**Supplementary Search String S1**

Search String S1:

(Hepatocellular OR liver) AND (carcinoma OR cancer) AND checkpoint inhibitor*; (Hepatocellular OR liver) AND (carcinoma OR cancer) AND checkpoint blockade; (Hepatocellular OR liver) AND (carcinoma OR cancer) AND Tremelimumab; (Hepatocellular OR liver) AND (carcinoma OR cancer) AND Ipilimumab; (Hepatocellular OR liver) AND (carcinoma OR cancer) AND (Nivolumab OR MDX-1106 OR BMS-936558); (Hepatocellular OR liver) AND (carcinoma OR cancer) AND (Pembrolizumab OR Lambrolizumab OR MK-3475 ); (Hepatocellular OR liver) AND (carcinoma OR cancer) AND (Tislelizumab OR BGB-A317); (Hepatocellular OR liver) AND (carcinoma OR cancer) AND (Camrelizumab OR SHR-1210); (Hepatocellular OR liver) AND (carcinoma OR cancer) AND (Cemiplimab or REGN2810); (Hepatocellular OR liver) AND (carcinoma OR cancer) AND (Spartalizumab OR PDR001); (Hepatocellular OR liver) AND (carcinoma OR cancer) AND (Sintilimab or IBI308); (Hepatocellular OR liver) AND (carcinoma OR cancer) AND (Toripalimab OR JS001); (Hepatocellular OR liver) AND (carcinoma OR cancer) AND AMP-224; (Hepatocellular OR liver) AND (carcinoma OR cancer) AND (Atezolizumab or MSB0010718C); (Hepatocellular OR liver) AND (carcinoma OR cancer) AND (Durvalumab OR MEDI4736); (Hepatocellular OR liver) AND (carcinoma OR cancer) AND (Avelumab OR MSB0010718C); (Hepatocellular OR liver) AND (carcinoma OR cancer) AND (BMS935559 OR MDX-1105). All searches were restricted to publications in English. References lists of related review articles were manually checked for additional studies. In addition, we searched the ASCO and ESMO libraries for relevant conference abstracts.

**Supplementary Table S1.**

Ongoing studies with checkpoint inhibitors in advanced/metastatic hepatocellular carcinoma

| Clinical trial.gov identifier | Treatment | Phase | Line of treatment | Patient characteristics | Number of patients | Primary end points | Estimated study completion |
|---|---|---|---|---|---|---|---|
| **PD-1/PD-L1 inhibitor, monotherapy** | | | | | | | |
| NCT03163992 | **Pembrolizumab** | II | 2. line | Not amenable to curative treatment or locoregional therapy or refractory to locoregional therapy<br>BCLC stage C or B<br>Child-Pugh A<br>Prior sorafenib | 60 | ORR | September 2020, recruiting |
| NCT03419481 | **Pembrolizumab** | II | Refractory | Advanced, not amenable to curative surgery or loco-regional ablation<br>HBV+ | 30 | RR | June 2021, recruiting |
| NCT03062358 (KEYNOTE-394) | **Pembrolizumab** + best supportive care<br>vs | III | 2. line | Not amenable to curative treatment or locoregional therapy or | 450 | OS | June 2021, active, not recruiting |

| Clinical trial.gov identifier | Treatment | Phase | Line of treatment | Patient characteristics | Number of patients | Primary end points | Estimated study completion |
|---|---|---|---|---|---|---|---|
| | Placebo + best supportive care | | | refractory to locoregional therapy<br>BCLC stage B or C<br>Child-Pugh A<br>Prior sorafenib or oxaliplatin-based chemotherapy | | | |
| NCT03419897<br>(RATIONALE-208) | **Tislelizumab** | II | ≥ 2. line | Not amenable for locoregional therapy<br>Child-Pugh A | 228 | ORR | September 2021, active, not recruiting, |
| NCT03412773<br>(RATIONALE-301) | **Tislelizumab**<br>vs<br>Sorafenib | III | 1. line | BCLC C or B<br>Child-Pugh A | 660 | OS | May 2022, recruiting |
| NCT04564313 | **Camrelizumab** | I | ≥ 2. line | Recurrence after liver transplantation<br>Child Pugh A and B7<br>PS 0-2 | 20 | ORR | July 2021, recruiting |

| Clinical trial.gov identifier | Treatment | Phase | Line of treatment | Patient characteristics | Number of patients | Primary end points | Estimated study completion |
|---|---|---|---|---|---|---|---|
| NCT03966209 | **Toripalimab** | I | NA | Recurrence or metastases after transplantation not suitable for local treatment<br>Child-Pugh A<br>Prior sorafenib | 20 | SAE, acute graft rejection rate | April 2021, recruiting |
| NCT03949231 | **Toripalimab**<br>vs<br>**Toripalimab** intrahepatic | III | 1. line | Unresectable/metastatic not amenable for locoregional treatment<br>Child-Pugh A or B7 | 200 | OS | January 2022, recruiting |
| **PD-1/PD-L1 inhibitor in combination with antiangiogenic drugs** | | | | | | | |
| NCT03382886 (NUANCE) | **Nivolumab** + bevacizumab | I | Any | Unresectable or metastatic<br>Child-Pugh A<br>Prior TKI | 12 | AE, MTD | March 2023, recruiting |
| NCT03418922 | **Nivolumab** + lenvatinib | Ib | 1. line | Unresectable, not eligible for resection or local ablation | 30 | DLT, safety<br>ORR | June 2020, active, not recruiting |

| **Clinical trial.gov identifier** | **Treatment** | **Phase** | **Line of treatment** | **Patient characteristics** | **Number of patients** | **Primary end points** | **Estimated study completion** |
|---|---|---|---|---|---|---|---|
| | | | | Child-Pugh A | | | |
| NCT01658878 (CheckMate040) | **Nivolumab**<br>**Nivolumab** + **ipilimumab**<br>**Nivolumab** + cabozantinib<br>**Nivolumab** + **ipilimumab** + cabozantibnib<br>Sorafenib | I/II | Any | Not candidate for locoregional therapy<br>Child-Pugh A + B 7 | 620 | Safety<br>ORR | Active not recruiting, partly published |
| NCT03841201 | **Nivolumab** + lenvatinib | II | 1. line | Unresectable, not eligible for resection or local ablation<br>Child-Pugh A | 50 | ORR, safety | July 2021, recruiting |
| NCT03439891 | **Nivolumab** + sorafenib | II | 1. line | Locally advanced/metastatic<br>Child-Pugh A or B7 | 40 | MTD<br>ORR | May 2020, recruiting |
| NCT04393220 | **Nivolumab**<br>+ bevacizumab | II, randomized | 1. line | Inegible for local treatment | 60 | PFS, OS | April 2021, active, not recruiting |

| Clinical trial.gov identifier | Treatment | Phase | Line of treatment | Patient characteristics | Number of patients | Primary end points | Estimated study completion |
|---|---|---|---|---|---|---|---|
| | Nivolumab<br>Bevacizumab | | | BCLC B or C<br>Child Pugh A | | | |
| NCT03347292 | **Pembrolizumab** + regorafenib | I | 1. line | BCLC stage C or B<br>Child-Pugh A | 40 | TEAE | June 2021, recruiting |
| NCT03211416 | **Pembrolizumab** + sorafenib | I/II | 1. line | Advanced or metastatic<br>Child-Pugh A<br>No prior sorafenib | 27 | ORR | September 2021, recruiting |
| NCT4442581 | **Pembrolizumab** +<br>cabozantinib | II | 1. line | Advanced<br>BCLC stage B or C<br>Child Pugh A | 29 | RR | September 2023, recruiting |
| NCT04696055 | **Pembrolizumab** +<br>regorafenib | II | Any | Unresectable advanced<br>BCLC stage B or C<br>Child Pugh A<br>Prior PD1/PD-L1 inhibitor | 119 | ORR | November 2022, recruiting |

| **Clinical trial.gov identifier** | **Treatment** | **Phase** | **Line of treatment** | **Patient characteristics** | **Number of patients** | **Primary end points** | **Estimated study completion** |
|---|---|---|---|---|---|---|---|
| NCT03713593 (LEAP -002) | Lenvatinib + **pembrolizumab**<br>vs<br>Lenvatinib + placebo | III | 1. line | Not amenable for local therapy or refractory to local therapy<br>BCLC stage B or C<br>Child-Pugh A | 750 | PFS, OS | July 2022, recruiting |
| NCT04401800 | **Tislelizumab** + lenvatinib | II | 1. line | Advanced/ metastatic<br>BCLC B or C<br>Child Pugh A | 66 | ORR | September 2022, recruiting |
| NCT04443309 | **Camrelizumab** + lenvatinib | I/II | 1. line | not suitable for surgical or local therapy<br>BCLC B or C<br>Child Pugh A | 53 | ORR | August 2022, recruiting |
| NCT04014101 | **Camrelizumab +** apatinib (VEGFR2 inhibitor) | II | 1. line | Advanced<br>BCLC stage B or C3<br>Child-Pugh A<br>Prior sorafenib/rivastatin | 40 | ORR | October 2019, recruiting? |

| **Clinical trial.gov identifier** | **Treatment** | **Phase** | **Line of treatment** | **Patient characteristics** | **Number of patients** | **Primary end points** | **Estimated study completion** |
|---|---|---|---|---|---|---|---|
| NCT03463876 | **Camrelizumab +** apatinib (VEGFR2 inhibitor) | II | 1. or 2. line | Advanced<br>BCLC stage B or C<br>Child-Pugh A | 190 | ORR | October 2019, active, not recruiting |
| NCT03793725 | **Camrelizumab +** apatinib (VEGFR2 inhibitor) | II | Any | Unresectable | 30 | R0 resection | January 2020, unknown |
| NCT04523662 | **Camrelizumab** + apatinib + radiotherapy | II | Any | Not suitable for surgical resection or local treatment, patients with lymph or lung metastasis<br>Child Pugh A | 27 | PFS | August 2022, not yet recruiting |
| NCT03764293 | **Camrelizumab +** apatinib (VEGFR2 inhibitor)<br>vs<br>Sorafenib | III | 1. line | Not suitable for local therapy<br>BCLC stage B or C<br>Child-Pugh A | 510 | OS<br>PFS | December 2021, recruiting |
| NCT04618367 | Oxaliplatin + 5 FU intra hepatic + | Not applicable | ?<br>Refused sorafenib | No extrahepatic disease<br>Portal vein tumor thrombus | 30 | PFS | December 2021, recruiting |

| **Clinical trial.gov identifier** | **Treatment** | **Phase** | **Line of treatment** | **Patient characteristics** | **Number of patients** | **Primary end points** | **Estimated study completion** |
|---|---|---|---|---|---|---|---|
| | lenvatinib + **sintilimab** | | | Child Pugh A or B<br>PS 0-2 | | | |
| NCT02988440 | **Spartalizumab** + sorafenib | I | 1. line | Advanced/metastatic not amenable for surgical or locoregional treatment<br>Child-Pugh A | 20 | AE | December 2019, completed |
| NCT04042805 | **Sintilimab** + lenvatinib | II | 1. line | BCLC B not amenable for resection or C<br>Child-Pugh score ≤7 | 566 | ORR | August 2022, not yet recruiting |
| NCT04052152 | **Sintilimab** + anlotinib (VEGFR/EGFR inhibitor) | II | 1. line | BCLC B or C<br>Child-Pugh score ≤7 | 20 | ORR<br>AE | December 2019, recruiting |
| NCT04411706 | **Sintilimab** + apatinib + capecitabine | II | 1.line | BCLC B and C<br>Child Pugh A | 46 | ORR | June 2021, recruiting |
| NCT04718909 | **Sintilimab** + regorafenib<br>vs | II, randomized | 2.line | Unresectable<br>Child Pugh A | 180 | PFS | June 2022, recruiting |

| Clinical trial.gov identifier | Treatment | Phase | Line of treatment | Patient characteristics | Number of patients | Primary end points | Estimated study completion |
|---|---|---|---|---|---|---|---|
| | Regorafenib | | | | | | |
| NCT03794440 | **Sintilimab** + IBI305 (anti-VEGF antibody)<br>Sorafenib | II/III | 1. line | BCLC B or C<br>Child-Pugh score ≤7 | 595 | OS, PFS | December 2022, active not recruiting |
| NCT04503902 | **Toripalimab** + donafenib (multikinase inhibitor) | I/II | Any | Advanced/metastatic<br>Not suitable for surgery | 46 | DLT, ORR | December 2022, not yet recruiting |
| NCT04368078 | **Toripalimab** + lenvatinib | II | 2. line | Advanced<br>BCLC B or C<br>Child Pugh A | 76 | ORR | April 2022, recruiting |
| NCT04605796 | **Toripalimab** + bevacizumab | II | 1. line | BCLC B or C<br>Child Pugh A | 60 | TEAE, ORR | March 2021, recruiting |
| NCT04627363 | Oxaliplatin + 5 FU intrahepatic + **toripalimab** + bevacizumab | II | 1. line | BCLC B or C<br>Child Pugh A or B | 30 | PFS | June 2022, not yet recruiting |

| Clinical trial.gov identifier | Treatment | Phase | Line of treatment | Patient characteristics | Number of patients | Primary end points | Estimated study completion |
|---|---|---|---|---|---|---|---|
| NCT04523493 | **Toripalimab** + lenvatinib<br>vs<br>Lenvatinib | III | 1. line | Advanced<br>BCLC stage B or C<br>Child Pugh A + B7 | 486 | OS, PFS | May 2024, recruiting |
| NCT04723004 | **Toripalimab** + bevacizumab<br>vs<br>Sorafenib | III | 1. line | Unsuitable surgery and local therapy<br>BCLC B or C<br>Child Pugh A | 280 | PFS, OS | August 2022, recruiting |
| NCT04732286 | **Atezolizumab** + bevacizumab | III, b<br>single arm | 1. line | Advanced/metastatic<br>Not amenable to surgery and local therapy | 100 | Discontinuation of atezolizumab due to AE | December 2022, not yet recruiting |
| NCT04487067 (AMETHISTA) | **Atezolizumab** + bevacizumab | III, b<br>single arm | 1. line | Not amenable to surgery and local therapy<br>Child Pugh A | 150 | AE grade 3-5 bleeding | October 2022, recruiting |
| NCT03755791 (COSMIC-312) | **Atezolizumab** + cabozantinib<br>vs<br>Sorafenib | III | 1. line | Not amenable to curative or locoregional therapy<br>BCLC B or C | 740 | PFS, OS | June 2021, recruiting |

| **Clinical trial.gov identifier** | **Treatment** | **Phase** | **Line of treatment** | **Patient characteristics** | **Number of patients** | **Primary end points** | **Estimated study completion** |
|---|---|---|---|---|---|---|---|
| | vs<br>Cabozantinib | | | Child-Pugh A | | | |
| NCT04770896<br>IMbrave251 | **Atezolizumanab** + lenvatinib<br>vs<br>**Atezolizumab** + sorafenib<br>vs<br>Lenvatinib<br>vs<br>Sorafenib | III | Any | Advanced /metastatic<br>Unresectable<br>Child Pugh A<br>Prior atezolizumab + bevacizumab | 554 | OS | September 2024, not yet recruiting |
| NCT03970616 | **Durvalumab** + tivozanib (VEGF inhibitor) | Ib/II | 1. line | Metastatic<br>Child-Pugh A | 42 | TEAE | August 2021, recruiting |
| NCT04443322<br>(DULECT2020-1) | **Durvalumab** + lenvatinib | Single group, not applicable | 1. line | Advanced/metastatic<br>Child Pugh A | 20 | PFS, RFS | December 2021, recruiting |

| **Clinical trial.gov identifier** | **Treatment** | **Phase** | **Line of treatment** | **Patient characteristics** | **Number of patients** | **Primary end points** | **Estimated study completion** |
|---|---|---|---|---|---|---|---|
| NCT03475953 (Regomune) | **Avelumab +** regorafenib | I/II<br>Including other tumor types | 2. line | Advanced/metastatic<br>Child-Pugh A | 362 | RP2D<br>ORR | November 2021, recruiting |
| **PD-1/PD-L1 inhibitor in combination with CTLA-4 inhibitor** | | | | | | | |
| NCT04039607 (CheckMate 9DW) | **Nivolumab + ipilimumab** vs<br>Sorafenib/lenvatinib | III | 1. line | Advanced HCC<br>Child-Pugh 5-6 | 1084 | OS | September 2023, recruiting |
| NCT04401813 | **Sintilimab** + IBI310 (CTLA-4 inhibitor) | I | Refractory | Advanced/metastatic | 47 | AE, ORR | April 2023, recruiting |
| NCT04720716 | **Sintilimab** + IBI310 (CTLA-4 inhibitor)<br>vs<br>Sorafenib | III | 1. line | BCLC B and C<br>Child Pugh A | 490 | OS, ORR | December 2023, recruiting |

| Clinical trial.gov identifier | Treatment | Phase | Line of treatment | Patient characteristics | Number of patients | Primary end points | Estimated study completion |
|---|---|---|---|---|---|---|---|
| NCT03482102 | **Durvalumab + tremelimumab +** radiation | II<br>Including biliary tract cancer | 2. line | Locally advanced/metastatic<br>Child-Pugh A + B7<br>Prior sorafenib | 70 | ORR | October 2021, recruiting |
| NCT02519348 | **Durvaluma**b vs **Tremelimumab** vs **Durvalumab** + **Tremelimumab vs Durvalumab +** bevacizumab | II, randomized | 2. line | Unresectable<br>Child-Pugh A-B7<br>Prior sorafenib | 440 | AE, DLT | December 2019, active, not recruiting |
| NCT03298451 (HIMALAYA) | **Durvalumab** vs **Durvalumab + tremelimumab** vs sorafenib | III | 1. line | Not amenable to local therapy<br>Child-Pugh A | 1310 | OS | March 2020, recruiting |
| **PD-1/PD-L1 inhibitor in combination with other agents** | | | | | | | |
| NCT03059147 | **Nivolumab** + SF1126 (Bromodomain inhibitor) | I | Any | Not candidate for local therapy<br>Child-Pugh A + B7<br>Prior sorafenib | 14 | DLT | October 2022, recruiting |

| Clinical trial.gov identifier | Treatment | Phase | Line of treatment | Patient characteristics | Number of patients | Primary end points | Estimated study completion |
|---|---|---|---|---|---|---|---|
| NCT03893695 | **Nivolumab +**<br>GT90001 (ALK1 antibody) | I | ≥ 2. line | BCLC B or C<br>Child-Pugh A | 20 | DLT | May 2020, active, not recruiting |
| NCT03655613 | **Nivolumab** or CBT501 (PD-1 inhibitor) + CBT-101 (cMet inhibitor) | I/II | Any | Advanced/metastatic<br>Prior sorafenib | 119 | DLT | September 2020, unknown |
| NCT02423343 | **Nivolumab** + galunisertib (Transforming growth factor-beta receptor I kinase inhibitor) | Ib/II | 2. line | Recurrent/refractory<br>Elevated alpha-fetoprotein<br>Child-Pugh A<br>Prior sorafenib | 75 | MTD<br>PFS | Completed |
| NCT02859324 | **Nivolumab** + CC-122 (E3 ligase inhibitor) | I/II | 1–3. line | Unresectable<br>≤ 2 prior systemic therapies | 50 | DLT, AE<br>ORR | Completed |
| NCT02705105 | **Nivolumab** + mogamulizumab (CC chemokine receptor 4 (CCR4) antibody) | I/II | ≥ 2. line | Advanced or metastatic<br>Child-Pugh A | 114 | MTD<br>ORR | Completed |

| Clinical trial.gov identifier | Treatment | Phase | Line of treatment | Patient characteristics | Number of patients | Primary end points | Estimated study completion |
|---|---|---|---|---|---|---|---|
| NCT03695250 | **Nivolumab + BMS-986205 (IOD1 inhibitor)** | I/II | ≤ 2. line | Not amenable for curative treatment<br>Child-Pugh A | 23 | | December 2021, recruiting |
| NCT03897543 | **Nivolumab +**<br>ABX196 (Natural Killer T cell agonist) | I/II | ≥2. line | Not amenable for curative treatment<br>Child-Pugh A | 48 | AE | January 2021, recruiting |
| NCT03071094 | **Nivolumab +** Pexa-Vec (intratumoral oncolytic immunotherapy) | I/II | 1. line | Advanced or metastatic<br>Child-Pugh A | 30 | DLT<br>ORR | October 2019, active not recruiting |
| NCT03781960 | **Nivolumab** + abemaciclib | II | Any | Advanced/metastatic<br>Retinoblastoma expression positive | 27 | ORR | January 2021, suspended (due to COVID-19) |
| NCT04567615 | **Nivolumab**<br>**Nivolumab**<br>+ relatlimab (2 doses) (LAG3 inhibitor) | II, randomized | ≥ 2. line | Advanced/metastatic<br>Child Pugh A | 250 | ORR | September 2023, not yet recruiting |

| Clinical trial.gov identifier | Treatment | Phase | Line of treatment | Patient characteristics | Number of patients | Primary end points | Estimated study completion |
|---|---|---|---|---|---|---|---|
| NCT03647163 | **Pembrolizumab** + VSV-IFNβ-NIS (oncolytic vesicular stomatitis virus) | I<br>Including non-SCLC | Any | Advanced/metastatic<br>Progression on PD-1/PD-L1 therapy | 23 | RR (expansion arm) | November 2020, recruiting |
| NCT03259867 | **Pembrolizumab** + transarterial tirazamine embolization | II Including colorectal cancer | 2. line | Advanced/metastatic<br>BCLC stage C<br>Child-Pugh score 5-7<br>Prior sorafenib | 20 | RR | December 2021, recruiting |
| NCT03519997 | **Pembrolizumab** + bivatuzumab (Anti-CD44 antibody) | II | 1. line | Advanced or metastatic, not amenable to curative treatment or locoregional therapy<br>Child-Pugh A | 34 | ORR | April 2021, recruiting |
| NCT02940496 | **Pembrolizumab** + Elbasvir/Grazoprevir | II | 2. line | Advanced with no curative option<br>Child-Pugh A | 30 | DLT | December 2021, active, not recruiting |
| NCT03836352 | **Pembrolizumab** + DPX-survivac + low dose cyclophosphamide | II | Refractory | Advanced/metastatic<br>Expression of survirin | 232 | Disease progression | December 2022, recruiting |

| **Clinical trial.gov identifier** | **Treatment** | **Phase** | **Line of treatment** | **Patient characteristics** | **Number of patients** | **Primary end points** | **Estimated study completion** |
|---|---|---|---|---|---|---|---|
| | | Including other tumor types | | | | | |
| NCT03605706 | **Camrelizumab** + FOLFOX<br>FOLFOX<br>Sorafenib | III | 1. line | Advanced/metastatic<br>Child-Pugh A or B7 | 448 | OS | February 2021, recruiting |
| NCT02795429 | **Spartalizumab** + INC280 (MET inhibitor)<br>**Spartalizumab** | I/II | 2. line | Recurrent or metastatic<br>Child-Pugh A<br>Prior sorafenib | 87 | DLT, MTD<br>ORR | December 2019, active, not recruiting |
| NCT04337463 | **Toripalimab + ATG-008** | Not applicable (+ solid tumor) | Refractory | BCLC B and C<br>Child Pugh A or B7 | 38 | MTD, RP2D, ORR | March 2021, recruiting |
| NCT04612504 | **Atezolizumab** + SynOV1 (Recombinant Oncolytic Adenovirus) | I/IIa | Refractory | Locally advanced or metastatic<br>AFP positive | 45 | DLT, MTD, RR | August 2023, not yet recruiting |

| Clinical trial.gov identifier | Treatment | Phase | Line of treatment | Patient characteristics | Number of patients | Primary end points | Estimated study completion |
|---|---|---|---|---|---|---|---|
| NCT03257761 | **Durvalumab** + guadecitabine (hypomethylating drug) | I<br>Including pancreatic bile duct and gallbladder cancer | 2. line | Not amenable to potentially curative resection, local treatment<br>Child-Pugh score ≤ 7<br>Prior sorafenib | 90 | DLT, RR | February 2021, recruiting |
| NCT03099109 | **LY3321367 (anti-TIM-3) +/- lodapolimab** | I | Refractory | Solid tumor | 275 | DLT | December 2019, active not recruiting |
| **PD-1/PD-L1 in combination with other treatment strategies** | | | | | | | |
| NCT04611165 | **Nivolumab** + external beam radiation | II | 1.or 2. line | Presence of major vascular invasion on dynamic CT or dynamic MRI<br>Child Pugh A | 50 | PFS | June 2022, recruiting |
| NCT04652440 | **Tislelizumab** + RFA | I/II | 1. line | Indication for RFA<br>BCLC B and C<br>Child Pugh A | 30 | Safety | December 2021, recruiting |

| **Clinical trial.gov identifier** | **Treatment** | **Phase** | **Line of treatment** | **Patient characteristics** | **Number of patients** | **Primary end points** | **Estimated study completion** |
|---|---|---|---|---|---|---|---|
| NCT04483284 | **Camrelizumab** + TACE | II | Any | Unable or unwilling to undergo surgical treatment<br>BCLC B and C<br>Child Pugh A- B7 | 60 | PFS | December 2020, recruiting? |
| NCT04724226 | Cryoablation → **Camrelizumab** + apatinib | II | ≤ 2. line | Advanced/metastatic<br>BCLC C<br>Child Pugh A | 34 | ORR | December 2021, not yet recruiting |
| NCT04592029 | **Sintilimab** + bevacizumab + TACE | I | 1.line | BCLC B and C<br>Child Pugh A-B7 | 36 | AE, PFS | June 2022, recruiting |
| NCT04599790 | **Sintilimab** + lenvatinib + TACE | II | 1.line | Advanced<br>BCLC C<br>Child Pugh A-B7 | 30 | OS | September 2022, recruiting |
| NCT03857815 | SBRT + **Sintilimab** | II | 1. line | Inoperable or unresectable | 30 | PFS | September 2020, recruiting |

| **Clinical trial.gov identifier** | **Treatment** | **Phase** | **Line of treatment** | **Patient characteristics** | **Number of patients** | **Primary end points** | **Estimated study completion** |
|---|---|---|---|---|---|---|---|
| NCT04547452 | **Sintilimab** + stereotatic body radiation (SBRT) | II | 2. line | Ineligible for curative intent therapy with surgical resection or liver<br>transplantation<br>Child Pugh A | 84 | PFS 24 weeks | July 2022, recruiting |
| NCT03864211 | **Toripalimab**<br>Thermal ablation → **Toripalimab** | I/II (randomized) | Any | Ineligible for curative therapy<br>One lesion suitable for ablation<br>Prior PD-1/PD-L1 inhibitor<br>Extrahepatic disease allowed<br>Child-Pugh A or B7 | 120 | AE<br>ORR | March 2021, recruiting |
| NCT04709380 | Radiotherapy + **toripalimab**<br>vs<br>Sorafenib | III | Any | Advanced<br>BCLC C<br>Portal vein tumor thrombosis | 85 | TTP | January 2022, not yet recruiting |

| Clinical trial.gov identifier | Treatment | Phase | Line of treatment | Patient characteristics | Number of patients | Primary end points | Estimated study completion |
|---|---|---|---|---|---|---|---|
| | | | | Child Pugh A-B7 | | | |
| NCT04430452 | Hypofractioned radiotherapy → **durvalumab + tremelimumab** | II | Any, | Advanced or metastatic; clinical indication for radiotherapy to any site<br>Child Pugh A - B7 | 30 | ORR | November 2022, not yet recruiting |

AE, adverse event; AEsi, adverse event of special interest; DLT, dose-limiting toxicity; BCLC, Barcelona Clinic liver cancer stage; MTD, maximum tolerated dose; RFS, recurrence-free survival; RR, response rate; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; RFA, radiofrequency ablation; RP2D, recommended phase II dose; SAE, serious adverse event; TEAE, treatment emergent adverse event; TTP, time to progression; vs, versus.

**Supplementary Table S2.**

Ongoing studies with checkpoint inhibitors in locally advanced hepatocellular carcinoma

| Clinical trial.gov identifier | Treatment | Phase | Line of treatment | Patient characteristics | Number of patients | Primary end points | Estimated study completion |
|---|---|---|---|---|---|---|---|
| **PD-1/PD-L1 monotherapy** | | | | | | | |
| NCT03916627 | **Cemiplimab** | II (includes other cancer cohorts) | Any | Determined to be candidate for resection | 94 | Significant tumor necrosis | June 2020, recruiting |
| **PD-1/PD-L1 in combination with local treatment** | | | | | | | |
| NCT02837029 | **Nivolumab** + Yttrium Y90-glass microspheres | I/Ib | Any | Advanced, not amenable to transplant or resection<br>Child-Pugh ≤ B8 | 35 | MTD | July 2019, active, not recruiting |
| NCT03143270 | **Nivolumab +** debTACE | I | 1. line | Locally advanced, not eligible for surgical resection or liver transplant<br>Child-Pugh A | 14 | AE | April 2022, recruiting |
| NCT03099564 | **Pembrolizumab** + Y90-radioembolization | I | 1. line | Locally advanced, not eligible for surgical resection or liver transplant<br>Child-Pugh ≤ B7 | 30 | PFS | July 2021, recruiting |

| **Clinical trial.gov identifier** | **Treatment** | **Phase** | **Line of treatment** | **Patient characteristics** | **Number of patients** | **Primary end points** | **Estimated study completion** |
|---|---|---|---|---|---|---|---|
| | | | | Limited extrahepatic disease allowed<br>No prior TAE or TACE | | | |
| NCT03380130 (NASIR-HCC) | Yttrium Y90-glass microspheres → **nivolumab** | II | Any | Inoperable, candidate for local therapy<br>Child-Pugh A<br>No extrahepatic disease | 40 | AE | Completed |
| NCT03572582 (IMMUTACE) | **Nivolumab** + TACE | II | 1. line | Not eligible for resection or local ablation<br>Child-Pugh A | 49 | ORR | December 2021, recruiting |
| NCT04340193 | **Nivolumab + ipilimumab** + TACE<br>vs<br>**Nivolumab** + placebo +TACE | III | Not specified | Eligible for TACE | 765 | PFS, OS | February 2026, recruiting |

| **Clinical trial.gov identifier** | **Treatment** | **Phase** | **Line of treatment** | **Patient characteristics** | **Number of patients** | **Primary end points** | **Estimated study completion** |
|---|---|---|---|---|---|---|---|
| | vs<br><br>Placebo + TACE | | | | | | |
| NCT03397654 (PETAL1) | TACE → **pembrolizumab** | I/II | 1. line | Ineligible surgical resection or liver transplantation<br><br>Child-Pugh score < 7<br><br>No extrahepatic metastasis | 26 | TEAE | December 2021, recruiting |
| NCT03753659 (IMMULAB) | **Pembrolizumab** + RFA/MWA | II | 1. line | Candidate for local ablation<br><br>Child-Pugh score ≤ 6 | 30 | ORR | March 2022, recruiting |
| NCT03316872 | **Pembrolizumab** + SBRT | II | 2. line | Intrahepatic HCC amenable to SBRT<br><br>Child-Pugh A<br><br>Prior sorafenib | 30 | ORR | November 2022, recruiting |
| NCT04652492 | **Tislelizumab** + TACE | II | 1. line | BCLC C<br><br>Suitable for TACE<br><br>Child Pugh A- B7 | 72 | TTP | November 2022, recruiting |

| Clinical trial.gov identifier | Treatment | Phase | Line of treatment | Patient characteristics | Number of patients | Primary end points | Estimated study completion |
|---|---|---|---|---|---|---|---|
| NCT04663035 | **Tislelizumab** + ablation<br>vs<br>Ablation | II, randomized | Any | Recurrent lesions within 3 to 12 months | 120 | RFS, 1 year | December 2023, recruiting |
| NCT04517227 | TACE or ablation → **durvalumab** | Pilot | Any | Not amenable for surgery or transplantation<br>Suitable for ablation<br>BCLC B<br>Child Pugh A-B7 | 30 | AE, SAE, AEsi, discontinuation rate | August 2024, not yet recruiting |
| **PD-1/PD-L1 in combination with angiogenic drugs and local therapy** | | | | | | | |
| NCT04559607 | TACE + **camrelizumab** + apatinib<br>vs<br>TACE | Not applicable, randomized | 1. line | China liver cancer stage IIb-IIIa<br>Child Pugh A | 188 | PFS | September 2021, recruiting |
| NCT04479527 | **Camrelizumab** + apatinib (VEGFR2 inhibitor) + TACE + FOLFOX | II | Any | Advanced<br>Surgical resection or local ablation is impossible | 34 | PFS | August 2023, not yet recruiting |

| Clinical trial.gov identifier | Treatment | Phase | Line of treatment | Patient characteristics | Number of patients | Primary end points | Estimated study completion |
|---|---|---|---|---|---|---|---|
| | | | | Child Pugh A- B7 | | | |
| NCT04599777 | **Tislelizumab** + sorafenib + TACE | II | 1. line | Advanced<br>Not amenable to curative therapies Amenable to TACE<br>Child Pugh A- B7 | 30 | OS | September 2022, recruiting |
| NCT04541173 | Y-90 TARE + **atezolizumab** + bevacizumab<br>vs<br>Y-90 TARE | II, randomized | 1. line | Not amenable to transplantation or resection At least BCLC B<br>No extrahepatic disease | 128 | PFS | November 2021, recruiting |
| NCT04727307 | **Atezolizumab** → RFA → **atezolizumab** + bevacizumab<br>vs<br>RFA | II, randomized | 1. line | Eligible for ablation<br>No extrahepatic disease<br>Child Pugh A | 202 | RFS | January 2025, recruiting |
| NCT04712643 | **Atezolizumab** + bevacizumab + TACE (on demand) | III | 1. line | Eligible for TACE<br>No extrahepatic disease | 342 | "TACE PFS", OS | February 2025, recruiting |

| Clinical trial.gov identifier | Treatment | Phase | Line of treatment | Patient characteristics | Number of patients | Primary end points | Estimated study completion |
|---|---|---|---|---|---|---|---|
| | vs<br><br>TACE (on demand) | | | Child Pugh A | | | |
| NCT03778957 (EMERALD-1) | TACE + **Durvalumab** + placebo vs<br><br>TACE + **durvalumab** + Bevacizumab vs<br><br>**TACE** + placebo | III | Any | Not amenable for resection, transplantation, curative ablation<br><br>Amenable for TACE<br><br>No extrahepatic disease<br><br>Child-Pugh A + B7 | 600 | PFS | September 2022, recruiting |
| **PD-1/PD-L1 in combination with CTLA-4 inhibitor and local therapy** | | | | | | | |
| NCT03203304 | **Nivolumab** + **ipilimumab** + SBRT<br><br>**Nivolumab** + SBRT | I | Any | Ineligible for curative intent therapy with surgical resection or liver transplantation<br><br>Child-Pugh A<br><br>Extrahepatic disease allowed | 50 | ORR | August 2020, recruiting |

| **Clinical trial.gov identifier** | **Treatment** | **Phase** | **Line of treatment** | **Patient characteristics** | **Number of patients** | **Primary end points** | **Estimated study completion** |
|---|---|---|---|---|---|---|---|
| NCT04472767 | **Nivolumab + ipilimumab +** cabozantinib + TACE | II | 1. line | Not candidate for resection or transplantation<br>No extrahepatic disease<br>Child Pugh A orB7<br>PS 0-2 | 35 | PFS at 6 months | March 2022, recruiting |
| NCT04605731 | Radioembolization → **durvalumab + tremelimumab** | Ib | Any | Unresectable, locally advanced<br>No extra-hepatic disease<br>Child Pugh A | 32 | AE, DLT, ORR | October 2024, not yet recruiting |
| NCT03638141 | **Durvalumab + tremelimumab** → TACE<br>**Tremelimumab** → TACE | II (parallel assignment) | 1. line | "Have disease that responds to TACE" | 30 | ORR | November 2023, recruiting |
| NCT04522544 (IMMUWIN) | **Durvalumab + tremelimumab** + Y-90 SIRT<br>**Durvalumab + tremelimumab** + TACE | II, randomized | 1. line | Not eligible for resection or local ablation<br>Child Pugh A | 84 | ORR | March 2024, recruiting |

AE, adverse event; BCLC, Barcelona Clinic liver cancer stage; deb-TACE, drug eluting bead transarterial chemoembolization; DLT, dose-limiting toxicity; MWA, microwave ablation; NA, not applicable; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; RFA, radiofrequency ablation; RFS recurrence-free survival; RR, response rate; SBRT, stereotactic body radiation; SIRT, selective internal radiation therapy; TACE, transarterial chemoembolization, TAE, transarterial embolization; TARE, transarterial radioembolization; TEAE, treatment emergent adverse event; vs, versus.

**Supplementary Table S3.**

Ongoing studies with checkpoint inhibitors in hepatocellular carcinoma in the preoperative or adjuvant setting

| Clinical trial.gov identifier | Treatment | Phase | Line of treatment | Patient characteristics | Number of patients | Primary end points | Estimated study completion |
|---|---|---|---|---|---|---|---|
| **Preoperative setting, eligible for surgical resection** | | | | | | | |
| NCT03812562 | Yttrium Y90-glass microspheres → **nivolumab** → resection | I | | Eligible for resection<br>Child-Pugh ≤ B8 | 12 | Recurrence rate | June 2021, recruiting |
| NCT03299946 | **Nivolumab** + cabozantinib → resection | I | | Locally advanced, borderline resectable<br>Adequate liver remnant and function | 15 | AE | December 2021, recruiting |
| NCT04658147 | **Nivolumab**<br>**Nivolumab**<br>+ relatlimab (LAG3 inhibitor) | I, randomized | Preoperatively | Technically resectable<br>No extrahepatic spread, no nodal disease, and no bilateral left | 20 | No patients completing treatment and proceed to surgery | April 2025, not yet recruiting |

| Clinical trial.gov identifier | Treatment | Phase | Line of treatment | Patient characteristics | Number of patients | Primary end points | Estimated study completion |
|---|---|---|---|---|---|---|---|
| | | | | and right branch portal vein involvement | | | |
| NCT03682276 (PRIME-HCC) | **Nivolumab + ipilimumab** → resection | I/II | | Planned liver resection<br>No extrahepatic disease<br>Child-Pugh A | 32 | Delay of surgery, TEAE | December 2020, recruiting |
| NCT03630640 | **Nivolumab** → electroporation → **nivolumab** | II | - | Eligible for electroporation<br>Child-Pugh A | 50 | Local recurrence free survival (2 years) | September 2020, recruiting |
| NCT03510871 | **Nivolumab**<br>**Nivolumab + ipilimumab** | II, randomized | Prior treatment allowed | Potential for resection<br>Child-Pugh A | 45 | AE | September 2022, recruiting |
| NCT03222076 | **Nivolumab**<br>**Nivolumab + ipilimumab** | II, randomized | Potential for resection<br>Child-Pugh A | Potential for resection<br>Child-Pugh A | 30 | AE | September 2022, active, not recruiting |
| NCT04425226 (PLENTY202001) | **Pembrolizumab +**<br>Lenvatinib<br>vs | Not applicable | Neoadjuvant<br>No prior systemic therapy | Exceeding Milan criteria before liver transplant | 192 | RFS | December 2022, recruiting |

| Clinical trial.gov identifier | Treatment | Phase | Line of treatment | Patient characteristics | Number of patients | Primary end points | Estimated study completion |
|---|---|---|---|---|---|---|---|
| | No intervention | | | Child Pugh A-B7 | | | |
| NCT04701060 | **Camrelizumab** + apatinib (VEGFR2 inhibitor) | II | Perioperative | Indication for resection<br>Child Pugh A | 30 | Safety, rate of enrollment (feasibility) | January 2022, not yet recruiting |
| NCT 03869034 | **Sintilimab** + FOLFOX (transarterial infusion) | II | | Locally advanced, potentially resectable<br>KPS ≥90<br>Child-Pugh A | 40 | PFS | March 2020, active, not recruiting |
| NCT04721132 | **Atezolizumab** + bevacizumab → surgery | II | Preoperative | Resectable disease with no evidence of extrahepatic spread<br>Child Pugh A | 30 | Safety<br>Pathological response rate | December 2022, not yet recruiting |
| **Adjuvant setting** | | | | | | | |
| NCT03383458 (CheckMate 9DX) | **Nivolumab**<br>**Placebo** | III | | Curative hepatic resection or ablation<br>Child-Pugh score 5 or 6 | 530 | RFS | April 2022, recruiting |

| Clinical trial.gov identifier | Treatment | Phase | Line of treatment | Patient characteristics | Number of patients | Primary end points | Estimated study completion |
|---|---|---|---|---|---|---|---|
| NCT03337841 (AURORA) | **Pembrolizumab** | II | Neoadjuvant + adjuvant (until progression) | Radical cure possible by resection or RFA<br>Child-Pugh A | 50 | 1-year RFS | October 2020, unknown |
| NCT03867084 (KEYNOTE-937) | **Pembrolizumab** vs<br>Placebo | III | | Confirmed complete surgical resection or local ablation<br>Child-Pugh score 5-6 | 950 | RFS<br>OS | July 2025, recruiting |
| NCT03722875 | **Camrelizumab +** apatinib (VEGFR2 inhibitor) | Single arm, pilot | | Complete surgical resection<br>BCLC stage B or C, no extrahepatic disease prior to resection<br>Child-Pugh A | 45 | RFS<br>OS | March 2019, unknown |

| Clinical trial.gov identifier | Treatment | Phase | Line of treatment | Patient characteristics | Number of patients | Primary end points | Estimated study completion |
|---|---|---|---|---|---|---|---|
| NCT03839550 | **Camrelizumab +** apatinib (VEGFR2 inhibitor) vs<br>Epirubicn + oxaliplatin intrahepatic | II, randomized | | Complete response after surgical resection<br>Child-Pugh A | 200 | RFS | February 2020?, not yet recruiting |
| NCT03914352 | **Camrelizumab +** portal vein thrombus<br>PD-l antibody + portal vein thrombus | Parallel assignment, randomized | | No intra- or extrahepatic recurrence<br>Child-Pugh A or B | 40 | OS<br>DFS | December 2019?, recruiting |
| NCT04639180 | **Camrelizumab** + apatinib<br>vs<br>Active surveillance | III | No prior treatment | Undergone a curative resection or ablation<br>No extrahepatic spread<br>Child Pugh A | 674 | RFS | July 2024, not yet recruiting |

| **Clinical trial.gov identifier** | **Treatment** | **Phase** | **Line of treatment** | **Patient characteristics** | **Number of patients** | **Primary end points** | **Estimated study completion** |
|---|---|---|---|---|---|---|---|
| NCT04653389 | **Sintilimab** + TACE +/- radiotherapy → surgery → **sintilimab** | II | Neoadjuvant and adjuvant<br>No prior therapy | Technically resectable<br>Child Pugh A-B7 | 30 | Event free survival | December 2022, recruiting |
| NCT04682210 | **Sintilimab** + bevacizumab<br>vs<br>Active surveillance | III | | Curative resection, high risk of recurrence | 246 | RFS | December 2023, not yet recruiting |
| NCT03859128 | **Toripalimab**<br>vs<br>Placebo | II, III | | No residual tumor<br>Child-Pugh A | 402 | RFS | October 2022, recruiting |
| NCT04649489 | **Surgery → atezolizumab** + bevacizumab<br>**Atezolizumab** + bevacizumab | ? randomized | No prior treatment | Feasibility for curative hepatic resection Portal vein tumor thrombosis<br>Child Pugh A | 198 | Time to treatment failure | September 2022, not yet recruiting |

| Clinical trial.gov identifier | Treatment | Phase | Line of treatment | Patient characteristics | Number of patients | Primary end points | Estimated study completion |
|---|---|---|---|---|---|---|---|
| NCT04102098 (IMBrave 050) | **Atezolizumab + bevazicumab**<br>vs<br>Active surveillance | III | | No residual tumor after surgical resection or ablation<br>Child-Pugh A<br>High risk of recurrence | 662 | RFS | March 2023, recruiting |
| NCT03847428 (EMERALD-2) | **Durvalumab +** bevacizumab vs<br>**Durvalumab +**<br>Placebo vs<br>Placebo + placebo | III | | Completed curative therapy (resection or ablation)<br>Child-Pugh score 5 or 6 | 888 | RFS | June 2022, recruiting |

AE, adverse event; DFS, disease-free survival; OS, overall survival; RFS, recurrence-free survival; TEAE, treatment emergent adverse event; vs, versus.