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Review

Optimizing Survival and the Changing Landscape of Targeted Therapy for Intermediate and Advanced Hepatocellular Carcinoma: A Systematic Review

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Abstract

Background: Systemic therapy for hepatocellular carcinoma (HCC) consisting of the tyrosine kinase inhibitor sorafenib has remained unchanged for over a decade, although results from phase III targeted therapy trials have recently emerged. This review considers available phase III evidence on the use and sequencing of targeted therapy for intermediate and advanced non-locoregional therapy (LRT) eligible HCC and discusses implications for clinical practice. Methods: Published and presented literature on phase III data reporting on targeted therapy for advanced HCC that was not eligible for loco-regional therapies was identified using the key search terms “hepatocellular cancer” AND “advanced” AND “targeted therapy” AND “phase III” OR respective aliases (PRISMA). Results: Ten phase III trials assessed targeted therapy first-line and eight following sorafenib. In the first-line, atezolizumab plus bevacizumab statistically significantly improved overall survival (OS) and patient-reported outcomes (PROs) compared with sorafenib, while lenvatinib demonstrated non-inferior OS. Following progression on sorafenib, statistically significant OS improvements over placebo were seen for cabozantinib and regorafenib in unselected patients and for ramucirumab in those with baseline α-fetoprotein$\geq$400 ng/mL. Based on improved OS and PROs, atezolizumab plus bevacizumab appears to be a preferred first-line treatment option for intermediate or advanced non-LRT eligible HCC. Phase III data informing sequencing of later lines of treatment is lacking. Therefore, sequencing principles are proposed that can be used to guide treatment selection. Conclusions: Ongoing trials will continue to inform optimal therapy. Multiple targeted therapies have improved OS in intermediate or advanced non-LRT eligible HCC, although optimal sequencing is an area of ongoing investigation.

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Liver cancer is one of the most common malignancies worldwide, with approximately 840 000 new cases and 780 000 deaths resulting from this type of cancer in 2018 (1). The majority of primary liver cancers (75%-85%) are hepatocellular carcinoma (HCC) (1,2), which is often associated with well-known risk factors such as hepatitis B/C infection, alcohol, diabetes, and other metabolic diseases (3,4). HCC is unique in that the majority of cases (70%-90%) occur within a background of chronic liver disease and cirrhosis (3), and approximately two-thirds of diagnosed HCC cases are not eligible for curative options (5). HCC represents a growing health threat with annual mortality rates increasing by approximately 2%-3% per year from 2003 to 2012 (6) and a 43% increase in the rate of death from HCC from 2000 to 2016 in the United States (7). Scoring systems have been developed to predict outcomes for HCC with some based on the Child-Pugh score (8-10), which uses the clinical parameters of encephalopathy and ascites as well as biochemical indicators (11). These can help predict potential efficacy of response based

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on hepatic reserve in addition to morphological features (12,13), both being factors for determining overall prognosis.

Treatment strategies in Western countries center around the Barcelona Clinic Liver Cancer (BCLC) staging system, which informs treatment approach based on disease burden presentation and underlying hepatic function (14). Initial curative options include transplant, resection, and/or ablation (BCLC 0 and A), with a progression to palliative locoregional therapies (LRT), with or without embolization, followed by systemic therapy in LRT-ineligible patients or those progressing on LRT (BCLC B and C) (11,14-16). Although initial LRT is considered, up to two-thirds of patients may become ineligible due to tumor burden or liver decompensation (15,17). Although conventional chemotherapy has not improved survival in this setting (18), initial (first-line systemic therapy) and subsequent lines of therapy (second- or third-line systemic therapy) using targeted agents have been evaluated.

Tyrosine kinases are key targets for HCC therapy because they catalyze transfer of the gamma phosphate group from adenosine triphosphate to target proteins that can drive tumor cell progression, proliferation, neovascularization, and metastasis while reducing apoptosis (19). A number of multi-target tyrosine kinase inhibitors (TKIs) exert antitumor activity by targeting components of the mitogen-activated protein kinase pathway (Raf/MEK/ERK) (20), which partially controls cellular processes as diverse as division, differentiation, movement, and apoptosis (21). TKIs also target factors involved in neovascularization, which otherwise stimulate tumor growth (20). The first-generation, oral, multi-TKI sorafenib was approved by the United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA) in 2007 (22) and became a convenient standard of care for the first-line systemic treatment of intermediate or advanced non-LRT-eligible HCC (16). Second- and subsequent-generation TKIs have also been investigated, including sunitinib (23), brivanib (24), linifanib (25), and lenvatinib (26) as first-line systemic therapy. Brivanib (27), regorafenib (28), tivantinib (29), and cabozantinib (30) have also been evaluated following progression on sorafenib.

In addition to TKIs, novel targeted agents have also been evaluated for advanced HCC in the last decade, including those targeting the mechanistic target of rapamycin (mTOR) (31), the immune system (32-34), and tumor vasculature (35,36), with the latter 2 most promising. Immune checkpoints modulate immune responses to reduce collateral damage to healthy tissues (37), in part through interactions between the programmed cell death protein 1 (PD-1) on activated T-cells and the programmed death ligand 1 (PD-L1) in peripheral tissues (37,38). Tumor cells also express PD-L1 to avoid immune attack (39), so recombinant monoclonal antibody (MoAb) immune checkpoint inhibitors (ICIs) that disrupt PD-1 and PD-L1 interactions have been extensively investigated as cancer therapies. The anti-PD-1 agents nivolumab and pembrolizumab and the anti-PD-L1 drug atezolizumab have been assessed either alone (33,34) or in combination with other targeted agents (32) for intermediate or advanced non-LRT-eligible HCC.

Solid tumors, through their inherent metabolism, generate a hypoxic environment that is presumed to drive the angiogenic pathway, resulting in increased tumor vascularity (40). Cooption of hepatic arterial inflow rather than sprouting is believed to be 1 possible cause of acquired sorafenib resistance, among others (41-44). Vascular endothelial growth factors (VEGFs) and their receptors (VEGFRs) are key regulators of angiogenesis, with VEGFR-2 expressed on almost all endothelial cells and VEGF-A integral to the formation and branching of new vasculature (40,45). Two MoAb inhibitors of angiogenesis (V-MoAbs), bevacizumab, which targets VEGF-A (45), and ramucirumab, which targets VEGFR-2 (20), have also been assessed in intermediate or advanced non-LRT-eligible HCC (32,35,36).

Many phase III trials in the past decade have evaluated newer targeted agents and immunotherapies alone or in combinations, although many have not been practice-changing (23-25,27,29,31,33,34,36,46,47). Positive trials were recently reported, however (26,28,30,32,35), requiring a careful review of new data and reevaluation of best treatment sequences and pathways. This review provides updated guidance on targeted therapies for intermediate or advanced non-LRT-eligible HCC based on randomized phase III data.

Methods

Targeted therapy was defined as small-molecule drugs or MoAbs that selectively target specific molecules on tumor cells or their microenvironment, thereby inhibiting tumor growth or spread. A search of published and presented literature identified phase III trials reporting efficacy outcomes on targeted therapy to treat advanced HCC patients not eligible for LRT. PubMed (all time to November 7, 2019), the proceedings from the American Society of Clinical Oncology, the European Society for Medical Oncology 2018 and 2019 annual meetings, and the European Society for Medical Oncology-Asia 2018 and 2019 Congress were searched for phase III trials assessing targeted therapy using the key search terms “hepatocellular cancer” AND “advanced” AND “targeted therapy” AND “phase III” OR respective aliases. A supplemental bibliographic search of review articles and pooled or meta-analyses was also conducted.

English language records were vetted at abstract level and confirmed at full text as needed. Excluded studies included those that were nonoriginal research; preclinical; correlative science; not specific to HCC; outside the intermediate or advanced non-LRT-eligible setting; retrospective; prospective phase I, II, IV, or undefined phase; duplicate or prior reports; studies without reported outcomes; and those that assessed combinations of targeted therapy and LRT. Categorization of studies by line of therapy was based on the number of lines of prior systemic therapy delivered in the advanced setting.

Findings

Literature Search Results

The literature search identified a total of 340 records, resulting in a total of 18 eligible phase III trials (Preferred Reporting Items for Systematic Reviews and Meta-Analyses; Figure 1) (23-36,46-49). Ten trials assessed targeted agents as first-line systemic therapy (23-26,32,34,46-49), and 8 trials evaluated these agents in patients who had progressed on sorafenib (27-31,33,35,36).

First-Line Systemic Therapy

Among studies assessing systemic first-line targeted agents, research has primarily focused on 2 major classes of drugs, TKIs and, more recently, ICIs.

Tyrosine Kinase Inhibitors

Eight phase III trials assessed TKIs as first-line systemic therapy either alone or in combination for intermediate or advanced

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Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses diagram. [a]Primary reports of eligible studies that were not identified through database search. ASCO = American Society of Clinical Oncology; ESMO = European Society for Medical Oncology; HCC = hepatocellular carcinoma; LRT = locoregional therapy.

non-LRT-eligible HCC (Table 1) (23-26,46-49). The benefits of TKIs in unresectable HCC were first confirmed in 2 pivotal phase III studies in 2008-2009, which demonstrated statistically significant improvements in overall survival (OS) for sorafenib compared with placebo (48,49). SHARP (n = 602) and Sorafenib Asia-Pacific (n = 226) showed statistically significant improvements in median OS (10.7 vs 7.9 months, hazard ratio [HR] = 0.69, 95% confidence interval [CI] = 0.55 to 0.87, $P < .001$; and 6.5 vs 4.2 months, HR = 0.68, 95% CI = 0.50 to 0.93, $P = .014$, respectively) and median time to radiologic progression (TTP, 5.5 vs 2.8 months, HR = 0.58, 95% CI = 0.45 to 0.74, $P < .001$; and 2.8 vs 1.4 months, HR = 0.57, 95% CI = 0.42 to 0.79, $P = .0005$), respectively, for sorafenib vs placebo (Table 1) (48,49). Rates of treatment discontinuation due to adverse events (AEs) were similar between treatments in SHARP and Sorafenib Asia-Pacific (38% vs 37% and 19.5% vs 13.3%, respectively), and the most common grade 3 or 4 AEs for sorafenib compared with placebo in the respective trials were hand-foot skin reactions (8% vs <1%, $P < .001$ and 10.7% vs 0), diarrhea (8% vs 2%, $P < .001$ and 6.0% vs 0), fatigue (approximately 4% vs <4%, $P = 1.0$ and 3.4% vs 1.3%), and hypertension (2% vs 1%, $P = .28$ and 2.0% vs 0). Drug-related deaths were not reported in SHARP (49) or in either arm of Sorafenib Asia-Pacific (48).

Since then, 5 phase III trials have evaluated, without success, either alternative TKIs or the addition of other agents to first-line sorafenib compared with sorafenib alone (23-25,46,47). Three trials, A6181170, BRISK-FL, and M10-963, compared sunitinib (23), brivanib (24), or linifanib (25), respectively, with sorafenib. In A6181170 (n = 1074), at a median follow-up of approximately 7.5 months, sunitinib showed no improvement in the primary endpoint of OS (HR = 1.30, $P = 1.0$) or TTP (HR = 1.13, $P = .83$) (Table 1) (23). In BRISK-FL (n = 1155) (24) and M10-963 (n = 1035) (25), neither brivanib nor linifanib statistically significantly improved the primary endpoint of OS compared with sorafenib (HR = 1.07, $P = .31$; HR = 1.05, P = not reported, respectively) (24,25), although improved TTP for linifanib was shown in M10-963 (HR = 0.76, 95% CI = 0.64 to 0.90, $P = .001$) (Table 1) (25). Two trials assessed the addition of either chemotherapy or targeted therapy to sorafenib (46,47). At a median follow-up of 36.1 months, CALGB 80802 (n = 356) showed no improvement in the primary endpoint of OS or TTP and greater toxicity with the addition of doxorubicin (47), and SEARCH (n = 720) showed a similar lack of improvement with the addition of the first-generation epidermal growth factor receptor TKI, erlotinib (Table 1) (46).

The phase III REFLECT trial compared lenvatinib with sorafenib in 954 patients. At a median follow-up of 27.7 months, lenvatinib was shown to be noninferior to sorafenib for the primary endpoint of median OS (13.6 vs 12.3 months, HR = 0.92, 95% CI = 0.79 to 1.06, upper limit of 2-sided 95% CI < 1.08) and demonstrated statistically significant improvements in TTP (8.9 vs 3.7 months, HR = 0.63, 95% CI = 0.53 to 0.73, $P < .0001$), progression-free survival (PFS = 7.4 vs 3.7 months, HR = 0.66, 95% CI = 0.57 to 0.77, $P < .0001$), and modified response evaluation criteria in solid tumors (mRECIST) overall response rate (ORR = 24.1% vs 9.2%, $P < .0001$) (Table 1) (26). AEs leading to treatment discontinuation occurred in 13.2% vs 9.1% of patients, grade 3 or greater treatment-related AEs (TRAEs) occurred in

Table 1. Efficacy outcomes of phase III trials assessing targeted therapy in intermediate and advanced non-LRT-eligible HCC

Trial name (reference)	Regimen(s)	No.	Median follow-up, mo (range)	ORR,[a] % OR (95% CI)	Median DoR, mo (95% CI) [range]	Median PFS,[a] mo HR (95% CI)	Median OS, mo HR (95% CI)
First-line therapy							
SHARP (49)	Sorafenib 400 mg BID	299	NR	2[b,c] P = .05	NR	5.5 (TTP)[b,c] HR = 0.58 (0.45 to 0.74) P < .001	10.7 HR = 0.69 (0.55 to 0.87) P < .001
	Placebo	303		1[b,c]	NR	2.8 (TTP)[b,c]	7.9
Sorafenib Asia-Pacific (48)	Sorafenib 400 mg BID	150	NR	3.3	NR	2.8 (TTP) HR = 0.57 (0.42 to 0.79) P = .0005	6.5 HR = 0.68 (0.50 to 0.93) P = .014
	Placebo	76		1.3	NR	1.4 (TTP)	4.2
A6181170 (23)	Sunitinib 37.5 mg/d	530	7.4	6.6	NR	3.6 (TTP) HR = 1.13 (0.99 to 1.30) P = .23	7.9 HR = 1.30 (1.13 to 1.50) P = .0014
	Sorafenib 400 mg BID	544	7.8	6.1	NR	3.0 (TTP)	10.2
BRISK-FL (24)	Brivanib 800 mg/d	577	NR	12.0 OR = 1.45 (0.99 to 2.13) P = .057	NR	4.2 (TTP) HR = 1.01 (0.88 to 1.16) P = .85	9.5 HR = 1.07 (0.94 to 1.23) P = .31
	Sorafenib 400 mg BID	578		8.8	NR	4.1 (TTP)	9.9
M10-963 (25)	Linifanib 17.5 mg/d	514	NR	13.0 P = .018	NR	5.4 (TTP) HR = 0.76 (0.64 to 0.90) P = .001	9.1 HR = 1.05 (0.90 to 1.22) P = NR
	Sorafenib 400 mg BID	521		6.9	NR	4.0 (TTP)	9.8
SEARCH (46)	Sorafenib 400 mg BID plus erlotinib 150 mg/d	362	NR	6.6 P = .10	NR	3.2 (TTP) HR = 1.14 (0.94 to 1.37) P = .18	9.5 HR = 0.93 (0.78 to 1.11) P = .41
	Sorafenib 400 mg BID plus placebo	358		3.9	NR	4.0 (TTP)	8.5
REFLECT (26)	Lenvatinib 12 mg or 8 mg/d[d]	478	27.7	24.1[e] OR = 3.13 (2.15 to 4.56) P < .0001	NR	7.4[e] HR = 0.66 (0.57 to 0.77) P < .0001	13.6 HR = 0.92 (0.79 to 1.06) (noninferior)
	Sorafenib 400 mg BID	476	27.2	9.2[e]	NR	3.7[e]	12.3

(continued)

Table 1. (continued)

Trial name (reference)	Regimen(s)	No.	Median follow-up, mo (range)	ORR,[a] % OR (95% CI)	Median DoR, mo (95% CI) [range]	Median PFS,[a] mo HR (95% CI)	Median OS, mo HR (95% CI)
CheckMate 459 (34)	Nivolumab 240 mg Q2W	371	22.8[f]	15[c]	23.3 [3.1-34.5+]	3.7[c]	16.4 HR = 0.85 (0.72 to 1.02) P = .075
	Sorafenib 400 mg BID	372		7[c]	23.4 [1.9+-28.7+]	3.8[c]	14.7
IMbrave150 (32,50)	Atezolizumab 1200 mg plus bevacizumab 15 mg/kg Q3W	336	8.6	33.2[c,e] P < .001	NE[c,e]	6.8[c] HR = 0.59 (0.47 to 0.76) P < .001	NE HR = 0.58 (0.42 to 0.79) P < .001
	Sorafenib 400 mg BID	165		13.3[c,e]	6.3[c,e] (4.9 to NE)	4.3[c]	13.2
CALGB 80802 (47)	Sorafenib 400 mg BID plus doxorubicin Q3W	180	36.1	10.0 P = .52	NR	4.0 HR = 0.93 (0.75 to 1.16) P = .54	9.3 HR = 1.05 (0.83 to 1.31) P = .68
	Sorafenib 400 mg BID	176		5.4	NR	3.7	9.4
Second-line therapy							
BRISK-PS (27)	Brivanib 800 mg/d plus BSC	263	NR	9.9 OR = 5.72 (1.41 to 23.25) P = .003	NR	4.2 (TTP) HR = 0.56 (0.42 to 0.76) P < .001	9.4 HR = 0.89 (0.69 to 1.15) P = .33
	Placebo plus BSC	132		1.5	NR	2.7 (TTP)	8.2
EVOLVE-1 (31)	Everolimus 7.5 mg/d plus BSC	362	24.6 (14.8-36.6)	2.2	NR	3.0 (TTP) HR = 0.93 (0.75 to 1.15) P = NR	7.6 HR = 1.05 (0.86 to 1.27) P = .68
	Placebo plus BSC	184		1.6	NR	2.6 (TTP)	7.3
REACH (36)	Ramucirumab 8 mg/kg Q2W plus BSC	283	8.3	7.1 P < .0001	NR	2.8 HR = 0.63 (0.52 to 0.75) P < .0001	9.2 HR = 0.87 (0.72 to 1.05) P = .14
	Placebo Q2W plus BSC	282	7.0	0.71	NR	2.1	7.6
RESORCE (28)	Regorafenib 160 mg/d plus BSC wk 1-3 Q4W	379	7.0	10.6[e] P = .005	3.5 (1.9 to 4.5)	3.1[e] HR = 0.46 (0.37 to 0.56) P < .0001	10.6 HR = 0.63 (0.50 to 0.79) P < .0001
	Placebo daily plus BSC wk 1-3 Q4W	194		4.1[e]	2.7 (1.9 to NE)	1.5[e]	7.8

(continued)

Table 1. (continued)

Trial name (reference)	Regimen(s)	No.	Median follow-up, mo (range)	ORR,[a] % OR (95% CI)	Median DoR, mo (95% CI) [range]	Median PFS,[a] mo HR (95% CI)	Median OS, mo HR (95% CI)
METIV-HCC (29)	Tivantinib 120 mg BID	226	18.1	0	NR	2.1 HR = 0.96 (0.75 to 1.22) P = .72	8.4 HR = 0.97 (0.75 to 1.25) P = .81
	Placebo	114		0	NR	2.0	9.1
CELESTIAL (30)	Cabozantinib 60 mg/d	470	NR	3.8 P = .009	NR	5.2 HR = 0.44 (0.36 to 0.52) P < .001	10.2 HR = 0.76 (0.63 to 0.92) P = .005
	Placebo daily	237		0.4	NR	1.9	8.0
REACH-2 (35)	Ramucirumab 8 mg/kg Q2W plus BSC	197	7.6	4.6 P = .17	NR	2.8 HR = 0.45 (0.34 to 0.60) P < .0001	8.5 HR = 0.71 (0.53 to 0.95) P = .02
	Placebo Q2W plus BSC	95		1.1	NR	1.6	7.3
KEYNOTE-240 (33)	Pembrolizumab 200 mg Q3W plus BSC	278	NR	18.3[c] P = .00007	13.8 [1.5+-23.6+]	3.0[c] HR = 0.72 (0.57 to 0.90) P < .002	13.9 HR = 0.78 (0.61 to 1.0) P = .024[g]
	Placebo Q3W plus BSC	135		4.4[c]	NYR [2.8-20.4+]	2.8[c]	10.6

[a]Based on investigator assessment by RECIST 1.1 or otherwise footnoted. BID = twice daily; BSC = best supportive care; CI = confidence interval; DoR = duration of response; HCC = hepatocellular carcinoma; HR = hazard ratio; LRT = locoregional therapy; NE = not estimable; NR = not reported; NYR = not yet reached; OR = odds ratio; ORR = overall response rate; OS = overall survival; PFS = progression free survival; QXW = every X weeks; TTP = time to progression.
[b]RECIST 2000.
[c]Independent review.
[d]12 mg/d for bodyweight 60 kg and over, and 8 mg/d for bodyweight less than 60 kg.
[e]mRECIST.
[f]Minimum follow-up.
[g]Did not reach statistical significance according to prespecified criteria.

Table 2. Safety outcomes of select phase III trials assessing targeted therapy in intermediate and advanced non-LRT-eligible HCC

Trial name (reference)	Treatment	Safety population	Treatment discontinuation due to TRAEs, %	Overall TRAEs, %		Deaths due to TRAEs, %
				Any grade	Grade 3 or 4	
First-line therapy						
REFLECT (26)	Lenvatinib	476	13.2 (Any AE)	93.9	56.7	2.3
	Sorafenib	475	9.1 (Any AE)	95.2	48.6	0.8
CheckMate 459 (34)	Nivolumab	367	4.4	NR	22.1	0.3
	Sorafenib	363	8.0	NR	49.3	0.3
IMbrave150 (32,50)	Atezolizumab plus bevacizumab	329	15.5 (Any AE)	83.9	35.6	1.8
	Sorafenib	156	10.3 (Any AE)	94.2	45.5	0.6
Second-line therapy						
REACH (36)	Ramucirumab plus BSC	277	10.1	97.4[a]	62.3[a]	2.5
	Placebo plus BSC	276	2.9	94.2[a]	48.0[a]	1.4
RESORCE (28)	Regorafenib	374	10.4	92.5	50.0	1.9
	Placebo plus BSC	193	3.6	51.8	16.6	1.0
CELESTIAL (30)	Cabozantinib	467	16.3	98.5 (Any AE)	67.7 (Any AE)	1.3
	Placebo	237	3.0	92.4 (Any AE)	36.3 (Any AE)	0.4
REACH-2 (35)	Ramucirumab	197	10.7	10.7	NR	3.0 (Any AE)
	Placebo plus BSC	95	3.2	5.3	NR	3.2 (Any AE)
KEYNOTE-240 (33,51)	Pembrolizumab plus BSC	279	6.5	60.9	18.3	0.4
	Placebo plus BSC	134	0.7	48.5	7.5	0

[a]Treatment-emergent AEs. AE = adverse event; BSC = best supportive care; HCC = hepatocellular carcinoma; LRT = locoregional therapy; NR = not reported; TRAE = treatment-related adverse event.

56.7% vs 48.6% of patients (Table 2), and grade 3 or 4 treatment-emergent AEs that occurred in more than 15% of patients for lenvatinib vs sorafenib included hypertension (23.3% vs 14.3%), decreased weight (7.6% vs 2.9%), decreased appetite (4.6% vs 1.3%), diarrhea (4.2% vs 4.2%), and fatigue (3.8% vs 3.6%). Deaths attributed to AEs occurred in 2.3% vs 0.8% of patients in the lenvatinib vs sorafenib arms, respectively.

Immune Checkpoint Inhibitors

Two phase III trials evaluated ICIs used either alone or with targeted therapy compared with sorafenib as first-line therapy for intermediate or advanced non-LRT-eligible HCC (32,34). At median follow-ups of 15.2 and 13.4 months for nivolumab and sorafenib, respectively, CheckMate 459 showed no statistically significant improvement in the primary endpoint of median OS (16.4 vs 14.7 months, HR = 0.85, 95% CI = 0.72 to 1.02, $P = .075$), PFS (3.7 vs 3.8 months, HR = 0.93, 95% CI = 0.79 to 1.10, P = not reported), or duration of response (23.3 vs 23.4 months) for nivolumab vs sorafenib (Table 1) (34). Nivolumab showed improvements over sorafenib in overall health-related quality-of-life (HRQoL) with fewer TRAEs leading to discontinuation (4.4% vs 7.9%) and grade 3 or 4 TRAEs overall (22.1% vs 49.3%) (Table 2). Approximate rates of the most common grade 3 or 4 TRAEs reported in the nivolumab and sorafenib arms, respectively, were aspartate aminotransferase (AST) increase (7% vs 4%), diarrhea (1% vs 5%), fatigue (1% vs 2%), pruritis (1% vs <1%), and HFSR (<1% vs 15%). Treatment-related deaths were reported in 0.3% of patients in each arm.

IMbrave150 randomly assigned 501 patients 2:1 to receive atezolizumab plus bevacizumab or sorafenib. At a median follow-up of 8.6 months, the coprimary endpoints of median OS (not estimable vs 13.2 months, HR = 0.58, 95% CI = 0.42 to 0.79, $P < .001$) and median PFS (6.8 vs 4.3 months, HR = 0.59, 95% CI = 0.47 to 0.76, $P < .001$) were statistically significantly improved for atezolizumab plus bevacizumab vs sorafenib, as was mRECIST ORR (33.2% vs 13.3%, $P < .001$) (Table 1) (32). The median time to deterioration in HRQoL also favored the atezolizumab plus bevacizumab arm (11.2 vs 3.6 months, HR = 0.63, 95% CI = 0.46 to 0.85). AEs leading to treatment discontinuation occurred in 15.5% vs 10.3% and grade 3 or 4 TRAEs occurred in 35.6% vs 45.5% of patients (Table 2) (50). Approximate rates of the most common grade 3 or 4 TRAEs reported for atezolizumab plus bevacizumab vs sorafenib were hypertension (10.3% vs 9.0%), AST increase (4.3% vs 2.6%), proteinuria (2.7% vs 0.6%), platelet count decrease (2.4% vs 0.6%), and infusion-related reactions or alanine aminotransferase increase (2.1% vs 0 for each) (32). Deaths due to TRAEs occurred in 1.8% vs 0.6% of patients who received atezolizumab plus bevacizumab and sorafenib, respectively (50).

Second-Line Systemic Therapy

Studies assessing targeted agents as second-line systemic therapy for intermediate or advanced non-LRT-eligible HCC have evaluated mTOR and VEGF-2 inhibitors (31,35,36) in addition to TKIs and ICIs (27-30,33).

VEGF-2 and mTOR and Inhibitors. Two phase III studies assessed the VEGF-2 inhibitor ramucirumab (35,36), with both agents compared with placebo for the second-line treatment of intermediate or advanced non-LRT-eligible HCC, and 1 phase III trial evaluated the mTOR inhibitor everolimus (31). REACH evaluated ramucirumab vs placebo in 565 patients and after a median follow-up of 8.3 and 7.0 months for ramucirumab and placebo, respectively, showed no statistically significant improvements in the primary endpoint of median OS (9.2 vs 7.6 months, HR = 0.87, 95% CI = 0.72 to 1.05, $P = .14$) (Table 1), although statistically significant OS improvements were seen in a prespecified analysis of 250 patients with baseline α-fetoprotein levels of at least 400 ng/mL (7.8 vs 4.2 months, HR = 0.67, 95% CI = 0.51 to 0.90, $P = .006$) (36). Based on these findings, REACH-2 randomly assigned 292 patients with baseline α-fetoprotein of at least 400 ng/mL 2:1 to receive ramucirumab or placebo. At a median follow-up of 7.6 months, statistically significant improvements were seen for ramucirumab vs placebo in the primary endpoint of median OS (8.5 vs 7.3 months, HR = 0.71, 95% CI = 0.53 to 0.95, $P = .02$) and median PFS (2.8 vs 1.6 months, HR = 0.45, 95% CI = 0.34 to 0.60, $P < .0001$) (Table 1) (35). TRAEs leading to discontinuation occurred in 10.7% vs 3.2% of patients receiving ramucirumab vs placebo, respectively, and overall rates of grade 3 or 4 TRAEs were not reported (Table 2). The most common TRAEs in the ramucirumab and placebo arms, respectively, were hypertension (7.6% vs 2.1%), proteinuria (2.0% vs 0), liver injury or failure (1.5% vs 0), peripheral edema (1.0% vs 0), and fatigue (1.0% vs 0). Deaths due to TRAEs occurred in 1.5% of patients receiving ramucirumab and in no patients receiving placebo. EVOLVE-1 randomly assigned 546 patients 2:1 to receive everolimus or placebo and at a median follow-up of 24.6 months showed no statistically significant differences between arms for OS (HR = 1.05, $P = .68$) or TTP (HR = 0.93, P = not tested; Table 1) (31).

Tyrosine Kinase Inhibitors

TKIs were also assessed for second-line intermediate or advanced non-LRT-eligible HCC in 4 phase III trials (27-30). In BRISK-PS (n = 395) (27) and METIV-HCC (n = 340) (29), brivanib and tivantinib, respectively, were compared with placebo either with (BRISK-PS) or without (METIV-HCC) best supportive care (BSC). With median follow-ups not reported for BRISK-PS and 18.1 months for METIV-HCC, neither trial showed statistically significant improvements in their primary end-points of OS (HR = 0.89, $P = .33$ and HR = 0.97, $P = .81$, respectively) (27,29), although brivanib showed statistically significantly improved TTP compared with placebo (HR = 0.56, 95% CI = 0.42 to 0.76, $P < .001$) (Table 1) (27).

RESORCE randomly assigned 573 patients 2:1 to regorafenib or placebo plus BSC. At a median follow-up of 7.0 months, regorafenib demonstrated statistically significant improvements in the primary endpoint of median OS (10.6 vs 7.8 months, HR = 0.63, 95% CI = 0.50 to 0.79, $P < .0001$), median PFS (3.1 vs 1.5 months, HR = 0.46, 95% CI = 0.37 to 0.56, $P < .0001$) (Table 1), and median TTP (3.2 vs 1.5 months, HR = 0.44, 95% CI = 0.36 to 0.55, $P < .0001$) compared with placebo (Table 1) (28). TRAEs leading to treatment discontinuation occurred in 10.4% vs 3.6% of patients, grade 3 or 4 TRAEs occurred in 50.0% vs 16.6% of patients (Table 2), and grade 3 or 4 TRAEs included hypertension (13.1% vs 3.1%), HFSR (12.6% vs 0.5%), increased blood bilirubin (6.7% vs 2.1%), fatigue (6.4% vs 1.6%), and increased AST (5.1% vs 5.2%). Deaths attributed to AEs occurred in 1.9% vs 1.0% of patients in the regorafenib vs placebo arms. CELESTIAL randomly assigned 707 patients 2:1 to receive cabozantinib or placebo. At the second interim analysis, cabozantinib also demonstrated statistically significant improvements over placebo in the primary endpoint of median OS (10.2 vs 8.0 months, HR = 0.76, 95% CI = 0.63 to 0.92, $P = .005$) and median PFS (5.2 vs 1.9 months, HR = 0.44, 95% CI = 0.36 to 0.52, $P < .001$) (Table 1) (30). TRAEs leading to discontinuation occurred in 16.3% vs 3.0% of patients, and any grade 3 or 4 AEs occurred in 67.7% vs 36.3% of patients in the cabozantinib vs placebo arms, respectively (Table 2). The most common grade 3 or 4 AEs included HFSR (16.9% vs 0), hypertension (15.8% vs 1.7%), increased AST (11.8% vs 6.8%), fatigue (10.5% vs 4.2%), and diarrhea (9.9% vs 1.7%). Treatment-related deaths occurred in 1.3% and 0.4% of patients in the cabozantinib and placebo arms, respectively.

An ICI has also been evaluated for second-line HCC following sorafenib in 1 phase III trial. KEYNOTE-240 randomly assigned 413 patients 2:1 to receive pembrolizumab or placebo plus BSC. At a median follow-up of 13.8 months for pembrolizumab and 10.6 months for placebo, numerical improvements were seen in the coprimary endpoints of median OS (13.9 vs 10.6 months, HR = 0.78, 95% CI = 0.61 to 1.0, $P = .024$) and PFS (3.0 vs 2.8 months, HR = 0.72, 95% CI = 0.57 to 0.90, $P = .002$; Table 1), which did not achieve statistical significance according to prespecified boundaries (OS, $P = .017$ at the final analysis and PFS, $P = .002$ at the first interim analysis) (33). TRAEs leading to discontinuation occurred in 6.5% vs 0.7% of patients (51) and grade 3 or 4 TRAEs occurred in 18.3% vs 7.5% of patients receiving pembrolizumab and placebo, respectively (Table 2) (33). Grade 3 or 4 TRAEs in the pembrolizumab vs placebo arms included increased AST (5.4% vs 1.5%), increased alanine aminotransferase (3.6% vs 1.5%), fatigue (1.1% vs 0.7%), and increased blood bilirubin and decreased appetite (1.1% vs 0 for each). Treatment-related deaths occurred in 0.4% of patients receiving pembrolizumab, with none reported in the placebo arm.

Discussion

With respect to the clinical benefit of first-line systemic therapy, statistically significant improvements in OS and/or HRQoL must be shown over standard of care in a phase III trial to warrant a change in clinical practice. During the last decade, multiple phase III trials have sought to improve OS and HRQoL using alternative strategies in this setting without success, including sunitinib, brivanib, and linifanib (23-25); the addition of erlotinib or chemotherapy to sorafenib (46,47); and the ICI nivolumab (34). Recently, however, 2 phase III trials have shown promise; 1 assessed lenvatinib (26) and the other the ICI atezolizumab plus the VEGF-A inhibitor bevacizumab (32). REFLECT demonstrated a statistically significant 34% reduced risk of progression for lenvatinib vs sorafenib (net 3.7 months, $P < .0001$) and over a 2.5-fold improvement in mRECIST ORR (24.1% vs 9.2%, $P < .0001$), although with only a noninferior median OS (HR = 0.92) (26). However, despite slightly higher rates of grade 3 or 4 TRAEs for lenvatinib compared with sorafenib (56.7% vs 48.6%), higher rates of overall AEs were mainly related to hypertension (any grade, 42.2% vs 30.3%; grade 3 or 4, 23.3% vs 14.3%), which is generally manageable, with decreased rates of HSFR (any grade, 26.9% vs 52.4%; grade 3 or 4, 2.9% vs 11.4%) suggesting a more favorable toxicity profile. IMbrave150 showed a statistically significant 42% reduction in the risk of death (HR = 0.58, $P < .001$), a 41% reduction in the risk of progression (HR = 0.59, $P < .001$), a 2.5-fold improved mRECIST ORR (33.2% vs 13.3%, $P < .001$), clear HRQoL benefits (HR = 0.63), and lower rates of grade 3 or 4

Table 3. OS outcomes for select subgroups for positive phase III trials assessing targeted therapy in intermediate and advanced non-LRT-eligible HCC[a]

Trial	Patient exclusions	BCLC Stage B % of patients HR (95% CI)	No MVI/EHS or both % of patients HR (95% CI)	Nonviral etiology % of patients HR (95% CI)	ECOG PS 0 % of patients HR (95% CI)	AFP at baseline <400 μg/L % of patients HR (95% CI)
First-line						
REFLECT (26)	Resectable Child-Pugh B,C ECOG PS 2-5	20.5% 0.91 (0.65 to 1.28)	30.3% 1.05 (0.79 to 1.40)	Alcohol, other, unknown: 5.9% 1.03 (0.47 to 2.28)	63.4% 0.88 (0.73 to 1.06)	<200 μg/L 56.7% 0.91 (0.74 to 1.12)
IMbrave150 (32)	Resectable Child-Pugh B,C ECOG PS 2-5	15.6% 1.09 (0.33 to 3.53)	24.6% 0.69 (0.29 to 1.65)	30.5% 0.91 (0.52 to 1.60)	62.3% 0.67 (0.43 to 1.06)	62.7% 0.52 (0.34 to 0.81)
Second-line						
RESORCE (28)	Resectable Child-Pugh B,C ECOG PS 2-5	12.7% NR	18.1% 0.98 (0.58 to 1.66)	No hepatitis B: 60.4% 0.73 (0.56 to 0.95) No hepatitis C: 76.8% 0.65 (0.51 to 0.82)	63.8% 0.61 (0.47 to 0.80)	54.8% 0.67 (0.50 to 0.90)
CELESTIAL (30)	Resectable Child-Pugh B,C ECOG PS 2-5	NR	15.4% 0.99 (0.59 to 1.65)	40.2% 0.72 (0.54 to 0.96)	53.2% 0.69 (0.53 to 0.89)	58.6% 0.81 (0.62 to 1.04)
REACH-2 (35)	Resectable Child-Pugh B,C ECOG PS 2-5	18.5% 0.69 (0.35 to 1.35)	No MVI: 64.7% 0.60 (0.42 to 0.87) No EHS: 27.7% 0.84 (0.48 to 1.48)	33.6% 0.63 (0.38 to 1.06)	57.5% 0.71 (0.49 to 1.04)	n/a

[a]AFP = α-fetoprotein; BCLC = Barcelona Clinic Liver Cancer; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; EHS = extrahepatic spread; HCC = hepatocellular carcinoma; HR = hazard ratio; LRT = locoregional therapy; MVI = macroscopic portal vein invasion; n/a = not applicable; NR = not reported; OS = overall survival; PS = performance status.

TRAEs (35.6% vs 45.5%) for the combination of atezolizumab plus bevacizumab compared with sorafenib (32). Approximate rates of treatment-related hypertension were similar (any grade, 30% vs 24%; grade 3 or 4, 15% vs 12%), and HSFR rates were substantially lower (any grade, 1% vs 48%; grade 3 or 4, 0 vs 9%) for atezolizumab plus bevacizumab vs sorafenib, respectively. Given the statistically significant improvements in OS, PFS, and ORR in addition to the favorable safety profile of atezolizumab plus bevacizumab, this regimen represents a new systemic first-line standard for intermediate or advanced non-LRT-eligible HCC and was approved by the FDA in this setting in 2020 (52). Lenvatinib received FDA approval in 2018 for first-line use (53), and lenvatinib or sorafenib could be considered in patients after liver transplant or in those who are ineligible for atezolizumab plus bevacizumab or infusion therapy. The benefits of LRT in patients with a morphologic response from systemic therapy are currently unknown.

Second-line systemic therapy for intermediate or advanced non-LRT-eligible HCC has historically been BSC following progression on sorafenib, and statistically significant OS and/or HRQoL improvements in a phase III trial would be needed to establish a new standard of care. Over the last decade, several phase III studies attempted to improve OS in this setting without success, including those assessing brivanib (27), tivantinib (29), everolimus (31), ramucirumab (36), and pembrolizumab (33). More promising results have been reported for ramucirumab in select patients (35), in addition to regorafenib and cabozantinib (28,30). Despite the lack of demonstrated OS benefit for ramucirumab compared with placebo among unselected patients in REACH (36), a follow-up trial in poor prognosis patients with α-fetoprotein concentrations of 400 ng/mL or greater (REACH-2) showed a statistically significant 29% reduction in the risk of death (net 1.2 months, $P = .02$), providing a safe alternative to TKIs for select patients in this setting (discontinuation due to TRAEs, 10.7% vs 10.4%-16.3%) (35). RESORCE and CELESTIAL also demonstrated clinically meaningful OS gains for both regorafenib and cabozantinib compared with placebo, respectively (28,30). Regorafenib was associated with a statistically significant 37% reduction in risk of death (net 2.8 months, $P < .0001$) in patients with demonstrated tolerance to sorafenib (28), and cabozantinib showed a statistically significant 24% reduced risk of death (net 2.2 months, $P = .005$) in both sorafenib tolerant and intolerant patients (30). Patterns of toxicity were comparable for both TKIs (28,30). Although regorafenib showed a fourfold increase (50.0% vs 16.6%) (28) and cabozantinib a twofold increase (67.7% vs 36.3%) (30) in overall grade 3 or 4 TRAEs, rates of grade 3 or 4 HSFR were low for both agents (regorafenib vs placebo, treatment-related, 12.6% vs 0.5% and cabozantinib vs placebo, any cause, 16.9% vs 0%) (28,30). Given the clinically meaningful OS gains for regorafenib and cabozantinib in unselected patients plus their comparable toxicity profiles and oral delivery, either agent is recommended in patients who have progressed on sorafenib. Regorafenib received FDA (54) and EMA (55) approval in 2017 and cabozantinib received EMA approval in 2018 (56) and FDA approval in 2019 (57) for patients with HCC previously treated with sorafenib. Ramucirumab received FDA and EMA approvals in 2019 (58,59) and may be a tolerable intravenous option for patients with

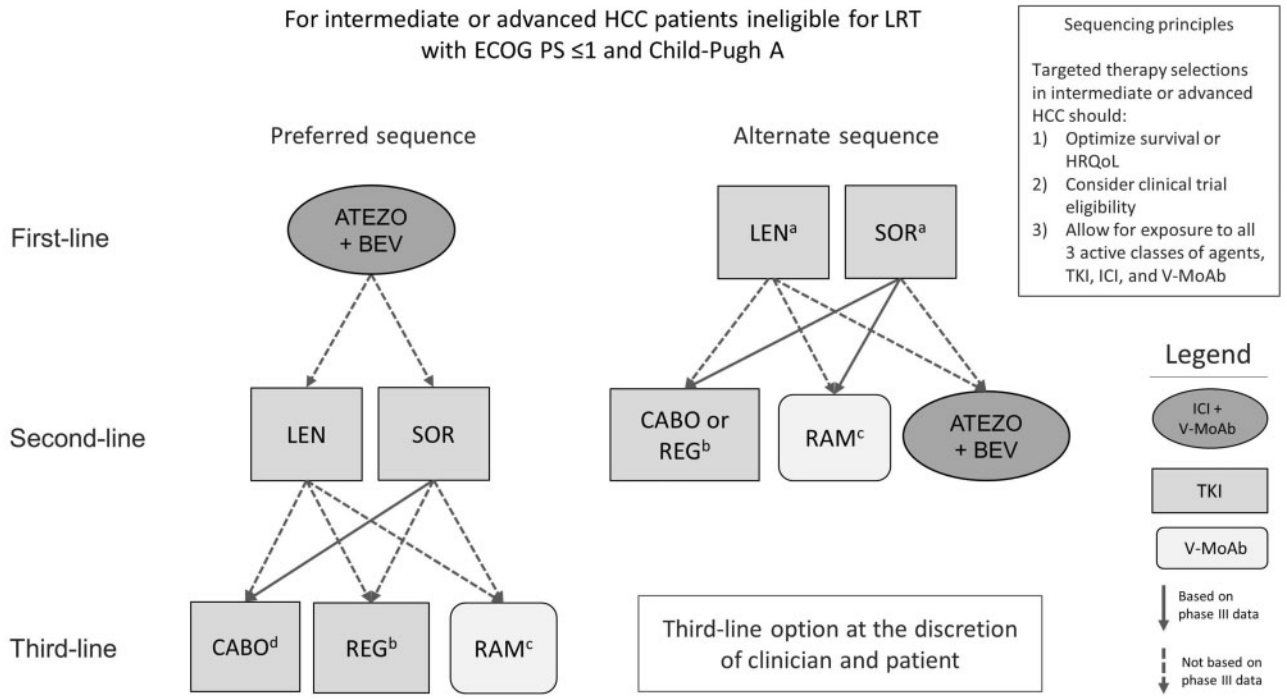

Figure 2. Potential systemic therapy treatment sequencing for advanced HCC. [a]Patients who are unsuitable for first-line ATEZO+BEV or those who started a TKI before ATEZO+BEV availability. [b]Patients with demonstrated ability to tolerate sorafenib. [c]Patients with baseline α-fetoprotein ≥400 ng/mL only. ATEZO = atezolizumab; BEV = bevacizumab; CABO = cabozantinib; ECOG = Eastern Cooperative Oncology Group; HCC = hepatocellular carcinoma; HRQoL = health-related quality of life. [d]Phase III subgroup data exists for this third-line option post-sorafenib, although not following the ICI combination; ICI = immune checkpoint inhibitor; LEN = lenvatinib; LRT = locoregional therapy; PS = performance status; RAM = ramucirumab; REG = regorafenib; SOR = sorafenib; TKI = tyrosine kinase inhibitor; V-MoAb = anti-VEGF(R) monoclonal antibody.

α-fetoprotein concentrations of at least 400 ng/mL. Nivolumab (2017) (60) and pembrolizumab (2018) (61) also received accelerated FDA approval for HCC following treatment with sorafenib, although neither agent has demonstrated statistically significantly improved survival compared with controls in a phase III trial (62,63).

Patient or disease characteristics and biomarkers would be helpful for selecting patients with intermediate or advanced non-LRT-eligible HCC who would benefit from a given therapy because multiple treatment options exist. Exploratory analyses of OS outcomes for subpopulations of interest from positive trials are summarized in Table 3. Predictive factors were not evident, although this may be due to the variability in patient populations and the reduced power of subgroup analyses to detect differences. Further research is needed to identify predictive factors that will help guide therapy selection for intermediate or advanced non-LRT-eligible HCC.

Treatment of advanced HCC involves care from a multidisciplinary team of specialists. Systemic therapy is indicated for patients with intermediate disease (BCLC B) who are ineligible for or have progressed on LRT, as well as for those with advanced disease (BCLC C) (16). Sorafenib has been the preferred systemic therapy for patients with Child-Pugh A disease and an Eastern Cooperative Oncology Group performance status of 2 or less for over a decade (64). Two additional classes of agents, ICIs and V-MoAbs, as well as next-generation TKIs have now demonstrated OS benefits in phase III trials compared with controls (28,30,32,35). These new treatments should not be given to patients with Child-Pugh B or Eastern Cooperative Oncology Group performance status 2 scores, although they can be administered to patients with active hepatitis B infection with the administration of antiviral therapy. Although the number of options is encouraging when systemic therapy is indicated, treatment selection can be challenging due to the lack of randomized data informing sequencing decisions. However, some insight might be gained by applying a few key sequencing principles for the selection of systemic therapy. Whenever possible, it is important to select therapies: 1) in a manner that optimizes survival or quality of life, 2) with consideration of clinical trial eligibility, and 3) to allow for exposure to all 3 active classes of agents: TKIs, an ICI, and a V-MoAb. Application of these principles could result in any number of sequences, preferably beginning with atezolizumab plus bevacizumab in suitable patients followed by a TKI (ICI + V-MoAb → TKI → Figure 2). The exact sequencing of subsequent therapies is unclear, and selection should be informed by demonstrated survival benefit following progression on sorafenib, TRAE risk, prior sorafenib tolerance [regorafenib was only assessed in sorafenib tolerant patients (28)], and α-fetoprotein levels [demonstrated OS benefit for ramucirumab in patients with baseline α-fetoprotein ≥400 ng/mL (35)]. A reasonable sequence in unselected patients following atezolizumab plus bevacizumab could consist of lenvatinib or sorafenib followed by cabozantinib or regorafenib (TKI → TKI). In some instances, the use of atezolizumab plus bevacizumab as first-line therapy may not be suitable, such as in patients with autoimmune disease or those who received a first-line TKI before atezolizumab plus bevacizumab availability. An alternate sequence to consider in these instances would be a first-line TKI (lenvatinib or sorafenib) followed by subsequent TKIs such as cabozantinib or regorafenib, ramucirumab

Table 4. Ongoing phase III clinical trials of combination targeted therapy in unresectable HCC[a]

Experimental agent(s) or approach	Trial ID (NCT No.) (reference)	Experimental regimen	Comparator	Primary endpoint(s)	Estimated PCD
Dual targeted therapy combinations					
Dual ICI combinations					
Durvalumab (PD-L1), tremelimumab (CTLA-4)	HIMALAYA (NCT03298451) (67)	Durvalumab with or without tremelimumab	Sorafenib	OS	Mar 2020
Nivolumab (PD-1), ipilimumab (CTLA-4)	CheckMate 9DW (NCT04039607) (68)	Nivolumab plus ipilimumab	Sorafenib or Lenvatinib	OS	Sep 2023
Checkpoint inhibitor plus TKI or V-MoAb combinations					
Cabozantinib (c-MET/VEGFR-2), atezolizumab (PD-L1)	COSMIC-312 (NCT03755791) (69)	Atezolizumab with or without cabozantinib	Sorafenib	PFS/OS	Aug 2020
SHR-1210 (PD-1), apatinib (VEGFR-2)	SHR-1210-III-310 (NCT03764293) (70)	SHR-1210 plus apatinib	Sorafenib	PFS/OS	Dec 2021
Pembrolizumab (PD-1)	LEAP-002 (NCT03713593) (71)	Pembrolizumab plus lenvatinib	Placebo plus Lenvatinib	PFS/OS	May 2022
Sintilimab (PD-1), IBI305 (VEGF-A)	ORIENT-32 (NCT03794440) (72)	Sintilimab plus IBI305	Sorafenib	ORR/OS	Dec 2022
CS1003 (PD-1), lenvatinib (VEGFR1-3)	CS1003-305 (NCT04194775) (73)	CS1003 plus lenvatinib	Placebo plus Lenvatinib	PFS/OS	Jun 2023
AK105 (PD-1), anlotinib (VEGFR/FGFR/PDGFR/c-kit)	ALTN-AK105-III-02 (NCT04344158) (74)	AK105 plus anlotinib	Sorafenib	OS	Jun 2024
LRT (or TACE or SBRT) in combination with TT					
SBRT	RTOG-1112 (NCT01730937) (75)	SBRT plus sorafenib	Sorafenib	OS	Jun 2020
TACE	SELECT (NCT01906216) (76)	TACE plus sorafenib	Sorafenib	OS	Sep 2020
TACE, SBRT	HEPIC2001 (NCT04387695) (77)	SBRT plus TACE plus sorafenib	Sorafenib	PFS	Jun 2021
TAI	B2019-076-01 (NCT04053985) (78)	TAI plus lenvatinib	Lenvatinib	PFS/OS	Dec 2022
TACE	TACE (NCT03905967) (79)	TACE plus lenvatinib	Lenvatinib	OS	Apr 2023
TKI (TKI, ICI, V-MoAb) in combination with LRT					
HAIC	HCC-S022 (NCT02856126) (80)	Sorafenib plus HAIC	Sorafenib plus TACE	OS	Feb 2020
Sorafenib (VEGFR)	E1208 (NCT01004978) (81)	Sorafenib plus TACE	Placebo plus TACE	PFS	Sep 2020
Durvalumab (PD-L1), bevacizumab (VEGF-A)	EMERALD-1 (NCT03778957) (82)	Durvalumab with or without bevacizumab plus TACE	Placebos plus TACE	PFS	Aug 2021
Sorafenib (VEGFR)	TREAT (NCT04103398) (83)	Sorafenib plus TACE	TACE	OS	Oct 2021
Sintilimab (PD-1)	ISBRT01 (NCT04167293) (84)	Sintilimab plus SBRT	SBRT	PFS	Nov 2021
Lenvatinib (VEGFR1-3)	HCC-S055 (NCT03775395) (85)	Lenvatinib plus HAIC	Sorafenib plus HAIC	OS	Dec 2021
PD-1 Inhibitor (PD-1), lenvatinib (VEGFR1-3)	DEEP (NCT04229355) (86)	PD-1 inhibitor or lenvatinib plus DEB-TACE	Sorafenib plus DEB-TACE	PFS	Dec 2022
Pembrolizumab (PD-1), lenvatinib (VEGFR1-3)	LEAP-012 (NCT04246177) (87)	Pembrolizumab plus lenvatinib plus TACE	Placebo plus TACE	PFS/OS	Apr 2025
Nivolumab (PD-1), ipilimumab (CTLA-4)	CheckMate 74W (NCT04340193) (88)	Nivolumab with or without ipilimumab plus TACE	Placebo plus TACE	TTTP/OS	Jun 2025
Nivolumab (PD-1)	TACE-3 (NCT04268888) (89)	Nivolumab plus DEB-TACE	DEB-TACE	OS[a]	Jun 2025

[a]TTTP was the primary endpoint of phase II stage of the trial. BSC = best supportive care; c-MET = tyrosine-protein kinase Met; CTLA-4 = cytotoxic T-lymphocyte-associated protein 4; DEB-TACE = drug-eluting beads transarterial chemoembolization; FGFR - human fibroblast growth factor receptor; FOLFOX = oxaliplatin = fluorouracil = and leucovorin; HAIC = hepatic artery infusion chemotherapy; HCC = hepatocellular carcinoma; ICI = immune checkpoint inhibitor; LRT = locoregional therapy; ORR = overall response rate; OS = overall survival; PCD = primary completion date; PD-1 = programmed cell death protein 1; PDGFR - platelet-derived growth factor receptor; PD-L1 = programmed death ligand 1; PFS = progression-free survival; SBRT = stereotactic body radiation therapy; TACE = transarterial chemoembolization; TAI = transarterial chemoinfusion; TKI = tyrosine kinase inhibitor; TTTP = time to TACE progression; VEGF = vascular endothelial growth factor; VEGFR = vascular endothelial growth factor receptor; V-MoAb = anti-VEGF(R) monoclonal antibody.

in patients with baseline α-fetoprotein 400 ng/mL or greater, or atezolizumab plus bevacizumab in appropriate patients.

First-line systemic treatment for intermediate or advanced non-LRT-eligible HCC is rapidly evolving. Moreover, phase III trials in patients who are LRT ineligible or have failed LRT continue to assess the merits of targeted therapies either alone (65,66), such as BGB-A317 (primary completion date [PCD], June 2021) (66), or as dual targeted therapy combinations (67-74). Results of multiple trials assessing the role of adding ICIs to a TKI are expected within the year, including COSMIC-312 (PCD, August 2020) (69), SHR-1210-III-310 (PCD, December 2021) (70), and LEAP-002 (PCD, May 2022) (Table 4) (71). Combinations of PD-1 inhibitors plus cytotoxic T-lymphocyte-associated protein 4 inhibitors are also an area of ongoing investigation. Nivolumab plus ipilimumab received accelerated FDA approval in patients who progressed on sorafenib in 2020 based on results from the phase I/II CheckMate 040 study (90,91), and phase III trials assessing dual ICIs such as HIMALAYA (PCD, March 2020) (67) and Checkmate 9DW (PCD, September 2023) (68) are ongoing. Combinations of PD-1 inhibitor plus a V-MoAb are also being assessed in ORIENT-32 (PCD, December 2022) (72).

There is an increasing recognition of the benefits of using targeted therapy in earlier stage disease as reflected by the Asian Pacific Consensus, which recommends use of targeted therapy before transarterial chemoembolization as a means of downstaging or achieving best overall response in high-burden intermediate HCC (92-95). There is also ongoing research into the benefits of combining targeted therapy with LRT in eligible patients either through adding LRT to first-line TKIs such as sorafenib or lenvatinib (Table 4) (75-79) or adding targeted therapy to LRT such as transarterial chemoembolization, hepatic artery infusion chemotherapy, or stereotactic body radiation (81-84,87-89).

Atezolizumab in combination with bevacizumab statistically significantly improved OS with clinically meaningful improvements in patient-reported outcomes compared with sorafenib as systemic first-line therapy in intermediate or advanced non-LRT-eligible HCC, and cabozantinib and regorafenib statistically significantly improved OS compared with BSC in unselected patients progressing on sorafenib. Atezolizumab plus bevacizumab appears to represent a new, preferred, first-line treatment in this setting, and there is a paucity of phase III data informing the sequencing of later lines of systemic therapy. The use of sequencing principles that optimize survival benefit and allow for exposure to all 3 active classes of agents, TKIs, ICIs, and V-MoAbs, is recommended. Research into additional first-line targeted therapy combinations and targeted therapy combined with LRT in earlier settings is ongoing.

REVIEW

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Data Availability

No new data were generated or analyzed in support of this research.

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