Regorafenib Combined With Sintilimab Versus Regorafenib as Second-line Treatment for Advanced Hepatocellular Carcinoma

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Abstract

**Purpose:** To evaluate the safety and efficacy of regorafenib combined with immune checkpoint inhibitor sintilimab (rego-sintilimab) as second-line treatment for advanced hepatocellular carcinoma (HCC) patients who failed prior sorafenib or lenvatinib.

**Methods:** This retrospective study evaluated consecutive patients with advanced HCC who received rego-sintilimab (rego-sintilimab group) or regorafenib alone (regorafenib group) as second-line treatment from January 2019 to December 2020. Adverse events, objective response rate (ORR), progression-free survival (PFS), and overall survival (OS) were compared between the two groups.

**Results:** Eighty-three patients were included: 48 received rego-sintilimab and 35 received regorafenib. Rego-sintilimab group had higher ORR (33.3% vs 14.3%, \( P = .049 \)), longer PFS (median, 5.1 vs 3.0 months; \( P = .001 \)), and better OS (median, 13.3 vs 9.1 months; \( P = .001 \)) than regorafenib group. Regorafenib alone, Child-Pugh B, and neutrophil-to-lymphocyte ratio (NLR) >3.5 were independent prognostic factors for poor OS in uni- and multi-variable analyses. Subgroup analyses showed that, in patients with Child-Pugh A (16.4 vs 11.5 months; \( P = .005 \)), Child-Pugh B (8.8 vs 6.4 months; \( P = .032 \)), or NLR \( \leq 3.5 \) (16.3 vs 11.5 months; \( P = .012 \)), rego-sintilimab group had significantly better median OS than regorafenib group, whereas median OS was not significantly different between the two groups in patients with NLR >3.5 (8.4 vs 7.0 months; \( P = .288 \)). The incidences of grade 3/4 adverse events were similar between the two groups (39.4% vs 34.1%; \( P = .445 \)).

**Conclusion:** Rego-sintilimab was tolerable and led to better OS than regorafenib as second-line treatment for advanced HCC patients, especially in those with NLR \( \leq 3.5 \).

Introduction

Despite recent improvements in surveillance programs, 50–75% of patients with hepatocellular carcinoma (HCC) are diagnosed at an advanced stage [1]. Multi-kinase inhibitor sorafenib and lenvatinib are the first-line treatments for advanced HCC, as recommended by updated Barcelona Clinical Liver cancer (BCLC) treatment algorithms [1]. However, these two drugs only result in a median progression free survival (PFS) of 3.7–7.3 months [2, 3], and a second-line treatment is needed after disease progression. Multi-kinase inhibitor regorafenib [4], cabozantinib [5], and VEGFR-2 inhibitor ramucirumab [6] are appropriate for pretreated patients with advanced HCC. Nonetheless, these second-line treatments only resulted in an objective response rate (ORR) of 4–11% and a median OS of 8.5–10.6 months versus a median OS of 7.3-8.0 months for placebo. Considering the low ORR and modest OS improvement, a more effective second-line treatment is needed.

Immunotherapy with immune checkpoint inhibitors (ICI) is currently a possible second-line option. Phase 1/2 data highlighted durable responses with ICI, such as nivolumab and pembrolizumab, for HCC patients who failed prior sorafenib treatment [7, 8]; however, phase 3 data of pembrolizumab has failed to demonstrate improved OS compared to placebo in second-line setting [9]. Since ICI monotherapy was not significantly effective, combination of ICI and tyrosine-kinase inhibitors or VEGF inhibitors is being widely considered [10]. Regorafenib is potent VEGFR2/3 inhibitor, which may lead to promising ORR in combination with ICI immunotherapy [11]. An HCC model has shown that the combination of regorafenib and ICI could increase intratumoral CD8+ T-cell infiltration by normalizing the tumor vasculature [12], and subsequently improve the efficacy of ICI immunotherapy.
Recently, ICI sintilimab combined with VEGF inhibitor (bevacizumab biosimilar) showed a significant OS benefit versus sorafenib in the first-line setting for Chinese HCC patients [13]. Sintilimab has a high programmed death-1 (PD-1) receptor occupancy rate (>95%) [14] and long occupancy duration on circulating T cells [15], which indicates that it may have a powerful anti-tumor immune effect. Considering the above characteristics of regorafenib and sintilimab, their combination (rego-sintilimab) may have an advantage over the current standard second-line regorafenib monotherapy. Therefore, this study aimed to investigate the safety and efficacy of rego-sintilimab, in comparison to regorafenib alone, for advanced HCC patients in a second-line setting.

**Materials And Methods**

**Patient Selection**

We reviewed the electronic medical records of consecutive patients with advanced HCC who receive rego-sintilimab or regorafenib after disease progression on sorafenib or lenvatinib treatment from January 2019 to December 2020 at our institution. Patients were assigned to receive rego-sintilimab or regorafenib according to patients’ decision under the attending physician’s suggestion. This retrospective study was approved by our institutional review board. Written informed consent was obtained from every patient prior to treatment.

HCC was diagnosed according to the European Association for the Study of Liver and American Association for the study of Liver Disease guidelines [16]. The inclusion criteria for the study population were as follows: (a) age between 18 and 75 years, (b) Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, (c) BCLC stage C HCC, (d) Child-Pugh A or B liver function, and (e) radiographic disease progression on first-line treatment with sorafenib or lenvatinib. Patients were excluded from this study if they (a) had previously received targeted therapy besides to sorafenib or lenvatinib monotherapy, (b) had previously received immunotherapy, (c) currently had or had a history of malignant tumors in addition to HCC, (d) had severe medical comorbidities including severe organ dysfunction and coagulation disorders, such as creatinine ≥ 1.5 upper limit of normal or international normalized ratio ≥ 1.5, or (e) had a follow-up less than 3 months.

**Data collection**

The baseline characteristics were collected within one week before the initiation of rego-sintilimab or regorafenib. Inflammation-based prognostic scores neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) were calculated based on the baseline data. NLR was calculated as the neutrophil count divided by the lymphocyte count and PLR as the platelet count divided by the lymphocyte count [17].

All the dynamic CT or MR imaging analyses, including tumor size, tumor number, macrovascular invasion, extrahepatic metastasis, and treatment response, were conducted independently by two diagnostic radiologists who were blinded to treatment allocation and clinical information. When there was any ambiguity, the final determination was made by consensus.

**Treatment protocol and adjustment**

Regorafenib was initially prescribed 120 mg/day, which might be adjusted to 160 or 80 mg/day according to the patients’ tolerance, during weeks 1–3 of each 4 week-cycle. Sintilimab (Innovent Biologics, Suzhou, China) was prescribed at a fixed dose of 200 mg every 3 weeks.
Follow-up of the patients was conducted at a 3- to 6-week interval. Treatment was discontinued in cases of progressive disease confirmed by the follow-up CT or MR or in patients who had hepatic decompensation with Child-Pugh C or clinical progression to ECOG performance status > 2, or intolerable toxicity even after the dose adjustment of regorafenib (to 80 mg/day) or treatment interruption. Patients who encountered intolerable toxicity in the rego-sintilimab group might discontinue one treatment of regorafenib or sintilimab and retained the other under the physician's suggestion. Patients with discontinuation of second-line treatment might receive post-line treatments, such as apatinib, and/or ICI immunotherapy other than sintilimab, and/or regional therapies, i.e. transarterial chemoembolization, or iodine125 seed implantation, for patients with Child-Pugh A/B and ECOG score 0-2, or best support treatment for patients with Child-Pugh C or ECOG score >2, according to the attending physicians' consensus.

Outcomes

Adverse events (AEs) related to treatment were recorded according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0 [18].

Treatment responses were assessed based on the dynamic CT or MR imaging, according to the Response Evaluation Criteria in Solid Tumors (RESICT) version 1.1 [19] and modified RESICT (mRESICT) [20]. ORR was defined as the incidence of complete response and partial response. Disease control rate (DCR) was defined as the incidence of complete response, partial response, and stable disease.

Progression-free survival (PFS) was defined as the time from the initiation of regorafenib until the date when tumor progression or death was confirmed or the last follow-up in censored data. OS was defined as the time from the initiation of regorafenib until death or the last follow-up in censored data.

Statistical Analyses

Categorical data was presented as number (percentage) and quantitative data as median value (Interquartile range [IQR]) unless otherwise indicated. Pearson \( \chi^2 \) test, correction of continuity, or Fisher's exact test were used to compare the categorical data of baseline patient characteristics, adverse events, and treatment responses between the two groups, as appropriate. Mann-Whitney \( U \) test or Student's \( t \) test were used to compare the quantitative data of baseline characteristics or mean dose of regorafenib between the two groups. Receiver operating characteristic (ROC) curve analyses were performed to determine the optimal cut-off values of lymphocyte, neutrophils, platelet, NLR, and PLR for predicting a 1-year survival. Curves of OS and PFS were determined by the Kaplan-Meier method and the log-rank test was used for comparisons. Univariate analyses and multivariate analyses of prognostic factors for OS and PFS were performed with Cox proportional hazard regression model. Variables with a \( P \) value < .10 in the univariate analysis were included into the multivariate analysis. All tests were 2-sided and \( P < .05 \) was considered statistically significant. All statistical analyses were performed using SPSS Statistics, version 22.0 (SPSS, Chicago, IL).

Results

Study Population

A total of 94 patients with advanced HCC who received rego-sintilimab or regorafenib as second-line treatment were assessed for eligibility during the study period. Eleven patients were excluded because they met the exclusion criteria
Finally, 83 patients were included in this study (rego-sintilimab group, \(n = 48\); regorafenib group, \(n = 35\)). The baseline characteristics between the two groups were not significantly different (Table 1).

In detail, 37.5% (18/48) of patients in rego-sintilimab group and 34.3% (12/35) in regorafenib group had Child-Pugh B liver function \((P = .763)\). 41.7% (20/48) of patients in rego-sintilimab group and 37.1% (13/35) in regorafenib group received lenvatinib in first-line treatment \((P = .678)\). Median time on first-line treatment was 8.0 months (IQR, 4.6–12.3) in rego-sintilimab group and 7.9 months (IQR, 5.2–13.7) in regorafenib group \((P = .941)\). Mean daily dose of regorafenib was 108.3 mg ± 23.3 in rego-sintilimab group and 114.3 mg ± 24.0 in regorafenib group \((P = .260)\). Median duration of second-line treatment with rego-sintilimab or regorafenib was 5.8 months (IQR, 3.5–9.4) in rego-sintilimab group and 3.9 months (IQR, 2.4–6.8) in regorafenib group.

## Safety

Treatment-related AEs are shown in Table 2. No treatment-related mortality occurred. The overall incidence of AEs was similar between rego-sintilimab group and regorafenib group (any grade: 93.8% vs 89.6%, \(P = .661\); grade 3/4: 39.6% vs 31.4%, \(P = .445\)). There was a higher incidence of any grade rash in rego-sintilimab group than in regorafenib group (22.9% vs 5.7%, \(P = .033\)). Incidences of other AEs were not significantly different between the two groups. AEs of any grade with an incidence over 20% in rego-sintilimab group included fatigue, hand–foot skin reaction, rash, hypertension, hypothyroidism, hyperbilirubinemia, diarrhea, and anorexia. Grade 3/4 AEs with an incidence over 5% in rego-sintilimab group included hand–foot skin reaction, hypertension, hyperbilirubinemia.

Treatment was discontinued because of AE in 12.5% (6/48) of patients in rego-sintilimab group and in 8.6% (3/35) in regorafenib group \((P = .833)\). Grade 4 skin toxicity was observed in 1 patient after 2 cycles of rego-sintilimab and grade 4 hyperbilirubinemia in 1 patient with immune-related hepatitis confirmed by liver biopsy after 6 cycles of rego-sintilimab, and both recovered from discontinuation of sintilimab and treatment with glucocorticoid. Other 4 cases of treatment discontinuation in rego-sintilimab group were caused by grade 3 AEs, i.e. rash in 1 patient, pneumonitis in 1 patient, and gastrointestinal hemorrhage in 2 patients.

## Treatment Response

Tumor responses of the two groups were shown in Table 3. Two patients (5%) in rego-sintilimab group versus no patients in regorafenib group had a complete response. The DCR for rego-sintilimab group was significantly higher than that observed in regorafenib group (72.9% vs 48.6% by RECIST 1.1, \(P = .024\); 72.9% vs 51.4% by mRECIST, \(P = .044\)). The ORR for rego-sintilimab group was significantly higher than that observed in regorafenib group when assessed by mRECIST (33.3% vs 14.3%, \(P = .049\)), but there was only a nonsignificant better ORR trend in rego-sintilimab group compared with regorafenib group when assessed by RECIST 1.1 (22.9% vs 8.6%, \(P = .085\)).

## ROC curve analyses

ROC curve analyses for predicting 1-year survival revealed that the optimal cut-off values for NLR, PLR, and neutrophils were 3.56 (area under the curve [AUC], .698; 95% CI, .579–.818; \(P = .004\)), 119 (AUC, .656; 95% CI, .530–.782; \(P = .022\)) and 4.53*10^9/L (AUC .699; 95% CI, .575–.822; \(P = .003\)), respectively. Thus, these variables were clarified into NLR ≤ 3.5/> 3.5, PLR ≤ 120/> 120, and neutrophils ≤ 4.5*10^9/L/> 4.5*10^9/L. The AUC for lymphocyte and platelet were not statistically significant \((P = 0.121 and 0.284, respectively)\), and thus their cut-off values were not determined by the ROC curve.
The median follow-up duration was 12.8 months (IQR, 7.0–16.5) for the rego-sintilimab group and 8.7 months (IQR, 5.3–12.4) for the regorafenib group. During follow-up, 41 of 48 (85.4%) patients in the rego-sintilimab group and 34 of 35 (97.1%) patients in the regorafenib group experienced tumor progression. The median PFS in rego-sintilimab group vs in regorafenib group were 5.1 months (95% CI, 3.4–6.8) vs 3.0 months (95% CI, 2.3–3.7), respectively \( (P = .001) \) (Fig. 2).

According to the uni- and multi-variate analyses, regorafenib alone (HR, 2.186; 95% CI, 1.353–3.532; \( P = .001 \)), \( \alpha \)-fetoprotein (HR per 10⁴ ng/mL, 1.044; 95% CI, 1.019–1.069; \( P = .001 \)), and NLR > 3.5 (HR, 1.769; 95% CI, 1.093–2.863; \( P = .020 \)) were independent prognostic factors for PFS (Table 4).

**Overall survival**

During the follow-up period, 32 of 48 (66.7%) patients in rego-sintilimab group and 27 of 35 (77.1%) patients in regorafenib group died. The 6-, 12-, and 24-month OS rates were 83.3%, 54.1%, and 36.3% (median OS, 13.3 months [95% CI, 9.5–17.1]), respectively, in rego-sintilimab group and 76.2%, 31.4%, and 0% (median OS, 9.1 months [95% CI, 5.6–12.5]), respectively, in regorafenib group \( (P = .001) \) (Fig. 3). According to the uni- and multi-variate analyses, regorafenib alone (HR, 2.141; 95% CI, 1.178–3.890; \( P = .012 \)), Child-Pugh B liver function (HR, 2.225; 95% CI, 1.301–3.804; \( P = .003 \)), and NLR > 3.5 (HR, 1.897; 95% CI, 1.075–3.348; \( P = .027 \)) were independent prognostic factors for OS (Table 5).

Subgroup analyses showed that, in patients with Child-Pugh A (16.4 vs 11.5 months; \( P = .005 \)) or B (8.8 vs 6.4 months; \( P = .032 \)) liver function, the median OS was significantly improved in rego-sintilimab group compared with regorafenib group (Fig. 4a and 4b). In patients with an NLR \( \leq \) 3.5, the median OS was significantly improved in rego-sintilimab group compared with regorafenib group (16.3 vs 11.5 months; \( P = .012 \)), whereas it was not significantly different between the two groups in patients with an NLR > 3.5 (8.4 vs 7.0 months; \( P = .288 \)) (Fig. 4c and 4d).

**Discussion**

Our study showed that rego-sintilimab conferred a significant survival benefit when compared with regorafenib in a second-line setting in advanced HCC patients who failed prior sorafenib or lenvatinib treatment. This finding was associated with an increase in median OS from 9.1 months to 13.3 months. In the multivariate analyses, combing sintilimab was an independent predictor for better OS and PFS. This survival benefit may be attributed to a higher ORR and DCR and a longer PFS in patients who received rego-sintilimab compared to those who received regorafenib alone. A recent phase 1b trial investigated regorafenib combined with ICI pembrolizumab in first-line treatment of HCC and showed a promising ORR of 28% by RECIST 1.1 [11], while the ORR by RECIST 1.1 in the rego-sintilimab group in our study was 22.9% in a second-line setting. These results indicated that rego-sintilimab had an advantage over regorafenib alone: regorafenib potently inhibited JAK1/2-STAT1 and MAPK signaling and subsequently attenuated the PD-L1 expression in the tumor [21], and increased intratumoral CD8 + T-cell infiltration through vasculature normalization by targeting VEGFR2/3 [12], which probably improve the efficacy of ICI sintilimab.

The median OS in the regorafenib group was 9.1 months, which seems to be poorer than the median OS of 10.3–12.1 months for second-line regorafenib treatment in previous studies [4, 22, 23]. It was worth noting that these studies included only patients with Child-Pugh A liver function, while there were about 35% of patients in our study had Child-Pugh B HCC. The OS of Child-Pugh B patients with regorafenib treatment was reported significantly poorer than the Child-Pugh A cohort in a multicentre study [24], which was consistent with the results in our study.
Nonetheless, an effective treatment is still demanded for Child-Pugh B patients. Casadei’s study showed that 35% of patients, who had Child-Pugh A HCC before sorafenib, might encountered a liver function deterioration to Child-Pugh B when sorafenib ceased [25]. The latest phase I/II study by Kudo M et al. showed that ICI immunotherapy had favorable safety for patients with Child-Pugh B HCC, comparable to that seen in Child-Pugh A patients [26]. Similarly, our subgroup analyses indicated that rego-sintilimab improved patient survival for Child-Pugh B HCC was well as for Child-Pugh A HCC when compared to regorafenib alone.

An effective prognostic biomarker for immunotherapy in HCC patients is currently lacking and urgently needed [27]. NLR is an easily accessed and widely available blood-based clinical biomarker. A lower NLR may delineate a healthy host immune anti-tumor response [28], and was an independent predictor for PFS and OS in our study. Its clinical relevance is thought to be that an elevated peripheral neutrophil count is a marker of chronic inflammation which often leads to impaired immunity [29], whereas the peripheral lymphocyte count is a hallmark of a healthy cytotoxic T-cell response [30]. In our subgroup analyses, for HCC patients with an NLR > 3.5, rego-sintilimab might not confer a survival benefit compared to regorafenib alone. This result may help to select patients suitable for second-line treatment with rego-sintilimab.

The safety profile of rego-sintilimab was generally consistent with historical data on regorafenib [4] and sintilimab [13], with no new AEs reported. Combining sintilimab did not increase the overall incidence of any grade or grade 3/4 AEs on the basis of regorafenib treatment. Treatment in 12.5% of patients in rego-sintilimab group were discontinued because of AEs, which was similar to the incidence previously reported with sintilimab–bevacizumab biosimilar treatment (14%) [13].

This study has several limitations. First, as a retrospective study, the comparison of rego-sintilimab and regorafenib may be subject to selection bias, and no matched pair analysis between the two groups was performed because of a small sample size. Instead, we conducted multivariate analyses and subgroup analyses to make a correction for confounding factors. Second, sample size in this study was relatively small. Results of the subgroup analyses should be cautiously interpreted and validation by further studies is needed. Third, the baseline NLR cut-off values are different (range 1.9-5.0) in each study [31]. This heterogeneity could hinder the application of NLR in the clinical setting. Thus, large cohort studies are required to establish the most appropriate NLR cut-off value in HCC patients with immunotherapy.

In conclusion, rego-sintilimab was tolerable and yielded promising outcomes in a second-line setting for patients with advanced HCC and Child-Pugh A or B liver function. These patients appeared to benefit from rego-sintilimab, and have better treatment responses, PFS, and OS, in comparison to regorafenib alone, especially in those who had an NLR ≤ 3.5.

**Declarations**

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**Conflict of interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.
**Ethics approval:** Appropriate Ethics Committee approval has been obtained for the research reported and the requirement to obtain informed consent for the study was waived.

**Consent to participate:** All patients were informed that regorafenib was standard second-line treatment and regorafenib combined with sintilimab was an alternative treatment. Moreover, all patients were informed of the economic cost and potential toxicity. Final treatment decisions were made by the patients.

**Availability of data and material:** All data generated or analyzed during this study are available by contacting the corresponding author.

**Authors' contributions:**

Jingjun Huang: conceptualization, methodology, validation, investigation, data curation, writing—original draft preparation, writing—review and editing, and funding acquisition. Yongjian Guo: conceptualization, methodology, validation, investigation, resources, data curation, writing—original draft preparation, writing—review and editing. Wensou Huang: conceptualization, methodology, validation, investigation, resources, data curation, writing—original draft preparation. Zining Xu: investigation, data curation, and writing—original draft preparation. Liteng Lin: investigation and writing—original draft preparation. Jingwen Zhou: investigation and writing—original draft preparation. Licong Liang: investigation and writing—review and editing. Yaqin Zhang: investigation and writing—review and editing. Juan Zhou: investigation and writing—review and editing. Mingyue Cai: methodology, formal analysis, investigation, writing—review and editing. Kangshun Zhu: conceptualization, writing—review and editing, supervision, project administration, and funding acquisition.

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**Tables**

**Table 1 Baseline patient characteristics at initiation of second-line treatment**
| Characteristic                                | Rego-sintilimab Group (N = 48) | Regorafenib Group (N = 35) | P value |
|----------------------------------------------|---------------------------------|-----------------------------|---------|
| Male                                         | 42 (87.5)                       | 30 (85.7)                   | > .999  |
| Age (year)                                   | 55 (40–61)                      | 51 (47–63)                  | .506    |
| ECOG score 1                                 | 16 (33.3)                       | 16 (45.7)                   | .252    |
| Positive for HBsAg                           | 40 (83.3)                       | 32 (91.4)                   | .455    |
| Child-Pugh B                                 | 18 (37.5)                       | 12 (34.3)                   | .763    |
| Presence of ascites                          | 11 (22.9)                       | 4 (11.4)                    | .179    |
| Tumor diameter (cm)                          | 5.9 (4.2–8.8)                   | 5.5 (4.3–7.0)               | .901    |
| > 3 intrahepatic tumors                      | 33 (68.8)                       | 25 (71.4)                   | .793    |
| Macrovascular invasion                       | 32 (66.7)                       | 20 (57.1)                   | .376    |
| Extrahepatic metastasis                      | 30 (62.5)                       | 21 (60.0)                   | .817    |
| First-line treatment with lenvatinib         | 20 (41.7)                       | 13 (37.1)                   | .678    |
| Time on first-line treatment (months)        | 8.0 (4.6–12.3)                  | 7.9 (5.2–13.7)              | .941    |
| Previous treatment procedures                |                                 |                             | .877    |
| Surgery or radical ablation                  | 11 (22.9)                       | 9 (25.7)                    |         |
| TACE or HAIC ^                               | 33 (68.8)                       | 24 (68.6)                   |         |
| Others ^                                     | 4 (8.3)                         | 2 (5.7)                     |         |
| Laboratory test                              |                                 |                             |         |
| α-fetoprotein (ng/mL)                        | 924 (22–15862)                  | 594 (12–7630)               | .625    |
| PIVKA-II (ng/mL)                             | 1445 (138–12512)                | 1984 (496–16625)            | .150    |
| Alanine aminotransferase (U/L)               | 29 (20–45)                      | 36 (28–49)                  | .177    |
| Aspartate aminotransferase (U/L)             | 43 (31–72)                      | 48 (26–67)                  | .340    |
| Total bilirubin (umol/L)                     | 12.7 (8.7–17.7)                 | 15.5 (9.7–23.7)             | .156    |
| Albumin (g/dL)                               | 35.4 (31.3–39.4)                | 35.9 (32.5–40.1)            | .678    |
| Lymphocyte (10^9/L)                          | 1.02 (.66–1.36)                 | .80 (.60–1.33)              | .262    |
| Neutrophils (10^9/L)                         | 2.63 (2.13–3.62)                | 2.95 (2.41–3.84)            | .612    |
| Platelet (10^9/L)                            | 125 (101–206)                   | 130 (84–177)                | .583    |
| Inflammation-based prognostic score          |                                 |                             |         |
| NLR                                          | 2.80 (1.94–5.25)                | 3.85 (2.01–6.08)            | .184    |
| PLR                                          | 153 (96–195)                    | 152 (79–267)                | .846    |
Categorical data was presented as number (percentage) and quantitative data as median value (Interquartile range).
rego-sintilimab = regorafenib combined with sintilimab, ECOG = Eastern Cooperative Oncology Group, HBsAg = hepatitis B surface antigen, TACE = transarterial chemoembolization, HAIC = hepatic arterial infusion chemotherapy, PIVKA-II = protein Induced by Vitamin K Absence or Antagonist-II, NLR = neutrophil-to-lymphocyte ratio, PLR = platelet-to-lymphocyte ratio.

& TACE or HAIC without surgery or radical ablation

^ Including palliative ablation, radiotherapy, or Iodine125 seed implantation, without surgery, radical ablation, TACE, or HAIC.

**Table 2 Adverse events in the two groups**
| Adverse events               | Any Grade | Regorafenib Group (N=35) | **P** value | Regorafenib Group (N=35) | **P** value |
|----------------------------|-----------|--------------------------|-------------|--------------------------|-------------|
|                            | Regosintilimab Group (N=48) |                |             |                          |             |
|                            | Overall incidence          | 45 (93.8)        | .661        | 19 (39.6)                | .445        |
|                            | Fatigue                  | 17 (35.4)        | .511        | 0                        | .175        |
|                            | Hand-foot skin reaction  | 14 (29.2)        | .620        | 3 (6.3)                  | .396        |
|                            | Rash                     | 11 (22.9)        | .033        | 2 (4.2)                  | .506        |
|                            | Pneumonitis              | 6 (12.5)         | .230        | 2 (4.2)                  | .506        |
|                            | Hypertension             | 13 (27.1)        | .662        | 7 (14.6)                 | .928        |
|                            | Hypothyroidism           | 11 (22.9)        | .325        | 0                        | —           |
|                            | Hyperthyroidism          | 4 (8.3)          | .570        | 0                        | —           |
|                            | Hyperbilirubinemia       | 11 (22.9)        | .750        | 3 (6.3)                  | .919        |
|                            | Increased GGT            | 5 (10.4)         | >.999       | 1 (2.1)                  | >.999       |
|                            | Increased AST            | 9 (18.8)         | >.999       | 2 (4.2)                  | >.999       |
|                            | Increased ALT            | 6 (12.5)         | .833        | 1 (2.1)                  | >.999       |
|                            | Leukopenia               | 6 (12.5)         | .511        | 2 (4.2)                  | 0           |
|                            | Lymphopenia              | 5 (10.4)         | .718        | 0                        | —           |
|                            | Neutropenia              | 4 (8.3)          | .924        | 1 (2.1)                  | >.999       |
|                            | Thrombocytopenia         | 5 (10.4)         | >.999       | 1 (2.1)                  | 1 (2.9)     |
|                            | Anemia                   | 6 (12.5)         | .511        | 1 (2.1)                  | >.999       |
|                            | Proteinuria              | 3 (6.3)          | .396        | 0                        | —           |
|                            | Increased creatinine     | 1 (2.1)          | >.999       | 0                        | 0           |
|                            | Diarrhea                 | 13 (27.1)        | .456        | 2 (4.2)                  | >.999       |
|                            | Nausea                   | 5 (10.4)         | >.999       | 0                        | 0           |
|                            | Anorexia                 | 12 (25.0)        | .822        | 0                        | 1 (2.9)     |
|                            | Weight loss              | 2 (4.2)          | .715        | 0                        | —           |
|                            | Constipation             | 3 (6.3)          | .919        | 0                        | 0           |
|                            | Presence of ascites      | 1 (2.1)          | >.999       | 0                        | 0           |
|                            | Gastrointestinal hemorrhage | 2 (4.2)     | >.999       | 2 (4.2)                  | >.999       |
|                            | Gingival bleeding        | 3 (6.3)          | .661        | 0                        | 0           |
|                            | Epistaxis                | 0                | .437        | 0                        | 0           |
|                | Regorafenib Group (N=35) | Sintilimab Group (N=48) | *P* value | Regorafenib Group (N=35) | Sintilimab Group (N=48) | *P* value |
|----------------|--------------------------|-------------------------|-----------|--------------------------|-------------------------|-----------|
| **CR**         | 2                        | 0                       | ...       | 0                        | 0                       | ...       |
| **PR**         | 14                       | 5                       | ...       | 11                       | 3                       | ...       |
| **SD**         | 19                       | 13                      | ...       | 24                       | 14                      | ...       |
| **PD**         | 13                       | 17                      | ...       | 13                       | 18                      | ...       |
| **ORR, %**     | 33.3                     | 14.3                    | 0.049     | 22.9                     | 8.6                     | 0.085     |
| **DCR, %**     | 72.9                     | 51.4                    | 0.044     | 72.9                     | 48.6                    | 0.024     |
| Factor                                      | Univariable analysis          | Multivariate analysis         |
|---------------------------------------------|------------------------------|-------------------------------|
|                                             | HR (95% CI)                  | P Value                      |
| Regorafenib alone                           | 2.188 (1.361–3.518)         | .001                         |
| Male                                        | 1.296 (.661–2.539)          | .450                         |
| ≥ 65 years                                  | .701 (.346–1.419)           | .324                         |
| ECOG score = 1                              | 1.142 (7.04–1.854)         | .591                         |
| Positive for HbsAg                          | .782 (.374–1.636)           | .513                         |
| Child-Pugh B                                | .930 (.567–1.525)           | .774                         |
| Presence of ascites                         | .903 (.494–1.649)           | .740                         |
| Tumor diameter (cm)                         | 1.168 (.721–1.891)          | .528                         |
| > 3 intrahepatic tumors                     | 1.606 (963–2.678)           | .069                         |
| Macrovacular invasion                       | .854 (.530–1.376)           | .516                         |
| Extrahepatic metastasis                     | 1.558 (965–2.513)           | .070                         |
| Firs-line treatment with lenvatinib         | .905 (5.526–1.154)          | .174                         |
| Time on first-line treatment (month)        | 1.008 (995–1.021)           | .215                         |
| Previous surgery or ablation                | .576 (291–1.141)            | .114                         |
| α-fetoprotein (10^4 ng/mL)                  | 1.047 (1.023–1.072)         | < .001                       |
| PIVKA-Ⅳ (10^4 mAU/mL)                       | 1.077 (1.017–1.141)         | .011                         |
| Alanine aminotransferase > 50 U/L           | 1.260 (7.30–2.176)          | .407                         |
| Aspartate aminotransferase > 40 U/L         | 1.036 (6.54–1.641)          | .881                         |
| Total bilirubin > 22 umol/L                 | 1.231 (6.91–2.195)          | .480                         |
| Albumin < 35 g/dL                           | .998 (6.26–1.590)           | .993                         |
| Lymphocyte < 1.0*10^9/L                     | 1.588 (996–2.530)           | .052                         |
| Neutrophils > 4.5*10^9/L                    | 1.908 (1.001–3.637)         | .050                         |
| Platelet of 100-200*10^9/L                  | Ref                         |                              |
| Platelet < 100*10^9/L                       | 1.899 (923–3.905)           | .081                         |
| Platelet > 200*10^9/L                       | 1.877 (945–3.725)           | .072                         |
| NLR > 3.5                                   | 1.979 (1.241–3.154)         | .004                         |
| PLR > 120                                   | 1.528 (939–2.489)           | .088                         |

The uni- and multi-variate analyses were performed using Cox proportional hazard regression model. HR = Hazard Ratio, CI = confidence interval, ECOG = Eastern Cooperative Oncology Group, HBsAg = hepatitis B surface antigen,
PIVKA-II = protein Induced by Vitamin K Absence or Antagonist-II, NLR = neutrophil-to-lymphocyte ratio, PLR = platelet-to-lymphocyte ratio.

Table 5 Analyses of prognostic factors for overall survival
| Factor                          | Univariable analysis |          | Multivariate analysis |          |
|--------------------------------|----------------------|----------|-----------------------|----------|
|                                | HR (95% CI)          | P Value  | HR (95% CI)           | P Value  |
| Regorafenib alone              | 2.481 (1.434–4.293)  | .001     | 2.141 (1.178–3.890)   | .012     |
| Male                           | 1.073 (.525–2.193)   | .846     |                       |          |
| ≥ 65 years                     | 1.245 (.561–2.765)   | .590     |                       |          |
| ECOG score = 1                 | 2.036 (1.218–3.403)  | .007     |                       | .309     |
| Positive for HbsAg             | .734 (.314–1.713)    | .474     |                       |          |
| Child-Pugh B                   | 1.977 (1.169–3.346)  | .011     | 2.225 (1.301–3.804)   | .003     |
| Presence of ascites            | 1.155 (.609–2.188)   | .659     |                       |          |
| Tumor diameter (per cm)        | 1.037 (.956–1.124)   | .384     |                       |          |
| > 3 intrahepatic tumors        | 1.735 (1.960–3.136)  | .068     |                       | .116     |
| Macrovascular invasion         | 1.091 (.639–1.863)   | .750     |                       |          |
| Extrahepatic metastasis        | 1.490 (.847–2.620)   | .167     |                       |          |
| First-line treatment with lenvatinib | .756 (.445–1.283) | .300     |                       |          |
| Time on first-line treatment (per month) | .991 (.970–1.012) | .385     |                       |          |
| Previous surgery or ablation   | .577 (.291–1.142)    | .114     |                       |          |
| α-fetoprotein (per 10⁴ ng/mL)  | 1.017 (.997–1.038)   | .095     |                       | .811     |
| PIVKA-Ⅲ (per 10⁴ mAU/mL)       | 1.059 (1.005–1.115)  | .031     |                       | .983     |
| Alanine aminotransferase > 50 U/L | 1.475 (.827–2.630) | .188     |                       |          |
| Aspartate aminotransferase > 40 U/L | 2.225 (1.297–3.816) | .004     |                       | .116     |
| Total bilirubin > 22 umol/L    | 1.898 (1.044–3.451)  | .036     |                       | .471     |
| Albumin < 35 g/dL              | 1.538 (.920–2.570)   | .100     |                       |          |
| Lymphocyte < 1.0*10⁹/L         | 1.920 (1.113–3.312)  | .019     |                       | .672     |
| Neutrophils > 4.5*10⁹/L        | 2.620 (1.318–5.209)  | .006     |                       | .176     |
| Platelet of 100-200*10⁹/L     | Ref                  |          |                       |          |
| Platelet < 100*10⁹/L          | 2.135 (1.054–4.327)  | .035     |                       | .682     |
| Platelet > 200*10⁹/L          | 2.136 (1.051–4.343)  | .036     |                       | .624     |
The uni- and multi-variate analyses were performed using Cox proportional hazard regression model. HR = Hazard Ratio, CI = confidence interval, ECOG = Eastern Cooperative Oncology Group, HBsAg = hepatitis B surface antigen, PIVKA-II = protein Induced by Vitamin K Absence or Antagonist-II, NLR = neutrophil-to-lymphocyte ratio, PLR = platelet-to-lymphocyte ratio.

**Figures**

**Figure 1**

Flow diagram shows exclusion in patients with advanced hepatocellular carcinoma (HCC) who receive regorafenib combined with sintilimab (rego-sintilimab) or regorafenib in a second-line setting.
Kaplan-Meier curves of progression-free survival (PFS) for patients with advanced hepatocellular carcinoma who receive regorafenib combined with sintilimab (rego-sintilimab) (median PFS, 5.1 months; 95% CI, 3.4–6.8) or regorafenib (median PFS, 3.0 months; 95% CI, 2.3–3.7; P = .001) in a second-line setting. CI = confidence interval.

Figure 2

| Number at risk | Time (month) |
|----------------|--------------|
| Rego-sintilimab | 48 15 7 2 0 |
| Regorafenib    | 35 6 1 0 0 |

Kaplan-Meier curves of progression-free survival (PFS) for patients with advanced hepatocellular carcinoma who receive regorafenib combined with sintilimab (rego-sintilimab) (median PFS, 5.1 months; 95% CI, 3.4–6.8) or regorafenib (median PFS, 3.0 months; 95% CI, 2.3–3.7; P = .001) in a second-line setting. CI = confidence interval.
Figure 3

Kaplan-Meier curves of overall survival (OS) for patients with advanced hepatocellular carcinoma who receive regorafenib combined with sintilimab (rego-sintilimab) (median OS, 13.3 months; 95% CI, 9.5–17.1) or regorafenib (median OS, 9.1 months; 95% CI, 5.6–12.5; P = .001) in a second-line setting. CI = confidence interval.
Figure 4

Kaplan-Meier curves of overall survival (OS) for (a) Child-Pugh A patients (rego-sintilimab group: median OS, 16.4 months [95% CI, 6.6–26.1]; regorafenib group: median OS, 11.5 months [95% CI, 7.5–15.5]; P = .005), (b) Child-Pugh B patients (rego-sintilimab group: median OS, 8.8 months [95% CI, 7.0–10.5]; regorafenib group: median OS, 6.4 months [95% CI, 5.4–7.3]; P = .027), (c) patients with NLR ≤ 3.5 (rego-sintilimab group: median OS, 16.3 months [95% CI, 13.4–19.2]; regorafenib group: median OS, 11.5 months [95% CI, 1.9–21.1]; P = .012), and (d) patients with NLR > 3.5 (rego-sintilimab group: median OS, 8.4 months [95% CI, 8.2–8.5]; regorafenib group: median OS, 7.0 months [95% CI, 3.7–10.2]; P = .274). CI = confidence interval, NLR = neutrophil-to-lymphocyte ratio.