REVIEW ARTICLE

Non-surgical management of advanced hepatocellular carcinoma: A systematic review by Cancer Care Ontario

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ABSTRACT

BACKGROUND: Hepatocellular carcinoma (HCC) is a global health problem, accounting for 4.7% of all new cancer cases and 8.2% of all cancer deaths worldwide in 2018. Resection and transplantation are the only modalities that offer a cure for HCC; however, most patients are diagnosed at an advanced stage, precluding these curative treatments. A number of local (ie, ablative therapies) and/or local-regional therapies (ie, chemo-embolization) are used and followed by systemic therapy for advanced or progressive disease. Other treatments are available, but their efficacy compared with these standards is not well known. **METHODS:** Literature searches (1/2000 to 1/2020 or 1/2005 to 1/2020, depending on the specific systematic review question) were conducted, including MEDLINE, Embase and the Cochrane Database of Systematic Reviews. **RESULTS:** Over 30,000 articles were identified. In total, 49 studies were included in the systematic review. **CONCLUSIONS:** There is no evidence to support the addition of sorafenib to any local or regional therapy. First-line systemic therapy options for unresectable or metastatic HCC include sorafenib, lenvatinib, and atezolizumab + bevacizumab. Regorafenib or cabozantinib provide survival benefits when given as second-line treatment.

KEYWORDS: hepatocellular carcinoma; non-surgical treatment; systematic review; systemic therapy; tyrosine kinase inhibitor

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GLOSSARY

Local therapies

- RFA – radiofrequency ablation
- SBRT – stereotactic body radiation therapy
- TEA – transarterial ethanol ablation

Regional therapies

- cTACE – conventional transarterial chemoembolization
- DEB-TACE – drug eluting bead transarterial chemoembolization
- SIRT – selective internal radiation therapy (same as TARE)
- TAE – bland transarterial embolization
- TARE – transarterial radioembolization

Other therapies

- BSC – best supportive care

Outcomes

- ORR – objective response rate
- OS – overall survival
- PFS – progression free survival
- TTP – time to progression

Other terms

- CI – confidence interval
- HR – hazard ratio
- NE – not estimable
- NR – not reported
- ns – not significant

Definitions (http://www.cancer.ca/en/cancer-information/cancer-type/liver/staging/?region=qc)

- Barcelona Clinic Liver Cancer (BCLC) Stage B (Intermediate stage)
  - Child-Pugh A or B
  - Multifocal disease but tumours are not causing symptoms
  - ECOG = 0
- Barcelona Clinic Liver Cancer (BCLC) Stage C (Advanced stage)
  - Child-Pugh A or B
  - Tumour(s) have grown into blood vessels or there has been spread to other body sites. Tumour(s) are causing symptoms.
  - ECOG = 1 or 2

BACKGROUND

The incidence of liver cancer steadily increased in Canadian men and women between 1989 and 2011 (1). Specifically, the incidence has increased by 3.8% and 2.7% per year in males and females, respectively. This rising incidence may partially be attributed to immigration from regions where exposure to liver cancer risk factors such as hepatitis B, hepatitis C, and aflatoxin are much more common (1). The mortality from liver cancer has also been steadily increasing. Since the mid-1990s, mortality has increased by 3.1% per year in males and 2.2% per year in females in Canada (1). Hepatocellular carcinoma (HCC) accounts for approximately 72% of all liver cancers in Canada. This disease is a global health problem, accounting for 4.7% of all new cancer cases and 8.2% of all cancer deaths worldwide in 2018 (2). In the province of Ontario in 2019, there will be an estimated 1,170 new-incident cases of liver cancer (39.3 % of the estimated new-incident liver cancer cases in Canada) and 550 deaths from liver cancer (39.9% of the estimated liver cancer deaths in Canada) (1). The predicted net observed survival for 2012 to 2014 for liver cancer was 19% (95% CI 18%–20%) for males and females combined (1).

Resection and transplantation are the foundations for a cure for HCC; however, most patients are diagnosed at an advanced stage, precluding these curative treatments. Non-curative treatments are usually transarterial chemoembolization (TACE) and, in the case of advanced disease, sorafenib. Other treatments are available, but their efficacy compared with TACE and sorafenib is not well known. The purpose of this systematic review is to evaluate the current evidence for treatment options for advanced, unresectable HCC.

RESEARCH QUESTIONS

This systematic review examined the evidence to answer the following questions in those with locally advanced or advanced HCC (Barcelona Clinic Liver Cancer [BCLC] Stage B or higher):

1. What are the benefits of other local therapies (transarterial ethanol ablation [TEA], bland transarterial embolization [TAE], radiofrequency ablation [RFA], transarterial radioembolization [TARE], stereotactic body radiation therapy [SBRT], and drug-eluting bead transarterial chemoembolization [DEB-TACE]), versus transarterial chemoembolization (TACE)?

2. What is the benefit of other systemic treatment regimens versus sorafenib?
3. What is the benefit of second-line systemic therapy following sorafenib?

METHODS

Search strategy and selection criteria

Clinical practice guidelines

A search was conducted for existing clinical practice guidelines. Only guidelines based on a systematic review and covering a question of interest were retained. All retained guidelines were evaluated for quality using the AGREE II framework (3).

Systematic reviews

A search was conducted for existing systematic reviews in the databases MEDLINE, Embase, and the Cochrane Database of Systematic Reviews, from 2005 to January 2020. English language systematic reviews that covered any of the current questions of interest were included.

Primary literature

A search for primary studies was undertaken for all questions. If more than one publication was available for a given trial, only the most recent publication was included. The search strategy for guidelines, systematic reviews, and primary studies is available upon request.

Study selection criteria and process

Selected studies had to be English language studies addressing the question of interest in adult participants (N = 30 minimally) with locally advanced or advanced HCC (BCLC Stage B or intermediate stage or higher) who were not suitable for transplant or surgery, included a comparison of interest, and included at least one outcome of interest. Randomized controlled trials were preferred. If none were available for a particular comparison, other comparative studies were included.

A review of the titles and abstracts that resulted from the search was independently conducted by one reviewer (author RC). A full-text review was conducted by one reviewer (RC). If there was any question regarding the eligibility of a given study, then two reviewers (RC and BMM) reviewed each item in collaboration to determine eligibility.

Data extraction and assessment of study quality and potential for bias

Data from all included studies were extracted by one member of the working group (RC). All extracted data were subsequently audited by an independent auditor.

RCTs were assessed for quality and potential bias using the Cochrane Risk of Bias tool (section 8 of the Cochrane's *and Handbook for Systematic Review of Interventions*, available at http://handbook.cochrane.org/). All non-RCTs were assessed using the ROBINS-I tool from *Cochrane Risk of Bias in Non-Randomized Studies – of Interventions* (available at https://sites.google.com/site/riskofbias-tool/). Systematic reviews were evaluated using the AMSTAR tool (4).

RESULTS

Search for existing clinical practice guidelines

A search for systematic reviews uncovered 11,279 documents. Of these, 398 underwent full-text review, and none were retained.

Search for existing systematic reviews

A search for systematic reviews uncovered 6,783 documents. Of these, 394 underwent full-text review and none were retained.

Search for primary literature

A search for primary studies uncovered 13,166 documents. Of these, 461 underwent a full-text review and 49 were retained, including one relevant pooled analysis. For a summary of the full literature search results (including guidelines and systematic reviews), please refer to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) study selection flow diagram in Figure 1.

Study design and quality

Randomized controlled trials

Forty RCTs published in 47 manuscripts (5–51) were included in this guidance document and were assessed using Cochrane's Risk of Bias tool. Many of the included RCTs could not be assessed on at least one element of the risk of bias tool. This was particularly evident in abstracts, which report very limited information. These items were therefore rated as "unclear." Overall, there were only 6 RCTs that had a low

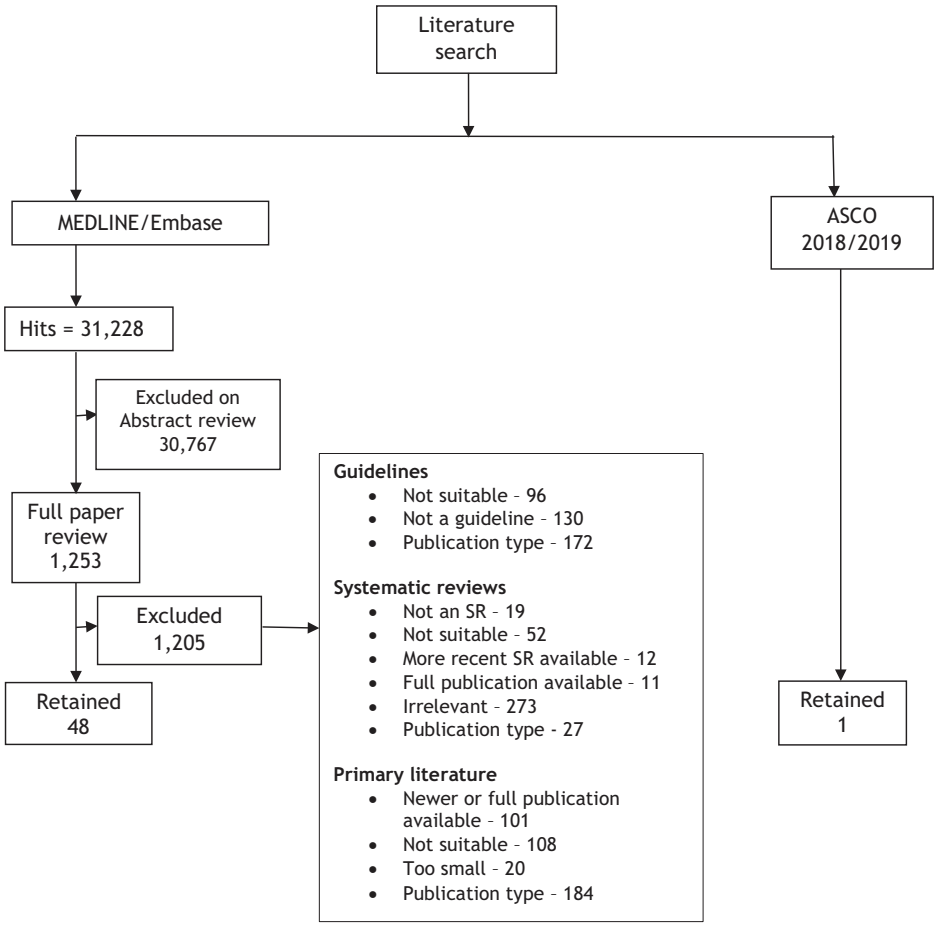

Figure 1: PRISMA flow diagram for literature search

PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses (http://www.prisma-statement.org/); ASCO = ASCO Publications (https://ascopubs.org/); SR = Systematic review

risk of bias (38,41,45,47,48,51). Eighteen RCTs (5,7,8,10,11,19,21–23,29,30,33,35,40,44,46,49,50) were considered to have an unclear risk of bias as at least one of the domains was rated as "unclear." Sixteen RCTs (6,9,12,13,18,20,24–28,31,32,34,36,37) were considered to have a serious risk of bias (risk of bias evaluations are available upon request).

Non-randomized controlled studies

This guidance document includes two non-RCTs (52,53) that were each assessed using the ROBINS-I tool. This tool assesses each trial on seven domains of bias as well as an overall assessment of risk of bias. These were only available in abstract form and therefore were assessed as "no information," as there was not enough information in the abstracts to evaluate risk of bias (risk of bias evaluations are available upon request from the corresponding author).

Outcomes

Question 1: What is the benefit of the addition of sorafenib to local therapies (TEA, TAE, RFA, TARE, SBRT, DEB-TACE, and TACE)?

TEA + sorafenib versus TEA

No studies were found.

TAE + sorafenib versus TAE

No studies were found.

RFA + sorafenib versus RFA

One trial of 62 participants, with lesions ranging from 3.1 to 5.0 cm, was retained (5). One-, 2-, and 3-year recurrence rates were significantly higher in the RFA-alone arm (87.5% versus 56.7%, $p < 0.01$). Median time to progression (TTP) was significantly longer in the RFA + sorafenib arm (17.0 months versus 6.1 months, $p < 0.05$). There were no

serious toxicities in the RFA arm. However, 8.1% and 6.5% of participants in the combination arm experienced a Grade 3 increase in alanine aminotransferase (ALT) and aspartate transaminase (AST), respectively. No subgroup analysis for tumour size was reported.

TARE + sorafenib versus TARE

No RCTs were found. However, 2 abstracts (one retrospective study and one case-control study) were retained. Ma et al (52) conducted a retrospective study of 55 participants in one centre. Median survival in the combined arm was significantly higher than in the TARE-only arm (21.0 months versus 7.0 months; p = 0.003). Adverse effects were reported in 1 participant in the combined treatment arm and 6 participants in the TARE-only arm. However, severities of the toxicities were not reported. Maccauro et al (53) conducted a case-control study of 15 cases and 30 controls. There were no significant differences between the groups on any reported outcome, including median PFS, median overall survival (OS), and ORR.

SBRT + sorafenib versus SBRT

No studies were found.

DEB-TACE + sorafenib versus DEB-TACE

Two trials were retained (10,11). The SPACE trial (10) included 307 participants with intermediate-stage HCC. TTP was not significantly different in the two study arms (HR 0.797; 95% CI 0.588–1.080; p = 0.072). OS was also not significantly different in the two study arms (HR 0.898, 95% CI 0.606–1.330; p = 0.295). ORR was 35.7% in the DEB-TACE/sorafenib arm and 28.1% in the DEB-TACE/placebo arm (p = NR). The TACE 2 trial (11) included 399 participants and was terminated early for futility. Median PFS (HR 0.99; 95% CI 0.77–1.27; p = 0.94) and median OS (HR 0.91; 95% CI 0.67–1.24; p = 0.57) were not significantly different in the two trial arms.

DEB-TACE + sorafenib versus DEB-TACE

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TACE + sorafenib versus TACE

Four trials were retained (6–9). Kudo et al (6) conducted a phase III trial of 458 participants with unresectable HCC. Median TTP was not significantly different in the two arms of the trial (HR 0.87; 95% CI 0.70–10.9; p = 0.252). Median OS was also not significantly different in the two arms of the study (p = 0.790). The incidence of drug-related adverse events (AEs) was higher in the TACE/sorafenib arm (18%) compared with the TACE/placebo arm (9%), but no p value is reported. Sansonno et al (7) conducted a smaller trial of 80 intermediate-stage HCC participants. There was a significantly longer TTP in the TACE/sorafenib arm compared with the TACE/placebo arm (9.2 months versus 4.9 months, p < 0.001). There were more drug-related AEs in the TACE/sorafenib arm; however, no p values are reported. Kudo et al (8) conducted a trial of 256 participants with unresectable HCC in 33 centres. Median PFS was significantly longer in the TACE/sorafenib arm compared with the TACE-alone arm (25.2 months versus 13.5 months [HR 0.56; 95% CI 0.38–0.83; p = 0.004]). Park et al (9) conducted a phase III trial of 330 participants with advanced HCC. Median OS was not significantly different in the two study arms (HR 0.91; 95% CI 0.69–1.21; p = 0.290). However, both median TTP (HR 0.67; 95% CI 0.53–0.85; p = 0.003) and median PFS (HR 0.73; 95% CI 0.59–0.91; p = 0.01) significantly favoured the TACE/sorafenib arm.

Question 2: What is the benefit of other systemic treatment regimens versus sorafenib?

Single drugs versus sorafenib alone

Lenvatinib versus sorafenib

A phase III non-inferiority trial of lenvatinib versus sorafenib was reported in one full publication (13), and 4 abstracts were retained (14–17). This trial enrolled 954 participants. The data indicate that lenvatinib is non-inferior to sorafenib with respect to median OS (HR 0.92; 95% CI 0.79–1.06). Median PFS (HR 0.66; 95% CI 0.57–0.77, p <0.0001), median TTP (HR 0.63; 95% CI 0.53–0.73, p <0.0001), and

Table 1: Outcomes from included studies on other systemic treatments versus sorafenib

Study	Treatment allocation	N (evaluated)	Median OS (months)	Median TTP (months)	Median PFS (months)	ORR No. (%)	Terminated early?
			Single drugs vs. sorafenib alone				
Linifanib vs. sorafenib							
Cainap, 2015 (12)	Linifanib	514 (510)	9.1	5.4	4.2	10.1%	Yes, for futility
	Sorafenib	521 (519)	9.8 HR 1.046; 95% CI 0.896–1.221; *p* = ns	4.0 HR 0.759; 95% CI 0.643–0.895; *p* = 0.001	2.9 HR 0.813; 95% CI 0.697–0.948; *p* = 0.008	6.1% *p* = 0.018	
Lenvatinib vs. sorafenib							
Kudo, 2018 (13)	Lenvatinib	478	13.6	8.9	7.4	115 (24)	No
	Sorafenib	476	12.3 HR 0.92; 95% CI 0.79–1.06; *p* = NR	3.7 HR 0.63; 95% CI 0.53–0.73; *p* <0.0001	3.7 HR 0.66; 95% CI 0.57–0.77; *p* <0.0001	44 (9) *p* <0.0001	
Han, 2017 (14), abstract	HBV-positive participants						
	Lenvatinib	259	13.4				
	Sorafenib	244	10.2 HR 0.83; 95% CI 0.68–1.02; *p* = NR				
	HBV-positive Asia-Pacific participants						
	Lenvatinib	218	13.1				
	Sorafenib	208	9.4 HR 0.82; 95% CI 0.66–1.02; *p* = NR				
Sunitinib vs. sorafenib							
Cheng, 2013 (18)	Sunitinib	530	7.9	4.1	3.6	NR	Yes, for futility and safety
	Sorafenib	544	10.2 HR 1.30; 95% CI 1.13–1.50; *p* = 0.9990	3.8 HR 1.13; 95% CI 0.98–1.31; *p* = 0.8312	3.0 HR 1.13; 95% CI 0.99–1.30; *p* = 0.8785		
Nintedanib vs. sorafenib							
Yen, 2018 (19)	Nintedanib	63	10.2	2.8	2.7	NR	No
	Sorafenib	32	10.7 HR 0.94; 95% CI 0.59–1.49; *p* = NR	3.7 HR 1.21; 95% CI 0.73–2.01; *p* = NR	3.7 HR 1.19; 95% CI 0.73–1.93; *p* = NR		
Palmer, 2015 (20), abstract	Nintedanib	62	11.9	5.5 (investigator assessed)	NR	NR	No

(*Continued*)

Study	Treatment allocation	N (evaluated)	Median OS (months)	Median TTP (months)	Median PFS (months)	ORR No. (%)	Terminated early?
	Sorafenib	31	11.4 HR 0.88; 95% CI 0.52–1.47; p = NR	3.8 (investigator assessed) HR 1.05; 95% CI 0.63–1.76; p = NR			
Brivanib vs. sorafenib							
BRISK-FL, 2013 (21)	Brivanib	577 (575)	9.5	4.2	NR	12%	No
	Sorafenib	578 (575)	9.9 HR 1.07; 95% CI 0.94–1.23; p = 0.3116	4.1 HR 1.01; 95% CI 0.88–1.16; p = 0.8532		9% p = 0.569	
Capecitabine vs. sorafenib							
Wahab, 2012 (22), abstract	Capecitabine	N total	5.07	NR	4	3.0%	No
	Sorafenib	52	7.05 p <0.016		6 p <0.005	14.5% p = NR	
Nivolumab vs. sorafenib							
Yau, 2019 (23), abstract	Nivolumab	371	16.4	NR	3.7	57 (15)	No
	Sorafenib	372	14.7 HR 0.85; 95% CI 0.72–1.02; p = 0.0752		3.8 p = NR	26 (7) p = NR	
Drug combinations vs. sorafenib alone							
Atezolizumab + bevacizumab vs. sorafenib **Nivolumab vs. sorafenib**							
Finn, 2020 (24)	Atezolizumab + bevacizumab	336	NE		6.8	27%	No
	Sorafenib	165	13.2 HR 0.58; 95% CI 0.42–0.79; p <0.001		4.3 HR 0.059; 95% CI 0.47–0.76; p <0.001	12% p <0.001	
Doxorubicin + sorafenib vs. sorafenib							
Soradox trial, 2015 (25), abstract	Doxorubicin + sorafenib	15 (11)	6.97	7.11	NR	NR	No
	Sorafenib	15 (12)	19.8 p = 0.14	8.45 p = 0.96			
CALGB 80802, 2019 (26)	Doxorubicin + sorafenib	180	9.3	4.7	4.0	15 (10)	Yes, for futility
	Sorafenib	176	9.4 HR 1.03; 95% CI 0.82–1.29; p = 0.83	4.2 HR 0.92; 95% CI 0.71–1.18; p = 0.49	3.7 HR 0.93; 95% CI 0.75–1.16; p = 0.54	8 (5.4) p = ns	

(*Continued*)

Study	Treatment allocation	N (evaluated)	Median OS (months)	Median TTP (months)	Median PFS (months)	ORR No. (%)	Terminated early?
GEMOX + sorafenib vs. sorafenib							
GONEXT trial, 2019 (27)	GEMOX + sorafenib	48 (40)	13.5	6.2	6.2	6 (15)	No
	Sorafenib	46 (38)	14.8 *p* = NR	4.6 *p* = NR	4.6 *p* = NR	4 (9) *p* = NR	
Tigatuzumab + sorafenib vs. sorafenib							
Cheng, 2015 (28)	Tigatuzumab (6/2mg/kg) + sorafenib	53 (53)	8.2	3.0	NR	5.7%	No
	Tigatuzumab (6/6mg/kg) + sorafenib	55 (54)	12.2	3.9		14.8%	
	Sorafenib	55 (55)	8.2 All pairwise comparisons; *p* = ns	2.8 All pairwise comparisons; *p* = ns		10.9%	
Mapatumumab + sorafenib vs. sorafenib + placebo							
Ciuleanu, 2016 (29)	Mapatumumab + sorafenib	50	10.0	4.1	3.2	NR	No
	Sorafenib + placebo	51	10.1 HR 1.195; 90% CI 0–1.651*; *p* = 0.7823	5.6 HR 1.192; 95% CI 0–1.737; *p* = 0.7382	4.2 HR 1.066; 90% CI 0–1.43*; *p* = NR		
Everolimus + sorafenib vs. sorafenib							
Koeberle, 2016 (30)	Everolimus + sorafenib	60 (50)	12	NR	5.7	6 (10)	No
	Sorafenib	46 (43)	10 *p* = NR		6.6 *p* = NR	0 (0) *p* = NR	
AEG35256 + sorafenib vs. sorafenib							
Lee, 2016 (31)	AEG35256 + sorafenib	31	6.5	NR	4.0	3 (9.7)	No
	Sorafenib	17	5.4		2.6	0 (0.0)	
Bevacizumab + erlotinib vs. sorafenib							
Thomas, 2018 (32)	Bevacizumab + erlotinib	47	8.6	NR	NR	15%	No
	Sorafenib	43	8.6 HR 0.92; 95% CI 0.57–1.47; *p* = NR			9% *p* = NR	
Erlotinib + sorafenib vs. sorafenib + placebo							
SEARCH, 2015 (33)	Erlotinib + sorafenib	362 (362)	9.5	3.2	NR	6.6%	No
	Sorafenib + placebo	358 (355)	8.5 HR 0.929; 95% CI 0.78–1.11; *p* = 0.408	4.0 HR 1.135; 95% CI 0.94–1.37; *p* = 0.18		3.9% *p* = 0.102	

(*Continued*)

Study	Treatment allocation	N (evaluated)	Median OS (months)	Median TTP (months)	Median PFS (months)	ORR No. (%)	Terminated early?
Pravastatin+sorafenib vs. sorafenib							
Blanc, 2018 (34), abstract	Pravastatin+ sorafenib	40	4.0	NR	3.4	NR	No
	Sorafenib	41	3.8 *p* = NR		3.2		
Resminostat + sorafenib vs. sorafenib							
Tak, 2018 (35)	Resminostat + sorafenib	86 (84)	11.8	2.8	NR	3 (3.6)	No
	Sorafenib	84 (84)	14.1 HR 1.046; 95% CI 0.70–1.55; *p* = 0.824	2.8 HR 0.984; 95% CI 0.68–1.41; *p* = 0.925		8 (9.5) *p* = NR	
Tegafur–uracil (UFT) + sorafenib vs. sorafenib							
Azim, 2018 (36)	UFT + sorafenib	36	8.2	7.5	6	NR	Yes, for futility
	Sorafenib	38	10.5 HR 1.58; 95% CI 0.90– 2.76; *p* = 0.112	8.2 HR 1.07; 95% CI 0.52–2.22; *p* = 0.855	6 HR 1.19; 95% CI 0.71–2.01; *p* = 0.508		

***** *Note this is a 90% confidence interval*
OS = Overall survival; TTP = Time to progression; PFS = Progression-free survival; ORR = Objective response rate; HR = Hazard ratio; CI = Confidence interval;
HBV = Hepatitis B virus; NR = Not reported; GEMOX = Gemcitabine/oxaliplatin; NE = Not estimable; ns = Not significant

ORR (24.1% versus 9.2%, p <0.0001) were all significantly better in the lenvatinib arm (15) (Table 1). This trial had very strict inclusion criteria. Specifically, only those with ECOG PS 0–1 were included, and those with main portal vein thrombosis were excluded. This limits the generalizability of the results. Subgroup analysis demonstrated that median OS was similar in the 2 study arms in HBV-positive participants in general (HR 0.83; 95% CI 0.68–1.02) and HBV-positive participants from the Asia-Pacific (HR 0.82; 95% CI 0.66–1.02) (14). Health-related QOL was reported in 3 abstracts (15–17). Lenvatinib was significantly better with respect to role function (p = 0.0098), pain (p = 0.006), diarrhea (p <0.0001), body image (p = 0.0041), and nutrition (p = 0.006).

Other single drugs versus sorafenib

All other comparisons of single drugs to sorafenib, including linifanib (12), sunitinib (18), nintedanib (19,20), brivanib (21), capecitabine (22), and nivolumab (23) were non-significant, not non-inferior, or too small to make any conclusions about (Table 1).

Drug combinations versus sorafenib alone

Atezolizumab + bevacizumab versus sorafenib

The phase III IMbrave150 trial comparing atezolizumab/bevacizumab versus sorafenib was retained (24). This trial is currently only available in abstract form and is technically an interim analysis, which would normally result in it not being included in the systematic review. However, since the results of the interim analysis have met the stated primary end points, they were considered final. This trial of 501 participants demonstrated significantly better median OS (HR 0.58; 95% CI 0.42–0.79; p <0.001) and median PFS (HR 0.059; 95% CI 0.47–0.76; p <0.001) for the combination arm compared with the sorafenib alone arm (Table1). These results are intriguing, but a final recommendation would only be made once the final publication is available.

Other drug combinations versus sorafenib

All comparisons of drug combination to sorafenib including doxorubicin/sorafenib (25,26), gemcitabine/oxaliplatin/sorafenib (27), tigatuzumab/sorafenib (28), mapatumumab/sorafenib (29), everolimus/sorafenib (30), AEG35256/sorafenib (31), becvacizumab/erlotinib (32), erlotinib/sorafenib (33), pravastatin/sorafenib (34), resminostat/sorafenib (35), and UFT/sorafenib (36) were non-significant (Table 1).

Question 3: What is the benefit of second-line systemic therapy following sorafenib?

Regorafenib + best supportive care (BSC) versus placebo + BSC

One full publication (41) and two abstracts (42,43) of the RESORCE trial were retained. This was a phase III RCT of regorafenib/BSC versus placebo/BSC. The authors (41) reported significantly better median OS (HR 0.63; 95% CI 0.50–0.79, p <0.0001), median PFS (HR 0.46; 95% CI 0.37–0.56, p <0.0001) and median TTP (HR 0.44; 95% CI 0.36–0.55, p <0.0001) in the regorafenib arm of the trial. ORR was also significantly better in the regorafenib arm (11% versus 4%; p = 0.0047 (Table 2). Updated OS results are very similar to the primary analysis (HR 0.62; 95% CI 0.50–0.75; p<0.0001) (42). Grade 3/4 toxicity was greater in the regorafenib arm overall (67% versus 39%) including hand-foot skin reaction (13% versus 1%), diarrhea (3% versus 0%), fatigue (9% versus 5%), and hypertension (15% versus 5%). No p values are reported (41). All measures of QOL were similar in the two treatment arms (43).

Cabozantinib versus placebo

One full publication of the phase III CELESTIAL trial of second- or third-line cabozntinib versus placebo was retained (44). Median OS (HR 0.76; 95% CI 0.63–0.92; p = 0.005), median PFS (HR 0.44; 95% CI 0.36–0.52, p <0.001) and ORR (4% versus < 1%; p = 0.009) were significantly better in the cabozantinib arm (Table 2). Grade 3/4 toxicity was greater in the cabozantinib arm compared with the placebo arm (68% versus 36%), including for hand-foot skin reaction (17% versus 0%), hypertension (16% versus 2%), fatigue (10% versus 4%), and diarrhea (10% versus 2%). No p values are reported.

Ramucirumab/BSC versus placebo/BSC

Two full publications (38,39) of the REACH trial were retained as well as one full publication (40) of the REACH-2 trial (Table 2). REACH is a phase III trial that compared second-line ramucirumab + BSC to placebo + BSC. Each of these REACH trial publications reports different outcomes. Zhu et al (38) report the main findings of the REACH trial. There was no significant difference between the groups with respect to median OS (HR 0.87; 95% CI 0.72–1.05; p = 0.14). The ramucirumab arm was significantly better than the placebo arm with respect to median PFS (HR 0.63; 95% CI 0.52–0.75; p <0.0001), median TTP (HR 0.59; 95% CI 0.49–0.72; p <0.0001), and ORR (7% versus <1%, p <0.0001). Although no p values are reported, ascites, hypertension, asthenia, and thrombocytopenia occurred more often in the ramucirumab arm. In contrast, increased AST, hyperbilirubinemia, and increased blood bilirubin occurred more often in the placebo group. Chau et al (39) reported participant-focused outcomes from the REACH trial using the FACT Hepatobiliary Symptom Indexes. There were no significant differences between the two arms of the trial. Therefore, treatment with ramucirumab did not lead to any improvement or impairment with respect to symptoms or participant functioning.

REACH-2 (40) was a phase III RCT of ramucirumab versus placebo/BSC in participants with elevated alpha-fetoprotein (AFP) at ≥400 ng/mL following first-line sorafenib. Median OS (HR 0.710; 95% CI 0.53–0.95; p = 0.0199) and median PFS (HR 0.452; 95% CI 0.34–0.60, p <0.0001) were both significantly better in the ramucirumab arm compared with placebo. There was no significant difference in ORR (Table 2).

All other second-line systemic therapy

All other second-line systemic therapy regimens including ADI-peg 20/BSC (37), S-1 (45), brivanib/BSC (46), tivantinib (47,48), RO5137382/GC33 (49), everlimus/BSC (50), and pembrolizumab (51) were non-significant or too small to make any conclusions about (Table 2).

DISCUSSION

The majority of those with newly diagnosed HCC are not eligible for curative therapies, including local or regional ablative therapies, hepatic resection, or transplant. Previous guidelines have reviewed the evidence for local or regional ablative therapies (54,55). In this systematic review, we reviewed the current evidence for treatment options for advanced, unresectable HCC. We focused on two areas: TACE and systemic therapies.

Table 2: Outcomes from included studies on the benefit of second-line systemic therapy following sorafenib

Study	Treatment allocation	N (evaluated)	Median OS (months)	Median TTP (months)	Median PFS (months)	ORR No. (%)	Terminated early?
Regorafenib + BSC vs. placebo + BSC							
Bruix, 2017 (41)	Regorafenib + BSC	379	10.6	3.2	3.1	40 (11)	No
	Placebo + BSC	194	7.8	1.5	1.5	8 (4)	
			HR 0.63; 95% CI 0.50–0.79; p <0.0001	HR 0.44; 95% CI 0.36–0.55; p <0.0001	HR 0.46; 95% CI 0.37–0.56; p <0.0001	p = 0.0047	
Cabozantinib vs. placebo							
Abou-Alfa, 2018 (44)	Cabozantinib	470	10.2	NR	5.2	18 (4)	Yes, for efficacy
	Placebo	237	8.0		1.9	1 (<1)	
			HR 0.76; 95% CI 0.63–0.92; p = 0.005		HR 0.44; 95% CI 0.36–0.52; p <0.001	p = 0.009	
Ramucirumab + BSC vs. placebo + BSC							
REACH – Zhu, 2015 (38)	Ramucirumab + BSC	283 (277)	9.2	3.5	2.8	20 (7)	No
	Placebo + BSC	282 (276)	7.6	2.6	2.1	2 (<1.0)	No
			HR 0.87; 95% CI 0.72–1.05; p = 0.14	HR 0.59; 95% CI 0.49–0.72; p <0.0001	HR 0.63; 95% CI 0.52–0.75; p <0.0001	p <0.0001	
REACH-2, 2019 (40)	Ramucirumab	197	8.5		2.8	9 (5)	
	Placebo + BSC	95	7.3		1.6	1 (1)	
			HR 0.710; 95% CI 0.53–0.95; p = 0.0199		HR 0.452; 95% CI 0.34–0.60; p <0.0001	p = 0.1697	
ADI-peg 20 + BSC vs. placebo + BSC							
Abou-Alfa, 2018 (37)	ADI-peg 20 + BSC	424	7.8	NR	2.6	2 (<1.0)	No
	Placebo + BSC	211	7.4		2.6	6 (2.8)	
			HR 1.022; 95% CI 0.847–1.233; p = 0.884		HR 1.175; 95% CI 0.964–1.432; p = 0.075	p = NR	
S-1 vs. placebo							
S-CUBE, 2017 (45)	S-1	222	11.1	2.6	2.6	12 (5)	No
	Placebo	111	11.2	1.4	1.4	1 (1)	
			HR 0.86; 95% CI 0.067–1.10; p = 0.220	HR 0.59; 95% CI 0.46–0.76; p <0.0001	HR 0.60; 95% CI 0.46–0.77; p <0.0001	p = 0.068	

(*Continued*)

Study	Treatment allocation	N (evaluated)	Median OS (months)	Median TTP (months)	Median PFS (months)	ORR No. (%)	Terminated early?
Brivanib + BSC vs. placebo + BSC							
BRISK-PS – Llovet, 2013 (46)	Brivanib + BSC	263 (261)	9.4	4.2	NR	10	No
	Placebo + BSC	132 (131)	8.2	2.7		2	
			HR 0.89; 95% CI 0.69–1.15; p = 0.3307	HR 0.56; 95% CI 0.42–0.76; p <0.001		p = 0.0030	
Tivantinib vs. placebo							
Santoro, 2013 (47)	Tivantinib	71	6.6	1.6	1.5	3	No
	Placebo	36	6.2	1.4	1.4	0	
			HR 0.90; 95% CI 0.57–1.40; p = 0.63	HR 0.64; 90% CI†, 0.43–0.94; p = 0.04	HR 0.67; 95% CI 0.44–1.04; p = 0.06		
Rimassa, 2018 (48)	Tivantinib	226	8.4	2.4	2.1	NR	No
	Placebo	114	9.1	3.0	2.0		
			HR 0.97; 95% CI 0.75–1.25; p = 0.81	HR 0.96; 95% CI 0.74–1.25; p = 0.76	HR 0.96; 95% CI 0.75–1.22; p = 0.72		
RO5137382/GC33 vs. placebo							
Yen, 2014 (49), abstract	RO5137382/GC33	121	6.8	2.9	2.6	NR	No
	Placebo	64	6.7	1.7	1.5		
			p = 0.99	p = 0.85	p = 0.87		
Everolimus + BSC vs. placebo + BSC							
Zhu, 2014 (50)	Everolimus + BSC	362	7.6	NR	NR	2.2	No
	Placebo + BSC	184	7.3	NR		1.6	
			HR 1.05; 95% CI 0.86–1.27; p = 0.68	HR 0.93; 95% CI 0.75–1.15; p = ns		p = NR	
Pembrolizumab + BSC vs. placebo + BSC							
Finn, 2019 (51)	Pembroli-zumab + BSC	278	13.9	3.8	3.0	51 (18.3)	No
	Placebo + BSC	135	10.6	2.8	2.8	6 (4.4)	
			HR 0.78; 95% CI 0.61–1.00; p = 0.0238‡	HR 0.69; 95% CI 0.54–0.88; p = 0.0011	HR 0.71; 95% CI 0.57–0.90; p = 0.0022‡	p = 0.00007	

† Note this is a 90% confidence interval
‡ Did not meet pre-specified boundaries for statistical significance set prior to the start of the trial
OS = Overall survival; TTP = Time to progression; PFS = Progression-free survival; ORR = Objective response rate; BSC = Best supportive care; HR = Hazard ratio; CI = Confidence interval; NR = Not reported; ns = Not significant

TACE

Following the treatment of local or regional therapies, there is no evidence to support the addition of sorafenib following this. The majority of these studies were small and of moderate to poor quality. Following the failure of local or regional therapies, those suitable for systemic therapy should be considered for treatment.

Even though some of the studies demonstrated an advantage for TACE/sorafenib over TACE alone with respect to TTP and PFS, this did not always ultimately translate into a survival advantage. It is not known that better TTP/PFS always translates to OS. It is possible that subsequent treatments will confound these endpoints. It is also likely that the timing of treatment (ex sorafenib pre-, post-, or concurrently with TACE) is an important factor. Finally, TACE protocols are heterogeneous and it becomes difficult to compare different studies.

Systemic therapies

For those who are either ineligible for local or regional therapies or have progressed following them, the number of systemic therapies now available has increased since earlier in the decade. First-line systemic therapy options for unresectable or metastatic HCC include sorafenib, lenvatinib, and atezolizumab + bevacizumab. In addition, the PD-L1 nivolumab is being compared with sorafenib in an active clinical trial (NCT0257650).

In the second-line setting, both regorafenib and cabozantinib have received approval by the US Food and Drug Administration (FDA) (the latter based on abstract publication only). In addition, nivolumab has received provisional approval (FDA/Health Canada) based on the response rates seen.

Gaps in knowledge

There are definite gaps in knowledge in the existing literature. Studies typically categorize patients by BCLC staging. For example, BCLC B with a large or multifocal HCC may have a worse prognosis than a small volume disease with a single metastatic lung or nodal metastasis. However, this prognostication is not well captured. Moreover, trials do not evaluate real-world experiences in treating patients; however, the concept of multi-modality therapy has been proposed by several groups (56,57). Nuanced sequencing of appropriate local and systemic therapy has not been addressed in any studies, but this approach likely more accurately portrays real-world, multidisciplinary teams.

CONCLUSIONS

There is no evidence to support the addition of sorafenib to any local or regional therapy. Single-agent sorafenib or lenvatinib, or a combination of atezolizumab + bevacizumab, are recommended for first-line systemic treatment of intermediate-stage HCC. Regorafenib or cabozantinib provide survival benefits when given as second-line treatment after progression on sorafenib. With immunotherapy combinations becoming a new standard of care, the assumptions regarding localized and sequencing lines of therapies will need further study. More active systemic regimens should move earlier in the treatment course for HCC patients. Lessons learned from the many studies reviewed systemically in this paper will help guide the next important questions.

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