sorafenib (NCT02774187), showed dramatically higher progression-free survival (PFS) and overall survival (OS) than sorafenib alone in treating AHCC [14, 15]. Although AHCC patients have suffered from extremely poor prognosis for years, many potential treatment approaches have been reported with convincing evidence in recent years, and it is urgent to properly organize these potent treatment approaches into strategies in order to achieve more effective outcomes. However, to date, there are no head-to-head comparisons of different molecular-targeted drugs (MTDs), immune checkpoint inhibitors (ICIs), hepatic arterial infusion chemotherapy (HAIC), and their combinations in AHCC. Therefore, we initiated this review to comprehensively compare the safety and efficacy of the abovementioned trials and to explore the optimal therapeutic regimens that compose a multidisciplinary approach in treating AHCC. We hypothesized that the efficacy and safety profiles differed across different anti-AHCC regimens.

## 3. Methods

The experimental arms in the abovementioned anti-AHCC studies, including MTDs, ICIs, HAIC, and their combinations, were included in the analysis [8–10, 12–16]. The baseline information of the eight enrolled studies is listed in **Supplementary Tables 1,2**, which includes trial-level characteristics and patient-level characteristics. The major assessed outcomes were adverse events (AEs), disease control rates (DCRs), objective response rates (ORRs), OS and PFS. AEs, DCRs and ORRs data were pooled up per regimen and are described as percentages. OS and PFS were pooled up and forest plots were drawn for comparisons. In details, the AEs is defined according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 3.0 [17]. ORR is defined as the proportion of patients who had a best response rating of complete response and partial response, which was maintained for at least 4 weeks from the first manifestation of that rating. And DCR is a composite of ORR and stable disease cases over the same time period [18].

To indirectly compare grade 1–5 and 3–5 adverse events in different regimens, the pooled odds ratios and 95% confidence intervals (CI) of each regimen were com-

pared one-to-one (Fig. 1b). The comparative incidences of AEs between different regimens were evaluated by the odds ratio (OR) and corresponding 95% CI using Fisher's exact test. For instance, OR >1 is considered to indicate a higher incidence of AEs than the other regimen. Given that the imaging evaluation of AHCC efficacy is dependent on either the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 or modified Response Evaluation Criteria in Solid Tumors (mRECIST), the effective data according to either of these imaging evaluation criteria were extracted from the enrolled studies if available. Forest plots were plotted based on the hazard ratios (HR) accompanying 95% CI for survival analysis outcomes in terms of OS and PFS on treatment allocations, respectively. Statistical analyses were performed using R version 3.5.2 (R Foundation for Statistical Computing, Vienna, Austria) and Review Manager, version 5.3 (Nordic Cochrane Centre, Oxford, England). A two-tailed $p < 0.05$ was considered statistically significant.

## 4. Results

### 4.1 Safety profile of the different regimens

8 studies from phase III clinical trials were included, the characteristics of the included studies are summarized in **Supplementary Tables 1**,**2**. The median sample size for antitumor therapy was 229 (range, 102–478), and the numbers of monotherapy and combination therapy were 6 and 2, respectively. Five of the eight (62.5%) studies investigated MTDs (28.6%) or ICIs (28.6%) in treating AHCC, while the other 3 studies (37.5%) investigated HAIC in treating AHCC with/without sorafenib. Around 70% of patients were diagnosed at the Barcelona Clinic Liver Cancer (BCLC) stage C among studies that reported tumor stages. Fig. 1 and **Supplementary Fig. 2** demonstrates the comparison of the safety profiles of MTDs, ICIs, HAIC, and their combinations. The pooled incidence rates of grade 1–5/3–5 AEs were 98.0%/48.6%, 98.3%/57.4%, 91.4%/22.0%, 96.4%/54.6%, 98.2%/61.1%, 86.3%/34.1%, 88.9%/9.4%, and 95.2%/53.2% for sorafenib, lenvatinib, nivolumab, pembrolizumab, atezolizumab plus bevacizumab, HAIC-cisplatin plus sorafenib, HAIC-oxaliplatin, and HAIC-oxaliplatin plus sorafenib, respectively (Fig. 1a). The incidence rate of grade 1–5 AEs was the lowest with HAIC-cisplatin plus sorafenib, while that of grade 3–5 AEs was the lowest with HAIC-oxaliplatin monotherapy. Treatment-related deaths were reported in patients receiving lenvatinib (hepatic failure, $n = 3$; cerebral hemorrhage, $n = 3$; respiratory failure, $n = 2$; tumor hemorrhage, $n = 1$; ischemic stroke, $n = 1$ and sudden death, $n = 1$), pembrolizumab (myocardial infarction, $n = 1$; esophageal variceal hemorrhage, $n = 1$; upper gastrointestinal hemorrhage, $n = 2$; death, $n = 1$; hepatic cirrhosis, $n = 1$ and malignant neoplasm pro-

gression, $n = 1$) and HAIC-oxaliplatin plus sorafenib (not reported; $n = 2$) (Fig. 1a). Treatment discontinuation due to AEs was most commonly recorded in HAIC-cisplatin plus sorafenib (29.5%) and HAIC-oxaliplatin plus sorafenib (25.8%), followed by sorafenib (19.5%), pembrolizumab (17.2%), nivolumab (11.2%), lenvatinib (8.9%), and atezolizumab plus bevacizumab (7.1%), while it was the lowest in HAIC-oxaliplatin monotherapy (0.0%) (Fig. 1a). Fisher's exact test indicated a noticeably lower risk of grade 1–5 AEs favoring HAIC-cisplatin plus sorafenib over most regimens, whereas dramatically higher risks of grade 1–5 AEs occurred with sorafenib over most regimens (Fig. 1b). Moreover, nivolumab and HAIC-oxaliplatin monotherapy demonstrated superior safety ranking compared with other regimens regarding grade 3–5 AEs (Fig. 1b). Generally, the risks of grade 1–5 and 3–5 AEs of HAIC-oxaliplatin monotherapy were obviously lower than those of the other treatments, while sorafenib, pembrolizumab and HAIC-oxaliplatin plus sorafenib shared the highest incidence of grade 1–5 and 3–5 AEs (Fig. 1b).

To profile the toxicity spectra in terms of different regimens, we further evaluated the incidence of class-specific AEs for grades 3–5 and 1–5, respectively (Fig. 1c and **Supplementary Fig. 2**). Fig. 1c showed that the majority of grade 3–5 AEs resulted from liver damage or myelosuppression, including alanine aminotransferase (ALT) increase (2.3%–14.8%), aspartate aminotransferase (AST) increase (4.2%–29.5%), anemia (2.2%–17.0%), neutropenia (1.5%–17.0%), and thrombocytopenia (1.8%–34.1%). In detail, the combination of HAIC and sorafenib therapies contributed the most to grade 3–5 AEs. HAIC-cisplatin or HAIC-oxaliplatin combined with sorafenib had the highest grade 3–5 AE incidence of AST increase (29.5%), hypertension (25.0%), lipase increase (29.5% and 29.0% for HAIC-cisplatin plus sorafenib and HAIC-oxaliplatin plus sorafenib, respectively), and thrombocytopenia (34.1%). Moreover, lenvatinib also suffered from a higher hypertension incidence (23.3%) than the most therapies. The majority of grade 1–5 AEs were systemic- and gastrointestinal-related and included fatigue (range, 20.1%–76.6%), weight loss (1.1%–39.8%), hand-foot skin reaction (2.9%–45.0%), rash or desquamation (9.7%–20.1%), hypertension (1.1%-52.3%), diarrhea (13.3%–38.7%), constipation (9.3%–21.7%), nausea (11.4%–79.8%), vomiting (9.5%–59.7%), abdominal pain (12.2%–43.8%), and decreased appetite (12.8%–34.0%). Moreover, the grade 1–5 AEs with an over 50.0% incidence rates mainly came from HAIC-related regimens, and HAIC-oxaliplatin plus sorafenib was the only regimen that suffered from two grade 1–5 AEs that were over 80.0% incidences: hypoalbuminemia (81.5%) and AST increase (80.7%). The majority of gastrointestinal-related AEs were mild and moderate (grade 1–2) and were recoverable if suspend the treatments. Of note, the systemic- and gastrointestinal-related AEs that had higher proportions of

**a**

| | Any grade AEs | Grade 3-5 AEs | Led to death | Led to discontinuation |
|---|---|---|---|---|
| Sorafenib | 98.0% | 48.6% | 0 | 19.5% |
| Lenvatinib | 98.3% | 57.4% | 2.3% | 8.9% |
| Nivolumab | 91.4% | 22.0% | 0 | 4.0% |
| Pembrolizumab | 96.4% | 54.6% | 2.5% | 17.2% |
| Atezolizuma + Bevacizumab | 98.2% | 61.1% | 0 | 7.1% |
| HAIC-cisplatin + Sorafenib | 86.3% | 34.1% | 0 | 29.5% |
| HAIC-oxaliplatin | 88.9% | 9.4% | 0 | 0 |
| HAIC-oxaliplatin + Sorafenib | 95.2% | 53.2% | 1.6% | 25.8% |

Grade 1-2 AEs (%)
Grade 3-5 AEs (%)

**b**

| | | | | | | | Adverse event |
|---|---|---|---|---|---|---|---|
| Sorafenib | 3.15 (0.96-16.41) P=0.054 | 4.58 (1.40-23.76) P=0.005 | 1.81 (0.46-10.38) P=0.556 | 0.51 (0.09-1.90) P=0.411 | 7.68 (2.06-42.86) P<0.001 | 6.06 (1.74-32.48) P<0.001 | 2.47 (0.51-15.56) P=0.308 |
| 0.62 (0.42-0.92) P=0.016 | Lenvatinib | 1.45 (0.83-2.55) P=0.181 | 0.57 (0.25-1.23) P=0.172 | 1.61 (0.80-3.43) P=0.198 | 2.45 (1.15-5.01) P=0.012 | 1.92 (1.00-3.63) P=0.044 | 0.78 (0.26-1.98) P=0.829 |
| 3.38 (2.21-5.19) P<0.001 | 5.44 (3.96-7.55) P<0.001 | Nivolumab | 0.39 (0.17-0.84) P=0.009 | 2.34 (1.17-4.95) P=0.013 | 1.68 (0.79-3.41) P=0.019 | 1.32 (0.69-2.47) P=0.355 | 0.54 (0.18-1.35) P=0.241 |
| 0.79 (0.51-1.20) P=0.258 | 1.27 (0.92-1.74) P=0.138 | 0.23 (0.16-0.33) P<0.001 | Pembrolizumab | 0.92 (0.36-2.32) P=1.000 | 4.26 (1.69-11.13) P=0.001 | 3.35 (1.45-8.24) P=0.001 | 1.37 (0.40-4.26) P=0.584 |
| 1.74 (1.15-2.63) P=0.006 | 1.08 (0.80-1.47) P=0.653 | 5.88 (4.17-8.35) P<0.001 | 1.37 (0.97-1.93) P=0.065 | Atezolizuma + Bevacizumab | 3.94 (1.65-9.47) P=0.002 | 3.10 (1.43-6.97) P=0.002 | 1.26 (0.38-3.66) P=0.606 |
| 1.83 (1.02-3.30) P=0.041 | 2.94 (1.78-4.94) P<0.001 | 0.54 (0.32-0.93) P=0.019 | 2.32 (1.37-4.00) P<0.001 | 3.18 (1.89-5.42) P<0.001 | HAIC-cisplatin + Sorafenib | 0.79 (0.36-1.77) P=0.570 | 0.32 (0.10-0.93) P=0.032 |
| 9.08 (4.76-18.28) P<0.001 | 14.68 (8.27-27.81) P<0.001 | 2.70 (1.48-5.22) P<0.001 | 11.58 (6.38-22.38) P<0.001 | 15.83 (8.78-30.38) P<0.001 | 4.96 (2.39-10.72) P<0.001 | HAIC-oxaliplatin | 0.41 (0.13-1.09) P=0.062 |
| 0.75 (0.44-1.25) P=0.266 | 1.20 (0.78-1.85) P=0.400 | 0.22 (0.14-0.35) P<0.001 | 0.95 (0.60-1.50) P=0.825 | 1.30 (0.83-2.03) P=0.271 | 0.41 (0.22-0.75) P=0.002 | 0.08 (0.04-0.16) P<0.001 | HAIC-oxaliplatin + Sorafenib |

Grade 1-5
Grade 3-5

**c**

Studies:
- Sorafenib
- Lenvatinib
- Nivolumab
- Pembrolizumab
- Atezolizuma + Bevacizumab
- HAIC–cisplatin + Sorafenib
- HAIC–oxaliplatin
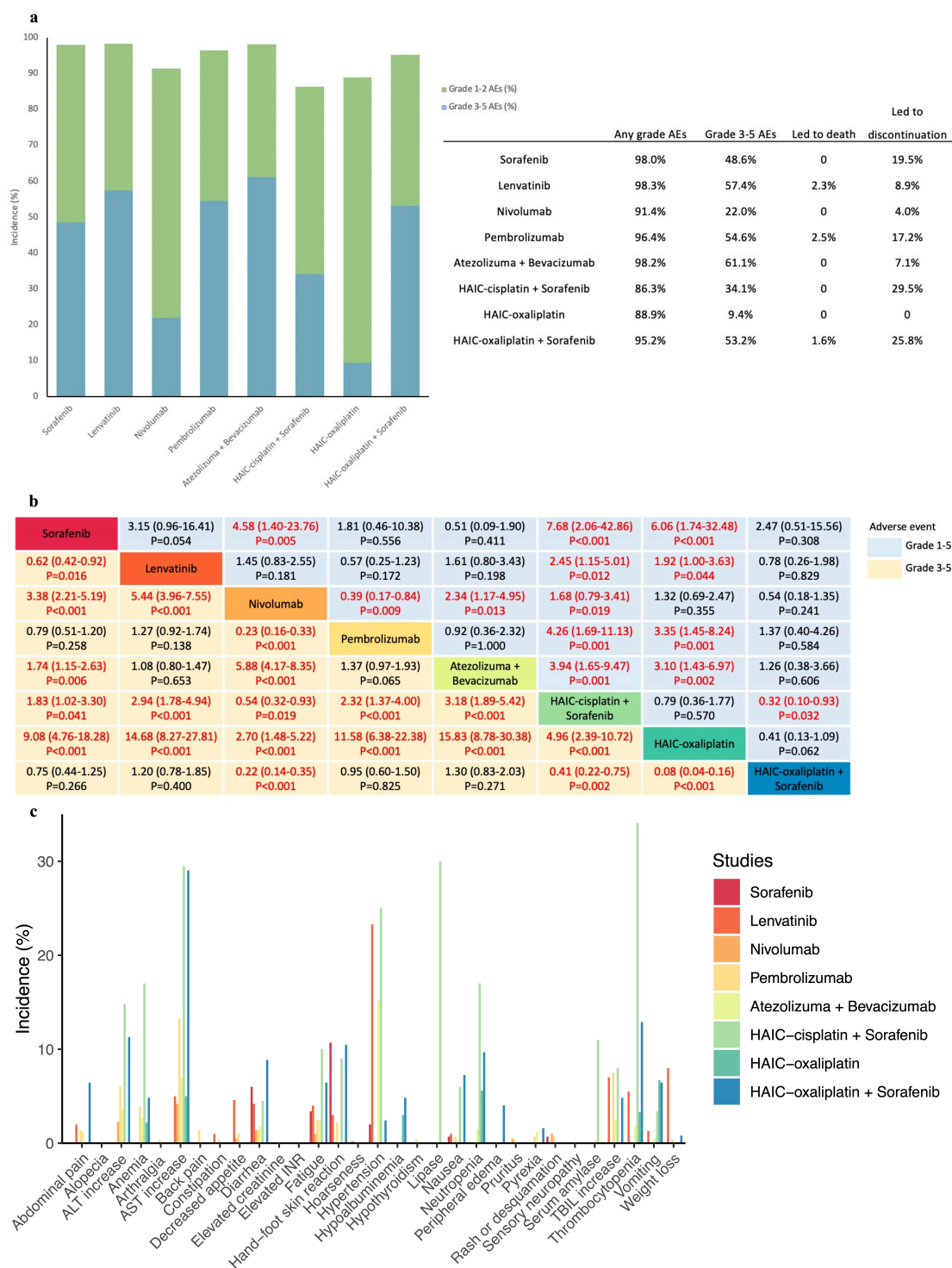- HAIC–oxaliplatin + Sorafenib

**Fig. 1. Safety profiles of molecularly targeted drugs, immune checkpoint inhibitors, hepatic arterial infusion chemotherapy alone, or their combinations in advanced hepatocellular carcinoma.** (a) Bar plot depicts the incidence rates of grade 1–5 adverse events (divided into grade 1–2 and 3–5) in sorafenib, lenvatinib, nivolumab, pembrolizumab, atezolizuma plus bevacizumab, hepatic arterial infusion chemotherapy (HAIC)-cisplatin plus sorafenib, HAIC-oxaliplatin, and HAIC-oxaliplatin plus sorafenib. The rates of deaths and discontinuation rates due to adverse events are also presented. (b) Indirect comparisons of grade 1–5 and 3–5 adverse events in different regimens. The pooled odds ratios and 95% confidence intervals indicate the result of the top regimen versus the bottom regimen. Each cell contains the pooled odds ratios and 95% confidence intervals; significant results are indicated in red. (c) Bar plot depicts the 3–5 grade toxicity spectra based on each of the specific adverse event. AE, adverse event; HAIC, hepatic arterial infusion chemotherapy; ALT, alanine aminotransferase; AST, aspartate aminotransferase; INR, international normalized ratio; TBIL, total bilirubin.

grade 1–5 AEs did not correspond to higher proportions of grade 3–5 AEs. However, compared to other regimens, HAIC-related therapies were always the major source of AEs for both grade 1–5 and grade 3–5 AEs. The details of AEs from each study were provided in supplementary materials (**Supplementary Table 3**).

### 4.2 Efficacy of the different regimens

Fig. 2 presents the efficacy of disease control of the different regimens according to RECIST 1.1 or mRECIST. Seven and five studies reported available data for analysis based on RECIST 1.1 and mRECIST, respectively. According to RECIST 1.1, lenvatinib (72.8%), atezolizumab plus bevacizumab (73.6%), HAIC-oxaliplatin (78.8%) and HAIC-oxaliplatin plus sorafenib (75.2%) showed higher DCRs than sorafenib (57.3%), nivolumab (33.9%), and pembrolizumab (62.3%) (Fig. 2a,b). Lenvatinib, nivolumab, pembrolizumab, and atezolizumab plus bevacizumab reported complete response (CR) cases among ORRs cases, with proportions of 0.4%, 3.7%, 2.2%, and 5.5%, respectively. Moreover, HAIC-oxaliplatin and its combination therapy had higher ORRs in partial response (PR) cases than the other regimens, which hit 29.4% and 40.8%, respectively. Notably, 54.0% of the DCRs of sorafenib and lenvatinib were stable disease (SD) cases, which resulted in the lowest ORRs of sorafenib among enrolled regimens. According to the mRECIST criteria, each enrolled study reached over 60.0% DCR, and the DCRs for lenvatinib, atezolizumab plus bevacizumab, HAIC-cisplatin plus sorafenib, HAIC-oxaliplatin, and HAIC-oxaliplatin plus sorafenib were 73.9%, 72.4%, 64.6%, 80.6%, and 76.0%, respectively (Fig. 2c). Impressively, when looking at the ORRs, the three combinations demonstrated higher CR rates than the other two monotherapies (10.2%, 7.8%, and 8.0% for atezolizumab plus bevacizumab, HAIC-cisplatin plus sorafenib, and HAIC-oxaliplatin plus sorafenib vs. 2.1% and 1.1% for lenvatinib and HAIC-oxaliplatin monotherapy, respectively). For PR rates of ORRs, HAIC-oxaliplatin based treatments had higher proportions than the other three treatments (47.8% and 46.4% for HAIC-oxaliplatin monotherapy and HAIC-oxaliplatin plus sorafenib vs. 38.5%, 23.1%, and 28.4% for lenvatinib, atezolizumab plus bevacizumab, and HAIC-cisplatin plus sorafenib, respectively). The SD rates of each regimen were no higher than 40.0% according to mRECIST.

For the survival analysis, the comparisons were divided into two parts regarding different control arms, compared to placebo or compared to sorafenib. 2 and 6 regimens with 639 and 3062 patients were compared in terms of OS and PFS, respectively. In the comparison to placebo, the pooled results demonstrated that receiving sorafenib or pembrolizumab were superior to placebo both in OS and PFS (HR 0.74, 95% CI 0.61–0.90, $p = 0.002$; HR 0.65, 95% CI 0.52–0.82, $p < 0.001$, respectively; Fig. 3a,c). More-

over, compared to sorafenib alone, the pooled results indicated that the therapies other than sorafenib were superior to single-use sorafenib for OS and PFS (HR 0.53, 95% CI 0.31–0.92, $p = 0.02$; HR 0.58, 95% CI 0.43–0.78, $p < 0.001$, respectively; Fig. 3b,d).

## 5. Discussion

This is the first review that comprehensively compared the safety and efficacy of different phase III MTDs, ICIs, HAIC and their combinations in AHCC, which provides preliminary evidence and integrative insights into future study designs and the implementation of novel treatment combination for clinical trials in AHCC. In the present study, the general safety of nivolumab, HAIC-cisplatin plus sorafenib and HAIC-oxaliplatin monotherapy ranked high, while their incidences of grade 3–5 AEs were relatively low. Integrating the specific toxicity spectra and regimens of each study, we postulate that HAIC-oxaliplatin monotherapy possess the lowest toxicity profile; the high incidence of all-grade AEs may be attributed to fatigue and AST increase, which are generally unthreatening and self-resolving. Moreover, the low incidence of all-grade and grade 3–5 AEs of HAIC-cisplatin plus sorafenib may be attributed to the low-dose regimen of cisplatin, whereas, it could compromise the treatment efficacy as results. The higher proportion of grade 3–5 liver damage may restrict the use of nivolumab compared to the other two interventional regimens [7, 15]. Interestingly, HAIC-oxaliplatin showed a markedly lower incidence of grade 3–5 AEs than the other treatments; however, once it was combined with sorafenib, the incidence of grade 3–5 AEs and the AE-related discontinue rate dramatically increased compared with HAIC-oxaliplatin alone, which suggests that the majority of AEs were mainly caused by sorafenib. This finding was also exactly supported by the counterpart control group from the same study that received sorafenib monotherapy, of which the proportion of grade 3–5 AEs was only 17.7% [15]. Moreover, this finding is also indirectly in accordance with the sorafenib arms in both the HAIC-cisplatin plus sorafenib and HAIC-oxaliplatin plus sorafenib studies [13, 14].

The response with HAIC-oxaliplatin based therapies for AHCC according to RECIST 1.1 or mRECIST both ranked at the forefront in terms of DCR and ORR. Additionally, although the incidence of all-grade AEs with HAIC-oxaliplatin monotherapy was high, the incidence of grade 3–5 AEs was substantially lower than those with other regimens. The ORR of HAIC-oxaliplatin monotherapy was not sufficiently satisfactory compared to that of HAIC-oxaliplatin plus sorafenib therapy, however, the combination therapy with sorafenib does not seem to be an efficient regimen because of its high AEs and low ORR. Instead, we believed that it provides preliminary inspiration that the combination of HAIC-oxaliplatin with other antitu-
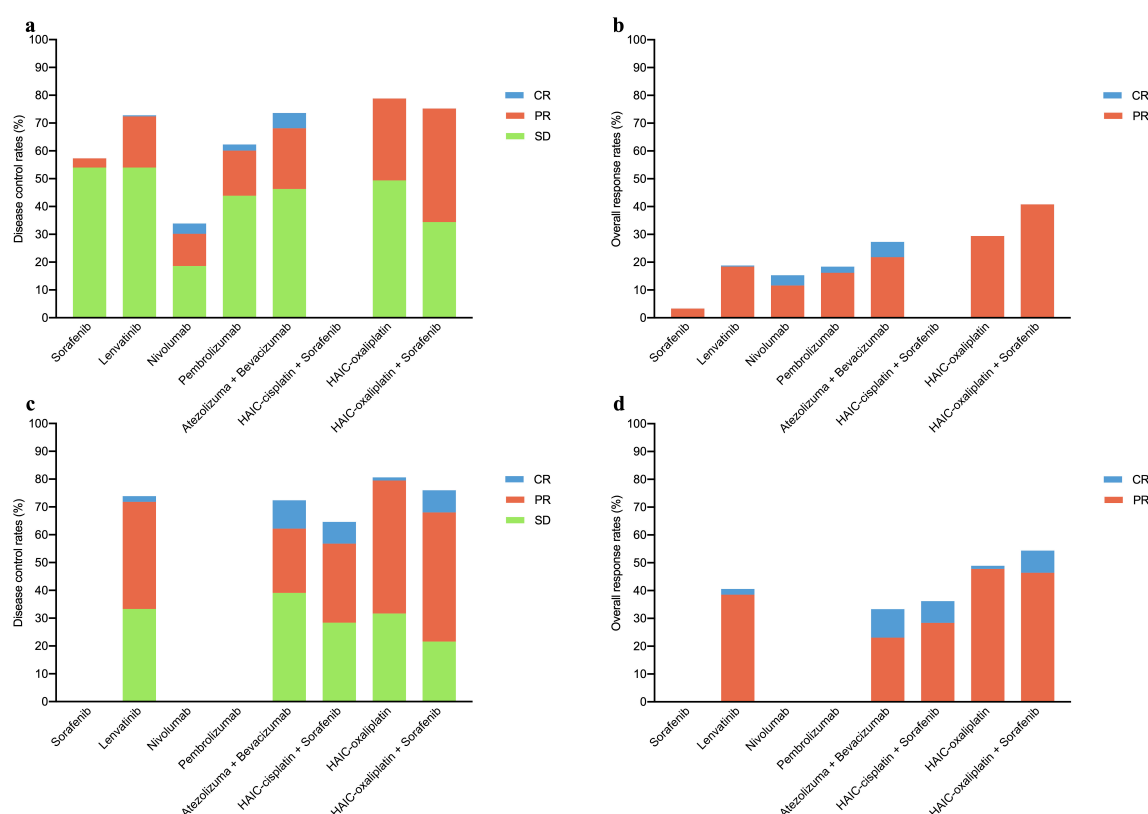
**Fig. 2. Efficacy of molecularly targeted drugs, immune checkpoint inhibitors, hepatic arterial infusion chemotherapy alone, or their combination in advanced hepatocellular carcinoma according to RECIST 1.1 or mRECIST.** Bar plot shows the disease control rates (a) and overall response rates (b) of patients with response to sorafenib, lenvatinib, nivolumab, pembrolizumab, atezolizuma plus bevacizumab, hepatic arterial infusion chemotherapy (HAIC)-cisplatin plus sorafenib, HAIC-oxaliplatin, and HAIC-oxaliplatin plus sorafenib according to RECIST 1.1; data were available from seven studies except the SILIUS study. Bar plot depicts disease control rates (c) and overall response rates (d) of patients with response to sorafenib, lenvatinib, nivolumab, pembrolizumab, atezolizuma plus bevacizumab, HAIC-cisplatin plus sorafenib, HAIC-oxaliplatin, and HAIC-oxaliplatin plus sorafenib according to mRECIST; data were available from five studies (REFLECT, IMbrave, SILIUS, HAIC-oxaliplatin, HAIC-oxaliplatin + Sorafenib). HAIC, hepatic arterial infusion chemotherapy; CR, complete response; PR, partial response; SD, stable disease; RECIST, Response Evaluation Criteria in Solid Tumors; mRECIST, modified Response Evaluation Criteria in Solid Tumors.

mor agents other than sorafenib is a "trial-worthy" approach to promote the ORR of anti-AHCC treatment.

Notably, we observed similarly higher CR rates (>7.0%) among the three combination therapies for intrahepatic disease than those of the other monotherapies. It supported that the combination therapies have synergized efficacy to improve the effect of single therapy, and it indicated that additionally systemic therapies, such as MTDs or ICIs, may be adequate to complete elimination of tumor cells (CR rate) when treating AHCC [19]. On the other hand, the responses of single lenvatinib, nivolumab, pembrolizumab, or HAIC were very limited, which was similar to other MTDs and ICIs [20–22]. It is reasonable enough to combine different treatments to substantially improve the tumor-killing efficacy (PR rate) under controllable toxicities (AE rates). Likewise, a phase 1b study by Ikeda and colleagues [23] reported encouraging ORRs (46.0%) and DCRs (92.0%) in treating unresectable HCC patients receiving lenvatinib plus pembrolizumab. Mean-

while, another phase 1 study led by Xu and colleagues [24] demonstrated that AHCC patients who received an anti-PD-1 agent, SHR-1210, combined with apatinib showed manageable AEs and relatively high ORR and DCR of 30.6% and 83.3%, respectively. These results implicate that the combination of MTDs with ICIs may achieve synergistic effects, and the substantially increased ORR may translate into patient survival benefits. To date, although there are several studies concerning the combination of MTDs and ICIs, trials of HAIC regimens combined with antitumor agents other than sorafenib are still lacking and are potentially accessible.

The majority of MTDs and ICIs are challenging because they benefit only small subsets of patients. Our prior studies found that a special tumor model, with vessels that encapsulated tumor clusters, demonstrated a better response and survival benefits to sorafenib [25], and there were also numerically higher ORRs in patients with PD-L1-positive AHCC than in those with PD-L1-negative
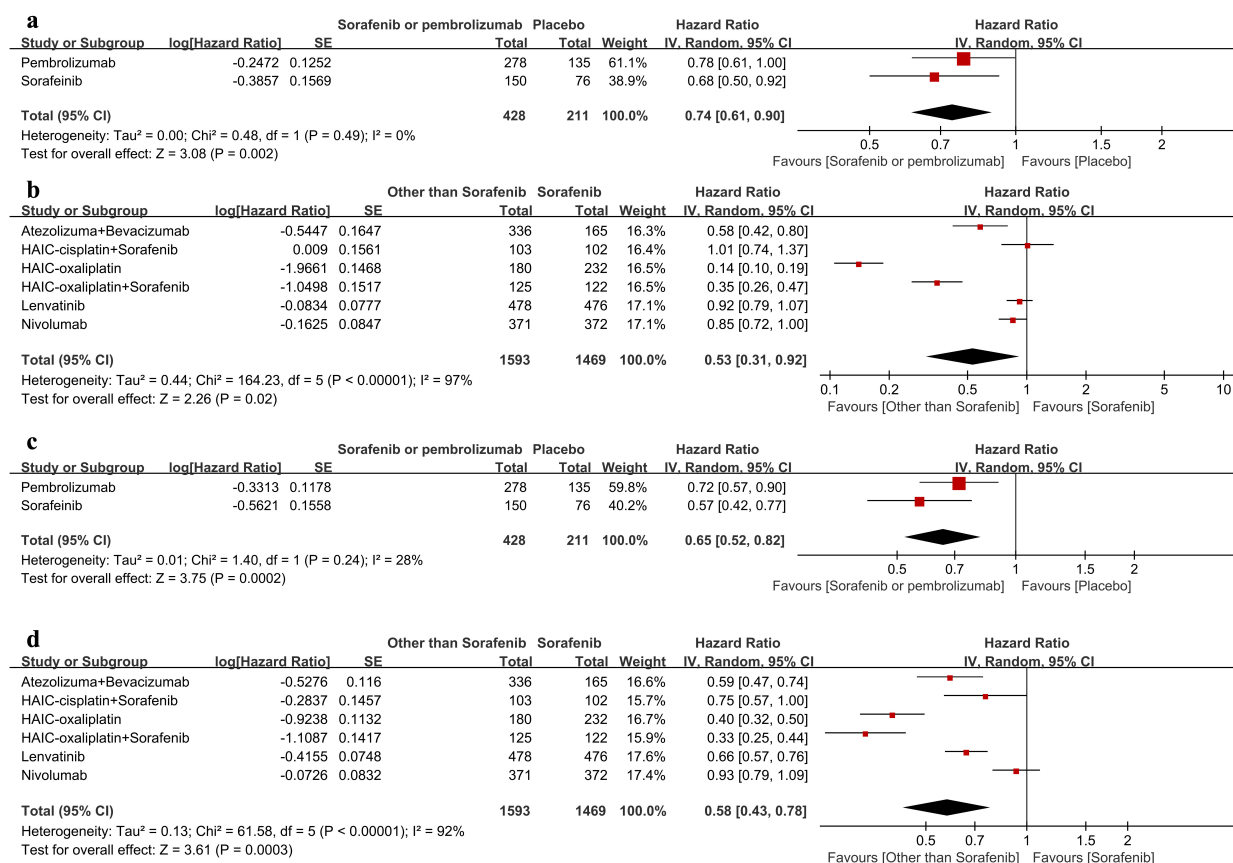
**Fig. 3. Forest plots demonstrating comparisons of overall survival (OS) and progression-free survival (PFS) among different therapies for advanced hepatocellular carcinoma.** (a) and (c) illustrate the comparisons between sorafenib or pembrolizumab and placebo in terms of OS and PFS, respectively. (b) and (d) illustrate the comparisons between therapies other than sorafenib and sorafenib in terms of OS and PFS, respectively.

AHCC when they received nivolumab [7]. Therefore, combining MTDs with ICIs might easily touch the ceiling and not be optimal enough to reach the best antitumor response. HAIC-oxaliplatin based local treatment has a remarkably higher ORR than other regimens, but the grade 3–5 AEs of HAIC-oxaliplatin plus sorafenib are relatively high. Based on the safety analysis of this study, we propose a potentially effective regimen that uses intrahepatic HAIC-oxaliplatin as a major regional treatment as well as this treatment combines with other systemic therapies, including MTDs and ICIs. Additionally, in the pooled comparison, those two HAIC-oxaliplatin based regimens enjoyed the best OS and PFS among other regimens, which also endorsed our hypothesis that HAIC-oxaliplatin is a proper candidate to synergize with other treatments.

We believe that future studies are warranted to identify a reliable and effective treatment combination in AHCC therapies, and improvements in treatment efficacy can be achieved by breakthroughs in combination regimens. Moving forward, these preliminary findings can construct a roadmap for the design of future trials to assess the efficacy of multidisciplinary anti-AHCC approaches. The results from relevant ongoing trials (e.g., NCT04053985,

NCT04135690, NCT04191889) are eagerly awaited.

One major limitation of this review is that the eligibility criteria are various among studies, there should be some effects on the outcomes because unable to calibrate. Moreover, our hypothesis needs to be verified in future large-scale, head-to-head, phase 3 trials. Second, the results of the toxicity spectra analysis should be interpreted with caution, in view of the gradual and in-depth comprehension of AEs assays [26].

## 6. Conclusions

Our review comprehensively compared the safety profiles and efficacies of MTDs, ICIs, HAIC and their combinations in patients with AHCC, providing an insightful possibility and evidence supports in terms of multidisciplinary therapy for HAIC-oxaliplatin-based regional plus systemic regimens.

## 7. Author contributions

YXP, RJW, DDH and WX made the study concepts, designed and drafted manuscript. JJH, YZF helped collect data and conduct data analysis. LX and YJZ helped manuscript preparation and revision. MSC and ZGZ were the guarantor of integrity of the entire study.

## 8. Ethics approval and consent to participate

Not applicable.

## 9. Acknowledgment

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## 11. Conflict of interest

The authors declare no conflict of interest.

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