

# AGA Technical Review on Systemic Therapies for Hepatocellular Carcinoma

**Authors:** Osama Altayar<sup>1, \*</sup>, Raj Shah<sup>2, \*</sup>, Charissa Chang<sup>3</sup>, Yngve Falck-Ytter<sup>4</sup>, Andrew J. Muir<sup>5</sup>

\*Authors share co-first authorship

**Affiliations:**

(1) Division of Gastroenterology, Department of Medicine, Washington University School of Medicine, St. Louis, MO.

(2) Division of Gastroenterology, Hepatology and Endoscopy. Brigham and Women's Hospital. Harvard Medical School. Boston, MA.

(3) Division of Liver Diseases, Icahn School of Medicine at Mount Sinai, New York, NY.

(4) Division of Gastroenterology and Hepatology, Veterans Affairs Northeast Ohio Health Care System, Cleveland, OH; Case Western Reserve University School of Medicine, Cleveland, OH.

(5) Division of Gastroenterology, Department of Medicine, School of Medicine, Duke University, Durham, NC.

**Correspondence:** Address correspondence to: Chair, Clinical Guidelines Committee, American Gastroenterological Association, National Office, 4930 Del Ray Avenue, Bethesda, Maryland 20814. e-mail: [clinicalpractice@gastro.org](mailto:clinicalpractice@gastro.org)

**Conflicts of interest:** The authors disclose no conflicting interest.

## Abbreviations

HCC, hepatocellular carcinoma

AFP, alpha-fetoprotein

BCLC, Barcelona Clinic Liver Cancer

CP score, Child-Pugh score

TACE, transarterial chemoembolization

TARE, transarterial radioembolization

FDA, Food and Drug Administration

PICO: population, intervention, comparator, and outcomes

PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses

RCT, randomized controlled trial

RFA, radiofrequency ablation

HRQOL, health-related quality of life

SAE, serious adverse event

HR, hazard ratio

CI, confidence interval

CoE, certainty of evidence

ECOG PS, Eastern Cooperative Oncology Group performance status

RR, relative risk

BSC, best supportive care

MELD, Model for End-Stage Liver Disease

mg/kg, milligram/kilogram

ng/mL, nanogram/milliliter

EORTC, European Organization for the Research and Treatment of Cancer

QLQ-C30, EORTC Quality of Life Questionnaire version 3

QLQ-HCC18, EORTC Quality of Life Questionnaire for Hepatocellular Carcinoma

GRADE, Grading of Recommendations Assessment, Development and Evaluation

## Introduction

Liver cancer is the seventh most common cancer worldwide, and the sixth leading cause of cancer-related mortality in the United States.<sup>1, 2</sup> Hepatocellular carcinoma (HCC), the most common histologic type of liver cancer, occurs most commonly in patients with cirrhosis. However, it can occur in the absence of cirrhosis, as is well-described in patients with chronic Hepatitis B. There are multiple options for screening and early detection including serial examination with liver ultrasound and/or serum alpha-fetoprotein (AFP). The diagnosis can be made by characteristic findings on multiphase cross-sectional imaging, and sometimes may require biopsy for confirmation where imaging is nondiagnostic. There are multiple staging schemes; however, the one that is used most commonly is the Barcelona Clinic Liver Cancer (BCLC) staging, which takes into account not only tumor burden, but also underlying liver function and overall performance status in guiding treatment options.<sup>3</sup> When the disease is detected at an early stage, curative treatment options include surgical resection, ablation, and liver transplantation. At intermediate stages, treatments include locoregional therapies, such as transarterial chemoembolization (TACE) and transarterial radioembolization (TARE). In patients with advanced-stage HCC, novel systemic therapies including targeted therapies (tyrosine kinase and vascular endothelial growth factor inhibitors) and immunotherapies have been shown to delay disease progression and improve survival. The first approved treatment was sorafenib, a tyrosine kinase inhibitor, which led to improved survival in 2 milestone clinical trials, the SHARP trial and the Asia Pacific trial.<sup>4, 5</sup> Since then, multiple agents have been added to the list of systemic therapies approved by the United States Food and Drug Administration (FDA) for advanced HCC.<sup>6</sup> Additionally, multiple trials have studied the role of different systemic therapies at early and intermediate stages of HCC, such as adjuvant therapies combined with curative resection or ablation. Therefore, the American Gastroenterological Association (AGA) prioritized this topic for the generation of clinical guidelines for systemic therapies of HCC.

## Methods

### Overview

The technical review and the accompanying guideline were conducted according to the GRADE framework.<sup>7</sup> The AGA Clinical Guideline Committee selected the members of the technical review and clinical guideline panels who were screened to minimize any conflict of interest. The guideline panel defined the scope of the guideline and developed focused clinical questions that were deemed relevant for clinical practice.

The technical review panel then formulated the clinical questions, identified, and defined patient-important outcomes, and reviewed the literature systematically to summarize the available body of evidence for each question.

## Formulating the Clinical Questions

The clinical questions aimed to assess the role of systemic therapies in patients with advanced-stage HCC as first- and second-line treatments, and assess their role as adjuvant and neoadjuvant therapies in patients receiving curative resection or ablation, locoregional therapies, and liver transplantation. The clinical questions were formulated using the PICO format which frames a clinical question by defining a specific patient population (P), intervention (I), comparator (C), and outcomes (O). The panel finalized 5 questions on the topic (Appendix 1).

## The Systematic Review Process and Literature Search Strategy

We conducted a systematic review and reported it according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.<sup>8</sup> The technical review panel developed a protocol to guide the systematic review a priori. An experienced librarian conducted a comprehensive search of the following databases from inception to December 4, 2020: MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials (CENTRAL). The Technical Review Panel guided the search, and both controlled vocabulary and keywords that were used to search the studies. The search was limited to English and human studies. The final search strategies are available in Figure 1. The references of previously published systematic reviews and clinical guidelines were reviewed to identify other relevant studies that may have been missed by the search strategy. Due to the evolving field and to keep the guideline abreast of recently published studies, the search was updated on a weekly basis until June 9, 2021. We also searched for the published articles of conference abstracts if they were relevant.

## Eligibility Criteria

We included randomized controlled trials (RCT) of any of the therapies of interest compared to standard or best supportive care, placebo, other therapies of interest, or no intervention. The therapeutic agents of interest were the medications approved by the United States Food and Drug Administration (FDA) for hepatocellular carcinoma and medications suggested by the panel: sorafenib, lenvatinib, regorafenib, cabozantinib, pemigatinib, pembrolizumab, bevacizumab/atezolizumab, ramucirumab, nivolumab, nivolumab/ipilimumab, and tremelimumab/durvalumab. For adjuvant, neoadjuvant, and concurrent therapy, we only included trials in which the co-interventions were given to both the intervention and comparison arms of the trial (e.g. concurrent sorafenib and TACE treatment versus TACE treatment alone). We included studies that used any of the following co-interventions: resection, radiofrequency ablation (RFA), liver transplantation, and TACE. We included trials of first- and second-line treatments.

We excluded studies that did not include a comparison or control arm, or single-arm pre-post studies. We excluded studies that used conventional cytotoxic chemotherapeutic agents, and studies of non-FDA approved agents including linafinib, tivantinib, erlotinib, everolimus, sunitinib, apatinib, and brivanib. We excluded studies that used hepatic arterial infusion chemotherapy. Conference abstracts were only included if they provided updated effect estimates based on a priori planned follow-up, otherwise we only included comparative effectiveness studies published with peer review.

## Study Selection and Data Extraction

We uploaded the references identified by the search strategy to *Rayyan*, a web-based platform for conducting systematic reviews.<sup>9</sup> Initially, the titles and abstracts were reviewed for eligibility by two independent blinded reviewers with complementary expertise, a clinical expert and a methodologist. The full texts of the eligible references were retrieved and reviewed by two independent blinded reviewers with complementary expertise. Disagreements were resolved by discussion with the rest of the technical review panel and reaching consensus. During the selection process, the identified references were classified based on which PICO question they informed to streamline the data extraction process. We also identified cost-effectiveness analyses to be taken into consideration in the evidence-to-decision framework.

A data extraction form was developed using Google Docs which was piloted using two studies and revised as needed. The extracted data included the inclusion and exclusion criteria, study protocol for interventions and assessment, the baseline characteristics of each arm (age, gender, Child-Pugh (CP) score, BCLC stage, and performance status), and the outcomes of interest (detailed below). If the results of a trial were published in multiple reports including conference abstracts, we combined the data and used the most recent effect estimates.

## Defining the Important Outcomes

The outcomes of interest were identified based on their importance for patients and decision making. Overall survival was defined as time between randomization and death from any cause, and mortality as the rate of death due to any cause at prespecified time points reported in the trials. We considered overall survival and mortality critical outcomes for decision making. Disease-related mortality was defined as death attributed to hepatocellular carcinoma. In studies of patients not eligible for curative treatment, we used progression-free survival and time-to-progression as outcomes when overall survival showed no difference between the intervention and control arms of the trial. Progression-free survival was defined as the time from randomization to disease progression (as defined by the trial) or death from any cause (whichever came first), while time-to-progression was defined as the time from randomization to disease progression (as defined by the trial). When disease progression was defined according to both Response Evaluation Criteria in Solid Tumors (RECIST) and the modified RECIST (mRECIST) criteria, we used the mRECIST definition. For studies of systemic therapies in combination with curative treatments, we used the recurrence-free survival and time-to-recurrence as outcomes critical for decision making. We also included health-related quality of life (HRQOL), serious adverse events (SAE) as defined by the FDA<sup>10</sup>, and adverse events leading to discontinuation of treatment as outcomes critical for decision making.

## Data Synthesis

When multiple trials informed a PICO question, we used the DerSimonian-Liard random-effects model to pool the relative effects, unless the number of studies was too small to allow precise estimation of between-study variance in which case we used the fixed-effects model.<sup>11, 12</sup> Due to the nature of the disease, time-to-event outcomes were used frequently and reported as the median time to the event and the associated hazard ratios (HR). The HR and its corresponding confidence interval (CI) were transformed using the natural log transformation to log HR and its standard error, pooled to provide pooled log HR with its standard error, then back-transformed to pooled HR with its corresponding 95% CI. We used the  $I^2$  statistic to quantify heterogeneity and used a threshold of 50% as an indicator of substantial heterogeneity.<sup>13</sup> When a sufficient number of studies was presented with no substantial heterogeneity, we planned to assess for publication bias using funnel plot asymmetry tests.<sup>14</sup> We used the package *meta* 4.19-1 in R 4.1.1 to conduct the analyses.<sup>15, 16</sup>

## Assessing the Quality of Evidence

The risk of bias in the individual trials was assessed using the Cochrane Collaboration's tool for assessing risk of bias in randomized trials.<sup>17</sup> An additional factor that we took into consideration when judging the risk of bias was the reporting of how post-protocol therapies, given after discontinuation of the trial intervention, were chosen and whether the study groups were allocated to similar post-protocol therapies. For example, if conventional cytotoxic chemotherapies were given preferentially to one group more than the other, it could have led to worse outcomes in that group as HCC is considered less responsive to conventional cytotoxic chemotherapy than other malignancies.

We used the GRADE approach to assess the certainty (quality) of evidence for the body of evidence from the systematic reviews and meta-analyses.<sup>7</sup> The evidence is rated for each outcome as high, moderate, low or very low. Evidence derived from RCTs starts at a high certainty of evidence, then it is rated down for risk of bias, inconsistency, indirectness, imprecision, and/or other factors. The overall certainty of evidence (CoE) for the PICO question is then rated based on the lowest rating for the critical outcomes.

As we defined HRQOL as a critical outcome for decision making, we could have rated the CoE for some of the PICO questions in which HRQOL was not reported as very low despite the rest of the body of evidence. To avoid that, we used discontinuation due to adverse events to assess the possibility of an important impact on HRQOL. For PICO questions that showed improved survival in the intervention group compared to the control group but did not report HRQOL data, we rated the CoE as very low when there was evidence of increased treatment discontinuation due to adverse events in the intervention group, and as low certainty of evidence when there was no difference in the rate of treatment discontinuation due to adverse events in the intervention and control groups.

## Evidence-to-Decision Framework

As this technical review was conducted to inform clinical practice guidelines, in addition to a comprehensive risk-to-benefit assessment, we also considered information about patients' preferences and values, resources utilization, cost-effectiveness, and health disparities, when available. As we were unable to identify evidence regarding patients preferences and values, we developed a scheme to evaluate the certainty in the patients' values and preference using the concordance or discordance between HRQOL and discontinuation due to adverse events. This scheme is summarized in Appendix 3. A systematic search for studies on health equity and disparities was performed using the MEDLINE/PubMed Health Disparities and Minority Health Search Strategy filter, and the identified references were reviewed and summarized.<sup>18</sup>

For resource utilization, we used the average wholesale price as obtained from UpToDate in June 2021.<sup>19</sup> The calculated estimated resource utilization that we presented were reported for transparency, but did not take into account the variability in acquisition price which varies widely between institutions, and they do not represent cost effectiveness or utilization analyses. We reviewed published economic evaluation (cost-effectiveness and utilization) studies and listed them in Appendix 4.

## Results

The search strategy identified 3,919 references as of December 4, 2020 and the weekly updates identified additional 553 references as of June 9, 2021. A total of 250 full texts were retrieved for review after title and abstract screening, and 41 references reporting 20 RCTs were finally included in the systematic review. Resource utilization is reported in the evidence profiles, and economic evaluation studies are listed in Appendix 4. The search for studies on health equity and disparities identified 5 references, only one of them met the inclusion criteria based on review of the titles but it was excluded after review of the abstract and full text article. The baseline characteristics of the included studies are presented in Appendix 5 and risk of bias assessment is presented in Appendix 6.

## PICO 1

**In patients with hepatocellular carcinoma who failed locoregional therapy, were ineligible for locoregional therapy, or have metastatic disease with preserved liver function, should systemic therapy be used?**

A priori, preserved liver function was defined as non-cirrhosis or CP score of A or B  $\leq 7$ , or BCLC B or C. It is noted that studies had overlap of inclusion patient population and could not adhere to this strict definition. A priori, poor liver function was defined as Child B  $> 7$  or CP C and BCLC C or D. These definitions were used as a guiding principle and the technical review team as a group discussed which definition fit each included study and noted that

there may be some overlap. If outcomes were reported by these sub-groups in a fashion that did not violate randomization, they were reported.

## First-Line Therapies

Evidence for first-line therapies were found for the following interventions: sorafenib monotherapy, lenvatinib monotherapy, and atezolizumab+bevacizumab combination therapy.

### Sorafenib vs. no Sorafenib

#### Key Message

In patients with HCC who failed/ineligible for locoregional therapy or have metastatic disease with preserved liver function, sorafenib may lead to moderate improvement in overall survival (2.3-2.8 months) and disease progression with similar quality of life between intervention and placebo, but moderate risk of adverse events leading to discontinuation of treatment (appear to be underestimated in the studies) and similar serious adverse event rates (*low overall CoE*).

#### Evidence Synthesis

Two RCTs assessed sorafenib (400 mg twice a day) versus placebo. Both trials included the majority of patients CP A and Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1 and a minority of patients with CP B and ECOG 2 (Appendix 5).<sup>4, 5</sup>

#### Benefits

Two RCTs were pooled for the outcome of mortality and disease progression with 449 patients in the sorafenib arm and 379 in the no sorafenib arm. The follow-up range was 19-23 months. Median overall survival in the SHARP trial was 10.7 (9.4-13.3) months in the sorafenib arm versus 7.9 (6.8-9.1) months in the no sorafenib arm (difference of 2.8 months).<sup>4</sup> In the ASIA-PACIFIC trial, the overall survival was found to be 6.5 (5.6-7.6) vs 4.2 (3.8-5.5) months (difference of 2.3 months).<sup>5</sup> In a pooled analysis, those in the sorafenib arm were 31% less likely to die than those without sorafenib during the study duration (HR 0.69, 95% CI 0.57-0.83). (CITE FP AND EP) For the outcome of disease progression, HR was found to be 0.58 (95% CI 0.47-0.70). The ASIA-PACIFIC trial reported no difference in the quality of life between the intervention and comparator arms and similar scores on the Function Assessment of Cancer Therapy- Hepatobiliary symptom Index (FHSI-8) and Functional Assessment of Cancer Therapy- Hepatobiliary (FACT-HP) questionnaire.

#### Harms

Serious adverse events (SAE) and discontinuation due to adverse events outcomes were based on a pooling of two RCTs with a total of 823 participants. Serious adverse events occurred in 52.5% (198/377) in the sorafenib group versus 50.2% (224/446) in the no sorafenib group (RR

0.97, 95% CI 0.85-1.11). Discontinuation due to adverse events occurred in 32.4% (122/377) in the sorafenib group versus 31.8% (142/446) in the no sorafenib group (RR 1.07, 95% CI 0.88-1.31). As the clinical experts in the panel raised concerns that the rate of harms did not match their clinical experience, we identified a systematic review that evaluated the risk of serious adverse events in RCTs that compared sorafenib to placebo or no intervention in patients with solid malignancies. The systematic review included 12 RCTs that comprised 6,797 patients with solid malignancies. Patients who received sorafenib had higher risk of developing serious adverse events (RR 1.49, 95% CI 1.18-1.89;  $I^2 = 81%$ ) compared to patients who received placebo or no intervention.<sup>20</sup>

#### Certainty of evidence

The certainty of evidence for the outcomes of mortality, disease progression, and harms was deemed to be moderate. For mortality, there was a serious risk of bias as it was unclear if blinding was intact for the decision making for post-protocol therapies. Furthermore, the delineated protocol of which intervention was given after treatment discontinuation was unclear. Disease progression was regarded to be an indirect surrogate of overall survival. Furthermore, the ASIA-PACIFIC study reported this outcome as a composite of radiologic and symptomatic progression. For the outcome of quality of life, it was deemed to be of low certainty as there was serious risk for both bias and imprecision due to the lack of reporting on result details and response rates and small sample size. In regards to harms, there was serious risk of imprecision as the confidence interval showed both appreciable benefit and harm. Driven by the outcome of quality of life, the overall certainty of evidence for this PICO was deemed to be low.

#### Lenvatinib vs. Sorafenib

##### Key Message

In patients with hepatocellular carcinoma who failed locoregional therapy, were ineligible for locoregional therapy, or have metastatic disease with preserved liver function, lenvatinib and sorafenib may lead to similar overall survival and overall decline in quality of life, however lenvatinib may lead to small improvements in progression-free survival and disease progression, but also small increase in serious adverse events and discontinuation due to adverse events (*low overall CoE*).

##### Evidence Synthesis

A non-inferiority RCT (REFLECT) assessed 478 patients on lenvatinib (8-12 mg/kg daily) versus 476 patients on sorafenib (400 mg twice daily) with the majority of the population having CP A and BCLC C and the minority being CP B and BCLC B in both cohorts.<sup>21</sup> Patients with main portal vein invasion were excluded (Appendix 5). Mortality, assessed with a follow up median of 27.2-27.7 months, was found to be 73.5% (350/476) versus 73.4% (351/478) (HR 0.92, 95% CI 0.79-1.06). Median overall survival was 13.6 months (95% CI 12.1-14.9) in the lenvatinib group and 12.3 months in the sorafenib group (95% CI 10.4-13.9). Median progression-free survival and median time to progression for patients on lenvatinib versus sorafenib were 7.3 versus 3.6

months (HR 0.64, 95% CI 0.55-0.75) and 7.4 versus 3.7 months (HR 0.60, 95% CI 0.51-0.71), respectively. Overall quality of life score between the two interventions was similar (HR 0.87, 95% CI 0.754-1.012), however specific domains for time to deterioration for role functioning, pain, diarrhea (EORTC QLQ-C30), nutrition and body image (based on EORTC QLQ Questionnaire for HCC, EORTC QLQ-HCC18) was reported to be earlier in the sorafenib arm. SAE rate and treatment discontinuation due to adverse event rate was found to be 43.1% and 13.2% respectively in the lenvatinib arm and 30.3% and 9.1% respectively in the sorafenib arm (RR 1.42, 95% CI 1.20-1.69; RR 1.46, 95% CI 1.01-2.11, respectively). The most common any grade adverse event was hypertension, occurring at a rate of 42.2% in the lenvatinib arm and 30.3% in the sorafenib arm. The next most common adverse events were diarrhea (39% in lenvatinib arm, 46% in sorafenib arm) and palmar erythrodysesthesia (27% in lenvatinib arm, 52.4% in sorafenib arm).

#### Certainty of Evidence (CoE)

Serious risk of bias was found for the outcomes of harms, decline in quality of life, and mortality due to the study being open label and unclear impact of lack of blinding on post-protocol therapies. Additionally, progression-free survival and disease progression were deemed indirect measures of overall survival and thus were deemed to have moderate certainty. Serious imprecision was also found for the outcomes of mortality, quality of life, and discontinuation due to adverse events due to either the confidence interval favoring either drug or small event rate. This led certainty to be low for the outcome of mortality and harms. Overall certainty of evidence for this PICO was deemed to be low.

#### Atezolizumab + Bevacizumab vs. Sorafenib

##### Key Message

In patients with hepatocellular carcinoma who failed locoregional therapy, were ineligible for locoregional therapy, or have metastatic disease with preserved liver function, atezolizumab+bevacizumab may lead to moderate benefit over sorafenib for overall survival (5.8 months), progression-free survival, and deterioration of quality of life, but may have a small increase in serious adverse events and discontinuation due to adverse events when compared to sorafenib (*low overall CoE*).

##### Evidence Synthesis

One RCT (IMbrave150) was included for this PICO question for the intervention of atezolizumab + bevacizumab (1200 mg atezolizumab +15 mg/kg bevcizumab every 3 weeks) with included outcomes of mortality, progression free survival, quality of life, and harms.<sup>22, 23</sup> The comparator group was sorafenib in this RCT with a total of 501 participants among both arms and median follow-up time of 8.6 months. The population studied had a better score than CP B7 with ECOG 0 or 1 and the majority were BCLC C (Appendix 5). Mortality occurred in 28.6% (96/336) in the atezolizumab + bevacizumab arm and 39.4% (65/165) in the sorafenib arm (HR 0.66, 95% CI 0.52-0.85). Median overall and progression free survival in the atezolizumab + bevacizumab

group was 19.2 and 6.8 months versus 13.4 and 4.3 months in the sorafenib group (difference of 5.8 and 2.5 months), respectively. For the outcome of deterioration of quality of life, the study authors used the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire version 3 (EORTC QLQ-C30) and found the median time to deterioration was 11.2 months with atezolizumab–bevacizumab and 3.6 months with sorafenib (HR 0.63, 95% CI 0.46-0.85).

In regards to harms, both SAE and treatment discontinuation due to adverse events were deemed critically important for decision making. Among the atezolizumab + bevacizumab group 38% (125/329) had a SAE versus 30.8% (48/156) in the sorafenib group (RR 1.23, 95 CI 0.94-1.62). Discontinuation of treatment due to an adverse event occurred in 15.5% (51/329) in the atezolizumab + bevacizumab group and 10.3% (16/156) in the sorafenib group (RR 1.51, 95 CI 0.89-2.56). Details for selected grade 5 adverse events for the atezolizumab-bevacizumab group events did include 3 gastrointestinal hemorrhage, a gastric ulcer perforation, and esophageal variceal hemorrhage. In this study, patients were required to have variceal evaluation with endoscopy and treatment if needed prior to enrollment. The study reported a 7% upper gastrointestinal bleeding rate in the atezolizumab + bevacizumab group versus 4.5% in the sorafenib group.

#### Certainty of evidence

The overall certainty across all outcomes was deemed to be low. For the outcome of mortality and progression free survival, there was serious risk of bias as the lack of blinding could have led to differentially effective post-protocol therapies. Also, for mortality there was a serious risk of imprecision due to the small number of events. The outcome of progression free survival was considered to be an indirect surrogate for overall survival. For the outcomes of quality of life and harms, there was risk of bias due to lack of blinding. Additionally, for quality of life, the transparency of completed questionnaires and missing values was of concern. Furthermore, for harms there was serious risk for imprecision as the confidence interval included both increased and decreased risk of adverse events.

#### Other Agents

We identified a trial, CheckMate 459, that compared the use of nivolumab (n=371) versus sorafenib (n=372) as first-line treatment in patients with hepatocellular carcinoma who failed/were ineligible for locoregional therapy or had metastatic disease with preserved liver function. The results of the trial were presented in conferences and were available on ClinicalTrials.gov. The median overall survival with nivolumab was 16.4 months compared to 14.7 months in patients who received sorafenib (HR 0.85, 95% CI 0.71-1.02). The median progression-free survival in patients who received nivolumab was 3.68 months compared to 3.75 months in patients who received sorafenib (HR 0.93, 95 CI 0.79-1.1). In terms of safety, nivolumab was associated with less serious adverse events (RR 0.89, 95% CI 0.81-0.98). As the results of the trial have not been published, this precluded assessment of the certainty of evidence.<sup>24</sup>

## Second-Line Therapies

### Regorafenib vs. no Regorafenib

#### Key Message

In patients with hepatocellular carcinoma who failed locoregional therapy, were ineligible for locoregional therapy, or have metastatic disease with preserved liver function and have progressed on sorafenib, regorafenib may lead to small increase in overall survival (2.8 months), increase in progression free survival, and improvement in disease progression along with a small increase in serious adverse events and discontinuation due to adverse events and no improvement in quality of life (*low overall CoE*).

#### Evidence Synthesis

One RCT (RESORCE) met inclusion criteria and compared 379 patients who received regorafenib (160 mg daily for 3 weeks every 4 weeks) to 194 patients who received a matching placebo.<sup>25, 26</sup> The majority of the studied population had CP A, BCLC C, ECOG 0 or 1 and the minority of the population was CP B, BCLC A or B (Appendix 5). Regorafenib (mortality: 76.5%, 290/379) compared to no regorafenib (mortality: 87.1%, 169/194) is likely to increase overall survival (HR 0.61, 95% CI 0.5-0.75). This was based on a median follow-up of 3.7 to 12.6 months and median overall survival of 10.6 months with regorafenib versus 7.8 months with placebo (difference of 2.8 months). Progression free survival and disease progression are also likely to be improved with regorafenib (HR 0.46, 95% CI 0.37-0.56; HR 0.44, 95% CI 0.36-0.55; respectively). HRQOL was reported to be similar between the two groups. SAE occurred in 44.4% (166/374) of those who took regorafenib versus 46.6% (90/193) of those who received placebo (RR 0.95, 95% CI 0.79-1.15). Treatment discontinuation due to adverse events occurred in 24.9% of those who took regorafenib versus 19.2% in those who took placebo (RR 1.30, 95% CI 0.92-1.82). The most frequently occurring adverse events leading to discontinuation in those with regorafenib was increase in liver aminotransferases and hand-foot skin reaction.

#### Certainty of Evidence (CoE)

Serious risk of bias (concern for the effect of post protocol therapies) was found for the outcome of mortality. Progression free survival and disease progression were downgraded as they were indirect measures of overall survival. Serious imprecision was found for harms due to the confidence interval including minimally important different thresholds for decision making. These outcomes were deemed to have moderate certainty. However, the critically important outcome of HRQOL was deemed to have low certainty as there was serious risk of bias (unclear response rate) and imprecision (confidence interval including both improvement and worsened quality of life). Thus, the overall certainty of evidence was deemed to be low for this PICO.

## Cabozantinib vs. no Cabozantinib

### Key Message

In patients with hepatocellular carcinoma who failed locoregional therapy, were ineligible for locoregional therapy, or have metastatic disease with preserved liver function and have progressed on sorafenib, cabozantinib may lead to a small increase in overall survival (2.2 months) and progression free survival, but is likely to increase harms such as serious adverse events and treatment discontinuation due to adverse events (*very low overall CoE*).

### Evidence Synthesis

One RCT (CELESTIAL) was found that assessed cabozantinib (470 participants) versus a matching placebo (237 participants) in patients who had progressed on sorafenib with preserved liver function.<sup>27</sup> The majority of participants were classified as CP A, BCLC C, ECOG 0 or 1 while a small minority of patients were CP B, BCLC B, and ECOG 2 (Appendix 5). For the outcome of mortality with a follow up range up to 45 months, 67.4% (317/470) of those who received cabozantinib died and 70.5% (167/237) of those who received placebo died (HR 0.76, 95% CI 0.63-0.92). Median overall survival was 10.2 months with cabozantinib versus 8 months with placebo (difference of 2.2 months). Median progression-free survival was 5.2 months in patients on cabozantinib versus 1.9 months in patients on placebo (HR 0.44, 95% CI 0.36-0.52). HRQOL was not reported. In regards to harms, SAE rates and treatment discontinuation due to adverse events in cabozantinib versus placebo occurred at rates of 49.7% versus 36.7% and 21% versus 4.6% (RR 1.35, 95% CI 1.12-1.64; RR 4.52, 95% CI 2.47-8.27; respectively).

### Certainty of Evidence (CoE)

Serious risk of bias was noted for the outcome of mortality due to imbalances for post protocol therapies. Progression-free survival was found to have indirectness as it was an indirect measure of survival. Due to a wide confidence interval, we downgraded the discontinuation due to adverse events as it was deemed imprecise. Although these outcomes were deemed to have moderate certainty, and high certainty for serious adverse events, quality of life was not reported. We used the discontinuation due to adverse events as a surrogate for quality of life. Based on *a priori* rules as described previously, there was an increase in discontinuation in the intervention arm and thus quality of life was deemed to have very low certainty. Thus, the overall evidence for this PICO was deemed to be very low.

## Ramucirumab vs. no Ramucirumab

### Key Message

In patients with hepatocellular carcinoma who failed locoregional therapy, were ineligible for locoregional therapy, or have metastatic disease with preserved liver function and AFP >400 ng/mL, and have progressed on sorafenib, ramucirumab may lead to trivial to small improvement in overall survival (1.2 months), progression free survival, disease progression, and quality of life, and a likely increase in serious adverse events and treatment discontinuation due to adverse events (*low overall CoE*).

## Evidence Synthesis

The REACH trial assessed 283 patients who received ramucirumab (8 mg/kg every 2 weeks) versus 282 patients who received placebo.<sup>28</sup> All patients were CP A with ECOG 0 or 1 performance status and the majority were BCLC stage C (Appendix 5). Overall survival did not differ at a follow-up of up to 37 months with HR 0.87 (95% CI 0.72-1.05). HRQOL was not reported. SAE with ramucirumab occurred at a rate of 44% (122/277) compared with 32.2% in the placebo arm (89/276) (RR 1.37, 95 CI 1.10, 1.70). Treatment discontinuation rates due to adverse events were 18.4% with ramucirumab and 8.7% with placebo (RR 2.10, 95 CI 1.34, 3.34).

The REACH 2 trial assessed patients with similar characteristics, but with an AFP 400 ng/ml or higher with a follow up of up to 28 months.<sup>29</sup> Mortality occurred in 74.6% (147/197) in those with ramucirumab and 77.9% (74/95) in those with placebo (HR 0.71, 95% CI 0.53-0.95). Median overall survival was 8.5 in patients who received ramucirumab compared to 7.3 months on placebo. Progression-free survival and disease progression outcomes improved on ramucirumab with HR 0.45 (95% CI 0.34-0.60) and HR 0.43 (95% CI 0.31-0.58), respectively. HRQOL assessed with deterioration in FHSI-8 score showed the median time to deterioration to be 3.7 versus 2.8 months (HR 0.799, 95% CI 0.54-1.17). In patients that received ramucirumab versus placebo, SAE occurred in 34.5% (68/197) versus 29.5% (28/95) (RR 1.17 95% CI 0.81-1.69) and discontinuation due to adverse events occurred in 17.8% (35/197) versus 10.5% (10/95) (RR 1.69, 95% CI 0.87-3.26).

## Certainty of Evidence (CoE)

The overall certainty of evidence for patients with AFP <400 ng/mL across all outcomes was low due to risk of bias (transparency in randomization for additional CP A patients as the trial initially included CP B patient then excluded them, and blinding for post-protocol therapies), indirectness (progression-free survival and disease progression are surrogates for overall survival) and/or imprecision (confidence interval showing both benefit and harm or low number of events).

For outcomes for patients with AFP >400 ng/mL, low certainty was found for the outcomes of mortality, progression-free survival, disease progression, and HRQOL. Serious risk of bias (due to unclear blinding of post-protocol therapies, high attrition, and early stopping for benefit) and imprecision (due to low event rate or confidence interval crossing threshold for harm and benefit) was found. Additionally, indirectness for the outcomes of progression free survival and disease progression (indirect marker of survival) was noted. For harms, there was moderate certainty, rated down due to serious risk of imprecision (low event rate and confidence interval crossing threshold for no harm and harm). Overall, the certainty of evidence was deemed to be low for this PICO.

## Pembrolizumab vs. no Pembrolizumab

### Key Message

In patients with hepatocellular carcinoma who failed locoregional therapy, were ineligible for locoregional therapy, or have metastatic disease with preserved liver function and have

progressed on sorafenib, pembrolizumab may lead to a small increase in overall survival (3.3 months), progression-free survival, and disease progression, no difference in quality of life, and likely increase in serious adverse events and discontinuation due to adverse events (*low overall CoE*).

#### Evidence Synthesis

The KEYNOTE-240 trial assessed the use of pembrolizumab (200 mg IV every 3 weeks) versus placebo and included patients with primarily CP A, BCLC C and ECOG 0 or 1 performance status.<sup>30</sup> A minority of CP B7 patients were included (see supplemental table xx: characteristics of included studies). Patients with main portal vein invasion or inferior vena cava or cardiac involvement of HCC on the basis of imaging were excluded. For the outcome of mortality with a follow up of up to 30 months, the mortality rate of those treated with pembrolizumab was 64.7% (180/278) versus 74.8% (101/135) for those who received placebo (HR 0.78, 95% CI 0.61-0.99). Median overall survival was 13.9 versus 10.6 months, respectively (difference of 3.3 months). Progression-free survival and disease progression improved in patients who received pembrolizumab compared to placebo, HR 0.72 (95% CI 0.57-0.90) and HR 0.69 (95% CI 0.54-0.88), respectively. HRQOL and time to deterioration using EORTC QLQ-C30 and QLQ-HCC18 scores were reported to be similar (Appendix 5). SAE occurred in 37.3% (104/279) of those who received pembrolizumab versus 27.6% (37/134) (RR 1.35, 95% CI 0.99-1.85) in patients who received placebo. The discontinuation due to adverse event rate was 17.2% in the pembrolizumab arm and 9.0% in the placebo arm (RR 1.92, 95% CI 1.06-3.49)

#### Certainty of Evidence (CoE)

Overall, the certainty of evidence for this PICO was deemed to be low, driven by the outcomes of mortality and quality of life. There was serious risk of bias for mortality due to unclear blinding and selection for post-protocol therapies. In addition, there was imprecision due to the low event rate. For HRQOL, there was concern for missing data as the compliance rate for surveys was 90%, but the completion rate was about 68%. The missing data could lead to a different conclusion and thus we downgraded for risk of bias. Additionally, due to the small number of events and confidence interval including both improvement and worsening HRQOL, we rated down for imprecision. Progression-free survival and disease progression were downgraded for indirectness as they were indirect measures of survival. There was moderate certainty for the harm outcomes. We downgraded for serious imprecision due to low event rate and wide confidence interval.

#### Other Agents

We identified a phase 1/2 randomized clinical trial, CheckMate 040, that compared the use of nivolumab 1mg/kg + ipilimumab 3 mg/kg every 3 weeks for total 4 doses followed by nivolumab 240 mg every 2 weeks (arm A, n=50), nivolumab 1mg/kg + ipilimumab 1 mg/kg every 3 weeks for total 4 doses followed by nivolumab 240 mg every 3 weeks (arm B, n=49), or nivolumab 3 mg/kg every 2 week + ipilimumab 1 mg/kg every 6 weeks (arm C, n=49). Patients had to have HCC not eligible for surgical/locoregional therapies, were intolerant of or progressed on sorafenib, and had preserved liver function. The median overall survival in arm A was 22.8

months in arm A, 12.5 months in arm B, and 12.7 months in arm C. The survival rate at 12 months and 24 months were 61% and 48% for arm A, 56% and 30% for arm B, and 51% and 42% for arm C. Patients in arm A had a higher rate of immune-mediated adverse events leading to discontinuation of treatment (16%) compared to arm B (6%) and arm C (4%). The trial results did not inform any of the PICO questions as the trial did not compare any of the interventions to placebo, best supportive care, or previously established treatment.<sup>31</sup>

We could not identify any trials that assessed the use of atezolizumab/bevacizumab as a second-line treatment in patients who failed a tyrosine kinase inhibitor, or tyrosine kinase inhibitors or immunotherapeutic agents as second-line treatments after first-line treatment with atezolizumab/bevacizumab.

We identified a few network meta-analyses that aimed to provide quantitative comparative assessment of the different treatment agents. However, we did not include their findings in the technical review due to the overall very low to low certainty of the evidence in the trials that provided direct comparisons.<sup>32-38</sup>

## PICO 2

**In patients with hepatocellular carcinoma who failed locoregional therapy, were ineligible for locoregional therapy, or have metastatic disease with *poor* liver function, should systemic therapy be used?**

We identified only one trial that evaluated the role of systemic therapy in patients with advanced HCC with poor liver function. The trial used sorafenib as systemic therapy, and we could not identify any trial that evaluated other systemic therapies in this population. A priori, poor liver function was defined as Child B > 7 or CP C and BCLC C or D.

Sorafenib vs. no Sorafenib

### Key Message

In patients with HCC who failed locoregional therapy, were ineligible for locoregional therapy, or have metastatic disease, and have poor liver function, sorafenib may lead to a trivial improvement in overall survival (0.5 months) and progression-free survival (0.3 months), no improvement in quality of life, and no to trivial increased risk of SAEs (*very low overall CoE*).

### Evidence Synthesis

Ji et al. randomized patients with HCC who had CP B (75%) or C (25%) disease with an estimated life time of at least 2 months and ECOG no more than 2 to either sorafenib 400 mg twice daily (n= 95) or best supportive care (BSC, n= 94; Appendix 5). The median overall survival in the sorafenib group was 4.0 months compared to 3.5 months in the BSC group (HR 0.48, 95% CI 0.35-0.68). The median progression-free survival was 2.2 month in the sorafenib group compared to 1.9 months in the BSC group (HR 0.55, 95% CI 0.4-0.75). The authors reported evaluating HRQOL using the FHSI-8 questionnaire with no significant difference

between the two groups. Patients who received sorafenib had two SAEs compared to the BSC group who had none (RR 5.1, 95% 0.25-105.00).<sup>39</sup>

#### Certainty of Evidence (CoE)

The CoE for all the outcomes was very low, rated down for very serious risk of bias (unclear if allocation was concealed or not, and lack of blinding), and serious imprecision (due to the low event rate and small sample size).

### PICO 3

#### **In patients with HCC undergoing curative surgical resection, should systemic therapies be used?**

We could not identify any RCT that evaluated the role of concurrent or neoadjuvant systemic therapies in patients with HCC undergoing curative surgical resection. However, we identified one trial that assessed the role of adjuvant therapy after surgical resection.<sup>40</sup>

#### Adjuvant Therapy after Curative Surgical Resection

##### Sorafenib vs. no Sorafenib

##### Key Message

In patients with HCC undergoing curative surgical resection, sorafenib may lead to no or trivial improvement in overall survival (1 month), recurrence-free survival (3 months), and time-to-recurrence (3 months), but increased risk of adverse events leading to discontinuation of treatment (*low overall CoE*).

##### Evidence Synthesis

We identified one RCT, the STORM trial, that assessed the use of adjuvant sorafenib therapy in patients who had curative surgical resection (Appendix 5).<sup>40</sup> The trial included patients who underwent curative surgical resection or curative local ablation treatments who had confirmed complete radiological response with CP score 5 to 7 (patients with CP score 7 were only allowed if they had no ascites), ECOG PS 0, and AFP less than 400 ng/mL. All the patients had moderate to high risk of recurrence based on tumor characteristics. The patients were randomized within 6-12 weeks of treatment to receive sorafenib 400 mg twice daily (n= 558, including 450 patients who had surgical resection) versus a matching placebo (n= 556, including 450 patients who had surgical resection), and they were stratified according to curative treatment that they received (surgical resection or RFA). The median duration of treatment was 12.5 months in the sorafenib group and 22.2 months in the placebo group, and the patients were followed up for up to 4 years.

In patients who underwent surgical resection, the median recurrence-free survival was 41.7 months in patients who received sorafenib versus 38.7 month in patients who received placebo (HR 0.94, 95% CI 0.76-1.17). The median overall survival in patients who received

sorafenib was 23 months versus 22 months in patients who received placebo (HR 0.99, 95% CI 0.76-1.30), but no separate results were reported for patients who underwent surgical resection. The median time to recurrence was 38.5 months in the sorafenib group versus 35.8 months in the placebo group (HR 0.89, 95% CI 0.73-1.08). More patients in the sorafenib group (24.1%) had adverse events that led to discontinuation of treatment compared to patients in the placebo group (7.4%; RR 3.2, 95% CI 2.3-4.5). The number of SAE was comparable in the sorafenib and placebo groups (40.7% vs. 41.2%; RR 0.99, 95% CI 0.86-1.14).

#### Certainty of Evidence (CoE)

The CoE for mortality and disease recurrence outcomes was low, rated down for serious indirectness (as they were reported for patients who had surgical resection and RFA together with unknown differential effect) and imprecision (the CI wide including both appreciable benefits and harms). The CoE for recurrence-free survival, SAE, and adverse events leading to discontinuation of treatment was moderate, rated down for serious imprecision (wide CI including both appreciable benefits and harms).

## PICO 4

**In patients with HCC undergoing liver transplantation, should systemic therapies be used?**

#### Sorafenib vs. no Sorafenib

We identified two studies that evaluated the role of sorafenib treatment in patients awaiting liver transplantation (Appendix 5).<sup>41, 42</sup> Both trials were very small in size leading to very serious imprecision, included different patient populations leading to serious heterogeneity, with serious risk of bias leading to very low CoE. Additionally, the trials did not report the outcomes that we predetermined as critical for decision making which made it difficult to reach a conclusion about the benefits/harms ratio. We summarize both studies here. Kulik et al. randomized patients with HCC who are candidates for liver transplantation to concurrent sorafenib and TARE using  $\beta$ -emitting yttrium-90 (n=11) versus TARE alone (n=12). The overall survival at 3 years was comparable in both groups (72% in the group that received concurrent sorafenib/TARE vs. 70% in the group that received TARE alone). In the patients who ended up undergoing liver transplantation, the study showed increased risk of post-transplant biliary complications in the concurrent treatment group compared to the TARE alone group (4 out of 8 vs 0 out of 9).<sup>41</sup> The HeiLivCa trial randomized patients with HCC suitable for liver transplantation who are undergoing TACE treatment to sorafenib (n=24) versus placebo (n=26). The study reported minimal to no difference in progression-free survival (HR 1.26, 95% CI 0.48-3.27) or SAE (RR 1.08, 95% CI 0.24-4.86), but increased risk of discontinuation due to adverse events (RR 6.5, 95% CI 0.84-50.14).<sup>42</sup>

## PICO 5

### **In patients with HCC undergoing locoregional therapy, should systemic therapies be used?**

We identified two studies that evaluated the role of sorafenib as adjuvant treatment after curative local ablation (including RFA), and seven studies that evaluated either sorafenib or bevacizumab as concurrent treatments in patients with HCC undergoing TACE treatment (Appendix 5).

#### Adjuvant Therapy after Curative Local Ablation

##### Sorafenib vs. no Sorafenib

##### Key Message

In patients with HCC undergoing curative local ablation, sorafenib may lead to no or trivial improvement in overall survival (1 month), recurrence-free survival (1.5 months less), and time-to-recurrence (3 months), but increased risk of adverse events leading to discontinuation of treatment (*low overall CoE*).

##### Evidence Synthesis

The STORM trial, summarized above under PICO 3, assessed the use of adjuvant sorafenib therapy in patients who had curative local ablation (using RFA or percutaneous ethanol injection) in addition to patients who underwent surgical resection.<sup>40</sup> The patients were randomized to receive sorafenib 400 mg twice daily (n= 558, including 108 patients who had local ablation) versus a matching placebo (n= 556, including 106 patients who had local ablation), and were followed up for up to 4 years.

In patients who underwent curative local ablation, the median recurrence-free survival was 19.6 months in patients who received sorafenib versus 22.1 months in patients who received placebo (HR 0.97, 95% CI 0.66-1.43). The remaining outcomes were reported for all the patients with trivial to no difference in overall survival (HR 0.99, 95% CI 0.76-1.30), time-to-recurrence (HR 0.89, 95% CI 0.73-1.08), and SAE (RR 0.99, 95% CI 0.86-1.14), but increased risk of adverse events leading to discontinuation of treatment (RR 3.2, 95% CI 2.3-4.5) in the sorafenib group compared to the placebo group.

A second study by Kan et al randomized patients undergoing curative RFA to sorafenib (n=30) versus no sorafenib (n=32). The study did not report any of the outcomes that we predetermined as critical for decision making, thus it did not contribute to the evidence synthesis.<sup>43</sup>

##### Certainty of Evidence (CoE)

As outlined under PICO 3, the CoE for the mortality and disease recurrence outcomes was low (rated down for serious indirectness and imprecision), and moderate for recurrence-free survival, SAE, and adverse events leading to discontinuation of treatment (rated down for serious imprecision).

## Concurrent Therapy with TACE

### Sorafenib vs. no Sorafenib

#### Key Message

In patients with HCC receiving TACE treatment, sorafenib may lead to no or trivial improvement in overall survival, progression-free survival, and time to progression, worsening of some HRQOL scales, and increased risk of SAE and adverse events leading to discontinuation of treatment (*very low overall CoE*).

#### Evidence Synthesis

We identified five trials that assessed the role of concurrent sorafenib therapy in patients receiving TACE treatments. The first trial, Kudo et al, randomized patients who had sustained response 1-3 months after TACE treatments to sorafenib (n= 229) or placebo (n=229).<sup>44</sup> There was trivial to no difference in overall mortality (HR 1.06, 95% CI 0.69-1.64) and time-to-progression (HR 0.87, 95% CI 0.70-1.09) with increased risk of SAE (RR 2.08, 95% CI 1.28-3.38) and adverse events leading to discontinuation of treatment (RR 7.09, 95% CI 4.09-12.30). Three of the trials included patients with CP score A who had no locally invasive disease and had measurable lesions on imaging studies, then randomized them to concurrent TACE and sorafenib treatment versus TACE alone or with placebo.<sup>45-48</sup> The HeiLivCa trial also informed this PICO question as it randomized patients awaiting liver transplantation and receiving TACE treatment to sorafenib versus placebo.<sup>42</sup> This trial did not report survival data and included patients listed awaiting liver transplantation specifically so it did not contribute to the outcomes of survival, disease progression, or HRQOL.

The trials showed no to trivial improvement in overall survival (pooled HR 0.89, 95% CI 0.73-1.09;  $I^2= 0\%$ ). Also, they showed no to trivial improvement in progression-free survival and time-to progression, however we are unable to provide a pooled estimate of the effect as they used different definitions for progression including untreatable progression, progression based on mRECIST, and progression based on RECIST version 1.1. There was a small increase in SAE (RR 1.30, 95% CI 1.16-1.69;  $I^2= 0\%$ ) and adverse events leading to discontinuation of treatment (RR 1.67, 95% CI 1.18-.2.36;  $I^2= 0\%$ ). The TACE-2 trial assessed changes in HRQOL using 3 different scales: the EORTC QLQ-C30, EORTC QLQ-HCC18, and the EuroQOL (EQ-5D) questionnaire at baseline, before TACE, week 10, and then every 6 weeks until disease progression. The trial reported worsening in some of the scales in patients receiving sorafenib compared to placebo, specifically the social and role functioning scales, diarrhea, appetite loss, and nutritional problems scores, but no difference was observed in the other HRQOL scales.<sup>46</sup>

#### Certainty of Evidence (CoE)

The CoE for improvement in mortality was low, rated down for serious risk of bias (lack of blinding and allocation concealment in some of the studies, and unclear contribution of post-protocol treatments to overall survival) and serious imprecision (the 95% CI included potential increase and decrease in mortality). The CoE for progression-free survival and time-to-progression were very low and low, rated down for serious risk of bias, indirectness (both outcomes are surrogates for overall survival), and/or serious imprecision (95% CI included

potential improvement and worsening of progression-free survival). The CoE for HRQOL was low after rating down for serious risk of bias (due to concerns about attrition bias) and imprecision (due to small sample size). The CoE for SAE and adverse events leading to discontinuation of treatment was moderate, rated down for serious risk of bias (unclear allocation concealment in some of the trials).

## Bevacizumab vs. no Bevacizumab

### Key Message

In patients with HCC receiving TACE treatment, bevacizumab may lead to worsening of overall survival and progression-free survival, no to trivial improvement in disease progression, and possible increased risk of SAE and adverse events leading to discontinuation of treatment (*very low overall CoE*).

### Evidence Synthesis

We identified two trials that evaluated the role of concurrent bevacizumab and TACE treatment versus TACE alone in patients with HCC who are not amenable to curative surgical or ablative therapy.<sup>49, 50</sup> Both trials included patients with no extrahepatic disease, and the majority of the patients had CP A disease. Britten et al. randomized patients receiving TACE treatment to either bevacizumab (n= 15) or observation (n= 15). All the patients who underwent observation only had CP A disease, while 13% of patients who received bevacizumab had CP B. They did not exclude patients awaiting liver transplantation as long as they had a Model for End-Stage Liver Disease (MELD) score less than 28, however they excluded patients with portal vein thrombosis. Patients who received bevacizumab had a median overall survival of 61 months compared to 49 months in patients who underwent observation only, with better progression-free survival at 16 weeks (RR 4.0, 95% CI 1.4-11.3). However, patients who received bevacizumab had more SAEs (RR 5.0, 95% CI 0.66-37.85) and adverse events leading to discontinuation of treatment (RR 3.0, 95% CI 0.1-68.3).<sup>49</sup> In the AVATACE trial, Pinter et al. randomized patients receiving TACE to bevacizumab (n= 16) or placebo (n= 16), and 31% of the patients had CP B disease. They included both treatment naive patients and patients with recurrent disease after resection or ablation. All the patients underwent upper endoscopy with variceal band ligation if they were found to have large varices. In the AVATACE trial, patients who received bevacizumab had a median overall survival of 5.3 months compared to 13.7 month in patients who had placebo (mortality HR 1.7, 95% CI 0.8-3.6). After 12 months of randomization, there were a total of 11 deaths in the bevacizumab group and 7 deaths in the placebo group. The trial was terminated prematurely due to safety reasons as severe septic (sepsis, abdominal abscesses, cholangitis) and vascular (myocardial infarction, arterial and venous thrombosis, and aneurysms) events occurred mostly in patients receiving bevacizumab. The median time-to-progression was 7.2 months in the bevacizumab group compared to 11.7 months in the placebo group.<sup>50</sup>

### Certainty of Evidence (CoE)

The CoE for the mortality (overall survival) outcome was very low, rated down for serious risk of bias (unclear allocation was concealed or not), inconsistency (the two trials showed

contradicting findings), and serious imprecision (due to the small number of patients enrolled in both trials). The CoE for the outcomes of progression-free survival, disease progression, adverse event leading to discontinuation of treatment, and SAE was very low, rated down for serious risk of bias and very serious imprecision.

## Discussion

### Summary

We identified 20 RCTs that evaluated the role of systemic therapies in patients with HCC. The majority of the trials (N=9) were conducted in patients with hepatocellular carcinoma who failed/were ineligible for locoregional therapy or had metastatic disease with preserved liver function. The initial milestone trials were the SHARP and ASIA-PACIFIC trials which showed that sorafenib as first-line treatment improved survival by 2.3 to 2.8 months compared to placebo.<sup>4, 5</sup> A decade later, the REFLECT trial showed that lenvatinib improved survival by 1.3 months over sorafenib, then the IMbrave150 trial showed that atezolizumab-bevacizumab improved overall survival by 5.8 months over sorafenib.<sup>21-23</sup> As for second-line treatments, 5 trials evaluated the role of different systemic therapies as compared to placebo in patients who failed sorafenib treatment and showed variable improvement in median overall survival: regorafenib (2.8 months), cabozantinib (2.2 months), ramucirumab (1.2 months in patients with AFP > 400), and pembrolizumab (3.3 months).<sup>25-30</sup> None of the first or second-line treatments led to improvement in quality of life, and all of them were associated with an increased risk of adverse events at different magnitudes. The overall certainty of evidence ranged between very low and low. The use of sorafenib as a first-line treatment in patients with poor liver function was assessed in one trial which showed that sorafenib led to an increase in median overall survival by 0.5 months with a comparable safety profile but very low certainty of evidence.<sup>39</sup>

Other trials evaluated the role of sorafenib as adjuvant therapy after curative surgery (1 RCT) or RFA (2 RCTs), or concurrent therapy with TACE (5 RCTs) with no to minimal improvement in overall survival (very low to low overall certainty of evidence).<sup>40, 42-48</sup> Two trials evaluated the role of bevacizumab as concurrent therapy with TACE with possible increase in mortality compared to placebo (very low certainty of evidence)<sup>49, 50</sup>, and two trials evaluated the role of sorafenib in patients with HCC awaiting liver transplantation with no survival benefit.<sup>41, 42</sup>

### Knowledge Gaps and Future Directions

The technical review team identified few knowledge gaps and limitations in the evidence that could inform clinical practice and future guidelines:

- The majority of the trials continued treatment until disease progression based on imaging studies or the development of serious adverse events. The effect of post-protocol treatments, treatments received after the discontinuation of the trial interventions, was not considered in the design of any of the trials, and only few trials performed post-hoc adjustments to account for those effects. Post-protocol treatments are administered after the trial treatment allocation is revealed, which may influence the

decision regarding post-treatments and lead to differences in overall survival. One possible solution for this issue would be to include the second-line treatments *a priori* in the study design and preserve the allocation concealment during the follow-up period even after disease progression. This will also allow for the evaluation of different sequences of treatments, for example, all the trials of second line treatment were in patients who failed sorafenib and none of the available RCTs evaluated the role of any of the treatments after atezolizumab + bevacizumab failure, making it a knowledge gap.

- The majority of the trials assessed changes in quality of life, however only few of them reported detailed results on quality of life which we consider a patient-important outcome that was critical for decision making. Reporting detailed quality of life assessment and the thresholds that were used to define minimally important clinical difference would allow
- Few of the studies did not blind outcome assessors although progression was a condition for discontinuation of treatment, and the lack of blinding could have affected the decision to discontinue treatment. Similarly, some of the trials did not blind patients to the intervention which may affect subjective outcomes such as quality of life.

## Limitations

This technical review had some limitations that we will outline. First, in the evidence profiles that we present in the Appendix, we included information on resource use. This document is not a coverage document and the reported cost data estimates were reported for transparency. We presented a list of studies that assessed cost effectiveness of different interventions in Appendix 4. Second, our inclusion criteria was limited to randomized controlled trials and we did not include observational studies that compared any of the included interventions. Some of those observational studies may inform clinicians in scenarios not covered in this document. Third, although we identified a few network meta-analyses that attempted to provide quantitative indirect comparison between the different systemic therapies, we did not perform or utilize network meta-analysis methods in this technical review due to their indirect nature and the limited number of trials that utilized FDA-approved therapies. Third, there are numerous RCTs that are being conducted and we anticipate this document to require an update in 2 years.

# Figures

Figure1. Flow Diagram

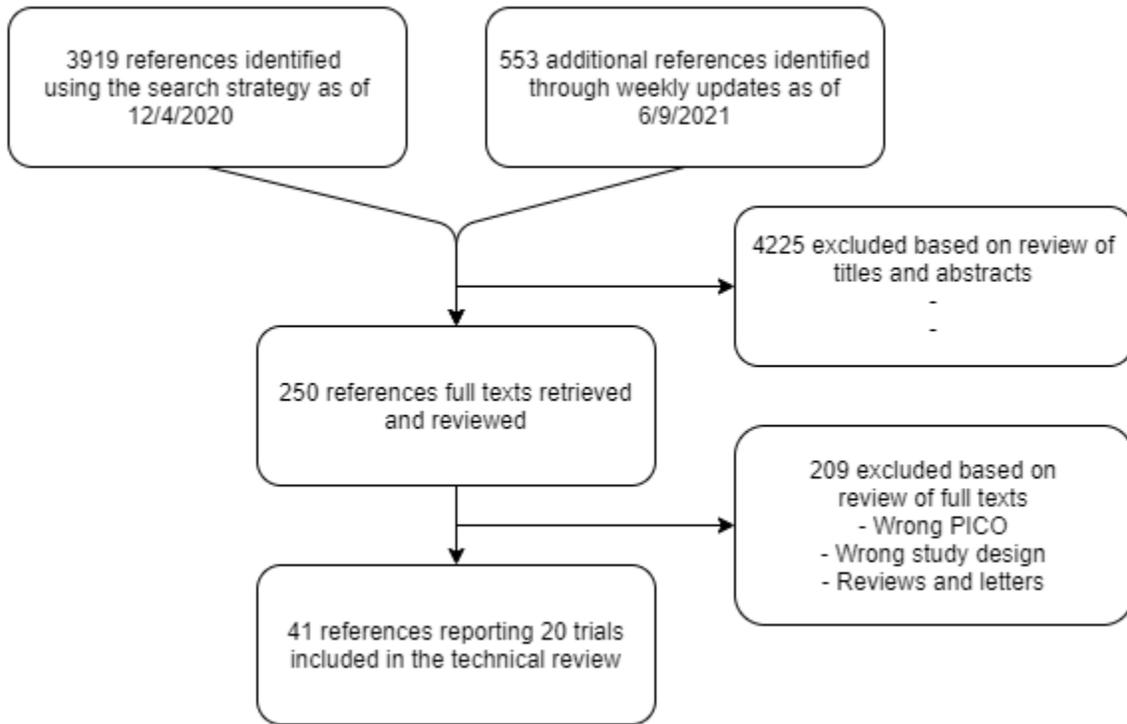


Figure 2a. Sorafenib as first line treatment in patients with hepatocellular carcinoma who failed locoregional therapy, were ineligible for locoregional therapy, or have metastatic disease with preserved liver function: Overall mortality

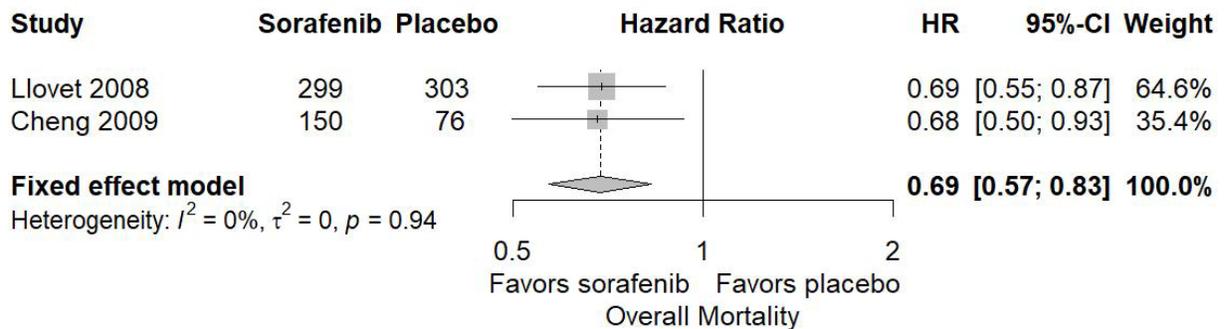


Figure 2b. Sorafenib as first line treatment in patients with hepatocellular carcinoma who failed locoregional therapy, were ineligible for locoregional therapy, or have metastatic disease with preserved liver function: Disease progression

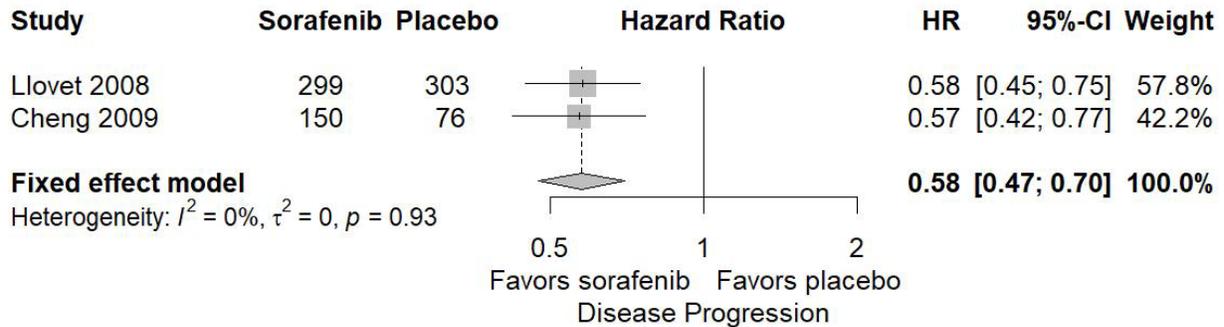


Figure 2c. Sorafenib as first line treatment in patients with hepatocellular carcinoma who failed locoregional therapy, were ineligible for locoregional therapy, or have metastatic disease with preserved liver function: Serious adverse events

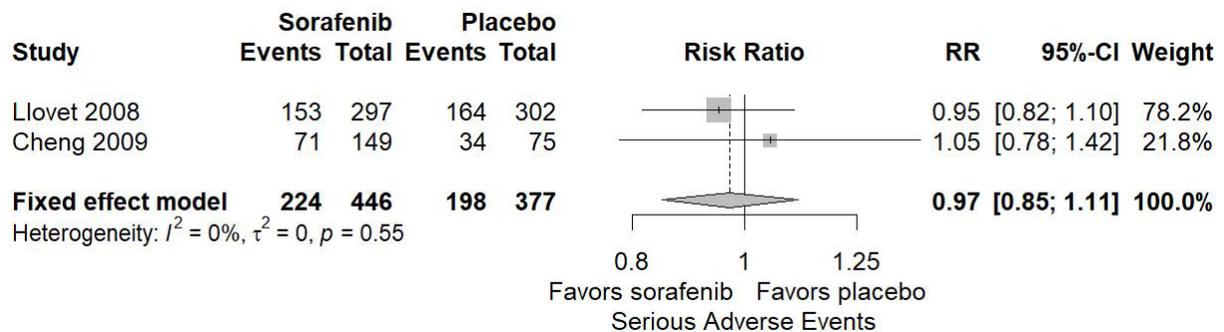


Figure 2d. Sorafenib as first line treatment in patients with hepatocellular carcinoma who failed locoregional therapy, were ineligible for locoregional therapy, or have metastatic disease with preserved liver function: Treatment discontinuation due to adverse events

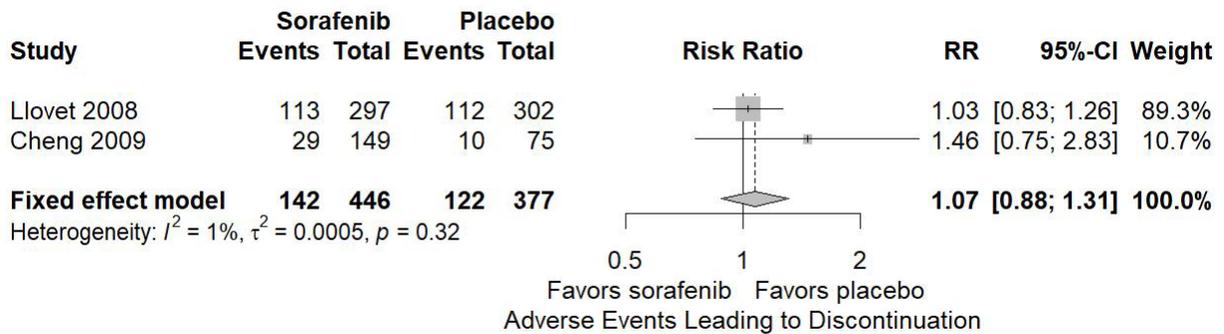


Figure 3a. Sorafenib as adjuvant/concurrent therapy in patients with hepatocellular carcinoma receiving TACE locoregional therapy: Overall survival

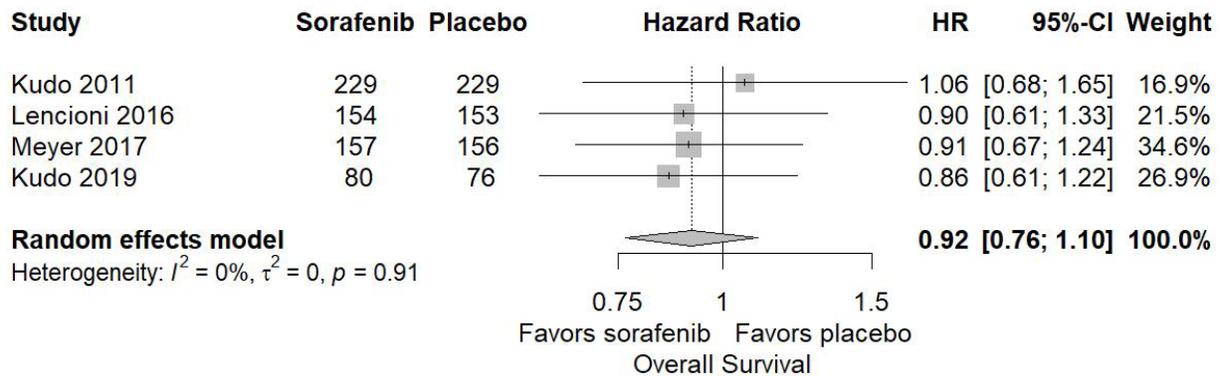


Figure 3b. Sorafenib as adjuvant/concurrent therapy in patients with hepatocellular carcinoma receiving TACE locoregional therapy: Serious adverse events.

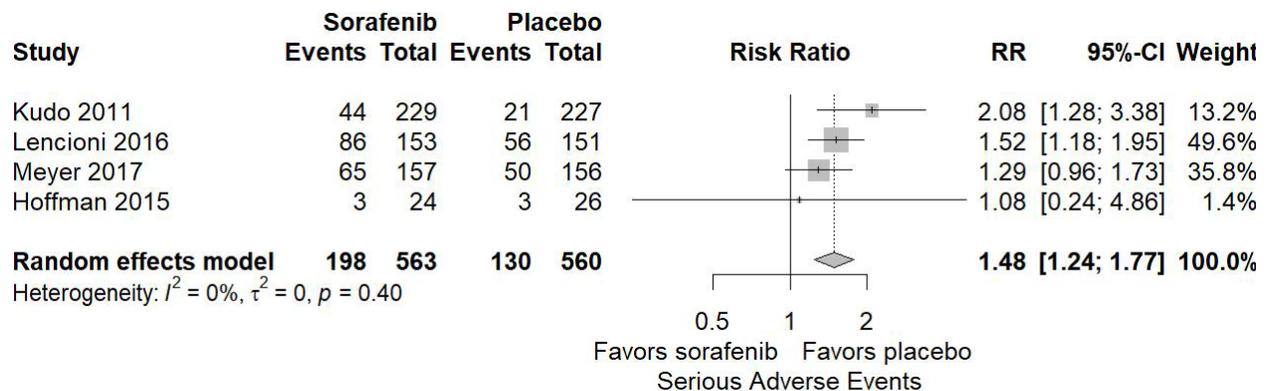


Figure 3c. Sorafenib as adjuvant/concurrent therapy in patients with hepatocellular carcinoma receiving TACE locoregional therapy: Treatment discontinuation due to adverse events.

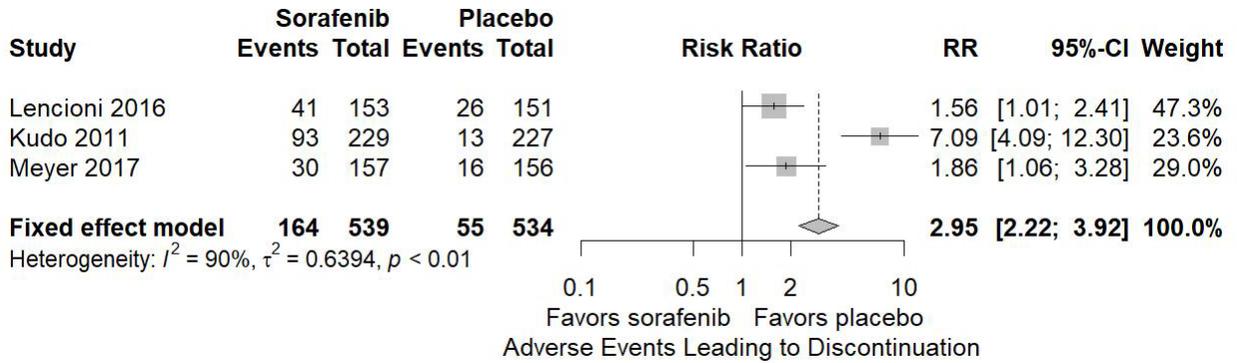
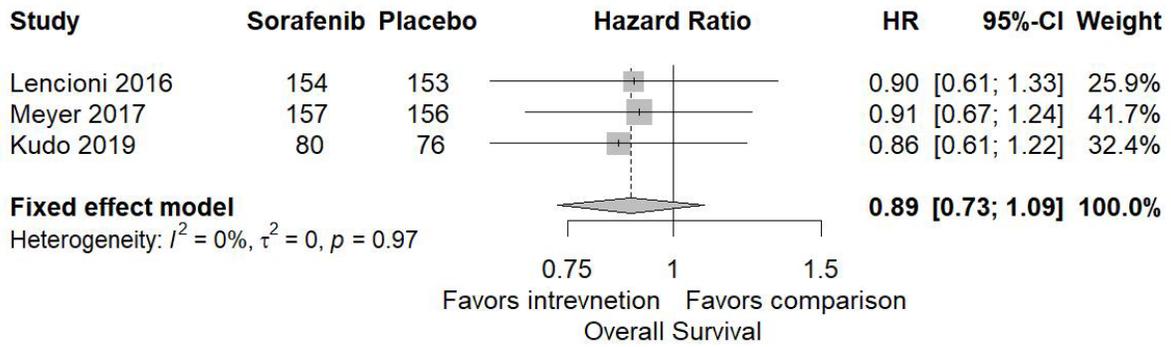


Figure 3d. Sorafenib as adjuvant therapy in patients with hepatocellular



carcinoma receiving TACE locoregional therapy: Overall survival

## References

1. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin* 2021;71:209-249.
2. American Cancer Society. Cancer Statistics Center. <http://cancerstatisticscenter.cancer.org>. Accessed: August 8, 2021.
3. Llovet JM, Bru C, Bruix J. Prognosis of hepatocellular carcinoma: the BCLC staging classification. *Semin Liver Dis* 1999;19:329-38.
4. Llovet JM, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med* 2008;359:378-90.
5. Cheng AL, Kang YK, Chen Z, et al. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. *Lancet Oncol* 2009;10:25-34.
6. National Cancer Institute. Drugs Approved for Liver Cancer. <https://www.cancer.gov/about-cancer/treatment/drugs/liver> Accessed: December 20, 2021.
7. Guyatt GH, Oxman AD, Schunemann HJ, et al. GRADE guidelines: a new series of articles in the Journal of Clinical Epidemiology. *J Clin Epidemiol* 2011;64:380-2.
8. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71.
9. Ouzzani M, Hammady H, Fedorowicz Z, et al. Rayyan-a web and mobile app for systematic reviews. *Syst Rev* 2016;5:210.
10. U.S. Food & Drug Administration. What is a Serious Adverse Event? <https://www.fda.gov/safety/reporting-serious-problems-fda/what-serious-adverse-event> Accessed September 28, 2021.
11. Lin E, Tong T, Chen Y, et al. Fixed-effects model: the most convincing model for meta-analysis with few studies. arXiv preprint arXiv:2002.04211 2020.
12. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;7:177-88.
13. Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. *BMJ* 2003;327:557-60.
14. Ioannidis JP, Trikalinos TA. The appropriateness of asymmetry tests for publication bias in meta-analyses: a large survey. *CMAJ* 2007;176:1091-6.
15. R Core Team. R: A Language and Environment for Statistical Computing. Vienna, Austria: R Foundation for Statistical Computing, 2021.
16. Balduzzi S, Rucker G, Schwarzer G. How to perform a meta-analysis with R: a practical tutorial. *Evid Based Ment Health* 2019;22:153-160.
17. Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;343:d5928.

18. MEDLINE®/PubMed® Health Disparities and Minority Health Search Strategy.  
[https://www.nlm.nih.gov/services/queries/health\\_disparities\\_details.html](https://www.nlm.nih.gov/services/queries/health_disparities_details.html)  
Accessed: June 1, 2021.
19. General drug information. UpToDate. Accessed: June 4, 2021.
20. Gyawali B, Shimokata T, Ando M, et al. Risk of serious adverse events and fatal adverse events with sorafenib in patients with solid cancer: a meta-analysis of phase 3 randomized controlled trials. *Ann Oncol* 2017;28:246-253.
21. Kudo M, Finn RS, Qin S, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. *Lancet* 2018;391:1163-1173.
22. Finn RS, Qin S, Ikeda M, et al. Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma. *N Engl J Med* 2020;382:1894-1905.
23. Finn RS, Qin S, Ikeda M, et al. IMbrave150: Updated overall survival (OS) data from a global, randomized, open-label phase III study of atezolizumab (atezo) + bevacizumab (bev) versus sorafenib (sor) in patients (pts) with unresectable hepatocellular carcinoma (HCC). *Journal of Clinical Oncology* 2021;39:267-267.
24. Yau T, Park JW, Finn RS, et al. CheckMate 459: A randomized, multi-center phase III study of nivolumab (NIVO) vs sorafenib (SOR) as first-line (1L) treatment in patients (pts) with advanced hepatocellular carcinoma (aHCC). *Annals of Oncology* 2019;30:v874-v875.
25. Bruix J, Qin S, Merle P, et al. Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* 2017;389:56-66.
26. Bruix J, Merle P, Granito A, et al. Updated overall survival (OS) analysis from the international, phase 3, randomized, placebo-controlled RESORCE trial of regorafenib for patients with hepatocellular carcinoma (HCC) who progressed on sorafenib treatment. *Annals of Oncology* 2017;28:iii140.
27. Abou-Alfa GK, Meyer T, Cheng AL, et al. Cabozantinib in Patients with Advanced and Progressing Hepatocellular Carcinoma. *N Engl J Med* 2018;379:54-63.
28. Zhu AX, Park JO, Ryou BY, et al. Ramucirumab versus placebo as second-line treatment in patients with advanced hepatocellular carcinoma following first-line therapy with sorafenib (REACH): a randomised, double-blind, multicentre, phase 3 trial. *Lancet Oncol* 2015;16:859-70.
29. Zhu AX, Kang YK, Yen CJ, et al. Ramucirumab after sorafenib in patients with advanced hepatocellular carcinoma and increased alpha-fetoprotein

- concentrations (REACH-2): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol* 2019;20:282-296.
30. Finn RS, Ryoo BY, Merle P, et al. Pembrolizumab As Second-Line Therapy in Patients With Advanced Hepatocellular Carcinoma in KEYNOTE-240: A Randomized, Double-Blind, Phase III Trial. *J Clin Oncol* 2020;38:193-202.
  31. Yau T, Kang YK, Kim TY, et al. Efficacy and Safety of Nivolumab Plus Ipilimumab in Patients With Advanced Hepatocellular Carcinoma Previously Treated With Sorafenib: The CheckMate 040 Randomized Clinical Trial. *JAMA Oncol* 2020;6:e204564.
  32. Vogel A, Rimassa L, Sun HC, et al. Comparative Efficacy of Atezolizumab plus Bevacizumab and Other Treatment Options for Patients with Unresectable Hepatocellular Carcinoma: A Network Meta-Analysis. *Liver Cancer* 2021;10:240-248.
  33. Solimando AG, Susca N, Argentiero A, et al. Second-line treatments for Advanced Hepatocellular Carcinoma: A Systematic Review and Bayesian Network Meta-analysis. *Clin Exp Med* 2021.
  34. Han Y, Zhi WH, Xu F, et al. Selection of first-line systemic therapies for advanced hepatocellular carcinoma: A network meta-analysis of randomized controlled trials. *World J Gastroenterol* 2021;27:2415-2433.
  35. Oranratnachai S, Rattanasiri S, Pooprasert A, et al. Efficacy of First Line Systemic Chemotherapy and Multikinase Inhibitors in Advanced Hepatocellular Carcinoma: A Systematic Review and Network Meta-Analysis. *Front Oncol* 2021;11:654020.
  36. Park R, Lopes da Silva L, Nissaisorakarn V, et al. Comparison of Efficacy of Systemic Therapies in Advanced Hepatocellular Carcinoma: Updated Systematic Review and Frequentist Network Meta-Analysis of Randomized Controlled Trials. *J Hepatocell Carcinoma* 2021;8:145-154.
  37. Delos Santos S, Udayakumar S, Nguyen A, et al. A systematic review and network meta-analysis of second-line therapy in hepatocellular carcinoma. *Curr Oncol* 2020;27:300-306.
  38. Sonbol MB, Riaz IB, Naqvi SAA, et al. Systemic Therapy and Sequencing Options in Advanced Hepatocellular Carcinoma: A Systematic Review and Network Meta-analysis. *JAMA Oncol* 2020;6:e204930.
  39. Ji YX, Zhang ZF, Lan KT, et al. Sorafenib in liver function impaired advanced hepatocellular carcinoma. *Chin Med Sci J* 2014;29:7-14.
  40. Bruix J, Takayama T, Mazzaferro V, et al. Adjuvant sorafenib for hepatocellular carcinoma after resection or ablation (STORM): a phase 3, randomised, double-blind, placebo-controlled trial. *Lancet Oncol* 2015;16:1344-54.
  41. Kulik L, Vouche M, Koppe S, et al. Prospective randomized pilot study of Y90+/-sorafenib as bridge to transplantation in hepatocellular carcinoma. *J Hepatol* 2014;61:309-17.

42. Hoffmann K, Ganten T, Gotthardt D, et al. Impact of neo-adjuvant Sorafenib treatment on liver transplantation in HCC patients - a prospective, randomized, double-blind, phase III trial. *BMC Cancer* 2015;15:392.
43. Kan X, Jing Y, Wan QY, et al. Sorafenib combined with percutaneous radiofrequency ablation for the treatment of medium-sized hepatocellular carcinoma. *Eur Rev Med Pharmacol Sci* 2015;19:247-55.
44. Kudo M, Imanaka K, Chida N, et al. Phase III study of sorafenib after transarterial chemoembolisation in Japanese and Korean patients with unresectable hepatocellular carcinoma. *Eur J Cancer* 2011;47:2117-27.
45. Kudo M, Ueshima K, Ikeda M, et al. Randomised, multicentre prospective trial of transarterial chemoembolisation (TACE) plus sorafenib as compared with TACE alone in patients with hepatocellular carcinoma: TACTICS trial. *Gut* 2020;69:1492-1501.
46. Meyer T, Fox R, Ma YT, et al. Sorafenib in combination with transarterial chemoembolisation in patients with unresectable hepatocellular carcinoma (TACE 2): a randomised placebo-controlled, double-blind, phase 3 trial. *Lancet Gastroenterol Hepatol* 2017;2:565-575.
47. Lencioni R, Llovet JM, Han G, et al. Sorafenib or placebo plus TACE with doxorubicin-eluting beads for intermediate stage HCC: The SPACE trial. *J Hepatol* 2016;64:1090-1098.
48. Kudo M, Ueshima K, Ikeda M, et al. TACTICS: Final overall survival (OS) data from a randomized, open label, multicenter, phase II trial of transcatheter arterial chemoembolization (TACE) therapy in combination with sorafenib as compared with TACE alone in patients (pts) with hepatocellular carcinoma (HCC). *Journal of Clinical Oncology* 2021;39:270-270.
49. Britten CD, Gomes AS, Wainberg ZA, et al. Transarterial chemoembolization plus or minus intravenous bevacizumab in the treatment of hepatocellular cancer: a pilot study. *BMC Cancer* 2012;12:16.
50. Pinter M, Ulbrich G, Sieghart W, et al. Hepatocellular Carcinoma: A Phase II Randomized Controlled Double-Blind Trial of Transarterial Chemoembolization in Combination with Biweekly Intravenous Administration of Bevacizumab or a Placebo. *Radiology* 2015;277:903-12.

## Appendix

### Appendix 1: PICO Question

Informal Question	PICO Question				Study design
	Population	Intervention	Comparator	Outcome	
1: In patients with HCC who failed LRT, are not eligible for LRT, or have metastatic disease with preserved liver function, what systemic therapy should be used?	Patients with HCC who failed/ineligible for LRT or have metastatic disease with preserved liver function (noncirrhotic, Child A, Child B $\leq$ 7)	<ul style="list-style-type: none"> <li>- sorafenib</li> <li>- lenvatinib</li> <li>- nivolumab</li> <li>- nivolumab/ ipilimumab</li> <li>- pembrolizumab</li> <li>- regorafenib</li> <li>- cabozantinib</li> <li>- ramucirumab</li> <li>- bevacizumab/ atezolizumab</li> <li>- tremmalimumab/ durvalumab</li> </ul>	<ul style="list-style-type: none"> <li>- none</li> <li>- best supportive care</li> <li>- placebo</li> <li>- sorafenib</li> <li>- lenvatinib</li> <li>- nivolumab</li> <li>- nivolumab/ ipilimumab</li> <li>- pembrolizumab</li> <li>- regorafenib</li> <li>- cabozantinib</li> <li>- ramucirumab</li> <li>- bevacizumab/ atezolizumab</li> <li>- tremmalimumab/ durvalumab</li> </ul>	<ul style="list-style-type: none"> <li>- Overall mortality</li> <li>- HCC-related mortality</li> <li>- Health-related quality of life</li> <li>- Disease progression (or recurrence)</li> <li>- Progression (or recurrence) free survival</li> <li>- Harms</li> <li>- Resource use</li> </ul>	Randomized controlled trials, or systematic reviews of randomized controlled trials
2: In patients with HCC with poor liver function who are not liver transplant candidates, should systemic therapies be used?	Patients with HCC who failed/ineligible for LRT or have metastatic disease with poor liver function (Child C, Child B $>$ 7)				
3: Should we use systemic therapies in patients with resectable HCC?	Patients with resectable HCC	Settings:			
4: In patients with HCC who are candidates for liver transplant, should systemic therapies be used?	Patients with HCC who are candidates for liver transplant	<ul style="list-style-type: none"> <li>- 1st or 2nd line</li> <li>- Alone or combination</li> <li>- Adjuvant, neoadjuvant, or concurrent</li> </ul>			
5: In patients with liver-confined HCC undergoing locoregional	Patient with liver-confined HCC undergoing				

therapy, should systemic therapies be used?	locoregional therapy (LRT)				
---	----------------------------	--	--	--	--

DRAFT

## Appendix 2: Search strategy

### I. Pubmed: Date 12/4/2020

Set #	Search Strategy	Results
1	"carcinoma, hepatocellular"[Mesh]	86,239
2	"hepatocellular cancer*" [tiab] OR "hepatocellular carcinoma*" [tiab] OR "hepatocellular neoplasm*" [tiab] OR hepatoma [tiab] OR "liver cell carcinoma*" [tiab] OR "liver cell cancer*" [tiab] OR "liver cell neoplasm*" [tiab] OR "hepatic cell cancer*" [tiab] OR "hepatic cell carcinoma*" [tiab] OR "hepatic cell neoplasm*" [tiab] OR (("hepatic cell" OR hepatocellular [tiab] OR "liver cell" [tiab]) AND (cancer* [tiab] OR carcinoma* [tiab] OR neoplasm* [tiab]))	123,034
3	1 OR 2	139,509
4	"bevacizumab"[Mesh] OR "ipilimumab"[Mesh] OR "nivolumab"[Mesh] OR "sorafenib"[Mesh]	20,464
5	"atezolizumab"[Supplementary Concept] OR "cabozantinib"[Supplementary Concept] OR "durvalumab"[Supplementary Concept] OR "lenvatinib"[Supplementary Concept] OR "pembrolizumab"[Supplementary Concept] OR "pemigatinib"[Supplementary Concept] OR "ramucirumab"[Supplementary Concept] OR "regorafenib"[Supplementary Concept] OR "tremelimumab"[Supplementary Concept]	4,089
6	"atezolizumab"[tiab] OR "bevacizumab"[tiab] OR "cabozantinib"[tiab] OR "durvalumab"[tiab] OR "ipilimumab"[tiab] OR "lenvatinib"[tiab] OR "nivolumab"[tiab] OR "pembrolizumab"[tiab] OR "pemigatinib"[tiab] OR "ramucirumab"[tiab] OR "regorafenib"[tiab] OR "sorafenib"[tiab] OR "tremelimumab"[tiab]	36,043
7	OR/4-7	39,985
8	3 AND 8	4,854
9	English[lang]	27,103,172

10	9 AND 10	4,650
11	"animals"[MeSH] NOT "humans"[MeSH]	4,762,683
12	10 NOT 11	4,571
13	"randomized controlled trial"[pt] OR "controlled clinical trial"[pt] OR "randomized"[tiab] OR "placebo"[tiab] OR "drug therapy"[Subheading] OR "randomly"[tiab] OR "trial"[tiab] OR "groups"[tiab]	4,924,288
14	12 AND 13	2,612

II. EMBASE: Date 12/4/2020

Set #	Search Strategy	Results
1	carcinoma, hepatic cell/exp OR 'carcinoma, hepatocellular'/exp OR 'carcinoma, liver'/exp OR 'carcinoma, liver cell'/exp OR 'hepatic carcinoma'/exp OR 'hepatic cell carcinoma'/exp OR 'hepatocarcinoma'/exp OR 'hepatocellular carcinoma'/exp OR 'hepatocellular carcinoma cell line'/exp OR 'hepatoma'/exp OR 'liver carcinoma'/exp OR 'liver carcinoma rupture'/exp OR 'liver cell carcinoma'/exp OR 'malignant hepatoma'/exp OR 'primary liver carcinoma'/exp	195,180
2	hepatic cell carcinoma':ti,ab OR 'hepatocellular cancer':ti,ab OR 'hepatocellular carcinoma':ti,ab OR 'hepatocellular neoplasm':ti,ab OR 'liver cell cancer':ti,ab OR 'liver cell carcinoma':ti,ab OR 'liver cell neoplasm':ti,ab OR 'hepatic carcinoma':ti,ab OR 'hepatic cell cancer':ti,ab OR 'hepatic cell neoplasm':ti,ab OR 'hepatocarcinoma':ti,ab OR 'hepatoma':ti,ab OR 'liver carcinoma':ti,ab OR 'liver carcinoma rupture':ti,ab OR 'malignant hepatoma':ti,ab OR 'primary liver carcinoma':ti,ab OR (('hepatic cell' OR hepatocellular OR 'liver cell') NEAR/2 (cancer* OR carcinoma* OR neoplasm*)):ti,ab)	173,626
3	1 OR 2	229,072

4	<p>1 [4 [ (6 carbamoyl 7 methoxy 4 quinolinyl) oxy] 2 chlorophenyl] 3 cyclopropylurea'/exp OR '3 (2, 6 difluoro 3, 5 dimethoxyphenyl) 1 ethyl 8 [ (4 morpholinyl) methyl] 1, 3, 4, 7 tetrahydro 2h pyrrolo [3', 2':5, 6] pyrido [4, 3 d] pyrimidin 2 one'/exp OR '3 (2, 6 difluoro 3, 5 dimethoxyphenyl) 1 ethyl 8 [ (morpholin 4 yl) methyl] 1, 3, 4, 7 tetrahydro 2h pyrrolo [3', 2':5, 6] pyrido [4, 3 d] pyrimidin 2 one'/exp OR '4 [3 chloro 4 [ (cyclopropylcarbamoyl) amino] phenoxy] 7 methoxyquinoline 6 carboxamide'/exp OR '4 [3 chloro 4 [ [(cyclopropylamino) carbonyl] amino] phenoxy] 7 methoxy 6 quinolinecarboxamide'/exp OR '4 [4 [ [[4 chloro 3 (trifluoromethyl) phenyl] carbamoyl] amino] 3 fluorophenoxy] n methylpyridine 2 carboxamide'/exp OR '4 [4 [ [[[4 chloro 3 (trifluoromethyl) phenyl] amino] carbonyl] amino] 3 fluorophenoxy] n methyl 2 pyridinecarboxamide'/exp OR '4 [4 [3 [4 chloro 3 (trifluoromethyl) phenyl] ureido] phenoxy] n methyl 2 pyridinecarboxamide'/exp OR 'abp 215'/exp OR 'abp215'/exp OR 'ainex'/exp OR 'altuzan'/exp OR 'ask b1202'/exp OR 'askb1202'/exp OR 'atezolizumab'/exp OR 'avastin'/exp OR 'bat 1706'/exp OR 'bat1706'/exp OR 'bay 43 9006'/exp OR 'bay 43-9006'/exp OR 'bay 439006'/exp OR 'bay43 9006'/exp OR 'bay43-9006'/exp OR 'bay439006'/exp OR 'bay 73 4506'/exp OR 'bay 73-4506'/exp OR 'bay 734506'/exp OR 'bay73 4506'/exp OR 'bay73-4506'/exp OR 'bay734506'/exp OR 'bcd 021'/exp OR 'bcd021'/exp OR 'bevacizumab'/exp OR 'bevacizumab awwb'/exp OR 'bevacizumab beta'/exp OR 'bevacizumab bvzr'/exp OR 'bevacizumab-awwb'/exp OR 'bevacizumab-bvzr'/exp OR 'bevax'/exp OR 'bevz 92'/exp OR 'bevz92'/exp OR 'bi 695502'/exp OR 'bi695502'/exp OR 'bms 734016'/exp OR 'bms734016'/exp OR 'bms 907351'/exp OR 'bms907351'/exp OR 'bms 936558'/exp OR 'bms936558'/exp OR 'bryxta'/exp OR 'cabometyx'/exp OR 'cabozantinib'/exp OR 'cabozantinib malate'/exp OR 'cabozantinib s malate'/exp OR 'cabozantinib s-malate'/exp OR 'chs 5217'/exp OR 'chs5217'/exp OR 'cmab 819'/exp OR 'cmab819'/exp OR 'cometriq'/exp OR 'cp 675 206'/exp OR 'cp 675, 206'/exp OR 'cp 675206'/exp OR 'cp675 206'/exp OR 'cp675, 206'/exp OR 'cp675206'/exp OR 'ct p16'/exp OR 'ctp16'/exp OR 'cyclopropane 1, 1 dicarboxylic acid [4 (6, 7 dimethoxyquinolin 4 yloxy) phenyl] amide (4 fluorophenyl) amide'/exp OR 'cyramza'/exp OR 'durvalumab'/exp OR 'e 7080'/exp OR 'e7080'/exp OR 'er 203492-00'/exp OR 'er203492-00'/exp OR 'fkb 238'/exp OR 'fkb238'/exp OR 'hd 204'/exp OR 'hd204'/exp OR 'hlx 04'/exp OR 'hlx04'/exp OR 'ibi 375'/exp OR 'ibi375'/exp OR 'imc 1121 b'/exp OR 'imc 1121b'/exp OR 'imc1121 b'/exp OR 'imc1121b'/exp OR 'imfinzi'/exp OR 'incb 054828'/exp OR 'incb 54828'/exp OR 'incb054828'/exp OR 'incb54828'/exp OR 'ipilimumab'/exp OR 'keytruda'/exp OR 'kisplyx'/exp OR 'krabeva'/exp OR 'kyomarc'/exp OR 'lambrolizumab'/exp OR 'lenvatinib'/exp OR 'lenvatinib mesilate'/exp OR 'lenvatinib mesylate'/exp OR 'lenvatinib methanesulfonate'/exp OR 'lenvima'/exp OR 'ly 3009806'/exp OR 'ly3009806'/exp OR 'mb 02'/exp OR 'mb02'/exp OR 'mdx 010'/exp OR 'mdx 101'/exp OR 'mdx010'/exp OR 'mdx101'/exp OR 'mdx 1106'/exp OR</p>	119,423
---	---	---------

'mdx1106'/exp OR 'medi 4736'/exp OR 'medi4736'/exp OR 'mil 60'/exp OR 'mil60'/exp OR 'mk 3475'/exp OR 'mk3475'/exp OR 'monoclonal antibody mpdl 3280a'/exp OR 'monoclonal antibody mpdl3280a'/exp OR 'mpdl 3280a'/exp OR 'mpdl3280a'/exp OR 'mvasi'/exp OR 'myl 14020'/exp OR 'myl 1402o'/exp OR 'myl14020'/exp OR 'myl1402o'/exp OR 'n [4 [ (6, 7 dimethoxyquinolin 4 yl) oxy] phenyl] n` (4 fluorophenyl) cyclopropane 1, 1 dicarboxamide'/exp OR 'n [4 (6, 7 dimethoxy 4 quinolinyloxy) phenyl] n` (4 fluorophenyl) 1, 1 cyclopropanedicarboxamide'/exp OR 'n [4 [ (6 carbamoyl 7 methoxyquinolin 4 yl) oxy] 2 chlorophenyl] n` cyclopropylurea'/exp OR 'nexavar'/exp OR 'nivolumab'/exp OR 'nsc 704865'/exp OR 'nsc704865'/exp OR 'ono 4538'/exp OR 'ono4538'/exp OR 'ons 1045'/exp OR 'ons 5010'/exp OR 'ons1045'/exp OR 'ons5010'/exp OR 'opdivo'/exp OR 'pemazyre'/exp OR 'pembrolizumab'/exp OR 'pemigatinib'/exp OR 'pf 06439535'/exp OR 'pf 6439535'/exp OR 'pf06439535'/exp OR 'pf6439535'/exp OR 'ql 1101'/exp OR 'ql1101'/exp OR 'ramucirumab'/exp OR 'regorafenib'/exp OR 'rg 435'/exp OR 'rg435'/exp OR 'rg 7446'/exp OR 'rg7446'/exp OR 'rhumab-vegf'/exp OR 'ro 4876646'/exp OR 'ro4876646'/exp OR 'sb 8'/exp OR 'sb8'/exp OR 'sch 900475'/exp OR 'sch900475'/exp OR 'sorafenib'/exp OR 'sorafenib tosylate'/exp OR 'stc 103'/exp OR 'stc103'/exp OR 'stivarga'/exp OR 'strentarga'/exp OR 'tecentriq'/exp OR 'tecnriq'/exp OR 'ticilimumab'/exp OR 'tremelimumab'/exp OR 'xl 184'/exp OR 'xl184'/exp OR 'yervoy'/exp OR 'zirabev'/exp

5	<p>1 [4 [ (6 carbamoyl 7 methoxy 4 quinolinyl) oxy] 2 chlorophenyl] 3 cyclopropylurea' OR '3 (2, 6 difluoro 3, 5 dimethoxyphenyl) 1 ethyl 8 [ (4 morpholinyl) methyl] 1, 3, 4, 7 tetrahydro 2h pyrrolo [3', 2':5, 6] pyrido [4, 3 d] pyrimidin 2 one' OR '3 (2, 6 difluoro 3, 5 dimethoxyphenyl) 1 ethyl 8 [ (morpholin 4 yl) methyl] 1, 3, 4, 7 tetrahydro 2h pyrrolo [3', 2':5, 6] pyrido [4, 3 d] pyrimidin 2 one' OR '4 [3 chloro 4 [ (cyclopropylcarbamoyl) amino] phenoxy] 7 methoxyquinoline 6 carboxamide' OR '4 [3 chloro 4 [ [(cyclopropylamino) carbonyl] amino] phenoxy] 7 methoxy 6 quinolinecarboxamide' OR '4 [4 [ [[4 chloro 3 (trifluoromethyl) phenyl] carbamoyl] amino] 3 fluorophenoxy] n methylpyridine 2 carboxamide' OR '4 [4 [ [[[4 chloro 3 (trifluoromethyl) phenyl] amino] carbonyl] amino] 3 fluorophenoxy] n methyl 2 pyridinecarboxamide' OR '4 [4 [3 [4 chloro 3 (trifluoromethyl) phenyl] ureido] phenoxy] n methyl 2 pyridinecarboxamide' OR 'abp 215' OR 'abp215' OR 'ainex' OR 'altuzan' OR 'ask b1202' OR 'askb1202' OR 'atezolizumab' OR 'avastin' OR 'bat 1706' OR 'bat1706' OR 'bay 43 9006' OR 'bay 43-9006' OR 'bay 439006' OR 'bay43 9006' OR 'bay43-9006' OR 'bay439006' OR 'bay 73 4506' OR 'bay 73-4506' OR 'bay 734506' OR 'bay73 4506' OR 'bay73-4506' OR 'bay734506' OR 'bcd 021' OR 'bcd021' OR 'bevacizumab' OR 'bevacizumab awwb' OR 'bevacizumab beta' OR 'bevacizumab bvzr' OR 'bevacizumab-awwb' OR 'bevacizumab-bvzr' OR 'bevax' OR 'bevx 92' OR 'bevx92' OR 'bi 695502' OR 'bi695502' OR 'bms 734016' OR 'bms734016' OR 'bms 907351' OR 'bms907351' OR 'bms 936558' OR 'bms936558' OR 'bryxta' OR 'cabometyx' OR 'cabozantinib' OR 'cabozantinib malate' OR 'cabozantinib s malate' OR 'cabozantinib s-malate' OR 'chs 5217' OR 'chs5217' OR 'cmab 819' OR 'cmab819' OR 'cometriq' OR 'cp 675 206' OR 'cp 675, 206' OR 'cp 675206' OR 'cp675 206' OR 'cp675, 206' OR 'cp675206' OR 'ct p16' OR 'ctp16' OR 'cyclopropane 1, 1 dicarboxylic acid [4 (6, 7 dimethoxyquinolin 4 yloxy) phenyl] amide (4 fluorophenyl) amide' OR 'cyramza' OR 'durvalumab' OR 'e 7080' OR 'e7080' OR 'er 203492-00' OR 'er203492-00' OR 'fkb 238' OR 'fkb238' OR 'hd 204' OR 'hd204' OR 'hlx 04' OR 'hlx04' OR 'ibi 375' OR 'ibi375' OR 'imc 1121 b' OR 'imc 1121b' OR 'imc1121 b' OR 'imc1121b' OR 'imfinzi' OR 'incb 054828' OR 'incb 54828' OR 'incb054828' OR 'incb54828' OR 'ipilimumab' OR 'keytruda' OR 'kispplx' OR 'krabeva' OR 'kyomarc' OR 'lambrolizumab' OR 'lenvatinib' OR 'lenvatinib mesilate' OR 'lenvatinib mesylate' OR 'lenvatinib methanesulfonate' OR 'lenvima' OR 'ly 3009806' OR 'ly3009806' OR 'mb 02' OR 'mb02' OR 'mdx 010' OR 'mdx 101' OR 'mdx010' OR 'mdx101' OR 'mdx 1106' OR 'mdx1106' OR 'medi 4736' OR 'medi4736' OR 'mil 60' OR 'mil60' OR 'mk 3475' OR 'mk3475' OR 'monoclonal antibody mpdl 3280a' OR 'monoclonal antibody mpdl3280a' OR 'mpdl 3280a' OR 'mpdl3280a' OR 'mvasi' OR 'myl 14020' OR 'myl 1402o' OR 'myl14020' OR 'myl1402o' OR 'n [4 [ (6 carbamoyl 7 methoxyquinolin 4 yl) oxy] 2 chlorophenyl] n` cyclopropylurea' OR 'n [4 (6, 7 dimethoxy 4 quinolinyl) oxy] n` (4 fluorophenyl) 1, 1 cyclopropanedicarboxamide' OR 'n [4 [ (6, 7 dimethoxyquinolin 4 yl) oxy]</p>	123,562
---	--	---------

	phenyl] n` (4 fluorophenyl) cyclopropane 1, 1 dicarboxamide' OR 'nexavar' OR 'nivolumab' OR 'nsc 704865' OR 'nsc704865' OR 'ono 4538' OR 'ono4538' OR 'ons 1045' OR 'ons 5010' OR 'ons1045' OR 'ons5010' OR 'opdivo' OR 'pemazyre' OR 'pembrolizumab' OR 'pemigatinib' OR 'pf 06439535' OR 'pf 6439535' OR 'pf06439535' OR 'pf6439535' OR 'ql 1101' OR 'ql1101' OR 'ramucirumab' OR 'regorafenib' OR 'rg 435' OR 'rg435' OR 'rg 7446' OR 'rg7446' OR 'rhumab-vegf' OR 'ro 4876646' OR 'ro4876646' OR 'sb 8' OR 'sb8' OR 'sch 900475' OR 'sch900475' OR 'sorafenib' OR 'sorafenib tosylate' OR 'stc 103' OR 'stc103' OR 'stivarga' OR 'strentarga' OR 'tecentriq' OR 'tecnetriq' OR 'ticilimumab' OR 'tremelimumab' OR 'xl 184' OR 'xl184' OR 'yervoy' OR 'zirabev'	
6	OR/4-5	123,562
7	3 AND 6	13,544
8	[english]/lim	32,260,551
9	7 AND 8	13,000
10	[animals]/lim NOT [humans]/lim	5,885,146

11	9 NOT 10	12,511
12	[conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim OR [editorial]/lim OR [erratum]/lim OR [letter]/lim OR [note]/lim	7,581,691
13	11 NOT 12	7,910
14	crossover procedure':de OR 'double-blind procedure':de OR 'randomized controlled trial':de OR 'single-blind procedure':de OR (random* OR factorial* OR crossover* OR cross NEXT/1 over* OR placebo* OR doubl* NEAR/1 blind* OR singl* NEAR/1 blind* OR assign* OR allocat* OR volunteer*):de,ab,ti	2,656,831
15	13 AND 14	1,697

### III. Cochrane: Date 12/4/2020

Set #	Search Strategy	Results
1	MeSH descriptor: [Carcinoma, Hepatocellular] explode all trees	1,744
2	"hepatocellular cancer*":ti,ab OR "hepatocellular carcinoma*":ti,ab OR "hepatocellular neoplasm*":ti,ab OR hepatoma:ti,ab OR "liver cell carcinoma*":ti,ab OR "liver cell cancer*":ti,ab OR "liver cell neoplasm*":ti,ab OR "hepatic cell cancer*":ti,ab OR "hepatic cell carcinoma*":ti,ab OR "hepatic cell neoplasm*":ti,ab OR (("hepatic cell":ti,ab OR hepatocellular:ti,ab OR "liver cell":ti,ab) AND (cancer*":ti,ab OR carcinoma*":ti,ab OR neoplasm*":ti,ab))	4,700
6	OR1/2	4,971
7	MeSH descriptor: [Bevacizumab] explode all trees	1,932
8	MeSH descriptor: [Ipilimumab] explode all trees	186
9	MeSH descriptor: [Nivolumab] explode all trees	441

10	MeSH descriptor: [Sorafenib] explode all trees	475
11	"atezolizumab":ti,ab OR "bevacizumab":ti,ab OR "cabozantinib":ti,ab OR "durvalumab":ti,ab OR "ipilimumab":ti,ab OR "lenvatinib":ti,ab OR "nivolumab":ti,ab OR "pembrolizumab":ti,ab OR "pemigatinib":ti,ab OR "ramucirumab":ti,ab OR "regorafenib":ti,ab OR "sorafenib":ti,ab OR "tremelimumab":ti,ab	12,854
12	OR/7-12	13,106
13	9 AND 12	1,093

### Appendix 3: Schema to evaluate the certainty in the patients' values and preferences

Discontinuation due to adverse events	HRQOL	Values and preferences
Increased discontinuation due to adverse events	No HRQOL data	Uncertainty about values and preference
No increase in discontinuation due to adverse events	No HRQOL data	Uncertainty about values and preference
Increased discontinuation due to adverse events	No difference/or better HRQOL	Possible variability in values and preferences
No increase in discontinuation due to adverse events	No difference/or batter HROQL	Probably no variability in values and preferences

### Appendix 4: Published economic evaluations

1. Carr BI, Carroll S, Muszbek N, et al. Economic evaluation of sorafenib in unresectable hepatocellular carcinoma. *J Gastroenterol Hepatol* 2010;25:1739-46.
2. Muszbek N, Shah S, Carroll S, et al. Economic evaluation of sorafenib in the treatment of hepatocellular carcinoma in Canada. *Curr Med Res Opin* 2008;24:3559-69.
3. Camma C, Cabibbo G, Petta S, et al. Cost-effectiveness of sorafenib treatment in field practice for patients with hepatocellular carcinoma. *Hepatology* 2013;57:1046-54.
4. Zhang P, Yang Y, Wen F, et al. Cost-effectiveness of sorafenib as a first-line treatment for advanced hepatocellular carcinoma. *Eur J Gastroenterol Hepatol* 2015;27:853-9.

5. Parikh ND, Marshall VD, Singal AG, et al. Survival and cost-effectiveness of sorafenib therapy in advanced hepatocellular carcinoma: An analysis of the SEER-Medicare database. *Hepatology* 2017;65:122-133.
6. Ho JC, Hsieh ML, Chuang PH, et al. Cost-Effectiveness of Sorafenib Monotherapy and Selected Combination Therapy with Sorafenib in Patients with Advanced Hepatocellular Carcinoma. *Value Health Reg Issues* 2018;15:120-126.
7. Cai H, Zhang L, Li N, et al. Lenvatinib versus sorafenib for unresectable hepatocellular carcinoma: a cost-effectiveness analysis. *J Comp Eff Res* 2020;9:553-562.
8. Ikeda S, Kudo M, Izumi N, et al. Cost-Effectiveness of Lenvatinib in the Treatment of Patients With Unresectable Hepatocellular Carcinomas in Japan: An Analysis Using Data From Japanese Patients in the REFLECT Trial. *Value Health Reg Issues* 2021;24:82-89.
9. Meyers BM, Vogel A, Marotta P, et al. The Cost-Effectiveness of Lenvatinib in the Treatment of Advanced or Unresectable Hepatocellular Carcinoma from a Canadian Perspective. *Can J Gastroenterol Hepatol* 2021;2021:8811018.
10. Kim JJ, McFarlane T, Tully S, et al. Lenvatinib Versus Sorafenib as First-Line Treatment of Unresectable Hepatocellular Carcinoma: A Cost-Utility Analysis. *Oncologist* 2020;25:e512-e519.
11. Chiang CL, Chan SK, Lee SF, et al. First-Line Atezolizumab Plus Bevacizumab versus Sorafenib in Hepatocellular Carcinoma: A Cost-Effectiveness Analysis. *Cancers (Basel)* 2021;13.
12. Su D, Wu B, Shi L. Cost-effectiveness of Atezolizumab Plus Bevacizumab vs Sorafenib as First-Line Treatment of Unresectable Hepatocellular Carcinoma. *JAMA Netw Open* 2021;4:e210037.
13. Zhang X, Wang J, Shi J, et al. Cost-effectiveness of Atezolizumab Plus Bevacizumab vs Sorafenib for Patients With Unresectable or Metastatic Hepatocellular Carcinoma. *JAMA Netw Open* 2021;4:e214846.
14. Wen F, Zheng H, Zhang P, et al. Atezolizumab and bevacizumab combination compared with sorafenib as the first-line systemic treatment for patients with unresectable hepatocellular carcinoma: A cost-effectiveness analysis in China and the United states. *Liver Int* 2021;41:1097-1104.
15. Liao W, Huang J, Hutton D, et al. Cost-effectiveness analysis of cabozantinib as second-line therapy in advanced hepatocellular carcinoma. *Liver Int* 2019;39:2408-2416.
16. Sieg M, Hartmann M, Settmacher U, et al. Comparative cost-effectiveness of cabozantinib as second-line therapy for patients with advanced hepatocellular carcinoma in Germany and the United States. *BMC Gastroenterol* 2020;20:120.
17. Zheng H, Qin Z, Qiu X, et al. Cost-effectiveness analysis of ramucirumab treatment for patients with hepatocellular carcinoma who progressed on sorafenib with alpha-fetoprotein concentrations of at least 400 ng/ml. *J Med Econ* 2020;23:347-352.
18. Soto-Perez-de-Celis E, Aguiar PN, Cordon ML, et al. Cost-Effectiveness of Cabozantinib in the Second-Line Treatment of Advanced Hepatocellular Carcinoma. *J Natl Compr Canc Netw* 2019;17:669-675.
19. Shlomai A, Leshno M, Goldstein DA. Cabozantinib for patients with advanced hepatocellular carcinoma: a cost-effectiveness analysis. *Therap Adv Gastroenterol* 2019;12:1756284819878304.

20. Chiang CL, Chan SK, Lee SF, et al. Cost-effectiveness of Pembrolizumab as a Second-Line Therapy for Hepatocellular Carcinoma. *JAMA Netw Open* 2021;4:e2033761.
21. Shlomai A, Leshno M, Goldstein DA. Regorafenib treatment for patients with hepatocellular carcinoma who progressed on sorafenib-A cost-effectiveness analysis. *PLoS One* 2018;13:e0207132.
22. Parikh ND, Singal AG, Hutton DW. Cost effectiveness of regorafenib as second-line therapy for patients with advanced hepatocellular carcinoma. *Cancer* 2017;123:3725-3731.
23. Tapper EB, Catana AM, Sethi N, et al. Direct costs of care for hepatocellular carcinoma in patients with hepatitis C cirrhosis. *Cancer* 2016;122:852-8.
24. Thein HH, Qiao Y, Zaheen A, et al. Cost-effectiveness analysis of treatment with non-curative or palliative intent for hepatocellular carcinoma in the real-world setting. *PLoS One* 2017;12:e0185198.
25. Sherrow C, Attwood K, Zhou K, et al. Sequencing Systemic Therapy Pathways for Advanced Hepatocellular Carcinoma: A Cost Effectiveness Analysis. *Liver Cancer* 2020;9:549-562.

## Appendix 5: Baseline characteristics tables

PICO 1: In patients with hepatocellular carcinoma who failed locoregional therapy, were ineligible for locoregional therapy, or have metastatic disease with preserved liver function, should systemic therapy be used?

Author, Yr, Design, Country	Baseline	Intervention/Comparator	Outcomes
<b>First Line Treatment</b>			
Sorafenib vs Placebo/BSC			
<p>Llovet 2008 (SHARP) NCT00105443</p> <p>RCT</p> <p>Global (21 countries)</p> <p>Follow-up: data cut off was approximately 19 months after randomization (from clinical trials.gov)</p>	<p><b>Inclusion:</b> Advanced-stage HCC, as confirmed by pathological analysis. No previous systemic therapy. Not eligible for or had disease progression after surgical or locoregional therapies. ECOG <math>\leq</math> 2. CP A. Life expectancy <math>\geq</math> 12 weeks. Adequate hematologic, hepatic, and renal functions. At least one untreated target lesion that could be measured in one dimension according to RECIST.</p> <p><b>Exclusion:</b> Previous molecular targeted or any other systemic treatment.</p> <p><b>Study Design:</b></p> <ul style="list-style-type: none"> <li>- Stratified according to region, ECOG, presence of absence of macrovascular invasion or extrahepatic spread.</li> <li>- Treatment continued until the occurrence of both</li> </ul>	<p><b>I: Sorafenib (299)</b> Dose: 400 mg twice daily Received Rx: 297 Age: 64.9 Male%: 87 CP: A: 95%, B: 5% BCLC: B: 18%, C: 82% ECOG: 0: 54% 1: 38%, 2: 8% Median 5.3 (range 0.2-16.1) months</p> <p><b>C: Placebo (303)</b> Dose: Matching placebo Received Rx: 302 Age: 66.3 Male%: 87 CP: A 98%, B 2% BCLC: B 17%, C 83% ECOG: 0: 54% 1: 39% 2: 7%</p>	<p><b>Overall Survival (mortality)</b> Events: 143 vs 178 Median: 10.7 (9.4-13.3) vs 7.9 (6.8-9.1) months HR: 0.69 (0.55-0.87) 1-year: 44% vs 33%</p> <p><b>Disease-Specific Survival</b> NR</p> <p><b>Progression-Free Survival</b> NR</p> <p><b>Time to Progression</b> Definition: RECIST Events: 107 vs 156 Median: 5.5 (4.1-6.9) vs 2.8 (2.7-3.9) months HR: 0.58 (0.45-0.74)</p>

	<p>radiologic (RECIST) and symptomatic FHSI8) progression, or the occurrence either unacceptable adverse events or death.</p> <ul style="list-style-type: none"> <li>- Tumor measured at screening, every 6 weeks during treatment, and at the end of treatment by CT/MRI.</li> <li>- unclear about subsequent study interventions</li> </ul>	<p>Median 4.3 (range 0.1-16.6) months</p>	<p><b>HRQOL</b> NR</p> <p><b>Harms (297 vs 302)</b> Discontinuation 2/2 AE:113/297 (GI events, fatigue, live dysfunction) vs 112/302</p> <p>SAE: 153/297 vs 164/302 (heaptobiliary 11 vs 9%, hemorrhagic 9 vs 13%, variceal bleeding 2 vs 4 %, renal failure &lt;1 vs 3%, cardiac ischemia/infarction 3 vs 1%; diarrhea 7 vs 5%; ascites 5 vs 4%)</p> <p><b>Overall Response</b> Definition: RECIST Events: 7 vs 2</p> <p><b>Disease Control</b> Definition: RECIST Events: 218 vs 206</p>
<p>Cheng 2009 (ASIA-PACIFIC) NCT00492752</p> <p>RCT</p> <p>23 sites in China, South Korea, Taiwan</p> <p>Follow-up: data cutoff was approximately 23</p>	<p><b>Inclusion:</b> Advanced (unresectable or metastatic) hepatocellular carcinoma. No previous systemic therapy. ECOG 0-2. CP A. Life expectancy of at least 12 weeks. Adequate renal, hematological and hepatic function. At least 1 tumor lesion (not previously treated with local therapy) that could be measured per RECIST. If received previous local therapy, then eligible if target lesion increased in size by 25% or more, or the target lesion had not been treated with local therapy. Local therapy had been stopped at least 4 weeks before study entry.</p> <p><b>Exclusion:</b> Previous or concomitant systemic therapy,</p>	<p><b>I:</b> Sorafenib (150) Dose: 400 mg twice daily Received Rx:149 Age: 51 Male%: 84.7 CP: A: 97.3%, B: 2.7% BCLC: C: 95.3% ECOG: 0: 25.3%, 1: 69.3%, 2: 5.3% Median duration: NR</p> <p><b>C:</b> Placebo (76) Dose: N/A</p>	<p><b>Overall Survival (mortality)</b> Events: NR Median: 6.5 months (5.6-7.6) vs 4.2 (3.8-5.5) HR: 0.68 (0.5-0.93) 6 month 53.3% vs 36.7</p> <p><b>Disease-Specific Survival</b> NR</p> <p><b>Progression-Free Survival</b> NR</p>

<p>months after randomization</p>	<p>known history of HIV, clinically serious infections, known substance abuse, history of organ allograft, history of cardiac disease, known CNS tumor, known GI bleeding up to 30 days prior to study entry, pregnancy or breastfeeding.</p> <p><b>Study Design:</b></p> <ul style="list-style-type: none"> <li>- Stratified by the presence or absence of macroscopic vascular invasion or extrahepatic spread (or both), ECOG 0-2, and geographical region.</li> <li>- Treatment continued until death, adverse events requiring termination in the opinion of the investigator, disease progression, pregnancy, deterioration of ECOG to 4, development of a second cancer, use of an illicit drug that could contribute to toxicity in the opinion of the investigator, withdrawal of consent, or loss to follow-up.</li> <li>- Tumor measurements done at screening and every 6 weeks thereafter. Patient visits every 3 weeks to monitor safety and drugs.</li> <li>- Subsequent treatment: NR.</li> <li>- Unplanned early termination</li> </ul>	<p>Received Rx:75 Age: 52 Male%: 86.8 CP: A: 97.4%, B: 2.6% BCLC: C: 96.1% ECOG: 0: 27.6%, 1: 67.1%, 2: 5.3% Median duration: NR</p>	<p><b>Time to Progression</b> Definition: RECIST or symptomatic progression (deterioration to ECOG PS 4 status or change from baseline FHSI-8) Events: Median: 2.8 (2.6-3.6) vs 1.4 (1.4-1.6) months HR: 0.57 (0.42-0.79)</p> <p><b>HRQOL</b> Similar FSHI-8 and FACT-HP scores and thus no difference in HRQOL (data not shown)</p> <p><b>Harms</b> Discontinuation 2/2 AE: 29/149 vs 10/75 SAE (life-threatening, death, patient hospitalization, prolongation of hospitalization persistent or significant disability or incapacity): 71/149 vs 34/75</p> <p><b>Overall Response</b> Definition: complete and partial response 5/150 vs 1/76</p> <p><b>Disease Control:</b> Definition: complete or partial response, or stable disease Events: 86/150 vs 22/76</p>
<p>Atezolizumab plus Bevacizumab versus Sorafenib</p>			
<p>Finn 2020 (IMbrave150) NCT03434379</p>	<p><b>Inclusion:</b> Locally advanced metastatic and/or unresectable HCC. No previous systemic therapies for liver cancer. Measurable disease per RECIST 1.1, not</p>	<p>I: Atezolizumab (A) plus Bevacizumab (Bev) (336) Dose: 1200 mg A +15 mg/kg</p>	<p><b>Overall Survival (mortality)</b> Events: 96 vs 65 Median: 19.2 vs 13.4 months</p>

<p>RCT</p> <p>Global: suspect USA and Taiwan</p> <p>Median follow up: 15.6 months</p>	<p>amenable to curative or locoregional therapies or progressed thereafter. CP A. ECOG 0 or 1. Adequate hematologic and organ function.</p> <p><b>Exclusion:</b> history of autoimmune disease, co-infection with hepatitis B/C and un- or incompletely treated EV/GV with bleeding or high risk of bleeding.</p> <p><b>Study Design:</b></p> <ul style="list-style-type: none"> <li>- Stratification based on geographic lesion (Asia excluding Japan vs others), macrovascular invasion or extrahepatic spread of disease, baseline alpha-fetoprotein (&lt; vs ≥400 ng/mL), and ECOG status (0 vs 1)</li> <li>- Patients received their assigned drugs until unacceptable toxic effects occurred or there was loss of clinical benefit. Patients could continue treatment beyond disease progression if the investigator observed evidence of clinical benefit and if symptoms and signs indicating unequivocal disease progression were absent.</li> <li>- Dose modification okay for Sorafenib, but not for AB, but could continue on single agent if investigator deemed benefit</li> <li>- Assessments by CT/MRI every 6 weeks until week 54 and then every 9 weeks thereafter</li> <li>- Post-discontinuation therapies reported in Table S3 of the article.</li> </ul>	<p>Bev q3 weeks Received Rx: 329 Age: 64 Male%: 82 CP: A5 72%, A6 28%, B7 &lt; 1%</p> <p>BCLC: A 2%, B 15%, C 82% ECOG: 0: 62%, 1: 28% Median duration 7.4 months</p> <p><b>C: Sorafenib (165)</b> Dose: 400 mg twice daily PO Received Rx: 156 Age: 66 Male%: 83 CP: A5 73%, A6 27%, B7 0% BCLC: A 4%, B 16%, C 81% ECOG: 0: 63%, 1: 27% Median duration 2.8 months</p>	<p>HR: 0.66 (0.52-0.85) Survival at 6 months: 84.8% vs 72.2% Survival at 12 months: 67.2% vs 54.6% Survival at 18 months: 52% vs 40%</p> <p><b>Disease-Specific Survival</b> NR</p> <p><b>Progression-Free Survival</b> Definition: time from randomization to disease progression according to RECIST 1.1 or death Events: 197 vs 109 Median: 6.8 (5.7-8.3) vs 4.3 (4-5.6) HR: 0.59 (0.47-0.76) PFS at 6 months: 54.5% vs 37.2%</p> <p><b>Time to Progression</b> NR</p> <p><b>HRQOL:</b> Definition: EORTC QLQ-C30 (Deterioration) Median time to deterioration: 11.2 (6-NE) vs 3.6 (3-7) HR 0.63 (0.46-0.85)</p> <p><b>Harms</b> Discontinuation 2/2 AE: pt with at least one event and d/c any component: 51/329 vs 16/156 SAE: 125/329 vs 48/156</p> <p><b>Overall Response</b> Definition: mRECIST Events: 108/325 vs 21/158</p>
---	--	--	--

			<b>Disease Control</b> Definition: mRECIST Events: 235/325 vs 87/158
Lenvatinib vs Sorafenib			
Kudo 2018 (REFLECT) NCT01761266  RCT  Global (20 countries)  Up to 3.8 years of follow-up	<b>Inclusion:</b> Unresectable HCC; one or measurable target lesions based on mRECIST, prior locoregional therapy allowed if they showed radiographic evidence of progression to be deemed target lesions; BCLC B or C; CP A; ECOG $\leq$ 1; controlled blood pressure and adequate liver, bone marrow, renal, pancreatic and blood function.  <b>Exclusion:</b> 50% or higher liver occupation; obvious invasion of the bile duct; invasion at the main portal vein; previous systemic therapy.  <b>Study Design:</b> - Stratified by region (Eastern vs Western); macroscopic portal vein invasion, extrahepatic spread, or both (yes vs no); ECOG (0 or 1); and bodyweight (< 60 vs $\geq$ 60 kg). - 28-day cycles - Tumor assessment every 8 weeks with CT or MRI until radiological disease progression, assessed using mRECIST by local investigators. If drug discontinued not due to progression, follow-up was continued until progression or starting of new treatment. - Follow-up for survival every 12 weeks, even after drug discontinuation, unless patient withdrew consent or sponsor terminated the study	<b>I: Lenvatinib (478)</b> Dose: 8-12 mg/kg daily depending on bodyweight Received Rx: 476 Age: 63 Male%: 85 CP: A 99%, B 1% BCLC: B 22%, C 78% ECOG: 0: 64%, 1: 36% Median: 5.7 (IQR 2.9-11.1) months  <b>C: Sorafenib (476)</b> Dose: 400 mg twice daily Received Rx: 475 Age: 62 Male%: 84 CP: A 99%, B 1% BCLC: B 19%, C 81% ECOG: 0: 63%, 1: 37% Median: 3.7 (IQR 1.8-7.4) months	<b>Overall Survival (mortality)</b> Events: 351 vs 350 Median: 13.6 (12.1-14.9) vs 12.3 (10.4-13.9) months HR: 0.92 (0.79-1.06; margin 1.08)  <b>Disease-Specific Survival</b> NR  <b>Progression-Free Survival</b> Definition: mRECIST Events: 349 vs 367 Median: 7.3 (5.6-7.5) vs 3.6 (3.6-3.7) HR: 0.64 (0.55-0.75)  <b>Time to Progression</b> Definition: mRECIST Events: 308 vs 343 Median: 7.4 (7.2-9.1) vs 3.7 (3.6-3.9) HR: 0.6 (0.51-0.71)  <b>HRQOL</b> Definition: EROTC QLQ-C30 and EROTC QLQ-HCC18 HR: 0.87 (0.754-1.013) "Baseline scores on the EORTC QLQ-C30 and EORTC QLQ-HCC18 health questionnaires were similar in the

DRAFT

lenvatinib and sorafenib treatment groups. Following treatment, scores declined in both groups. Analysis of time to clinically meaningful deterioration showed that role functioning (nominal  $p=0.0193$ ), pain (nominal  $p=0.0105$ ), and diarrhoea (nominal  $p<0.0001$ ) from EORTC QLQ-C30, and nutrition (nominal  $p=0.0113$ ) and body image (nominal  $p=0.0051$ ) from EORTC QLQ-HCC18 were observed earlier in patients treated with sorafenib than in those treated with lenvatinib. For between-group comparison, the summary score was not significantly different between the treatment arms (HR 0.87, 95% CI 0.754–1.013)”, quoted from study

**Harms (476 vs 475)**

SAE treatment-related: 205 vs 144  
Discontinuation 2/2 AE: 63 vs 43  
Death: 11 (3 hepatic failure, 3 cerebral hemorrhage, 2 respiratory failure) vs 4 (tumor hemorrhage, ischemic stroke, respiratory failure, sudden death)

**Overall Response**

Definition: mRECIST  
Events: 194 vs 59

**Disease Control**

Definition: mRECIST  
Events: 353 vs 278

## Second-Line Treatment

### Regorafenib vs Placebo

Bruix 2017  
(RESORCE)  
NCT01774344

RCT

Global  
21 countries

Follow-up 7.0 m  
(3.7-12.6)

**Inclusion:** Adults with HCC with at least one measurable lesion by mRECIS and RECIST 1.1. BCLC B or C, and could not benefit from resection, local ablation or chemoembolization. Documented radiological progression during sorafenib treatment, tolerated sorafenib ( $\geq 400$  mg daily for at least 20 of the 28 days before discontinuation), and received the last dose within 10 weeks of randomization. CP A.

**Exclusion:** Received any other systemic treatment of HCC, or discontinued sorafenib for toxicity.

**Study design:**

- Stratified by geographical region (Asia vs others), macrovascular invasion, extrahepatic disease,  $\alpha$ -fetoprotein concentration ( $<$  vs  $\geq 400$  ng/mL), ECOG status (0 vs 1)
- Proportion recruited from Asia limited to 40%
- Treatment continued until disease progression as defined by mRECIS, clinical progression (ECOG  $\geq 3$  or symptomatic deterioration), death, unacceptable toxicity, withdrawal of consent, or decision by treating

**I: Regorafenib (379)**  
Dose: 160 mg daily for 3 weeks every 4 weeks  
Received Rx: 374  
Age: 64  
Male%: 88%  
CP: A 98%, B 1%  
BCLC: A  $<1\%$ , B 14%, C 86%  
ECOG: 0: 65%, 1: 35%  
Median duration: 3.6 (IQR 1.6-7.6) months

**C: Placebo (194)**  
Dose: Matching placebo  
Received Rx: 193  
Age: 62  
Male%: 88%  
CP: A 97%, B 3%  
BCLC: A 0%, B 11%, C 89%  
ECOG: 0: 67%, 1: 33%  
Median duration: 1.9 (IQR 1.4-3.9) months

**Overall Survival (mortality)**

Events: 233 vs 140  
Median: 10.6 (9.1-12.1) vs 7.8 (6.3-8.8)  
HR: 0.63 (0.50-0.79)  
Survival at 12 months: 47% vs 28%  
Survival at 18 months: 32% vs 16%  
Survival at 30 months: 16% vs 7%

**Disease-Specific Survival**

NR

**Progression-Free Survival**

Definition: Time from randomization to radiological (mRECIST) or clinical progression, or death  
Events: NR  
Median: 3.1 (2.8-4.2) vs 1.5 (1.4-1.6)  
HR: 0.46 (0.37-0.56)

**Time to Progression**

Definition: mRECIST  
Events: 149 vs 120  
Median: 3.2 (2.9-4.2) vs 1.5 (1.4-1.6)  
HR: 0.44 (0.36-0.55)

**HRQOL**

Definition: FACT-G, FACT-Hep, EQ-5D, EQ-VAS  
"No clinically meaningful differences were noted between the regorafenib and

physician that discontinuation would be in the patient's best interest. Treatment could be continued beyond progression if the investigator judged that the patient would benefit from continued treatment. Patients assigned to placebo could receive regorafenib after the primary analysis.

- Follow-up every 6 weeks for the first 8 cycles, and every 12 weeks thereafter.
- Treatment interruptions and dose reductions were allowed to manage toxicity.

placebo groups in HRQOL. Overall changes from baseline in EQ-5D and FACT-Hep were similar in the two groups. In the LSM time-adjusted AUC analysis of the EQ-5D and FACT-Hep, the scores were lower in the regorafenib group than in the placebo group, and specifically the scores of the FACT-Hep Total and Trial Outcome Index (a subscale of the FACT-Hep) were statistically lower in the regorafenib group than in the placebo group ( $p=0.0006$  and  $p<0.0001$ , respectively); however, minimally important thresholds for the differences as established in the literature were not met", quoted from the study.

**Harms**

Discontinuation 2/2 AE: 93 vs 37  
SAE: 166 vs 90

**Overall Response**

Definition: mRECIST  
Events: 40 vs 8

**Disease Control**

Definition: mRECIST  
Events: 274 vs 70

Abou-Alfa 2018  
(CELESTIAL)  
NCT01908426

RCT

Global (19  
countries and 95  
centers)

Up to 45 months  
of follow-up.

**Inclusion:** HCC not amenable to curative treatment; CP A (5-6); **received previous treatment with Sorafenib** and had disease progression after at least one (max 2; 27% did this) systemic treatment; ECOG 0 or 1; adequate hematologic and renal measures.

**Exclusion:** previous treatment with cabozantinib; uncontrolled clinically significant illness.

**Study design:**

- Stratified based on etiologic factor, geographic region, and evidence of extrahepatic spread, macrovascular invasion or both.
- Allowed to have the assigned drug (cabozantinib or placebo) beyond radiographic progression as long as they continued to have clinical benefit, as judged by the investigator, or until they had unacceptable toxic effects.
- Tumors assessed by CT or MRI at baseline, then every 8 weeks, until 8 weeks after radiographic progression or discontinuation of drug. They used RECIST 1.1.

**I: Cabozantinib (470)**

Dose: 60 mg daily

Received Rx: 467

Age: 64

Male%: 81

CP: A 98%, B 1%, Missing  $\leq$ 1%

BCLC: B 9%, C 91%

ECOG: 0: 52%, 1: 48%, 2:

<1%

Median duration: 3.8 months

**C: Matching placebo (237)**

Dose: matching

Received Rx: 237

Age: 64

Male%: 85

CP: A 99%, B 1%

BCLC: B 10%, C 90%

ECOG: 0: 55%, 1: 45%, 2:

0%

Median duration: 2.0 months

**Overall Survival**

Events: 317/470 vs 167/237

Median: 10.2 (9.1-12) vs 8 (6.8-9.4)  
months

HR: 0.76 (0.63-0.92)

12 months: 46% vs 34%

24 months: 18% vs 13%

**Disease-Specific Survival**

NR

**Progression-Free Survival**

Definition: time from randomization to radiographic progression or death from any cause, whichever 1st. (KM graph out to 24 months)

Events: 349/470 vs 205/237

Median: 5.2 (4-5.5) vs 1.9 (1.9 vs 1.9)

HR: 0.44 (0.36-0.52)

**Time to Progression**

NR

**HRQOL**

NR

**Harms (467 vs 237)**

Discontinuation 2/2 AE: 98 vs 11 (more palmar-plantar erythrodysesthesia, fatigue, decreased appetite, diarrhea, nausea)

SAE: 232 vs 87

**Overall Response (RECIST 1.1)**

complete or partial

Events: 18/470 vs 1/237

DRAFT

**Disease Control**  
Events: complete/partial/stable  
300/470 vs 79/237

Ramucirumab vs Placebo

Zhu 2015  
(REACH)  
NCT01140347

RCT  
Global (27  
countries)

7.0-8.3 (3.2-4.0  
to 12.9-14.9)  
months. Up to 37  
months of follow-  
up.

**Inclusion:** HCC not amenable to locoregional therapy; BCLC C or B; CP A; previously treated with and discontinued sorafenib for at least 14 days, and had radiographically documented disease progression during sorafenib treatment or after discontinuation of sorafenib treatment; ECOG 0 or 1; adequate hematological and biochemical parameters.

**Exclusion:** major surgery or hepatic locoregional therapy within 28 days before randomisation; previous systemic therapy with VEGF or VEGFR inhibitors other than sorafenib; ongoing therapeutic anticoagulation or antiplatelet therapy; history of or current hepatic encephalopathy or current clinically meaningful ascites; arterial thrombotic event within 6 months before randomisation; high bleeding risk from esophageal or gastric varices; uncontrolled arterial hypertension.

**Study Design:**

- At the beginning they included CP B but due to imbalance between CP A and B in the two groups, they stopped recruiting CP B initially. Later, data from sorafenib trials showed that CP B were a clinically distinct population so they excluded them completely and replaced them with CP A patients.
- Stratified by region and cause of liver disease
- Treatment continued until progression, unacceptable toxicity or withdrawal of consent
- Disease assessment done every 6 weeks in the first 6 months then every 9 weeks

**I: Ramucirumab (283)**  
Dose: 8 mg/kg every 2 weeks  
Received Rx: 277  
Age: 64  
Male%: 83  
CP: A 100%  
BCLC: B 12%, C 88%  
ECOG: 0: 56%, 1: 44%  
Median: 12 (6.0-29.4) weeks

**C: Placebo (282)**  
Dose: IV over 1 hour every 2 weeks  
Received Rx: 276  
Age: 62  
Male%: 86  
CP: A 100%  
BCLC: B 12%, C 88%  
ECOG: 0: 54%, 1: 46%  
Median: 8 (6.0-17.8) weeks

**Overall Survival**

Events: 218 vs 224  
Median: 9.2 (8.1-10.6) vs 7.6 (6.0-9.3) months  
HR: 0.87 (0.72-1.05)

**Disease-Specific Survival**

NR

**Progression-Free Survival**

Definition: RECIST 1.1  
Events: 240 vs 263  
Median: 2.8 (2.7-3.9) vs 2.1 (1.6-2.7)  
HR: 0.63 (0.52-0.75)

**Time to Progression**

Definition: RECIST 1.1  
Events: 164 vs 218  
Median: 3.5 (2.8-4.5) vs 2.6 (1.6-2.8)  
HR: 0.59 (0.49-0.72)

**HRQOL**

NR

**Harms (277 vs 276)**

SAE: 122 vs 89  
Discontinuation due to AE: 51 vs 24 (flowchart)  
Death: 7 (2 hepatic failure, 1 multiorgan failure, 1 renal failure, 1 acute liver failure, 1 unknown cause, 1 sepsis, 1 UTI) vs 4 (1 PE, 1 esophageal variceal bleeding, 1 septic shock, 1 ARDS)

			<p><b>Overall Response</b> Definition: RECIST 1.1 Events: 20 vs 2</p> <p><b>Disease Control</b> Definition: RECIST 1.1 Events: 159 vs 129</p>
<p>Zhu 2019 (REACH-2) NCT02435433</p> <p>RCT</p> <p>Global: 20 countries</p> <p>Up to 28 months of follow-up.</p>	<p><b>Inclusion:</b> HCC diagnosis based on histopathological or cytological and if not available classic imaging. BCLC B or C that was refractory or not amenable to locoregional therapy, CPA, ECOG 0 or 1, <b>AFP 400 ng/ml or higher</b>, adequate hematologic and biochemical parameters. <math>\geq</math> 18 year old. <b>Sorafenib only previous systematic treatment allowed and discontinued 14 days prior to starting due to intolerance or disease progression.</b> Adequate organ function with measurable lesion based on RECIST v 1.1. Able to include if ascites were on stable regimen for at least 3 months.</p> <p><b>Exclusion:</b> hepatic locoregional therapy after sorafenib, major surgery in the 28 days before randomisation, history of or current hepatic encephalopathy, previous liver transplantation, esophageal or gastric varices requiring endoscopic treatment and uncontrolled arterial hypertension. Clinically meaningful ascites (worse than grade 1 of CTCAE version 4.0).</p> <p><b>Study Design:</b></p> <ul style="list-style-type: none"> <li>- Stratified by geographical region, macrovascular invasion, and ECOG performance</li> <li>- Treatment continued until disease progression, unacceptable toxicity or withdrawal of consent.</li> </ul>	<p><b>I:</b> IV Ramucirumab (197) Dose: 8mg/kg every 2 weeks Received Rx: 197 Age: 64 Male%: 78 CP: A5: 62%, A6 38% BCLC: B 17%, C 83% ECOG: 0: 57%, 1: 43% Median duration 12 w (IQR 6-28)</p> <p><b>C:</b> Placebo (95) Dose: N/A Received Rx: 95 Age: 64 Male%: 83 CP: A5 57%, A6 43% BCLC: B 21%, C 79% ECOG: 0: 58%, 1: 42% Median duration: 8 w (IQR 6-13)</p>	<p><b>Overall Survival</b> Events: 147 vs 74 Median: 8.5 (7-10.6) vs 7.3 (5.4-9.1) months HR: 0.710 (0.531-0.949)</p> <p><b>Overall survival censored for post-discontinuation therapies (post-hoc):</b> Median 8.1 (6.7-9.9) vs 6.6 (5.2-8.5) HR: 0.647 (0.462-0.907)</p> <p><b>Disease-Specific Survival</b> NR</p> <p><b>Progression-Free Survival</b> Definition: Time from randomization to radiographic progression or death Events: 172 vs 86 Median: 2.8 (2.8-4.1) vs 1.6 (1.5-2.7) months HR: 0.452 (0.339-0.603)</p> <p><b>Time to Progression</b> Definition: time from randomization to radiographic progression Events: 129 vs 77 Median: 3 (2.8-4.2) vs 1.6 (1.5-2.7)</p>

- Best supportive care including concomitant drugs were allowed by investigator. Supportive care with use of concomitant drugs for 195 in Ram and 91 in Placebo group seemed similar across groups (data not shown).  
- Tumours assessed by CT or MRI at baseline, every 6w for 1st 6 months and every 9 wks after.

months  
HR: 0.427 (0.313-0.582)

**HRQOL**

Time to deterioration of FHSI-8 score from randomization to the first meaningful deterioration (greater than equal to 3 points) in total score  
Time to deterioration performance status: from randomization to performance status of 2 or higher  
Events: NR  
Median time to deterioration 3.7 months (2.8 - 4.4) vs 2.8 months (1.6-2.9)  
HR: 0.799 (0.535-1.171)

**Harms**

Discontinuation 2/2 any AE: 35/197 vs 10/95  
SAE: 68/197 vs 28/95  
Death: for any reason on therapy or within 30 days of treatment discontinuation: 39/197 vs 16/95  
While on treatment 6 vs 3 died on treatment because of adverse events  
3 deemed to be due to RAM

**Overall Response**

Events: 9 vs 1

**Disease Control**

Events: 197 vs 37

<p>Finn 2020 (KEYNOTE-240) NCT02702401</p> <p>RCT</p> <p>Global (27 countries)</p> <p>13.8 (range 0.9-30.4) vs 10.6 (range 0.9-29.5) months. Up to 30 months.</p>	<p><b>Inclusion:</b> HCC with radiographic progression during or intolerance to sorafenib treatment; BCLC B or C; not amenable to or refractor to locoregional therapy; CP A; ECOG 0 or 1; otherwise adequate organ function.</p> <p><b>Exclusion:</b> Prior immunotherapy including anti-PD-1, anti-PD-1 ligand, or anti-PD-L2 agent, or previous systemic therapy for HCC in the advanced setting other than sorafenib; clinically apparent ascites on physical examination; main portal vein invasion or inferior vena cava or cardiac involvement of HCC on the basis of imaging; or clinically diagnosed hepatic encephalopathy within the past 6 months.</p> <p><b>Study Design:</b></p> <ul style="list-style-type: none"> <li>- Stratified by geographic region, macrovascular invasion, and alpha-fetoprotein level (&lt; 200 vs ≥ 200 ng/mL).</li> <li>- Treatment continued until disease progression according to RECIST 1.1, unacceptable toxicity, withdrawal of consent, investigator decision to withdraw the patient, or 35 cycles of study drug received.</li> <li>- Tumore imaging at baseline, 6 weeks after random assignment, and every 6 weeks thereafter until progression. They used RECIST 1.1.</li> <li>- Patients contacted every 12 weeks for survival assessment during follow-up.</li> <li>- At progression during study treatment, systemic anticancer therapies were used by 116 patients (41.7%) in the pembrolizumab group and 64 (47.4%) in the placebo group; at any given time after random assignment, the percentage of patients who received poststudy therapy was higher in the placebo arm. Two post-hoc sensitivity analyses were done to adjust for treatment switches to subsequent anticancer therapies in both arms: IPCW model (13.9 v 9.3 months; HR, 0.67;</li> </ul>	<p><b>I: Pembrolizumab (278)</b>  Dose: 200 mg IV every 3 weeks  Received Rx: 279  Age: 67  Male%: 81.3  CP: A5 63.3%, A6 36.3%, B7 0.4%  BCLC: B 20.1%, C 79.9%  ECOG: 58.3%, 1: 41.7%  Median 3.5 (range 0.0-24.4) months</p> <p><b>C: Placebo (135)</b>  Dose: Saline IV infusion every 3 weeks  Received Rx: 134  Age: 65  Male%: 83  CP: A5 63.7%, A6 34.8%, B7 1.5%  BCLC: B 21.5%, C 78.5%  ECOG: 0: 52.6%, 1: 47.4%  Median 2.8 (range 0.0-24.2) months</p>	<p><b>Overall Survival</b>  Events: 180 vs 101  Median: 13.9 (11.6-16.0) vs 10.6 (8.3 vs 13.5) months  HR: 0.781 (0.611-0.998)</p> <p><b>Disease-Specific Survival</b>  NR</p> <p><b>Progression-Free Survival</b>  Definition: RECIST 1.1  Events:  Median: 3.0 (2.8-4.1) vs 2.8 (1.6-3.0)  HR: 0.718 (0.570-0.904)</p> <p><b>Time to Progression</b>  Definition: RECIST 1.1  Events: 173 vs 100  Median: 3.8 (2.8-4.4) vs 2.8 (1.6-2.9) months  HR: 0.688 (0.540-0.877)</p> <p><b>HRQOL</b>  NR</p> <p><b>Harms (279 vs 134)</b>  Discontinuation 2/2 AE: 48 vs 12  Death attributed to treatment: 1 vs 0  Death: 7 vs 4  Serious AE: 104 vs 37</p> <p><b>Overall Response</b>  Definition: RECIST 1.1  Events: 51 vs 6</p> <p><b>Disease Control</b></p>
---	--	---	--

	95% CI, 0.48 to 0.92; nominal one-sided P = 0.0066) and a two-stage survival analysis model (10.6 v 7.6 months; HR, 0.68; 95% CI, 0.53 to 0.86; nominal one-sided P = 0.0011).		Definition: RECIST 1.1 Events: 173 vs 72
--	--	--	---

Abbreviations: CP, Child Pugh score; ECOG, Eastern Cooperative Oncology Group performance status; RECIST, Response Evaluation Criteria in Solid Tumors; CNS, central nervous system; HIV, human immunodeficiency virus; GI, gastrointestinal; FHSI-8, Functional Assessment of Cancer Therapy–Hepatobiliary Symptom Index; FACT–HP, Functional Assessment of Cancer Therapy–Hepatobiliary

PICO 2: In patients with hepatocellular carcinoma who failed locoregional therapy, were ineligible for locoregional therapy, or have metastatic disease with poor liver function, should systemic therapy be used?

Author, Yr, Design, Country	Baseline	Intervention/Comparator	Outcomes
Sorafenib vs BSC as First-Line in CP B or C			
Ji 2014 RCT China Follow-up NR PICO 5	<p><b>Inclusion:</b> Advanced HCC. CP B or C, BCLC B or C, and estimated life time <math>\geq 2</math> months. Failed to respond or ineligible to locoregional treatment. Local therapy must be completed at least 4 weeks prior to baseline scan. ECOG <math>\leq 2</math>. Adequate renal function. One or more evaluable target lesion that could be measured in one dimension according to RECIST 1.1</p> <p><b>Exclusion:</b> Prior molecular target therapy.</p> <p><b>Study Design:</b> - Randomization with dynamic balancing with respect to performance status (based on WHO performance scale</p>	<p><b>I:</b> Sorafenib (95) Dose: 400 mg twice daily Received Rx: 89 Age: 59.4 Male%: 85 CP: B 76%, C 24% BCLC: B 12%, C 88% ECOG: 1: 25% 2: 75%</p> <p><b>C:</b> Best supportive care (94) Dose: none Received Rx: 91 Age: 58.6 Male%: 83 CP: B 74%, C 26% BCLC: B 13%, C 87%</p>	<p><b>Overall Survival</b> Events: 64 vs 75 Median: 4.0 vs 3.5 months HR: 0.48 (0.35-0.68)</p> <p><b>Disease-Specific Survival</b> NR</p> <p><b>Progression-Free Survival</b> Definition: RECIST 1.1 Events: NR Median: 2.2 vs 1.9 months HR: 0.55 (0.4-0.75)</p> <p><b>Time to Progression</b> NR</p>

	<p>measuring activity), sex, HBV or HCV infection history, and BCLC stage.</p> <ul style="list-style-type: none"> <li>- Treatment continued until disease progression (RECIST 1.1) and symptomatic progression (FHSI-8), liver function worsened to CP C or ECOG to grade 3, requested by patients or physicians, or uncontrollable serious adverse effects or death.</li> <li>- Two dose reductions permitted</li> <li>- Tumor measurements at screening and every 4 weeks thereafter</li> <li>- Quality-of-life questionnaires were administered at baseline, on day 1 of each cycle, and at the off treatment visit (within 30 days of the final administration of study drug)</li> </ul>	<p>ECOG: 1: 29% 2: 71%</p>	<p><b>HRQOL</b> The quality of life of the 2 groups did not differ significantly at baseline or during the treatment, according to the response to the FHSI-8 questionnaire</p> <p><b>Harms</b> Discontinuation 2/2 AE: 2 (diarrhea) vs 0 Death: 0 vs 0</p> <p><b>Overall Response</b> Definition: RECIST 1.1 Events: 1 vs 0</p> <p><b>Disease Control</b> Definition: RECIST 1.1 Events: 41 vs 27</p>
--	--	----------------------------	--

PICO 3: In patients with HCC undergoing curative surgical resection, should systemic therapies be used?

Author, Yr, Design, Country	Baseline	Intervention/Comparator	Outcomes
<p>Bruix 2015 (STORM) NCT00692770  RCT  28 countries</p>	<p><b>Inclusion:</b> Confirmed first diagnosis of HCC suitable for curative treatment with confirmed complete radiological response based on masked central independent review (3 weeks after resection or 7 weeks after local ablation with RFA or percutaneous ethanol injection). No more than 4 months between initial staging scan and completion of curative treatment. Patients had a surgically resectable lesion regardless of size, or a</p>	<p><b>I:</b> Sorafenib (556) Dose: 400 mg twice daily for up to 4 years or until disease recurrence. Received Rx: 553 Age: median 58 Male%: 81% CP: 5: 77%, 6: 20%, 7: 3%</p>	<p><b>Overall Survival</b> Follow-up: median 23 (IQR 12.7-36.0) vs 22.0 (14.4-35.5) months Median: NR vs NR Events: 104 vs 113 HR 0.995 (0.761-1.300)</p> <p><b>Disease-Specific Survival</b></p>

<p>Median 8.5 (IQR 2.9-19.5) vs 8.4 (2.9-19.8) months. Up to 4 years of follow-up.</p> <p>(Also listed under PICO 3)</p>	<p>single 5 cm or smaller lesion or no more than 3 lesions 3 cm or smaller for ablation.  CP 5-7 (7 only allowed if had no ascites), ECOG 0, AFP &lt; 400 ng/mL, adequate bone marrow, liver and renal function within 14 day before randomization.  Patients with intermediate (resection: a single tumour of 2 cm or larger with well differentiated or moderately differentiated microscopic appearance, and the absence of microvascular invasion or satellite tumours; ablation: a single tumour 2-3 cm in size) or high (resection: one tumour of any size plus microvascular invasion, satellite tumours, or poorly differentiated microscopic appearance, or two or three tumours each 3 cm or smaller in size; ablation: a tumour 3-5 cm in size or two or three tumours each 3 cm or smaller) risk of recurrence based on tumor characteristics as established by pathology report.</p> <p><b>Exclusion:</b> recurrent HCC; macrovascular invasion; a history of cardiovascular disease (myocardial infarction &gt;6 months before study entry was allowed); infection with HIV or other clinically serious infections; seizure disorder requiring drugs; and previous anticancer treatment for HCC, including sorafenib.</p> <p><b>Design:</b></p> <ul style="list-style-type: none"> <li>- Stratified based on type curative treatment, geographical region, CP (A5/6 vs B7), and risk of recurrence.</li> <li>- Randomization occurred 6-12 weeks after curative treatment.</li> <li>- Treatment interruptions and up to two levels of dose reductions (first to 400 mg once a day and then to 400 mg every other day) were allowed if drug-related adverse events were recorded. If further dose reductions were needed, treatment was to be discontinued.</li> </ul>	<p>BCLC: NR  ECOG: 0: 99%, 1: &lt;5%  Treatment: resection 450, ablation 106  Risk: intermediate 298, high 258  Duration median 12.5 (IQR 2.6-35.8)</p> <p><b>C:</b> Placebo (558)  Dose: matching placebo  Received Rx: 554  Age: 60  Male%: 81  CP: 5: 77%, 6: 19%, 7: 3%, 8: &lt;1%  BCLC: NR  ECOG: 0: 100%, 1: &lt;1%  Treatment: resection 450, ablation 108  Risk: intermediate 308, high 250  Duration median 22.2 (IQR 8.1-38.8)</p>	<p>NR</p> <p><b>Recurrence-free survival</b>  Definition: time from randomization to the first documented disease recurrence by independent radiological assessment (intrahepatic or extrahepatic) or death by any cause  Median 33.3 (27.6-44.0) vs 33.7 (27.6-39.0) months  Events: 194 vs 270  HR 0.94 (0.78-1.134)</p> <p><u>Subgroups:</u>  Resection 0.937 (0.759-1.156); median 41.7 vs 38.7 months  Ablation: 0.970 (0.656-1.434); median 19.6 vs 22.1 months</p> <p><b>Time to recurrence</b>  Definition: time from randomization to the first documented disease recurrence by independent radiological assessment  Median 38.5 (30.4-NE) vs 35.8 (30.3-41.4)  HR 0.891 (0.735-1.081)</p> <p><b>HRQOL</b>  NR</p> <p><b>Harms</b>  Discontinuation due to AE 133 vs 41  Serious adverse events 225 vs 228  Death 15 vs 9</p>
--	---	---	---

PICO 4: In patients with HCC undergoing liver transplantation, should systemic therapies be used?

Author, Yr, Design, Country	Baseline	Intervention/Comparator	Outcomes
<p>Kulik 2014 NCT00846131 RCT</p> <p>USA</p> <p>PICO: 2</p> <p>Median follow-up after transplant 29.9 months</p>	<p><b>Inclusion:</b> HCC confirmed by histology or imaging, CP &lt;= B8, potential candidate for OLT per UCS criteria</p> <p><b>Exclusion:</b> extrahepatic disease, vascular invasion, performance status &gt;2, or biological/clinical abnormalities contraindicating sorafenib/Y90</p> <p>Discontinuation rules: self-withdrawal, deterioration of performance status to P3, &gt;12 months of sorafenib or &gt;2 Y90 treatments.</p>	<p><b>I:</b> Sorafenib + Y90 (11) Dose: 400 mg bid Received Rx: 10 Age: 58 Male%: 80 CP: A 8%, B 2% BCLC: A 7%, B 1%, C 2% ECOG: 0: 8%, 1: 2%</p> <p><b>C:</b> Y90 alone (12) Dose: NA Received Rx: 10 Age: 60 Male%: 50 CP A 6% , B 4 % BCLC: A 5%, B 1%, C 4% ECOG: 0: 6%, 1: 3%, 2: 1%</p>	<p><b>Overall Survival</b> 3 year: SY90 72% vs Y90 70%</p> <p><b>Recurrence rate at 3 years:</b> 0 both arms</p> <p><b>Transplanted</b> SY90: 8 vs Y90: 9 Time to transplant: 7.8 months (range: 4.2–20.3) and similar between groups (p= 0.35)</p> <p><b>Harms:</b> Discontinuation of sorafenib due to side effects: 50% Among non transplanted: 1 in SY90 had hepatic resection, 1 died HCC progression. 1 died from sepsis in Y90. 3 Transplanted died: Y90: complications of CABG at 120 days, at 49 days one with multisystem failure and cerebrovascular event. SY90: 1 at 970 days with sepsis/renal failure.</p> <p>Post transplant biliary complication: SY90: 3 biliary anastomotic</p>

			<p>strictures and 1 leak due to anastomotic stricture vs 0 biliary complications in Y90</p> <p>SY90: 3/8 acute cellular rejection vs Y90: 0/9</p> <p><b>Disease-Specific Survival</b> NR</p> <p><b>Progression-Free Survival</b> NR</p> <p><b>Time to Progression</b> NR</p> <p><b>HRQOL</b> NR</p>
<p>Hoffman 2015 (HeiLivCa trial) RCT</p> <p>Germany</p>	<p><b>Inclusion:</b> HCC according to Milan and suitable for liver transplantation, measurable disease parameters according to mRECIST, no evidence of radiologically defined major vascular invasion or extrahepatic metastases, Karnofsky index &gt; 80%, adequate liver, renal and hematological function, negative pregnancy test.</p> <p><b>Exclusion:</b> prior systemic, anticancer therapy or local tumor therapy, thrombotic or embolic events, hemorrhage/bleeding event of Grade III within four weeks of first dose of study drug, any reported cardiovascular disease, uncontrolled infection and HIV seropositive patients.</p> <p><b>Study Design:</b> - Treatment continued until progression of disease or</p>	<p><b>I:</b> Sorafenib (24) Dose: 400 mg bid Received Rx: 24 Age: 58.5 CP A 58.3%, B 37.5%, C 4.2% labMELD 11 (6-15) BCLC: NR Duration median 4.17 (range 0.03-12.7) months</p> <p><b>C:</b> Placebo (26) Dose: NA Received Rx: 25 Age: 58.0 CP A 76.9%, B 23.1% labMELD 11 (6-37) BCLC: NR</p>	<p><b>Overall Survival</b> NR</p> <p><b>Disease-Specific Survival</b> NR</p> <p><b>Progression-Free Survival</b> Definition: time between the date of the first dose of the study medication and the date of the first indication of disease progression or death due to any cause, provided that the death occurred before tumour progression was documented. Events: NR HR 1.259 (0.485-3.270)</p>

liver transplantation. Medication stopped 3 days before and after TACE. TACE performed every 4 weeks until devascularization of the treated nodule.

Duration median 5.7 (range 0.03-12.2) months

Overall population: male: 90%

**Time to Progression**

Definition: time between the first dose of the study medication and the first documentation of tumour progression (mRECIST)

Events 7 vs 7

Median 2.4 (range 0.03-13.1) vs 2.8 (0.03-13.5) months

HR 1.106 (0.387-3.162)

**HRQOL**

NR

**Harms**

Discontinuation 2/2 AE: 6 vs 1

SAE: 3 vs 3

Death: no tx related deaths

**Objective response rate**

Definition: mRECIST

Events: 5 vs 7

**Disease control rate**

Definition: mRECIST

Events: 16 vs 19

**Time-to-LT**

Definition: time between first dose and LT

Transplantation 5 vs 12

Median 5.1 (1.0-11.3) vs 5.8 (1.2-10.5) months

153 (31-339) vs 174 (37-351)

HR 0.575 (0.192-1.721)

Recurrence: 0 vs 2

PICO 5: In patients with HCC undergoing locoregional therapy, should systemic therapies be used?

Author, Yr, Design, Country	Baseline	Intervention/Comparator	Outcomes
Sorafenib + Curative Locoregional Therapy			
Kan 2015 RCT China	<p><b>Inclusion::</b> HBV related HCC (3.1-5 cm), no previous treatment for HCC, CP A or B, ECOG 0-2, PT ≤ 18, unwilling to undergo partial hepatectomy.</p> <p><b>Study Design:</b></p> <ul style="list-style-type: none"> <li>- Clinical exam, CT and blood work at 4 and 3rd month following ablation and same examination every 2 month</li> <li>- TACE was performed 7-10 days before RFA if the tumor was hypervascular.</li> <li>- CT repretated 4-6 weeks after RFA. If a viable tumor was present, repeat RFA was done if appropriate.</li> </ul>	<p><b>I:</b> Sorafenib and RFA (30)                      Dose: 400 mg bid on day 4-7 after RFA                      Received Rx: NR                      Age: 53.7                      Male%: 80                      CP: A 40%, B 60%                      BCLC: B: 26.7%, C: 73.3%                      Duration: NR</p> <p><b>C:</b> RFA alone (32)                      Dose: NA                      Received Rx: NR                      Age: 52.4                      Male%: 78.1                      CP: A 43.8%, B 56.2%                      BCLC: B 43.6%, C 56.4%                      Duration: NR</p>	<p><b>Overall Survival</b>                      NR (majority of patients were alive)</p> <p><b>Disease-Specific Survival</b>                      NR</p> <p><b>Recurrence-Free Survival</b>                      NR</p> <p><b>Time to Recurrence</b>                      1-year-recurrence rate: 11 vs 20                      2-year-recurrence rate: 13 vs 25                      3-year-recurrence rate: 17 vs 28</p> <p><b>Time to Progression</b>                      Definition: NR                      Events: NR                      Median: 17 months vs 6.1 months                      HR: NR</p> <p><b>HRQOL</b>                      NR</p> <p><b>Harms</b>                      Discontinuation 2/2 AE: NR                      SAE: NR</p>
Bruix 2015	<b>Inclusion:</b> Confirmed first diagnosis of HCC suitable for	<b>I:</b> Sorafenib (556)	<b>Overall Survival</b>

<p>(STORM) NCT00692770</p> <p>RCT</p> <p>28 countries</p> <p>Median 8.5 (IQR 2.9-19.5) vs 8.4 (2.9-19.8) months. Up to 4 years of follow-up.</p> <p>(Also listed under PICO 1)</p>	<p>curative treatment with confirmed complete radiological response based on masked central independent review (3 weeks after resection or 7 weeks after local ablation with RFA or percutaneous ethanol injection). No more than 4 months between initial staging scan and completion of curative treatment. Patients had a surgically resectable lesion regardless of size, or a single 5 cm or smaller lesion or no more than 3 lesions 3 cm or smaller for ablation.</p> <p>CP 5-7 (7 only allowed if had no ascites), ECOG 0, AFP &lt; 400 ng/mL, adequate bone marrow, liver and renal function within 14 day before randomization.</p> <p>Patients with intermediate (resection: a single tumour of 2 cm or larger with well differentiated or moderately differentiated microscopic appearance, and the absence of microvascular invasion or satellite tumours; ablation: a single tumour 2-3 cm in size) or high (resection: one tumour of any size plus microvascular invasion, satellite tumours, or poorly differentiated microscopic appearance, or two or three tumours each 3 cm or smaller in size; ablation: a tumour 3-5 cm in size or two or three tumours each 3 cm or smaller) risk of recurrence based on tumor characteristics as established by pathology report.</p> <p><b>Exclusion:</b> recurrent HCC; macrovascular invasion; a history of cardiovascular disease (myocardial infarction &gt;6 months before study entry was allowed); infection with HIV or other clinically serious infections; seizure disorder requiring drugs; and previous anticancer treatment for HCC, including sorafenib.</p> <p><b>Design:</b> - Stratified based on type curative treatment, geographical region, CP (A5/6 vs B7), and risk of recurrence.</p>	<p>Dose: 400 mg twice daily for up to 4 years or until disease recurrence.</p> <p>Received Rx: 553</p> <p>Age: median 58</p> <p>Male%: 81%</p> <p>CP: 5: 77%, 6: 20%, 7: 3%</p> <p>BCLC: NR</p> <p>ECOG: 0: 99%, 1: &lt;5%</p> <p>Treatment: resection 450, ablation 106</p> <p>Risk: intermediate 298, high 258</p> <p>Duration median 12.5 (IQR 2.6-35.8)</p> <p><b>C: Placebo (558)</b></p> <p>Dose: matching placebo</p> <p>Received Rx: 554</p> <p>Age: 60</p> <p>Male%: 81</p> <p>CP: 5: 77%, 6: 19%, 7: 3%, 8: &lt;1%</p> <p>BCLC: NR</p> <p>ECOG: 0: 100%, 1: &lt;1%</p> <p>Treatment: resection 450, ablation 108</p> <p>Risk: intermediate 308, high 250</p> <p>Duration median 22.2 (IQR 8.1-38.8)</p>	<p>Follow-up: median 23 (IQR 12.7-36.0) vs 22.0 (14.4-35.5) months</p> <p>Median: NR vs NR</p> <p>Events: 104 vs 113</p> <p>HR 0.995 (0.761-1.300)</p> <p><b>Disease-Specific Survival</b> NR</p> <p><b>Recurrence-free survival</b> Definition: time from randomization to the first documented disease recurrence by independent radiological assessment (intrahepatic or extrahepatic) or death by any cause</p> <p>Median 33.3 (27.6-44.0) vs 33.7 (27.6-39.0) months</p> <p>Events: 194 vs 270</p> <p>HR 0.94 (0.78-1.134)</p> <p><u>Subgroups:</u> Resection 0.937 (0.759-1.156); median 41.7 vs 38.7 months</p> <p>Ablation: 0.970 (0.656-1.434); median 19.6 vs 22.1 months</p> <p><b>Time to recurrence</b> Definition: time from randomization to the first documented disease recurrence by independent radiological assessment</p> <p>Median 38.5 (30.4-NE) vs 35.8 (30.3-41.4)</p> <p>HR 0.891 (0.735-1.081)</p> <p><b>HRQoL</b></p>
--	--	---	---

	<p>- Randomization occurred 6-12 weeks after curative treatment.</p> <p>- Treatment interruptions and up to two levels of dose reductions (first to 400 mg once a day and then to 400 mg every other day) were allowed if drug-related adverse events were recorded. If further dose reductions were needed, treatment was to be discontinued.</p>		<p>NR</p> <p><b>Harms</b>  Discontinuation due to AE 133 vs 41  Serious adverse events 225 vs 228  Death 15 vs 9</p>
<b>Sorafenib + TACE</b>			
<p>Kudo 2011 NCT00494299</p> <p>RCT Japan and South Korea</p> <p>Follow up 3.9 w (0.2-25.8) vs 4.6 w (0.5-33.2) months</p>	<p><b>Inclusion:</b> adults with unresectable HCC; CP A; sustained a response 1-3 months after TACE (defined as <math>\geq 25\%</math> tumor necrosis and/or shrinkage); life expectancy <math>\geq 12</math> weeks; maximum target lesion of 7 cv; <math>\leq 10</math> target lesions; ECOG PS 0 or 1; adequate bone marrow, renal and hepatic function; amylase and lipase <math>\leq 2 \times \text{ULN}</math>.</p> <p><b>Exclusion:</b> macroscopic vascular invasion; renal failure; history of cardiac disease; active clinically serious infection; history of HIV infection; symptomatic metastatic brain or meningeal tumor; extrahepatic metastasis; seizure disorder requiring medication; prior use of systemic agents for advanced HCC (prior use of interferon, retinoid and/or vitamin K as adjuvant treatment after curative local treatment was allowed); use of hematopoietic growth factors within 3 weeks before start of study drug; concomitant treatment with cytokines after the last course of TACE; history of organ allograft; documented history of substance abuse; pregnancy or Breast-feeding.</p>	<p><b>I: Sorafenib (229)</b>  Dose: 400 mg twice daily  Received Rx: NA  Age: 69  Male%: 76%  CP: A 100%  BCLC: NR  ECOG: 0: 87.8%, 1: 12.2%</p> <p><b>C: Placebo (229)</b>  Dose: twice daily  Received Rx: 227  Age: 70  Male%: 73.4%  CP: A 100%  BCLC: NR  ECOG: 0: 88.2% 1: 11.8%</p>	<p><b>Overall Survival (mortality)</b>  Events: 43 vs 41  1-year: 94.6%vs 94.1%  2-year: 72.1% 73.8%  Median f/u: 29.7 m (28.6-NR) vs NR  HR: 1.06 (0.69-1.64)</p> <p><b>Disease-Specific Survival</b> NR</p> <p><b>Progression-Free Survival</b> NR</p> <p><b>Time to Progression (central review)</b>  Definition: time to recurrence in patients with complete remission and progression (<math>\geq 25\%</math> increase in tumour size or development of a new lesion) in patients with incomplete remission.  Events: 137 vs 187</p>

	<p><b>Study design:</b></p> <ul style="list-style-type: none"> <li>- stratified by: TACE response of complete (100% tumor necrosis or shrinkage) vs non complete response (25% ≤ to &lt;100% necrosis or shrinkage); ECOG PS; number of courses of TACE.</li> <li>- treatment continued until radiologic progression or recurrence of HCC, unacceptable toxicity associated with study drug, or withdrawal of consent</li> <li>- safety and compliance assessed every 2 weeks of cycles 1-3 (28-day cycles), and every 4 weeks thereafter.</li> <li>- tumors evaluated centrally at image registration centre ≤ 28 days before the first drug dose and every 8 weeks thereafter, or when evaluating recurrence/progression. Evaluation was done by dynamic CT.</li> </ul>		<p>Median f/u: 5.4 m (3.8-7.2) vs 3.7 (3.5-4.0) HR: 0.87 (0.70-1.09)</p> <p><b>HRQOL</b> NR</p> <p><b>Harms (229 vs 227)</b> Discontinuation 2/2 AE: 93/229 vs 13/227 Death: 0 vs 0 Drug-related SAE 44/229 vs 21/227</p> <p><b>Overall Response</b> NR</p> <p><b>Disease Control</b> NR</p>
<p>Kudo 2020 (TACTICS) NCT01217034.</p> <p>RCT</p> <p>33 Japan centers</p> <p>Follow-up 28 months</p>	<p><b>Inclusion:</b> unresectable HCC; age ≥ 20 years; life expectancy ≥ 12 weeks; tumors confined to the liver without vascular invasion/extrahepatic spread (EHS); treatable by TACE; maximum tumor diameter 10 cm; maximum number of nodules 10; max number of TACE procedures allowed before enrolment was 2, with at least 6 months since prior TACE (all who had a history of prior TACE achieved complete response, but recurred more than 6 months later at the study entry); ECOG PS 0 or 1; CP ≤ 7 points; and adequate organ function. Prior resection or ablation allowed.</p> <p><b>Exclusion:</b> another previous or current malignant</p>	<p><b>I:</b> Sorafenib + TACE (80) Dose: 400 mg twice daily 2-3 weeks prior to first TACE. Discontinued 2 days before and after TACE. Received Rx: 77 Age: 72 Male%: 78.8% CP: 5 80%, 6 18.8%, 7 1.3% BCLC: A 33.8%, B 55%, C 11.3% ECOG: 0: 88.8%, 1: 11.3</p> <p><b>C:</b> TACE alone (76) Dose: twice daily</p>	<p><b>Overall Survival</b> Events: NR 1-year: 96.2% vs 82.7% 2-year: 77.2% vs 64.6% Median time: 36.2 vs 30.8 months. HR: 0.861 (0.607-1.223)</p> <p><b>Disease-Specific Survival</b> NR</p> <p><b>Progression-Free Survival</b> Definition: time to unTACEable progression or death Events: NR Median time: 22.8 m vs 13.5</p>

	<p>tumour, except for early stage cancer with low risk of recurrence or a malignant tumour curatively treated &gt;3 years prior; cardiac disease or a serious and active infection, except HBV and HCV; diffuse tumour lesions, extrahepatic metastases, vascular invasion, hepatic encephalopathy, uncontrolled ascites or pleural effusion; previously treated for advanced HCC, including systemic chemotherapy, and those treated with CYP3A4- inducing agents; decompensated liver function.</p> <p><b>Study Design:</b></p> <ul style="list-style-type: none"> <li>- stratified by: study center; meeting or not meeting Milac criteria; number or prior TACE sessions</li> <li>- treatment continued until untreatable progression, progression to meet TACE refractoriness criteria, unacceptable toxicity, or withdrawal of consent</li> <li>- tumors assessed 4 weeks after TACE then every 8 weeks. Assessment done with dynamic CT or MRI.</li> <li>- Definitions: <ul style="list-style-type: none"> <li>= complete response: complete lipiodol retention within the nodule)</li> <li>= incomplete response: 50-100% lipiodol retention within the nodule</li> <li>= progression: JSH criteria for TACE failure/refractoriness, 2 or more consecutive insufficiency responses of the treated tumor (viable lesion &gt;50%) or two or more consecutive unnumbered increases in liver tumor number as determined by dynamic CT/MRI</li> </ul> </li> </ul>	<p>Received Rx: 71  Age: 73  Male%: 72.4%  CP: 5 71.1%, 6 22.4%, 7 5.6%  BCLC: A 43.4%, B 44.7%, C 11.8%  ECOG: 0: 88.2%, 1: 11.8%</p>	<p>months  HR: 0.661 (0.466-0.938)</p> <p><b>Time to Progression</b>  Definition: untreatable progression (inability to receive or benefit from TACE for reasons that included intrahepatic tumor progression according to RECICL, transient deterioration of liver function to CP C after TACE, macrovascular invasion, or extrahepatic spread); new hepatic lesion not regarded as progressive disease  Events: NR  Median f/u: 26.7 vs 16.4 m  HR: 0.54 (0.35-0.83)</p> <p><b>HRQOL</b>  NR</p> <p><b>Harms</b>  Discontinuation 2/2 AE: NR  Death: NR  SAE: NR</p> <p><b>Overall Response</b>  4 weeks after TACE: 57 vs 47  Not evaluable: 11 vs 14</p> <p><b>Disease Control</b>  4 weeks after TACE: 67 vs 59  Not evaluable: 11 vs 14</p>
Lencioni 2016	<b>Inclusion:</b> unresectable, multinodular, asymptomatic	I: Sorafenib + TACE (154)	<b>Overall survival</b>

<p>(SPACE) NCT00855218</p> <p>RCT</p> <p>13 countries</p> <p>Up to 28 months of follow-up.</p>	<p>HCC (BCLC stage B), with measurable lesions on CT or MRI; no macrovascular invasion or extrahepatic spread; CP A and compensated liver function; ECOG 0, no ascites; age <math>\geq 18</math> with life expectancy <math>\geq 12</math> months; adequate bone marrow, liver and kidney functions</p> <p><b>Exclusion:</b> diffuse HCC; vascular invasion (including segmental portal obstruction); extrahepatic tumor spread; advanced liver disease; contraindications for embolization; target lesion had previously undergone local treatment, including resection, radiofrequency ablation, percutaneous ethanol injection, or TACE; if they had received local therapy within 4 weeks of a baseline scan; had prior transarterial embolization or TACE; were previously treated with a kinase inhibitor; or had received anthracyclines or radiotherapy for HCC.</p> <p><b>Study Design:</b></p> <ul style="list-style-type: none"> <li>- Every patient received DEB-TACE. 300-500 micrometer beads; 150 mg doxorubicin. Treatment was divided into 4-week cycles from starting the study drug. First TACE was performed 3-7 days later, then on day 1 (+/- 4 days) of cycles 3, 7 and 14 and every 6 cycles thereafter.</li> <li>- Stratified based on geographical region, and serum AFP (&lt;400 vs <math>\geq 400</math>)</li> </ul>	<p>Dose: 400 mg bid Received Rx: 153 Age: 64.5 Male%: 87.7 CP: 5: 63.6%, 6: 35.7%, 7: 0.6% BCLC: B 100% Duration median 6.7 months</p> <p>C: Placebo + TACE (153) Dose: matching placebo Received Rx: 151 Age: 63.0 Male%: 82.4 CP: 5: 68.6%, 6: 30.7%, 7: 0%, missing: 0.7% BCLC: B 100% Duration median 7.8 months</p>	<p>Events: 52 (after 270 days) vs 49 (after 272 days) Median time: not reached in either group HR 0.898 (0.606-1.330)</p> <p><b>Disease-Specific Survival:</b> NR</p> <p><b>Progression-Free Survival</b> NR</p> <p><b>Time to Progression</b> Definition: mRECIST Events: NR Median time: 5.6 (5.5-7.3) vs 5.5 (3.8-5.6) months HR: 0.797 (0.588-1.080)</p> <p><b>HRQOL</b> NR</p> <p><b>Harms (153 vs 151)</b> Discontinuation 2/2 AE: 41 vs 26 SAE: 86 vs 56 Death 4 (liver dysfunction, constitutional, other syndrome) vs 1 (duodenal perforation)</p> <p><b>Overall Response</b> Definition: mRECIST Events: 55 vs 43 Not evaluable: 27 vs 18</p> <p><b>Disease Control</b> Definition: mRECIST</p>
--	--	--	---

			Events: 107 vs 99 Not evaluable: 27 vs 18
Meyer 2017 (TACE 2) NCT01324076  RCT  U.K.  Median 20.7 (95% CI, 19.1- 23.1) months follow-up.	<p><b>Inclusion:</b> histological or non-invasive diagnosis of HCC, at least one unidimensional lesion measurable according to RECIST v1.1, not a candidate for surgical resection or liver transplant, ECOG 1 or less, CP A, adequate bone marrow, liver, and renal functions.</p> <p><b>Exclusion:</b> extrahepatic metastasis, previous embolization, systemic therapy or radiotherapy for hepatocellular carcinoma, any contraindication to hepatic embolization, previous investigational therapy, major surgery or history of bleeding within 4 weeks of trial entry, hepatic encephalopathy, occlusion of the hepatic artery or main portal vein, myocardial infarction within 6 months or prolonged QT/QTc of more than 450 ms.</p> <p><b>Study Design:</b></p> <ul style="list-style-type: none"> <li>- Every patient received DEB-TACE. 100-500 micrometer beads; 150 mg doxorubicin. Treatment was given 2-5 weeks post-randomization, then follow-up treatment based on follow-up imaging.</li> <li>- Stratified based on serum AFP (&lt;400 vs &gt;=400)</li> <li>- Previous resection/ablation 7% vs 13%</li> <li>- Medication continued until disease progression according to RECIST v1.1, unacceptable toxicity, dose interruption of more than 30 days, patient choice, or the recommendation of the investigator.</li> <li>- On progression, patients were unmasked and entered the post-study treatment period. Unmasking was done based on local review first.</li> <li>- Trial terminated early due to lack of benefit based on interim analysis.</li> </ul>	<p><b>I: Sorafenib + TACE (157)</b> Dose: 400 mg twice a day Received Rx: 157 Age: 65 Male%: 89% CP: 5: 68%, 6: 25%, 7: 3%, 8: 1%, Unknown: 4% BCLC: NR Duration median 4 (IQR 1.4-8.9) months</p> <p><b>C: Placebo + TACE (156)</b> Dose: matching placebo Received Rx: 156 Age: 68 Male%: 88% CP: 5: 73%, 6: 22%, 7: 1%, 8: 1%, Unknown: 3% BCLC: NR Duration median 5.4 (IQR 2.3-10.8) months</p>	<p><b>Overall Survival</b> Events: NR (total 164) Median time: 21.0 (14.6-29.3) vs 19.9 (16.7-23.2) months HR 0.91 (0.67-1.24)</p> <p><b>Disease-Specific Survival:</b> NR</p> <p><b>Progression-Free Survival</b> Definition: RECIST v1.1 Events: NR (total 246) Median time: 7.9 (7.4-9.4) vs 7.8 (7.0-10.7) months HR: 0.99 (0.77-1.27)</p> <p><b>Time to Progression</b> Definition: RECIST v1.1 Events: NR Median time: 10.9 (8-13.7) vs 10.7 (7.8-13.3) months HR: 0.88 (0.67-1.17)</p> <p><b>HRQOL</b> 140/157 vs 149/156 returned at least one QOL questionnaire form. "According to multilevel regression of QLQ-C30 score over 12 months, both the mean social and role functioning scales were found to be up to 6% lower (p=0.045 and p=0.050) for patients in the</p>

			<p>sorafenib group. Of the symptom scales, mean diarrhoea score was up to 13% higher on average in the sorafenib group (p=0.0095) and mean appetite loss score was up to 10% higher (p=0.0018). According to HCC18, mean nutritional problem scores were up to 7% worse in the sorafenib group (p=0.0084). No evidence of non-zero interactions was observed. No significant differences were observed in other QOL scales.”, quoted from the study.</p> <p><b>Harms</b>  Discontinuation 2/2 AE: 30 vs 16  SAE: 65 vs 50  Death: 3 (acute liver failure, infection, HRS) vs 1</p> <p><b>Overall Response</b>  Definition: mRECIST  Events: 84/157 vs 81/156</p> <p><b>Disease Control</b>  Definition: mRECIST  Events:117/157 vs 120/156</p>
Bevacizumab + TACE			
Britten 2012 NCT00049322  RCT	<b>Inclusion:</b> HCC by EASL diagnostic imaging criteria or biopsy; TACE candidates with at least 1 lesion ≥ 3 cm and no lesion ≥ 15 cm and no more than 3 lesions	<b>I: Bevacizumab + TACE (15):</b> Dose: bevacizumab at a dose of 10 mg/kg IV every 14 days beginning 1 week prior to TACE	<b>Overall Survival</b> Median: 61 vs 49 months  <b>Disease-Specific Survival</b>

<p>USA</p> <p>16 weeks follow-up.</p>	<p>total; <i>awaiting OLT eligible if MELD less than 28 upon entry</i></p> <p><b>Exclusion:</b> CP C, ECOG &gt; 2; hepatic dysfunction; extrahepatic disease; thrombosis of the main portal vein; contraindications to Bevacizumab; thrombocytopenia.</p> <p><b>Study Design:</b></p> <ul style="list-style-type: none"> <li>- TACE on day 8 of all lesions. Angiogram during week 10 and 14 to assess tumor vascularity. Second TACE offered at week 14 if second TACE was performed if a previously embolized feeding vessel recanalized, there was residual tumor blush in a treated area, and a feeding vessel was visualized, or new lesions had developed that were amenable to TACE.</li> <li>- All patients had triple phase CT and/or MRI within 4 weeks of protocol treatment, then for disease assessment every 8 weeks.</li> <li>- Drug continued until unacceptable toxicity, developed tumor progression, their MELD score increased to &gt; 28 points, or patient request.</li> <li>- Safety evaluation 30 and 60 days after intervention</li> <li>- Follow up 16 weeks then institutional practice follow up with every 3 month survival assessment</li> </ul>	<p>and every 2 weeks 10 mg/kg as long as serum transaminases returned to pre TACE levels or within normal range.</p> <p>Received Rx: 15 Age: 61 Male%: 87% CP: A 87%, B 13% BCLC: A 7%, B 67%, C 27%</p> <p><b>C: Observation + TACE (15):</b> Dose: NA Received Rx: 14 Age: 58 Male%: 80% CP: A 100% BCLC: A 20%, B 67%, C 13%</p> <p>Received transplant: 4 vs 4</p>	<p>NR</p> <p><b>Progression-Free Survival</b> Definition: censored at last disease assessment, OLT, second TACE if performed without progressive disease, administration of a test dose of chemoembolization material. Events (16 weeks): 3 vs 12</p> <p><b>Time to Progression</b> Definition: increase in sum bidimensional products of all known disease by at least 25%, increase in enhancement of previously treated lesion, appearance of a new lesion, or evidence of neovascularization by angiography at week 14.</p> <p><b>HRQOL</b> NR</p> <p><b>Harms</b> Discontinuation 2/2 AE: 1 vs 0 SAE: 5 vs 1 Death: NR</p> <p><b>Overall Response</b> NR</p> <p><b>Disease Control</b> NR</p>
<p>Pinter 2015</p>	<p><b>Inclusion:</b> histologically confirmed early HCC (BCLC A)</p>	<p>I: Bevacizumab (16)</p>	<p><b>Overall survival</b></p>

(AVATACE)  
NCT00280007

RCT  
U.K.

not amenable to surgical or local ablative therapy, or intermediate HCC (BCLC B). Single or multifactorial HC with no lesion larger than 15 cm, or larger who had no contraindication to TACE. Treatment naive patients or subjects with recurrence after resection or ablation.

**Exclusion:** recurrence after liver transplantation, heart failure, BCLC C or D, prior transarterial or experimental therapy, acute variceal bleeding within 2 weeks prior to inclusion, large esophageal varices without prophylactic ligation, major surgical procedures within the past 4 weeks, use of anticoagulation, uncontrolled hypertension, clinically important cardiovascular disease within the past 6 months, serious impairment in wound healing, impaired hematologic or renal function, life expectancy less than 3 months.

**Every patient received conventional TACE**

25-75mg doxorubicin

After the first treatment, it was repeated twice at 4-week intervals if it was clinically feasible and if contrast enhancement of nodules was present at follow-up. Additional cycles applied if clinically indicated.

Dose: 5 mg/kg  
Received Rx: NA  
Age: m 61.1  
Male%: 81%  
CP: A 69%, B 31%  
BCLC: A: 13%, B: 88%

**C:** Placebo (16)  
Dose: Saline matching  
Received Rx: NA  
Age: 61.3  
Male%: 100  
CP: A 69%, B 31%  
BCLC: 13%, 88%

Median: 5.3 months (0.8-9.9) vs 13.7 (5.3-22.2)  
HR 1.7 (0.8-3.6)  
1 yr survival: 31% vs 55%  
Have CP breakdown if needed

**Disease-Specific Survival:**  
NR

**Progression-Free Survival**  
NR

**Time to Progression**

Definition: NR  
Events: NR  
Median time: 7.2 (4.1-10.3) vs 11.7 (4.9-18.6)  
HR 0.9 (0.3-2.4)

**HRQOL**  
NR

**Harms**

Discontinuation 2/2 AE:: NR  
Death 11 vs 7  
Fatal adverse events from the drug: 8 vs 1

**Overall Response**

Definition: European Association for the Study of the Liver Criteria  
1 year: 5 vs 3

**Disease Control**

Definition: European Association for the Study of the Liver Criteria

			1 year: 5 vs 3
--	--	--	----------------

DRAFT

## Appendix 6: Risk of Bias Assessment

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias (including post-protocol therapy)
Abou-Alfa 2018 (CELESTIAL)	+	+	+	+	+	+	?
Britten 2012	+	?	?	?	+	+	+
Bruix 2015 (STORM)	+	+	+	+	+	+	+
Bruix 2017 (RESORCE)	+	+	+	+	+	+	?
Cheng 2009 (ASIA-PACIFIC)	+	+	+	?	+	+	?
Finn 2020 (IMbrave150)	+	+	+	-	-	+	?
Finn 2020 (KEYNOTE-240)	+	+	+	+	+	+	?
Hoffman 2015 (HeiLivCa trial)	+	+	+	?	+	?	+
Kan 2015	+	+	+	+	+	+	+
Kudo 2011	?	?	+	+	+	+	+
Kudo 2018 (REFLECT)	+	+	-	+	+	+	?
Kudo 2020 (TACTICS)	+	+	-	?	+	-	+
Lencioni 2016 (SPACE)	?	?	+	+	+	+	+
Llovet 2008 (SHARP)	+	+	+	+	+	+	?
Meyer 2017 (TACE 2)	+	+	+	-	+	+	-
Pinter 2015 (AVATACE)	+	?	+	?	+	+	-
Zhu 2015 (REACH)	+	+	+	-	+	+	-
Zhu 2019 (REACH-2)	+	+	+	+	+	+	-

## Appendix 7: Evidence profiles

Separate file

DRAFT