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Comparative efficacy of active first-line systemic therapies for unresectable hepatocellular carcinoma: a systematic review and network meta-analysis protocol of randomized controlled trials

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ADMINISTRATIVE INFORMATION

Support - No specific financial support has been received for this systematic review and network meta-analysis.

Review Stage at time of this submission - Preliminary searches.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 26 August 2026 and was last updated on 26 August 2026.

INTRODUCTION

Review question / Objective Among adults with unresectable or advanced hepatocellular carcinoma (HCC) who have not received prior systemic therapy, what are the comparative efficacy outcomes of active pharmacologic systemic treatments used as first-line therapy?

Population: Adults (≥18 years) with unresectable or advanced HCC who have not previously received systemic therapy for advanced disease.

Intervention: Active pharmacologic systemic treatments administered as first-line therapy, including tyrosine kinase inhibitors, immune checkpoint inhibitors, antiangiogenic agents, and systemic combination regimens.

Comparator: Other active pharmacologic systemic treatments. Sorafenib will be used as the reference treatment in the network meta-analysis because it is the most frequently used active comparator across pivotal first-line randomized trials and provides a well-connected anchor for indirect comparisons. Placebo or best supportive care without active systemic anticancer treatment will not be considered eligible comparators.

Outcomes: The primary outcome will be overall survival (OS). Secondary outcomes will include progression-free survival (PFS) and objective response rate (ORR).

Study design: Phase III randomized controlled trials.

Objective: To systematically synthesize direct and indirect randomized evidence and compare the efficacy of active first-line systemic pharmacologic treatments for unresectable or advanced HCC using network meta-analysis.Among adults with unresectable or advanced hepatocellular carcinoma who have not received prior systemic therapy, what are the comparative efficacy outcomes of active pharmacologic systemic

treatments evaluated as first-line therapy in randomized controlled trials?

Rationale Hepatocellular carcinoma (HCC) is a leading cause of cancer-related mortality worldwide. The therapeutic landscape for unresectable or advanced HCC has evolved substantially from sorafenib monotherapy to multiple active systemic options, including tyrosine kinase inhibitors, immune checkpoint inhibitor monotherapy, dual immune checkpoint inhibition, and immune checkpoint inhibitor–antiangiogenic combinations.

Several pivotal randomized controlled trials have compared these treatments with active systemic comparators, most commonly sorafenib. However, head-to-head randomized comparisons among contemporary active regimens remain limited, making direct determination of their relative efficacy difficult.

Previous network meta-analyses have evaluated broad treatment networks that may include historical placebo-controlled trials, investigational regimens, and, in some analyses, combinations of systemic and locoregional therapies. While such analyses provide a comprehensive overview of the available evidence, they may not directly address the clinical decision faced when choosing among active systemic pharmacologic treatments.

Therefore, this systematic review and network meta-analysis will focus specifically on randomized comparisons involving active systemic pharmacologic treatments used in the first-line setting for unresectable or advanced HCC. Placebo-controlled comparisons and treatment strategies incorporating locoregional interventions will be excluded. Sorafenib will serve as the reference treatment because it has been the most extensively used active comparator across pivotal first-line randomized trials and provides a well-connected and clinically interpretable anchor for the treatment network.

This approach is intended to provide comparative estimates that are directly relevant to treatment selection among active systemic therapeutic options.

Condition being studied Unresectable or advanced hepatocellular carcinoma.

Patients with unresectable or advanced HCC who are candidates for first-line systemic therapy have several pharmacologic treatment options. Because most contemporary systemic regimens have been evaluated against an established active comparator rather than directly against each other, their relative efficacy remains uncertain.

METHODS

Participant or population Adults aged ≥18 years with unresectable or advanced hepatocellular carcinoma who have not previously received systemic therapy for advanced disease.

Studies including mixed populations will be eligible only when data for the population meeting the eligibility criteria can be separately extracted.

Intervention Any active pharmacologic systemic therapy evaluated as first-line treatment for unresectable or advanced HCC, including tyrosine kinase inhibitors, immune checkpoint inhibitors, antiangiogenic agents, and systemic combination regimens.

Eligible interventions must consist exclusively of pharmacologic systemic treatment.

Comparator Active pharmacologic systemic therapy.

Trials will be eligible when both randomized treatment groups receive active systemic pharmacologic treatments. Sorafenib will be prespecified as the reference treatment for the network meta-analysis because of its extensive use as an active comparator across pivotal first-line HCC randomized trials and its central position within the anticipated treatment network.

Placebo or best supportive care without an active systemic anticancer treatment will not be considered eligible comparators.

Study designs to be included Phase III randomized controlled trials.

Eligibility criteria Inclusion

Studies will be included if they: (1) are randomized controlled trials; (2) enroll adults with unresectable or advanced HCC; (3) evaluate first-line systemic therapy in patients without previous systemic treatment for advanced disease; (4) compare two or more active systemic pharmacologic treatment strategies; and (5) report at least one prespecified efficacy outcome.

Exclusion

Studies will be excluded if they: (1) use placebo or best supportive care without active systemic anticancer treatment as the comparator; (2) evaluate TACE, HAIC, radiotherapy, radioembolization, ablation, or other locoregional interventions as part of the randomized treatment strategy; (3) evaluate adjuvant or neoadjuvant therapy; (4) evaluate second-line or later-line systemic therapy; (5) are non-randomized or single-arm studies; or (6) do not provide sufficient outcome data for quantitative synthesis.

Information sources MEDLINE via PubMed, Embase, and Scopus will be searched from inception to the final search date. In addition, the reference lists of included studies and relevant systematic reviews and network meta-analyses will be manually screened to identify additional eligible randomized controlled trials.

Main outcome(s) Primary outcome

Overall survival (OS), expressed as a hazard ratio (HR) with 95% confidence interval (CI).

Secondary outcomes

Progression-free survival (PFS), expressed as HR with 95% CI.

Objective response rate (ORR), expressed as risk ratio or odds ratio with 95% CI according to the prespecified statistical model.

Quality assessment / Risk of bias analysis Two reviewers will independently assess the risk of bias of each eligible randomized trial using the Cochrane Risk of Bias 2 (RoB 2) tool. Disagreements will be resolved by discussion or consultation with a third reviewer.Risk of bias will be independently assessed by two reviewers using the Cochrane Risk of Bias 2 (RoB 2) tool. Disagreements will be resolved through discussion or, when necessary, adjudication by a third reviewer (C.C.).

Strategy of data synthesis A network meta-analysis will be conducted to estimate the comparative efficacy of eligible active first-line systemic treatments. Sorafenib will be used as the reference treatment.

For time-to-event outcomes, hazard ratios and corresponding 95% confidence intervals will be analyzed on the natural logarithmic scale. Direct and indirect evidence will be synthesized within a random-effects network meta-analysis framework.

Network geometry will be presented graphically, with nodes representing treatment strategies and edges representing direct randomized comparisons. The size of nodes and thickness of edges may be weighted according to the number of participants and studies, respectively.

Heterogeneity will be assessed using the estimated between-study variance and relevant heterogeneity statistics. The assumption of transitivity will be evaluated by comparing the distribution of potential effect modifiers across treatment comparisons, including age, ECOG performance status, Child–Pugh class, BCLC stage, viral etiology, AFP concentration, macrovascular invasion, extrahepatic spread, and geographic region.

Where closed loops containing both direct and indirect evidence are available, inconsistency will be assessed using appropriate local and/or global methods.

Treatments will be ranked using P-scores or SUCRA values, as appropriate to the selected frequentist or Bayesian analytical framework. Treatment rankings will be interpreted alongside effect estimates and their uncertainty rather than in isolation.

Subgroup analysis Where sufficient data are available, subgroup analyses will explore treatment effects according to underlying HCC etiology (HBV, HCV, or non-viral disease) and geographic region.

Sensitivity analysis Sensitivity analyses will be conducted, where data permit, by:

(1) excluding trials judged to have a high risk of bias;
(2) restricting the analysis to currently approved first-line systemic treatment regimens; and
(3) excluding trials with clinically important differences in population characteristics or treatment definitions that may threaten the transitivity assumption.

Country(ies) involved Thailand.

Keywords hepatocellular carcinoma; systemic therapy; first-line treatment; active treatment; randomized controlled trial; network meta-analysishepatocellular carcinoma; systemic therapy; first-line treatment; sorafenib; immunotherapy;.

Contributions of each author

Author 1 - Chaichana Chantharakhit - Conceived and designed the study, developed the review methodology and search strategy, will supervise the review process and statistical analysis, resolve disagreements between reviewers, interpret the findings, and draft and critically revise the manuscript.
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