Entecavir plus Biejia-Ruangan compound reduces the risk of hepatocellular carcinoma in Chinese patients with chronic hepatitis B

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Fig. S1. Cumulative incidence of clinical outcomes in the ITT Population.

(A) HCC. (B) Liver-related deaths. (C) Non-HCC events. (D) Non-liver-related deaths.

The HRs indicate the incidence of clinical outcomes in the ETV+BRC group as compared with the ETV group, the \( p \) values are calculated using the Log-rank test and the Cox proportional regression. A two-tailed \( p \) value of <0.05 is considered statistically significant.

BRC, Biejia-Ruangan compound; CI, confidence interval; ETV, entecavir; HCC, hepatocellular carcinoma; HR, hazard ratio; ITT, intention-to-treat.
**Fig. S2. Cumulative incidence of clinical outcomes in the PP Population.**

(A) HCC. (B) Liver-related deaths. (C) Non-HCC events. (D) Non-liver-related deaths.

The HRs indicate the incidence of clinical outcomes in the ETV+BRC group as compared with the ETV group, the \( p \) values are calculated using the Log-rank test and the Cox proportional regression. A two-tailed \( p \) value of <0.05 is considered statistically significant.

BRC, Biejia-Ruangan compound; CI, confidence interval; ETV, entecavir; HCC, hepatocellular carcinoma; HR, hazard ratio; PP, per-protocol.
Fig. S3. The cutoff values of continuous variables by Kaplan-Meier curve.

The re-defined cutoff values of baseline age, BMI, and HBsAg level were 44 years, 26.9 kg/m², and 5000 IU/mL. Regarding HBsAg level, there is no well-documented definition for classifying high and low categories, 5839 IU/mL of HBsAg level deduced from Kaplan-Meier curve was poor clinical usability, and percentage of patients with HBsAg≥5839 were relatively low, so 5000 IU/mL was chosen as the cutoff value.

The $p$ values are calculated using the Log-rank test. A two-tailed $p$ value of $<0.05$ is considered statistically significant.

BMI, body mass index.
**Fig. S4.** Hazard ratios for the incidence of HCC by baseline prognostic factors in the ITT population.

Each square represents the estimated HR, the horizontal lines represent the 95% CIs, and the diamond corresponds to the estimated HR and the 95% CI for the entire population. The *p* value is calculated using the Cox proportional regression or Fisher’s exact test, if appropriate. The *p* value for interaction is analyzed by use of the Breslow-Day test. A two-tailed *p* value of <0.05 is considered statistically significant.

BMI, body mass index; BRC, Biejia-Ruangan compound; CI, confidence interval; ETV, entecavir; HCC, hepatocellular carcinoma; HR, hazard ratio; ITT, intention-to-treat; LC, liver cirrhosis; LSM, liver stiffness measurement.

| HCC/patients | ETV+BRC | ETV | Significant | Not significant | HR (95% CI) | *p* value | *P* interaction |
|--------------|---------|-----|-------------|----------------|-------------|-----------|----------------|
| Sex          | 15/346  | 31/353 |             |              | 0.489 (0.263–0.903) | 0.022 | 0.933          |
| Male         | 6/154   | 11/147 |             |              | 0.512 (0.189–1.385) | 0.187 |               |
| Female       | 9/192   | 19/199 |             |              | 0.579 (0.240–1.398) | 0.224 |               |
| Age (years)  | 9/280   | 13/280 |             |              | 0.469 (0.244–0.902) | 0.023 |               |
| <64          | 13/210  | 29/220 |             |              | 0.611 (0.342–1.066) | 0.093 |               |
| >64          | 2/61    | 12/71  |             |              | 0.187 (0.042–0.836) | 0.028 |               |
| BMI (kg/m²)  | 19/439  | 30/429 |             |              | 0.564 (0.309–1.031) | 0.063 |               |
| <26.9        | 4/114   | 14/124 |             |              | 0.372 (0.112–1.086) | 0.056 |               |
| ≥26.9        | 3/3     | 2/3    |             |              |              |          |               |
| Family history of HCC | 0/3 | 0/3 |              |              |              |          | 0.890          |
| No           | 17/386  | 28/376 |             |              | 0.489 (0.262–0.903) | 0.012 |               |
| Yes          | 4/114   | 14/124 |             |              | 0.422 (0.082–2.175) | 0.390 |               |
| HBV DNA (log₁₀ IU/mL) | 17/317 | 37/327 |             |              | 0.451 (0.254–0.800) | 0.007 |               |
| ≤3.3         | 2/161   | 5/170  |             |              | 0.601 (0.125–2.935) | 0.470 |               |
| ≥3.3–7.0     | 19/336  | 37/327 |             |              | 0.490 (0.262–0.903) | 0.012 |               |
| >7.0         | 13/213  | 21/204 |             |              | 0.566 (0.264–1.134) | 0.109 |               |
| HBsAg (IU/mL) | 4/189 | 5/184  |             |              | 0.391 (0.174–0.856) | 0.024 |               |
| <5000        | 17/317  | 37/327 |             |              | 0.451 (0.254–0.800) | 0.007 |               |
| ≥5000        | 2/161   | 5/170  |             |              | 0.601 (0.125–2.935) | 0.470 |               |
| Negative     | 13/213  | 21/204 |             |              | 0.566 (0.264–1.134) | 0.109 |               |
| Positive     | 7/329   | 13/321 |             |              | 0.519 (0.207–1.302) | 0.162 |               |
| LSM (kPa)    | 14/171  | 28/179 |             |              | 0.491 (0.263–0.943) | 0.032 |               |
| <13.0        | 7/329   | 13/321 |             |              | 0.519 (0.207–1.302) | 0.162 |               |
| ≥13.0        | 14/171  | 28/179 |             |              | 0.491 (0.263–0.943) | 0.032 |               |
| Liver cirrhosis | 0/229 | 6/243   |             |              | 0.573 (0.333–0.988) | 0.045 |               |
| No           | 21/271  | 34/267 |             |              | 0.492 (0.292–0.832) | 0.008 |               |
| Yes          | 0/229   | 6/243   |             |              |              |          |               |
Fig. S5. Hazard ratios for the incidence of HCC by baseline prognostic factors in the PP population.

Each square represents the estimated HR, the horizontal lines represent the 95% CIs, and the diamond corresponds to the estimated HR and the 95% CI for the entire population. The $p$ value is calculated using the Cox proportional regression or Fisher’s exact test, if appropriate. The $p$ value for interaction is analyzed by use of the Cochran-Mantel-Haenszel test. A two-tailed $p$ value of <0.05 is considered statistically significant.

BRC, Biejia-Ruangan compound; CI, confidence interval; ETV, entecavir; HCC, hepatocellular carcinoma; HR, hazard ratio; LC, liver cirrhosis; LSM, liver stiffness measurement; PP, per-protocol.
Fig. S6. Histological assessment of liver fibrosis regression.

(A) The percentage of patients achieved regression of liver fibrosis in mITT population.

(B) The representative liver biopsies of treatment baseline, 1.5-year, and 5-year post-treatment from 2 patients receiving ETV-based treatment.

BRC, Biejia-Ruangan compound; ETV, entecavir; IFS, Ishak fibrosis score; mITT, modified intention-to-treat.

Categorical variables are presented as numbers and percentages [n (%)]. The \( p \) value is investigated by chi-squared test. A two-tailed \( p \) value of \(<0.05\) is considered statistically significant.
Fig. S7. Cumulative incidence of HCC by on-treatment prognostic factors in the ITT population.

(A) Virological response at week 48 after randomization. (B) Histological response at week 72 after randomization.

The HRs and p values are estimated with the use of the Cox proportional regression. A two-tailed p value of <0.05 is considered statistically significant.

BRC, Biejia-Ruangan compound; CI, confidence interval; ETV, entecavir; HCC, hepatocellular carcinoma; HR, hazard ratio; ITT, intention-to-treat; REG, regression of fibrosis; VR, virological response.
Fig. S8. Cumulative incidence of HCC by on-treatment prognostic factors in the PP population.

(A) Virological response at week 48 after randomization. (B) Histological response at week 72 after randomization.

The HRs and p values are estimated with the use of the Cox proportional regression. A two-tailed p value of <0.05 is considered statistically significant.

BRC, Biejia-Ruangan compound; CI, confidence interval; ETV, entecavir; HCC, hepatocellular carcinoma; HR, hazard ratio; PP, per-protocol; REG, regression of fibrosis; VR, virological response.
Table S1. Baseline clinical characteristics of enrolled patients in the PP population.

|                          | Total      | ETV+BRC   | ETV       | p value |
|--------------------------|------------|-----------|-----------|---------|
| n                        | 925        | 485       | 440       | –       |
| Age (years)              | 42.0 (35.0-49.0) | 42.0 (35.0-49.0) | 42.0 (35.0-49.0) | 0.930   |
| Male sex                 | 647 (69.9) | 334 (68.9) | 313 (71.1) | 0.496   |
| Family history of HCC    | 219 (23.7) | 106 (21.9) | 113 (25.7) | 0.197   |
| Hypertension             | 91 (9.8)   | 56 (11.5)  | 35 (8.0)  | 0.085   |
| Diabetes mellitus        | 39 (4.2)   | 21 (4.3)   | 18 (4.1)  | 0.987   |
| BMI (kg/m²)              | 22.9 (21.0-25.0) | 22.9 (20.8-24.8) | 22.9 (21.3-25.3) | 0.243   |
| HBsAg (log₁₀ IU/mL)      | 3.5 (3.1-4.0) | 3.5 (3.1-4.0)  | 3.5 (3.1-4.0)  | 0.461   |
| HBeAg positive           | 538 (58.2) | 277 (57.1) | 261 (59.3) | 0.540   |
| HBVDNA (log₁₀ IU/mL)     | 6.1 (4.9-7.5) | 6.1 (4.8-7.4)  | 6.1 (4.9-7.6)  | 0.684   |
| PLT (×10⁹/L)             | 157 (119-198) | 157 (122-200) | 157 (117-195) | 0.593   |
| PT (s)                   | 12.7 (11.5-13.8) | 12.6 (11.4-13.8) | 12.8 (11.7-13.8) | 0.280   |
| ALB (g/L)                | 42.0 (39.0-45.0) | 42.1 (39.1-45.0) | 42.0 (39.0-45.0) | 0.728   |
| ALT (IU/L)               | 53.0 (32.0-99.0) | 51.0 (31.0-91.0) | 55.0 (32.8-105.2) | 0.141   |
| AST (IU/L)               | 44.0 (29.0-74.0) | 42.0 (29.0-69.0) | 44.0 (29.0-78.2) | 0.382   |
| TBIL (μmol/L)            | 13.9 (10.8-19.0) | 13.6 (10.4-18.5) | 14.1 (11.0-19.4) | 0.151   |
| eGFR (mL/min/1.73m²)     | 107 (90-126) | 105 (88-127)  | 107 (94-125)  | 0.269   |
| AFP (ng/mL)              | 5.0 (2.8-11.0) | 5.0 (2.7-11.0)  | 5.0 (2.9-11.0)  | 0.703   |
| APRI                     | 0.7 (0.4-1.4) | 0.7 (0.4-1.3)   | 0.8 (0.4-1.5)   | 0.250   |
| LSM (kPa)                | 9.9 (6.8-16.3) | 9.6 (6.6-16.1)  | 10.4 (6.8-16.5) | 0.231   |
| LC                       | 505 (54.6)  | 262 (54.0)   | 243 (55.2)   | 0.763   |
| Modified HAI (points)    | 0.467      |            |           |         |
| 0-3                      | 92 (9.9)   | 50 (10.3)   | 42 (9.5)    |         |
| 4-8                      | 609 (65.8) | 323 (66.6)  | 286 (65.0)  |         |
| 9-12                     | 209 (22.6) | 107 (22.1)  | 102 (23.2)  |         |
| 13-18                    | 15 (1.6)   | 5 (1.0)     | 10 (2.3)    |         |
| IFS (points)             | 0.263      |            |           |         |
| 3                        | 229 (24.8) | 113 (23.3)  | 116 (26.4)  |         |
| 4                        | 191 (20.6) | 110 (22.7)  | 81 (18.4)   |         |
| 5                        | 188 (20.3) | 103 (21.2)  | 85 (19.3)   |         |
| 6                        | 317 (34.3) | 159 (32.8)  | 158 (35.9)  |         |

Continuous variables are expressed as medians and interquartile ranges (IQRs) and compared using the Mann-Whitney test. Categorical variables are presented as...
numbers (percentages) and compared using the chi-square or Fisher’s exact test, if appropriate. A two-tailed p value of <0.05 is considered statistically significant.

AFP, alpha-fetoprotein; ALB, albumin; ALT, alanine aminotransferase; APRI, AST-to-platelet ratio index; AST, aspartate aminotransferase; BMI, body mass index; eGFR, estimated glomerular filtration rate; HAI, histologic activity index; IFS, Ishak fibrosis score; LSM, liver stiffness measurement; PLT, platelet; PP, per-protocol; PT, prothrombin time; TBIL, total bilirubin.
Table S2. Baseline clinical characteristics of HCC patients in the ITT population.

|                     | Total   | ETV+BRC | ETV       | p value |
|---------------------|---------|---------|-----------|---------|
| n                   | 63      | 42      | 21        | –       |
| Age (years)         | 47.0 (40.5-51.0) | 47.0 (40.5-51.0) | 46.0 (41.0-51.0) | 0.620   |
| Male sex            | 46 (73.0) | 31 (73.8) | 15 (71.4) | 1.000   |
| Family history of HCC | 18 (28.6) | 14 (33.3) | 4 (19.0)  | 0.375   |
| Hypertension        | 4 (6.3)  | 3 (7.1)  | 1 (4.8)   | 1.000   |
| Diabetes mellitus   | 0 (0.0)  | 0 (0.0)  | 0 (0.0)   | –       |
| BMI (kg/m²)         | 22.9 (21.2-25.6) | 23.5 (21.7-27.3) | 22.9 (20.2-24.1) | 0.234   |
| HBsAg (log₁₀ IU/mL) | 3.2 (2.8-3.5) | 3.2 (2.8-3.5) | 3.2 (2.9-3.4) | 0.961   |
| HBeAg positive      | 29 (46.0) | 21 (50.0) | 8 (38.1)  | 0.532   |
| HBVDNA (log₁₀ IU/mL)| 5.1 (4.6-6.2) | 5.4 (4.6-6.4) | 4.8 (4.4-5.5) | 0.122   |
| PLT (×10⁹/L)        | 115 (79-157) | 117 (83-157) | 110 (74-156) | 0.466   |
| PT (s)              | 13.1 (11.9-13.9) | 12.6 (11.8-13.6) | 13.6 (12.7-14.6) | 0.047   |
| ALB (g/L)           | 42.0 (38.1-45.3) | 42.2 (39.0-45.0) | 42.0 (35.0-45.6) | 0.615   |
| ALT (IU/L)          | 57.0 (37.5-93.0) | 58.0 (41.5-104.5) | 49.0 (26.0-68.0) | 0.149   |
| AST (IU/L)          | 49.0 (30.0-80.0) | 53.0 (30.0-84.0) | 44.0 (31.0-61.0) | 0.374   |
| TBIL (μmol/L)       | 16.4 (11.8-20.2) | 16.5 (11.3-20.0) | 16.4 (14.0-25.4) | 0.521   |
| eGFR (mL/min/1.73m²) | 104 (85-121) | 106 (88-120) | 101 (82-122) | 0.590   |
| AFP (ng/mL)         | 12.0 (8.0-21.7) | 10.8 (6.2-22.4) | 12.6 (9.8-17.0) | 0.353   |
| APRI                 | 1.3 (0.5-2.7) | 1.5 (0.6-2.9)  | 1.2 (0.5-2.1)  | 0.726   |
| LSM (kPa)           | 17.6 (10.2-21.6) | 18.1 (9.5-21.7) | 17.0 (10.9-21.1) | 0.907   |
| LC                  | 55 (87.3) | 34 (81.0) | 21 (100.0) | 0.082   |
| Modified HAI (points)|  0-3 | 6 (9.5)  | 6 (14.3)  | 0 (0.0)  |
|                     |        | 4-8     | 44 (69.8) | 27 (64.3) | 17 (81.0) |
|                     |        | 9-12    | 12 (19.0) | 8 (19.0)  | 4 (19.0)  |
|                     |        | 13-18   | 1 (1.6)   | 1 (2.4)   | 0 (0.0)   |
| IFS (points)        | 3       | 3 (4.8)  | 3 (7.1)   | 0 (0.0)   |
|                     | 4       | 5 (7.9)  | 5 (11.9)  | 0 (0.0)   |
|                     | 5       | 14 (22.2)| 8 (19.0)  | 6 (28.6)  |
|                     | 6       | 41 (65.1)| 26 (61.9) | 15 (71.4) |

Continuous variables are expressed as medians and interquartile ranges (IQRs) and compared using the Mann-Whitney test. Categorical variables are presented as numbers (percentages) and compared using the chi-square or Fisher’s exact test, if appropriate. A two-tailed p value of <0.05 is considered statistically significant.
AFP, alpha-fetoprotein; ALB, albumin; ALT, alanine aminotransferase; APRI, AST-to-platelet ratio index; AST, aspartate aminotransferase; BMI, body mass index; eGFR, estimated glomerular filtration rate; HAI, histologic activity index; IFS, Ishak fibrosis score; ITT, intention-to-treat; LSM, liver stiffness measurement; PLT, platelet; PT, prothrombin time; TBIL, total bilirubin.
Table S3. Cumulative clinical events occurred in the ITT/PP population at year 7 after starting treatment.

| ITT population | Total | ETV+BRC | ETV | p value |
|----------------|-------|---------|-----|---------|
| n              | 1000  | 500     | 500 | –       |
| Treatment discontinued | 33 (3.3) | 15 (3.0) | 18 (3.6) | 0.595 |
| HBsAg loss | 15 (1.5) | 5 (1.0) | 10 (2.0) | 0.193 |
| HBeAg seroconversion† | 246 (42.3) | 121 (42.2) | 125 (42.2) | 0.987 |
| Virological response | 919 (91.9) | 461 (92.2) | 458 (91.6) | 0.728 |
| Regression of liver fibrosis‡ | 312 (67.8) | 174 (76.7) | 138 (59.2) | <0.001 |
| HCC | 63 (6.3) | 21 (4.2) | 42 (8.4) | 0.006 |
| Liver-related deaths | 10 (1.0) | 1 (0.2) | 9 (1.8) | 0.026 |
| Non-HCC events§ | 17 (1.7) | 7 (1.4) | 10 (2.0) | 0.179 |
| Non-liver-related deaths¶ | 5 (0.5) | 1 (0.2) | 4 (0.8) | 0.370 |
| All-cause deaths | 15 (1.5) | 2 (0.4) | 13 (2.6) | 0.009 |

| PP population | n | ITT population | ETV+BRC | ETV | p value |
|---------------|---|----------------|---------|-----|---------|
| n             | 925 | 485  | 440 | – |
| Treatment discontinued | 0 (0.0) | 0 (0.0) | 0 (0.0) | – |
| HBsAg loss | 15 (1.6) | 5 (1.0) | 10 (2.3) | 0.134 |
| HBeAg seroconversion† | 236 (43.9) | 121 (43.7) | 115 (44.1) | 0.930 |
| Virological response | 877 (94.8) | 461 (95.1) | 416 (94.5) | 0.798 |
| Regression of liver fibrosis‡ | 296 (69.5) | 174 (76.7) | 122 (61.3) | <0.001 |
| HCC | 59 (6.4) | 21 (4.3) | 38 (8.6) | 0.007 |
| Liver-related deaths | 10 (1.1) | 1 (0.2) | 9 (2.0) | 0.017 |
| Non-HCC events§ | 17 (1.8) | 7 (1.4) | 10 (2.3) | 0.348 |
| Non-liver-related deaths¶ | 5 (0.5) | 1 (0.2) | 4 (0.9) | 0.314 |
| All-cause deaths | 15 (1.6) | 2 (0.4) | 13 (3.0) | 0.005 |

† The denominator is the number of patients who had a positive HBeAg at baseline (583 [ETV+BRC: 287; ETV: 296] in the ITT population, 538 [ETV+BRC: 277; ETV: 261] in the PP population).

‡ The denominator is the number of patients who underwent a third liver biopsy at year 5 after starting treatment (460 [ETV+BRC: 227; ETV: 233] in the ITT population, 426 [ETV+BRC: 227; ETV: 199] in the PP population).

# One patient received liver transplantation.
In the ETV+BRC group, 2 cases with hepatic encephalopathy, 1 case with esophageal variceal bleeding, 1 case with liver failure, 2 cases with gastric and colorectal cancers, 1 case with thyroid cancer; In the ETV group, 4 cases with esophageal variceal bleeding, 2 cases with gastric and colorectal cancers, 1 case with thyroid cancer, 1 case with pancreatic cancer, 1 case with acute kidney injury, and 1 case with lower extremity deep vein thrombosis.

In the ETV+BRC group, 1 case died of cardiovascular disease; In the ETV group, 2 cases died of cardiovascular disease, 1 case died of pancreatic cancer, and 1 case died from a traffic accident.

Categorical variables are presented as numbers and percentages [n (%)]. The p value is investigated by chi-squared test or Fisher exact test if appropriate. A two-tailed p value of <0.05 is considered statistically significant.

BRC, Biejia-Ruangan compound; ETV, entecavir; HCC, Hepatocellular carcinoma; ITT, intention-to-treat; PP, per-protocol.
Table S4. Baseline clinical characteristics of 42 treatment-converted patients by HCC development.

|                         | Total          | Non-HCC        | HCC            | p value |
|-------------------------|----------------|----------------|----------------|---------|
| n                       | 42             | 38             | 4              | –       |
| Age (years)             | 43.5 (40.0-48.0) | 43.5 (40.0-48.0) | 44.0 (40.2-45.8) | 0.864   |
| Male sex                | 26 (61.9)      | 23 (60.5)      | 3 (75.0)       | 0.979   |
| Family history of HCC   | 11 (26.2)      | 10 (26.3)      | 1 (25.0)       | 0.999   |
| Hypertension            | 6 (14.3)       | 6 (15.8)       | 0 (0.0)        | 0.915   |
| Diabetes mellitus       | 2 (4.8)        | 2 (5.3)        | 0 (0.0)        | 1.000   |
| BMI (kg/m²)             | 24.1 (21.5-25.6) | 23.3 (21.0-25.4) | 27.0 (24.7-32.4) | 0.065   |
| HBsAg (log₁₀ IU/mL)    | 3.5 (3.1-4.2)  | 3.5 (3.1-4.2)  | 3.4 (3.2-3.9)  | 0.898   |
| HBeAg positive          | 24 (57.1)      | 22 (57.9)      | 2 (50.0)       | 1.000   |
| HBVDNA (log₁₀ IU/mL)   | 6.0 (4.5-7.5)  | 6.0 (4.5-7.5)  | 5.8 (4.8-6.8)  | 0.898   |
| PLT (×10⁹/L)            | 165 (131-202)  | 165 (131-199)  | 186 (152-217)  | 0.466   |
| PT (s)                  | 11.9 (11.2-12.6) | 11.9 (11.2-13.2) | 11.9 (11.0-12.1) | 0.548   |
| ALB (g/L)               | 43.0 (39.0-45.0) | 42.6 (38.0-45.0) | 45.5 (44.5-46.0) | 0.107   |
| ALT (IU/L)              | 49.0 (34.5-143.8) | 52.0 (32.5-143.8) | 43.5 (40.0-129.0) | 0.881   |
| AST (IU/L)              | 37.4 (28.2-73.5) | 37.4 (29.0-73.5) | 33.0 (26.5-92.8) | 0.814   |
| TBIL (μmol/L)           | 12.2 (10.0-15.1) | 12.3 (10.0-15.1) | 11.8 (10.7-14.5) | 0.932   |
| eGFR (mL/min/1.73m²)    | 99 (91-118)    | 97 (91-112)    | 174 (157-183)  | 0.003   |
| AFP (ng/mL)             | 5.3 (3.5-10.7) | 5.1 (3.1-9.9)  | 9.8 (8.7-11.6) | 0.079   |
| APRI                    | 0.7 (0.4-1.1)  | 0.7 (0.4-1.1)  | 0.6 (0.4-1.2)  | 0.732   |
| LSM (kPa)               | 8.8 (6.9-13.7) | 8.8 (6.3-13.7) | 8.9 (8.1-12.1) | 0.607   |
| LC                      | 9 (21.4)       | 8 (21.1)       | 1 (25.0)       | 1.000   |
| Modified HAI (points)   |                |                |                | 0.097   |
| 0-3                     | 5 (11.9)       | 3 (7.9)        | 2 (50.0)       |         |
| 4-8                     | 32 (76.2)      | 30 (78.9)      | 2 (50.0)       |         |
| 9-12                    | 4 (9.5)        | 4 (10.5)       | 0 (0.0)        |         |
| 13-18                   | 1 (2.4)        | 1 (2.6)        | 0 (0.0)        |         |
| IFS (points)            |                |                |                | 0.738   |
| 3                       | 18 (42.9)      | 17 (44.7)      | 1 (25.0)       |         |
| 4                       | 15 (35.7)      | 13 (34.2)      | 2 (50.0)       |         |
| 5                       | 9 (21.4)       | 8 (21.1)       | 1 (25.0)       |         |

Continuous variables are expressed as medians and interquartile ranges (IQRs) and compared using the Mann-Whitney test. Categorical variables are presented as...
numbers (percentages) and compared using the chi-square or Fisher’s exact test, if appropriate. A two-tailed $p$ value of $<0.05$ is considered statistically significant.

AFP, alpha-fetoprotein; ALB, albumin; ALT, alanine aminotransferase; APRI, AST-to-platelet ratio index; AST, aspartate aminotransferase; BMI, body mass index; BRC, Biejia-Ruangan compound; eGFR, estimated glomerular filtration rate; ETV, entecavir; HAI, histologic activity index; HCC, Hepatocellular carcinoma; IFS, Ishak fibrosis score; LC, liver cirrhosis; LSM, liver stiffness measurement; PLT, platelet; PT, prothrombin time; TBIL, total bilirubin.
Table S5. Baseline clinical characteristics of enrolled patients in the mITT population by HCC development.

|                                      | Total      | Non-HCC    | HCC        | p value   |
|--------------------------------------|------------|------------|------------|-----------|
| n                                    | 1000       | 940        | 60         | –         |
| ETV+BRC treatment                    | 500 (50.0) | 479 (51.0) | 21 (35.0)  | 0.024     |
| Age (years)                          | 42.0 (35.0-49.0) | 41.5 (34.0-49.0) | 47.0 (40.0-51.2) | <0.001 |
| Male sex                             | 699 (69.9) | 656 (69.8) | 43 (71.7)  | 0.871     |
| Family history of HCC                | 238 (23.8) | 221 (23.5) | 17 (28.3)  | 0.488     |
| Hypertension                         | 99 (9.9)   | 95 (10.1)  | 4 (6.7)    | 0.521     |
| Diabetes mellitus                    | 43 (4.3)   | 43 (4.6)   | 0 (0.0)    | 0.172     |
| BMI (kg/m²)                          | 22.9 (21.0-25.1) | 22.9 (21.0-25.1) | 22.9 (21.1-25.0) | 0.920     |
| HBsAg (log₁₀ IU/mL)                  | 3.5 (3.1-4.0) | 3.5 (3.1-4.0) | 3.2 (2.8-3.4) | <0.001 |
| HBeAg positive                       | 583 (58.3) | 556 (59.1) | 27 (45.0)  | 0.043     |
| HBVDNA (log₁₀ IU/mL)                 | 6.1 (4.9-7.5) | 6.2 (4.9-7.6) | 5.1 (4.5-6.1) | <0.001 |
| PLT (×10⁹/L)                         | 158 (120-199) | 161 (123-201) | 113 (76-153) | <0.001 |
| PT (s)                               | 12.6 (11.5-13.8) | 12.6 (11.4-13.8) | 13.1 (12.0-13.9) | 0.072     |
| ALB (g/L)                            | 42.0 (39.0-45.0) | 42.0 (39.2-45.0) | 42.0 (38.0-45.1) | 0.323     |
| ALT (IU/L)                           | 53.0 (32.0-99.0) | 53.0 (32.0-99.0) | 60.0 (37.5-101.5) | 0.510     |
| AST (IU/L)                           | 43.0 (29.0-74.0) | 42.0 (29.0-72.0) | 51.0 (30.8-81.8) | 0.106     |
| TBIL (μmol/L)                        | 13.8 (10.8-18.7) | 13.6 (10.7-18.4) | 16.7 (11.9-20.2) | 0.008     |
| eGFR (mL/min/1.73m²)                 | 107 (90-125) | 107 (91-126) | 103 (84-1120) | 0.063     |
| AFP (ng/mL)                          | 5.0 (2.8-11.0) | 4.7 (2.7-9.7) | 12.2 (8.0-21.9) | <0.001 |
| APRI                                 | 0.7 (0.4-1.4) | 0.7 (0.4-1.3) | 1.4 (0.6-2.7) | <0.001 |
| LSM (kPa)                            | 9.7 (6.8-16.1) | 9.4 (6.7-15.3) | 17.8 (10.4-21.8) | <0.001 |
| LC                                   | 528 (52.8) | 474 (50.4)  | 54 (90.0)   | <0.001    |
| Modified HAI (points)                |            |            |            | 0.751     |
| 0-3                                  | 102 (10.2) | 98 (10.4)  | 4 (6.7)    |           |
| 4-8                                  | 661 (66.1) | 618 (65.7) | 43 (71.7)  |           |
| 9-12                                 | 221 (22.1) | 209 (22.2) | 12 (20.0)  |           |
| 13-18                                | 16 (1.6)   | 15 (1.6)   | 1 (1.7)    |           |
| IFS (points)                         |            |            |            | <0.001    |
| 3                                    | 257 (25.7) | 254 (27.0) | 3 (5.0)    |           |
| 4                                    | 215 (21.5) | 212 (22.6) | 3 (5.0)    |           |
| 5                                    | 204 (20.4) | 191 (20.3) | 13 (21.7)  |           |
| 6                                    | 324 (32.4) | 283 (30.1) | 41 (68.3)  |           |


Continuous variables are expressed as medians and interquartile ranges (IQRs) and compared using the Mann-Whitney test. Categorical variables are presented as numbers (percentages) and compared using the chi-square or Fisher’s exact test, if appropriate. A two-tailed $p$ value of $<0.05$ is considered statistically significant.

AFP, alpha-fetoprotein; ALB, albumin; ALT, alanine aminotransferase; APRI, AST-to-platelet ratio index; AST, aspartate aminotransferase; BMI, body mass index; BRC, Biejia-Ruangan compound; eGFR, estimated glomerular filtration rate; ETV, entecavir; HAI, histologic activity index; HCC, Hepatocellular carcinoma; IFS, Ishak fibrosis score; LC, liver cirrhosis; LSM, liver stiffness measurement; mITT, modified intention-to-treat; PLT, platelet; PT, prothrombin time; TBIL, total bilirubin.
Table S6. Baseline clinical characteristics of enrolled patients in the ITT population by HCC development.

|                             | Total      | Non-HCC    | HCC        | p value |
|-----------------------------|------------|------------|------------|---------|
| n                           | 1000       | 937        | 63         | –       |
| ETV+BRC treatment           | 500 (50.0) | 479 (51.1) | 21 (33.3)  | 0.009   |
| Age (years)                 | 42.0 (35.0-49.0) | 41.0 (34.0-49.0) | 47.0 (40.5-51.0) | <0.001 |
| Male sex                    | 699 (69.9) | 653 (69.7) | 46 (73.0)  | 0.678   |
| Family history of HCC       | 238 (23.8) | 220 (23.5) | 18 (28.6)  | 0.444   |
| Hypertension                | 99 (9.9)   | 95 (10.1)  | 4 (6.3)    | 0.449   |
| Diabetes mellitus           | 43 (4.3)   | 43 (4.6)   | 0 (0.0)    | 0.156   |
| BMI (kg/m²)                 | 22.9 (21.0-25.1) | 22.9 (21.0-25.1) | 22.9 (21.2-25.6) | 0.530   |
| HBsAg (log₁₀ IU/mL)         | 3.5 (3.1-4.0) | 3.5 (3.1-4.0) | 3.2 (2.8-3.5) | <0.001 |
| HBeAg positive              | 583 (58.3) | 554 (59.1) | 29 (46.0)  | 0.056   |
| HBVDNA (log₁₀ IU/mL)        | 6.1 (4.9-7.5) | 6.2 (4.9-7.6) | 5.1 (4.6-6.2) | <0.001 |
| PLT (×10⁹/L)                | 158 (120-199) | 161 (123-201) | 115 (79-157) | <0.001 |
| PT (s)                      | 12.6 (11.5-13.8) | 12.6 (11.4-13.8) | 13.1 (11.9-13.9) | 0.154   |
| ALB (g/L)                   | 42.0 (39.0-45.0) | 42.0 (39.1-45.0) | 42.0 (38.1-45.3) | 0.517   |
| ALT (IU/L)                  | 53.0 (32.0-99.0) | 53.0 (32.0-99.0) | 57.0 (37.5-93.0) | 0.638   |
| AST (IU/L)                  | 43.0 (29.0-74.0) | 42.0 (29.0-72.0) | 49.0 (30.0-80.0) | 0.217   |
| TBIL (μmol/L)               | 13.8 (10.8-18.7) | 13.6 (10.7-18.4) | 16.4 (11.8-20.2) | 0.010   |
| eGFR (mL/min/1.73m²)        | 107 (90-125) | 107 (91-125) | 104 (85-121) | 0.243   |
| AFP (ng/mL)                 | 5.0 (2.8-11.0) | 4.7 (2.7-9.5) | 12.0 (8.0-21.7) | <0.001 |
| APRI                        | 0.7 (0.4-1.4) | 0.7 (0.4-1.3) | 1.3 (0.5-2.7) | <0.001 |
| LSM (kPa)                   | 9.7 (6.8-16.1) | 9.4 (6.6-15.3) | 17.6 (10.2-21.6) | <0.001 |
| LC                          | 528 (52.8) | 473 (50.5)  | 55 (87.3)  | <0.001 |
| Modified HAI (points)‡      |           |            |            | 0.928   |
| 0-3                         | 102 (10.2) | 96 (10.2)  | 6 (9.5)    |         |
| 4-8                         | 661 (66.1) | 617 (65.8) | 44 (69.8)  |         |
| 9-12                        | 221 (22.1) | 209 (22.3) | 12 (19.0)  |         |
| 13-18                       | 16 (1.6)   | 15 (1.6)   | 1 (1.6)    |         |
| IFS (points)                |           |            |            | <0.001  |
| 3                           | 257 (25.7) | 254 (27.1) | 3 (4.8)    |         |
| 4                           | 215 (21.5) | 210 (22.4) | 5 (7.9)    |         |
| 5                           | 204 (20.4) | 190 (20.3) | 14 (22.2)  |         |
| 6                           | 324 (32.4) | 283 (30.2) | 41 (65.1)  |         |
Continuous variables are expressed as medians and interquartile ranges (IQRs) and compared using the Mann-Whitney test. Categorical variables are presented as numbers (percentages) and compared using the chi-square or Fisher’s exact test, if appropriate. A two-tailed $p$ value of $<0.05$ is considered statistically significant.

AFP, alpha-fetoprotein; ALB, albumin; ALT, alanine aminotransferase; APRI, AST-to-platelet ratio index; AST, aspartate aminotransferase; BMI, body mass index; BRC, Biejia-Ruangan compound; eGFR, estimated glomerular filtration rate; ETV, entecavir; HAI, histologic activity index; HCC, Hepatocellular carcinoma; IFS, Ishak fibrosis score; ITT, intention-to-treat; LC, liver cirrhosis; LSM, liver stiffness measurement; PLT, platelet; PT, prothrombin time; TBIL, total bilirubin.
Table S7. Baseline clinical characteristics of enrolled patients in the PP population by HCC development.

|                                | Total       | Non-HCC     | HCC         | p value |
|--------------------------------|-------------|-------------|-------------|---------|
| n                              | 925         | 866         | 59          | –       |
| ETV+BRC treatment              | 485 (52.4)  | 464 (53.6)  | 21 (35.6)   | 0.011   |
| Age (years)                    | 42.0 (35.0-49.0) | 42.0 (34.2-49.0) | 47.0 (40.5-51.5) | <0.001   |
| Male sex                       | 647 (69.9)  | 604 (69.7)  | 43 (72.9)   | 0.718   |
| Family history of HCC          | 219 (23.7)  | 202 (23.3)  | 17 (28.8)   | 0.423   |
| Hypertension                   | 91 (9.8)    | 87 (10.0)   | 4 (6.8)     | 0.556   |
| Diabetes mellitus              | 39 (4.2)    | 39 (4.5)    | 0 (0.0)     | 0.183   |
| BMI (kg/m²)                    | 22.9 (21.0-25.0) | 22.9 (21.0-25.0) | 22.9 (21.0-25.2) | 0.966   |
| HBsAg (log₁₀ IU/mL)            | 3.5 (3.1-4.0) | 3.5 (3.1-4.0) | 3.2 (2.8-3.4) | <0.001   |
| HBeAg positive                 | 538 (58.2)  | 511 (59.0)  | 27 (45.8)   | 0.063   |
| HBVDNA (log₁₀ IU/mL)           | 6.1 (4.9-7.5) | 6.2 (4.9-7.6) | 5.1 (4.6-6.2) | <0.001   |
| PLT (×10⁹/L)                   | 157 (119-198) | 161 (123-200) | 110 (76-150) | <0.001   |
| PT (s)                         | 12.7 (11.5-13.8) | 12.6 (11.5-13.8) | 13.1 (11.9-13.9) | 0.074   |
| ALB (g/L)                      | 42.0 (39.0-45.0) | 42.0 (39.2-45.0) | 42.0 (38.0-44.6) | 0.291   |
| ALT (IU/L)                     | 53.0 (32.0-99.0) | 53.0 (32.0-99.0) | 59.0 (37.0-93.0) | 0.656   |
| AST (IU/L)                     | 44.0 (29.0-74.0) | 43.0 (29.0-73.5) | 50.0 (30.5-80.0) | 0.183   |
| TBIL (μmol/L)                  | 13.9 (10.8-19.0) | 13.6 (10.7-18.5) | 17.0 (12.8-20.2) | 0.006   |
| eGFR (mL/min/1.73m²)           | 107 (90-126) | 107 (90-126) | 102 (83-119) | 0.049   |
| AFP (ng/mL)                    | 5.0 (2.8-11.0) | 4.7 (2.7-10.0) | 12.4 (8.0-22.0) | <0.001   |
| APRI                           | 0.7 (0.4-1.4) | 0.7 (0.4-1.3) | 1.4 (0.6-2.7) | <0.001   |
| LSM (kPa)                      | 9.9 (6.8-16.3) | 9.6 (6.6-15.3) | 17.9 (10.7-21.8) | <0.001   |
| LC                             | 505 (54.6)  | 451 (52.1)  | 54 (91.5)   | <0.001   |
| Modified HAI (points)          | 0-3         | 92 (9.9)    | 88 (10.2)   | 4 (6.8)  |
|                                | 4-8         | 609 (65.8)  | 567 (65.5)  | 42 (71.2) |
|                                | 9-12        | 209 (22.6)  | 197 (22.7)  | 12 (20.3) |
|                                | 13-18       | 15 (1.6)    | 14 (1.6)    | 1 (1.7)  |
| IFS (points)                   | 3           | 229 (24.8)  | 227 (26.2)  | 2 (3.4)  |
|                                | 4           | 191 (20.6)  | 188 (21.7)  | 3 (5.1)  |
|                                | 5           | 188 (20.3)  | 175 (20.2)  | 13 (22.0) |
|                                | 6           | 317 (34.3)  | 276 (31.9)  | 41 (69.5) |

Continuous variables are expressed as medians and interquartile ranges (IQRs) and compared using the Mann-Whitney test. Categorical variables are presented as
numbers (percentages) and compared using the chi-square or Fisher’s exact test, if appropriate. A two-tailed $p$ value of $<0.05$ is considered statistically significant.

AFP, alpha-fetoprotein; ALB, albumin; ALT, alanine aminotransferase; APRI, AST-to-platelet ratio index; AST, aspartate aminotransferase; BMI, body mass index; BRC, Biejia-Ruangan compound; eGFR, estimated glomerular filtration rate; ETV, entecavir; HAI, histologic activity index; HCC, Hepatocellular carcinoma; IFS, Ishak fibrosis score; LC, liver cirrhosis; LSM, liver stiffness measurement; PLT, platelet; PP, per-protocol; PT, prothrombin time; TBIL, total bilirubin.
Table S8. Baseline factors associated with HCC incidence by univariable and multivariable Cox analyses.

|                  | mITT population | ITT population | PP population |
|------------------|-----------------|----------------|---------------|
|                  | Univariable Cox analysis | Multivariable Cox analysis | Univariable Cox analysis | Multivariable Cox analysis |
|                  | HR        | 95% CI       | p value | HR        | 95% CI       | p value | HR        | 95% CI       | p value |
| Age (years)      | 1.047     | 1.020-1.070  | <0.001  | 1.030     | 1.000-1.061  | 0.049   | 1.049     | 1.020-1.080  | <0.001  |
| HBsAg (log_{10} IU/mL) | 0.546     | 0.410-0.730  | <0.001  | 0.735     | 0.501-1.080  | 0.117   | 0.544     | 0.400-0.730  | <0.001  |
| HBeAg positive   | 0.584     | 0.350-0.970  | 0.038   | 1.016     | 0.579-1.785  | 0.955   | 0.603     | 0.360-1.0100 | 0.053   |
| APRI             | 1.081     | 1.010-1.160  | 0.034   | 1.061     | 0.971-1.159  | 0.189   | 1.079     | 1.000-1.160  | 0.042   |
| HBVDNA (log_{10} IU/mL) | 0.728     | 0.610-0.860  | <0.001  | 0.781     | 0.633-0.963  | 0.021   | 0.736     | 0.620-0.870  | <0.001  |
| TBIL (μmol/L)    | 1.005     | 0.990-1.020  | 0.409   | –         | –            | –       | 1.005     | 0.990-1.020  | 0.409   |
| AFP (ng/mL)      | 1.000     | 1.000-1.000  | 0.658   | –         | –            | –       | 1.000     | 1.000-1.000  | 0.660   |
| LSM (kPa)        | 1.053     | 1.030-1.070  | <0.001  | 1.032     | 1.007-1.059  | 0.014   | 1.052     | 1.030-1.070  | <0.001  |
| LC               | 7.888     | 3.390-18.330 | <0.001  | 3.833     | 1.572-9.344  | 0.003   | 6.338     | 3.020-13.310 | <0.001  |
| ETV+BRC treatment| 0.489     | 0.290-0.830  | 0.008   | 0.405     | 0.230-0.710  | 0.002   | 0.492     | 0.290-0.830  | 0.008   |

The HRs and p values are estimated with the use of the Cox proportional regression.

A two-tailed p value of <0.05 is considered statistically significant.
AFP, alpha-fetoprotein; APRI, AST-to-platelet ratio index; BRC, Biejia-Ruangan compound; ETV, entecavir; HCC, Hepatocellular carcinoma; ITT, intention-to-treat; LC, liver cirrhosis; LSM, liver stiffness measurement; mITT, modified intention-to-treat; PP, per-protocol; TBIL, total bilirubin.