Supplementary Table 1. Best objective response evaluated by RECIST1.1 in different Child-Pugh class and tumor risk subgroups

| Parameter, n(%) | Child-Pugh class | Tumor risk |  |
|-----------------|------------------|------------|---|
|                 | Child A (n=51)   | Child B (n=20) | p Value | Low-risk tumors (n=43) | High-risk tumors (n=28) | p Value |
| CR              | 1(2)             | 0(0)       | 1.000   | 1(2.3)                  | 0(0)                    | 1.000   |
| PR              | 14(27.5)         | 5(25)      | 0.834   | 12(27.9)                | 7(25)                   | 0.787   |
| SD              | 26(51)           | 10(50)     | 0.941   | 19(44.2)                | 17(60.7)                | 0.173   |
| PD              | 10(19.6)         | 5(25)      | 1.000   | 11(25.6)                | 4(14.3)                 | 0.181   |
| ORR             | 15(29.4)         | 5(25)      | 0.710   | 13(30.2)                | 7(25)                   | 0.632   |
| DCR             | 41(80.4)         | 15(75)     | 0.748   | 32(74.4)                | 24(85.7)                | 0.254   |

CR, complete response; DCR, disease control rate; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.
## Supplementary Table 2. Treatment related adverse events

| Symptom, n(%)                          | Any grade                          | Grade 3 or 4                      |           |
|----------------------------------------|-------------------------------------|----------------------------------|-----------|
|                                        | All patients                        | Systemic therapy-experienced     |           |
|                                        | (n=71)                              | (n=44)                           | (n=27)    |           |
|                                        | First-line setting                  | First-line setting               |           |
|                                        |                                    |                                  |           |
| Fatigue                                | 40(56.3)                            | 15(55.6)                         | 1(1.4)    |
|                                        | 25(56.8)                            | 10(37)                           | 1(2.3)    |
|                                        |                                     |                                  | 0(0)      |
|                                        | 0.917                               |                                  |           |
| Hypertension                           | 35(49.3)                            | 9(33.3)                          | 1(1.4)    |
|                                        | 25(56.8)                            | 10(37)                           | 1(2.3)    |
|                                        |                                     |                                  | 0(0)      |
|                                        | 0.106                               |                                  |           |
| Palmar-plantar syndrome                 | 33(46.5)                            |                                  |           |
|                                        | 24(54.5)                            | 9(33.3)                          | 1(1.4)    |
|                                        |                                     |                                  | 1(2.3)    |
|                                        |                                     |                                  | 0(0)      |
|                                        | 0.082                               |                                  |           |
| Decreased appetite                      | 29(40.8)                            |                                  |           |
|                                        | 19(43.2)                            | 10(37)                           | 3(4.2)    |
|                                        |                                     |                                  | 2(4.5)    |
|                                        |                                     |                                  | 1(3.7)    |
|                                        | 0.609                               |                                  |           |
| Hypothyrodism                           | 27(38)                              |                                  |           |
|                                        | 20(45.5)                            | 7(25.9)                          | 0(0)      |
|                                        |                                     |                                  | 0(0)      |
|                                        |                                     |                                  | 0(0)      |
|                                        | 0.100                               |                                  |           |
| Decreased appetite                      |                                     |                                  |           |
|                                        |                                     |                                  |           |
| Diarrhea                                | 20(28.2)                            |                                  |           |
|                                        | 11(25)                              | 9(33.3)                          | 2(2.8)    |
|                                        |                                     |                                  | 1(2.3)    |
|                                        |                                     |                                  | 1(3.7)    |
|                                        | 0.449                               |                                  |           |
| Pruritis                                | 19(26.8)                            |                                  |           |
|                                        | 7(15.9)                             | 12(44.4)                         | 0(0)      |
|                                        |                                     |                                  | 0(0)      |
|                                        |                                     |                                  | 0(0)      |
|                                        | 0.008                               |                                  |           |
| Laryngeal inflammation                 | 18(25.4)                            |                                  |           |
|                                        | 13(29.5)                            | 5(18.5)                          | 0(0)      |
|                                        |                                     |                                  | 0(0)      |
|                                        |                                     |                                  | 0(0)      |
|                                        | 0.300                               |                                  |           |
| Proteinuria*                            | 17(25.8)                            |                                  |           |
|                                        | 12(30)                              | 5(19.2)                          | 0(0)      |
|                                        |                                     |                                  | 0(0)      |
|                                        |                                     |                                  | 0(0)      |
|                                        | 0.328                               |                                  |           |
| Hepatitis                               | 8(11.3)                             |                                  |           |
|                                        | 5(11.4)                             | 3(11.1)                          | 5(7)      |
|                                        |                                     |                                  | 3(6.8)    |
|                                        |                                     |                                  | 2(7.4)    |
|                                        | 0.974                               |                                  |           |
| Poriasis                                | 3(4.2)                              |                                  |           |
|                                        | 3(6.8)                              | 0(0)                             | 3(4.2)    |
|                                        |                                     |                                  | 3(6.8)    |
|                                        |                                     |                                  | 0(0)      |
|                                        | 0.283                               |                                  |           |
| Pneumonitis                             | 3(4.2)                              |                                  |           |
|                                        | 3(6.8)                              | 0(0)                             | 2(2.8)    |
|                                        |                                     |                                  | 2(4.5)    |
|                                        |                                     |                                  | 0(0)      |

*Available data for 66 patients, including 40 patients in first-line setting.
### Supplementary Table 3. Treatment related adverse events in different Child-Pugh class and tumor risk subgroups

| Symptom, n(%) | Child-Pugh class | Tumor risk | Any grade | Grade 3 or 4 | Any grade | Grade 3 or 4 |
|---------------|------------------|------------|-----------|--------------|-----------|--------------|
|               | Child A (n=51)   | Child B (n=20) | Child A (n=51) | Child B (n=20) | Low-risk tumor (n=43) | High-risk tumor (n=28) | Low-risk tumor (n=43) | High-risk tumor (n=28) |
| Fatigue       | 30(58.8)         | 10(50)     | 0(0)      | 1(5)         | 23(53.5) | 17(60.7) | 0(0) | 1(3.6) |
| Hypertension  | 26(51)           | 9(45)      | 2(3.9)    | 1(5)         | 20(46.5) | 15(53.6) | 3(7) | 0(0) |
| Palmar-plantar syndrome | 26(51) | 7(35) | 1(2) | 0(0) | 24(55.8) | 9(32.1) | 0(0) | 1(3.6) |
| Decreased appetite | 20(39.2) | 9(45) | 1(2) | 2(10) | 15(34.9) | 14(50.0) | 0(0) | 3(10.7) |
| Hypothyroidism | 19(37.3) | 8(40) | 0(0) | 0(0) | 15(34.9) | 12(42.9) | 0(0) | 0(0) |
| Diarrhea      | 16(31.4) | 4(20) | 1(2) | 1(5) | 13(30.2) | 7(25) | 1(2.3) | 1(3.6) |
| Pruritus       | 16(31.4) | 3(15) | 0(0) | 0(0) | 13(30.2) | 6(21.4) | 0(0) | 0(0) |
| Laryngeal inflammation | 13(15.5) | 5(25) | 0(0) | 0(0) | 8(18.6) | 10(35.7) | 0(0) | 0(0) |
| Proteinuria*  | 12(26.1) | 5(25) | 0(0) | 0(0) | 10(25.6) | 7(25.9) | 0(0) | 0(0) |
| Hepatitis     | 6(11.8) | 2(10) | 3(5.9) | 2(10) | 5(11.6) | 3(10.7) | 2(4.7) | 3(10.7) |
| Poriasis      | 2(3.9) | 1(5) | 2(3.9) | 1(5) | 2(4.7) | 1(3.6) | 2(4.7) | 1(3.6) |
| Pneumonitis   | 2(3.9) | 1(5) | 1(2) | 1(5) | 2(4.7) | 1(3.6) | 1(2.3) | 1(3.6) |
### Supplementary Table 4. Univariate and multivariate analyses for factors associated with progression free survival based on RECIST1.1

| Characteristics                        | Univariate Analysis |                  |       | Multivariate Analysis Model 1 |                  |       | Multivariate Analysis Model 2 |                  |       |
|----------------------------------------|---------------------|------------------|-------|-------------------------------|------------------|-------|-------------------------------|------------------|-------|
|                                        | HR                  | 95% CI           | p Value | HR                           | 95% CI           | p Value | HR                           | 95% CI           | p Value |
| Age(yr) >60 vs. ≤60                   | 1.544               | 0.816-2.923      | 0.182  |                              |                   |        |                              |                   |        |
| Gender Male vs. Female                | 1.282               | 0.503-3.272      | 0.603  |                              |                   |        |                              |                   |        |
| ECOG ≥1 Yes vs. No                    | 1.916               | 1.022-3.591      | 0.043  | 1.628                         | 0.848-3.124      | 0.143  | 1.542                         | 0.803-2.962      | 0.193  |
| Etiology (Viral hepatitis) Yes vs. No | 0.625               | 0.317-1.234      | 0.176  |                              |                   |        |                              |                   |        |
| Tumor number Multiple vs. single       | 0.934               | 0.476-1.833      | 0.843  |                              |                   |        |                              |                   |        |
| Tumor ≥50% liver volume Yes vs. No    | 0.941               | 0.447-1.977      | 0.872  |                              |                   |        |                              |                   |        |
| Main portal vein invasion Yes vs. No  | 0.881               | 0.406-1.909      | 0.881  |                              |                   |        |                              |                   |        |
| Bile duct involvement Yes vs. No      | 2.225               | 0.530-9.340      | 0.274  |                              |                   |        |                              |                   |        |
| Extrahepatic metastasis Yes vs. No    | 0.976               | 0.525-1.815      | 0.939  |                              |                   |        |                              |                   |        |
| BCLC stage Stage C vs. B              | 0.990               | 0.457-2.145      | 0.980  |                              |                   |        |                              |                   |        |
| AFP, ng/mL >400 vs. ≤400              | 1.321               | 0.714-2.445      | 0.375  |                              |                   |        |                              |                   |        |
| NLR >2.5 vs. ≤2.5                     | 0.965               | 0.470-1.979      | 0.922  |                              |                   |        |                              |                   |        |
| INR >1.2 vs. ≤1.2                     | 0.546               | 0.282-1.057      | 0.073  | 0.537                         | 0.275-1.050      | 0.069  | 0.617                         | 0.315-1.206      | 0.158  |
| Platelet count >100 vs. ≤100          | 0.581               | 0.295-1.143      | 0.116  |                              |                   |        |                              |                   |        |
| ALT, U/L >40 vs. ≤40                  | 0.622               | 0.334-1.158      | 0.134  |                              |                   |        |                              |                   |        |
| AST, U/L >40 vs. ≤40                  | 0.662               | 0.353-1.244      | 0.200  |                              |                   |        |                              |                   |        |
| Child–Pugh class Class B vs. A        | 1.701               | 0.873-3.317      | 0.119  |                              |                   |        |                              |                   |        |
| ALBI grade m2b/3 vs. 1/ m2a           | 1.111               | 0.593-2.083      | 0.742  |                              |                   |        |                              |                   |        |
| Fib-4 score >6.5 vs. ≤6.5             | 1.514               | 0.771-2.973      | 0.228  |                              |                   |        |                              |                   |        |
| Systemic treatment ≥2nd line vs. 1st line | 1.687               | 0.912-3.121      | 0.096  | 1.651                         | 0.872-3.127      | 0.124  |                              |                   |        |
| MKI experience Yes vs. No             | 1.475               | 0.791-2.747      | 0.221  |                              |                   |        |                              |                   |        |
| Nivolumab experience Yes vs. No       | 3.966               | 1.846-8.518      | <0.001 | 3.253                         | 1.473-7.183      | 0.004  |                              |                   |        |
| Early AFP response (≥10%)             | 1.099               | 0.469-2.577      | 0.828  |                              |                   |        |                              |                   |        |
| Early AFP response (any)              | 0.681               | 0.290-1.602      | 0.379  |                              |                   |        |                              |                   |        |

*53 patients with baseline AFP ≥10 ng/ml were analyzed; *AFP reduction ≥10% within 4 weeks according to 10-10 rule. *AFP reduction in any degree within 4 weeks.

AFP, alpha-fetoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BCLC, Barcelona-Clinic-Liver-Cancer; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; INR, international normalized ratio; MKI, multikinase inhibitor; NLR, neutrophil-to-lymphocyte ratio.
Supplementary Table 5. Association of the expression level of Programmed death-ligand 1 (PD-L1) with clinical outcomes\textsuperscript{a}

|                      | Best objective response\textsuperscript{b} | Progression free survival\textsuperscript{b} | Overall survival\textsuperscript{b} |
|----------------------|---------------------------------------------|-----------------------------------------------|----------------------------------|
|                      | (<1% vs. >1%)                               | (≥1% vs. <1%)                                 |                                  |
| Combined positive score | 7(23.3%) 9(50%)                            | 0.058                                         | 0.489 0.203-1.177 0.110           | 0.226 0.049-1.032 0.055           |
| Tumor proportion score | 9(25%) 7(58.3%)                            | 0.073                                         | 0.537 0.200-1.439 0.216           | 0.208 0.027-1.599 0.131           |

\textsuperscript{a}Of 48 patients with available PD-L1 expression data. \textsuperscript{b}Best objective response and progression-free survival are reviewed by RECIST v1.1. \textsuperscript{c}p values are for the association of PD-L1 expression with overall survival and progression-free survival by use of Cox regression.
Supplementary Figure 1. Kaplan-Meier curves of patients with nivolumab +/- MKI or MKI alone treatment experienced compared with patients received lenvatinib plus pembrolizumab as first-line treatment. (a) progression-free survival [PFS] by RECIST v1.1 (b) Overall survival [OS]