Supplemental Tables

Supplemental Table 1. PICOS Criteria for the SLR

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| --- | --- | --- |
|  | **Inclusion Criteria** | **Exclusion Criteria** |
| **P**opulation | Persons (ages ≥ 18 years) with unresectable advanced or metastatic HCC receiving systemic treatment in the 1L setting | Persons with HCC undergoing loco-regional treatment, resection, ablation, or liver transplant |
| **I**ntervention | 1L:Atezolizumab + bevacizumabLenvatinib Nivolumab Sorafenib FOLFOX | 2L:CabozantinibLenvatinibNivolumab ± ipilimumabPembrolizumab RamucirumabRegorafenibSorafenib | Interventions other than those listed |
| **C**omparators | Any, placebo, or none | Not applicable |
| **O**utcomes | Efficacy: mDOR, mOS, mPFS, mTTP, proportion survival at 6, 12, and 24 months; tumor response (DCR and ORR)Safety: Incidence of grade ≥3 adverse events, serious adverse events, adverse events leading to discontinuation | Outcomes other than those listed |
| **S**tudy design | Randomized controlled trials or single arm trials (including dose-finding trials)Systematic reviews (for identification of primary studies only) | Observational studiesCase reports/case seriesNon-systematic reviewsTrials terminated due to clinical efficacy/safety outcomesPost-hoc or pooled analyses of original trial data |
| Publication type | Journal articles indexed in Embase or MEDLINE and published any timeConference abstracts from 2016-2021 from American Society of Clinical Oncology Annual Meeting, Gastrointestinal Cancers Symposium, European Association for the Study of Liver International Liver Congress, European Society for Medical Oncology Congress, European Society for Medical Oncology Asia Congress, and American Association for the Study of Liver Diseases Liver MeetingClinical trial registries with results | NotesEditorialsLettersNewspaper articles |
| Other  | English language | Non-English language |
| Abbreviations: 1L, first line; 2L, second line; DCR, disease control rate; FOLFOX, folinic acid (leucovorin calcium), fluorouracil, and oxaliplatin combination; HCC, hepatocellular carcinoma; mDOR, median duration of response; mOS, median overall survival; mPFS, median progression-free survival; mTTP, median time to progression; ORR, objective response rate; PICOS, population, intervention, comparators, outcomes, study design. |

Supplemental Table 2. Search Strings and Results

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Database** | **Topic** | **Search** | **Search String** | **Results** |
| ProQuest |
| Embase | Population | S1 | TI,AB(“hepatocellular carcinoma”) | 134 116 |
| S2 | EMB.EXACT.EXPLODE("liver cell carcinoma") OR EMB.EXACT.EXPLODE("liver cell carcinoma") | 175 322 |
| S3 | S1 OR S2 | 189 660 |
| Intervention and comparators | S4 | TI,AB(sorafenib OR Nexavar OR lenvatinib OR Lenvima OR regorafenib OR Stivarga OR cabozantinib OR Cabometyx OR Cometriq OR ramucirumab OR Cyramza OR pembrolizumab OR Keytruda OR nivolumab OR Opdivo OR atezolizumab OR Tecentriq OR (oxaliplatin AND fluorouracil AND leucovorin) OR FOLFOX) | 47 472 |
| S5 | EMB.EXACT(sorafenib OR lenvatinib OR regorafenib OR cabozantinib OR ramucirumab OR pembrolizumab OR nivolumab OR atezolizumab) | 67 398 |
| S6 | S4 OR S5 | 75 471 |
| Study design | S7 | TI,AB((clinical NEAR/1 trial\*) OR ((doubl\* OR treb\* OR tripl\*) NEAR/1 (blind[\*3] OR mask[\*3] OR dummy)) OR ((control\* OR equivalence OR superiority OR non-inferiority OR noninferiority OR pragmatic OR practical OR quasiexperimental OR quasi-experimental OR experimental OR phase) NEAR/3 (study OR studies OR trial\* OR group\*)) OR sham OR placebo\* OR random\* OR RCT) | 3 427 416 |
| S8 | EMB.EXACT(“clinical trial” OR “multicenter study” OR "phase 1 clinical trial" OR "phase 2 clinical trial" OR “phase 3 clinical trial” OR “phase 4 clinical trial” OR “double blind procedure” OR “crossover procedure” OR “placebo” OR “control group” OR “prospective study”) OR EMB.EXACT.EXPLODE(“randomization” OR “randomized controlled trial as topic” OR “controlled clinical trial”) | 2 849 494 |
| S9 | S7 OR S8 | 4 770 161 |
| Combined searches | S10 | S3 AND S6 AND S9 | 5834 |
| English language only | S11 | S10 AND LA(English) | 5652 |
| Not conference abstracts | S12 | S11 NOT DTYPE("Conference abstract") | 3765 |
| MEDLINE | Population | S13 | TI,AB(“hepatocellular carcinoma”) | 91 449 |
| S14 | MESH.EXACT.EXPLODE("Carcinoma, Hepatocellular")  | 87 206 |
| S15 | S13 OR S14 | 120 343 |
| Intervention and comparators | S16 | TI,AB(sorafenib OR Nexavar OR lenvatinib OR Lenvima OR regorafenib OR Stivarga OR cabozantinib OR Cabometyx OR Cometriq OR ramucirumab OR Cyramza OR pembrolizumab OR Keytruda OR nivolumab OR Opdivo OR atezolizumab OR Tecentriq OR (oxaliplatin AND fluorouracil AND leucovorin) OR FOLFOX) | 21 911 |
| S17 | MESH.EXACT(Sorafenib OR Nivolumab) | 7900 |
| S18 | S16 OR S17 | 23 210 |
| Study design | S19 | TI,AB((clinical NEAR/1 trial\*) OR ((doubl\* OR treb\* OR tripl\*) NEAR/1 (blind[\*3] OR mask[\*3] OR dummy)) OR ((control\* OR equivalence OR superiority OR non-inferiority OR noninferiority OR pragmatic OR practical OR quasiexperimental OR quasi-experimental OR experimental OR phase) NEAR/3 (study OR studies OR trial\* OR group\*)) OR sham OR placebo\* OR random\* OR RCT) | 2 434 175 |
| S20 | MESH.EXACT(“Randomized Controlled Trials as Topic” OR “Randomized Controlled Trial” OR “Random Allocation” OR “Double Blind Method” OR “Clinical Trial” OR “Placebos”) OR MESH.EXACT.EXPLODE(“Clinical Trials as Topic”) | 586 908 |
| S21 | S19 OR S20 | 2 644 147 |
| Combined searches | S22 | S15 AND S18 AND S21 | 1348 |
| English language only | S23 | S22 AND LA(English) | 1305 |
| Not conference abstracts | S24 | S23 NOT DTYPE("Conference abstract") | 1305 |
| Embase or MEDLINE | Not conference abstracts |  | S12 OR S24 | 3922 |
| Conference abstracts only | S25 | (S11 OR S24) AND DTYPE(“Conference abstract”) AND PD(>2015) | 1033 |
| Conference abstracts of interest |  | Identified manually | 512 |
| Cochrane Library |
|  | Population | #1 | (“Hepatocellular carcinoma”):ti,ab,kw | 4558 |
| #2 | MeSH descriptor: [Carcinoma, Hepatocellular] explode all trees | 1761 |
| Intervention |  | (sorafenib OR Nexavar OR lenvatinib OR Lenvima OR regorafenib OR Stivarga OR cabozantinib OR Cabometyx OR Cometriq OR ramucirumab OR Cyramza OR pembrolizumab OR Keytruda OR nivolumab OR Opdivo OR atezolizumab OR Tecentriq OR (oxaliplatin AND fluorouracil AND leucovorin) OR FOLFOX):ti,ab,kw  | 8833 |
|  | MeSH descriptor: [Sorafenib] explode all trees | 476 |
|  | MeSH descriptor: [Nivolumab] explode all trees | 448 |
| Combined searches |  | (#1 OR #2) AND (#3 OR #4) in Cochrane Reviews, Trials | 1124 |
| Trial Registries |
| Clinicaltrials.gov | Population AND Intervention |  | Hepatocellular carcinoma AND (sorafenib OR Nexavar OR lenvatinib OR Lenvima OR regorafenib OR Stivarga OR cabozantinib OR Cabometyx OR Cometriq OR ramucirumab OR Cyramza OR pembrolizumab OR Keytruda OR nivolumab OR Opdivo OR atezolizumab OR Tecentriq) OR (oxaliplatin AND fluorouracil AND leucovorin) OR FOLFOX) AND Has Results | 73 |
| EU Clinical Trials Register | Population AND Intervention |  | “Hepatocellular carcinoma” AND (sorafenib OR Nexavar OR lenvatinib OR Lenvima OR regorafenib OR Stivarga OR cabozantinib OR Cabometyx OR Cometriq OR ramucirumab OR Cyramza OR pembrolizumab OR Keytruda OR nivolumab OR Opdivo OR atezolizumab OR Tecentriq OR (oxaliplatin AND fluorouracil AND leucovorin) OR FOLFOX) AND Has Results | 43 |

Supplemental Table 3. Extraction Variables

|  |  |
| --- | --- |
| **Category** | **Variables Extracted** |
| Trial characteristics | CitationClinicalTrials.gov NCT numberPublication typeTrial designTrial phaseCountriesTreatment lineBlindingSponsorStart and end date (month, year)Inclusion/exclusion criteriaPrimary and secondary endpointsMinimum age for enrolment |
| Patient characteristics | Treatment arm sample size (N, ITT)Age (mean, median, SE)Sex (n, % males)Proportion from Asia-Pacific region, %Presence of vascular invasion, %Presence of extrahepatic spread, %Presence of ascites, %Presence of portal vein thrombosis, %AFP, % over threshold or mean/medianPrior surgery or loco-regional treatment, type and %Prevalence of comorbidities (hepatitis B, hepatitis C, HIV, alcoholism), %ECOG performance status, %Child-Pugh class, %BCLC disease stage, %TNM disease stage, % |
| Continuous outcomes (i.e., mOS, mPFS, mTTP, mDOT) | Outcome definitionOutcome qualifier (mean or median, if applicable)Timepoint (mean/median/equals, if applicable) ValueError (SE or CI)Within-trial comparison (HR and error) |
| Dichotomous outcomes (i.e., CR, PR, SD, DCR, ORR, TEAEs) | Outcome definitionN (ITT or safety as applicable)n (cases) |
| Abbreviations: AFP, alpha fetoprotein; BCLC, Barcelona Clinic Liver Cancer; CI, confidence interval; CR, complete response; DCR, disease control rate; ECOG, Eastern Cooperative Oncology Group; HIV, human immunodeficiency virus; HR, hazard ratio; ITT, intent to treat; mDOT, median duration of treatment; mOS, median overall survival; mPFS, median progression-free survival; mTTP, median time to progression; NCT, Clinicaltrials.gov identifier; ORR, objective response rate; PR, partial response; SD, stable disease; SE, standard error; TEAE, treatment-emergent adverse events; TNM, tumor-node-metastasis; TRAEs, treatment-related adverse events.  |

Supplemental Table 4. Trials Not Included in the Similarity Assessment (RCT with 1 Comparator Not of Interest)

|  |  |  |  |
| --- | --- | --- | --- |
| **Primary Citation** | **Trial Acronym** | **NCT** | **Interventions** |
| Abdel-Rahman, 2013[45] | NR | NR | Sorafenib Capecitabine |
| Abou-Alfa, 2019[46] | CALGB 80802 | NCT01015833 | Sorafenib Sorafenib + doxorubicin |
| Assenat, 2019[47] | PRODIGE-10 | NCT00941967 | SorafenibSorafenib + gemcitabine + oxaliplatin |
| Bi, 2020[48] | ZGDH3 | NCT02645981 | SorafenibDonafenib |
| Blanc, 2021[49] | PRODIGE-21 | NCT01357486 | SorafenibPravastatinSorafenib + pravastatinBest supportive care |
| Cainap, 2015[50] | M10-963 | NCT01009593 | Sorafenib Linifanib |
| Cheng, 2015[51] | NR | NCT01033240 | Sorafenib Sorafenib + tigatuzumab  |
| Eli Lilly and Co[52] | H9H-MC-JBAS | NCT02178358 | SorafenibGalunisertibSorafenib + galunisertib |
| Haruna, 2017[53] | NR | NR | Sorafenib Sorafenib + vitamin K |
| Jouve, 2019[54] | PRODIGE-11 | NCT01075555 | SorafenibSorafenib + pravastatin |
| Johnson, 2013[55] | BRISK-FL | NCT00858871 | SorafenibBrivanib |
| Koeberle, 2016[56] | NR | NCT01005199 | SorafenibSorafenib + everolimus |
| Lee, 2016[57] | NR | NCT00882869 | Sorafenib Sorafenib + AEG35156 |
| Merck KgaA[58] | NR | NCT01988493 | SorafenibTepotinib |
| Novartis Pharmaceuticals[59] | NR | NCT01232296 | Sorafenib Dovitinib |
| Palmer, 2018[60] | NR | NCT01004003 | Sorafenib Nintedanib |
| Qin, 2013[61] | EACH | NCT00471965 | FOLFOXDoxorubicin |
| Rangegowda, 2016[62] | NR | NCT02259647 | Sorafenib Sorafenib + vitamin K1 |
| Ren, 2020[63] | ORIENT-32 | NCT03794440 | SorafenibSintilimab + bevacizumab biosimilar |
| Ryoo, 2018[64] | NR | NCT01988493 | SorafenibTepotinib |
| SillaJen, Inc[65] | PHOCUS | NCT02562755 | SorafenibSorafenib + Pexa-Vec |
| Tak, 2018[66] | NR | NCT02400788 | Sorafenib Resminostat |
| Thomas, 2018[67] | NR | NCT00881751 | SorafenibBevacizumab + erlotinib |
| Yau, 2019c[68] | NR | NCT02716766 | SorafenibSorafenib + capecitabine + oxaliplatin |
| Yen, 2018[69] | NR | NCT00987935 | SorafenibNintedanib |
| Zhu, 2015[70] | SEARCH | NCT00901901 | Sorafenib Sorafenib + erlotinib |
| Abbreviations: NCT, Clinicaltrials.gov identifier; NR, not reported; RCT, randomized controlled trial. |

Supplemental Table 5. Risk of Bias in 1L Single Arm or Dose-Finding Studies

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Trial Citation (Acronym)** | Abou-Alfa, 2006 (NR)[30] | Furuse, 2008(NR)[31] | Yau, 2009(NR)[32] | Hidaka, 2015(NR)[33] | Ikeda, 2017(NR)[34] | Suzuki, 2018(NR)[35] | Lee, 2020(GO30140)[44] a |
| Representativeness of the exposed cohort  | Unclear | Yes | Yes | Yes | Yes | Yes | Yes |
| Assessment of outcome  | Yes | Unclear | Yes | Unclear | Yes | Unclear | Yes |
| Sufficient length of follow-up  | Nob | Unclear | Unclear | Unclear | Unclear | Unclear | Yes |
| Adequacy of follow up of cohorts  | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Adapted from the Newcastle-Ottawa Scale for nonrandomised cohort studies.[21] Criteria for “selection of the non-exposed cohort”, “ascertainment of exposure”, “demonstration that outcome of interest was not present at start of study,” and “comparability of cohorts on the basics of the design or analysis” are not applicable to any of these trials and therefore not included. Representativeness: “yes” refers to truly or somewhat representative; “no” refers to selected group; “unclear” refers to no description. Assessment of outcome: “yes” refers to independent blind assessment; “no” refers to unblind assessment or written self-report; “unclear” refers to no description. Sufficient follow up: “yes” refers to adequate follow-up time for outcome of interest to occur; “no” refers to inadequate follow-up. Adequacy of follow up cohorts: “yes” refers to complete follow-up or adequate proportion followed unlikely to introduce bias; “no” refers to inadequate proportion followed; “unclear” refers to no statement.a Refers to Group A, the single arm component of the trial.b Median follow up was 3.4 months. |

Supplemental Table 6. Risk of Bias in 1L RCTs

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Trial Number (Acronym)** | Llovet, 2008 (SHARP)[36] | Cheng, 2009 (Sorafenib AP)[37] | Ji, 2014 (NR)[38] | Kudo, 2018 (REFLECT)[39] | Yau, 2019a (CheckMate 459)[40] | Finn, 2020b (IMbrave150)[42] | Lee, 2020 (GO30140)[44]a |
| Was randomisation carried out appropriately? | Yes | Yes | Unclear | Yes | Yes | Yes | Yes |
| Was the concealment of treatment allocation adequate? | Yes | Yes | Unclear | Yes | Yes | Yes | Yes |
| Were the groups similar at the outset of the study in terms of prognostic factors?  | Yes | Yes | Yes | Nob  | Unclearc | Yes | Yes |
| Were the care providers, participants and outcome assessors blind to treatment allocation? | Yes | Yes | No  | No  | No  | No  | No  |
| Were there any unexpected imbalances in drop-outs between groups? | No | Yesd  | No | No | Yese  | Yesf  | No |
| Is there any evidence to suggest that the authors measured more outcomes than they reported? | Unclear | Unclear | Unclear | Unclear | Nog  | Unclear | Unclear |
| Did the analysis include an intention-to-treat analysis? | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| If so, was this appropriate and were appropriate methods used to account for missing data? | Unclear | Unclear | Unclear | Unclear | Unclear | Unclear | Unclear |
| Abbreviations: AE, adverse events; RCT, randomized controlled trial.Adapted from the Centre for Reviews and Dissemination.[20] a Refers to Group F, the RCT component of the trial.b Lenvatinib and sorafenib groups differed in proportions with hepatitis B (19% versus 26%) and α-fetoprotein < 200 ng/mL (53% versus 60%).c Patient and disease characteristics at baseline were not reported.d Of patients assigned to sorafenib (n = 149) and placebo (n = 75), the sorafenib group experienced a higher proportion of patients who discontinued due to AEs (15% versus 9%) and a higher proportion of deaths (8% versus 3%).e Of patients assigned to nivolumab (n = 371) and sorafenib (n = 372), the sorafenib group had a higher proportion of patients who discontinued due to patient request (5% versus 2%) and who withdrew consent (3% versus 1%). f Of patients assigned to atezolizumab + bevacizumab (n = 336) and sorafenib (n = 165), the sorafenib group had a higher proportion of patients who withdrew consent (12% versus 4%).g The protocol is available at the trial registry entry, and all outcomes measured appear to have been reported. |

Supplemental Table 7. Risk of Bias in 2L Single Arm or Dose-Finding Studies

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Trial Citation (Acronym)** | Ikeda, 2016(NR)[71] | Kudo, 2020 (NR)[72] | Bruix, 2013(NR)[73] | Zhu, 2018(KEYNOTE 224)[74] | Feun, 2019(NR)[76] | El-Khoueiry, 2017(CheckMate 040) [83]a | Yau, 2020a(CheckMate 040) [84]b |
| Representativeness of the exposed cohort | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Assessment of outcome | No | No | Unclear | Yes | Unclear | Yes | Yes |
| Sufficient length of follow-up | Unclear | No | Unclear | Yes | Yes | Unclear | Yes |
| Adequacy of follow up of cohorts | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Adapted from the Newcastle-Ottawa Scale for nonrandomised cohort studies.[21] Criteria for “selection of the non-exposed cohort”, “ascertainment of exposure”, “demonstration that outcome of interest was not present at start of study,” and “comparability of cohorts on the basics of the design or analysis” are not applicable to any of these trials and therefore not included.Representativeness: “yes” refers to truly or somewhat representative; “no” refers to selected group; “unclear” refers to no description. Assessment of outcome: “yes” refers to independent blind assessment; “no” refers to investigator assessment; “unclear” refers to no description. Sufficient follow up: “yes” refers to adequate follow-up time for outcome of interest to occur; “no” refers to inadequate follow-up. Adequacy of follow up cohorts: “yes” refers to complete follow-up or adequate proportion followed unlikely to introduce bias; “no” refers to inadequate proportion followed; “unclear” refers to no statement.a Refers to the single arm component of the trial that compares nivolumab monotherapy dosing schedules.b Refers to the single arm component of the trial that compares nivolumab + ipilimumab combination therapy dosing schedules. |

Supplemental Table 8. Risk of Bias in 2L RCTs

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Trial Citation (Acronym)** | Abou-Alfa, 2018 (CELESTIAL)[77] | Zhu, 2015 (REACH)[78] | Bruix, 2017 (RESORCE)[79] | Zhu, 2019 (REACH-2)[80] | Finn, 2020c (KEYNOTE 240)[81] | Yau, 2020b (CheckMate 040)[86]a |
| Was randomisation carried out appropriately? | Yes | Yes | Yes | Yes | Yes | Unclear |
| Was the concealment of treatment allocation adequate? | Yes | Yes | Yes | Yes | Yes | Unclear |
| Were the groups similar at the outset of the study in terms of prognostic factors?  | Yes | Yes | Yes | Nob | Yes | Unclear |
| Were the care providers, participants and outcome assessors blind to treatment allocation? | Yes | Yes | Yes | Yes | Yes | No  |
| Were there any unexpected imbalances in drop-outs between groups? | Yesc | No | Yesd | Yese | Yesf | Unclear |
| Is there any evidence to suggest that the authors measured more outcomes than they reported? | Yesg | Unclear | Unclear | Noh | Unclear | Unclear |
| Did the analysis include an intention-to-treat analysis?  | Yes | Yes | Yes | Yes | Yes | Unclear |
| If so, was this appropriate and were appropriate methods used to account for missing data? | Unclear | Unclear | Unclear | Unclear | Unclear | NA |
| Abbreviations: AE, adverse events; RCT, randomized controlled trial.Adapted from the Centre for Reviews and Dissemination.[20]a Refers to the randomized component of the trial, which was reported in a conference abstract only; most assessments are unclear due to minimal reporting.b Ramucircumab and placebo groups differed in the median α-fetoprotein levels (3920 versus 2741 ng/mL), which authors ascribe as likely due to chance.c Of patients assigned to cabozantinib (n = 470) and placebo (n = 237), the cabozantinib group had a higher proportion who discontinued due to AEs (21% versus 5%).d Of patients assigned to regorafenib (n = 379) and placebo (n = 194), the regorafenib group had a higher proportion of patients who withdrew (7% versus 3%).e Of patients assigned to ramucirumab (n = 197) and placebo (n = 95), the ramucirumab group had a higher proportion of patients who withdrew content (4% versus 1%), discontinued due to AEs (15% versus 7%), or discontinued for other reasons (3% versus 1%).f Of patients assigned to pembrolizumab (n = 278) and placebo (n = 135), the pembrolizumab group had a higher proportion of patients who discontinued due to AEs (17% versus 8%).g The protocol is available at the trial registry entry and lists health-related quality of life measures not identified in the literature search.h The protocol is available at the trial registry entry, and all outcomes measured appear to have been reported. |

Supplemental Table 9. Trial Design

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Drug Class** | **Primary Citation** | **Trial Acronym** | **Study Start-****Completion Dates** | **Blinding** | **Phase** | **Region: Countries** | **Proprotion from Asia-Pacific, %** |
| 1L, single arm |
| TKI | Abou-Alfa, 2006[30] | NR | August 2002-February 2008 | Open label | 2 | Non-AP: Belgium, France, Israel, Italy, United States | 0 |
| Furuse, 2008[31] | NR | April 2004-January 2005 | Open label | 1 | AP: Japan | 100 |
| Yau, 2009[32] | NR | November 2006-January 2008 | Open label | 2 | AP: Hong Kong | 100 |
| Hidaka, 2015[33] | NR | September 2009-June 2013 | Open label | NR | AP: Japan | 100 |
| Ikeda, 2017[34] | NR | July 2009-August 2015 | Open label | 2 | AP: Japan, South Korea | 100 |
| Suzuki, 2018[35] | NR | April 2010-January 2012 | Open label | 2 | AP: Japan | 100 |
| 1L, RCT |
| TKI vs none | Llovet, 2008[36] | SHARP | Mar 2005-November 2008 | Double blind | 3 | Non-AP: Argentina, Australia, Belgium, Brazil, Bulgaria, Canada, Chile, Croatia, France, Germany, Greece, Israel, Italy, Mexico, New Zealand, Peru, Poland, Romania, Russia, Spain, Switzerland, United Kingdom, United States | 0 |
| Cheng, 2009[37] | Sorafenib AP | October 2005-July 2009 | Double blind | 2 | AP: China, South Korea, Taiwan | 100 |
| Ji, 2014[38] | NR | November 2011-May 2013 | Open label | NR | AP: China | 100 |
| TKI vs TKI | Kudo, 2018[39] | REFLECT | March 2013-July 2020 (estimated) | Open label | 3 | Global: Australia, Belgium, Canada, China, France, Germany, Hong Kong, Israel, Italy, Japan, Malaysia, Philippines, Poland, Russia, Singapore, South Korea, Spain, Taiwan, Thailand, United Kingdom, United States | 67 |
| IO vs TKI | Yau, 2019a[40] | CheckMate 459 | November 2015-December 2021 (estimated) | Open label | 3 | Global: Australia, Austria, Belgium, Canada, China, Czech Republic, France, Germany, Hong Kong, Israel, Italy, Japan, Poland, Russia, Singapore, South Korea, Spain, Sweden, Switzerland, Taiwan, United Kingdom, United States | 45 |
| IO + VEGFRI vs TKI | Finn, 2020b[42]  | IMbrave150 | March 2018-June 2022 (estimated) | Open label | 3 | Global: Australia, Canada, China, Czech Republic, France, Germany, Hong Kong, Italy, Japan, Poland, Russia, Singapore, South Korea, Spain, Taiwan, United Kingdom, United States | 41a |
| 1L, single arm and RCT |
| IO + VEGFRI (vs IO) | Lee, 2020[44] | GO30140 | April 2016-September 2021 (estimated) | Open label | 1b | Global: Australia, China, Japan, New Zealand, South Korea, Taiwan, United States | 61a |
| 2L, single arm |
| TKI | Ikeda, 2016[71] | NR | August 2009-November 2011 | Open label | 1 | AP: Japan | 100 |
| Kudo, 2021[72] | NR | August 2018-March 2021 (estimated) | Open label | 2 | AP: Japan | 100 |
| VEGFRI | Bruix, 2013[73] | NR | September 2009-March 2013 | Open label | 2 | Global: Germany, Italy, South Korea, Spain | 28 |
| IO | Zhu, 2018[74] | KEYNOTE 224 | May 2016-May 2021 (estimated) | Open label | 2 | Global: Belgium, Canada, France, Germany, Hong Kong, Italy, Japan, Taiwan, United Kingdom, United States | 13 |
| Feun, 2019[76] | NR | May 2016-November 2022 (estimated) | Open label | 2 | Non-AP: United States | 0 |
| 2L, RCT |
| TKI vs none | Abou-Alfa, 2018[77] | CELESTIAL | September 2013-October 2019 (estimated) | Double blind | 3 | Global: Australia, Belgium, Canada, France, Germany, Hong Kong, Ireland, Italy, Netherlands, New Zealand, Poland, Romania, Singapore, South Korea, Spain, Taiwan, Turkey, United Kingdom, United States | 25 |
| VEGFRI vs none | Zhu, 2015[78] | REACH | October 2010-March 2015 | Double blind | 3 | Global: Australia, Austria, Belgium, Brazil, Bulgaria, Canada, Czech Republic, Finland, France, Germany, Hong Kong, Hungary, Israel, Italy, Japan, Netherlands, Norway, Philippines, Portugal, Romania, South Korea, Spain, Sweden, Switzerland, Taiwan, Thailand, United States | 45 |
| Bruix, 2017[79] | RESORCE | May 2013-July 2019 | Double blind | 3 | Global: Argentina, Australia, Austria, Belgium, Brazil, China, Czech Republic, France, Germany, Hungary, Italy, Japan, Netherlands, Russia, Singapore, South Korea, Spain, Switzerland, Taiwan, United Kingdom, United States | 38 |
| Zhu, 2019[80] | REACH-2 | July 2015-December 2021 (estimated) | Double blind | 3 | Global: Australia, Austria, Belgium, Brazil, Canada, China, Czech Republic, France, Germany, Hong Kong, Israel, Italy, Japan, Poland, South Korea, Spain, Switzerland, Taiwan, United Kingdom, United States | 48 |
| IO vs none | Finn, 2020c[81]  | KEYNOTE 240 | May 2016-June 2021 (estimated) | Double blind | 3 | Global: Canada, China, France, Japan, Russia, South Korea, Taiwan, United States (not provided in registry) | 38 |
| 2L, single arm and RCT |
| IO (vs various) | El-Khoueiry, 2017[83] Yau, 2020a[84]Yau, 2020b[86] | CheckMate 040 | September 2012-April 2022 (estimated) | Open label | 1/2 | Global: Canada, France, Germany, Hong Kong, Italy, Japan, Puerto Rico, Singapore, South Korea, Spain, Taiwan, United Kingdom, United States | NR |
| Abbreviations: 1L, first-line; 2L, second-line; AP, Asia-Pacific; IO, immuno-oncology agent; NR, not reported; RCT, randomized controlled trial; TKI, tyrosine kinase inhibitor; VEGFRI, vascular endothelial growth factor receptor inhibitor.Note: Trials are arranged by 1L or 2L, single arm or RCT, drug class, and publication year.a Refers to Asia excluding Japan. |

Supplemental Table 10. Study Inclusion Criteria, General Disease Characteristics

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Drug Class** | **Primary Citation** | **Trial Name** | **BCLC Stage** | **ECOG Performance Status** | **Child-Pugh Class** | **Loco-regional Treatment a** |
| 1L, single arm |
| TKI | Abou-Alfa, 2006[30] | NR | NR | NR | **A or B** | NR |
| Furuse, 2008[31] | NR | NR | 0 or 1 | **A or B** | None |
| Yau, 2009[32] | NR | NR | NR | NR | NR |
| Hidaka, 2015[33] | NR | NR | 0 or 1 | A | NR |
| Ikeda, 2017[34] | NR | NR | 0 or 1 | A | None |
| Suzuki, 2018[35] | NR | NR | **0, 1, or 2** | **A, B7, or B8** | None |
| 1L, RCT |
| TKI vs none | Llovet, 2008[36] | SHARP | NR | **0, 1, or 2** | A | NR |
| Cheng, 2009[37] | Sorafenib AP | NR | **0, 1, or 2** | A | None |
| Ji, 2014[38] | NR | B or C | **0, 1, or 2** | **B or C** | None |
| Kudo, 2018[39] | REFLECT | B or C | 0 or 1 | A | None |
| IO vs TKI | Yau, 2019a[40] | CheckMate 459 | NR | 0 or 1 | A | None |
| IO + VEGFRI vs TKI | Finn, 2020b[42]  | IMbrave150 | NR | 0 or 1 | A | None |
| 1L, single arm and RCT |
| IO + VEGFRI | Lee, 2020[44] | GO30140 | NR | 0 or 1 | **A or B7** | NR |
| 2L, single arm |
| TKI | Ikeda, 2016[71] | NR | NR | 0 or 1 | NR | NR |
| Kudo, 2021[72] | NR | NR | 0 or 1 | A | None |
| VEGFRI | Bruix, 2013[73] | NR | **A, B, or C** | 0 or 1 | A | None |
| IO | Zhu, 2018[74] | KEYNOTE 224 | B or C | 0 or 1  | A  | NR |
| Feun, 2019[76] | NR | NR | 0 or 1 | **A or B7** | None |
| 2L, RCT |
| TKI vs none | Abou-Alfa, 2018[77] | CELESTIAL | NR | 0 or 1 | A | NR |
| VEGFRI vs none | Zhu, 2015[78] | REACH | B or C | 0 or 1 | A | None |
| Bruix, 2017[79] | RESORCE | B or C | 0 or 1 | A | None |
| Zhu, 2019[80] | REACH-2 | B or C | 0 or 1 | A | None |
| IO vs none | Finn, 2020c[81]  | KEYNOTE 240 | B or C | 0 or 1 | A | None |
| 2L, single arm and RCT |
| IO (vs various) | El-Khoueiry, 2017[83] Yau, 2020a[84]Yau, 2020b[86] | CheckMate 040 | NR | 0 or 1 | Ab | NR |
| Abbreviations: 1L, first-line; 2L, second-line; IO, immuno-oncology agent; NR, not reported; RCT, randomized controlled trial; TKI, tyrosine kinase inhibitor; VEGFRI, vascular endothelial growth factor receptor inhibitor.Note: Trials are arranged by 1L or 2L, single arm or RCT, drug class, and publication year. Bold formatting notes characteristics that differed from majority of trials.a "None" refers to ineligibility and at least 4 weeks since loco-regional treatment was received.b El-Khoueiry, 2017 was A or B7 for the dose-escalation phase and A for the dose-expansion phase. |

Supplemental Table 11. Study Inclusion Criteria, Specific Disease Characteristics

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Drug Class** | **Citation** | **Trial Name** | **Hepatic Encephalopathy** | **Ascites** | **Bleeding** | **Excluded Viral Infections** | **Hepatitis B, %** | **Hepatitis C, %** |
| 1L single arm |
| TKI | Abou-Alfa, 2006[30] | NR | NR | NR | NR | NR; HBV and HCV are allowed | 17 | 48 |
| Furuse, 2008[31] | NR | NR | NR | NR | NR | 7 | 79 |
| Yau, 2009[32] | NR | NR | NR | NR | NR | 90 | 6 |
| Hidaka, 2015[33] | NR | NR | NR | NR | NR | 16 | 62 |
| Ikeda, 2017[34] | NR | NR | None requiring drainage | No hemorrhagic or thrombotic events within 4 weeks of study entry | NR | 33 | 59 |
| Suzuki, 2018[35] | NR | NR | NR | NR | NR | 21 | 48 |
| 1L RCT |
| TKI | Llovet, 2008[36] | SHARP | NR | NR | No clinically significant gastrointestinal bleeding within 30 days of study entry | HIV or clinically serious infections | 19 | 28 |
| Cheng, 2009[37] | NR | NR | NR | No clinically significant gastrointestinal bleeding within 30 days of study entry | HIV or clinically serious infections | 73 | 8 |
| Ji, 2014[38] | NR | NR | NR | NR | NR | 84 | 3 |
| Kudo, 2018[39] | REFLECT | NR | NR | No gastrointestinal bleeding, active hemoptysis, or gastric or esophageal varices requiring interventional treatment (aside from beta-blockers) within 4 weeks of randomization; no bleeding or thrombotic disorders or use of anticoagulants requiring therapeutic INR monitoring | HIV or active infection requiring treatment except for hepatitis | 50 | 23 |
| IO vs TKI | Yau, 2019a[40] | CheckMate 459 | NR | NR | NR | NR | NR | NR |
| IO + VEGFRI vs TKI | Finn, 2020b[42]  | IMbrave150 | No history of encephalopathy allowed | No moderate or severe ascites allowed | No bleeding from esophageal and/or gastric varices within 6 months prior to study treatment initiation; no evidence of bleeding diathesis or significant coagulopathy | Tuberculosis; co-infection of HBC and HCV | 48 | 22 |
| 1L, single arm or RCT |
| IO + VEGFRI (vs IO) | Lee, 2020[44] | GO30140 | None allowed | No moderate or severe ascites allowed | No untreated or incompletely treated varices with bleeding or high risk for bleeding | HBV (acute or chronic), HIV, tuberculosis; any severe infections with 4 weeks or significant infection within 2 weeks of Day 1 | 52 | 23 |
| 2L single arm |
| TKI | Ikeda, 2016[71] | NR | NR | None within 4 weeks of study entry | No hemorrhagic or thrombotic events within 4 weeks of study entry | HIV or other serious infection | 35 | 45 |
| Kudo, 2021[72] | NR | NR | No moderate or severe ascites allowed | No gastric bleeding requiring transfusion/hospitalization within 6 months of study entry | HIV, untreated active HBV or HCV, or other active infection requiring systemic treatment | 21 | 32 |
| VEGFRI | Bruix, 2013[73] | NR | NR | NR | No bleeding risk allowed, including major surgery, traumatic injury, or clinically significant bleeding within 1 month; thromboembolic event within 6 months; no esophageal varices | NR | 39 | 36 |
| IO | Zhu, 2018[74] | KEYNOTE 224 | No history of hepatic encephalopathy in last 6 months | No current clinically apparent ascites | No esophageal or gastric variceal bleeding within 6 months of study entry | HIV, untreated active HBV, co-infection with HBV and HCV | 21 | 25 |
| Feun, 2019[76] | NR | NR | NR | NR | HIV, tuberculosis, or other active infection (HBV or HCV may be allowed) | 17 | 31 |
| 2L RCT |
| VEGFRI vs none | Abou-Alfa, 2018[77] | CELESTIAL | NR | NR | NR | NR | 39 | 24 |
| Zhu, 2015[78] | REACH | No history of or current encephalopathy allowed | None if clinically meaningful | No grade ≥3 gastrointestinal bleeding or any variceal bleeding requiring intervention within 3 months prior to randomization; no esophageal or gastric varices that require intervention or represent high bleeding risk; any patients with history of portal hypertension or variceal bleeding must undergo endoscopy | NR | 36 | 27 |
| Bruix, 2017[79] | RESORCE | NR | None if uncontrolled | No grade ≥3 bleeding within 30 days of randomization; no arterial or venous thrombotic or embolic events, deep vein thrombosis, or pulmonary embolism within 6 months of treatment initiation | No ongoing infection > grade 2; HBV or HCV are allowed if no active replication or no antiviral treatment required, respectively | 38 | 21 |
| Zhu, 2019[80] | REACH-2 | No history of or current encephalopathy allowed | None if clinically meaningful | No grade ≥3 gastrointestinal bleeding or any life-threatening bleeding episode; no esophageal or gastric varices that require intervention or represent high bleeding risk; any patients with history of portal hypertension or prior bleeding must undergo endoscopy | HIV or active/uncontrolled clinically serious infection (chronic viral hepatitis is eligible) | 37 | 26 |
| IO vs none | Finn, 2020c[81]  | KEYNOTE 240 | None within past 6 months | None if clinically apparent | No esophageal or gastric variceal bleeding within 6 months of study entry | No active infection requiring systemic therapy; no co-infection with HBV and HCV | 24 | 16 |
| 2L, single arm or RCT |
| IO (vs various) | El-Khoueiry, 2017[83] Yau, 2020a[84]Yau, 2020b[86] | CheckMate 040 | No history of hepatic encephalopathy allowed | No prior or current clinically significant ascites | NR | NR | NR | NR |
| Abbreviations: 1L, first-line; 2L, second-line; BSC, best supportive care; CTCAE; Common Terminology Criteria for Adverse Events; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IO, immuno-oncology agent; NR, not reported; RCT, randomized controlled trial; TKI, tyrosine kinase inhibitor; VEGFRI, vascular endothelial growth factor receptor inhibitor.Note: Trials are arranged by 1L or 2L, single arm or RCT, drug class, and publication year.  |

Supplemental Table 12. Trial Inclusion Criteria for Second-Line Treatment

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Drug Class** | **Citation** | **Trial Name** | **Prior Systemic Treatment**  | **Prior Immunotherapy** |
| 2L, single arm |
| TKI | Ikeda, 2016[71] | NR | Resistance to standard therapies, including sorafenib | NR |
| Kudo, 2021[72] | NR | Disease progression following prior systemic anticancer therapy | NR |
| VEGFRI | Bruix, 2013[73] | NR | Disease progression or intolerance to sorafenib only | None allowed |
| IO | Zhu, 2018[74] | KEYNOTE 224 | Disease progression or intolerance to sorafenib only | None allowed |
| Feun, 2019[76] | NR | Disease progression, intolerance, or refusal of sorafenib;  | No prior anti-PD-L1 or anti-PD-L2 therapy allowed |
| 2L, RCT |
| TKI vs none | Abou-Alfa, 2018[77] | CELESTIAL | Disease progression following sorafenib and up to 1 other systemic therapy; no prior cabozantinib | NR |
| VEGFRI vs none | Zhu, 2015[78] | REACH | Disease progression or intolerance to sorafenib only | None allowed |
| Bruix, 2017[79] | RESORCE | Disease progression following sorafenib only | None allowed |
| Zhu, 2019[80] | REACH-2 | Disease progression or intolerance to sorafenib only | None allowed |
| IO vs none | Finn, 2020c[81]  | KEYNOTE 240 | Disease progression or intolerance to sorafenib only | None allowed |
| 2L, single arm and RCT |
| IO (vs various) | El-Khoueiry, 2017[83] Yau, 2020a[84]Yau, 2020b[86] | CheckMate 040 | Disease progression or intolerance to at least 1 line of systemic therapy (including sorafenib) | None allowed |
| Abbreviations: 2L, second-line; IO, immuno-oncology agent; NR, not reported; PD-L1, programmed death-ligand 1; PD-L2, programmed death-ligand 2; RCT, randomized controlled trial; TKI, tyrosine kinase inhibitor; VEGFRI, vascular endothelial growth factor receptor inhibitor. |

Supplemental Table 13. Median Time to Progression, Duration of Treatment, and Duration of Response Reporting

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Drug Class** | **Primary Citation** | **Trial Name** | **Intervention(s)** | **mTTP** | **mDOT** | **mDOR** |
| 1L single arm |
| TKI | Abou-Alfa, 2006[30] | NR | Sorafenib | 🗸 |  |  |
| Furuse, 2008[31] | NR | Sorafenib | 🗸 |  |  |
| Yau, 2009[32] | NR | Sorafenib |  | 🗸 |  |
| Hidaka, 2015[33] | NR | Sorafenib |  | 🗸 |  |
| Ikeda, 2017[34] | NR | Lenvatinib | 🗸 | 🗸 |  |
| Suzuki, 2018[35] | NR | Sorafenib |  |  |  |
| IO + VEGFRI | Lee, 2020[44] | GO30140 Group A | Atezolizumab + bevacizumab  | 🗸 |  |  |
| 1L RCT |
| TKI vs none | Llovet, 2008[36] | SHARP | SorafenibPlacebo | 🗸 | 🗸 |  |
| Cheng, 2009[37] | Sorafenib AP | SorafenibPlacebo | 🗸 |  |  |
| Ji, 2014[38] | NR | SorafenibBSC |  |  |  |
| TKI vs TKI | Kudo, 2018[39] | REFLECT | LenvatinibSorafenib | 🗸 | 🗸 |  |
| IO vs TKI | Yau, 2019a[40] | CheckMate 459 | NivolumabSorafenib |  |  |  |
| IO + VEGFRI vs TKI | Finn, 2020b[42]  | IMbrave150 | Atezolizumab + bevacizumabSorafenib |  | 🗸 | 🗸 |
| IO + VEGFRI vs IO | Lee, 2020[44] | GO30140 Group F | Atezolizumab + bevacizumab Atezolizumab  | 🗸 | 🗸 |  |
| 2L single arm |
| TKI | Ikeda, 2016[71] | NR | Lenvatinib |  |  |  |
| Kudo, 2021[72] | NR | Cabozantinib |  | 🗸 |  |
| VEGFRI | Bruix, 2013[73] | NR | Regorafenib | 🗸 | 🗸 | 🗸 |
| IO | El-Khoueiry, 2017[83]  | CheckMate 040 | Nivolumab  | 🗸 |  | 🗸 |
| Zhu, 2018[74] | KEYNOTE 224 | Pembrolizumab | 🗸 | 🗸 | 🗸 |
| Feun, 2019[76] | NR | Pembrolizumab |  |  |  |
| IO + IO | Yau, 2020a[84] | CheckMate 040 | Nivolumab + ipilimumab |  | 🗸 | 🗸 |
| 2L RCT |
| TKI vs none | Abou-Alfa, 2018[77] | CELESTIAL | CabozantinibPlacebo |  | 🗸 |  |
| VEGFRI vs none | Zhu, 2015[78] | REACH | RamucirumabPlacebo | 🗸 | 🗸 |  |
| Bruix, 2017[79] | RESORCE | RegorafenibPlacebo | 🗸 | 🗸 | 🗸 |
| Zhu, 2019[80] | REACH-2 | RamucirumabPlacebo | 🗸 | 🗸 |  |
| IO vs none | Finn, 2020c[81]  | KEYNOTE 240 | PembrolizumabPlacebo | 🗸 | 🗸 | 🗸 |
| IO + VEGFRI vs IO + VEGFRI + IO | Yau, 2020b[86] | CheckMate 040 | Nivolumab + cabozantinibNivolumab + cabozantinib + ipilimumab |  |  |  |
| Abbreviations: 1L, first-line; 2L, second-line; BSC, best supportive care; IO, immuno-oncology agent; mDOR, median duration of response; mDOT, median duration of therapy; mTTP, median time to progression; NR, not reported; RCT, randomized controlled trial; TKI, tyrosine kinase inhibitor; VEGFRI, vascular endothelial growth factor receptor inhibitor.Note: the check mark indicates that data are available for a given trial and outcome.  |