Clinical Trials in Hepatocellular Carcinoma: An Update

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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-\(\beta\), 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, 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...
| Treatment                              | Trial phase/design | Line of treatment | No. of evaluable patients | ORR<sup>a</sup> (%) | DCR<sup>a</sup> (%) | 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]        |
| • Sunitinib 50 mg po qd for 4weeks, q6w |                    |                   | 544                       | N/A                  | N/A                  | 4.0               | 10.0        |            |
| Sorafenib 400 mg po bid                |                    |                   |                           |                      |                      |                   |             |            |
| • Sunitinib 50 mg po qd               | II                 | First             | 34                        | 12<sup>e</sup> (4 PR) | N/A                  | 2.8               | 5.8         | [4]        |
| Brivanib (VEGFR, PDGFR, FGFR)         |                    |                   |                           |                      |                      |                   |             |            |
| • Brivanib 800 mg po qd               | III, RC, DB        | First             | 299                       | 12<sup>e</sup>       | 66<sup>c, e</sup>    | 4.2 (NS)          | 9.5 (NS)     | [5]        |
| Sorafenib 400 mg po bid                |                    |                   |                           |                      |                      |                   |             |            |
| • Brivanib 800 mg po qd               | III, RC, DB        | Second            | 263                       | 11.5<sup>c</sup>     | 71.2<sup>c, e</sup>  | 4.2 (P = 0.0001)  | 9.4 (P = 0.33) | [6]        |
| Placebo                                |                    |                   | 132                       | 1.9<sup>f</sup>      | 49.1<sup>c, e</sup>  | 2.7               | 8.2         |            |
| • Brivanib 800 mg po qd               | II                 | First             | 55                        | 7.3<sup>d</sup> (1 CR, 3 PR) | 47.3<sup>d</sup> | (2.7)           | 10          | [7]        |
| • Brivanib 800 mg po qd               | II                 | Second            | 46                        | 4.3<sup>d</sup> (2 PR) | 45.7<sup>d</sup>     | 2.7               | 9.8         | [8]        |
| Linifanib (ABT-869) (VEGFR, PDGFR)    |                    |                   |                           |                      |                      |                   |             |            |
| • Linifanib 17.5 mg po qd             | III, RC, OL        | First             | 1035                      | 13.0                 | N/A                  | 5.4 (NS)          | 9.1 (NS)    | [9]        |
| Sorafenib 400 mg po bid                |                    |                   |                           |                      |                      |                   |             |            |
| • Linifanib 0.25 mg/kg po qd (CP A) or qod (CP B) | II                 | First             | 44                        | 7.9 (CP A); 3.7 (CP B) | N/A     | 9.7 (CP B) | 3.7 (CP B) | [10]      |
| Treatment                                      | Trial phase/ design | Line of treatment | No. of evaluable patients | ORR<sup>a</sup> (%) | DCR<sup>a</sup> (%) | TTP (PFS) (months) | OS (months) | References |
|-----------------------------------------------|---------------------|-------------------|---------------------------|-----------------------|---------------------|-------------------|-------------|------------|
| Lenvatinib (E7080) (VEGFR, PDGFR, FGFR, RET, KIT) |                     |                   |                           |                       |                     |                   |             |            |
| • Lenvatinib 12 (or 8) mg po qd               | III, RC, DB         | First             |                           |                       |                     |                   |             |            |
| Sorafenib 400 mg po bid                       |                     |                   |                           |                       |                     |                   |             | 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<sup>e</sup>         | N/A                 | N/A               | N/A         | [12]       |
| Ramucirumab (IMC-1121B) (VEGFR2)              |                     |                   |                           |                       |                     |                   |             |            |
| • Ramucirumab 8 mg/kg iv q2w                  | III, RC, DB         | Second            |                           |                       |                     |                   |             | NCT01140347 |
| Placebo                                       |                     |                   |                           |                       |                     |                   |             |            |
| 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   | III, RC, DB         | Second            |                           |                       |                     |                   |             | NCT01774344 |
| Placebo                                       |                     |                   |                           |                       |                     |                   |             |            |
| Bevacizumab (VEGF)                            |                     |                   |                           |                       |                     |                   |             |            |
| • Bevacizumab 5 or 10 mg/kg iv q2w            | II                  | Second or beyond  | 43                        | 14                    | 42<sup>c</sup>       | N/A               | N/A         | [13]       |
| • Bevacizumab iv q2w + sorafenib 400 mg po bid| I/II, RC, OL        | First             | 6 PR                      | 15                    | 6.7                 | N/A               | N/A         | N/C        |
| Sorafenib 400 mg po bid                       |                     |                   |                           |                       |                     |                   |             | [14]       |
| Axitinib (VEGFR, PDGFR)                       |                     |                   |                           |                       |                     |                   |             |            |
| • Axitinib 5 mg po bid                        | II, RC, DB          | Second (prior antiangiogenic therapy) |                       |                       |                     |                   |             | NCT01210495 |
| Placebo                                       |                     |                   |                           |                       |                     |                   |             |            |
| • Axitinib 5 mg po bid                        | II                  | Second (prior antiangiogenic therapy) | 15                       | 6.7                  | 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 | II, RC, OL | First | | | | | | NCT01232296 |
| Sorafenib 400 mg po bid |                       |                   |                          |                |                |                   |             |            |
| **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 |
| Treatment                          | Trial phase/ design | Line of treatment | No. of evaluable patients | ORR (%) | DCR (%) | TTP (PFS) (months) | OS (months) | References |
|-----------------------------------|---------------------|-------------------|---------------------------|---------|---------|-------------------|-------------|------------|
| **AMG386 (Angiopoietin)**         |                     |                   |                           |         |         |                   |             |            |
| • AMG386 10, 15 mg/kg iv qw +    | II                  | First             |                           |         |         |                   |             |            |
| sorafenib 400 mg po bid           |                     |                   |                           |         |         |                   |             | NCT00872014 |
| **TRC 105 (CD105; endolin)**      |                     |                   |                           |         |         |                   |             |            |
| • TRC 105                          | II                  | Second            |                           |         |         |                   |             | NCT01375569 |
| • TRC 105 iv weekly +             | I/II                | First             |                           |         |         |                   |             | NCT01306058 |
| sorafenib 400 mg po bid           |                     |                   |                           |         |         |                   |             |            |
| **2. EGFR inhibitor**             |                     |                   |                           |         |         |                   |             |            |
| • Erlotinib 100 mg po qd +        | III, RC, DB         | First             | 362                       | N/A     | 43.9    | 3.2 (NS)          | 9.5 (NS)   | [22]       |
| sorafenib 400 mg po bid           |                     |                   |                           |         |         |                   |             |            |
| Sorafenib 400 mg po bid           | II, RC, OL          | First             | 358                       | N/A     | 52.5    | 4.0              | 8.5        | NCT00881751 |
| • Erlotinib po qd +               | II, RC, OL          | First             |                           |         |         |                   |             |            |
| bevacizumab iv q2w                |                     |                   |                           |         |         |                   |             |            |
| Sorafenib 400 mg po bid           |                     |                   |                           |         |         |                   |             |            |
| • Erlotinib 150 mg po qd +        | II                  | First             | 18                        | N/A     | N/A     | 2.6              | 8.3        | [23]       |
| bevacizumab 15 mg/kg iv q3w       |                     |                   |                           |         |         |                   |             |            |
| • Erlotinib 150 mg po qd +        | II                  | First             | 27                        | 3.7 (1 PR) | 44.4    | 3.0              | 9.5        | [24]       |
| bevacizumab 10 mg/kg iv q2w       | (≤1 prior systemic or local therapy) |                   |                           |         |         |                   |             |            |
| • Erlotinib 150 mg po qd +        | II                  | Second            | 10                        | N/A     | N/A     | 1.8              | 4.4        | [25]       |
| bevacizumab 10 mg/kg iv q2w       |                     |                   |                           |         |         |                   |             |            |
| **3. mTOR inhibitors**            |                     |                   |                           |         |         |                   |             |            |
| • Everolimus 7.5 mg po qd         | III, RC, DB         | Second            |                           |         |         |                   |             | NCT01035229 |
| Placebo                           |                     |                   |                           |         |         |                   |             |            |
| **Everolimus 5 mg po qd +         | II, RC, OL          | First             |                           |         |         |                   |             | NCT01005199 |
| Sorafenib 400 mg po bid           |                     |                   |                           |         |         |                   |             |            |
| Treatment | Trial phase/design | Line of treatment | No. of evaluable patients | ORR<sup>a</sup> (%) | DCR<sup>a</sup> (%) | TTP (PFS) (months) | OS (months) | References |
|-----------|-------------------|-------------------|--------------------------|---------------------|---------------------|-------------------|-------------|------------|
| **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 | N/A | | | | | NCT01687673 |
| **Temsirolimus 10, 20, 25 mg iv qw + sorafenib 200 mg bid** | I/II | First | 39 | N/A | 6 (7.4) | | | NCT01335074 |
| **Temsirolimus 25 mg iv qw + bevacizumab 10 mg/kg iv q2w** | II | First | 25 | 8 (2 PR) | N/A | 6 | 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 | N/A | | | | | NCT01567930 |
| **Temsirolimus** | I/II | (Refractory patients) | N/A | | | | | 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) | N/A | | | | | NCT00999882 |
| Treatment | Trial phase/design | Line of treatment | No. of evaluable patients | ORR<sup>a</sup> (%) | DCR<sup>a</sup> (%) | TTP (PFS) (months) | OS (months) | References |
|-----------|-------------------|-------------------|---------------------------|---------------------|---------------------|------------------|------------|------------|
| **Tivantinib (ARQ 197) (c-Met)** | | | | | | | | |
| **Tivantinib 240 mg po bid** | III, RC, DB | Second (MET-high HCC) | 71 | 1.4 | 43.7 | 1.6 (all)/2.7 (MET-high) (P = 0.04/0.03) | 6.6 (all)/7.2 (MET-high) (P = 0.63/0.01) | NCT01755767 |
| Placebo | | | 36 | 0 | 30.6 | 1.4 (total)/ 1.4 (MET-high) | 6.2 (total)/3.8 (MET-high) | |
| **Tivantinib 360→240 mg po bid** | II, RC, DB | Second | 71 | 1.4 | 43.7 | 1.6 (all)/2.7 (MET-high) (P = 0.04/0.03) | 6.6 (all)/7.2 (MET-high) (P = 0.63/0.01) | [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 | 21 | 0 | 56 | 3.3 | N/A | NCT00827177 |
| **Tivantinib 360 mg po bid** | | (<≤2 prior systemic therapies) | 21 | 0 | 56 | 3.3 | N/A | NCT00827177 |
| **Tivantinib 240 mg po bid** | I | Second | 33 | 9 (week 12) | 71 | N/A | N/A | [36] |
| **Cabozantinib (XL-184) (c-Met, RET, VEGFR2)** | | | | | | | | |
| **Cabozantinib 100 mg po qd for 12 weeks** | II, RD, DB | ≤2 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 | 38 | 24<sup>e</sup> | 79<sup>h,e</sup> | 4.2 | 15.7 | NCT01737827 |
| **Foretinib (GSK 136089) (c-Met, RON, AXI, Tie-2, VEGFR)** | | | | | | | | |
| **Foretinib 30, 45 mg po qd** | I/II | First | 38 | 24<sup>e</sup> | 79<sup>h,e</sup> | 4.2 | 15.7 | [39] |
| Treatment | Trial phase/design | Line of treatment | No. of evaluable patients | ORR<sup>a</sup> (%) | DCR<sup>a</sup> (%) | 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<sup>*</sup> | 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<sup>b</sup> | 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-1, 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] |
| BIB022 (IGF-1R) | | | | | | | | |
| • BIB022 + sorafenib | I | First | | | | NCT00956436 | |
| MEDI-573 (IGF-1, IGF-2) | | | | | | | | |
| • MEDI-573 + sorafenib | I | First | | | | NCT01498952 | |
| Treatment | Trial phase/ design | Line of treatment | No. of evaluable patients | ORR\(^a\) (%) | DCR\(^a\) (%) | TTP (PFS) (months) | OS (months) | References |
|-----------|--------------------|-------------------|---------------------------|---------------|---------------|-------------------|-----------|------------|
| 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) | (phase II) | 42 | 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 | | | | | | | | |
| 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 (≤1 prior systemic regimen) | I/II | | | | | | | NCT00966251 |
| • BMS-936558 (≥1 prior systemic therapy) | I | | | | | | | NCT01658878 |
| Treatment | Trial phase/design | Line of treatment | No. of evaluable patients | ORR$^a$ (%) | DCR$^a$ (%) | TTP (PFS) (months) | OS (months) | References |
|-----------|-------------------|-------------------|--------------------------|-------------|-------------|-------------------|-------------|------------|
| 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 | II, RC, DB | (≥1 prior systemic therapy) | N/A | N/A | 6.1 (high glypican 3 expression) vs. 1.7 (low glypican 3 expression) | N/A | NCT01507168 |
| • GC33 2.5-20 mg/kg iv weekly | I | (Refractory patients) | 20 | N/A | N/A | N/A | 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 | N/A | N/A | N/A | N/A | 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 | N/A | N/A | N/A | N/A | NCT01545804 |
| • Lenalidomide + sorafenib 400 mg po bid | I | First | N/A | N/A | N/A | N/A | NCT01348503 |
| • Thalidomide 50-200 mg/day + sorafenib 400 mg po bid | I/II | First | N/A | N/A | N/A | N/A | 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 | II, RC, DB | Second | N/A | N/A | N/A | N/A | NCT00687596 |
| Placebo | | | | | | | | |
| • TAC-101, 20, 30 mg po qd | I | (Refractory patients) | 13 | 0 | 23 | N/A | N/A | [56] |
| Treatment | Trial phase/design | Line of treatment | No. of evaluable patients | ORR<sup>a</sup> (%) | DCR<sup>a</sup> (%) | TTP (PFS) (months) | OS (months) | References |
|-----------|--------------------|-------------------|--------------------------|-----------------------|------------------|-------------------|-------------|------------|
| 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.<sup>a</sup>The tumor response was defined per conventional RECIST unless otherwise indicated.<sup>b</sup>CR + PR + SD lasting for ≥ 3 months.<sup>c</sup>CR + PR + SD lasting for ≥ 4 months.<sup>d</sup>The tumor response was defined per modified WHO criteria.<sup>e</sup>The tumor response was defined per modified RECIST.<sup>*</sup>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 (3.2 months 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 ($\geq 2+$ staining intensity in $\geq 50\%$ 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-
| 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 | N/A | 5.4 | 3.7 | 29.7 | [58] |
| Sorafenib 400 mg po bid Placebo (7 days after TACE) | DEB-TACE | III, RC, DB | Target: 412 | N/A | 5.6 | 5.5 | Not reached | NCT01324076 (TACE2 trial) |
| Sorafenib 400 mg po bid Placebo (2 weeks before TACE) | TACE | III, RC, DB | 31 | 100* | 9.2 | 4.9 | N/A | [59] |
| Sorafenib 400 mg po bid Placebo (concurrently) | DEB-TACE | II, RC, DB | 154 | N/A | 5.8 | 5.5 | N/A | [60] (SPACE trial) |
| Sorafenib 400 mg po bid Placebo (3 days after TACE) | TACE | II, RC, OL | Target: 228 | N/A | 9.3 | Not reached | 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 | N/A | N/A | N/A | NCT01833299 |
| Sorafenib 400 mg po bid Placebo (concurrently) | RFA | II, RC, DB | Target: 290 | N/A | N/A | N/A | NCT01126645 (SORAMIC trial; local ablation group) |
| Sorafenib 400 mg po bid (concurrently) | RT | II | Target: 45 | N/A | N/A | N/A | NCT01319942 |
| Sorafenib 400 mg po bid (concurrently) | RT | I | Target: 44 | N/A | N/A | N/A | NCT00892658 (SHEP trial) |
| 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               |        |              |             |            |
| **Sunitinib** 37.5 mg po qd Placebo (7–10 days before TACE) | TACE                  | II/III, RC, DB     | Target: 190              |        |              |             |            |
| **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 (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              |        |              |             |            |
| **Orantinib** 200 mg po bid No antitumor therapy | TACE                  | II, RC, OL         | Total: 103               | N/A    | 5.2          | 4.0         | NA [68]    |
| **Brivanib** 200 mg po qd Placebo (2–21 days after TACE) | TACE                  | III, RC, DB        | Target: 870              |        |              |             |            |
| **Axitinib** 5 mg po qd                         | TACE                  | II                 | Target: 50               |        |              |             |            |
| **Thalidomide** (4 weeks before TACE)           | TACE                  | II                 | Target: 75               |        |              |             |            |
| **Everolimus** 7.5 mg po qd Placebo             | DEB-TACE              | II, RC, DB         | Target: 80               |        |              |             |            |
| **Everolimus** Placebo                         | DEB-TACE              | I/II, RC, DB       | Target: 98               |        |              |             |            |

RR = response rate; RT = radiotherapy. * randomization only for complete responders.
Evaluating 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 (TURNET trial), orantinib (ORIENTAL trial) and brivanib (BRIISK-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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**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 | Surgery or local ablation | III, RC, DB | Target: 1,114 | NCT00692770 (STORM trial) |
| Sorafenib 400 mg po qd | Surgery | II, OL | 14 16 | Not reached 6 (P = 0.008) |
| Sorafenib 400 mg po qd | OLT | II, RC, DB | Target: 356 | NCT01624285 |
| PI-88 160 mg sc qd | Surgery | III, RC, DB | Target: 500 | NCT01402908 |
| PI-88 160 and 250 mg sc qd for nine 4-week treatment cycles | Surgery | II, RC, OL | 168 | 10.8* (160 mg/day) 5.1* (P = 0.13) |

OLT = orthotopic liver transplant; sc = subcutaneous injection. * Time-to-recurrence at the 36th percentile.
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 updated versions of this article on a regular basis.

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