Risk versus Benefit of Tyrosine Kinase Inhibitors for Hepatocellular Carcinoma: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Although the treatment landscape has rapidly evolved over the last years, hepatocellular carcinoma (HCC) is one of the most lethal cancers. With recent advances, both immunotherapy and tyrosine kinase inhibitors (TKIs)-based chemotherapy constitute the standard treatment for advanced HCC. A systematic search of randomized clinical trials employing TKIs was performed in 17 databases, obtaining 25 studies evaluating the prognosis, tumor response, and presence of adverse events (AEs) related to TKIs in HCC. Overall effect sizes were estimated for the hazard ratios (HR) and odds ratios (OR) with 95% confidence interval (CI), either extracted or calculated with the Parmar method, employing STATA 16. Heterogeneity was assessed by Chi-square-based *Q*-test and inconsistency (I^2) statistic; source of heterogeneity by meta-regression and subgroup analysis; and publication bias by funnel plot asymmetry and Egger's test. The research protocol was registered in PROSPERO (CRD42023397263). Meta-analysis revealed a correlation between survival and tumor response parameters and TKI treatment vs. placebo, despite detecting high heterogeneity. Combined TKI treatment showed a significantly better objective response rate (ORR) with no heterogeneity, whereas publication bias was only detected with time to progression (TTP). Few gastrointestinal and neurological disorders were associated with TKI treatment vs. placebo or with combined treatment. However, a higher number of serious AEs were related to TKI treatment vs. sorafenib alone. Results show positive clinical benefits from TKI treatment, supporting the approval and maintenance of TKI-based therapy for advanced HCC, while establishing appropriate strategies to maximize efficacy and minimize toxicity.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ Hepatocellular carcinoma (HCC) constitutes one of the deadliest types of cancer. Although treatment landscape rapidly evolved over the years, tyrosine kinase inhibitors (TKIs) remain an alternative therapy for advanced HCC.

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ Are TKIs-based systemic treatment's effectiveness and safety for HCC patients being doubted after the appearance of immunotherapy?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ Treatment with TKIs correlated with a higher survival, tumor response rate, and the presence of few manageable adverse events (AEs) in patients suffering from HCC.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

☑ TKIs treatment has a positive impact in patients' prognosis and tumor response. Despite the presence of AEs, results support maintaining TKI-based therapy as one of the standard treatment for advanced HCC.

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Primary liver cancer is the third leading cause of cancer-related deaths, with a rising incidence and mortality worldwide.[1] Hepatocellular carcinoma (HCC) accounts for about 80–85% of all liver cancer cases, and regardless of etiology, it is usually diagnosed in the context of liver cirrhosis.[2–4] HCC is characterized by high recurrence rates, making patient's management a continuously challenging issue as well as a constant burden for healthcare systems.[3,5] The landscape for HCC treatment has improved over the years, and comprises a wide variety of therapeutic options established by the main staging system Barcelona Clinic Liver Cancer (BCLC) algorithm.[6,7] BCLC classification system is helpful in predicting a patient's prognosis accounting for tumor burden, liver function, and the performance status of the patients, grading HCC from early (BCLC 0-A) to terminal stage (BCLC D).[8]

Unfortunately, most HCC cases are diagnosed in advanced stages (BCLC C), where only systemic therapy (chemotherapy and immunotherapy) can have some beneficial effect.[7,9] Sorafenib, an orally administered tyrosine kinase inhibitor (TKI), exhibited promising results in the sorafenib in advanced hepatocellular carcinoma (SHARP) and Asia-Pacific clinical trials, which led to its approval as a first-line systemic treatment by the Food and Drug Administration in 2007.[10,11] Nonetheless, its efficacy rapidly declined due to the development of sorafenib-resistant HCC cells.[12,13] The scarcity of effective systemic therapy for HCC was reflected in the efforts of the scientific community to improve HCC treatment effectiveness, which resulted in the approval of regorafenib more than a decade later for patients that progressed after sorafenib.[14] Moreover, novel TKIs, such as lenvatinib and cabozantinib, have been proposed as alternative drugs due to their positive results in first and second-line treatment, respectively.[7]

Although HCC systemic therapy demonstrated great clinical benefit, adverse events (AEs) are a common issue that needs to be taken into account and managed to maximize treatment effectiveness.[15] Most AEs developed due to drug overexposure are tolerable and controllable (including hypertension, diarrhea, rash, nausea, vomiting, or fatigue); however, some high toxicity unexpected conditions can be life-threatening, causing dose interruption or treatment discontinuation.[15–19]

Considering the wide range of therapeutic options available for advanced HCC, we performed this unique systematic review with meta-analysis to determine the potential risk-to-benefit relationship of employing approved and unapproved TKIs as first- or second-line therapy for advanced HCC through analyzing survival and tumor response parameters as well as serious AEs that emerged in the clinical trials included in the present study.

METHODS

Study objectives

We performed this unique systematic review with meta-analysis to determine the potential risk-to-benefit relationship of employing approved and unapproved TKIs as first or second-line therapy for advanced HCC through analyzing survival and tumor response parameters, as well as serious AEs that emerged in clinical trials employing TKIs in the experimental or control arms.

This systematic review with meta-analysis was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (**Tables S1 and S2**).[20] Moreover, the study protocol was registered in the International Prospective Register for Systematic Reviews (PROSPERO), being ascribed the registration code CRD42023397263.

Clinical trials search strategy

We performed an exhaustive clinical trials search in the following clinical trials databases: the Australian New Zealand Clinical Trials Registry (ANZCTR), the Brazilian Clinical Trials Registry (ReBEC), the Chinese Clinical Trial Register (ChiCTR), the Clinical Research Information Service (Republic of Korea) (CriS), ClinicalTrials.gov, the Clinical Trials Registry (India) (CTRI), the Cuban Public Registry of Clinical Trials (RPCEC), the EU Clinical Trials Register (EUCTR), the German Clinical Trials Register (DRKS), the Iranian Registry of Clinical Trials (IRCT), the International Traditional Medicine Clinical Trial Registry (ISRCTN), the Japan Primary Registries Network (JPRN), the Pan African Clinical Trial Registry (PACTR), the Peruvian Clinical Trials Registry (REPEC), the Sri Lanka Clinical Trials Registry (SLCTR), the Thai Clinical Trials Register (TCTR) and The Netherlands National Trial Register (NTR). We established January 31st 2023 as the study inclusion deadline date.

The following search strategy was employed for clinical trials identification: («hepatocellular carcinoma» OR «hepatocarcinoma» OR «HCC»).

Inclusion and exclusion criteria

Studies that met the following criteria were selected for this systematic review and meta-analysis: (i) patients diagnosed with HCC; (ii) clinical trials that evaluated individual TKIs treatment or TKIs effects in combined treatments; (iii) studies that included a control arm; (iv) association of TKI treatment with survival parameters, tumor response or AEs with reported data or that can be estimated.

Studies complying with the following criteria were excluded from this meta-analysis: (i) no clinical trials; (ii) phase I or IV clinical trials; (iii) no randomization for experimental and control arms; (iv) no results available (no data provided or that cannot be estimated).

Data extraction and quality assessment

Four authors performed the studies screening, data extraction, and quality assessment of all included studies. All discrepancies were resolved by discussion and final consensus.

Studies included in the qualitative analysis were subjected to a quality assessment employing a modified version of the Jadad score (scoring from 0 to 10 points),[21] and the Delphi list (scoring from 0 to 9 points).[22] A high-quality cutoff of ≥6 and ≥5 was established for the Jadad and Delphi scores, respectively. Clinical trials that failed to comply with the quality thresholds for any of the scales were considered low-quality and were excluded from the analysis.

The main characteristics and data related to the extracted or estimated parameters of the key outcomes of each clinical trial are summarized in **Table 1**. All survival parameters and tumor response data were extracted from published articles of each clinical trial, except for NCT02279719 (amcasertib + sorafenib vs. sorafenib) and NCT02178358 (galunisertib or galunisertib + sorafenib vs. sorafenib + placebo), in which data were extracted from ClinicalTrials.gov. In contrast, ClinicalTrials.gov was employed to assess and extract data of the most frequent serious AEs, defined as the ones found and evaluated at least in 15 studies. Nevertheless, NCT01009593,[23] NCT00858871,[24] and NCT00825955[25] AEs data were only available in published articles.

Statistical analysis

The statistical software STATA version 16 (College Station, TX) was employed to analyze the survival parameters, tumor response rates, and AEs derived from TKIs treatment in patients diagnosed with HCC.

Table 1 Baseline characteristics of the clinical trials included in the meta-analysis

Clinical trial ID	Masking	Phase	Setting	Treatment arm	Control arm	Treatment/ Control arm of survival parameters (*n*)	Treatment/ Control arm of tumor response parameters (*n*)	Treatment/ Control arm of adverse events (*n*)	Follow-up (months)	Jadad score	Delphi score	Parameters evaluated
NCT02279719	Open	II	First-line	Amcasertib + sorafenib	Sorafenib	NR	10/31	7/36	NR	7	5	ORR, DCR, AEs
NCT02178358	Double	II	First-line	Galunisertib	Sorafenib	20/38	20/38	20/38	24	9	6	OS, ORR[a], AEs
				Galunisertib + sorafenib		74/38	74/38	74/38				
NCT01988493[29]	Open	II	First-line	Tepotinib	Sorafenib	38/37[b]	38/37	45/44	28.3	8	5	ORR, DCR, AEs
NCT01761266[30]	Open	III	First-line	Lenvatinib	Sorafenib	478/476	478/476	476/475	41	8	6	OS, PFS, TTP, ORR, DCR, AEs
NCT01774344[31]	Quadruple	III	Second-line	Regorafenib	Placebo	379/194	379/194	374/193	33	10	9	OS, PFS, TTP, ORR, DCR, AEs
NCT01755767[32]	Quadruple	III	Second-line	Tivantinib 120 mg	Placebo	226/114	NR	225/114	36	10	9	OS, PFS, TTP, AEs
				Tivantinib 240 mg		NR	NR	28/15				
NCT01465464[33]	Quadruple			Orantinib	Placebo	444/444 for OS	NR	444/444	42	10	9	OS, TTP, AEs
		III	First-line			442/443 for TTP						
NCT01232296[34]	Open	II	First-line	Dovitinib	Sorafenib	82/83	82/83	79/83	29.9	6	5	OS, TTP, ORR, DCR, AEs
NCT01210495[35]	Double	II	Second-line	Axitinib	Placebo	134/68	134/68	133/68	34	10	7	OS, PFS, TTP, ORR, DCR, AEs
NCT01164202[36]	Quadruple	II	First-line	Sunitinib	Placebo	39/38 for OS	36/34	39/38	36	8	9	OS[c], PFS[c], ORR, AEs
						38/38 for PFS						
NCT01009593[23]	Open	III	First-line	Linifanib	Sorafenib	512/521 for OS	514/521	510/519	27.5	6	5	OS, PFS, TTP, ORR, AEs
						514/521 for PFS and TTP						
NCT00987935[37]	Open	II	First-line	Nintedanib	Sorafenib	63/32	63/32	63/32	35	7	6	OS, PFS, TTP, ORR, DCR, AEs
NCT01004003[38]	Open	II	First-line	Nintedanib	Sorafenib	62/31	62/31	62/31	32	7	6	OS, PFS, TTP, ORR, DCR, AEs
NCT00901901[39]	Double	III	First-line	Erlotinib + sorafenib	Sorafenib + placebo	362/358	362/358	362/355	32	10	7	OS, PFS, TTP, ORR, DCR, AEs
NCT00858871[24]	Quadruple	III	First-line	Brivanib	Sorafenib	577/578	577/578	575/575	35	10	9	OS, TTP, ORR, DCR, AEs
NCT00855218[40]	Quadruple	II	First-line	Sorafenib + TACE	Placebo + TACE	154/153	154/153	153/151	26.6	7	9	OS, TTP, ORR, DCR, AEs
NCT00825955[25]	Quadruple	III	Second-line	Brivanib	Placebo	263/132	266/108	261/131	30	10	9	OS, TTP, ORR, DCR, AEs
NCT00699374[41]	Open	III	First-line	Sunitinib	Sorafenib	530/544	530/544	526/542	30.5	8	6	OS, PFS, TTP, ORR, DCR, AEs
NCT00692770[42]	Quadruple	III	Second-line	Sorafenib	Placebo	556/558	NR	559/548	64	9	9	OS, AEs

(Continued)

Table 1 (Continued)

Clinical trial ID	Masking	Phase	Setting	Treatment arm	Control arm	Treatment/ Control arm of survival parameters (*n*)	Treatment/ Control arm of tumor response parameters (*n*)	Treatment/ Control arm of adverse events (*n*)	Follow-up (months)	Jadad score	Delphi score	Parameters evaluated
NCT00508001[43]	Quadruple	II	First-line	Vandetanib 100 mg	Placebo	25/23	25/23	25/23	12	8	9	OS, PFS, ORR, DCR, AEs
				Vandetanib 300 mg		19/23	19/23	19/23				
NCT00494299[44]	Triple	III	First-line	Sorafenib	Placebo	229/229	NR	229/227	34	7	8	OS, TTP, AEs
NCT00492752[11]	Triple	III	First-line	Sorafenib	Placebo	150/76	150/76	149/75	21.5	8	8	OS, TTP, TTSP, ORR, DCR, AEs
NCT00108953[45]	Double	II	First-line	Sorafenib + doxorubicin	Placebo + doxorubicin	47/49	47/49	47/48	25	9	7	OS, PFS, TTP, TTSP, ORR, AEs
NCT00105443[10]	Double	III	First-line	Sorafenib	Placebo	299/303	299/303	297/302	17	9	7	OS, TTP, TTSP, ORR, DCR, AEs
NCT01908426[46]	Quadruple	III	Second-line	Cabozantinib	Placebo	470/237	470/237	467/237	41	10	9	OS, PFS, ORR, DCR, AEs

Abbreviations: AEs, adverse events; DCR, disease control rate; NR, no reported; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; TACE, transarterial chemoembolization; TKI, tyrosine kinase inhibitor; TTP, time to progression; TTSP, time to symptomatic progression. [a]Not included due to data being incorrect. [b]Not included due to 90% CI. [c]Estimated by Parmar method.

We pooled the overall survival (OS), progression-free survival (PFS), time to progression (TTP), and time to symptomatic progression (TTSP) by hazard ratio (HR) and 95% confidence interval (CI). OS, PFS, TTP, and TTSP were determined from the start of the study treatment until the last follow-up date, disease progression, the first symptom appearance, or the death of the patient. We used the Parmar method[26] to estimate these data when no information was directly provided in the study. HR with 95% CI were combined throughout the studies.

The association between TKI treatment and the objective response rate (ORR), the disease control rate (DCR), and the presence of AEs was assessed by odds ratio (OR) with 95% CI. Combined HR <1 and OR >1 represented a higher benefit in prognosis or a higher tumor response and presence of AEs in the experimental arm, respectively. These associations were considered statistically significant when *P*-value <0.05.

Heterogeneity was assessed by Chi-squared-based Q-test along with the inconsistency (I^2) statistic, ranging from 0% (no heterogeneity) to 100% (maximal heterogeneity). Heterogeneity was considered significant when $I^2 \geq 50\%$ and/or *Q*-test *P*-value was <0.10, where the restricted maximum likelihood (REML) method was used as the random-effects model. Otherwise, the inverse variance (IV) method was employed as the fixed-effects model.[27]

To evaluate the source of heterogeneity, subgroup analysis based on the follow-up was performed, as well as meta-regression.[28]

Risk of publication bias was analyzed by funnel plot asymmetry and Egger's test, considering significance when asymmetry was found and Egger's test *P*-value was <0.05, in which case the trim-and-fill method was used to estimate a corrected effect size adjustment.

RESULTS

Clinical trials selection and characteristics

After a comprehensive search was performed in several public databases, a total of 310 clinical trials were identified. After duplicated records were eliminated and removal after screening was made, we obtained a total of 25 randomized clinical trials that were included for data extraction and quantitative analysis[10,11,23–25,29–46] (plus NCT02279719 and NCT02178358, which results were obtained from ClinicalTrials.gov) (**Table 1**, **Figure S1**). Out of the 25 studies, 12 were evaluating TKI treatment vs. placebo as the control arm,[10,11,25,31–33,35,36,42–44,46] eight assessed the effect of TKI treatment vs. sorafenib as the control arm,[23,24,29,30,34,37,38,41] four determined the effect of TKIs in combined treatments[39,40,45] (plus NCT02279719) and one had both TKI in monotherapy and combined TKI treatment vs. sorafenib (NCT02178358). For this, three groups were established for subsequent analyses (vs. placebo, vs. sorafenib and combined TKI treatment).

Overall survival

TKI treatment was significantly correlated with a higher OS in HCC patients compared with placebo ($n = 13$) (HR 0.81, 95% CI 0.72–0.92, $P < 0.001$). However, heterogeneity across studies was found to be statistically significant ($I^2 = 51.67\%$ and *Q*-test $P = 0.01$) (**Figure 1a**).

No improvement in the patient's OS was significant in the vs. sorafenib group ($n = 8$), although global HR indicated a slightly more favorable outcome in the sorafenib treatment arm (HR 1.07, 95% CI 0.95–1.20, $P = 0.26$). In this group, heterogeneity was also found to be significant ($I^2 = 51.92\%$ and *Q*-test $P = 0.05$) (**Figure 1a**).

Finally, OS was higher but not significant in the combined TKI treatment compared with the control arm ($n = 4$) (HR 0.88, 95%

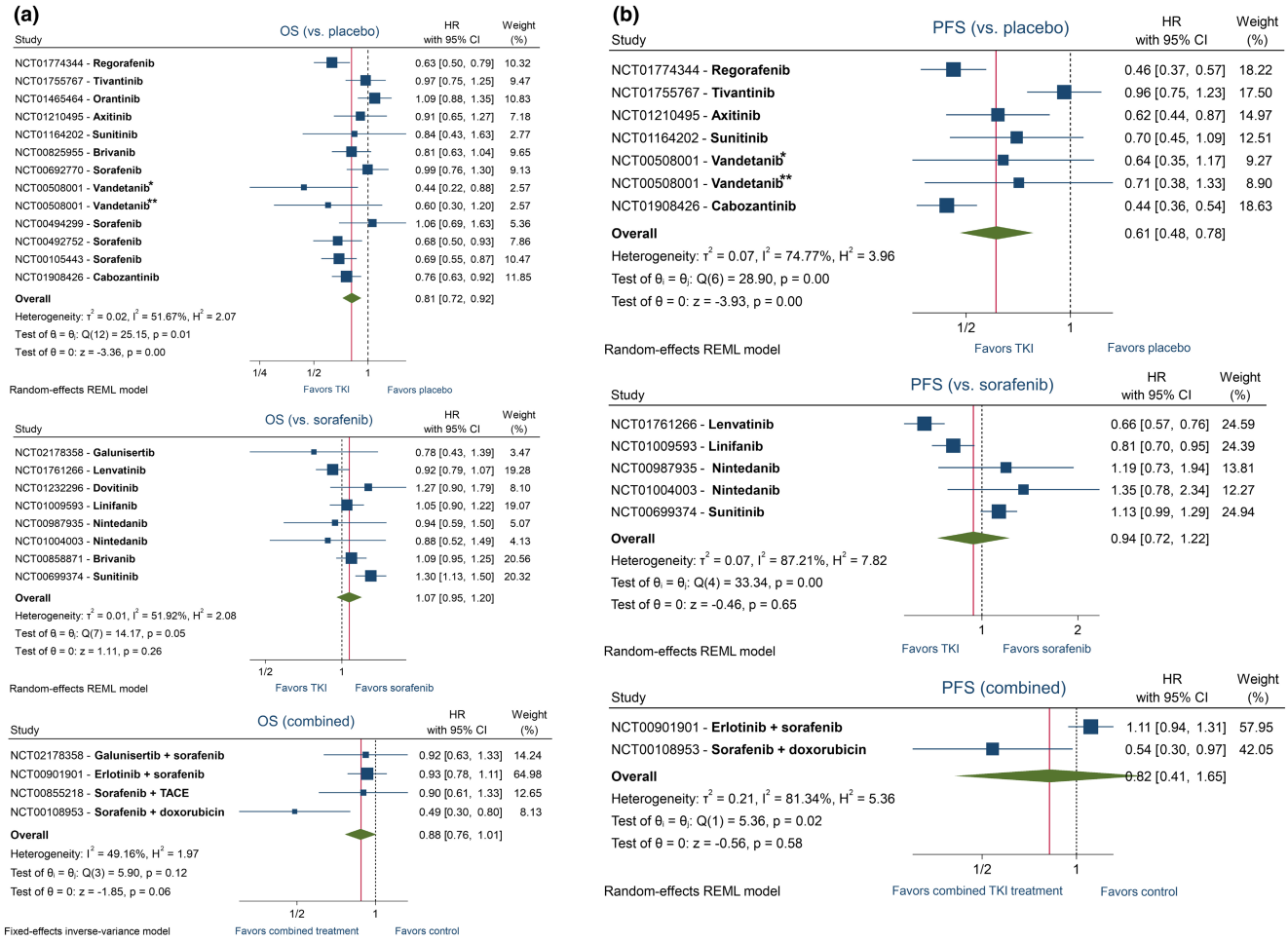

Figure 1 Forest plots of studies evaluating the association between (**a**) OS or (**b**) PFS and TKI therapy in the vs. placebo group, the vs. sorafenib group, and the combined TKI treatment group by HR in HCC patients. For each trial, the drug employed in the experimental arm is described. DCR, disease control rate; HCC, hepatocellular carcinoma; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; REML, restricted maximum likelihood; TACE, transarterial chemoembolization; TKI, tyrosine kinase inhibitor. *100 mg dose, **300 mg dose.

CI 0.76–1.01, $P = 0.06$). Remarkably, a moderate heterogeneity was detected among studies in this group ($I^2 = 49.16\%$ and Q-test $P = 0.12$) (**Figure 1a**).

Progression-free survival

The vs. placebo group ($n = 7$) showed a statistically significant correlation between TKI treatment and a higher PFS in HCC patients (HR 0.61, 95% CI 0.48–0.78, $P < 0.001$). Despite this, heterogeneity across trials was significantly elevated ($I^2 = 74.77\%$ and Q-test $P < 0.001$) (**Figure 1b**).

In the vs. sorafenib group ($n = 5$), PFS was not improved with TKI treatment, being slightly more favorable in the TKI treatment over sorafenib (HR 0.94, 95% CI 0.72–1.22, $P = 0.65$). However, heterogeneity was also found to be remarkably high among studies ($I^2 = 87.21\%$ and Q-test $P < 0.001$) (**Figure 1b**).

Regarding the combined TKI treatment group ($n = 2$), there was no relevant association with PFS compared with the control group, although global HR resulted favorable toward combined treatment (HR 0.82, 95% CI 0.41–1.65, $P = 0.58$). In this case, heterogeneity was also significantly increased among studies ($I^2 = 81.34\%$ and Q-test $P = 0.02$) (**Figure 1b**).

Time to progression and time to symptomatic progression

A marked significance was found in the correlation between TKI treatment and a higher TTP in the vs. placebo group ($n = 8$) (HR 0.67, 95% CI 0.55–0.81, $P < 0.001$), finding an elevated heterogeneity ($I^2 = 81.78\%$ and Q-test $P < 0.001$) (**Figure 2a**). Moreover, when TTSP was analyzed in this group ($n = 2$), no association with TKI treatment (HR 1.02, 95% CI 0.86–1.21, $P = 0.82$) was found, and no heterogeneity among studies ($I^2 = 0.00\%$ and Q-test $P = 0.33$) (**Figure 2b**) was observed.

As the aforementioned analysis exhibited, TTP was also not significantly associated with TKI treatment (HR 0.99, 95% CI 0.79–1.25, $P = 0.95$) in the vs. sorafenib group ($n = 7$), while a high heterogeneity was detected ($I^2 = 87.53\%$ and Q-test $P < 0.001$) (**Figure 2a**).

Finally, the combined TKI treatment group ($n = 3$) did not show any improvement in TTP of patients diagnosed with HCC (HR 0.81, 95% CI 0.52–1.26, $P = 0.34$), exhibiting an elevated heterogeneity ($I^2 = 83.59\%$ and Q-test $P < 0.01$) (**Figure 2a**).

Tumor response rates

In the vs. placebo group ($n = 9$ for ORR; $n = 9$ for DCR), both ORR (OR 2.41, 95% CI 1.09–5.33, $P = 0.03$) and DCR (OR

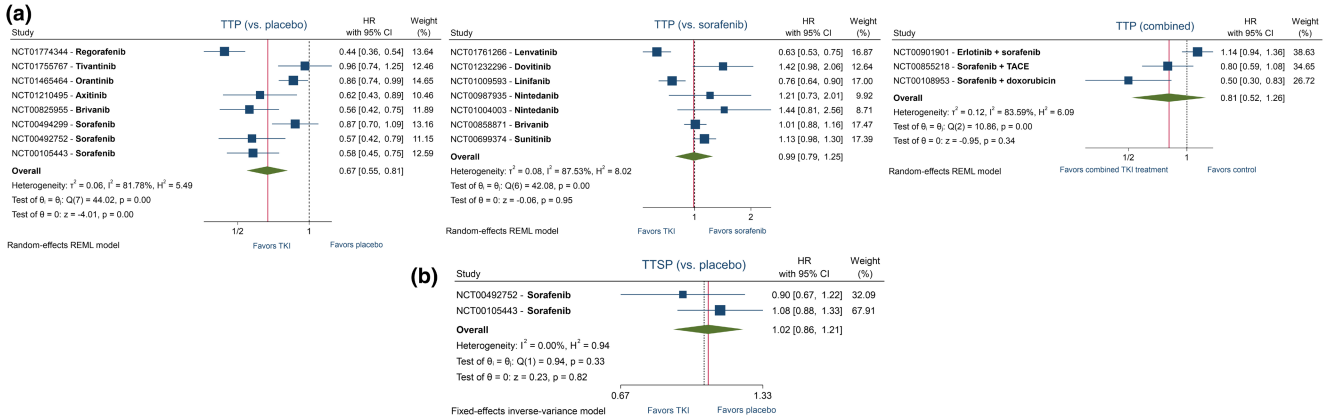

Figure 2 Forest plots exhibiting HR for the association of TKI treatment with (**a**) TTP in the vs. placebo group, the vs. sorafenib group, and the combined TKI treatment group or with (**b**) TTSP in the vs. placebo group. For each trial, the drug employed in the experimental arm is described. HR, hazard ratio; REML, restricted maximum likelihood; TACE, transarterial chemoembolization; TKI, tyrosine kinase inhibitor; TTP, time to progression; TTSP, time to symptomatic progression.

2.31, 95% CI 1.68–3.17, $P < 0.001$) were found to be significantly correlated to TKI treatment, although a high heterogeneity was detected among pooled OR ($I^2 = 53.72\%$ and Q-test $P = 0.03$ for ORR; $I^2 = 64.22\%$ and Q-test $P < 0.01$ for DCR) (**Figure 3a**).

On the other hand, ORR ($n = 8$) and DCR ($n = 7$) were not associated with TKI treatment in the vs. sorafenib group, which could be explained due to the heterogeneity observed in both cases ($I^2 = 85.19\%$ and Q-test $P < 0.001$ for ORR; $I^2 = 86.05\%$ and Q-test $P < 0.001$ for DCR) (**Figure 3b**).

Finally, combined TKI treatment group ($n = 4$ for ORR; $n = 3$ for DCR) only showed a significant correlation with ORR (OR 1.50, 95% CI 1.02–2.21, $P = 0.04$) with no heterogeneity detected among studies ($I^2 = 0.00\%$ and Q-test $P = 0.78$) (**Figure 3c**).

Adverse events

Dehydration (OR 2.45, 95% CI 1.07–5.60, $P = 0.03$), diarrhea (OR 2.88, 95% CI 1.56–5.33, $P < 0.001$) and hepatic encephalopathy (OR 2.03, 95% CI 1.14–3.62, $P = 0.02$) were significantly correlated to TKI treatment in the vs. placebo group, not finding any heterogeneity across studies (**Table 2**). However, in the vs. sorafenib group, dehydration (OR 3.07, 95% CI 1.36–6.93, $P = 0.01$), diarrhea (OR 1.37, 95% CI 1.00–1.86, $P = 0.049$), nausea (OR 2.63, 95% CI 1.07–6.44, $P = 0.03$), vomiting (OR 3.91, 95% CI 2.07–7.37, $P < 0.001$), fatigue (OR 2.00, 95% CI 1.39–2.88, $P < 0.001$), hypoglycemia (OR 2.29, 95% CI 1.09–4.84, $P = 0.03$), hyponatremia (OR 2.01, 95% CI 1.24–3.26, $P < 0.01$), and hepatic encephalopathy (OR 2.56, 95% CI 1.75–3.75, $P < 0.001$) were significantly higher in the experimental arm (**Table 2**). Moreover, hyperbilirubinemia (OR 2.40, 95% CI 1.01–5.70, $P = 0.049$) and increased AST (OR 4.41, 95% CI 1.09–17.93, $P = 0.04$) were found to be related to combined TKI treatment in HCC patients (**Table 2**). Heterogeneity was not found in any cases, except for the encephalopathy in TKI combined treatment group ($I^2 = 68.15\%$ and Q-test $P = 0.08$) (**Table 2**).

Meta-regression

The potential sources of heterogeneity found in all survival and tumor response parameters analyses were evaluated by performing a meta-regression, employing follow-up as the only available moderator (**Table 3**, **Figure S2**).

As shown in **Table 3**, follow-up was found to be mostly responsible for the high heterogeneity observed across studies for OS and DCR in the vs. placebo group ($I^2 = 34.68\%$, Q-test $P = 0.16$; $I^2 = 35.43\%$, Q-test $P = 0.15$; respectively), for OS in the vs. sorafenib group ($I^2 = 44.91\%$ and Q-test $P = 0.10$) and TTP in the combined TKI treatment group ($I^2 = 16.47\%$ and Q-test $P = 0.27$) after performing meta-regression. However, follow-up could partially or not explain the heterogeneity found in the rest of the parameters evaluated in all three groups (**Table 3**, **Figure S2**).

Subgroup analysis

Heterogeneity associated with TKI treatment and OS was resolved with follow-up as a moderator for the subgroups involving clinical trials performed in less than or equal to 20, 30 and 40 months ($I^2 = 0.00\%$, Q-test $P = 0.47$; $I^2 = 0.00\%$, Q-test $P = 0.52$; $I^2 = 34.37\%$, Q-test $P = 0.13$; respectively) in the vs. placebo group, maintaining a significant correlation with OS in all cases (**Table 4**). However, the subgroup comprising TKIs not approved for HCC treatment did not show a significant correlation with OS (HR 0.92, 95% CI 0.81–1.03, $P = 0.15$), although no heterogeneity was found in the analysis ($I^2 = 36.12\%$ and Q-test $P = 0.15$) (**Table 4**). In regard to PFS, only the subgroup comprising studies evaluated in less than or equal to 30 months ($I^2 = 0.00\%$ and Q-test $P = 0.81$) and both subgroups of not approved and approved TKI treatment exhibited a reduced heterogeneity ($I^2 = 23.09\%$, Q-test $P = 0.27$; $I^2 = 0.00\%$, Q-test $P = 0.77$; respectively), having a significant association with this survival parameter in the last two subgroups (HR 0.78, 95% CI 0.66–0.93, $P < 0.01$; HR 0.45, 95% CI 0.39–0.52, $P < 0.001$; respectively) (**Table 4**). For TTP, heterogeneity was only solved in studies performed in less than or equal to 30 months

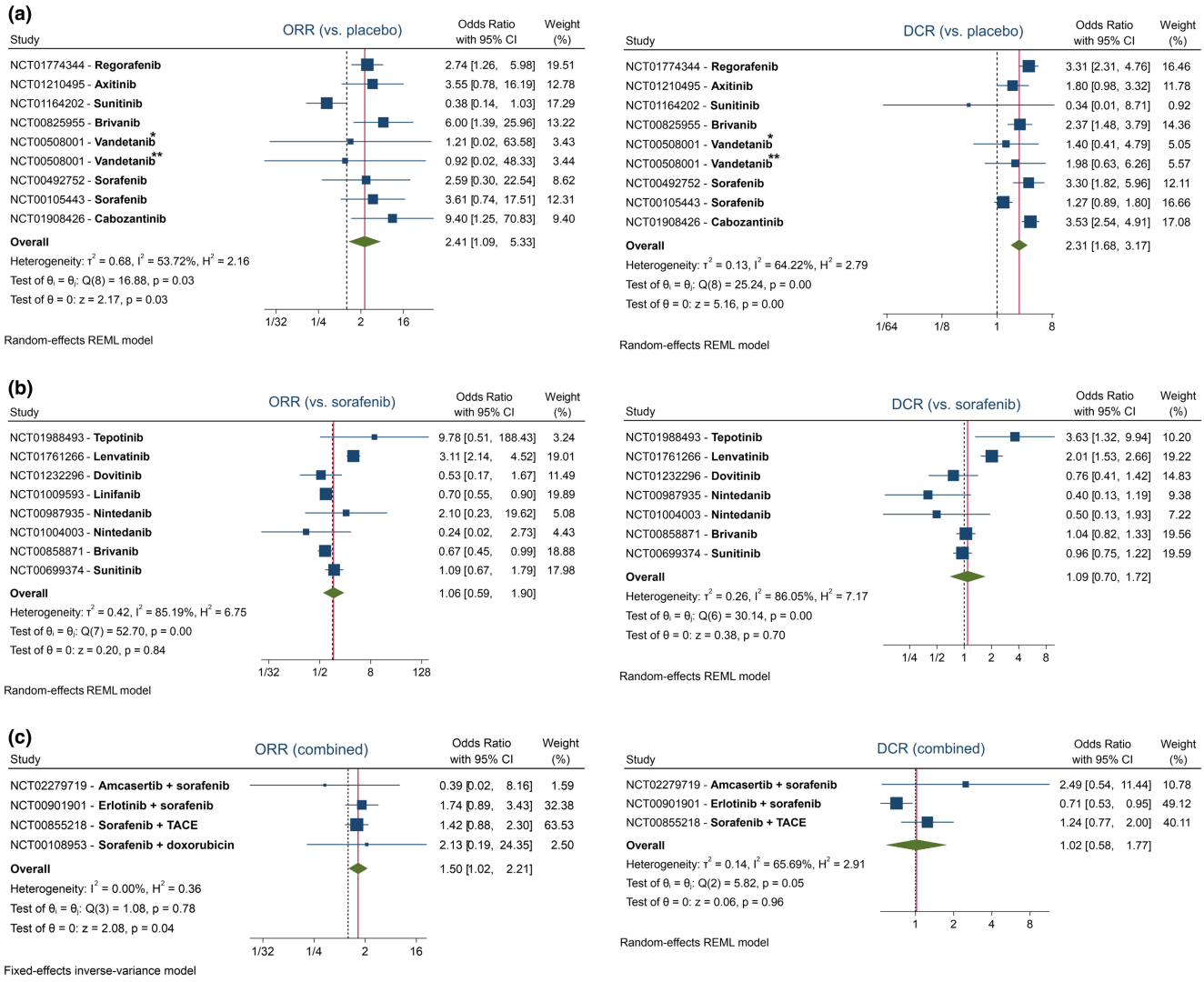

Figure 3 Forest plots assessing the association of TKI treatment with ORR and DCR by OR in studies from (**a**) the vs. placebo group, (**b**) the vs. sorafenib group, and (**c**) the combined TKI treatment group. DCR, disease control rate; OR, odds ratio; ORR, objective response rate; REML, restricted maximum likelihood; TACE, transarterial chemoembolization; TKI, tyrosine kinase inhibitor. *100 mg dose, **300 mg dose.

($I^2 = 0.00\%$ and Q-test $P = 0.96$). Finally, subgroup analysis for tumor response parameters was performed in the vs. placebo group (**Table 4**). Studies performed in less than or equal to 20 and 30 months ($I^2 = 0.00\%$, Q-test $P = 0.75$; $I^2 = 0.00\%$, Q-test $P = 0.86$; respectively) and with approved TKIs and sorafenib in the experimental arm ($I^2 = 0.00\%$, Q-test $P = 0.73$; $I^2 = 0.00\%$, Q-test $P = 0.81$; respectively) appeared to be covariates responsible for the high heterogeneity found in the association of TKI treatment with ORR meta-analysis (**Table 4**). In regard to the association of DCR with TKI treatment, heterogeneity was markedly reduced for follow-up ≤20 ($I^2 = 0.00\%$ and Q-test $P = 0.76$) and > 20/30 months ($I^2 = 25.41\%$, Q-test $P = 0.24$; $I^2 = 45.89\%$, Q-test $P = 0.14$; respectively) and for neither approved nor sorafenib treatment in the experimental arm ($I^2 = 0.00\%$, Q-test $P = 0.72$; $I^2 = 28.29\%$, Q-test $P = 0.21$) (**Table 4**).

For the vs. sorafenib group, heterogeneity across studies analyzed for OS and ORR parameters was found to be solved. Specifically, follow-up of less than and equal to 30 months ($I^2 = 8.80\%$ and Q-test $P = 0.33$) and follow-up of less than or equal to 40 months/not approved TKI treatment in experimental arm ($I^2 = 30.06\%$ and Q-test $P = 0.20$) were found to be potential sources of heterogeneity for OS, while observing a significant association with this survival parameter in the last subgroup (HR 1.13, 95% 1.05–1.22, $P < 0.01$) (**Table 4**). Meanwhile, follow-up of less than or equal than 30 months ($I^2 = 38.84\%$ and Q-test $P = 0.19$) and follow-up of less than or equal to 40 months/not approved TKI treatment in the experimental arm ($I^2 = 23.23\%$ and Q-test $P = 0.25$) subgroups resolved heterogeneity for the ORR parameter (**Table 4**). In both cases, a significant association with this tumor response parameter was found after heterogeneity resolution (ORR 0.70, 95% CI 0.55–0.90, $P < 0.01$; ORR 0.74, 95% CI 0.61–0.90, $P < 0.01$; respectively) (**Table 4**).

Conversely, the combined TKI treatment group subgroup analysis did not solve heterogeneity in any cases (**Table 4**).

Table 2 Assessment of AEs correlation with TKI treatment in the three groups

Adverse events		Clinical trials analyses (*n*)	Pooled OR			Test for heterogeneity		
			OR	95% CI	*P*-value	I^2	*Q*-test *P*-value	Model used
vs. placebo								
GI disorders (1)	Abdominal pain	14	0.74	(0.50–1.10)	0.14	2.51%	0.42	FEM
	Ascites	12	1.11	(0.78–1.58)	0.56	2.64%	0.42	FEM
	Dehydration	9	2.45	(1.07–5.60)	0.03*	0.00%	0.83	FEM
	Diarrhea	12	2.88	(1.56–5.33)	0.00*	0.00%	0.99	FEM
GI disorders (2)	Esophageal varices hemorrhage	12	0.87	(0.55–1.38)	0.56	0.00%	0.77	FEM
	GI hemorrhage	9	1.40	(0.61–3.23)	0.43	0.00%	0.84	FEM
	Nausea	5	1.07	(0.29–3.97)	0.92	0.00%	0.63	FEM
	Upper GI hemorrhage	11	0.89	(0.50–1.59)	0.99	0.00%	0.99	FEM
	Vomiting	10	0.93	(0.46–1.86)	0.83	0.00%	0.84	FEM
General, hepatobiliary disorders and infections	Fatigue	11	1.16	(0.60–2.22)	0.66	0.00%	0.77	FEM
	Pyrexia	14	1.26	(0.77–2.06)	0.35	0.00%	0.96	FEM
	Hepatic failure	10	0.96	(0.61–1.51)	0.86	0.00%	0.57	FEM
	Hyperbilirubinemia	10	1.14	(0.55–2.35)	0.72	0.00%	0.87	FEM
	Cellulitis	10	1.22	(0.44–3.35)	0.70	0.00%	0.98	FEM
	Pneumonia	12	1.38	(0.80–2.38)	0.25	0.00%	0.75	FEM
Metabolic, nervous and respiratory disorders	AST	9	1.99	(0.76–5.23)	0.16	0.00%	1.00	FEM
	Hypoglycemia	8	1.46	(0.59–3.59)	0.41	0.00%	0.88	FEM
	Hyponatremia	9	0.78	(0.29–2.09)	0.62	0.00%	0.72	FEM
	Encephalopathy	10	1.28	(0.63–2.61)	0.49	0.00%	0.54	FEM
	Hepatic encephalopathy	8	2.03	(1.14–3.62)	0.02*	0.00%	0.82	FEM
	Dyspnea	9	1.94	(0.93–4.05)	0.08	0.00%	0.90	FEM
vs. sorafenib								
GI disorders (1)	Abdominal pain	10	1.15	(0.78–1.69)	0.48	0.00%	0.81	FEM
	Ascites	9	1.37	(0.95–1.96)	0.09	0.00%	0.68	FEM
	Dehydration	5	3.07	(1.36–6.93)	0.01*	0.00%	0.44	FEM
	Diarrhea	9	1.37	(1.00–1.86)	0.049*	0.00%	0.96	FEM
GI disorders (2)	Esophageal varices hemorrhage	7	1.36	(0.74–2.51)	0.32	0.00%	0.98	FEM
	GI hemorrhage	7	1.30	(0.67–2.52)	0.44	0.00%	0.56	FEM
	Nausea	7	2.63	(1.07–6.44)	0.03*	0.00%	0.66	FEM
	Upper GI hemorrhage	8	1.28	(0.71–2.30)	0.41	0.00%	0.77	FEM
	Vomiting	7	3.91	(2.07–7.37)	0.00*	0.00%	0.70	FEM
General, hepatobiliary disorders and infections	Fatigue	8	2.00	(1.39–2.88)	0.00*	0.00%	0.97	FEM
	Pyrexia	7	1.09	(0.69–1.71)	0.71	26.09%	0.23	FEM
	Hepatic failure	8	1.18	(0.71–1.95)	0.52	0.00%	0.78	FEM
	Hyperbilirubinemia	7	1.39	(0.91–2.14)	0.13	0.00%	0.96	FEM
	Cellulitis	6	3.15	(0.84–11.86)	0.09	0.00%	0.99	FEM
	Pneumonia	6	1.08	(0.55–2.13)	0.82	0.00%	0.81	FEM
Metabolic, nervous and respiratory disorders	AST	7	1.00	(0.71–1.41)	0.99	0.00%	0.88	FEM
	Hypoglycemia	7	2.29	(1.09–4.84)	0.03*	0.00%	0.69	FEM
	Hyponatremia	7	2.01	(1.24–3.26)	0.00*	26.71%	0.22	FEM
	Encephalopathy	4	2.03	(0.71–5.82)	0.19	0.00%	0.57	FEM
	Hepatic encephalopathy	9	2.56	(1.75–3.75)	0.00*	0.00%	0.52	FEM
	Dyspnea	4	1.39	(0.53–3.62)	0.50	0.00%	0.67	FEM

(Continued)

Table 2 (Continued)

Adverse events		Clinical trials analyses (*n*)	Pooled OR			Test for heterogeneity		
			OR	95% CI	*P*-value	I^2	*Q*-test *P*-value	Model used
Combined TKI treatment								
GI disorders (1)	Abdominal pain	5	0.92	(0.53–1.60)	0.76	0.00%	0.53	FEM
	Ascites	4	1.34	(0.70–2.56)	0.38	0.00%	0.75	FEM
	Dehydration	4	2.14	(0.89–5.14)	0.09	0.00%	0.86	FEM
	Diarrhea	4	2.62	(1.00–6.86)	0.05	12.47%	0.33	FEM
GI disorders (2)	Esophageal varices hemorrhage	3	0.63	(0.28–1.40)	0.25	0.00%	0.43	FEM
	GI hemorrhage	2	3.32	(0.29–37.75)	0.33	0.00%	0.81	FEM
	Nausea	5	1.53	(0.37–6.37)	0.56	0.00%	0.74	FEM
	Upper GI hemorrhage	4	1.41	(0.63–3.13)	0.40	0.00%	0.64	FEM
	Vomiting	4	1.11	(0.32–3.83)	0.86	0.00%	0.41	FEM
General, hepatobiliary disorders and infections	Fatigue	4	1.40	(0.63–3.15)	0.41	10.07%	0.34	FEM
	Pyrexia	5	1.04	(0.54–2.01)	0.91	0.00%	0.70	FEM
	Hepatic failure	2	1.57	(0.16–15.78)	0.70	0.00%	1.00	FEM
	Hyperbilirubinemia	3	2.40	(1.01–5.70)	0.049*	0.00%	0.73	FEM
	Cellulitis	4	0.88	(0.24–3.31)	0.86	3.05%	0.38	FEM
	Pneumonia	5	1.36	(0.59–3.17)	0.47	0.00%	0.62	FEM
Metabolic, nervous and respiratory disorders	AST	2	4.41	(1.09–17.93)	0.04*	0.00%	0.33	FEM
	Hypoglycemia	3	1.15	(0.25–5.37)	0.86	0.00%	0.77	FEM
	Hyponatremia	2	1.50	(0.31–7.25)	0.62	0.00%	0.97	FEM
	Encephalopathy	2	1.68	(0.19–14.80)	0.64	68.15%	0.08	REM
	Dyspnea	3	2.33	(0.89–6.13)	0.09	0.00%	0.97	FEM

AEs, adverse events; AST, aspartate aminotransferase; CI, confidence interval; FEM, fixed-effects model; GI, gastrointestinal; OR, odds ratio; REM, random-effects model; TKI, tyrosine kinase inhibitor.*Significant correlation, *P*-value <0.05.

Publication bias assessment

We analyzed the risk of publication bias present in this meta-analysis by assessing funnel plot asymmetry along with Egger's test outcome (**Table 5**, **Figures S3–S6**). While no significant publication bias was found in the association of TKI treatment with OS (**Figure S3A**), PFS (**Figure S3B**), TTSP (**Figure S3C**), ORR or DCR (**Figure S3D**), funnel plot asymmetry, and positive Egger's test outcome was found in combined TKI treatment for TTP (**Table 5**, **Figure S3C**). Sensitivity analysis by trim-and-fill method was performed, imputing two missing studies and modifying the global effect size (HR 1.14, 95% CI 0.68–1.91), switching the effect of TTP to being favorable toward the control arm after publication bias determination (**Table 5**). For AEs, no presence of publication bias was reported (**Table 5**, **Figures S4–S6**).

DISCUSSION

HCC is a highly lethal disease, constituting nowadays a major public health issue.[1,5] The need to improve HCC therapy has been reflected in the approval of several TKIs that exhibited high efficacy by significantly extending patients' life expectancy.[10,30,31,46]

In this study, we aimed to address the clinical benefits of approved and unapproved TKIs in advanced HCC as well as the presence of AEs derived from the treatments detected in randomized clinical trials. Although several authors analyzed the clinical efficacy of TKIs alone or in combined treatment in various types of cancer,[47–50] our work constitutes the first systematic review with meta-analysis to address the risk vs. benefit evaluation of TKI treatment in patients with HCC.

Data from 25 high-quality randomized clinical trials comprising a total of 11,720 HCC patients treated with both approved and unapproved TKIs as first or second-line therapy were retrieved and included in the quantitative analysis. After performing statistical analysis, pooled results indicated that TKI treatment was correlated to a higher OS, PFS, and TTP compared with placebo. Surprisingly, treatment with the unapproved TKI vandetanib showed promising results for both OS and PFS but did not improve sorafenib outcome.[43] Treatment with TKIs was also found to be associated with a higher tumor response rate, being this response was more than two times higher in the experimental group than in the placebo one, which demonstrates a high effectiveness of any TKI for the treatment of advanced HCC. In addition, AEs positively correlated to TKI treatment vs. placebo included dehydration, diarrhea, and hepatic encephalopathy, which is a common and reversible neuropsychiatric condition associated with liver cirrhosis.[51] Data obtained by Tavakoli *et al.*[52] showed promising results regarding 15-year OS and disease-free survival, with an incidence of 65.70% and 57.83%,

Table 3 Estimation of the source of heterogeneity by meta-regression in global OS, PFS, TTP, ORR and DCR in all three groups

						Residual heterogeneity	
Variables	Beta coefficient	*z*	*P*-value	95% CI	I^2	*Q*-test *P*-value	R^2
vs. placebo							
OS							
Follow-up	1.01	2.56	0.01	(1.00–1.02)	34.68%	0.16[a]	49.31%
PFS							
Follow-up	0.99	−0.45	0.65	(0.97–1.02)	77.35%	0.00	0.00%
TTP							
Follow-up	1.02	1.43	0.15	(0.99–1.04)	77.58%	0.00	16.38%
ORR							
Follow-up	1.00	0.07	0.95	(0.91–1.11)	58.33%	0.02	0.00%
DCR							
Follow-up	1.03	2.27	0.02	(1.00–1.06)	35.43%	0.15[a]	64.84%
vs. sorafenib							
OS							
Follow-up	0.99	−0.93	0.35	(0.97–1.01)	44.91%	0.10[a]	13.98%
PFS							
Follow-up	0.98	−0.84	0.40	(0.93–1.03)	85.07%	0.00	0.00%
TTP							
Follow-up	0.97	−1.04	0.30	(0.92–1.03)	86.38%	0.00	0.00%
ORR							
Follow-up	1.10	1.98	0.048	(1.00–1.20)	66.10%	0.00	50.54%
DCR							
Follow-up	1.02	0.33	0.74	(0.91–1.15)	86.42%	0.01	0.00%
Combined TKI treatment							
TTP							
Follow-up	1.09	2.69	0.01	(1.02–1.17)	16.47%	0.27[a]	93.71%
DCR							
Follow-up	–	–	–	–	–	–	–

CI, confidence interval; DCR, disease control rate; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; TKI, tyrosine kinase inhibitor; TTP, time to progression. [a]Heterogeneity solved.

respectively, after treatment with imatinib in patients with chronic myeloid leukemia. Additionally, a recent clinical trial performed with cabozantinib achieved a 12-week PFS with stable disease or better in 45% of the patients enrolled with refractory, metastatic colorectal cancer, while being fatigue, diarrhea, hypertension, nausea, or decreased appetite were the most frequently detected AEs.[53] Interestingly, placebo-controlled studies included in Haber *et al.*[48] systematic review and meta-analysis reached a positive end point for OS, but no significant correlation was found with the disease etiology (viral or non-viral) in HCC patients treated with TKIs or antivascular endothelial growth factor therapies. With all, outcomes from our meta-analysis including placebo as control arm demonstrated that treatment with TKI achieves greater clinical benefits with a low presence of AEs and that can be controllable.

Regarding the vs. sorafenib group, primary pooled results found no positive association between TKI treatment and survival or tumor response parameters, although subgroup analysis exhibited significance in OS and ORR. However, global HR indicated that sorafenib treatment achieved a slightly greater OS benefit compared with the TKI treatment. The lack of significant improvement in sorafenib treatment can be partially explained by the presence of lenvatinib, the alternative to sorafenib as a first-line therapy for advanced HCC,[7] as well as linifanib, in the experimental arm, which modifies the global effect analysis by slightly favoring TKI treatment. Likewise, sorafenib benefit did not manifest in 184 HCC patients in the study performed by Öcal *et al.*,[54] and no significant improvement in OS, TTP, or treatment response was found by El Shorbagy *et al.*,[55] comparing to metformin plus sorafenib treatment in HCC. With respect to AEs evaluation in our study, dehydration, diarrhea, nausea, vomiting, fatigue, hypoglycemia, hyponatremia, and hepatic encephalopathy were significantly more frequent in the experimental arm than in the sorafenib one. Mostly low-grade GI or dermatologic AEs, such as diarrhea, abdominal pain, vomiting, rash, or hand-foot syndrome are detected after sorafenib[55–58] or sunitinib[59] treatment in several clinical trials. Curiously, several studies confirmed the positive association between a better prognosis and the presence of AEs

Table 4 Subgroup analysis of OS, PFS, TTP, ORR and DCR association with TKI treatment in the three groups

Subgroup	Clinical trials analyses (*n*)	Cases (*n*)	Pooled HR or OR			Test for heterogeneity		Model used
			HR or OR	95% CI	*P*-value	I^2	*Q*-test *P*-value	
vs. placebo								
OS								
Follow-up (months)								
>20	10	4,980	0.85	(0.75–0.97)	0.02*	52.5%	0.03	REM
≤20	3	692	0.66	(0.53–0.80)	0.00*	0.00%	0.47	FEM†
>30	8	4,359	0.88	(0.76–1.03)	0.11	56.98%	0.02	REM
≤30	5	1,313	0.71	(0.61–0.81)	0.00*	0.00%	0.52	FEM†
>40	3	2,709	0.93	(0.74–1.17)	0.53	67.88%	0.04	REM
≤40	10	2,963	0.76	(0.69–0.84)	0.00*	34.37%	0.13	FEM†
>50	1	1,114	0.99	(0.76–1.30)	–	–	–	–
≤50	12	4,558	0.80	(0.70–0.90)	0.00*	51.36%	0.02	REM
Approved treatment								
No	7	1992	0.92	(0.81–1.03)	0.15	36.12%	0.15	FEM†
Yes	6	3,680	0.76	(0.66–0.89)	0.00*	49.11%	0.08	REM
Sorafenib treatment								
No	9	3,272	0.81	(0.69–0.95)	0.01*	55.21%	0.02	REM
Yes	4	2,400	0.82	(0.65–1.02)	0.08	56.27%	0.08	REM
PFS								
Follow-up (months)								
>30	5	1898	0.60	(0.45–0.81)	0.00*	83.87%	0.00	REM
≤30	2	90	0.67	(0.44–1.04)	0.07	0.00%	0.81	FEM†
>40	1	707	0.44	(0.36–0.54)	–	–	–	–
≤40	6	1,281	0.66	(0.51–0.85)	0.00*	66.48%	0.00	REM
Approved treatment								
No	5	708	0.78	(0.66–0.93)	0.00*	23.09%	0.27	FEM†
Yes	2	1,280	0.45	(0.39–0.52)	0.00*	0.00%	0.77	FEM†
TTP								
Follow-up (months)								
>20	7	3,079	0.68	(0.54–0.85)	0.00*	83.75%	0.00	REM
≤20	1	602	0.58	(0.45–0.75)	–	–	–	–
>30	6	2,853	0.70	(0.54–0.90)	0.00*	86.35%	0.00	REM
≤30	2	828	0.58	(0.47–0.71)	0.00*	0.00%	0.96	FEM†
>40	1	885	0.86	(0.74–0.99)	–	–	–	–
≤40	7	2,796	0.64	(0.51–0.79)	0.00*	78.09%	0.00	REM
Approved treatment								
No	4	1822	0.75	(0.58–0.96)	0.02*	74.53%	0.01	REM
Yes	4	1859	0.60	(0.45–0.80)	0.00*	82.3%	0.00	REM
Sorafenib treatment								
No	5	2,395	0.66	(0.50–0.89)	0.01*	87.23%	0.00	REM
Yes	3	1,286	0.67	(0.51–0.89)	0.01*	70.68%	0.03	REM
ORR								
Follow-up (months)								
>20	6	2,112	2.50	(0.94–6.65)	0.07	67.95%	0.01	REM
≤20	3	692	2.68	(0.68–10.62)	0.16	0.00%	0.75	FEM†

(Continued)

Table 4 (Continued)

Subgroup	Clinical trials analyses (*n*)	Cases (*n*)	Pooled HR or OR			Test for heterogeneity		Model used
			HR or OR	95% CI	*P*-value	I^2	*Q*-test *P*-value	
>30	4	1,552	2.10	(0.56–7.80)	0.27	78.35%	0.00	REM
≤30	5	1,252	3.64	(1.46–9.04)	0.01*	0.00%	0.86	FEM†
>40	1	707	9.40	(1.25–70.83)	–	–	–	–
≤40	8	2097	2.09	(0.92–4.76)	0.08	53.79%	0.04	REM
Approved treatment								
No	5	696	1.64	(0.42–6.36)	0.48	62.01%	0.02	REM
Yes	4	2,108	3.22	(1.71–6.05)	0.00*	0.00%	0.73	FEM†
Sorafenib treatment								
No	7	1976	2.29	(0.85–6.16)	0.10	63.49%	0.01	REM
Yes	2	828	3.21	(0.90–11.51)	0.07	0.00%	0.81	FEM†
DCR								
Follow-up (months)								
>20	6	2,112	2.99	(2.47–3.62)	0.00*	25.41%	0.24	FEM†
≤20	3	692	1.32	(0.96–1.83)	0.09	0.00%	0.76	FEM†
>30	4	1,552	3.11	(2.48–3.89)	0.00*	45.89%	0.14	FEM†
≤30	5	1,252	1.96	(1.28–3.01)	0.00*	56.25%	0.05	REM
>40	1	707	3.53	(2.54–4.91)	–	–	–	–
≤40	8	2097	2.12	(1.51–2.97)	0.00*	57.50%	0.01	REM
Approved treatment								
No	5	696	2.02	(1.44–2.83)	0.00*	0.00%	0.72	FEM†
Yes	4	2,108	2.62	(1.59–4.31)	0.00*	84.71%	0.00	REM
Sorafenib treatment								
No	7	1976	2.68	(2.05–3.49)	0.00*	28.29%	0.21	FEM†
Yes	2	828	1.98	(0.78–5.05)	0.15	86.52%	0.01	REM
vs. sorafenib								
OS								
Follow-up (months)/Approved treatment								
>30	5	3,371	1.06	(0.90–1.25)	0.46	66.39%	0.02	REM
≤30	3	1,256	1.06	(0.92–1.22)	0.4	8.8%	0.33	FEM†
>40/Yes	1	954	0.92	(0.79–1.07)	–	–	–	–
≤40/No	7	3,673	1.13	(1.05–1.22)	0.00*	30.06%	0.20	FEM†
PFS								
Follow-up (months)/Approved treatment								
>30	4	2,216	1.00	(0.71–1.40)	0.98	87.89%	0.00	REM
≤30	1	1,035	0.81	(0.70–0.95)	–	–	–	–
>40/Yes	1	954	0.66	(0.57–0.76)	–	–	–	–
≤40/No	4	2,297	1.04	(0.82–1.31)	0.77	72.16%	0.01	REM
TTP								
Follow-up (months)/Approved treatment								
>30	5	3,371	0.99	(0.75–1.31)	0.97	87.79%	0.00	REM
≤30	2	1,200	1.01	(0.55–1.87)	0.96	89.05%	0.00	REM
>40/Yes	1	954	0.63	(0.53–0.75)	–	–	–	–
≤40/No	6	3,617	1.07	(0.88–1.30)	0.52	76.73%	0.00	REM

(Continued)

Table 4 (Continued)

Subgroup	Clinical trials analyses (*n*)	Cases (*n*)	Pooled HR or OR			Test for heterogeneity		Model used
			HR or OR	95% CI	*P*-value	I^2	*Q*-test *P*-value	
ORR								
Follow-up (months)/Approved treatment								
>30	5	3,371	1.21	(0.56–2.63)	0.63	85.74%	0.00	REM
≤30	3	1,275	0.70	(0.55–0.90)	0.00*	38.84%	0.19	FEM†
>40/Yes	1	954	3.11	(2.14–4.52)	–	–	–	–
≤40/No	7	3,692	0.74	(0.61–0.90)	0.00*	23.23%	0.25	FEM†
DCR								
Follow-up (months)/Approved treatment								
>30	5	3,371	0.98	(0.60–1.62)	0.95	88.1%	0.00	REM
≤30	2	240	1.58	(0.34–7.26)	0.65	84.97%	0.01	REM
>40/Yes	1	954	2.01	(1.53–2.66)	–	–	–	–
≤40/No	6	2,657	0.98	(0.84–1.15)	0.85	0.00%	0.05	REM
Combined TKI treatment								
TTP								
Follow-up (months)/vs. sorafenib								
>30/Yes	1	720	1.14	(0.94–1.36)	–	–	–	–
≤30/No	2	403	0.66	(0.42–1.04)	0.07	57.68%	0.12	REM
DCR								
Sorafenib treatment								
No	1	307	1.24	(0.77–2.00)	–	–	–	–
Yes	2	761	1.05	(0.34–3.31)	0.93	60.25%	0.11	REM

CI, confidence interval; DCR, disease control rate; FEM, fixed-effects model; HR, hazard ratio; OR, odds ratio; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; REM, random-effects model; TKI, tyrosine kinase inhibitor; TTP, time to progression.*Significant association, *P*-value <0.05.
†Heterogeneity solved (I^2 < 50% and *Q*-test *P*-value >0.10).

in HCC patients.[57,58,60–62] In line with our results, this indicates that the presence of AEs might play a crucial role in determining clinical outcomes in patients treated with sorafenib, being positively correlated with higher survival rates.

No significant association between combined TKI treatment in survival or DCR was observed in our meta-analysis. Nonetheless, the ORR was found to be slightly higher than in the control arm. Besides, hyperbilirubinemia and increased levels of AST were related to combined TKI treatment. In contrast, results obtained by Wu *et al.*[63] exhibited a high median PFS and tumor response, while detecting mild or moderate AEs that are easily manageable in patients suffering from retroperitoneal soft tissue sarcoma treated with anlotinib plus camrelizumab. Nevertheless, a recent meta-analysis evaluated the efficacy of transarterial chemoembolization (TACE) combined with TKIs in HCC patients with portal vein tumor thrombus. Treatment with TACE and sorafenib or apatinib enhanced OS and both ORR and DCR comparing to TACE alone, while TACE plus lenvatinib exhibited higher ORR and TTP than TACE and sorafenib.[47] Ding *et al.*[64] also assessed the presence of AEs in HCC patients receiving combined TACE plus sorafenib and TACE plus lenvatinib, being the incidence of AEs of any grade 96.9% and 100%, respectively. Altogether, combined TKI treatment showed diverse outcomes regarding survival, tumor response, and the presence of AEs, while not providing a clear clinical benefit.

The present study constitutes the first complete and detailed systematic review with meta-analysis evaluating the efficacy and safety of a wide range of TKIs employed in HCC patient's treatment. Although previous studies demonstrated systemic therapy effectiveness for advanced HCC,[48,65] no analysis of the risk and clinical benefit of approved and unapproved TKIs was performed. It should be highlighted that the presence of heterogeneity among studies and the risk of publication bias was evaluated, and sources of heterogeneity were analyzed by meta-regression and subgroup analysis. Notwithstanding this, our investigation has several limitations that need to be addressed to improve the comprehension of the advanced HCC treatment landscape and help develop future investigations in this field.

In our study design, no randomization was established as an exclusion criterion to minimize allocation and selection bias, leading to the rejection of 176 potentially useful clinical trials. Moreover, four initially selected clinical trials did not have publicly available results, which excludes likely relevant data to be used for this meta-analysis. Furthermore, eight trials did not employ any blinding strategy to prevent patient's performance bias.

Etiology plays an important role in determining HCC development and response to treatment[7]; however, this information was missing in most studies included, which could lead to the misinterpretation of the outcomes achieved. While demographic information was missing in some investigations, others included only Asian

Table 5 Risk of publication bias assessment for survival, tumor response parameters and AEs

Survival parameter	Clinical trials analyses (*n*)	Egger's test *P*-value	Model used	Trim-and-fill analysis		Imputed studies (*n*)
				HR	95% CI	
vs. placebo						
OS	13	0.38	REM	–	–	–
PFS	7	0.46	REM	–	–	
TTP	8	0.51	REM	–	–	–
TTSP	2	0.33	REM	–	–	–
vs. sorafenib						
OS	8	0.32	REM	–	–	–
PFS	5	0.19	REM	–	–	–
TTP	7	0.10	REM	–	–	–
Combined TKI treatment						
OS	4	0.11	FEM	–	–	–
PFS	2	**	REM	–	–	–
TTP	3	0.00*	REM	1.14	(0.68–1.91)	2

Tumor response parameter	Clinical trials analyses (*n*)	Egger's test *P*-value	Model used	Trim-and-fill analysis		Imputed studies (*n*)
				OR	95% CI	
vs. placebo						
ORR	9	0.85	REM	–	–	–
DCR	9	0.19	REM	–	–	–
vs. sorafenib						
ORR	8	0.76	REM	–	–	–
DCR	7	0.47	REM	–	–	–
Combined TKI treatment						
ORR	4	0.73	FEM	–	–	–
DCR	3	0.09	REM	–	–	–

Adverse events		Clinical trials analyses (*n*)	Egger's test *P*-value	Model used	Trim-and-fill analysis		Imputed studies (*n*)
					OR	95% CI	
vs. placebo							
GI disorders (1)	Abdominal pain	14	0.24	FEM	–	–	–
	Ascites	12	0.80	FEM	–	–	–
	Dehydration	9	0.94	FEM	–	–	–
	Diarrhea	12	0.96	FEM	–	–	–
GI disorders (2)	Esophageal varices hemorrhage	12	0.39	FEM	–	–	–
	GI hemorrhage	9	0.97	FEM	–	–	–
	Nausea	5	0.65	FEM	–	–	–
	Upper GI hemorrhage	11	0.59	FEM	–	–	–
	Vomiting	10	0.86	FEM	–	–	–
General, hepatobiliary disorders and infections	Fatigue	11	0.52	FEM	–	–	–
	Pyrexia	14	0.66	FEM	–	–	–
	Hepatic failure	10	0.30	FEM	–	–	–
	Hyperbilirubinemia	10	0.67	FEM	–	–	–
	Cellulitis	10	0.73	FEM	–	–	–
	Pneumonia	12	0.64	FEM	–	–	–

(Continued)

Table 5 (Continued)

Adverse events		Clinical trials analyses (*n*)	Egger's test *P*-value	Model used	Trim-and-fill analysis		Imputed studies (*n*)
					OR	95% CI	
Metabolic, nervous and respiratory disorders	AST	9	0.59	FEM	–	–	–
	Hypoglycemia	8	0.79	FEM	–	–	–
	Hyponatremia	9	0.60	FEM	–	–	–
	Encephalopathy	10	0.65	FEM	–	–	–
	Hepatic encephalopathy	8	0.63	FEM	–	–	–
	Dyspnea	9	0.92	FEM	–	–	–
vs. sorafenib							
GI disorders (1)	Abdominal pain	9	0.36	FEM	–	–	–
	Ascites	9	0.99	FEM	–	–	–
	Dehydration	5	0.33	FEM	–	–	–
	Diarrhea	9	0.91	FEM	–	–	–
GI disorders (2)	Esophageal varices hemorrhage	7	0.45	FEM	–	–	–
	GI hemorrhage	7	0.56	FEM	–	–	–
	Nausea	7	0.48	FEM	–	–	–
	Upper GI hemorrhage	8	0.72	FEM	–	–	–
	Vomiting	7	0.49	FEM	–	–	–
General, hepatobiliary disorders and infections	Fatigue	8	0.59	FEM	–	–	–
	Pyrexia	7	0.62	FEM	–	–	–
	Hepatic failure	8	0.87	FEM	–	–	–
	Hyperbilirubinemia	7	0.85	FEM	–	–	–
	Cellulitis	6	0.67	FEM	–	–	–
	Pneumonia	6	0.59	FEM	–	–	–
Metabolic, nervous and respiratory disorders	AST	7	0.92	FEM	–	–	–
	Hypoglycemia	7	0.78	FEM	–	–	–
	Hyponatremia	7	0.53	FEM	–	–	–
	Encephalopathy	4	0.48	FEM	–	–	–
	Hepatic encephalopathy	9	0.83	FEM	–	–	–
	Dyspnea	4	0.83	FEM	–	–	–
Combined TKI treatment							
GI disorders (1)	Abdominal pain	5	0.23	FEM	–	–	–
	Ascites	4	0.66	FEM	–	–	–
	Dehydration	4	0.93	FEM	–	–	–
	Diarrhea	4	0.18	FEM	–	–	–
GI disorders (2)	Esophageal varices hemorrhage	3	0.19	FEM	–	–	–
	GI hemorrhage	2	0.81	FEM	–	–	–
	Nausea	5	0.63	FEM	–	–	–
	Upper GI hemorrhage	4	0.70	FEM	–	–	–
	Vomiting	4	0.19	FEM	–	–	–
General, hepatobiliary disorders and infections	Fatigue	4	0.93	FEM	–	–	–
	Pyrexia	5	0.88	FEM	–	–	–
	Hepatic failure	2	1.00	FEM	–	–	–
	Hyperbilirubinemia	3	0.54	FEM	–	–	–
	Cellulitis	4	0.15	FEM	–	–	–
	Pneumonia	5	0.73	FEM	–	–	–

(Continued)

Table 5 (Continued)

Adverse events		Clinical trials analyses (*n*)	Egger's test *P*-value	Model used	Trim-and-fill analysis		Imputed studies (*n*)
					OR	95% CI	
Metabolic, nervous and respiratory disorders	AST	2	0.33	FEM	–	–	–
	Hypoglycemia	3	0.96	FEM	–	–	–
	Hyponatremia	2	0.97	FEM	–	–	–
	Encephalopathy	2	–	REM	–	–	–
	Dyspnea	3	0.92	FEM	–	–	–

AST, aspartate aminotransferase; CI, confidence interval; DCR, disease control rate; FEM, fixed-effects model; GI, gastrointestinal; HR, hazard ratio; OR, odds ratio; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; REM, random-effects model; TKI, tyrosine kinase inhibitor; TTP, time to progression.*Significant publication bias, *P*-value <0.05.**Convergence not achieved during tau2 estimation.

population or patients from both Asia and Western regions. Since some etiology factors are more prominent in certain regions,[1] this could lead to the presence of deviation in the results obtained in the present meta-analysis. HCC pathology was assessed based on different criteria such as diverse versions of the Response Evaluation Criteria in Solid Tumors (RECIST).[66–68] Moreover, patients with slightly distinct tumor grades, but still eligible for systemic therapy, and having received different doses of TKIs as well as treatment (first, second-line or adjuvant therapy) before trial enrollment, were included in our research. All this could contribute to the high heterogeneity described among studies in most of the analyses performed.

Clinical outcomes obtained in the present systematic meta-analysis were not consistent among the clinical trials selected. In addition, one study did not retrieve information about survival parameters[36] but could be estimated from Kaplan–Meier curves using Parmar method, causing a slight variation in the global effect obtained in the analysis. Curiously, the majority of included studies presented different sample sizes for survival parameters, tumor response, and AEs evaluation, possibly due to treatment discontinuation before achieving expected end points. Missing information about patient's outcomes could lead to an inaccurate interpretation of results.

Regarding treatment efficacy and safety, a small number of patients had to discontinue treatment or undergo dose reduction due to disease progression or high toxicity levels, triggering the development of AEs that could threaten patient's life. This led to the loss of relevant information that could contribute to a better understanding of the effect of TKI treatment for advanced HCC.

Overall, these results support the beneficial effects of HCC treatment with TKIs, but also provide a broader insight into different aspects that must be considered in the clinical setting. This systematic review with meta-analysis exhibits a complete and global analysis of both the effectiveness and risks of TKIs treatment in HCC patients affecting their outcomes, therefore providing a useful tool to take more accurate clinical decisions.

SUPPORTING INFORMATION

Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website (www.cpt-journal.com).

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CONFLICT OF INTEREST

The authors declared no competing interests for this work.

AUTHOR CONTRIBUTIONS

T.P.-S., C.M.-B., P.F.-P. and J.M.-G wrote the manuscript; M.R., J.J.O.-U., J.G.-G., J.J.G.M, J.L.M. and B.S.-M designed the research; T.P.-S., C.M.-B., P.F.-P. and J.M.-G performed the research; T.P.-S., C.M.-B., P.F.-P. and J.M.-G analyzed the data.

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