*Supplementary Appendix*

***Systemic Treatment Options in Hepatocellular Carcinoma***

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**Short Title:** Systemic Treatment Options in Hepatocellular Carcinoma

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Supplementary Table 1**.** Prior phase III trials of systemic treatment regimens in advanced HCC with negative results

| **Study Name/Identifier** | **Patients** | **Interventions** | **Primary Endpoint Results** | **Reference** |
| --- | --- | --- | --- | --- |
| **Phase III Studies in the First-Line Setting** |
| BRISK-FL/ [NCT00858871](https://clinicaltrials.gov/ct2/show/NCT00858871) | Advanced HCC; Child Pugh A; no prior systemic therapy(*N*=1150) | Brivanib vs. sorafenib | Primary endpoint of OS noninferiority was not met (mOS: 9.5 vs. 9.9 months; HR=1.06; 95.8% CI: 0.93–1.22) | Johnson et al. 2013[[1](#_ENREF_1)] |
| [NCT00699374](https://clinicaltrials.gov/ct2/show/NCT00699374) | Locally advanced or metastatic HCC; Child Pugh A; no prior systemic therapy(*N*=1074) | Sunitinib vs. sorafenib | Sunitinib significantly inferior to sorafenib (mOS: 7.9 vs. 10.2 months; HR=1.30; 95% CI: 1.13–1.50; *p*=0.0014) | Cheng et al. 2013 [[2](#_ENREF_2)] |
| [NCT01009593](https://clinicaltrials.gov/ct2/show/NCT01009593) | Advanced HCC; Child Pugh A; no prior systemic therapy(*N*=1035) | Linifanib vs. sorafenib | No difference in OS (mOS: 9.1 vs. 9.8 months; HR=1.046; 95% CI: 0.896–1.221)  | Cainap et al. 2015 [[3](#_ENREF_3)] |
| SEARCH/ [NCT0901901](https://clinicaltrials.gov/ct2/show/NCT00901901) | Advanced HCC; underlying Child Pugh class A cirrhosis; no prior systemic therapy(*N*=720) | Sorafenib plus erlotinib vs. sorafenib plus placebo | No difference in OS (mOS: 9.5 vs. 8.5 months; HR=0.929; 95% CI: 0.78–1.11; *p*=0.408) | Zhu et al. 2015 [[4](#_ENREF_4)] |
| CALGB 80802/ [NCT01015833](https://clinicaltrials.gov/ct2/show/NCT01015833) | Advanced HCC; no prior systemic therapy; Child Pugh A(*N*=346) | Doxorubicin plus sorafenib vs. sorafenib | No difference in OS (mOS: 9.3 vs. 10.5 months; HR=1.06; 95% CI: 0.8–1.4) | Abou-Alfa et al. 2016 [[5](#_ENREF_5)] |
| SARAH/ [NCT01482442](https://clinicaltrials.gov/ct2/show/NCT01482442) | Locally advanced or unresectable HCC or HCC after failed TACE(*N*=467) | Selective internal radiation therapy (SIRT) with yttrium-90 resin microspheres vs. sorafenib | No difference in OS (mOS: 8.0 vs. 9.9 months; HR=1.15; 95% CI: 0.94–1.41; *p*=0.18) | Vilgrain et al. 2017 [[6](#_ENREF_6)] |
| SIRveNIB/ [NCT01135056](https://clinicaltrials.gov/ct2/show/NCT01135056) | Locally advanced HCC; no extrahepatic disease; no prior systemic therapy(*N*=360) | SIRT with yttrium-90 resin microspheres radioembolization vs. sorafenib | No difference in OS (mOS: 8.8 vs. 10.0 months; HR=1.1; 95% CI: 0.9–1.4; *p*=0.36) | Chow et al. 2018 [[7](#_ENREF_7)] |
| **Phase III Studies in the Second-Line Setting** |
| BRISK PS/ [NCT00825955](https://clinicaltrials.gov/ct2/show/NCT00825955)  | Advanced HCC; progressed on/after or were intolerant to sorafenib(*N*=395) | Brivanib + BSC vs. placebo+ BSC | No difference in OS (mOS: 9.4 vs. 8.2 months; HR=0.89; 95.8% CI: 0.69–1.15; *p*=0.3307) | Llovet et al. 2013 [[8](#_ENREF_8)] |
| EVOLVE-1/ NCT01035229 | BCLC stage B or C HCC; progressed on/after or were intolerant to sorafenib(*N*=546) | Everolimus + BSC vs. placebo + BSC | No difference in OS (mOS: 7.6 vs. 7.3 months; HR=1.05; 95% CI: 0.86–1.27; *p*=0.68) | Zhu et al. 2014 [[9](#_ENREF_9)]  |
| REACH/NCT01140347 | BCLC stage B or C; progressed on/after or were intolerant to sorafenib(*N*=565) | Ramucirumab + BSC vs. placebo + BSC | No difference in OS (mOS: 9.2 vs. 7.6 months; HR=0.87; 95% CI: 0.72–1.05; *p*=0.14) | Zhu et al. 2015 [[10](#_ENREF_10)] |
| S-CUBE/JapicCTI-090920 (Japan only trial) | Advanced HCC; progressed on/after or were intolerant to sorafenib(*N*=334) | S-1 (tegafur/gimeracil/oteracil potassium) vs. placebo | No difference in OS (mOS: 11.1 vs. 11.2 months; HR=0.86; 95% CI: 0.67–1.10; *p*=0.220) | Kudo et al. 2017[[11](#_ENREF_11)] |
| METIV-HCC/ NCT01755767 | Advanced HCC with high MET expression; confirmed progression after sorafenib(*N*=340) | Tivantinib vs. placebo | No difference in OS (mOS: 8.4 vs. 9.1 months; HR=0.97; 95% CI: 0.75–1.25; *p*=0.81) | Rimassa et al. 2018 [[12](#_ENREF_12)] |
| JET-HCC/ NCT02029157 | Advanced HCC with high MET expression; progressed on/after or were intolerant to sorafenib(*N*=195) | Tivantinib vs. placebo | No difference in PFS (mPFS: 2.8 vs. 2.3 months; HR=0.72; 95% CI: 0.51–1.02; *p*=0.065) (Japan) | Kobayashi et al. 2017 [[13](#_ENREF_13)]  |
| ADI-PEG 20/ NCT01287585 | Advanced HCC; prior systemic therapy(*N*=635) | ADI-PEG 20 (arginine deiminase formulated with polyethylene glycol) vs. placebo | No difference in OS (mOS: 7.8 vs. 7.4 months; HR=1.02; 95% CI: 0.847–1.233; *p*=0.88) | Abou-Alfa et al. 2018 [[14](#_ENREF_14)]  |

BCLC, Barcelona Clinic Liver Cancer; BSC, best supportive care; CI, confidence interval; HCC, hepatocellular carcinoma; HR, hazard ratio; MET, mesenchymal-epithelial transition; mOS, median overall survival; mPFS, median progression-free survival; OS, overall survival; PFS, progression-free survival.

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