

## ORIGINAL ARTICLE

# Ranking of transarterial and targeted therapies for advanced hepatocellular carcinoma in the era of immuno-oncology: A network meta-analysis of randomized sorafenib-controlled trials

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## Abstract

To date, no studies have compared the new first-line atezolizumab+bevacizumab with transarterial therapies combined with the prior standard-of-care, sorafenib, in patients with advanced hepatocellular carcinoma (HCC). We compared and ranked all relevant transarterial and targeted treatments competing with atezolizumab+bevacizumab for such disease, based on direct and indirect evidence. This network meta-analysis was conducted as a systematic review of phase 2 and 3 randomized sorafenib-controlled trials investigating systemic treatment strategies for HCCs unsuitable for or that progressed after surgery or locoregional treatments as first-line option published between 2008 and 2021. We ranked the treatments based on overall survival (OS) as the primary outcome, together with progression-free survival (PFS) and grade 3–4 adverse events. Subgroup analyses were also implemented to estimate intervention efficacies in particular groups. We identified 3451 publications, 15 trials consisting of 7158 patients, using 14 different therapies including combinations of sorafenib with transarterial chemoembolization (TACE), hepatic arterial chemoinfusion, and radioembolization. Regarding OS, atezolizumab+bevacizumab was the only regimen significantly superior to sorafenib (hazard ratio 0.42; 95% confidence interval [CI] 0.25–0.70), and it ranked first. This combination was also the best in the PFS analysis (0.59; 0.47–0.74), followed by lenvatinib (0.66; 0.57–0.76) and TACE+sorafenib (0.73; 0.59–0.91); all had significantly better outcomes than sorafenib alone. TACE+sorafenib (0.52; 0.27–1.00) was ranked first based on OS in a subset with portal invasion, but not in the metastatic series, with atezolizumab+bevacizumab second (0.58; 0.38–0.89). Lenvatinib (odds ratio 1.76; 95% CI 1.35–2.30) and TACE+sorafenib (2.02; 1.23–3.32), but not atezolizumab+bevacizumab (1.38; 0.93–2.05), were significantly less safe than sorafenib monotherapy. **Conclusion:** Our results indicate that

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atezolizumab+bevacizumab is the best first-line clinically relevant systemic modality in advanced HCC. TACE+sorafenib may also be considered for the disease with portal invasion. (PROSPERO No. CRD42021250701).

## INTRODUCTION

Since the approval of sorafenib (Sora) for hepatocellular carcinoma (HCC) in 2007, based on improved survival, Sora has been widely acknowledged as the standard first-line regimen for advanced patients.<sup>[1,2]</sup> However, the limited effectiveness of Sora monotherapy in terms of response rate and survival advantage made clinicians hesitant to use it, especially for massive or diffuse intrahepatic tumors.<sup>[3]</sup> Thereafter, a decade of clinical trials comparing compounds targeting other molecules with Sora failed to meet their primary endpoints until the emergence of lenvatinib (Lenv).<sup>[4]</sup> On the other hand, multiple trials of liver-directed therapies, involving transarterial chemoembolization (TACE), selective internal radiation therapy (SIRT), and hepatic arterial infusion chemotherapy (HAIC) in combination with Sora, have also been carried out in patients with extrahepatic metastasis and/or portal vein tumor thrombosis (PVTT), with some positive outcomes specifically for surrogate endpoints such as progression-free survival (PFS) and time to progression (TTP).<sup>[5–8]</sup> Such encouraging data have resulted in them being recommended as alternative first-line options to the standard molecular or immune-targeted therapies in the current pan-Asian guidelines.<sup>[9]</sup> The intrahepatic phenotype of HCC is a robust prognosis-predicting and response-predicting factor identified in trials of diverse systemic drugs.<sup>[10,11]</sup> Conversely, anti-HCC studies have highlighted the significance of intrahepatic tumor control for the longevity of patients with systemic disease.<sup>[3,12,13]</sup> In the pre-Sora era, the overall survival (OS) of good TACE responders with hepatic tumors was reported to reach 33.2% at 1 year even in metastatic cases.<sup>[12]</sup>

Most recently, a landmark head-to-head confrontation and subsequent network meta-analyses (NMAs) demonstrated the superiority of combined atezolizumab and bevacizumab (Atez+Beva) over Sora alone in improving all short-term and long-term parameters of patients with unresectable HCC.<sup>[14–16]</sup> This combination was the first chemotherapeutic regimen with a survival rate superior to Sora since the REFLECT trial showed the noninferiority of Lenv to the standard-of-care for advanced-stage HCC.<sup>[4]</sup> However, there are potential concerns about poorer responsiveness to immunotherapy of HCC within the liver compared with extrahepatic disease due to the adaptive and innate tolerogenic hepatic microenvironment.<sup>[17]</sup> No studies of any design have ever compared this new immunotherapeutic combination with combinations of transarterial

therapies primarily targeting intrahepatic lesions with Sora in patients with HCC.

In the current dramatically changing landscape of treatments for advanced-stage HCC, we performed an NMA comparing the outcomes of diverse systemic strategies, including transarterial approaches combined with Sora, in randomized Sora-controlled trials. Our aim was to provide useful information for making accurate evidence-based decisions about the best-in-class first-line option in the various tumor settings of metastatic and/or locally advanced HCC.

## METHODS

The report was prepared according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) extension statement for systematic reviews incorporating NMAs.<sup>[18]</sup> The institutional review board of Asan Medical Center approved this trial-level NMA and waived the informed consent of individual patients (internal review board No. 2021–0688). This review has been registered on the PROSPERO website as No. CRD42021250701.

### Literature search and systematic review

Together with the phase 3 trial on Atez+Beva, we aimed to identify all phase 2 or 3 randomized controlled trials (RCTs) that investigated single or combination regimens using targeted drugs and catheter-based intra-arterial therapies concurrent with Sora in patients with HCC indicated for Sora therapy as recommended by the guidelines,<sup>[19,20]</sup> such as those for tumors not amenable to surgical or locoregional treatments or tumors that had progressed after such treatments (Table S1). The following studies were excluded: (1) trials on hepatic artery-directed monotherapies without combined Sora; (2) those not sharing a Sora control arm; and (3) those including participants with locally advanced HCCs without metastatic disease, in whom only transarterial monotherapies (e.g., TACE, SIRT, or HAIC alone) were tested. We developed a sensitive search algorithm using MeSH Terms and text words in combination with an RCT filter (Table S2). Using this algorithm, we searched PubMed, Embase, and the Cochrane Central Register of Controlled Trials for studies reported from January 1, 2008, to February 28, 2021. Only full text articles published in peer-reviewed journals in English

were included. The list of titles and abstracts was independently screened for potentially relevant studies by two reviewers (J. An and J. H. Shim) using a Cochrane online systematic review tool (i.e., Covidence). After excluding duplicated and irrelevant studies, the remaining articles were reviewed in full text. Any disagreement was resolved in consensus.

## Outcomes and data extraction

The primary outcome was OS, defined as the time from the date of randomization to death from any cause, measured in the intent-to-treat population. The secondary outcome was PFS, defined as the interval from random assignment to either disease progression or death, whichever came first. In trials in which PFS was not reported as an endpoint, time elapsed until objective tumor progression (i.e., TTP) was substituted as the secondary outcome in the NMA.<sup>[21]</sup> Progressive disease was determined according to Response Evaluation Criteria in Solid Tumors (RECIST) and modified RECIST in 10 and 6 studies, respectively.<sup>[22]</sup> We also carried out an exploratory analysis reporting the proportions of patients with serious adverse events (SAEs) defined as grade 3 or worse, classified according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4 (grade 1, mild; grade 2, moderate; grade 3, severe or medically significant; grade 4, life-threatening). Details of the study design, therapeutic interventions, and patient and tumor characteristics including age, sex, Eastern Cooperative Oncology Group performance status, race/region, Child-Turcotte-Pugh (CTP) class, hepatitis B virus (HBV) infection, hepatitis C virus (HCV) infection, Barcelona Clinic Liver Cancer (BCLC) stage, and presence of PVTT and extrahepatic metastasis were extracted from each selected study. Hazard ratios (HRs) and associated 95% confidence intervals (CIs) for OS, PFS, and TTP were extracted, when reported. The proportions (%) of SAEs were used to calculate their estimated odds ratios (ORs). All data used were publicly available or computable from the included studies, and were extracted by the two independent investigators, with all items reaching consensus.

## Risk of bias assessment

The Cochrane Risk of Bias Tool was implemented to assess the risk of bias for each RCT included.<sup>[23]</sup> Bias was assigned as a judgment (high, low, or unclear) for individual elements from seven domains: random sequence generation and allocation concealment (both within the domain of selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessors (detection bias), incomplete outcome

data (attrition bias), selective reporting (reporting bias), and an auxiliary domain (other bias). The two reviewers evaluated trial quality independently. Disagreements were resolved by discussion.

## Statistical methods

We performed NMAs for direct and indirect comparisons between interventions and control (i.e., Sora). We used the most common approach to NMAs, which is based on weighted least squares regression.<sup>[24]</sup> Results from the fixed-effects models were reported because, for treatment comparisons examined in RCTs, all comparisons other than HAIC+Sora versus Sora were examined in only one trial, which did not allow the estimation of a heterogeneity parameter.<sup>[25,26]</sup> Effect sizes for the HRs or ORs according to survival or the binary outcomes were represented by forest plots. We created a network plot to summarize the studies and the associations between treatments and clinical endpoints. We produced a league table in the form of a square matrix showing all pairwise comparisons between interventions. Point estimates and 95% CIs we presented alongside, in the league table. To rank the treatments to show superiority, we computed the P-score of each treatment, which measures how much better a treatment is than the others. We also produced a rankogram and surface under the cumulative ranking probability curve (SUCRA) values. The rankogram represents the probability that each treatment is the most effective one, while the SUCRA value ranges from 0 to 1, and the value for the best treatment would be close to 1. For OS outcomes, we created survival curves according to the estimated effect sizes from the NMA, using the Weibull regression model, and extracted baseline survival rates for the control (i.e., Sora) from the SHARP study.<sup>[1]</sup>

We evaluated the plausibility of transitivity assumption by comparing the distributions of the following potential confounders grouped by intervention across studies: age, sex, CTP class A, HBV infection, HCV infection, BCLC stage C, and presence of PVTT and extrahepatic metastasis.<sup>[27,28]</sup> The global consistency of the direct and indirect evidence could not be assessed, as the interventions were compared with the common comparator (i.e., Sora) in all included RCTs, with no closed loops in the whole network.<sup>[29]</sup> To evaluate the local consistency assumption, we conducted a frequentist pairwise meta-analysis of the only comparison, HAIC+Sora versus Sora, with direct evidence from multiple studies,<sup>[5,30,31]</sup> and compared the OS and PFS results with the corresponding pooled HRs from the NMA.

Subgroup analyses relating to OS were performed based on the presence of PVTT and extrahepatic metastasis and the underlying viral etiology of chronic liver disease. We also conducted sensitivity analyses to

assess the stability of the OS results by restricting the original NMA to phase 3 RCTs and studies investigating transarterial therapies with Sora in addition to the Ate+Bev trial. All data analyses were performed using R software, version 4.0.4. In particular, the R packages of *netmeta* and *gemtc* were used to conduct the main NMA and obtain rank probabilities and SUCRA values.

## RESULTS

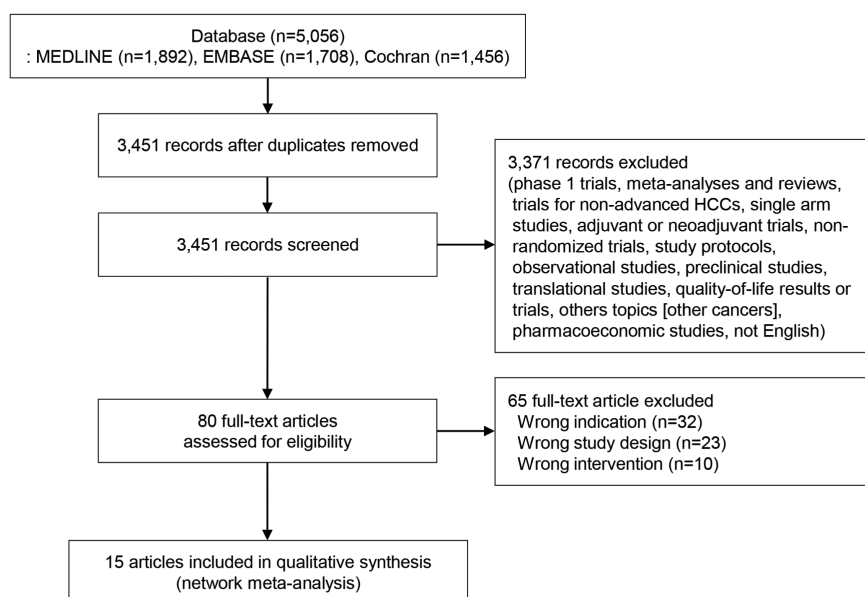
### Study selection

Figure 1 shows a flowchart of the study selection process. A total of 3451 titles and abstracts of potentially relevant studies were screened using Covidence, of which 80 fulfilled the eligibility criteria for full-text assessment. We finally retained seven phase 2 and eight phase 3 RCTs with a Sora arm in the first-line setting for the NMA; these evaluated 10 molecularly targeted regimens used in 6013 patients and three transarterial treatments with Sora used in 1145 patients, as follows: Atez+Beva, Lenv, linifinib (Lini), brivanib, sunitinib (Suni), dovitinib, Beva+erlotinib (Beva+Erlo), mapatumumab+Sora (Mapa+Sora), Erlo+Sora, tigatuzumab 6 (loading)/2 (maintenance) mg/kg+Sora (Tiga6/2+Sora), and tigatuzumab 6/6 mg/kg+Sora (Tiga6/6+Sora) in one three-arm trial, and HAIC, TACE, and SIRT in combination with Sora, respectively.<sup>[4,5,7,8,14,30–39]</sup> A network graph of treatment comparisons is presented in Figure S1. The circle size reflects the number of participants, while the line width reflects the number of direct comparisons. The absence of a connecting line between two treatments indicates that there was no direct comparison.

The characteristics of the 15 studies included in the network are summarized in Table 1 and Table S3. The sample numbers of the Sora arm and their counterparts were 3484 (range, 33–578) and 3674 (range, 35–577), respectively, in all RCTs. All patients did not receive any previous systemic therapy as treatment for HCC, with 95.9% and 4.1% of the participants having CTP class A and B7, respectively. The percentages of patients in BCLC stages B and C ranged from 2% to 40%, and from 54.3% to 98%, respectively, in these trials. Information on BCLC stage was not reported in Cheng 2015.<sup>[39]</sup> All included trials were designed with OS as the primary endpoint.

### Risk of bias profile

All of the trials were assessed as having low risks of bias for most of the seven domains. However, 12 had a high risk of bias in terms of blinding participants and personnel. However, the effect of performance bias was mitigated using objective outcomes.<sup>[40]</sup> In relation to detection bias, the outcome assessors were blinded to the interventions received by the study participants in four trials, whereas the other 11 were either aware of the interventions or unclear about them. The open-label assessment of outcomes may have been influenced by knowledge of the intervention received. Although double blinding was almost impossible to implement in trials investigating treatments that used different approaches or routes similar to our modalities, the results should be interpreted with caution, as trials that do not use double blinding tend to overestimate the efficacy of the treatment studied.<sup>[40]</sup> The selection of reported



**FIGURE 1** PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram of the process of screening and selecting studies. HCC, hepatocellular carcinoma.

**TABLE 1** Baseline characteristics of the study participants in the 15 selected randomized controlled trials

| Study name                        | Arm       | No. of patients | ECOG PS                              | Median age, years (range) | Race/Region                                              | Sex (male) | CTP class              | HBV   | HCV   | BCLC stage                         | PVTT  | EHM   |
|-----------------------------------|-----------|-----------------|--------------------------------------|---------------------------|----------------------------------------------------------|------------|------------------------|-------|-------|------------------------------------|-------|-------|
| Finn 2020 (IMBRAVE)               | Atez+Beva | 336             | 0 (62%), 1 (38%)                     | 64 (26–88)                | White (37%), Asian (56%)                                 | 82%        | A (99%), B (1%)        | 49%   | 21%   | A (2%)<br>B (15%)<br>C (82%)       | 38%   | 63%   |
|                                   | Sora      | 165             | 0 (62%), 1 (38%)                     | 66 (33–87)                | White (32%), Asian (58%)                                 | 83%        | A (100%)               | 46%   | 22%   | A (4%)<br>B (16%)<br>C (81%)       | 43%   | 56%   |
| Park 2019 (STAH)                  | TACE+Sora | 170             | 0 (80%), 1 (19.4%), 2 (0.6%)         | 60.2 (9.6) <sup>b</sup>   | Asian (100%)                                             | 80%        | A (87.1%)<br>B (12.9%) | 78.8% | 4.7%  | A (1.8%)<br>B (22.9%)<br>C (75.3%) | 40%   | 36.5% |
|                                   | Sora      | 169             | 0 (82.8%), 1 (16.6%), 2 (0.6%)       | 61.3 (9.6) <sup>b</sup>   | Asian (100%)                                             | 87%        | A (87.0%)<br>B (13.0%) | 71.0% | 9.5%  | A (0%)<br>B (26.0%)<br>C (74.0%)   | 37.3% | 34.9% |
| Ricke 2019 (SORAMIC)              | SIRT+Sora | 216             | NA                                   | 66 (53–79) <sup>a</sup>   | NA                                                       | 85.4%      | A (90.0%)<br>B (10.0%) | 8.0%  | 11.6% | A (2.8%)<br>B (29.4%)<br>C (67.8%) | 43.1% | 24.6% |
|                                   | Sora      | 208             | NA                                   | 66 (53–79) <sup>a</sup>   | NA                                                       | 85.5%      | A (90.0%)<br>B (8.2%)  | 11.6% | 23.2% | A (1.5%)<br>B (30.1%)<br>C (68.4%) | 43.7% | 22.2% |
| Kondo 2019 (SCOOP-2)              | HAIC+Sora | 35              | NA                                   | 72.0 (7.0) <sup>b</sup>   | Asian (100%)                                             | 80.0%      | A (88.6%)<br>B (11.4%) | 8.6%  | 60%   | A (5.7%)<br>B (40%)<br>C (54.3%)   | 60%   | 28.6% |
|                                   | Sora      | 33              | NA                                   | 70.9 (9.1) <sup>b</sup>   | Asian (100%)                                             | 81.8%      | A (87.9%)<br>B (12.1%) | 12.1% | 60.6% | A (6.1%)<br>B (39.4%)<br>C (54.5%) | 66.7% | 24.2% |
| Kudo 2018 <sup>[1]</sup> (SILIUS) | HAIC+Sora | 103             | 0 (87%), 1 (13%)                     | 69 (62–75) <sup>a</sup>   | Asian (100%)                                             | 87%        | A (88%)<br>B (12%)     | 26%   | 46%   | B (31%)<br>C (69%)                 | 70.9% | 27%   |
|                                   | Sora      | 103             | 0 (88%), 1 (12%)                     | 68 (62–75) <sup>a</sup>   | Asian (100%)                                             | 85%        | A (90%)<br>B (10%)     | 21%   | 45%   | B (26%)<br>C (74%)                 | 72.8% | 25%   |
| Kudo 2018 <sup>[2]</sup>          | Lenv      | 478             | 0 (64%), 1 (36%)                     | 63 (20–88)                | White (28%), Asian (70%), Other (2%)                     | 85%        | A (99%), B (1%)        | 53%   | 19%   | B (22%)<br>C (78%)                 | 23%   | 61%   |
|                                   | Sora      | 476             | 0 (63%), 1 (37%)                     | 62 (22–88)                | White (30%), Asian (68%), Other (2%)                     | 84%        | A (99%), B (1%)        | 48%   | 26%   | B (19%)<br>C (81%)                 | 19%   | 62%   |
| Cheng 2013                        | Suni      | 530             | 0 (52.5%), 1 (46.8%), Missing (0.7%) | 59 (18–85)                | White (20.9%), Black (1.1%), Asian (77.5%), Other (0.4%) | 82.3%      | A (99.8%)              | 54.7% | 21.3% | B (12.6%)<br>C (87.2%)             | NA    | NA    |
|                                   | Sora      | 544             | 0 (52.9%), 1 (46.7%), Missing (0.4%) | 59 (18–84)                | White (20.6%), Black (1.8%), Asian (76.8%), Other (0.7%) | 84.4%      | A (99.4%)              | 52.9% | 21.9% | B (16.4%)<br>C (83.5%)             | NA    | NA    |
| Cainap 2013                       | Lini      | 514             | 0 (62.8%), 1 (37.2%)                 | 59 (21–84)                | Outside Asia (33.4%), Asian (66.6%)                      | 86.4%      | A (93.2%), B (5.8%)    | 53.5% | 25.3% | B (15.8%)<br>C (84.2%)             | 46.3% | 59.7% |
|                                   | Sora      | 521             | 0 (66.2%), 1 (33.8%)                 | 60 (23–87)                | Outside Asia (32.8%), Asian (67.2%)                      | 83.7%      | A (95%), B (5%)        | 53%   | 24.8% | B (19.6%)<br>C (80.4%)             | 40.5% | 56.8% |

(Continues)

TABLE 1 (Continued)

| Study name    | Arm                                | No. of patients | ECOG PS                              | Median age, years (range) | Race/Region                                           | Sex (male) | CTP class            | HBV   | HCV   | BCLC stage                         | PVTT  | EHM   |
|---------------|------------------------------------|-----------------|--------------------------------------|---------------------------|-------------------------------------------------------|------------|----------------------|-------|-------|------------------------------------|-------|-------|
| Johnson 2013  | Briv                               | 577             | 0 (64%), 1 (36%)                     | 61 (19–87)                | Asia (60%), Europe (23%), America (15%), Other (2%)   | 84%        | A (92%), B (8%)      | 44%   | 20%   | A (8%)<br>B (17%)<br>C (77%)       | 27%   | 49%   |
|               | Sora                               | 578             | 0 (61%), 1 (39%)                     | 60 (25–89)                | Asia (64%), Europe (23%), America (11%), Other (1%)   | 84%        | A (92%), B (8%)      | 45%   | 21%   | A (5%)<br>B (17%)<br>C (78%)       | 27%   | 50%   |
| Thomas 2017   | Beva+Erla                          | 47              | 0 (32%), 1 (68%),                    | 61 (43–82)                | White (60%), Other (40%)                              | NA         | A (83%), B (17%)     | NA    | NA    | A (2%)<br>B (30%)<br>C (68%)       | 17%   | 40%   |
| Ikeda 2016    | Sora                               | 43              | 0 (40%), 1 (50%), 2 (2%)             | 61 (44–81)                | White (72%), Other (28%)                              | NA         | A (88%), B (12%)     | NA    | NA    | A (9%)<br>B (26%)<br>C (65%)       | 25%   | 17%   |
|               | HAIC+Sora                          | 66              | 0 (76.9%), 1 (23.1%)                 | 66 (25–79)                | Asian (100%)                                          | 86.2%      | A (87.7%), B (12.3%) | 33.8% | 27.7% | B (29.2%)<br>C (70.8%)             | 77.5% | 29.2% |
| Ciuleanu 2016 | Sora                               | 42              | 0 (80.5%), 1 (19.5%)                 | 64 (42–78)                | Asian (100%)                                          | 78.1%      | A (95.1%), B (4.9%)  | 22.0% | 48.8% | B (39.0%)<br>C (61.0%)             | 76.5% | 31.7% |
|               | Mapa+Sora                          | 50              | 0 (36%), 1 (58%), 2 (6%)             | 60 (33–84)                | White (96%), Black (4%), Asian (4%)                   | 52%        | A (100%)             | NA    | NA    | A (1.5%)<br>B (30.1%)<br>C (68.4%) | 14.0% | 15.7% |
| Cheng 2016    | Sora                               | 51              | 0 (33.3%), 1 (58.8%), 2 (7.8%)       | 64 (21–80)                | White (94%), Black (2%), Asian (4%)                   | 77%        | A (100%)             | NA    | NA    | A (1.5%)<br>B (30.1%)<br>C (68.4%) | 66.0% | 49.0% |
|               | Dovi                               | 82              | 0 (63%), 1 (37%)                     | 56 (27–82)                | Asian (100%)                                          | 89%        | A (100%)             | NA    | NA    | B (2%)<br>C (98%)                  | NA    | NA    |
| Zhu 2015      | Sora                               | 83              | 0 (64%), 1 (35%), Missing (1%)       | 56 (27–83)                | Asian (99%), Other (1%)                               | 81%        | A (99%), B (1%)      | NA    | NA    | B (2%)<br>C (98%)                  | NA    | NA    |
|               | Erla+Sora                          | 362             | 0 (61%), 1 (39%)                     | 60.5                      | America (24.3%), Europe (51.4%), Asia-Pacific (24.3%) | 81.5%      | A (98.4%), B (1.6%)  | 33.7% | 29.6% | B (16.6%)<br>C (83.4%)             | 38.1% | 56.6% |
| Cheng 2015    | Sora                               | 358             | 0 (61%), 1 (39%)                     | 60                        | America (23.7%), Europe (51.1%), Asia-Pacific (24.1%) | 79.9%      | A (96.4%), B (3.6%)  | 37.2% | 23.5% | B (13.4%)<br>C (86.6%)             | 42.7% | 61.2% |
|               | Tiga6 (low dose, 6/2 mg/kg)+ Sora  | 53              | 0 (60.4%), 1 (39.6%),                | 63 (27–82)                | Asian (98.1%)<br>Other (1.9%)                         | 84.9%      | A (100%)             | 62.3% | 32.1% | NA                                 | NA    | NA    |
| Sora          | Tiga6 (high dose, 6/6 mg/kg)+ Sora | 55              | 0 (57.4%), 1 (42.6%),                | 62.5 (39–84)              | Asian (98.1%)<br>Other (1.9%)                         | 83.3%      | A (100%)             | 46.3% | 38.9% | NA                                 | NA    | NA    |
|               | Sora                               | 55              | 0 (54.5%), 1 (45.5%), Missing (1.8%) | 66 (39–84)                | Asian (98.2%)<br>Other (1.8%)                         | 80%        | A (100%)             | 45%   | 34.5% | NA                                 | NA    | NA    |

Abbreviations: BCLC, Barcelona Clinic Liver Cancer; CTP, Child-Turcotte-Pugh; ECOG, Eastern Cooperative Oncology Group; EHM, extrahepatic metastasis; HBV, hepatitis B virus; HCV, hepatitis C virus; NA, not available; PS, performance status; PVTT, portal vein tumor thrombosis.

<sup>a</sup>Median (interquartile range).

<sup>b</sup>Mean (SD).

results raised concerns of bias in only one trial for PFS. All of the included trials had low risks in terms of selection and attrition biases. The details for these assessments are presented in Figure S2.

## Efficacy outcomes

### OS analysis

The HR estimates by NMA suggested that, in comparison with Sora, only Atez+Beva significantly improved OS (HR [95% CI], 0.58 [0.42–0.80]; Figure 2A). Conversely, Suni was associated with significantly worse OS than Sora (1.30 [1.13–1.50]). In addition to the nonsignificant findings for other targeted drugs, no survival advantage of Sora in combination with any transarterial therapy was found over Sora alone. In pairwise comparisons within the entire network of 15 trials, there were OS benefits of Atez+Beva compared with every other treatment except Tige6/6+Sora and Beva+Erlo (Figure 3). We also found that Lenv (0.71 [0.58–0.87]), Erlo+Sora (0.71 [0.57–0.89]), and Lini (0.80 [0.65–0.99]), as well as TACE+Sora (0.70 [0.51–0.95]), showed significantly better OS than Suni. When ordered from the most to the least effective based on P-score and SUCRA analyses, Atez+Beva was ranked the highest in terms of treatment effect size of all 15 treatment classes, and had a 98.2% probability of being the best treatment to improve OS. Tige6/6+Sora and Lenv had the second-best and third-best treatment effect sizes, respectively, and Tige6/2+Sora had the highest probability (31.8%) of being the lowest-ranked regimen on rankogram (Figure 2A, Figure S3A, and Table S4A). The same trend for the ranking of individual treatments with respect to OS was noted in the further NMA of parametric survival curves over time (Figure 4).

### PFS analysis

The PFS analysis involved 14 studies investigating 13 therapeutic options in 6734 patients. Nine of the trials reported HRs for PFS, whereas it was replaced by TTP data in five studies. A study of SIRT+Sora did not report both PFS and TTP data.<sup>[8]</sup> When compared with Sora monotherapy, we found that Atez+Beva and Lenv had significantly better PFS (HRs [95% CIs], 0.59 [0.47–0.74] and 0.66 [0.57–0.76]), respectively (Figure 2B). In addition, there was a PFS benefit associated with adding TACE to Sora (0.73 [0.59–0.91]). In the NMA, Atez+Beva ranked the highest for PFS based on either SUCRA value (0.947) or P-score (0.947), followed by Lenv, Beva+Erlo, and TACE+Sora (0.873, 0.816, and 0.768 for P-score; and 0.873, 0.816, and 0.768 for SUCRA value; respectively). The 14 pairwise treatment comparisons indicated no significant advantage

of Atez+Beva over Lenv, Beva+Erlo, TACE+Sora, HAIC+Sora, or Lini in improving PFS (Figure 3). Rankograms indicated that Atez+Beva had the highest probability of being best for PFS (54.9%) (Table S4B and Figure S3B).

### Safety analysis

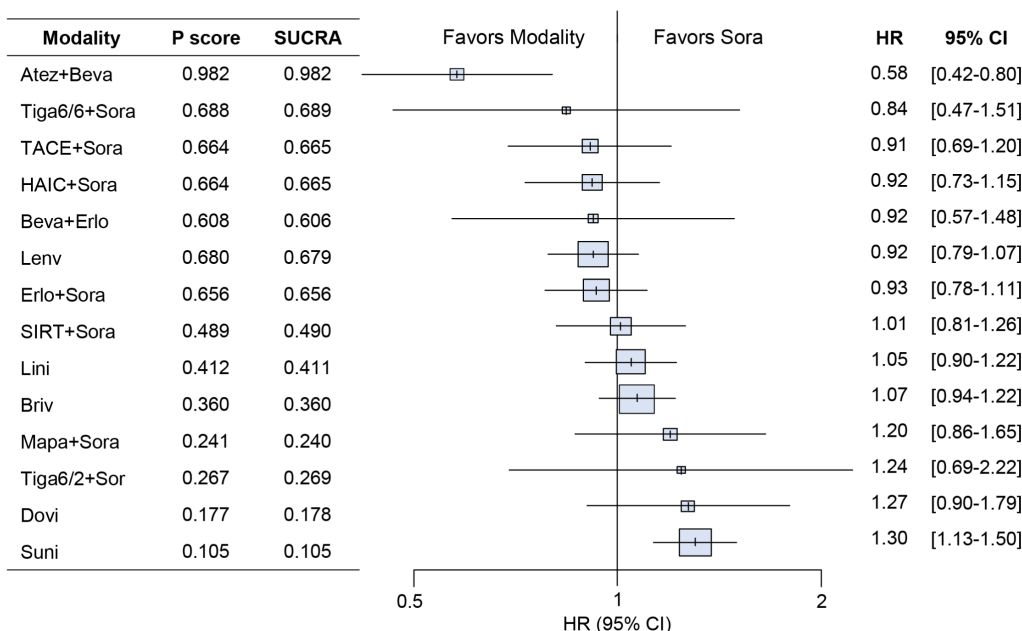
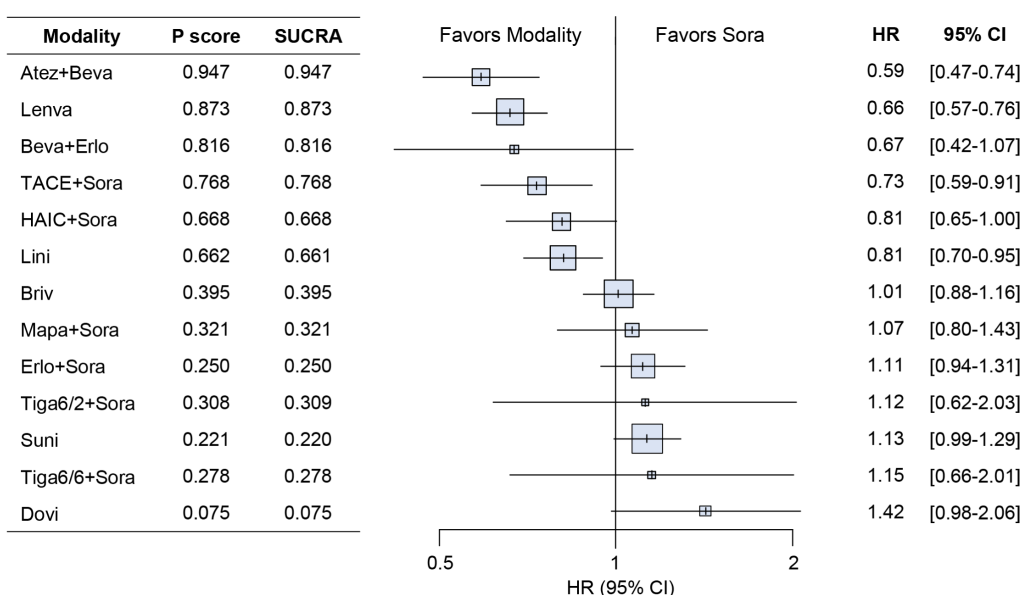
To estimate safety in terms of intertreatment associations with risk of SAE, we analyzed the relevant data from 10 RCTs that reported frequencies of adverse events for a total of 10 different therapies in 6468 patients (Figure 5A). Among them, Lenv, Lini, Suni, and TACE+Sora had significantly higher rates of SAE than Sora (ORs [95% CIs], 1.76 [1.37–2.25], 1.76 [1.35–2.30], 6.31 [4.77–8.34], and 2.02 [1.23–3.32], respectively). When ordered by SUCRA value, the rate of SAE of Atez+Beva was in the sixth rank out of 11 modalities, with a true rank probability of 0.503, which was not significantly different from every other treatment except Suni (0.22 [0.13–0.35]), as shown in the staircase table (Figure 5A,B). The probability that Atez+Beva, Lenv, or TACE+Sora was the least safe of the 10 interventions was very low (Table S4C).

### Sensitivity analysis

Figure 6 presents the results of two sensitivity analyses. In the first, individual sensitivity analysis of eight phase 3 studies of eight therapeutic interventions explicitly reporting primary OS comparisons with a Sora counterpart yielded consistent outcomes without any differences from the main analysis, in which Atez+Beva was ranked highest (Figure 6A, Table S5A, and Figure S4A). In the other, a comparative analysis based on five trials with 1646 patients pointed to a significant benefit of Atez+Beva versus any of the three categories of transarterial therapies added to Sora in terms of OS, with a probability of ranking highest of nearly 100% (Figure 6B, Table S5B, and Figure S4B).

### Subgroup analysis

Of the 15 selected RCTs, 9 were included in a network created to analyze HRs for OS in a subset of patients with PVTT. Figure 7A reveals a significant HR of 0.58 (95% CI, 0.38–0.89) for OS in the Atez+Beva group, with the second lowest risk of death by ranking probability (89.7%). TACE+Sora had borderline higher OS than Sora alone and ranked first based on both SUCRA value and its equivalent P-score, with the highest probability (91.4%) of the transarterial combination being the most effective of the eight treatment arms comprising the PVTT subgroup. There

**(A) Overall survival****(B) Progression-free survival**

**FIGURE 2** Forest plots of the fixed-effect network meta-analysis models for overall survival (OS) (A) and progression-free survival (PFS) (B), with treatment ranking by the probability of being the best based on P-score and surface under the cumulative ranking (SUCRA) value in the finally selected trials. (A) OS model. Data from all 15 trials involving the 7158 patients that were finally selected for this study were used for OS analyses. (B) The PFS model. Data from 14 trials investigating 13 treatment modalities in 6734 patients were used for the PFS analyses. Atez+Beva, combined atezolizumab and bevacizumab; Briv, brivanib; CI, confidence interval; Dovi, dovitinib; Erlo, erlotinib; HAIC, hepatic arterial infusion chemotherapy; HR, hazard ratio; Lenv, lenvatinib; Lini, linifanib; Mapa+Sora, combined mapatumumab and sorafenib; SIRT, selective internal radiation therapy; Sora, sorafenib; TACE, transarterial chemoembolization; Suni, sunitinib; Tiga6/6+Sora, tigatuzumab 6/6 mg/kg+Sora.

were null differences in OS estimates between the two first-ranked and second-ranked interventions in the pairwise comparison matrix (HR [95% CI], 0.90 [0.41–1.96]; Figure S5A). Additional subgroup analyses based on metastatic disease and underlying viral HBV and HCV involving six, eight, and seven RCTs,

respectively, revealed that Atez+Beva versus Sora possessed all of the significant benefits for OS where the ranking profile was generally consistent with the original NMA ranking, with that combination regimen being always the best option in any set of conditions (Figure 7B–D, Table S6, and Figure S5B–D).

| Overall survival    | Progression-free survival |                     |                     |                     |                     |                     |                     |                     |                     |                     |                     |                     |                     |                     |                     |
|---------------------|---------------------------|---------------------|---------------------|---------------------|---------------------|---------------------|---------------------|---------------------|---------------------|---------------------|---------------------|---------------------|---------------------|---------------------|---------------------|
|                     | Atez+Beva                 | 0.51<br>(0.28-0.94) | 0.89<br>(0.68-1.17) | 0.73<br>(0.53-1.00) | 0.80<br>(0.59-1.10) | 0.53<br>(0.40-0.70) | 0.88<br>(0.52-1.48) | 0.59<br>(0.47-0.74) | NA                  | 0.73<br>(0.55-0.96) | 0.58<br>(0.45-0.76) | 0.53<br>(0.28-0.99) | 0.55<br>(0.38-0.80) | 0.42<br>(0.27-0.64) | 0.52<br>(0.40-0.68) |
|                     | 0.69<br>(0.35-1.35)       | Tiga6/6+Sora        | 0.57<br>(0.32-1.02) | 0.70<br>(0.39-1.28) | 0.64<br>(0.35-1.16) | 1.04<br>(0.58-1.85) | 0.58<br>(0.28-1.20) | 0.87<br>(0.50-1.52) | NA                  | 0.71<br>(0.40-1.26) | 0.88<br>(0.49-1.56) | 0.97<br>(0.43-2.20) | 0.93<br>(0.49-1.74) | 0.81<br>(0.41-1.58) | 1.02<br>(0.57-1.80) |
|                     | 0.63<br>(0.44-0.90)       | 0.91<br>(0.50-1.67) | Lenv                | 0.82<br>(0.63-1.06) | 0.90<br>(0.69-1.17) | 0.59<br>(0.48-0.74) | 0.99<br>(0.60-1.61) | 0.66<br>(0.57-0.76) | NA                  | 0.81<br>(0.66-1.00) | 0.65<br>(0.53-0.80) | 0.59<br>(0.32-1.09) | 0.62<br>(0.45-0.86) | 0.46<br>(0.31-0.69) | 0.58<br>(0.48-0.71) |
|                     | 0.63<br>(0.43-0.94)       | 0.92<br>(0.49-1.72) | 1.00<br>(0.76-1.32) | HAIC+Sora           | 0.91<br>(0.67-1.23) | 0.73<br>(0.55-0.96) | 0.83<br>(0.50-1.39) | 0.81<br>(0.65-1.00) | NA                  | 0.99<br>(0.76-1.30) | 0.80<br>(0.62-1.03) | 0.72<br>(0.38-1.36) | 0.76<br>(0.53-1.09) | 0.57<br>(0.37-0.87) | 0.71<br>(0.55-0.92) |
|                     | 0.64<br>(0.42-0.98)       | 0.92<br>(0.48-1.77) | 1.01<br>(0.74-1.39) | 1.01<br>(0.70-1.44) | TACE+Sora           | 0.66<br>(0.50-0.87) | 0.91<br>(0.55-1.53) | 0.73<br>(0.59-0.91) | NA                  | 0.90<br>(0.69-1.18) | 0.73<br>(0.56-0.94) | 0.65<br>(0.35-1.23) | 0.69<br>(0.48-0.99) | 0.52<br>(0.34-0.79) | 0.65<br>(0.50-0.84) |
|                     | 0.62<br>(0.43-0.90)       | 0.90<br>(0.49-1.67) | 0.99<br>(0.79-1.25) | 0.99<br>(0.74-1.31) | 0.98<br>(0.71-1.36) | Erlo+Sora           | 0.60<br>(0.37-0.99) | 0.90<br>(0.76-1.06) | NA                  | 0.73<br>(0.58-0.92) | 0.91<br>(0.73-1.13) | 1.01<br>(0.54-1.87) | 0.96<br>(0.68-1.34) | 0.78<br>(0.52-1.17) | 0.98<br>(0.80-1.22) |
|                     | 0.63<br>(0.35-1.12)       | 0.91<br>(0.43-1.95) | 1.00<br>(0.61-1.65) | 1.00<br>(0.59-1.69) | 0.99<br>(0.57-1.72) | 1.01<br>(0.61-1.68) | Beva+Erlo           | 0.67<br>(0.42-1.07) | NA                  | 0.82<br>(0.50-1.35) | 0.66<br>(0.41-1.08) | 0.60<br>(0.28-1.27) | 0.63<br>(0.36-1.09) | 0.47<br>(0.26-0.86) | 0.59<br>(0.36-0.96) |
|                     | 0.58<br>(0.42-0.80)       | 0.84<br>(0.47-1.51) | 0.92<br>(0.79-1.07) | 0.92<br>(0.73-1.15) | 0.91<br>(0.69-1.20) | 0.93<br>(0.78-1.11) | 0.92<br>(0.57-1.48) | Sora                | NA                  | 0.81<br>(0.70-0.95) | 0.99<br>(0.86-1.14) | 0.89<br>(0.49-1.62) | 0.94<br>(0.70-1.26) | 0.70<br>(0.49-1.02) | 0.88<br>(0.78-1.01) |
|                     | 0.57<br>(0.39-0.85)       | 0.83<br>(0.44-1.56) | 0.91<br>(0.70-1.19) | 0.91<br>(0.66-1.25) | 0.90<br>(0.63-1.28) | 0.92<br>(0.69-1.22) | 0.91<br>(0.54-1.54) | 0.99<br>(0.79-1.23) | SIRT+Sora           | NA                  | NA                  | NA                  | NA                  | NA                  | NA                  |
|                     | 0.55<br>(0.39-0.79)       | 0.80<br>(0.44-1.47) | 0.88<br>(0.71-1.09) | 0.88<br>(0.67-1.15) | 0.87<br>(0.63-1.19) | 0.89<br>(0.70-1.12) | 0.88<br>(0.53-1.45) | 0.96<br>(0.82-1.12) | 0.97<br>(0.74-1.26) | Lini                | 0.80<br>(0.65-0.99) | 0.73<br>(0.39-1.34) | 0.76<br>(0.55-1.06) | 0.57<br>(0.38-0.86) | 0.72<br>(0.59-0.88) |
|                     | 0.54<br>(0.38-0.77)       | 0.79<br>(0.43-1.43) | 0.86<br>(0.70-1.05) | 0.86<br>(0.66-1.11) | 0.85<br>(0.63-1.15) | 0.87<br>(0.70-1.08) | 0.86<br>(0.52-1.41) | 0.93<br>(0.82-1.06) | 0.94<br>(0.73-1.22) | 0.98<br>(0.80-1.20) | Briv                | 0.90<br>(0.49-1.66) | 0.95<br>(0.69-1.31) | 0.71<br>(0.48-1.06) | 0.89<br>(0.74-1.08) |
|                     | 0.47<br>(0.24-0.91)       | 0.68<br>(0.30-1.55) | 0.74<br>(0.41-1.36) | 0.74<br>(0.40-1.38) | 0.73<br>(0.38-1.40) | 0.75<br>(0.41-1.38) | 0.74<br>(0.35-1.58) | 0.81<br>(0.45-1.45) | 0.81<br>(0.44-1.52) | 0.84<br>(0.46-1.54) | 0.86<br>(0.47-1.57) | Tiga6/2+Sora        | 0.95<br>(0.49-1.84) | 0.79<br>(0.39-1.59) | 0.99<br>(0.54-1.82) |
|                     | 0.49<br>(0.31-0.77)       | 0.70<br>(0.36-1.37) | 0.77<br>(0.54-1.10) | 0.77<br>(0.52-1.14) | 0.76<br>(0.50-1.17) | 0.78<br>(0.54-1.12) | 0.77<br>(0.43-1.37) | 0.84<br>(0.61-1.16) | 0.85<br>(0.57-1.25) | 0.88<br>(0.61-1.25) | 0.90<br>(0.63-1.27) | 1.04<br>(0.53-2.02) | Mapa+Sora           | 0.75<br>(0.47-1.20) | 0.94<br>(0.68-1.30) |
|                     | 0.46<br>(0.28-0.73)       | 0.66<br>(0.33-1.31) | 0.72<br>(0.50-1.06) | 0.72<br>(0.48-1.09) | 0.72<br>(0.46-1.11) | 0.73<br>(0.50-1.08) | 0.72<br>(0.40-1.31) | 0.79<br>(0.56-1.11) | 0.80<br>(0.53-1.20) | 0.82<br>(0.56-1.20) | 0.84<br>(0.58-1.22) | 0.98<br>(0.50-1.92) | 0.94<br>(0.59-1.51) | Dovi                | 0.80<br>(0.54-1.18) |
| 0.45<br>(0.31-0.63) | 0.65<br>(0.35-1.18)       | 0.71<br>(0.58-0.87) | 0.71<br>(0.54-0.92) | 0.70<br>(0.51-0.95) | 0.71<br>(0.57-0.89) | 0.71<br>(0.43-1.17) | 0.77<br>(0.67-0.88) | 0.78<br>(0.60-1.01) | 0.80<br>(0.65-0.99) | 0.82<br>(0.68-1.00) | 0.95<br>(0.52-1.74) | 0.92<br>(0.65-1.31) | 0.98<br>(0.67-1.42) | Suni                |                     |

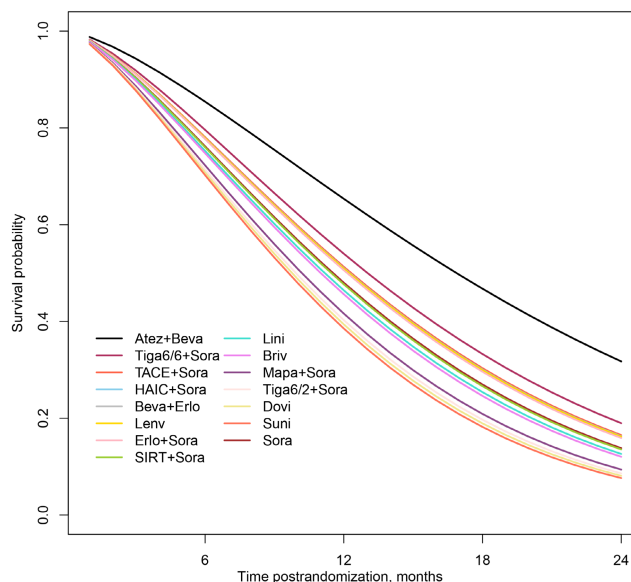
**FIGURE 3** League table showing HRs for pairwise comparisons of OS and PFS between treatments. Comparisons should be read from left to right. HRs (95% CIs) for comparisons are in the cells shared by the column-defining and row-defining interventions. Bold cells are significant. For OS, an HR < 1 favors the row-defining treatment. For PFS, an HR < 1 favors the column-defining treatment. NA, not applicable.

## Assessment of transitivity and consistency

Overall, the transitivity assumption was not challenged without significant differences in the examined baseline parameters for evaluating its plausibility (Figure S6). Results of the comparisons in HAIC+Sora versus Sora were consistent in terms of OS and PFS between pairwise and network meta-analyses (Table S7).

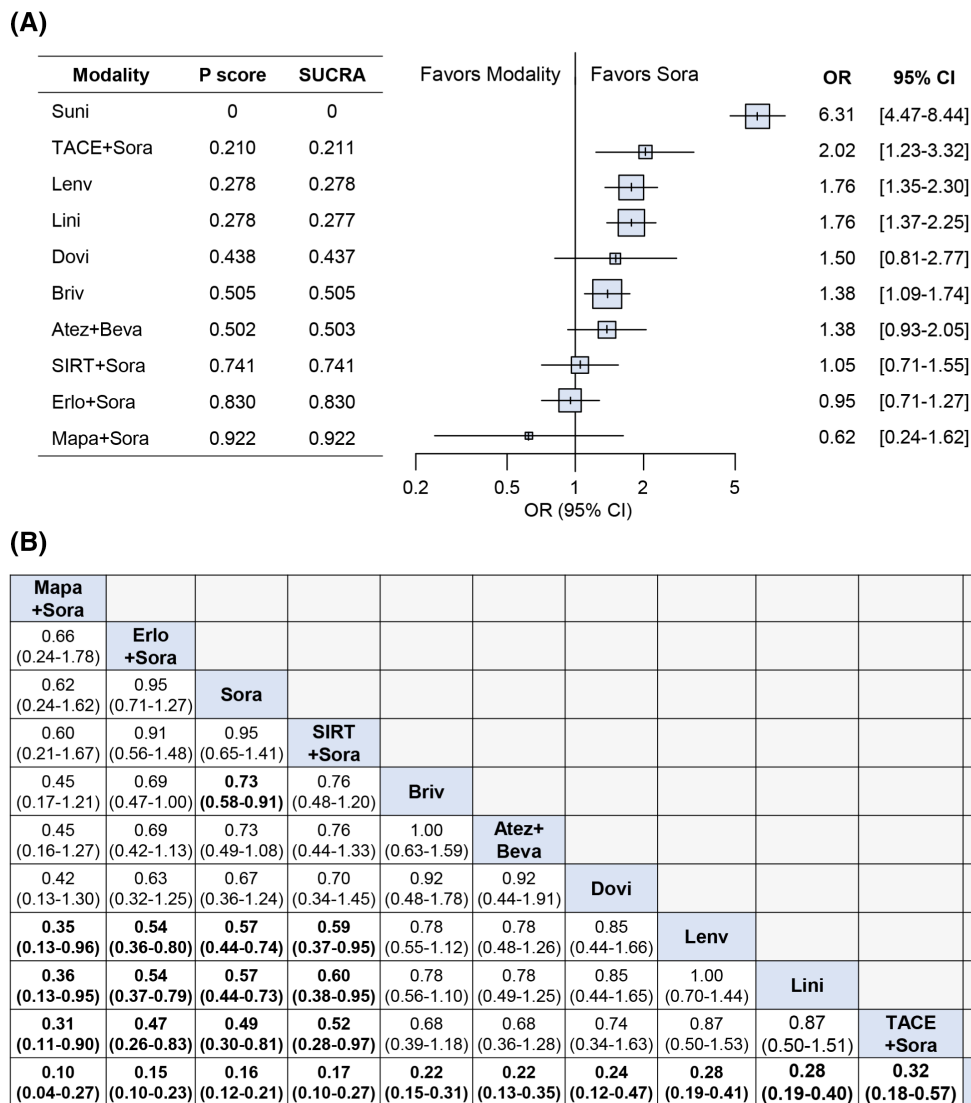
## DISCUSSION

Since the recent shift in systemic treatment paradigm for advanced HCC due to Atez+Beva, polytherapies have not been much tested compared with combinations of Sora and transarterial interventions, which have given encouraging results in head-to-head studies of previously untreated patients.<sup>[7,14,16]</sup> This systematic review and NMA has unequivocally confirmed that Atez+Beva provides the best first-line systemic care for most patients with metastatic and/or locally advanced HCC in any setting of tumor status and hepatitis virus, and has tolerable side effects. This immunotherapeutic combination achieved the top rank position with significant advantages in terms of extending survival and delaying progression, overriding the achievements of three liver-directed procedures with global accreditation for HCC when combined with Sora. Its solid ranking was



**FIGURE 4** Survival probabilities with time for each treatment, based on estimates of the relative effects of treatments.

maintained in coherent comparisons with every other agent primarily targeting fibroblast growth factor and its receptor, platelet-derived growth factor receptor, epidermal growth factor receptor, tumor necrosis factor-related apoptosis-inducing ligand death receptors, as well as vascular endothelial growth factor and its



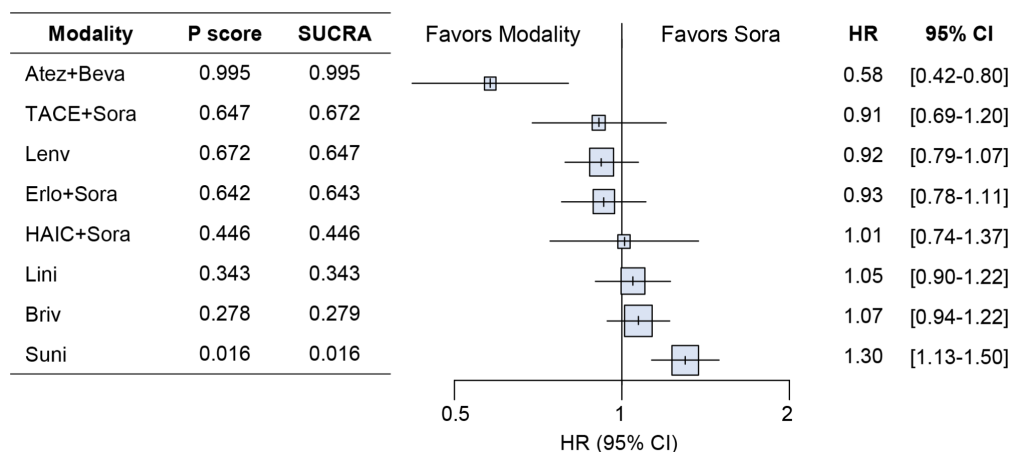
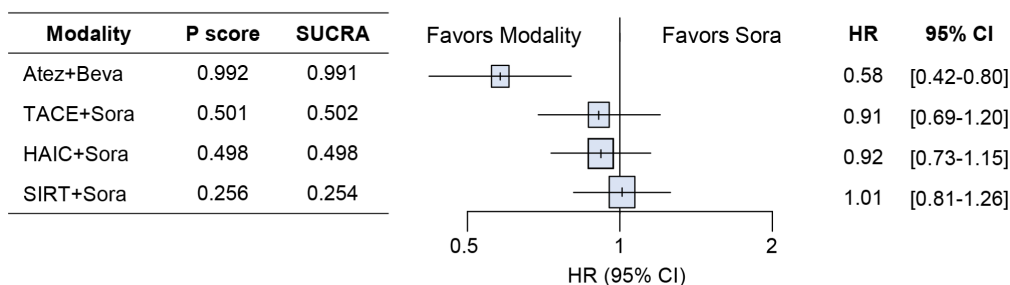
**FIGURE 5** Safety analysis. (A) Forest plot depicting the proportions of serious adverse events (SAEs), and rankings of safety of the interventions by P-score and SUCRA value. SAE analyses included 10 trials with 6468 patients. (B) Relative treatment effect estimates for all possible pairwise treatment comparisons of SAEs. Comparisons should be read from left to right. Odds ratios (ORs [95% CIs]) for comparisons are in the cells shared between column-defining and row-defining interventions. Bold cells are significant.

receptor, as monotherapy or in combination.<sup>[4,32–39]</sup> The top-placed OS effects of Atez+Beva based on direct and indirect evidence were recapitulated in the ranking metrics based on the estimated time-varying HRs of each treatment.

Unfortunately, solid organ or bone marrow transplant recipients, for whom suppression of the immune system is of vital importance, are excluded from treatments using immune checkpoint inhibitors (e.g., Atez).<sup>[41]</sup> Autoimmune rheumatic disease can also be excluded in clinical guidelines because of substantial concerns about increased risk of toxicity in the form of either immune-related adverse events or flares of pre-existing disease.<sup>[42,43]</sup> There are also additional vulnerabilities specific to immune stimulation, albeit less absolute, such as particular individuals continuing to use immunosuppressants for any condition (e.g.,

brain metastases and interstitial lung disease).<sup>[44]</sup> On the other hand, where there is a high risk of hemorrhage, especially from varices, the harm from the use of Beva may outweigh the benefit.<sup>[14,45,46]</sup> In these exceptional circumstances, the equivalent treatment effects of Lenv and Sora determined by the current rank statistics for OS, together with considerations about the practical availability of the drugs, are more likely to prompt the use of either one as the optimal alternative modality in spite of Lenv's estimated advantage in terms of PFS.

Indeed, this study is the first report of an NMA including all RCTs of the three major transarterial procedures combined with Sora in treating patients with HCC requiring systemic therapy. It is of practical importance to note that in our investigation the combined use of TACE with Sora, the prior standard-of-care,

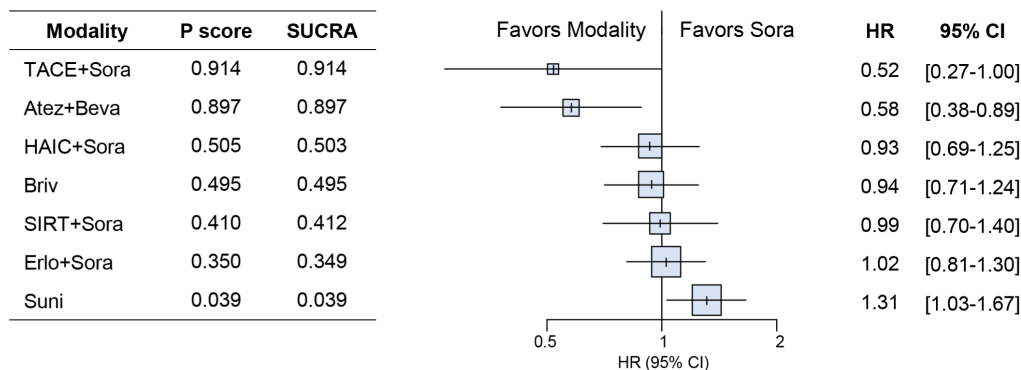
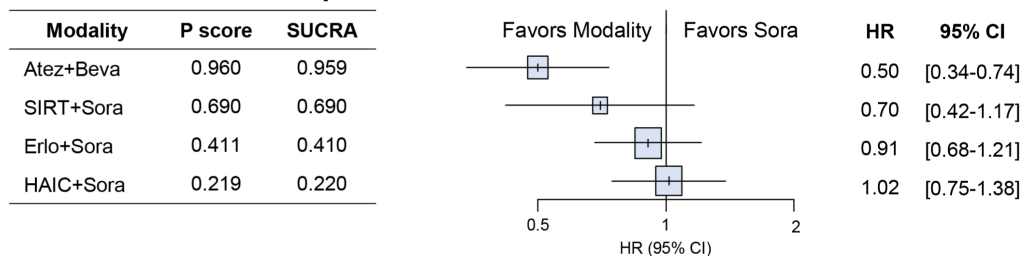
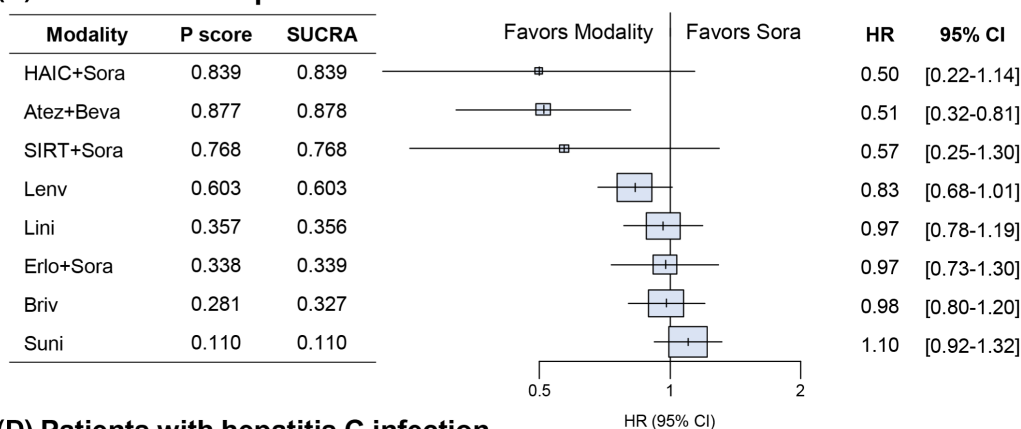
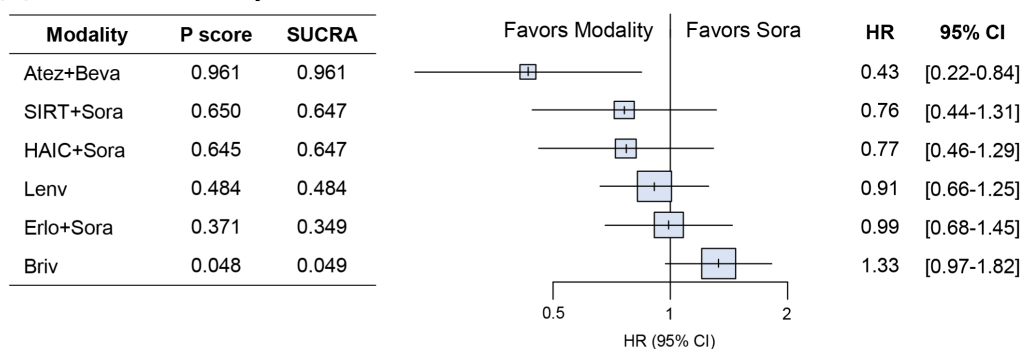
**(A) Phase 3 trials****(B) Comparisons of transarterial therapies with Sora and Atez+Beva**

**FIGURE 6** Treatment effects and rankings for OS in the sensitivity analysis based on phase 3 randomized controlled trials (A) and comparisons of transarterial therapies with Sora and Atez+Beva (B). Eight phase 3 trials and five studies of transarterial combinations were included in these network meta-analyses.

appeared to provide more benefit than Sora alone in prolonging survival in the subseries with PVTT; it was ranked first above Atez+Beva, unlike the competing transarterial combinations of HAIC or SIRT. Because the RCTs that were included were at comparable tumor stages (Table 1), this outcome does not appear to have been affected by any potential advantage conferred by the status of the tumors. Although TACE for hepatic lesions *per se* often induces an adverse inflammatory response to ischemic or necrotic tissues—as a result of arterial embolization in addition to the systemic effects of the chemotherapeutics—as the cost of the increased response rate, it should always be noted that the long-term prognosis depends, at least in part, on the efficient control of intrahepatic tumors, regardless of HCC stage.<sup>[7,19,47]</sup> In a recent single-center phase 2 RCT that enrolled 90 non-metastatic Korean patients with HCC invading the portal vein only (which were therefore excluded from our NMA of systemic therapies not limited to options specific for intrahepatic disease), TACE coupled with radiotherapy primarily targeting PVTT had a more favorable effect on OS than Sora, without causing greater hepatic damage, and met the

study's secondary endpoint with a 34% reduction in mortality risk.<sup>[48]</sup> These findings support the view that TACE+Sora has a meaningful role in HCC with PVTT, as suggested by our subgroup analysis. Moreover, the general contraindications to treatment with immune checkpoint inhibitors, another potential application of TACE combinations, could be as a second-line option after failure of Atez+Beva in the PVTT setting. Until now, the benefit of any rescue therapy has not been convincingly established in patients failing the new front-line combination for advanced HCC. Indeed, it will take several years to disseminate to the public the results of ongoing clinical trials aimed at obtaining robust evidence on this issue.

Our results should be interpreted in the context of their inherent limitations, shared by all NMAs, namely, the inclusion of data derived from indirect comparisons for most of the evidence in the network, as well as the fact that the estimates are based on study-level data, not individual patient data. We attempted to minimize these limitations by using only RCT data in the form of published articles with a common comparator (i.e., Sora). Another consideration is the use of surrogate data in place of missing

**(A) Patients with portal vein tumor thrombosis****(B) Patients with extrahepatic metastasis****(C) Patients with hepatitis B infection****(D) Patients with hepatitis C infection**

**FIGURE 7** Network meta-analysis results for OS in subgroups with portal vein tumor thrombosis (A), metastatic disease (B), and hepatitis B (C) and hepatitis C (D) infection from nine, six, eight, and even studies, respectively.

endpoints for some trials. A strong trial-level correlation has already been documented between PFS and TTP.<sup>[49]</sup> However, differences between the radiographic progressions defined by conventional

and modified RECIST across trials could result in less precise comparisons. Very recently, the front-line combination of durvalumab and tremelimumab significantly improved the OS, compared with Sora,

as reported in the phase 3 HIMALAYA trial, which met its primary endpoint of OS, but not the secondary endpoint of PFS.<sup>[50]</sup> Hence, further analysis including the newest regimen as an additional network node is warranted to provide a more useful reference when making clinical treatment decisions in the future.

In conclusion, our NMA results, based on officially published RCT data regarding different systemic anti-HCC agents and types, support the current NCCN guidelines favoring the preferential use of Atez+Beva, likely followed by Lenv or Sora, in the first-line setting of advanced-stage tumors. Selected patients with PVTT may benefit from treatment strategies containing TACE, where there is a critical need to avoid the potential risk of toxicity related to immunotherapy, or in second line. For higher confidence in the specific evidence, direct comparisons of efficacy between the multimodal interventions are needed, along with parametric estimation of cost-effectiveness and quality of life.

## AUTHOR CONTRIBUTIONS

*Study concept and design; and data acquisition, analysis, and interpretation:* Jihyun An and Ju Hyun Shim. *Manuscript draft:* Jihyun An, Ju Hyun Shim, S. Han, and Ha Il Kim. *Critical revision of the manuscript for important intellectual content:* Jihyun An, Ju Hyun Shim, Seungbong Han, and Ha Il Kim. *Verification of the underlying data:* Jihyun An, Ju Hyun Shim, Seungbong Han, and Ha Il Kim. *Statistical analysis:* Seungbong Han.

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## CONFLICT OF INTEREST

Nothing to report.

## ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The institutional review board of Asan Medical Center approved this trial-level network meta-analysis and waived the informed consent of individual patients (internal review board No. 2021–0688).

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### SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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