

# Alternative treatment strategies to sorafenib in patients with advanced hepatocellular carcinoma: a meta-analysis of randomized Phase III trials

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**Introduction:** This meta-analysis was conducted to evaluate efficacy and safety in patients treated with sorafenib vs other tyrosine-kinase inhibitors (TKIs) or selective internal radiotherapy (SIRT) for advanced hepatocellular carcinoma (HCC).

**Methods:** Electronic databases were systematically reviewed for randomized Phase III trials comparing sorafenib with other TKIs or SIRT in advanced HCC. Sorafenib was defined as the control arm. Other TKIs or SIRT was defined as the experimental arm. Overall survival (OS), time to progression (TTP), objective response rate (ORR), disease-control rate (DCR), and adverse events (AEs) were reviewed. Four trials in the other-TKI group (n=4,218) and two in the SIRT group (n=819) were eligible.

**Results:** Compared with sorafenib, other TKIs showed similar benefit on OS (HR 1.08, 95% CI 0.93–1.24;  $P=0.31$ ) and TTP (HR 0.86, 95% CI 0.66–1.12;  $P=0.26$ ) for advanced HCC. A significant increase in ORR (RR 1.67, 95% CI 1.15–2.43;  $P=0.008$ ) was found with other TKIs, but no increase in DCR (RR 1.11, 95% CI 0.98–1.26;  $P=0.11$ ) was observed. Other TKIs were associated with more frequent grade 3/4 AEs than sorafenib, including hypertension ( $P<0.00001$ ), thrombocytopenia ( $P=0.002$ ), fatigue ( $P<0.00001$ ), decreased appetite ( $P<0.00001$ ), and vomiting ( $P<0.0001$ ). For locally advanced HCC, neither OS (HR 1.14, 95% CI 0.98–1.32;  $P=0.09$ ) nor TTP (HR 0.87, 95% CI 0.74–1.02;  $P=0.10$ ) differed significantly in SIRT and sorafenib. There was an increase in ORR (RR 2.60, 95% CI 1.69–4.00;  $P<0.0001$ ), but no improvement in DCR (RR 0.91, 95% CI 0.81–1.02;  $P=0.11$ ) in the SIRT group. Fewer patients treated with SIRT had grade 3/4 AEs than those treated with sorafenib, including diarrhea ( $P<0.0001$ ), fatigue ( $P=0.0006$ ), and hand-foot syndrome ( $P=0.0002$ ). Other TKIs were noninferior to sorafenib in OS and TTP in advanced HCC, but with increased risk of toxicities.

**Conclusion:** Patients with locally advanced HCC treated with SIRT got similar efficacy with less toxicity to those treated with sorafenib.

**Keywords:** sorafenib, tyrosine-kinase inhibitors, selective internal radiotherapy, hepatocellular carcinoma, meta-analysis

## Introduction

Hepatocellular carcinoma (HCC) is the fifth-most common cancer in males and the seventh in females worldwide. Patients in developing countries account for about 85% of victims globally.<sup>1</sup> Hepatitis B virus (HBV) infection is the leading cause of HCC in Asia, while hepatitis C virus (HCV) infection is the main pathogen in Europe and North America.<sup>2</sup> Over the past few decades, the incidence of HCC has been increasing in Western countries, particularly in the population infected with HCV.<sup>3</sup> Surgery or liver transplantation are regarded as optimal treatment options, but only about 20% of HCC patients are suitable for potentially curative resection. Patients with intermediate stage

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HCC may obtain limited survival benefit from locoregional treatment.<sup>4</sup> Although early- and intermediate-stage HCC can be controlled temporarily, most patients may progress to an advanced stage after the initial therapy.

Sorafenib is an oral multitarget tyrosine-kinase inhibitor (TKI), which acts by blocking the activities of Raf kinase and VEGFR and inhibiting tumor angiogenesis and proliferation.<sup>5</sup> Sorafenib has been recognized as a standard therapy for advanced HCC, resulting from the approval of it for a modest overall survival (OS) benefit.<sup>6,7</sup> The successful approval of sorafenib has greatly stimulated the development of other TKIs in advanced HCC. There have been six randomized controlled trials to evaluate efficacy and safety of other TKIs, including sunitinib, brivanib, linifanib, dovitinib, lenvatinib, and nintedanib, and all demonstrated noninferiority to sorafenib in OS in patients with advanced HCC.<sup>8–13</sup> However, linifanib and lenvatinib showed significant improvement in time to progression (TTP) and objective response rate (ORR) to sorafenib.<sup>10,12</sup>

Although sorafenib is the reference treatment in advanced HCC, dose reduction or discontinuation of sorafenib are frequently necessary, due to such adverse events (AEs) as diarrhea, fatigue and hand–foot syndrome.<sup>6,7,14</sup> Selective internal radiation (SIRT) might be an alternative therapy to sorafenib with less toxicity in locally advanced HCC patients.<sup>15,16</sup> SIRT with yttrium 90 (<sup>90</sup>Y) microspheres is a therapeutic procedure applied via the hepatic artery, delivering brachytherapy directly to liver tumors. In the SARAH and SIRVENIB trials, OS and TTP in the SIRT group were similar to the sorafenib group among patients with locally advanced HCC. However, ORR and AE frequency were improved with SIRT over sorafenib.<sup>15,16</sup>

As mentioned, other TKIs and SIRT might be alternative treatments to sorafenib for advanced HCC. We conducted this meta-analysis with only large prospective randomized trials included to examine efficacy and safety of other TKIs and SIRT vs sorafenib comprehensively. The main end points were OS and TTP. Secondary end points were ORR, disease-control rate (DCR) and AEs.

## Methods

### Literature-search strategy

Databases were searched systematically, including PubMed, Embase, Chinese National Knowledge Infrastructure, and Wanfang, for titles including “sorafenib” for identification of sorafenib, “tyrosine kinase inhibitor” or “TKI” for identification of TKIs, “selective internal radiotherapy” or “selective internal radiation” for identification of SIRT, and

“(hepatocellular or liver) and (cancer or carcinoma)” or “hepatoma” or “HCC” for identification of HCC.

### Inclusion and exclusion criteria

We included studies based on the following inclusion criteria: randomized Phase III trials, OS or TTP reported, one treatment group receiving sorafenib and the other receiving other TKIs or SIRT, and HCC patients with Child–Pugh A or B liver-function status, performance status (PS) 0–1, and Barcelona Clinic Liver Cancer B or C enrolled. Reviews, retrospective studies, studies unrelated to the topics, or studies without outcomes of interest were excluded. Publication language was not limited.

### Data extraction and quality assessment

We reviewed trials and abstracts of potentially eligible studies and extracted information from studies that met the inclusion criteria, including authors, publication year, sample size, patient characteristics, treatment regimens, and treatment efficacy, such as OS, TTP, ORR, and DCR. The Jadad scoring system was used to assess study quality, graded 0–5 depending on randomization, blinding, and dropout.

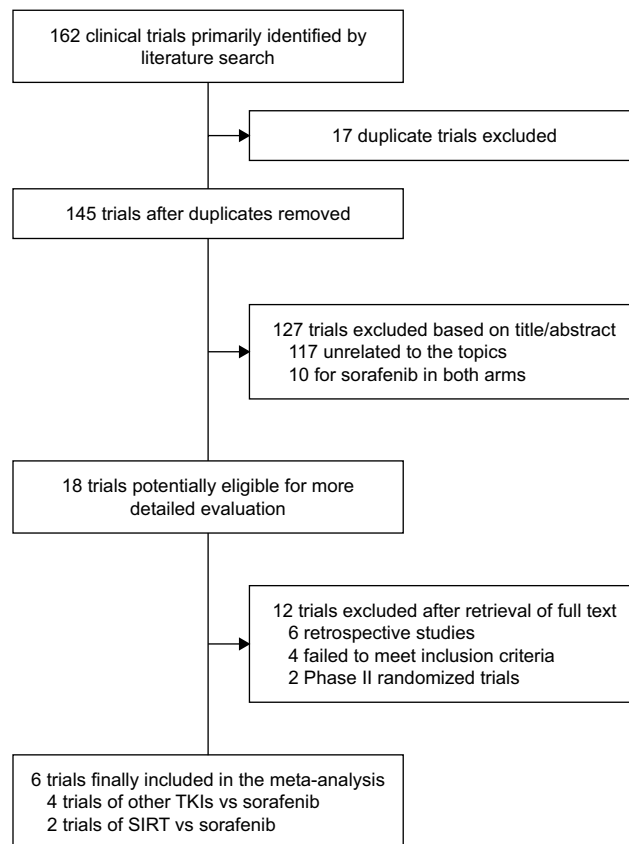
### Statistical analysis

The main end points were OS and TTP. OS was defined as time from random assignment to death from any cause. TTP was defined as time from randomization until disease progression. Secondary end points were ORR and DCR. Results for OS and TTP were expressed as HRs with 95% CIs. HRs and 95% CIs were used directly if reported in the trial. Otherwise, we worked out HR and 95% CI values by a method previously reported.<sup>17</sup> Results for ORR and DCR are expressed as relative risk. Results of grade 3/4 AEs are also expressed as relative risk. The meta-analysis was performed using RevMan 5.3. To evaluate statistical heterogeneity across the studies,  $\chi^2$  and  $I^2$  statistics were used, with predefined significance for  $\chi^2$   $P$ -value  $<0.1$  or  $I^2 >50\%$ . HR and ORR were calculated with a fixed-effect model if heterogeneity was not observed. Otherwise, a random-effect model was used.  $P < 0.05$  (two-sided) was considered statistically significant.

## Results

### Study characteristics

After exclusion of 156 studies, a total of four trials in the other-TKI group and two trials in the SIRT group were eligible (selection process in Figure 1; detailed information



**Figure 1** Study-selection procedure.

**Abbreviations:** TKIs, tyrosine-kinase inhibitors; SIRT, selective internal radiotherapy.

listed in Table 1). Based on the data available for all eligible trials, patients were mostly male, median age 56 and 66 years, with good PS (0–1), good liver function (Child–Pugh A and B) and advanced HCC (Barcelona Clinic Liver Cancer B and C). The results of assessing the quality of all eligible studies are also shown in Table 1.

**Table 1** Demographic and disease characteristics of studies included

Study	Regimen	Patients	Median age, years (range)	Asian (yes/no)	Male/female	Etiology (HBV/HCV)	CP (A/B)	PS (0/1)	BCLC (B/C)	MVI/EHS (yes/no)	Jadad score
Cheng et al <sup>8</sup>	Sunitinib	530	57 (18–85)	411/119	436/94	290/113	529/0	278/248	67/462	418/112	3
Johnson et al <sup>9</sup>	Sorafenib	544	59 (18–84)	418/126	459/85	288/119	541/1	288/254	89/454	415/129	5
Cainap et al <sup>10</sup>	Brivanib	577	61 (19–87)	346/231	483/94	254/116	531/46	361/216	95/444	361/216	3
Kudo et al <sup>12</sup>	Sorafenib	578	60 (25–89)	372/206	484/94	258/119	531/47	352/226	97/449	361/217	5
Vilgrain et al <sup>15</sup>	Linifanib	514	59 (21–84)	339/175	444/70	275/130	484/30	323/191	81/433	362/152	3
Chow et al <sup>16</sup>	Sorafenib	521	60 (23–87)	350/171	436/85	276/129	493/26	344/176	102/418	364/157	3
Cheng et al <sup>8</sup>	Lenvatinib	478	63 (20–88)	321/157	405/73	NA	475/3	304/174	104/374	329/149	5
Johnson et al <sup>9</sup>	Sorafenib	476	62 (22–88)	319/157	401/75	NA	471/5	301/175	92/384	336/140	3
Cheng et al <sup>8</sup>	SIRT	237	66 (60–72)	0/237	212/25	13/55	196/39	145/92	66/162	149/88	3
Johnson et al <sup>9</sup>	Sorafenib	222	65 (58–73)	0/222	202/20	15/49	187/35	139/83	61/149	128/94	3
Chow et al <sup>16</sup>	SIRT	182	60 (47–72)	182/0	147/35	93/26	165/14	135/47	93/88	56/126	3
Cheng et al <sup>8</sup>	Sorafenib	178	58 (47–68)	178/0	151/27	104/19	160/16	141/37	97/80	54/124	3

**Abbreviations:** SIRT, selective internal radiotherapy; HBV, hepatitis B virus; HCV, hepatitis C virus; PS, performance status; BCLC, Barcelona Clinic Liver Cancer; CP, Child–Pugh; MVI, macrovascular invasion; EHS, extrahepatic spread; NA, not available.

## Other TKIs vs sorafenib

### Main analyses of OS and TTP

Survival analyses were based on 4,218 patients from four trials. Other TKIs showed similar benefit on OS to sorafenib for advanced HCC (HR 1.08, 95% CI 0.93–1.24;  $P=0.31$ ) (Figure 2). There was heterogeneity among the trials ( $P=0.008$ ,  $I^2=74\%$ ), so a random-effect model was used. The pooled HR of TTP was 0.86 (95% CI 0.66–1.12,  $P=0.26$ ) with significantly high heterogeneity ( $I^2=92\%$ ,  $P<0.00001$ ) using a random-effect model, as shown in Figure 3.

### Subgroup analyses of OS

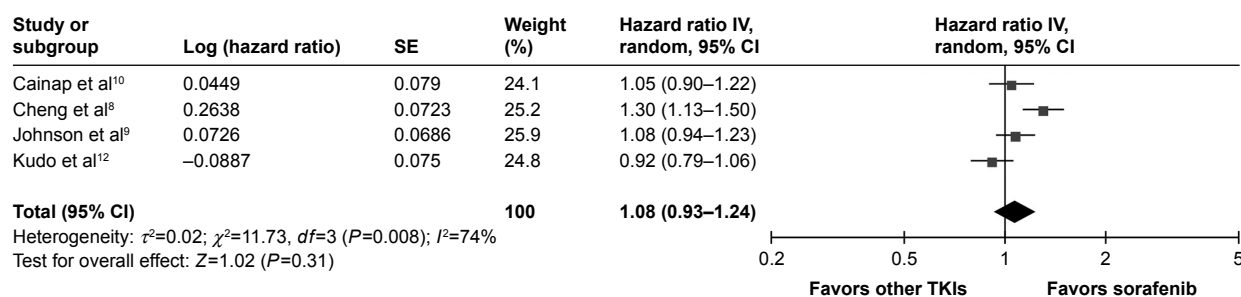
Subgroup analyses identified baseline factors as prognostic of OS: region, AFP level, PS, etiology, and tumor burden. There were no significant differences in OS benefit between sorafenib and other TKIs in subgroups (Table 2).

### Analyses of ORR and DCR

Other TKIs showed greater ORR than sorafenib (RR 1.67, 95% CI 1.15–2.43;  $P=0.008$ ); however, other TKIs failed to show improvement compared with sorafenib for DCR (RR 1.11, 95% CI 0.98–1.26;  $P=0.11$ ; Table 3).

### AEs

Compared with sorafenib, other TKIs were associated with higher incidence of hypertension (RR 1.99, 95% CI 1.67–2.39;  $P<0.00001$ ), fatigue (RR 1.79, 95% CI 1.42–2.26;  $P<0.00001$ ), thrombocytopenia (RR 4.18, 95% CI 1.66–10.56;  $P=0.002$ ), decreased appetite (RR 2.21, 95% CI 1.62–3.01;  $P<0.00001$ ), and vomiting (RR 3.15, 95% CI 1.88–5.26;  $P<0.0001$ ). However, hand–foot



**Figure 2** Overall survival and pooled estimates of other TKIs vs sorafenib.

**Abbreviations:** TKIs, tyrosine-kinase inhibitors; IV, inverse variance.

syndrome (RR 0.39, 95% CI 0.19–0.82;  $P=0.01$ ) and rash (RR 0.34, 95% CI 0.17–0.68;  $P=0.002$ ) occurred less frequently in the other-TKI group than the sorafenib group (Table 4).

## SIRT vs sorafenib

### Main analyses of OS and TTP

Two trials of SIRT vs sorafenib involving 819 patients reported HRs with 95% CIs of OS and TTP. Pooled HRs for OS and TTP were 1.14 (95% CI 0.98–1.32,  $P=0.09$ ; Figure 4) and 0.87 (95% CI 0.74–1.02,  $P=0.10$ ; Figure 5) and showed similar efficacy in the SIRT and sorafenib groups. There was no heterogeneity between the trials for OS ( $P=0$ ,  $P=0.87$ ; Figure 4) or TTP ( $P=0$ ;  $P=0.94$ ; Figure 5), so a fixed-effect model was used.

### Analyses of ORR and DCR

The ORR was significantly greater (RR 2.60, 95% CI 1.69–4.00;  $P<0.0001$ ) in the SIRT group than the sorafenib group, but no improvement in DCR (RR 0.91, 95% CI 0.81–1.02;  $P=0.11$ ) was identified in the SIRT group (Table 3).

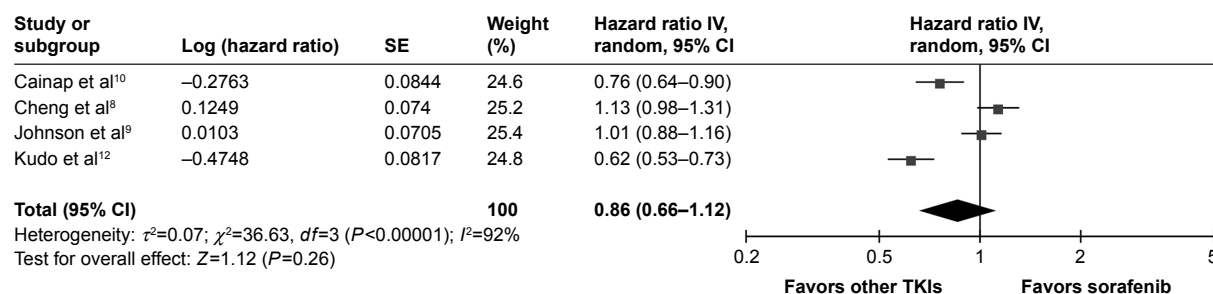
### AEs

The incidence of diarrhea (RR 0.10, 95% CI 0.03–0.28;  $P<0.0001$ ), fatigue (RR 0.42, 95% CI 0.26–0.69;

$P=0.0006$ ), and hand–foot syndrome (RR 0.04, 95% CI 0.01–0.22;  $P=0.0002$ ) in patients treated with SIRT was significantly lower than those treated with sorafenib. However, there were no significant differences between SIRT and sorafenib in the occurrence of pyrexia ( $P=0.15$ ), nausea ( $P=0.78$ ), abdominal pain ( $P=0.23$ ), ascites ( $P=0.62$ ) gastric ulcer ( $P=0.22$ ), or upper gastrointestinal hemorrhage ( $P=0.34$ ; Table 5).

## Discussion

Our meta-analysis included more data than previous meta-analyses, in which recent published clinical trials have not been updated.<sup>12,15,16,18–20</sup> In addition, our meta-analysis included randomized Phase III trials only. As such, our findings are more comprehensive and reliable. Based on four trials and 4,218 patients, results demonstrated similar efficacy of other TKIs to sorafenib on both OS and TTP for advanced HCC patients. Subgroup analyses identified AFP level, PS, etiology, and tumor burden as key prognostic indicators. No differences on OS were found in any subgroups. Pooled results of two trials comprising 819 patients did not show a difference in OS and TTP between SIRT and sorafenib among locally advanced HCC patients. Therefore, other TKIs and SIRT might be alternative treatments to sorafenib for advanced HCC.



**Figure 3** Time to progression and pooled estimates of other TKIs vs sorafenib.

**Abbreviations:** TKIs, tyrosine-kinase inhibitors; IV, inverse variance.

**Table 2** Results of subgroup analyses for OS in studies of sorafenib vs other TKIs

	HR(95% CI)	P-value
Region		
Asia	1.04 (0.91–1.20)	0.55
No Asia	1.23 (0.97–1.58)	0.09
AFP		
<200 ng/mL	1.03 (0.81–1.30)	0.83
≥200 ng/mL	0.91 (0.69–1.19)	0.48
ECOG PS		
0	1.00 (0.90–1.11)	0.98
I	1.04 (0.91–1.19)	0.56
Etiology		
HBV(+)	0.97 (0.88–1.07)	0.57
HCV(+)	1.23 (0.91–1.65)	0.18
Tumor burden		
MVI/EHS	1.00 (0.91–1.11)	0.95
No MVI/EHS	1.04 (0.89–1.21)	0.63

**Abbreviations:** HBV, hepatitis B virus; HCV, hepatitis C virus; MVI, macrovascular invasion; EHS, extrahepatic spread; OS, overall survival; TKIs, tyrosine-kinase inhibitors.

Broad-spectrum TKIs have been developed and tested in first- and second-line therapy for advanced HCC.<sup>8–13,21–23</sup> Four randomized Phase III trials have investigated the use of other TKIs (sunitinib/brivanib/linifanib/lenvatinib) as first-line therapy, all including sorafenib as the control. Our results suggested that other TKIs had similar benefits on OS and TTP when compared with sorafenib. We also conducted subgroup analyses to demonstrate the efficacy of sorafenib vs other TKIs in advanced-HCC patients with various clinical characteristics. Patients from different geographic regions, with different AFP levels, with various PS, and with different tumor burden obtained similar benefits in OS. However, there was a trend of patients treated with sorafenib who were HCV-infected having increased hazard than those treated with other TKIs, although this showed no statistically significant evidence. Consistently, Shao et al and Jackson et al reported improved OS for patients positive for HCV when treated with sorafenib, but no evidence of any improvement in OS attributable to sorafenib for patients positive for HBV and negative for HCV.<sup>18,20</sup> Meanwhile, a retrospective study of patients who received sorafenib for advanced HCC found that

**Table 3** Summary of the RRs of treatment response rates

	Other TKIs vs sorafenib		SIRT vs sorafenib	
	RR (95% CI)	P-value	RR (95% CI)	P-value
ORR	1.67 (1.15–2.43)	0.008	2.60 (1.69–4.00)	<0.0001
DCR	1.11 (0.98–1.26)	0.11	0.91 (0.81–1.02)	0.11

**Abbreviations:** TKIs, tyrosine kinase inhibitors; SIRT, selective internal radiotherapy; RR, risk ratio; CI, confidence interval; vs, versus; ORR, objective response rate; DCR, disease control rate.

**Table 4** Summary of the RRs of grade 3/4 adverse events incidences in trials of other TKIs vs sorafenib

Adverse events	RR	95% CI	P-value
Hypertension	1.99	1.67–2.39	<0.00001
Fatigue	1.79	1.42–2.26	<0.00001
Thrombocytopenia	4.18	1.66–10.56	0.002
Decreased appetite	2.21	1.62–3.01	<0.00001
Vomiting	3.15	1.88–5.26	<0.0001
Hand-foot syndrome	0.39	0.19–0.82	0.01
Rash	0.34	0.17–0.68	0.002

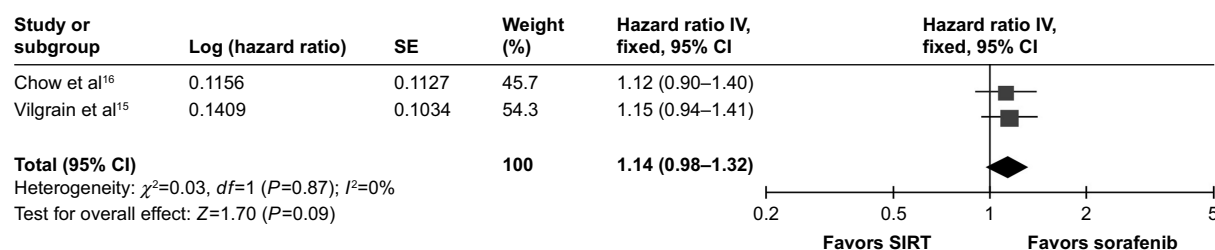
**Abbreviations:** TKIs, tyrosine kinase inhibitors; RR, risk ratio.

HCV infection but not ethnicity was associated with OS.<sup>24</sup> As for mechanism, HCC development and progression are relevant to Raf1–MAPK pathway activation and HCV proteins activate the Raf1–Mek–ERK pathway.<sup>25–27</sup> Moreover, a study has suggested that HCV-related HCC exhibits higher expression of VEGF than HBV-related disease.<sup>28</sup> Sorafenib can mediate inhibition of VEGFR and Raf1, and this may explain the efficacy of sorafenib in HCV-related patients. Therefore HCV-related HCC patients may get better efficacy from sorafenib than other etiologic factor-related disease.<sup>5</sup>

Pooled ORR was significantly higher in advanced-HCC patients treated with other TKIs than those treated with sorafenib, but DCRs were similar between sorafenib and other TKIs. Unfortunately, the improvement in ORR did not translate into a survival advantage. The incidence of grade 3/4 AEs was higher for other TKIs than sorafenib. Notably, differences were seen in the toxicity profile between sorafenib and other TKIs, with higher rates of grade 3/4 hypertension, fatigue, decreased appetite, vomiting, and thrombocytopenia occurring in those treated with other TKIs, whereas patients on sorafenib had higher rates of grade 3/4 rash and hand–foot syndrome. Although other TKIs have similar efficacy compared with sorafenib, other factors, such as toxicity and cost-effectiveness, will determine their roles in the future management of advanced HCC.<sup>29</sup>

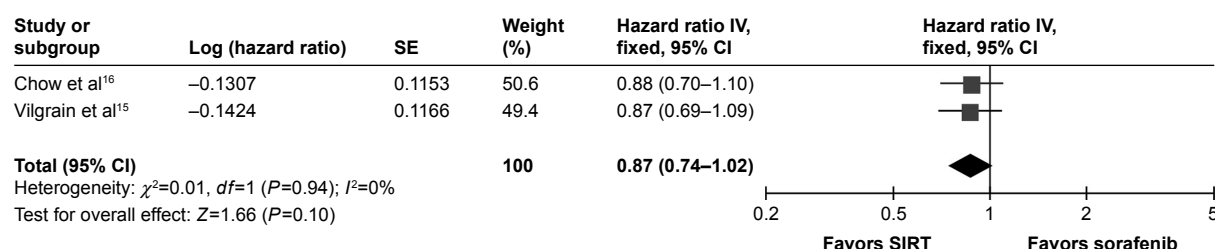
SIRT with <sup>90</sup>Y resin microspheres is an effective treatment for advanced unresectable HCC.<sup>30</sup> Several retrospective trials have indicated that SIRT can offer similar OS for patients with locally advanced HCC compared with sorafenib, but with fewer AEs and better quality of life.<sup>31–33</sup> Consistently, our meta-analysis, including two randomized Phase III trials, suggested that OS and TTP in the SIRT group was similar to that in the sorafenib group. It can be seen that SIRT is an alternative treatment to sorafenib in patients with locally advanced HCC. Besides, the ORR was significantly higher on SIRT compared with sorafenib for patients with locally





**Figure 4** Overall survival (OS) and pooled estimates of SIRT vs sorafenib.

**Abbreviations:** IV, inverse variance; TKIs, tyrosine-kinase inhibitors; SIRT, selective internal radiotherapy.



**Figure 5** Time to progression (TTP) and pooled estimates of SIRT vs sorafenib.

**Abbreviations:** IV, inverse variance; TKIs, tyrosine-kinase inhibitors; SIRT, selective internal radiotherapy.

advanced HCC, while no increase in DCR was observed. Importantly, tolerability was significantly better in the SIRT than the sorafenib arm. Common grade 3/4 AEs, including hand–foot syndrome, diarrhea, and fatigue, occurred more frequently in patients treated with sorafenib than those treated with SIRT, which is consistent with treatment discontinuation that has previously been observed.<sup>6,7</sup> SIRT-related AEs were as expected.

Conclusively, other TKIs and sorafenib resulted in similar OS and TTP in advanced HCC. ORR favored other TKIs, whereas safety results favored sorafenib. For patients with locally advanced HCC, OS did not differ significantly between SIRT and sorafenib. Moreover, SIRT was associated with higher ORR and fewer AEs than sorafenib.

**Table 5** Summary of the RRs of grade 3/4 adverse events incidences in trials of SIRT vs sorafenib

Adverse events	RR	95% CI	P-value
Diarrhea	0.10	0.03–0.28	<0.0001
Fatigue	0.42	0.26–0.69	0.0006
Hand-foot syndrome	0.04	0.01–0.22	0.0002
Pyrexia	0.21	0.03–1.75	0.15
Nausea	0.66	0.04–11.68	0.78
Abdominal pain	0.61	0.27–1.36	0.23
Ascites	1.20	0.58–2.48	0.62
Gastric ulcer	3.13	0.50–19.68	0.22
Upper gastrointestinal hemorrhage	0.61	0.22–1.67	0.34

**Abbreviations:** SIRT, selective internal radiotherapy; RR, risk ratio.

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## Disclosure

The authors report no conflicts of interest in this work.

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