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Review

Clinical Trials in Hepatocellular Carcinoma: An Update

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Key Words
Clinical trial · Hepatocellular carcinoma · Molecular targeted therapy

Abstract
The success of sorafenib has spurred an explosive increase of clinical trials testing novel molecular targets and other agents in the treatment of hepatocellular carcinoma (HCC). The paradigm of the studies has been characterized by three noticeable changes. First, the molecular targets of interest have expanded from angiogenesis to cancer cell-directed oncogenic signaling pathways for advanced HCC treatment. Agents targeting EGFR, FGFR, PI3K/Akt/mTOR, TGF-β, c-Met, MEK, IGF signaling, and histone deacetylase have been actively explored. Second, the target indication has shifted from advanced stage to early or intermediate stages of disease. The feasibility of combining locoregional therapies and targeted agents, and the use of novel agents after curative treatments are currently under active investigation. Finally, the therapeutic strategy has shifted from monotherapy to combination targeted therapy. We aim to provide a comprehensive overview of newly disclosed and ongoing clinical trials for the treatment of HCC.

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Sorafenib, a multi-target anti-angiogenic agent, was the first systemic therapy approved for the treatment of advanced hepatocellular carcinoma (HCC) [1, 2]. The success of sorafenib has spurred an explosive increase of clinical trials testing many novel molecular targeted agents in HCC. In recent years, the paradigm of the studies has been characterized by some noticeable changes. First, the molecular targets of interest have expanded from angiogenesis to cancer cell-directed oncogenic signaling pathways. Second, the target indication has shifted from advanced HCC toward early or intermediate HCC. Third, the therapeutic strategy has moved from monotherapy to combination therapy. In this article, we will provide a comprehensive, up-to-date review of clinical trials in HCC.

We searched for all interventional studies in HCC in ClinicalTrials.gov. Studies that met the following criteria were selected: (1) molecular targeted therapy as palliative treatment for advanced or intermediate HCC (in combination with locoregional therapies) or adjuvant treatment for early HCC following curative treatment; (2) studies which were open for recruitment (recruiting or not yet recruiting) as of February 2013 or studies which were closed (active but not recruiting, completed, suspended or terminated) after 2011. We also searched PubMed and meeting abstracts of the American Society of Clinical Oncology (ASCO), the American Association for the Study of Liver Diseases (AASLD), the International Liver Congress, the International Liver Cancer Association (ILCA), and the Asian Pacific Association for the Study of Liver (APASL) from January 2011 to February 2013 for full or interim reports of those included trials. The following data from published studies are shown in the tables: number of evaluable patients, objective response rate (ORR), disease control rate (DCR), time-to-progression (TTP), progression-free survival (PFS) and overall survival (OS).

Clinical Trials of Molecular Targeted Therapy for Advanced HCC

Data from clinical trials on a variety of molecular targeted therapies for advanced HCC are shown in table 1 [3–56].

Anti-angiogenic Agents

Angiogenesis is so far the most extensively studied therapeutic target of HCC. The efficacy of novel anti-angiogenic tyrosine kinase inhibitors (TKI) for sorafenib-naive advanced HCC has been investigated in several phase III, randomized, controlled trials. However, to date, none of these novel anti-angiogenic TKIs has exhibited superior efficacy to sorafenib. Sunitinib [3] and linifanib (ABT-869) [9], both primarily targeting vascular endothelial growth factor receptor (VEGFR) and platelet-derived growth factor receptor (PDGFR), failed to prolong OS compared to sorafenib (8.1 months for sunitinib vs. 10.0 months for sorafenib, $P = 0.0019$; 9.1 months for linifanib vs. 9.8 months for sorafenib, $P > 0.05$), and were associated with relatively more grade 3 or 4 adverse events than sorafenib was. Brivanib, which targets VEGFR, PDGFR and fibroblast growth factor receptor (FGFR), also failed to prolong OS (9.5 months for brivanib vs. 9.9 months for sorafenib, $P > 0.05$) but had a more favorable toxicity profile than sorafenib [5]. Lenvatinib (E7080), a TKI of VEGFR, PDGFR, FGFR, RET and c-Kit, resulted in a high ORR of 33% per modified response evaluation criteria in solid tumors (mRECIST) in a phase I/II trial [12], and is currently undergoing phase III investigation.

The efficacy of brivanib after sorafenib failure has also been investigated in a phase III, randomized, placebo-controlled study (BRISK-PS study) [6]. Brivanib, compared to placebo, resulted in a higher ORR (11.5% vs. 1.9%; per mRECIST) and a longer median TTP (4.3 months vs. 2.7 months, $P = 0.0001$), but did not significantly increase the OS (9.4 months

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Table 1. Clinical trials of molecular targeted therapy for advanced HCC

Treatment	Trial phase/ design	Line of treatment	No. of evaluable patients	ORR[a] (%)	DCR[a] (%)	TTP (PFS) (months)	OS (months)	References
1. Anti-angiogenic agents (targets)								
Sunitinib (VEGFR, PDGFR, KIT, RET, Flt-3)								
• **Sunitinib** 37.5 mg po qd	III, RC, OL	First	529	N/A	N/A	4.1 (NS)	8.1 (P = 0.0019)	[3]
Sorafenib 400 mg po bid			544	N/A	N/A	4.0	10.0	
• **Sunitinib** 50 mg po qd for 4weeks, q6w	II	First	34	12 (4 PR)	N/A	2.8	5.8	[4]
Brivanib (VEGFR, PDGFR, FGFR)								
• **Brivanib** 800 mg po qd	III, RC, DB	First	299	12[e]	66[c, e]	4.2 (NS)	9.5 (NS)	[5]
Sorafenib 400 mg po bid			303	9[e]	65[c, e]	4.1	9.9	
• **Brivanib** 800 mg po qd	III, RC, DB	Second	263	11.5[e]	71.2[c, e]	4.2 (P = 0.0001)	9.4 (P = 0.33)	[6]
Placebo			132	1.9[f]	49.1[c, e]	2.7	8.2	
• **Brivanib** 800 mg po qd	II	First	55	7.3[d] (1 CR, 3 PR)	47.3[d]	(2.7)	10	[7]
• **Brivanib** 800 mg po qd	II	Second	46	4.3[d] (2 PR)	45.7[d]	2.7	9.8	[8]
Linifanib (ABT-869) (VEGFR, PDGFR)								
• **Linifanib** 17.5 mg po qd	III, RC, OL	First	1035 (1:1)	13.0	N/A	5.4 (NS)	9.1 (NS)	[9]
Sorafenib 400 mg po bid				6.9	N/A	4.0	9.8	
• **Linifanib** 0.25 mg/kg po qd (CP A) or qod (CP B)	II	First	44 (38, CP A; 6, CP B)	7.9 (CP A); 0 (CP B)	N/A	3.7	9.7	[10]

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Treatment	Trial phase/ design	Line of treatment	No. of evaluable patients	ORR[a] (%)	DCR[a] (%)	TTP (PFS) (months)	OS (months)	References
Lenvatinib (E7080) (VEGFR, PDGFR, FGFR, RET, KIT)								
• **Lenvatinib** 12 (or 8) mg po qd Sorafenib 400 mg po bid	III, RC, DB	First						NCT01761266
• **Lenvatinib** 8, 12, 16 mg po qd	I/II	First	20 (phase I)	N/A	N/A	N/A	N/A	[11]
• **Lenvatinib** 12 mg po qd	I/II	First	42 (phase II)	33[e] (14 PR)	N/A	N/A	N/A	[12]
Ramucirumab (IMC-1121B) (VEGFR2)								
• **Ramucirumab** 8 mg/kg iv q2w Placebo	III, RC, DB	Second						NCT01140347
Regorafenib (RET, VEGFR, KIT, PDGFR, FGFR, TIE2, DDR2, Trk2A, Eph2A, RAF-1, BRAF, BRAFV600E, SAPK2, PTK5, Bcr-Abl)								
• **Regorafenib** 160 mg po qd for 3 weeks, q4w Placebo	III, RC, DB	Second						NCT01774344
Bevacizumab (VEGF)								
• **Bevacizumab** 5 or 10 mg/kg iv q2w	II	Second or beyond	43	14 (6 PR)	42[c]	N/A	N/A	[13]
• **Bevacizumab** iv q2w **+** sorafenib 400 mg po bid Sorafenib 400 mg po bid	I/II, RC, OL	First						NCT00867321
Axitinib (VEGFR, PDGFR)								
• **Axitinib** 5 mg po bid Placebo	II, RC, DB	Second (prior antiangiogenic therapy)						NCT01210495
• **Axitinib** 5 mg po bid	II	Second (prior antiangiogenic therapy)	15	6.7 (1 PR); 0[e]	N/A	N/A	N/A	[14]
• **Axitinib** 5 mg po bid	II	Second						NCT01273662

Treatment	Trial phase/ design	Line of treatment	No. of evaluable patients	ORR[a] (%)	DCR[a] (%)	TTP (PFS) (months)	OS (months)	References
Cediranib (AZD2171) (VEGFR)								
• **Cediranib** 30 mg po qd	II	Second or beyond	17	0	29	(5.3)	11.7	[15]
• **Cediranib** 45 mg po qd	II	Second or beyond	28	0	25	2.8	5.8	[16]
Dovitinib (TKI-258) (VEGFR, PDGFR, FGFR)								
• **Dovitinib** 500 mg po qd 5 days on, 2 days off Sorafenib 400 mg po bid	II, RC, OL	First						NCT01232296
Vandetanib (VEGFR, EGFR)								
• **Vandetanib** 300 mg po qd	II, RC, DB	First	19	0	5.3[c]	1.05 (P = 0.31)	5.95 (P = 0.15)	[17]
• **Vandetanib** 100 mg po qd			25	0	16[c]	1.7 (P = 0.15)	5.75 (P = 0.02)	
Placebo			23	0	8.7[c]	0.95	4.27	
Pazopanib (VEGFR, PEGFR)								
• **Pazopanib** 200–800 mg po qd	I/II	First	28	8 (2 PR)	73	(4.1)	N/A	[18]
Orantinib (TSU-68) (VEGFR, PDGFR, FGFR)								
• **Orantinib** 200, 400 mg po bid (phase I); 200 mg po bid (phase II)	I/II	First	35	8.6 (1 CR, 2 PR)	51.4	2.1	13.1	[19]
Nintedanib (BIBF 1120) (VEGFR, PDGFR, FGFR)								
• **Nintedanib** 50–200 mg po bid	I/II (RC for phase II)	First	35 (phase I)	N/A	N/A	N/A	N/A	[20]
• **Nintedanib** 50–200 mg po bid	I/II (RC for phase II)	First	28 (phase I)	N/A	N/A	N/A	N/A	[21]
• **Nintedanib**	I	(≤1 prior systemic therapy)						NCT01594125
RO5323441 (placental growth factor; PIGF)								
• **RO5323441** iv q2w + sorafenib 400 mg po qod-bid	I	First						NCT01308723

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AMG386 (Angiopoietin)								
• **AMG386** 10, 15 mg/kg iv qw + sorafenib 400 mg po bid	II	First						NCT00872014
TRC 105 (CD105; endolin)								
• **TRC 105**	II	Second						NCT01375569
• **TRC 105** iv weekly + sorafenib 400 mg po bid	I/II	First						NCT01306058
2. EGFR inhibitor								
• **Erlotinib** 100 mg po qd + sorafenib 400 mg po bid	III, RC, DB	First	362	N/A	43.9	3.2 (NS)	9.5 (NS)	[22]
Sorafenib 400 mg po bid			358	N/A	52.5	4.0	8.5	
• **Erlotinib** po qd + bevacizumab iv q2w	II, RC, OL	First						NCT00881751
Sorafenib 400 mg po bid								
• **Erlotinib** 150 mg po qd + bevacizumab 15 mg/kg iv q3w	II	First	18	N/A	N/A	2.6	8.3	[23]
• **Erlotinib** 150 mg po qd + bevacizumab 10 mg/kg iv q2w	II	(≤1 prior systemic or local therapy)	27	3.7 (1 PR)	44.4	3.0	9.5	[24]
• **Erlotinib** 150 mg po qd + bevacizumab 10 mg/kg iv q2w	II	Second	10	N/A	N/A	1.8	4.4	[25]
• **Erlotinib** 150 mg po qd + bevacizumab 10 mg/kg iv q2w	II	Second						NCT01180959
3. mTOR inhibitors								
• **Everolimus** 7.5 mg po qd	III, RC, DB	Second						NCT01035229
Placebo								
• **Everolimus** 5 mg po qd + Sorafenib 400 mg po bid	II, RC, OL	First						NCT01005199
Sorafenib 400 mg po bid								

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• **Everolimus** 2.5, 5 mg po qd + Sorafenib 400 mg po bid	I/II	First	30	0	62.5 (2.5 mg); 35.7 (5 mg)	3.5 (2.5 mg); 3.6 (5 mg)	N/A	[26]
• **Everolimus** 5 mg po qd + Bevacizumab 5 mg/kg iv q2w	II	First (prior sorafenib use <3 months is allowed)	33	0	N/A	2.0	9.0	[27]
• **Everolimus** 5, 10 mg po qd	I/II	(0–2 prior regimens)	27	4	N/A	(3.8)	N/A	[28]
• **Everolimus** 2.5–10 mg po qd vs. 20–70 mg po qw	I, RC, OL	(Refractory patients)	39	N/A	71.4 (daily); 44.4 (weekly)	N/A	N/A	[29]
• **Temsirolimus** 10, 15 mg iv qw + sorafenib 200–800 mg/day po	I	First	21	10	N/A	N/A	N/A	[30]
• **Temsirolimus** 10 mg iv qw + sorafenib 200 mg bid	II	First						NCT01687673
• **Temsirolimus** 10, 20, 25 mg iv qw + sorafenib 200 mg bid	I/II	First						NCT01335074
• **Temsirolimus** 25 mg iv qw **+** bevacizumab 10 mg/kg iv q2w	II	First	25	8 (2 PR)	N/A	6 (7.4)	8.3	[31]
• **Temsirolimus** 25 mg iv qw + bevacizumab 10 mg /kg iv q2w	II	Second	13	30.7 (4 PR)	N/A	N/A	N/A	[32]
• **Temsirolimus**	II	Second						NCT01567930
• **Temsirolimus**	I/II	(Refractory patients)						NCT01251458
• **Sirolimus** 20 mg/w for 4 weeks then 30 mg/w	II	First	25	8 (1 CR, 1 PR)	40	3.6	6.2	[33]
• **Sirolimus** 1–5 mg po qd + bevacizumab 5 mg/kg iv q2w	I	(Refractory patients)	18	5.6 (1 CR)	55.6	6.6	7.5	[34]
• **AZD8055**	I	(Refractory patients)						NCT00999882

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4. c-Met inhibitors (targets)								
Tivantinib (ARQ 197) (c-Met)								
• **Tivantinib** 240 mg po bid Placebo	III, RC, DB	Second (MET-high HCC)						NCT01755767
• **Tivantinib** 360→240 mg po bid	II, RC, DB	Second	71	1.4	43.7	1.6 (all)/ 2.7 (MET-high) (P = 0.04/ P = 0.03)	6.6 (all)/ 7.2 (MET-high) (P = 0.63/ P = 0.01)	[35]
Placebo			36	0	30.6	1.4 (total)/ 1.4 (MET-high)	6.2 (total)/ 3.8 (MET-high)	
• **Tivantinib** 240, 360 mg bid **+** sorafenib 200, 400 mg bid	I	First						NCT00827177
• **Tivantinib** 360 mg po bid	I	(≤2 prior systemic therapies)	21	0	56	3.3	N/A	[36]
• **Tivantinib** 240 mg po bid	I	Second						NCT01656265
Cabozantinib (XL-184) (c-Met, RET, VEGFR2)								
• **Cabozantinib** 100 mg po qd for 12 weeks	II, RD, DB	(≤1 prior regimen)	33	9 (week 12)	71	N/A	N/A	[37]
Golvatinib (E7050) (c-Met, KIT, RON, VEGFR2)								
• **Golvatinib** 200, 300, 400 mg po qd + sorafenib 400 mg po bid	I/II	(≤2 prior regimens including sorafenib)	12 (phase I)	17 (2 PR)	50	N/A	N/A	[38]
INC280 (c-Met)								
• **INC280** 300 mg po bid	II	First						NCT01737827
Foretinib (GSK 136089) (c-Met, RON, AXL, Tie-2, VEGFR)								
• **Foretinib** 30, 45 mg po qd	I/II	First	38 (phase II)	24[e]	79[b,e]	4.2	15.7	[39]

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Treatment	Trial phase/ design	Line of treatment	No. of evaluable patients	ORR[a] (%)	DCR[a] (%)	TTP (PFS) (months)	OS (months)	References
5. MEK inhibitors								
• **Selumetinib (AZD6244)** 100 mg po bid	II	First	19	0	N/A	1.8	N/A	[40]
• **Selumetinib (AZD6244)** 50–100 mg po bid + sorafenib 400 mg po bid	I	First	11	27.3*	N/A	N/A	N/A	[41]
• **BAY86-9766** 50 mg po bid + sorafenib 400 mg po bid	II	First	58	5	N/A	4	N/A	[42]
6. Inhibitors of IGF signaling (targets)								
Cixutumumab (IMC-A12) (IGF-1R)								
• **Cixutumumab** 6 mg/kg iv qw	II	First	24	0	29[b]	N/A	8	[43]
• **Cixutumumab** 10 mg/kg iv q3w + sorafenib 400 mg po bid	II	First						NCT00906373
• **Cixutumumab** iv qw + sorafenib 400 mg po bid	I	First						NCT01008566
OSI-906 (IGF-1R, IR)								
• **OSI-906** 150 mg po bid Placebo	II, RC, DB	Second						NCT01101906
• **OSI-906** 150 mg po bid + sorafenib 400 mg po bid	II	First						NCT01334710
AVE1642 (IGF-1R)								
• **AVE1642** 1, 3, 6 mg/kg iv qw + sorafenib 400 mg po bid	I	First	13	0	N/A	N/A	N/A	[44]
BIIB022 (IGF-1R)								
• **BIIB022** + sorafenib	I	First						NCT00956436
MEDI-573 (IGF-1, IGF-2)								
• **MEDI-573** + sorafenib	I	First						NCT01498952

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7. Histone deacetylase (HDAC) inhibitors								
• **Resminostat (4SC-201)** 200, 400, 600, 800 mg po qd for 5 days every 14 days + sorafenib 200, 400 mg po bid	II, RC, OL	Second (PD under sorafenib)	26	0	N/A	(4.7)	(8.0)	[45]
Resminostat (4SC-201) 200, 400, 600, 800 mg po qd for 5 days every 14 days			19	0	N/A	(2.2)	(4.1)	
• **Vorinostat** + sorafenib	I	First						NCT01075113
• **Belinostat (PXD101)** 600–1400 mg/kg/day iv D1-5, q3w	I/II	(Refractory patients)	42 (phase II)	2.4	47.6	(2.84)	6.6	[46]
8. Others (targets)								
Mapatumumab (tumor necrosis factor-related apoptosis-inducing ligand receptor-1; TRAIL-R1)								
• **Mapatumumab** 30 mg/kg iv q3w + sorafenib 400 mg po bid	II, RC, DB	First						NCT01258608
Sorafenib 400 mg po bid								
• **Mapatumumab** 30 mg/kg iv q3w + sorafenib 400 mg po bid	Ib	First	19	10.5	N/A	N/A	N/A	[47]
Tigatuzumab (CS-1008) (Death receptor 5)								
• **CS-1008** 2,4, 6 mg/kg iv qw + sorafenib 400 mg po bid	II, RC, OL	First	9 (phase I)	22 (2 PR)	66.7	N/A	N/A	[48])
AEG35156 (X-linked inhibitor of apoptosis protein; XIAP)								
• **AEG35156** 300 mg iv qw + sorafenib 400 mg po bid	II, RC, OL	First	31	N/A	N/A	(4.0)	N/A	[49]
Sorafenib 400 mg po bid			17	N/A	N/A	(2.6)	N/A	
Tremelimumab (CP 675,206) (Cytotoxic T-lymphocyte antigen 4; CTLA-4)								
• **Tremelimumab** 15 mg/kg iv every 90 days	II	Second or beyond	20	12 (2 PR)	76.4	6.4	7.5	[50]
CT-011 and BMS-936558 (programmed death-1; PD-1)								
• **CT-101**	I/II	(≤1 prior systemic regimen)						NCT00966251
• **BMS-936558**	I	(≥1 prior systemic therapy)						NCT01658878

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CF102 (A3 adenosine receptor)								
• **CF102** 1,5, 25 mg po bid	I/II	(Refractory patients)	18	0	22.2[c]	N/A	7.8	[51]
GC33 (Glypican 3)								
• **GC33** 1600 mg iv q2w Placebo	II, RC, DB	(≥1 prior systemic therapy)						NCT01507168
• **GC33** 2.5-20 mg/kg iv weekly	I	(Refractory patients)	20	N/A	N/A	6.1 (high glypican 3 expression) vs. 1.7 (low glypican 3 expression)	N/A	[52]
• **GC33** 5, 10, 20 mg/kg iv weekly	I	(Refractory patients)	13	0	23.1	N/A	N/A	[53]
• **GC33** +sorafenib 400 mg bid or qd	I	First						NCT00976170
Lenalidomide and thalidomide (Immune modulation)								
• **Lenalidomide** 25 mg po qd for 3 weeks every 4 weeks	II	Second	37	22 (2 CR, 6 PR)	N/A	N/A	N/A	[54]
• **Lenalidomide** 25 mg po qd for 3 weeks every 4 weeks	II	Second						NCT01545804
• **Lenalidomide** + sorafenib 400 mg po bid	I	First						NCT01348503
• **Thalidomide** 50-200 mg/day+ sorafenib 400 mg po bid	I/II	First						NCT00971126
Bortezomib (proteasome)								
• **Bortezomib** 1.3 mg/m2 iv bolus on days 1, 4, 8, and 11 every 21 days	II	First	35	2.9 (1 PR)	N/A	1.6	6.0	[55]
TAC-101 (retinoid receptor)								
• **TAC-101** 20 mg po qd for 14 days, every 3 weeks Placebo	II, RC, DB	Second						NCT00687596
• **TAC-101**10, 20, 30 mg po qd	I	(Refractory patients)	13	0	23	N/A	N/A	[56]

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Z-208 (Peroxisome proliferator-activated receptor α; PPARα)								
• **Z-208**	I/II	(Refractory patients)						NCT00731445
Bavituximab (phospholipid)								
• **Bavituximab** + sorafenib	I/II	First						NCT01264705
Dasatinib (Kit, Src, Bcr-Abl								
• **Dasatinib**	II	(Refractory patients)						NCT00459108
LY2157299 (TGFβ)								
• **LY2157299** 160, 300 mg po qd for 14 days every 28 days	II, RC, OL	Second						NCT01246986
MK2206 (AKT)								
• **MK2206** po D1, 8, 15, 22, every 28 days	II	Second						NCT01239355
OPB-31121 (STAT 3)								
• **OPB-31121** 400, 600 mg po qd	I/II	Second						NCT01406574
PD-0332991 (Cyclin-dependent kinases 4/6; CDK 4/6)								
• **PD-0332991** 125 mg po qd for 3 weeks every 4 weeks	II	(Refractory patients)						NCT01356628

ORR = complete response (CR) + partial response (PR); DCR = CR + PR + stable disease (SD); RC = randomized controlled; RD = randomized discontinuation; OL = open-label; DB = double-blind; N/A = not available; NS = non-significant; CP A = Child-Pugh A; CP B = Child-Pugh B; PD = progressive disease. [a] The tumor response was defined per conventional RECIST unless otherwise indicated. [b] CR + PR + SD lasting for ≥ 3 months. [c] CR + PR + SD lasting for ≥ 4 months. [d] The tumor response was defined per modified WHO criteria. [e] The tumor response was defined per modified RECIST. * The evaluation criteria was not mentioned.

vs. 8.2 months, P = 0.33). The efficacy of other second-line anti-angiogenic agents (ramucirumab, regorafenib and axitinib) remains undetermined.

EGFR Inhibitor

The combination of anti-angiogenic therapy and erlotinib has been investigated. In a phase III, randomized, controlled, double-blind trial (SEARCH trial) [22], sorafenib plus erlotinib, compared to sorafenib plus placebo, did not prolong either TTP (3.2months vs. 4.0 months, P > 0.05) or OS (9.5 months vs. 8.5 months; P > 0.05). In several completed phase II single-arm studies, bevacizumab (anti-VEGF monoclonal antibody) plus erlotinib resulted in a modest anti-tumor activity compared to the historical control of sorafenib or bevacizumab [23–25].

mTOR Inhibitors

Everolimus (RAD001) is the most extensively studied mTOR inhibitor for the treatment of HCC. The recommended phase II dose of everolimus was 7.5 or 10 mg per day for monotherapy in HCC patients [28, 29]. A phase III, randomized, placebo-controlled trial testing the efficacy of everolimus 7.5 mg po qd after sorafenib failure has completed patient recruitment, and the results will be available by the end of 2013. The maximum tolerated dose of everolimus was determined to be 2.5 mg per day for combination with sorafenib [26]. However, everolimus at this dose level was considered biologically inactive and unlikely to improve the efficacy of sorafenib through mTOR inhibition.

A phase II trial testing the efficacy of temsirolimus 25 mg iv weekly plus bevacizumab 10 mg/kg iv biweekly for first-line treatment was prematurely stopped due to futility [31]. However, the same combination regimen resulted in a higher ORR (per conventional RECIST) of 30.7% and fair tolerability in the first 13 patients in a phase II trial for patients in whom sorafenib failed [32].

c-Met Inhibitors

c-Met signaling is considered essential for hepatocarcinogenesis [57]. Foretinib (GSK 136089), the first multi-target c-MET TKI to undergo clinical investigation, produced a promising ORR (per mRECIST) of 24%, median TTP of 4.2 months, and median OS of 15.7 months in 38 sorafenib-naïve HCC patients [39]. Other c-Met inhibitors have been primarily evaluated in HCC patients in whom sorafenib had failed. Tivantinib (ARQ 197), a selective non-ATP competitive inhibitor of c-MET, has been tested in a phase II, randomized, placebo-controlled trial [35]. Tivantinib, compared to placebo, improved median TTP from 1.4 to 1.6 months in molecularly unselected HCC patients with a hazard ratio (HR) of 0.64 (P = 0.04). Importantly, tivantinib almost doubled median TTP (2.7 months vs. 1.4 months, HR = 0.43, P = 0.03) and median OS (7.2 months vs. 3.8 months, HR = 0.38, P = 0.01) in patients with high c-Met-expressing tumors (≥2+ staining intensity in ≥50% of tumor cells by an immunohistochemical method). A confirmatory phase III, randomized, placebo-controlled trial was subsequently launched to evaluate the efficacy of tivantinib in HCC patients who had high c-Met expression in their tumors and developed progressive disease under sorafenib therapy. c-Met inhibitors are generally well tolerated except for increased incidence of grade 3 or 4 neutropenia, anemia and thrombocytopenia (14.1, 11.3 and 5.6%, respectively).

MEK Inhibitors

Selumetinib (AZD6244) 100 mg po bid resulted in a short TTP of 1.8 months in the first 19 treatment-naïve HCC patients of a phase II trial, although it did induce down-regulation of ERK phosphorylation in post-treatment tumor tissue [40]. Selumetinib [41] and BAY86-9766 [42] were investigated in early-phase trials for their combination activity with

sorafenib. The combination of sorafenib and selumetinib resulted in an ORR of 27.3% in the first 11 patients, but this finding needs to be validated.

Inhibitors of IGF Signaling

Several IGF- or IGF-1R-targeted agents, either as single agents or in combination with sorafenib, have undergone early-phase investigations [43, 44]. However, several toxicities, such as hyperglycemia, hyperbilirubinemia and elevation of liver enzymes, following combination therapy have limited the development of OSI-906, AVE1642 and BIIB022.

Other Molecular Targeted Agents

Many other signaling pathways are also involved in hepatocarcinogenesis, including histone deacetylase (HDAC), tumor necrosis factor-related apoptosis-inducing ligand receptor-1 (TRAIL-R1), death receptor 5 (DR5), X-linked inhibitor of apoptosis protein (XIAP), proteasome, retinoid receptor, peroxisome proliferator-activated receptor α (PPARα), phospholipid, transformation growth factor-β (TGF-β), AKT, STAT3 and cyclin-dependent kinases. In addition, some molecular targets expressed either on immune cells (such as cytotoxic T-lymphocyte antigen and programmed death-1) or cancer cells (such as A3 adenosine receptor and glypican 3) provide opportunities for immunotherapy. Corresponding targeted agents are being actively studied in phase I/II or II trials for their feasibility. Noticeably, lenalidomide (an immune moderator) resulted in a higher ORR of 22% per conventional RECIST (two complete responders and six partial responders) in 37 American patients in whom sorafenib had failed [54]. Another study testing the efficacy of lenalidomide as second-line treatment is ongoing in Asian HCC patients.

Clinical Trials of Molecular Targeted Therapy in Combination with Locoregional Therapy

Data from clinical trials on a variety of molecular targeted therapies in combination with locoregional therapy are shown in table 2 [58–68].

Sorafenib

The feasibility of combining locoregional therapy and sorafenib for HCC treatment has been evaluated in many clinical trials. In a phase III, randomized, placebo-controlled trial, patients whose hepatic tumors had ≥25% tumor necrosis/shrinkage after one or two sessions of transarterial chemoembolization (TACE) were randomized to sorafenib or placebo. However, the addition of sorafenib failed to prolong TTP (5.4 months vs. 3.7 months; HR = 0.87; P = 0.252) [58]. Subsequently, a number of phase II trials evaluating the efficacy and safety of conventional TACE or TACE with doxorubicin-eluting beads (DEB) with concurrent sorafenib (which started within 14 days before or after TACE was carried out) revealed inconsistent results [59–64]. The diversity of study designs created confounding factors including primary endpoints, patient populations, TACE procedures, timing of randomization, and drug administration may account for these conflicting results [69]. Another two phase III, randomized, placebo-controlled trials evaluating the efficacy of sorafenib in combination with conventional TACE or DEB-TACE are ongoing.

In the phase II SORAMIC trial (local ablation group), patients with early HCC receive a maximum of two curative radiofrequency ablation (RFA) sessions. Randomization to sorafenib or placebo was performed after completion of RFA. Several phase I or II trials eval-

Table 2. Clinical trials of molecular targeted therapy in combination with locoregional therapy for HCC

Molecular targeted therapy (time of initiation)	Loco-regional therapy	Trial phase/design	No. of evaluable patients	RR (%)	TTP (months)	OS (months)	References
Sorafenib 400 mg po bid Placebo (sequential to TACE)	TACE	III, RC, DB	229 229	N/A	5.4 3.7 (HR = 0.87, P = 0.252)	29.7 Not reached	[58]
Sorafenib 400 mg po bid Placebo (7 days after TACE)	DEB-TACE	III, RC, DB	Target: 412				NCT01324076 (TACE2 trial)
Sorafenib 400 mg po bid Placebo (2 weeks before TACE)	TACE	III, RC, DB	Target: 400				NCT01004978
Sorafenib 400 mg po bid Placebo (sequential to TACE)	TACE	II, RC, DB	31 31	100*	9.2 4.9 (HR = 2.5, P < 0.001)	N/A	[59]
Sorafenib 400 mg po bid Placebo (concurrently)	DEB-TACE	II, RC, DB	154 153	N/A	5.6 5.5 (HR = 0.797, P = 0.072)	N/A	[60] (SPACE trial)
Sorafenib 400 mg po bid Placebo (3 days after TACE)	TACE	II, RC, OL	Target: 228				NCT01217034 (TACTICS trial)
Sorafenib 400 mg po bid (4–7 days after TACE)	TACE	II	147	52	9.3	Not reached	[61] (START trial)
Sorafenib 400 mg po bid (3 days after TACE)	TACE	II	50	44	7.1	N/A	[62]
Sorafenib 400 mg po bid (1 week before TACE)	DEB-TACE	II	35	58	N/A	N/A	[63]
Sorafenib 400 mg po bid (2 weeks before TACE)	TACE	II	15	70	5.2	10.6	[64]
Sorafenib 400 mg po bid Placebo (2–4 weeks after TACE)	TACE	IV	Target: 120				NCT01833299
Sorafenib 400 mg po bid Placebo (concurrently)	RFA	II, RC, DB	Target: 290				NCT01126645 (SORAMIC trial; local ablation group)
Sorafenib 400 mg po bid (concurrently)	RT	II	Target: 45				NCT01319942
Sorafenib 400 mg po bid (concurrently)	RT	I	Target: 44				NCT00892658 (SHEP trial)

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Molecular targeted therapy (time of initiation)	Loco-regional therapy	Trial phase/design	No. of evaluable patients	RR (%)	TTP (months)	OS (months)	References
Sorafenib 400 mg po bid (concurrently)	RT	I	Target: 30				NCT01618253
Sunitinib 37.5 mg po qd Placebo (7–10 days before TACE)	TACE	II/III, RC, DB	Target: 190				NCT01164202 (SATURNE trial)
Sunitinib 37.5 mg po qd (7 days before TACE)	TACE	II	16	12.5	8.0	14.9	[65]
Bevacizumab 10 mg/kg iv every 2 weeks Placebo (1 week before TACE)	TACE	II, RC, OL	15 15	N/A	(PFS at 16 weeks: 79% vs. 10%, P = 0.021)	49 61 (P = 0.21)	[66]
Bevacizumab 10 mg/kg iv every 2 weeks (2 weeks before TACE)	TACE	II	26	60	7.2	10.8	[67]
Orantinib 200 mg po bid Placebo (≥3 days after TACE)	TACE	III, RC, DB	Target: 880				NCT01465464 (ORIENTAL trial)
Orantinib 200 mg po bid No antitumor therapy	TACE	II, RC, OL	Total: 103	N/A	5.2 4.0 (HR = 0.699; P = 0.054)	NA	[68]
Brivanib 200 mg po qd Placebo (2–21 days after TACE)	TACE	III, RC, DB	Target: 870				NCT00908752 (BRISK-TA trial)
Axitinib 5 mg po qd	TACE	II	Target: 50				NCT01352728
Thalidomide (4 weeks before TACE)	TACE	II	Target: 75				NCT00006016
Everolimus 7.5 mg po qd Placebo	DEB-TACE	II, RC, DB	Target: 80				NCT01379521 (TRACER trial)
Everolimus Placebo	DEB-TACE	I/II, RC, DB	Target: 98				NCT01009801

RR = response rate; RT = radiotherapy. * randomization only for complete responders.

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Table 3. Clinical trials of adjuvant molecular targeted therapy following curative treatment for HCC

Treatment	Curative treatment	Trial phase/design	No. of evaluable patients	Recurrence-free survival (months)	References
Sorafenib 400 mg po qd Placebo	Surgery or local ablation	III, RC, DB	Target:1,114		NCT00692770 (STORM trial)
Sorafenib 400 mg po qd Placebo	Surgery	II, OL	14 16	Not reached 6 (P = 0.008)	[70]
Sorafenib 400 mg po qd Placebo	OLT	II, RC, DB	Target: 356		NCT01624285
PI-88 160 mg sc qd Placebo	Surgery	III, RC, DB	Target: 500		NCT01402908
PI-88 160 and 250 mg sc qd for nine 4-week treatment cycles No adjuvant treatment	Surgery	II, RC, OL	168	10.8* (160 mg/day) 5.1* (P = 0.13)	[71]

OLT = orthotopic liver transplant; sc = subcutaneous injection. * Time-to-recurrence at the 36th percentile.

uating the efficacy and/or safety of radiotherapy in combination with sorafenib in patients with early HCC are actively recruiting patients.

Other Anti-angiogenic Agents and Everolimus

Several phase II trials explored the efficacy of combining TACE and anti-angiogenic agents, such as sunitinib [65], bevacizumab [66, 67] and orantinib (TSU-68) [68]. Most of these trials demonstrated promisingly long TTP. Further phase III, randomized, controlled trials exploring the combinations of TACE and sunitinib (TURNE trial), orantinib (ORIENTAL trial) and brivanib (BRISK-TA trial) are ongoing. In addition, the efficacy of DEB-TACE with everolimus is currently being explored in two phase II, randomized, controlled trials.

Clinical Trials of Adjuvant Molecular Targeted Therapy Following Curative Treatment

The potential of molecular targeted agents as adjuvant therapy after curative surgery, local ablation or liver transplantation is under active investigation; most studies are still ongoing. In a phase II trial with a limited number of patients (30 patients in total), sorafenib following curative surgery resulted in a lower tumor recurrence rate (33.3% vs. 73.6%), compared to surgery alone [70]. A large-scale, phase III, randomized, placebo-controlled trial (STORM trial) evaluating the efficacy of sorafenib after curative surgery or local ablation has completed accrual.

PI-88, a heparanase inhibitor, has been testing as adjuvant therapy for HCC after curative resection. A phase II study suggested that PI-88 at 160 mg/day is potentially effective as adjuvant therapy in postoperative HCC patients [71]. A phase III, randomized, placebo-controlled trial exploring the value of PI-88 in the adjuvant setting is ongoing. Data from clinical trials of adjuvant molecular targeted therapy following curative treatment are shown in table 3 [70,71].

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Conclusion

We have provided a comprehensive overview of recently reported and ongoing clinical trials in HCC. The trials are categorized in a way that helps investigators from diverse disciplines to grasp easily a full picture of research in this field. We intend to provide updated versions of this article on a regular basis.

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