# Sorafenib improves the survival of patients with advanced hepatocellular carcinoma: a meta-analysis of randomized trials

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**There is no effective systemic therapy for patients with advanced hepatocellular carcinoma (HCC) except liver transplantation. Sorafenib, a multikinase inhibitor, has been shown to significantly increase overall survival (OS) in a randomized, placebo-controlled, phase III trial of patients with HCC (SHARP). The aim of this study was to evaluate the effectiveness of sorafenib for advanced HCC by carrying out a meta-analysis of randomized controlled trials that compared sorafenib-based therapy with other agent-based therapy. Randomized controlled trials comparing sorafenib or combined chemotherapy with placebo or combined chemotherapy in advanced HCC between 2000 and 2008 were identified and the data were extracted from reports. Outcomes analyzed were objective response rate, time to progression (TTP), OS, and toxicity. The summary hazard ratios (HRs), odds ratios, and their 95% confidence intervals (CIs) for mortality, objective response rate, and toxicity were estimated. All statistical tests were two-sided. Three trials including 924 patients were identified. Sorafenib-based chemotherapy was also associated with a 79% prolongation of TPP (HR = 0.58, 95% CI = 0.49–0.69, $P < 0.001$), and a 37.3% increase in OS (HR = 0.66, 95% CI = 0.55–0.78, $P < 0.001$). Despite significant increases in the frequencies of hand–foot syndrome and diarrhea in patients receiving sorafenib-containing chemotherapy, no significant difference in other toxic events was observed. This meta-analysis suggests that sorafenib-based chemotherapy is superior to placebo-based chemotherapy in terms of TPP and OS without increase in severe toxic effects. *Anti-Cancer Drugs* 21:326–332 © 2010 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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## Introduction

Hepatocellular carcinoma (HCC) is the fifth leading cancer in the world with more than 1 million deaths annually [1]. More than 80% of cases occur in Asia. The most common cause is the increase in the incidence of hepatitis B and C. Chronic hepatitis B viral infection is prevalent in Asian countries and accounts for most of the cases of HCC [2]. In contrast, chronic hepatitis C viral infection is more common in Europe and the US [3]. Approximately 80% of HCC cases develop from a cirrhotic liver, which is caused by chronic hepatitis B or C infection, with an annual incidence of 2–6% for hepatitis B virus carriers and 3–5% for hepatitis C virus-infected individuals. Effective treatments for HCC include liver resection, transplantation and various local ablative and trans-arterial therapies. The surgical resection and liver transplantation will remain the main curative treatment option [4–7]. The median survival for patients with early-stage cancer after treatment is 6–9 months (single or three nodules $\leq 3$ cm) [8]. However, even in the developed countries, most (60–70%) of the patients are diagnosed with advanced stage of HCC, having 1–2 months median survival time after treatment [8].

Sorafenib (Nexavar; Bayer Pharmaceuticals Corporation, West Haven, Connecticut, USA) is an oral multi-kinase inhibitor that blocks tumor-cell proliferation and increases the rate of apoptosis [9,10]. Its targets include the serine–threonine kinases, Raf-1 and B-Raf, the receptor tyrosine kinase of vascular endothelial growth factor receptors (VEGFRs) [11], and platelet-derived growth factor receptor-β [9,10]. Growth factors and receptors of the Raf/mitogen-activated protein kinase/extracellular-signal-regulated kinase and VEGF pathways are often overexpressed or dysregulated in HCC [11]. Some preclinical studies had proved that sorafenib could suppress tumor angiogenesis, block tumor-cell signaling, and increased tumor-cell apoptosis in a mouse xenograft model [12]. Several randomized controlled clinical trials comparing sorafenib with placebo in the treatment of advanced HCC are proceeding, and three of them have

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reported results. On the basis of these data, we conducted a meta-analysis to assess the efficacy and safety of sorafenib in patients with advanced HCC.

## Materials and methods

### Search for trials

Both published and unpublished trials reported between January 2000 and December 2008 were identified through a computer-based search of the PUBMED database and abstracts from the past 10 conferences of the American Society of Clinical Oncology and the past 10 conferences of the European Society for Medical Oncology. We searched using the following terms: 'advanced hepatocellular carcinoma', 'Sorafenib or Nexavar'. We also examined reference lists of original articles and the Physician Data Query Registry of clinical trials.

### Selection of trials

If sorafenib alone or sorafenib-based combination chemotherapy were included in a randomized controlled trial (RCT), it was considered to be eligible. Trials had to fulfill the following inclusion criteria: (i) patients were randomly assigned to treatment, (ii) sorafenib or sorafenib-based combination chemotherapy was compared with other agent or agent-based combination chemotherapy without confounding by other agents or interventions, and (iii) only patients with diagnosis of advanced HCC were included.

### Validity assessment

Assessment of the trials was carried out openly with the instrument reported by Moher *et al.* [13], and there was no significant difference observed among the trials. Therefore, the result of the validity assessment was not considered in this meta-analysis.

### Data abstraction

The following information was extracted from each report: study design, regimen details, allocated patients, cause of disease, Barcelona Clinic liver cancer stage, extra-hepatic spread status, Eastern Cooperative Oncology Group performance status, macroscopic vascular invasion, Child–Pugh class, biochemical analysis, earlier therapy, median follow-up, ratios (HRs) for the whole study populations, and the year of reporting. Data were independently extracted from each report by Su and Liu, who were blinded to each other, using a standardized data recording form. After extraction, data were reviewed and compared by Zhang and Cheng. All data were checked for internal consistency, and any disagreements were resolved by discussion among the investigators. We also tried to contact the principal investigators of the trials to confirm or update both published and unpublished data.

### Statistical analysis

The primary endpoints in the meta-analysis were overall survival (OS) and time to progression (TTP). The secondary endpoints were objective response rate (ORR) and toxic events. Except toxic events, all analysis was conducted on an intention-to-treat basis, and all randomly assigned patients were included in the analyses according to the allocated treatment. We looked for heterogeneity among the trials based on standard methods [14]. The DerSimonian and Laird Q statistic (Q test) was used to test for heterogeneity among trials [15]. Begg's funnel plots [16] and Egger's test [17] were used to detect possible publication bias. On the basis of the results of the Q test we applied a fixed-effects model to estimate the summary HR, odds ratios (ORs) and their 95% confidence intervals (CIs). We also used a random-effect model [15], which usually yields wider CIs, resulting in a more conservative statistical claim. If HRs or its 95% CIs could not be obtained from reports, crude log HR and its variance were calculated according to the method proposed by Parmar *et al.* [18]. All statistical analyses were conducted with STATA Version10.1 software (College Station, Texas, USA). All statistical tests were two-sided, and $P$ values of 0.05 were considered to be statistically significant.

## Results

### Trial flow

The flow chart of our study is shown in Fig. 1. Ultimately, only three RCT studies involving 924 patients with advanced HCC were analyzed in this meta-analysis [19–21]. Although we did not limit language in the process of searching, all the trials were published in English. All the three trials were randomized double-blind placebo-controlled trials and the results were based on intention-to-treat analysis except toxic events. One trial that compared sorafenib plus Transcatheter arterial chemoembolization with sorafenib alone in 105 patients was excluded because this phase III study was ongoing and the data were not available [22,23].

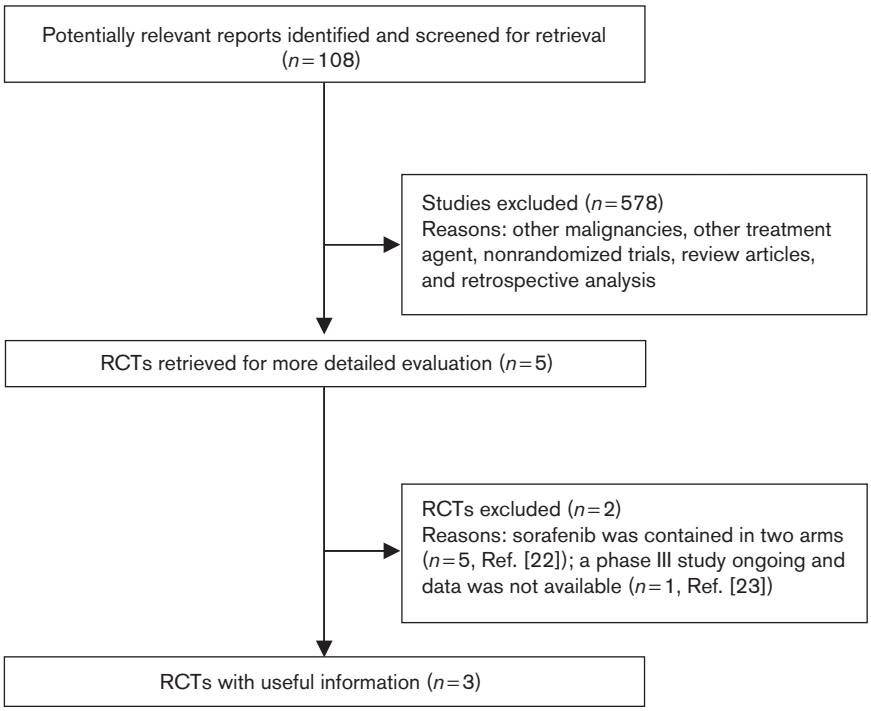
### Characteristics of the three trials

The characteristics of the three trials are listed in Table 1. In total, 924 patients were randomized to receive a sorafenib or sorafenib-based doublet (496 patients) or a placebo therapy (428 patients). Three hundred patients enrolled in one trial were excluded before randomization [19]. Two trials were a phase III studies and one was a phase II study. Further information on one unpublished trial [21] was obtained by contacting the principal authors. No potential sources of heterogeneity including sex, age, Child–Pugh status, macroscopic vascular invasion, extrahepatic disease, Child–Pugh class were associated with significant differences in outcomes.

### Objective response rate

Information on ORR was available for all three trials (Table 2). On the basis of intention-to-treat analysis including all randomized patients, the ORR to a sorafenib or sorafenib-based doublet therapy was more than

**Fig. 1**




A flow chart showing the progress of trials through the review. RCT, randomized controlled trials.

**Table 1 Characteristics of the three trials included in this meta analysis**

| Authors | Year | Publication form | Patients | Chemotherapy regimen | Sex (male, %) | PS 0–1 (%) | Age (years) | Child–Pugh status A (%) | Macroscopic vascular invasion (%) | Extraheptic disease (%) |
|---|---|---|---|---|---|---|---|---|---|---|
| Llovet *et al.* | 2008 | Full text | 299 | Sorafenib 400 mg, placebobid | 87 | 92 | 64.9 | 95 | 36 | 53 |
| | | | 303 | Placebo 2 tablets placebo bid | 87 | 93 | 66.3 | 98 | 41 | 50 |
| Cheng *et al.* | 2009 | Abstract | 150 | Sorafenib 400 mg, twice, daily | 85 | 94 | 51 | 97 | 36 | 69 |
| | | | 76 | Placebo 2 tablets placebo bid | 87 | 95 | 52 | 97 | 34 | 68 |
| Abou-Alfa *et al.* | 2008 | Abstract | 47 | Doxorubicin 60 mg/m$^2$, day 1, q3 weeks + sorafenib 400 mg placebo bid | 66 | 85 | 63 | 100 | 28 | 51 |
| | | | 49 | Doxorubicin 60 mg/m$^2$, day 1, q3 weeks + P 2 tablets placebo bid | 86 | 84 | 62 | 96 | 33 | 65 |

All trials were randomized controlled phase III trials except for the trial by Abou-Alfa which was designed as a randomized controlled phase II trial.
PS, performance status.

**Table 2 Responses in the three trials**

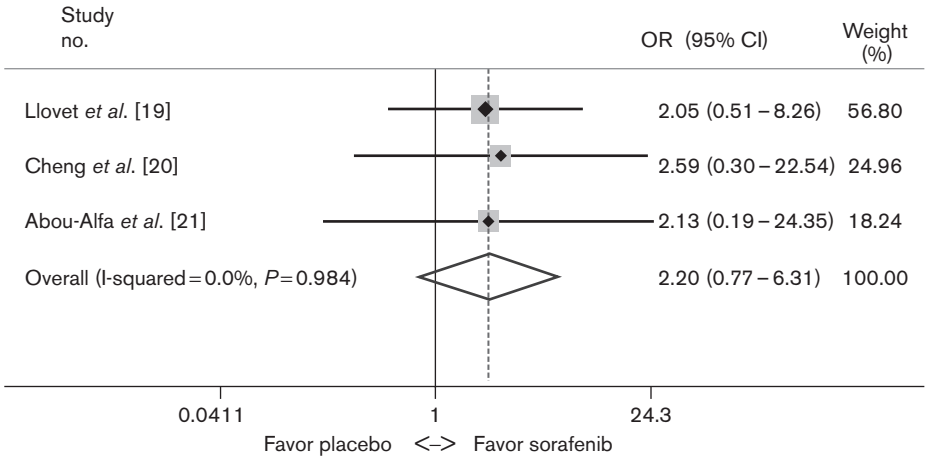
| Authors | Chemotherapy regimen | Patients with complete or partial response | Patients with stable disease | Randomized patients | Objective response rate (%) |
|---|---|---|---|---|---|
| Llovet *et al.* | Sorafenib | 6 | 212 | 299 | 2 |
| | Placebo | 3 | 203 | 303 | 1 |
| Cheng *et al.* | Sorafenib | 5 | 81 | 150 | 3 |
| | Placebo | 1 | 21 | 76 | 1 |
| Abou-Alfa *et al.* | Sorafenib + doxorubicin | 2 | 36 | 47 | 2 |
| | Placebo + doxorubicin | 1 | 27 | 49 | 1 |

two-fold higher than a placebo or placebo-based doublet therapy but had no significant difference (OR = 2.20, 95% CI = 0.77–6.31, $P = 0.14$, Fig. 2). Neither a Begg's funnel plot nor a rank correlation test regarding response rate indicated the existence of publication bias ($Z = 0.00$, $P = 1.000$). The results of Egger' test were similar. The heterogeneity test did not yield a significant result ($P = 0.98$).

### Time to progression and overall survival

Data of TTP and OS were available from all the three trials (Table 3). On the basis of the intention-to-treat analysis, TPP and survival analyses were carried out in all three trials. Sorafenib or sorafenib-based doublet therapy was associated with a 79% improvement in TPP (HR = 0.58, 95% CI = 0.49–0.69, $P < 0.001$, Fig. 3). Similarly, a funnel plot and rank correlation test regarding survival confirmed the absence of publication bias ($Z = 0.00$, $P = 1.000$). The results of Egger' test was similar. The heterogeneity test did not yield a significant

**Fig. 2**



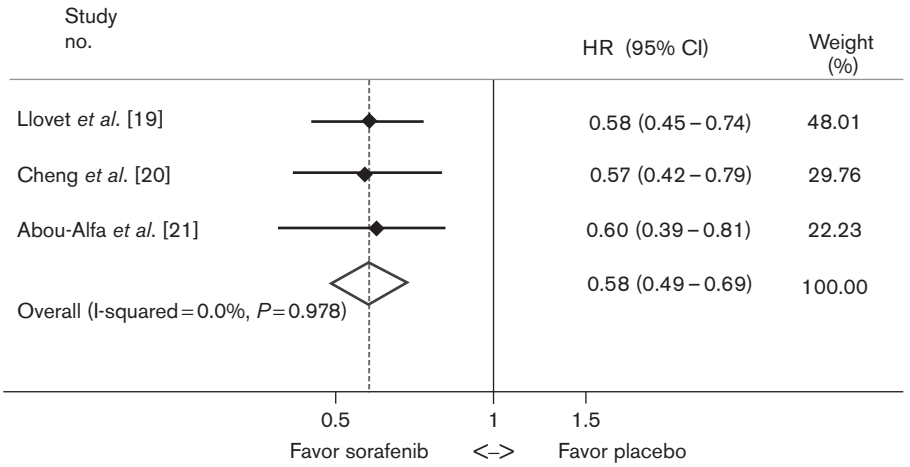

Response to a sorafenib containing chemotherapy compared with a placebo containing chemotherapy. The heterogeneity test did not yield a significant result ($P = 0.98$). CI, confidence interval; OR, odds ratio.

**Table 3 Time to progression and overall survival in the three trials**

| Authors | Chemotherapy regimen | ITT analysis | Randomized patients | Median TTP (month) | *P* value | Median overall survival time (month) | *P* value |
|---|---|---|---|---|---|---|---|
| Llovet *et al.* | Sorafenib | Yes | 299 | 5.5 (4.1–6.9) | <0.001 | 10.7 (9.4–13.3) | <0.001 |
| | Placebo | | 303 | 2.8 (2.7–3.9) | | 7.9 (6.8–9.1) | |
| Cheng *et al.* | Sorafenib | Yes | 150 | 2.8 (2.6–3.6) | <0.001 | 6.5 (5.6–7.6) | 0.014 |
| | Placebo | | 76 | 1.4 (1.3–1.5) | | 4.2 (3.7–5.5) | |
| Abou-Alfa *et al.* | Sorafenib + doxorubicin | Yes | 47 | 8.6 (4.8–12.6) | 0.076 | 13.8 (9.1–NA) | 0.013 |
| | Placebo + doxorubicin | | 49 | 4.8 (2.8–8) | | 6.5 (4.9–11.3) | |

ITT, intention-to-treat; TTP, time to progression.

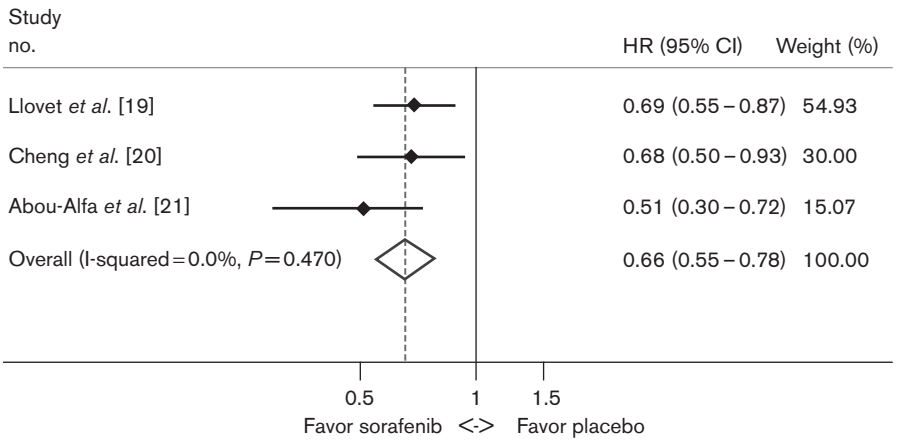
**Fig. 3**




Time to progression with a sorafenib containing chemotherapy compared with a placebo containing chemotherapy. The heterogeneity test yielded no significant result ($P = 0.98$). CI, confidence interval; HR, hazard ratio.

result ($P = 0.98$). Sorafenib or sorafenib-based doublet therapy was associated with a 37.3% improvement in OS (HR = 0.66, 95% CI = 0.55–0.78, $P < 0.001$, Fig. 4). Similarly, a funnel plot and rank correlation test regarding survival confirmed the absence of publication bias ($Z = 1.04$, $P = 0.30$). The results of Egger' test was similar. The heterogeneity test did not yield a significant result ($P = 0.47$).

**Fig. 4**




Overall survival with a sorafenib containing chemotherapy compared with a placebo containing chemotherapy. The heterogeneity test yielded no significant result ($P=0.47$). CI, confidence interval; HR, hazard ratio.

**Table 4 Toxic events in trials comparing sorafenib-containing regimen with placebo containing regiment (grades 3 and 4)**

| | | Sorafenib containing therapy | | Placebo containing therapy | | | |
|---|---|---|---|---|---|---|---|
| Toxicity | No. of evaluable trials | Patients with toxicity (%) | Evaluable patients | Patients with toxicity (%) | Evaluable patients | OR (95% CI) | *P* value for Q test |
| Fatigue | 3 | 14 | 494 | 11 | 426 | 1.19 (0.51–2.74) | 0.69 |
| Diarrhea[a] | 3 | 19 | 494 | 7 | 426 | 2.41 (0.99–5.86) | 0.05 |
| Hand–foot syndrome[a] | 3 | 23 | 494 | 0 | 426 | 13.43 (3.53–71.47) | 0.002 |
| Hypertension | 3 | 4 | 494 | 1 | 426 | 2.25 (0.34–14.80) | 0.40 |
| Abdominal pain | 2 | 7 | 345 | 5 | 351 | 1.47 (0.45–4.83) | 0.53 |
| Rash/desquamation | 2 | 2 | 446 | 0 | 377 | 2.18 (0.23–21.06) | 0.50 |
| Nausea | 2 | 1 | 446 | 2 | 377 | 0.41 (0.05–3.33) | 0.41 |
| Neutropenia | 1 | 26 | 48 | 22 | 49 | 1.45 (0.45–3.23) | 0.36 |
| Febrile neutropenia | 1 | 2 | 48 | 7 | 49 | 0.26 (0.05–1.33) | 0.11 |
| Anorexia | 1 | 0 | 297 | 1 | 302 | 0.34 (0.01–8.33) | 0.51 |
| Bilirubin | 1 | 5 | 48 | 3 | 49 | 1.78 (0.40–7.92) | 0.45 |
| LV dysfunction | 1 | 1 | 48 | 0 | 49 | 3.13 (0.12–78.66) | 0.49 |

Heterogeneity tests showed no significant results for all toxic events.
CI, confidence interval; LV, left ventricle; OR, odds ratio.
[a]The result had a significant difference.

### Toxicity

All three trials included 920 patients, which provided toxicity results (Table 4). No data for rash/desquamation and nausea were available in one trial [21]; data for abdominal pain were not available in one trial [20], data for neutropenia, febrile neutropenia, bilirubin, and left venticle dysfunction were not available in two trials [19,20], and data for anorexia could only be obtained from one trial [19]. The heterogeneity test found no statistical significance for all toxic events. Comparing with placebo or placebo-based doublet therapy, sorafenib or sorafenib-based doublet therapy significantly increased the frequency of hand–foot syndrome and diarrhea, whereas there was no significant difference in other toxic events.

## Discussion

Sorafenib (Nexavar; Bayer Pharmaceuticals Corporation) was initially found in a screen for agents to block the Raf proteins, C-Raf, and B-Raf. Further examination showed that this compound also blocked other kinases including VEGFR-2 and VEGFR-3, platelet-derived growth factor receptor, and the receptors for Flt-3 legend and stem cell factor [9,24]. Sorafenib was initially used to treat renal cell carcinoma, which could increase median progression-free survival time from 2.8 months to 5.5 months according to the Treatment Approaches in Renal Cancer Global Evaluation Trial study [25]. In 2006, Huitzil-Melendez *et al.*, [26] reported that single-agent sorafenib might have a beneficial therapeutic effect in an uncontrolled phase II study involving 137 patients with advanced HCC and Child–Pugh class A or B status. The median OS was 9.2 months and a median TPP was 5.5 months. For the treatment of advanced HCC, these results were really exciting. But because this trial was not a RCT trial, we did not include it in our meta-analysis.

In this meta-analysis, we identified only three RCT trials, and the largest accounted for 602 randomly assigned patients. The data of a single trial are not sufficient to provide reliable evidence to endorse or refuse the use of sorafenib as a treatment of advanced HCC. Therefore, we believed it was necessary to integrate the data together with these RCT trials comparing sorafenib-based therapy with placebo and evaluate the evidence.

The results of this meta-analysis showed that sorafenib-based chemotherapy significantly prolonged the TPP (HR = 0.58, 95% CI = 0.49–0.69, $P < 0.001$), and improved OS (HR = 0.66, 95% CI = 0.55–0.78, $P < 0.001$) compared with placebo-based chemotherapy. But sorafenib-based chemotherapy is not inferior in terms of the ORR (OR = 2.20, 95% CI = 0.77–6.31, $P = 0.14$). Meanwhile, sorafenib-based chemotherapy showed no significant difference in toxic events except for hand–foot syndrome (OR = 13.43, 95% CI = 7.53–71.47, $P = 0.002$), and diarrhea (OR = 2.41, 95% CI = 0.99–5.86, $P = 0.05$). The results of the meta-analysis are consistent with the results of all the three RCT trials. Neither the Begg's funnel plot for publication bias nor the heterogeneity test yielded a significant result. As the results based on random effect model were similar to the results based on a fixed-effect model, we did not show the results based on a random-effect model.

However, there are still several limitations in this meta-analysis. First, this analysis is based on aggregated data, not individual patient data (IPD). An IPD meta-analysis would give a more robust estimate of the association but it takes a long time to obtain those data [27]. However, as opposed to IPD meta-analysis, our meta-analysis offers the most comprehensive insight into sorafenib-based therapy as soon as possible and may help physicians and their patients worldwide to make a better-informed decision regarding the most appropriate adjuvant therapy. Second, as far as we know, only three RCT trials including 924 patients reported their results. However, all the three trials are double blind and carried out on an intention-to-treat analysis. Therefore, we consider that our meta-analysis based on these trials is believable. Third, a possible publication bias is also a potential threat in our study, although we did not detect it statistically.

In conclusion, this is the first published meta-analysis, to our knowledge, of randomized trials of sorafenib-based therapy versus placebo-based therapy in treating advanced HCC. Although there are some limitations, the survival improvement obtained with sorafenib-based therapy in comparison with placebo-based therapy indicates that sorafenib may be a new effective therapy for treating advanced HCC.

## Acknowledgement

Conflict of interest: none declared.

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