**Supplementary materials**

**Supplementary table S1. Characteristics of the randomized clinical trials from which model data were extracted.**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Trial (reference)** | **Treatments** | **N of patients in each arm** | **Characteristics of includedpatients** | **Median**  **OS (mo.)** | **Median PFS (mo.)** | **Median TTP (mo.)** | **ORR (%)** | **SAEs (%)** |
| **First-line** | | | | | | | |  |
| IMBrave150 (4) | Atezolizumab+Bevacizumab; Sorafenib | 336;165 | Locally advanced or metastatic and/or unresectable HCC; No prior systemic therapy; measurable disease defined by RECIST 1.1; ECOG-PS 0 or 1; Child-Pugh A. Patients with history of autoimmune diseases. coinfection HBV/HCV and untreated esophageal or gastric varices were excluded. | NE;13.2 | 6.8;4.3 | - | 27;12 | 61;60.9 |
| **Second-line** | | | | | | | | |
| SHARP (3) | Sorafenib; Placebo | 299;303 | Advanced and/or unresectable HCC. No prior systemic therapy. At least one untreated target lesion defined by RECIST;Child Pugh A. ECOG PS of 2 or less. | 10.7; 7.9 | - | 5.5; 2.8 | 2;1 | - |
| Asian-Pacific (11) | Sorafenib; Placebo | 150; 76 | Histologically proven advanced hepatocellular carcinoma. No prior systemic therapy. At least one measurable lesion according to RECIST criteria. Child-Pugh A. ECOG PS 2 or less. | 6.5; 4.2 |  | 2.8; 1.4 | 3.3; 1.3 | - |
| Johnson et al. (12) | Sorafenib; Brivanib | 578; 577 | Advanced and unresectable HCC. No prior systemic therapies; at least one untreated measurable lesion. Child- Pugh A; ECOG PS 0- 1 | 9.9; 9.5 | - | 4.1; 4.2 | 9; 12 | 65; 67 |
| SUN1170 (13) | Sorafenib; Sunitinib | 544;530 | Histologically confirmed. locally advanced  or metastatic HCC candidate for systemic anticancer treatment. Child-Pugh A; ECOG-PS 0 or 1 | 10.2; 7.9 | 3.0; 3.6 | 3.8; 4.1 | 6.1; 6.6 | 74.2; 82.1 |
| Cainap et al. (14) | Sorafenib; Linifanib | 521; 514 | Unresectable and/or metastatic HCC. No prior systemic therapy and at least a measurable lesion according to RECIST v1.1; no prior loco regional treatment within 4 weeks before stufy drug administration. Child-Pugh A; ECOG PS 0-1 | 9.8; 9.1 | 2.9;4.2 | 4.0; 5.4 | 6.9; 13 | 75; 85.3 |
| SEARCH (15) | Sorafenib; Sorafenib plus Erlotinib | 358; 362 | Advanced and/or metastatic HCC. At least one measurable lesion according to RECIST criteria. No prior local therapies within 4 weeks before study entry. Child-Pugh A; ECOG PS 0-1. | 8.5; 9.5 | - | 4.0; 3.2 | 3.9 ; 6.6 | 84; 87 |
| REFLECT (16) | Sorafenib; Lenvatinib | 476;478 | Unresectable HCC BCLC B or C; Child-Pugh A; ECOG-PS 0 or 1; one or more measurable  target lesions.  Patients with 50% or higher  liver occupation. invasion of the bile duct. or invasion at the main portal vein and patients previously treated with systemic therapy were excluded. | 12.3;13.6 | 3.7;7.4 | 3.7; 8.9 | 12.4;40.6 | 66.5; 75 |
| RESORCE (5) | Regorafenib; Placebo | 379;194 | HCC BCLC B or C not amenable to curative treatment; Child-Pugh A; ECOG-PS 0 or 1;  documented radiological progression during Sorafenib  treatment; tolerance to Sorafenib (≥400 mg daily for at least 20 of the 28 days before discontinuation); last Sorafenib dose within 10 weeks of randomization.  Patients with previous systemic treatment for HCC or  discontinuation of Sorafenib for toxicity were excluded. | 10.6; 7.8 | 3.1; 1.5 | 3.2; 1.5 | 11; 4 | 79.7; 58.5 |
| CELESTIAL (6) | Cabozantinib; Placebo | 470;237 | HCC not amenable to curative  Treatment; Child-Pugh class A; ECOG-PS 0 or 1 previous treatment with Sorafenib; disease progression after at least one systemic treatments (up to 2) | 10.2; 8.0 | 5.2; 1.9 | - | 4; 1 | 79.4; 48.1 |
| REACH-2 (7) | Ramucirumab; Placebo | 197;95 | BCLC C or B refractory or not amenable to locoregional  therapy; Child-Pugh A ; ECOG-PS 0 or 1; previous treatment with Sorafenib (stopped because of progression or intolerance).Alphafetoprotein levels higher than 400 ng/mL | 8.5;7.3 | 2.8;1.6 | - | 5;1 | NA |
| REACH (18) | Ramucirumab; Placebo | 283;282 | BCLC C or B refractory or not amenable to locoregional  therapy; Child-Pugh A ; ECOG-PS 0 or 1; previous treatment with Sorafenib (stopped because of progression or intolerance). | 9.2; 7.6 | 2.8; 2.1 | 3.5; 2.6 | 7; <1 | 70.4; 54.3 |

HCC.Hepatocellular carcinoma. BCLC.Barcelona Clinic Liver Cancer. PS. Performance status. OS. Overall Survival. PFS. Progression-Free Survival. TTP. Time To Progression. ORR. Objective Response Rate. Mo.. months. SAEs. Severe (grade ≥ 3) adverse events.

**Supplementary Table S2.** Study- and patient-level covariates reported in randomized controlled trials of tyrosine-kinase inhibitors for advanced hepatocellular carcinoma and used for meta-regression analysis.

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Trial (reference)** | **Year of publication** | **Treatment** | **N of patients** | **Median Age (years)** | **Male sex (n,%)** | **Asian ethnicity (n,%)** | **ECOG-PS 1 (n,%)** | **HBV infection (n,%)** | **HCV infection (n,%)** | **Non-viral etiology (n,%)** | **Child-Pugh B (n,%)** | **BCLC C (n,%)** | **ALBI grade 2 (n,%)** | **AFP>400 ng/mL (n,%)** | **Macrovascular invasion (n,%)** | **Extrahepatic**  **spread (n,%)** |
| SHARP (3) | 2008 | Sorafenib | 299 | 64.9 | 260 (87.0) | 0 (0.0) | 128 (42.8) | 56 (18.7) | 87 (29.1) | 156 (52.2) | 14 (4.7) | 244 (81.6) |  | - | 108 (36.1) | 159 (53.2) |
| Asian-Pacific (11) | 2009 | Sorafenib | 150 | 51 | 127 (84.7) | 100 (66.7) | 112 (74.7) | 106 (70.7) | 16 (10.7) | 28 (18.7) | 4 (2.7) | 143 (95.3) |  | - | 54 (36.0) | 103 (68.7) |
| Johnson et al. (12) | 2013 | Sorafenib | 578 | 60 | 484 (83.7) | 372 (64.4) | 226 (39.1) | 258 (44.6) | 119 (20.6) | 120 (20.8) | 47 (8.1) | 449 (77.7) |  | 278 (48.1) | 158 (27.3) | 291 (50.3) |
| SUN1170 (13) | 2013 | Sorafenib | 544 | 59 | 459 (84.4) | 410 (75.4) | 254 (46.7) | 288 (52.9) | 119 (21.9) | 137 (25.2) | 1 (0.2) | 454 (83.5) |  | - | - | - |
| Cainap et al. (14) | 2014 | Sorafenib | 521 | 59 | 444 (85.2) | 339 (65.1) | 191 (36.7) | 275 (52.8) | 130 (25.0) | 109 (20.9) | 30 (5.8) | 433 (83.1) |  | - | 238 (45.7) | 307 (58.9) |
| SEARCH (15) | 2015 | Sorafenib | 358 | 60 | 286 (79.9) | 90 (25.1) | 142 (39.7) | 133 (37.2) | 84 (23.5) | 141 (39.4) | 13 (3.6) | 310 (86.6) |  | - | 153 (42.7) | 219 (61.2) |
| RESORCE (5) | 2016 | Regorafenib | 379 | 64 | 333 (87.9) | 156 (41.2) | 132 (34.8) | 143 (37.7) | 78 (20.6) | 146 (38.5) | 5 (1.3) | 325 (85.8) |  | 162 (42.7) | 110 (29.0) | 265 (69.9) |
| REFLECT (16) | 2018 | Sorafenib | 476 | 62 | 405 (85.1) | 326 (68.5) | 175 (36.8) | 228 (47.9) | 126 (26.5) | 122 (25.6) | 5 (1.1) | 384 (80.7) | 134 (28.15) | - | 90 (18.9) | 295 (62.0) |
| REFLECT (16) | 2018 | Lenvatinib | 478 | 63 | 405 (84.7) | 334 (69.9) | 174 (36.4) | 251 (52.5) | 91 (19.0) | 136 (28.5) | 3 (0.6) | 374 (78.2) | 158 (33.05) | - | 109 (22.8) | 291 (60.9) |
| CELESTIAL (6) | 2018 | Cabozantinib | 470 | 64 | 379 (80.6) | 116 (24.7) | 225 (47.9) | 178 (37.9) | 113 (24.0) | 179 (38.1) | 0 (0.0) | - | 282 (60.0) | 192 (40.9) | 129 (27.4) | 369 (78.5) |
| IMBRAVE 150 (4) | 2020 | Sorafenib | 165 | 66 | 137 (83.0) | 68 (41.2) | 62 (37.6) | 76 (46.1) | 36 (21.8) | 53 (32.1) | 0 (0.0) | 133 (80.6) |  | 61 (37.0) | 71 (43.0) | 93 (56.4) |
| Pooled analysis of REACH and REACH-2 (17) | 2021 | Ramucirumab | 316 | 63 | 246 (77.85) | 162 (51.27) | 143 (45.25) | 124 (39.24) | 83 (26.26) | 140 (44.3) | 126 (39.87) | 286 (90.51) | 176 (55.7) | 316 (100) | 113 (40) | 226 (79) |

ECOG-PS: Eastern Cooperative Oncology Group-Performance status. BCLC: Barcelona Clinic Liver Cancer. AFP: alpha-fetoprotein.

**Supplementary Table S3.** Predictors of overall survival by univariate meta-regression analysis.

|  |  |  |  |
| --- | --- | --- | --- |
|  | Coefficient | 95%Confidence interval | *p*-value |
| Sorafenib RCTs publication year\*  After 2018 | 3.54 | 1.29;5.78 | 0.002 |
| Treatment\*  Lenvatinib  Regorafenib  Cabozantinib  Ramucirumab | 4.34  1.34  0.94  -1.15 | 1.42;7.25  -1.54;4.21  -2.03;3.91  -4.37;2.07 | 0.004  0.36  0.54  0.48 |
| Sex  Male | 0.23 | -0.19;0.65 | 0.28 |
| Ethnicity  Asian | 0.003 | -0.05;0.06 | 0.9 |
| Etiology of liver disease  HBV  HCV  Nonviral | -0.03  0.13  Reference | -0.13;0.07  -0.14;0.39  - | 0.54  0.35  - |
| Child-Pugh  Class B | -0.02 | -0.06;0.01 | 0.19 |
| ALBI  Grade 2 | -0.12 | -0.24;-0.01 | 0.04 |
| BCLC  Stage C | -0.34 | -0.50;-0.18 | <0.001 |
| Patients with AFP > 400 ng/mL | -0.06 | -0.11;-0.001 | 0.05 |
| Presence of macrovascular invasion | -0.09 | -0.24;0.06 | 0.27 |
| Presence of extrahepatic spread | -0.09 | -0.24;0.08 | 0.29 |

\*Reference: Sorafenib trials published before 2018.