Combination of transcatheter arterial chemoembolization and interrupted dosing sorafenib improves patient survival in early–intermediate stage hepatocellular carcinoma
A post hoc analysis of the START trial

Teng-Yu Lee, MD, PhD, Chen-Chun Lin, MD, Chiung-Yu Chen, MD, Tsang-En Wang, MD, Gin-Ho Lo, MD, Chi-Sen Chang, MD, PhD, Yee Chao, MD, PhD

Abstract
Background/Objective: The survival benefit of treatment for unresectable hepatocellular carcinoma (HCC) with transcatheter arterial chemoembolization (TACE) combined with sorafenib remains uncertain. We compared the survival of patients treated with TACE and sorafenib with that of patients treated with TACE alone.

Methods: This was a post hoc analysis of the Study in Asia of the Combination of TACE with Sorafenib in Patients with HCC (START) trial. All patients who received TACE and interrupted dosing of sorafenib for early or intermediate-stage HCC in Taiwan from 2009 to 2010 were recruited into the TACE and sorafenib group. They were randomly matched 1:1 by age, sex, Child–Pugh score, tumor size, tumor number, and tumor stage with patients from Taichung Veterans General Hospital in Taiwan who received TACE alone and who fulfilled the selection criteria of the START trial during the same time period (control group). Patient survival [cumulative incidence and hazard ratio (HR)] of the 2 groups were analyzed and compared.

Results: The baseline characteristics of the 36 patients in each group were similar. Tumor response rates were significantly better in the TACE and sorafenib group (P < .04). Overall survival of the TACE and sorafenib group was also significantly better than that of the control (TACE alone) group over the 2 years [78%, 95% confidence interval (95% CI) 64–91 vs 49, 95% CI 32–66; P = .012]. In the multivariate regression analysis, TACE and sorafenib was found to be independently associated with a decreased risk of mortality (HR 0.33, 95% CI 0.12–0.93; P = .015). Multivariate stratified analyses verified this association in each patient subgroup (all HR < 1.0).

Conclusion: With a high patient tolerance to an interrupted sorafenib dosing schedule, the combination of TACE with sorafenib was associated with improved overall survival in early–intermediate stage HCC when compared with treatment with TACE alone.

Abbreviations: AFP = alpha-fetoprotein, BCLC = Barcelona Clinic Liver Cancer, CI = confidence interval, CR = complete response, HCC = hepatocellular carcinoma, HR = hazard ratio, OS = overall survival, PD = progressive disease, PR = partial response, RCT = randomized controlled trial, RECIST = Response Evaluation Criteria In Solid Tumors, SD = stable disease, START = Study in Asia of the Combination of TACE with Sorafenib in Patients with HCC, TACE = transcatheter arterial chemoembolization, TTP = time to progression.

Keywords: hepatoma, molecular targeted therapy, patient outcome, therapeutic embolization
1. Introduction

Hepatocellular carcinoma (HCC) is a highly fatal malignancy and remains one of the leading causes of cancer death worldwide. Even with progress in HCC surveillance, only a small proportion of new cases can receive curative treatment; potentially palliative treatments, such as transcatheter arterial chemoembolization (TACE), are frequently used for unresectable HCC. Under current practice guidelines, TACE is the recommended standard of care for intermediate-stage HCC. Moreover, TACE is used to treat early-stage HCC patients in whom curative treatment has failed or is infeasible. However, the clinical outcomes of patients who receive TACE remain unsatisfactory. In previous randomized controlled trials (RCTs) wherein patients with good liver condition were strictly selected, the 3-year survival rates of the TACE groups were only around 30%. There is a great need to improve the survival rates of patients who receive TACE.

Sorafenib has been shown to be successful in improving patient survival in advanced-stage HCC, so some experts have reasonably hypothesized that the combination of sorafenib with TACE for the treatment of locoregional HCCs would improve survival. However, the survival benefit of this combination strategy has not been demonstrated in RCTs. With the discrepancy between the hypothesis and previous trial results on the TACE and sorafenib combination, concerns related to study heterogeneity in previous clinical trials have been raised, and a positive result demonstrating clear survival benefit from a clinical trial is still pending.

In our recently published Phase II clinical trial [Study in Asia of the Combination of TACE with Sorafenib in Patients with HCC (START)], we showed that the combination of TACE and sorafenib is not only well tolerated but also efficacious. An interrupted sorafenib dosing schedule helped to reduce the number of adverse events caused by the combination treatment, and even improved patient compliance and clinical outcomes. However, a comparator arm in which patients received TACE alone was lacking in the START trial. We therefore conducted a post hoc analysis to compare patient survival in the TACE and sorafenib group and a matched control TACE alone group.

2. Methods

2.1. Study design and participants

We conducted a post hoc analysis of our recently published clinical trial (START; ClinicalTrials.gov registration #NCT00990860). START was a Phase II, investigator-initiated, prospective, single-arm multinational study that evaluated sorafenib in combination with TACE in patients with locoregional HCC. Patients were enrolled from 2009 to 2010. A detailed description of the study methods, inclusion and exclusion criteria, are available in the previously published report by Chung et al.

In this post hoc analysis, all Taiwanese patients with early or intermediate-stage HCC in the START trial were recruited into a TACE and sorafenib group. They were then randomly matched 1:1 by age, sex, Child-Pugh score, tumor size, tumor number, and tumor stage with patients from Taichung Veterans General Hospital who received TACE alone and who fulfilled the patient selection criteria of the START trial during the same time period (control group). Patients with advanced HCC were excluded from this present study. The clinical outcomes of the TACE and sorafenib group and the control group were compared. This study was conducted in accordance with the principles in the Declaration of Helsinki on human research. Approval from the institutional review board of Taichung Veterans General Hospital (No. CE14263A) was also obtained for this study.

2.2. TACE procedure

Conventional TACE was performed by experienced radiologists. The feeding vessels of tumors were selectively catheterized to preserve as much of the liver parenchyma as possible. Transarterial chemotherapy was performed using a mixture of lipiodol and a chemotherapeutic agent. Afterwards, embolization with absorbable particles (Gelfoam; Pfizer Inc., New York, NY) was done until complete flow stagnation was achieved. The detailed procedures which we followed for TACE were as previously described. Dynamic computed tomography (or, alternatively, magnetic resonance imaging) of the abdomen with contrast agent administration was used to evaluate the need for subsequent TACE 4 to 8 weeks after the index TACE. TACE was repeated on demand according to clinician judgment. If no viable tumor was found on dynamic imaging study, follow-up computed tomography (or magnetic resonance imaging) was arranged at 3-month intervals. If dynamic imaging study revealed new lesions, the patient was evaluated to determine whether new TACE treatment would be feasible.

2.3. The interrupted schedule of sorafenib therapy

In the START trial, patients were initially started on sorafenib therapy (400 mg BID) on day 4 (to day 7) after the index TACE (day 1). If a follow-up imaging study showed viable HCC, another course of TACE would be scheduled. Sorafenib therapy would be interrupted after the evening dose on day 4 before each subsequent TACE, and sorafenib therapy would be restarted on day 4 (to day 7) after each subsequent TACE. If patients did not receive further TACE, then they would receive continuous sorafenib therapy. The detailed schedules of sorafenib therapy were as previously described. The maximum duration of sorafenib treatment was 2 years after the index TACE. Sorafenib was used until stage migration during the study period. In contrast, none of the patients in the control (TACE alone) group received sorafenib therapy during the study period.

2.4. Outcome measures

We used modified RECIST (Response Evaluation Criteria In Solid Tumors) criteria to measure tumor size and tumor response. Apart from patients with extrahepatic metastasis, a maximum of 2 lesions in the liver were designated as target lesions by dynamic imaging study at the time of assessment. Tumor response was evaluated after comprehensively examining target lesions and nontarget lesions within or outside the liver. Tumor responses were classified as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD) according to the modified RECIST criteria. We also evaluated time to progression (TTP) and overall survival (OS).

2.5. Statistical analysis

Using a logistic model with age, sex, Child-Pugh score, tumor size, tumor number, and tumor stage, propensity scores were measured and patients in the 2 groups were matched. Data of continuous variables are presented as mean ± standard deviation.
deviation and median (interquartile range). Data of discrete variables are presented as number (%). Continuous variables were compared using the Mann–Whitney U test, and discrete variables were compared using Fisher exact test. Cumulative incidences for time-to-event (tumor progression or patient mortality) were calculated, and death before tumor progression was considered a competing risk event. Cumulative incidences of the TACE and sorafenib group and the control (TACE alone) group were compared using a modified Kaplan–Meier method, and differences in the full time-to-event distributions were compared using a modified log-rank test. After adjusting for age, sex, serum bilirubin level, serum albumin level, Child–Pugh score, tumor size, tumor number, Barcelona Clinic Liver Cancer (BCLC) tumor stage, and serum alpha-fetoprotein (AFP) level, multivariate regression analyses were conducted to determine the independent prognostic factors for OS. Hazard ratios (HRs) were also determined by means of a modified Cox proportional hazard model in the presence of competing risk events. A P value of less than .05 was considered to be statistically significant. Data analyses were carried out using IBM SPSS Statistics for Windows, Version 20.0 (IBM Corp., Armonk, NY).

### 3. Results

#### 3.1. Baseline demographic characteristics

There were 36 patients with early or intermediate-stage HCC in the TACE and sorafenib group, and 36 patients with early or intermediate-stage HCC in the TACE-alone control group. As summarized in Table 1, the baseline demographic data of patients in both groups were similar. The majority of patients in both groups were male (> 80%) and in late middle age. Liver function was generally well compensated, and the mean and median values of serum bilirubin and albumin were within normal limits. The median Child–Pugh score of each group was 5.0. Tumor burden, including maximum tumor size and tumor number, was also similar in both groups. Although the proportion of patients in BCLC stage A was slightly lower in the TACE and sorafenib group (25.0%) than in the control group (41.7%), the difference was not statistically significant (P = .21). The mean and median values of serum AFP were also similar in both groups. In the TACE and sorafenib group, the mean daily dose of sorafenib was 660.6 ± 152.0mg (median, 752.8mg), and the mean duration of sorafenib treatment was 378.2 ± 223.7 days (median, 394.0 days).

#### Table 1

Baseline characteristics of study participants.

| Characteristics                  | TACE and sorafenib group | Control (TACE alone) group | P  |
|----------------------------------|--------------------------|---------------------------|----|
| Age, y                           |                          |                           |    |
| Mean                             | 62.3 ± 8.9               | 62.6 ± 9.1                | .89|
| Median (interquartile range)     | 60.0 (57.0–69.0)         | 62.0 (66.8–69.3)          | .80|
| Sex, no. (%)                     |                          |                           | .73|
| Male                             | 30 (83.3)                | 32 (88.9)                 |    |
| Female                           | 6 (16.7)                 | 4 (11.1)                  |    |
| Sorafenib dosage, mg             |                          |                           |    |
| Mean                             | 660.6 ± 152.0            |                           |    |
| Median (interquartile range)     | 752.8 (517.3–800.0)      |                           |    |
| Sorafenib duration, d            |                          |                           |    |
| Mean                             | 378.2 ± 223.7            | —                         |    |
| Median (interquartile range)     | 394.0 (192.5–555.0)      | —                         |    |
| Albumin, g/dL                    |                          |                           |    |
| Mean                             | 3.8 ± 0.8                | 3.7 ± 0.4                 | .81|
| Median (interquartile range)     | 3.9 (3.3–4.2)            | 3.8 (3.6–4.0)             | .24|
| Total bilirubin, mg/dL           |                          |                           |    |
| Mean                             | 0.9 ± 0.4                | 1.0 ± 0.5                 | .41|
| Median (interquartile range)     | 0.8 (0.6–1.3)            | 1.1 (0.6–1.4)             | .55|
| Child–Pugh score                 |                          |                           |    |
| Mean                             | 5.3 ± 0.6                | 5.4 ± 0.8                 | .30|
| Median (interquartile range)     | 5.0 (5.0–5.0)            | 5.0 (5.0–6.0)             | .57|
| Max. tumor size, cm              |                          |                           |    |
| Mean                             | 3.5 ± 2.2                | 3.8 ± 2.7                 | .53|
| Median (interquartile range)     | 2.9 (1.9–4.1)            | 3.0 (2.0–5.0)             | .55|
| Tumor number                     |                          |                           |    |
| Mean                             | 3.8 ± 2.3                | 3.4 ± 2.6                 | .50|
| Median (interquartile range)     | 3.0 (2.0–4.3)            | 2.0 (1.0–6.0)             | .21|
| BCLC stage, no. (%)              |                          |                           |    |
| A                                | 9 (25.0)                 | 15 (41.7)                 | .21|
| B                                | 27 (75.0)                | 21 (58.3)                 |    |
| Serum AFP, ng/mL                 |                          |                           |    |
| Mean                             | 2420.9 ± 8060.8          | 14,439.4 ± 46,349.7       | .13|
| Median (interquartile range)     | 26.8 (11.3–232.3)        | 30.6 (12.6–1140.0)        | .40|

AFP = alpha-fetoprotein, BCLC = Barcelona Clinic Liver Cancer, TACE = transcatheter arterial chemembolization.
3.2. Tumor responses and time to progression

Radiological responses were evaluated by modified RECIST criteria. The tumor responses observed in the TACE and sorafenib group were significantly better than those in the control group (CR, 55.6% vs 33.3%; PR, 33.3% vs 38.9%; SD, 11.1% vs 11.1%; PD: 0% vs 16.7%; \( P = 0.04 \)). The disease control rate (CR + PR + SD) of the TACE and sorafenib group was significantly higher than that of the control group (100.0% vs 83.3%, \( P = 0.03 \)). However, although median TTP in the TACE and sorafenib group was longer than that in the control group, the difference was not statistically significant (0.65 (0.44–1.08) vs 0.38 (0.21–0.95) years; \( P = 0.14 \)).

3.3. Overall survival

As shown in Fig. 1, the 2-year OS in the TACE and sorafenib group was significantly higher than that of the control group [1-year survival probabilities: 0.86 (95% confidence interval, 95% CI, 0.75–0.98) vs 0.64 (95% CI, 0.47–0.80); 2-year survival probabilities: 0.78 (95% CI, 0.64–0.91) vs 0.49 (95% CI, 0.32–0.66); \( P = .012 \)]. Furthermore, TACE and sorafenib combination (HR, 0.35; 95% CI, 0.16–0.81), Child-Pugh score (HR, 2.21; 95% CI, 1.39–3.51), maximum tumor size (HR, 1.34; 95% CI, 1.18–1.52), BCLC stage A (HR, 0.31; 95% CI, 1.29–5.95), and tumor responder (CR + PR) (HR, 0.43; 95% CI, 0.19–0.97) were associated with improved patient survival in the univariate regression analysis (Table 2). However, in the multivariate regression analysis, only TACE and sorafenib combination (HR, 0.35; 95% CI, 0.15–0.81), Child-Pugh score (HR, 1.84; 95% CI, 1.09–3.09), maximum tumor size (HR, 1.29; 95% CI, 1.10–1.52), and serum AFP > 200 ng/mL (HR, 2.55; 95% CI, 1.08–6.00) were independent prognostic factors for patient survival.

We also analyzed OS among patients with intermediate-stage HCC. As shown in Fig. 2, the 2-year OS was significantly higher in the TACE and sorafenib group than in the control group [1-year survival probabilities: 0.85 (95% CI, 0.72–0.99) vs 0.48 (95% CI, 0.25–0.70); 2-year survival probabilities: 0.74 (95% CI, 0.56–0.91) vs 0.29 (95% CI, 0.08–0.49); \( P = .002 \)].

![Figure 1. Overall survival of patients with early-intermediate stage hepatocellular carcinoma in the TACE and sorafenib group and the control (TACE alone) group over the 2-year study period. TACE = transcatheter arterial chemoembolization.](image)

![Figure 2. Overall survival of patients with intermediate stage hepatocellular carcinoma in the TACE and sorafenib group and the control (TACE alone) group over the 2-year study period. TACE = transcatheter arterial chemoembolization.](image)

### Table 2

| Variables                      | Univariate analysis | Multivariate analysis |
|--------------------------------|---------------------|-----------------------|
|                                | HR (95% CI)         | \( P \)               | HR (95% CI)         | \( P \)               |
| TACE and sorafenib vs Control  | 0.35 (0.16–0.81)    | 0.013                 | 0.35 (0.15–0.81)    | 0.015                 |
| Age, y                         | 1.01 (0.97–1.05)    | 0.750                 |                      |                       |
| Male                           | 0.89 (0.81–2.52)    | 0.822                 |                      |                       |
| Total bilirubin, mg/dL         | 0.85 (0.35–2.09)    | 0.722                 |                      |                       |
| Albumin, g/dL                  | 0.41 (0.15–1.17)    | 0.096                 |                      |                       |
| Child-Pugh score               | 2.21 (1.39–3.51)    | <.001                 | 1.84 (1.09–3.09)     | 0.022                 |
| Max. tumor size, cm            | 1.34 (1.18–1.52)    | <.001                 | 1.29 (1.10–1.52)     | 0.002                 |
| Tumor number                   | 1.09 (0.94–1.27)    | .260                  |                      |                       |
| BCLC stage A vs B              | 0.31 (0.11–0.91)    | .034                  | 0.49 (0.14–1.73)     | .268                  |
| AFP >200 mg/mL                 | 2.77 (1.20–5.05)    | .009                  | 2.55 (1.08–6.00)     | .032                  |
| CR+PR vs SD+PD                 | 0.43 (0.19–0.97)    | .042                  | 2.08 (0.62–7.00)     | .236                  |

**Note:** Diabetes, hypertension, alcohol intake, BMI, PT, INR, platelet. 

\( \alpha \)-fetoprotein, BCLC = Barcelona Clinic Liver Cancer, CI = confidence interval, CR = complete response, HR = hazard ratio, PD = progressive disease, PR = partial response, SD = stable disease, TACE = transcatheter arterial chemoembolization.
OS in the TACE and sorafenib group at the 3-year mark was not significantly different from that of the control group [3-year survival probabilities: 0.42 (95% CI, 0.25–0.59) vs 0.38 (95% CI, 0.21–0.54); \( P = .245 \); see Figure, Supplemental Content, http://links.lww.com/MD/B865].

### 3.4. Multivariate stratified analyses in subgroups of patients

Multivariate stratified analyses for survival benefit of TACE and sorafenib combination therapy was performed in subgroups of patients (subgroups shown in Fig. 3). TACE and sorafenib combination therapy was associated with decreased overall mortality in each patient subgroup (all HR <1.0). Furthermore, regarding the association between TACE and sorafenib combination and reduced overall mortality risk, statistical significance was reached in some subgroups (age >60 years, male sex, BCLC stage A or B, Child–Pugh class A5, tumor size >3 cm, AFP ≤200 ng/mL, and tumor response CR and PR).

### 3.5. Discussion

Although some Phase II clinical trials have shown encouraging results that TACE combined with sorafenib could be efficacious in the management of locoregional HCC,[15,19,20] RCTs have failed to demonstrate any survival benefit from combined therapy.[13,21] However, variations in treatment regimens, such as the timing of sorafenib discontinuation or repeating TACE, have been observed in different regions.[21,22] In 1 study, Asian patients appeared to have a greater survival benefit from TACE and sorafenib than non-Asian patients.[21] It is also possible that TACE operators in different regions may contribute to differences in outcome.[22] In this study, because patients were recruited from the same region, heterogeneity in the treatment process may be reduced. We demonstrated that patient survival was improved by TACE and sorafenib compared with TACE alone. Our findings provide a basis for conducting well-designed RCTs in the future.

On the basis of previous RCTs of TACE and sorafenib for locoregional HCC, sustaining sorafenib therapy for a sufficient period of time has been considered an important prognostic factor.[14] For example, compared with non-Asian patients in the SPACE trial, longer duration of sorafenib treatment was associated with longer OS in Asian patients (median duration 30 vs 17 weeks). Similarly, compared with Japanese patients in the Japan–Korea trial, longer duration of sorafenib treatment was associated with longer TTP in Korean patients (median duration 31 vs 16 weeks). In this study, the median duration of sorafenib therapy was 394 days (56 weeks); the good survival benefit we observed may have been related to the lengthy duration of sorafenib treatment. According to the START findings, an interrupted sorafenib dosing schedule (in which sorafenib administration was stopped for 4 days before and after TACE) contributed to considerably fewer adverse events than observed in other trials of combination therapy; this dosing strategy may help patients tolerate a longer duration of sorafenib therapy.

![Figure 3. Multivariate stratified analysis of the association between TACE and sorafenib combination treatment and mortality risk.](http://links.lww.com/MD/B865)

| Subgroup                          | Control | TACE + sorafenib | HR (95% CI) |
|-----------------------------------|---------|------------------|-------------|
| **Age, year**                     |         |                  |             |
| ≤ 60                              | 8       | 15               | 0.52 (0.14-2.01) |
| > 60                              | 10      | 21               | 0.04 (0.00-0.57) |
| **Sex**                           |         |                  |             |
| Male                              | 16      | 32               | 0.25 (0.10-0.63) |
| Female                            | 2       | 4                | 0.25 (0.10-0.63) |
| **BCLC stage**                    |         |                  |             |
| A                                 | 3       | 15               | 0.27 (0.10-0.71) |
| B                                 | 15      | 21               | 0.27 (0.11-0.68) |
| **Child–Pugh class**              |         |                  |             |
| A5                                | 11      | 26               | 0.10 (0.02-0.43) |
| A6-B7                             | 7       | 10               | 0.24 (0.04-1.53) |
| **Max. tumor size**               |         |                  |             |
| ≤ 3 cm                            | 7       | 20               | 0.12 (0.00-5.61) |
| > 3 cm                            | 11      | 16               | 0.28 (0.09-0.82) |
| **Tumor number**                  |         |                  |             |
| ≤ 3                               | 9       | 22               | 0.39 (0.14-1.13) |
| > 3                               | 9       | 14               | 0.18 (0.01-2.42) |
| **Serum AFP, ng/mL**              |         |                  |             |
| ≤ 200 ng/mL                       | 9       | 22               | 0.07 (0.02-0.27) |
| > 200 ng/mL                       | 9       | 14               | 0.32 (0.07-1.39) |
| **Tumor response**                |         |                  |             |
| CR+PR                             | 10      | 26               | 0.23 (0.09-0.60) |
| SD+PD                             | 8       | 10               | 0.32 (0.09-0.60) |
| **Total**                         | 18      | 36               | 0.32 (0.14-0.73) |
Tumor response was significantly better among patients who received TACE and sorafenib than among those who received TACE alone in this study. Improved tumor response rates in the TACE and sorafenib group may also have contributed to better patient survival. Due to the hypoxic effect in tumor cells induced by arterial embolization, TACE can result in a rapid release of tumor neoangiogenesis within tumor mass leading to much higher than that of patients with intermediate-stage HCC, so the observation that TACE and sorafenib combination therapy could improve patient survival remains unchanged.

In conclusion, with high patient tolerance to an interrupted sorafenib dosing schedule, the combination of TACE and sorafenib was associated with improved OS in early–intermediate stage HCC compared with TACE alone.

References

[1] Torre LA, Bray F, Siegel RL, et al. Global cancer statistics, 2012. CA Cancer J Clin 2015;65:87–108.
[2] Ulahannan SV, Duffy AG, McNeil TS, et al. Earlier presentation and application of curative treatments in hepatocellular carcinoma. Hepatology 2014;60:1637–44.
[3] Altekruse SF, McGlynn KA, Reichman ME. Hepatocellular carcinoma incidence, mortality, and survival trends in the United States from 1973 to 2005. J Clin Oncol 2009;27:1485–91.
[4] European Association for the Study of the Liver, European Organisation for Research and Treatment of Cancer. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol 2012;56:908–943. Erratum in: J Hepatol 2012;56:1430.
[5] Forner A, Gilabert M, Bruix J, et al. Treatment of intermediate-stage hepatocellular carcinoma. Nat Rev Clin Oncol 2014;11:325–33.
[6] Bruix J, Sherman M. American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma: an update. Hepatology 2011;53:1020–2.
[7] Kinugasa H, Nousu K, Takeuchi Y, et al. Risk factors for recurrence after transarterial chemoembolization for early-stage hepatocellular carcinoma. J Gastroenterol 2012;47:421–6.
[8] Lo CM, Ngan H, Tso WK, et al. Randomized controlled trial of transarterial lipidol chemoembolization for unresectable hepatocellular carcinoma. Hepatology 2002;35:1164–71.
[9] Llovet JM, Real ML, Montaña X, et al. Barcelona Liver Cancer Group. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. Lancet 2002;359:64–69.
[10] Llovet JM, Bacigalupo A, Mazzucchelli L, et al. SHARP Investigators Study Group. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 2008;359:378–90.
[11] Cheng AL, Kang YK, Chen Z, et al. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. Lancet Oncol 2009;10:25–34.
[12] Kudo M, Ueshima K. Positioning of a molecular-targeted agent, sorafenib, in the treatment algorithm for hepatocellular carcinoma and implications of many complete remission cases in Japan. Oncology 2010;78(Suppl 1):154–66.
[13] Zeng J, Lv L, Mei ZC. Efficacy and safety of transarterial chemoembolization plus sorafenib for early or intermediate stage hepatocellular carcinoma: a systematic review and meta-analysis of randomized controlled trials. Clin Res Hepatol Gastroenterol 2016;40:688–97.
[14] Hsu C, Po Ching L, Morita S, et al. Perspectives on the design of clinical trials combining transarterial chemoembolization and molecular-targeted therapy. Liver Cancer 2012;1:148–76.
[15] Chao Y, Chung YH, Han G, et al. The combination of transcatheter arterial chemoembolization and sorafenib is well tolerated and effective in Asian patients with hepatocellular carcinoma: final results of the START trial. Int J Cancer 2013;136:1458–67.
[16] Chung YH, Han G, Yoon JH, et al. Interventional analysis of START: study in Asia of the combination of TACE (transcatheter arterial chemoembolization) with sorafenib in patients with hepatocellular carcinoma. Int J Cancer 2013;132:2448–58.
[17] Lencioni R, Llovet JM. Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. Semin Liver Dis 2010;30:52–60.
[18] Gray RJ. A class of K-sample tests for comparing the cumulative incidence of a competing risk. Ann Stat 1988;16:1141–34.
[19] Lencioni R, Llovet JM, Han G, et al. TACE plus sorafenib for the treatment of hepatocellular carcinoma: results of the multicenter, phase II SOCRATES trial. Cancer Chemother Pharmacol 2014;74:947–54.
[20] Sansonno D, Lautletta G, Russi S, et al. Transarterial chemoembolization plus sorafenib: a sequential therapeutic scheme for HCV-related intermediate-stage hepatocellular carcinoma: a randomized clinical trial. Oncologist 2012;17:359–66.
[21] Lencioni R, Llovet JM, Han G, et al. Sorafenib or placebo plus TACE with doxorubicin-eluting beads for intermediate stage HCC: the SPACE trial. J Hepatol 2016;64:1090–8.
[22] Kudo M, Imanaka K, Chida N, et al. Phase III study of sorafenib after transarterial chemoembolization in Japanese and Korean patients with unresectable hepatocellular carcinoma. Eur J Cancer 2011;47:2117–27.
[23] Chaparro J, Geschwind JF. Percutaneous therapies of hepatocellular carcinoma: an update. Chin Clin Oncol 2013;2:16.
[24] Carmeliet P, Jain RK. Angiogenesis in cancer and other diseases. Nature 2000;407:249–57.
[25] Sergio A, Cristofori G, Cardin R, et al. Transcatheter arterial chemoembolization (TACE) in hepatocellular carcinoma (HCC): the role of angiogenesis and invasiveness. Am J Gastroenterol 2008;103:914–21.
[26] Llovet JM, Peña CE, Labia CD, et al. SHARP Investigators Study Group. Plasma biomarkers as predictors of outcome in patients with advanced hepatocellular carcinoma. Clin Cancer Res 2012;18:2290–300.
[27] Wilhelm SM, Carter C, Tang L, et al. BAY 43-9006 exhibits broad spectrum oral antitumor activity and targets the RAF/MEK/ERK pathway and receptor tyrosine kinases involved in tumor progression and angiogenesis. Cancer Res 2004;64:7099–109.
[28] Carlonago F, Anaganti S, Guida T, et al. BAY 43-9006 inhibition of oncogenic RET mutants. J Natl Cancer Inst 2006;98:326–34.

[29] Chao Y, Wu CY, Kuo CY, et al. Cytokines are associated with postembolization fever and survival in hepatocellular carcinoma patients receiving transcatheter arterial chemoembolization. Hepatol Int 2013;7:883–92.

[30] Poullenot F, Bioulac-Sage P, Laumonier H, et al. Hepatocellular carcinoma treated by sorafenib with complete radiological response according to mRECIST criteria: could we stop the treatment? About four cases. Acta Oncol 2014;53:420–3.

[31] Wada Y, Takami Y, Tateishi M, et al. The efficacy of continued sorafenib treatment after radiologic confirmation of progressive disease in patients with advanced hepatocellular carcinoma. PLoS One 2016;11:e0146456.

[32] Zhang Y, Fan W, Zhu K, et al. Sorafenib continuation or discontinuation in patients with unresectable hepatocellular carcinoma after a complete response. Oncotarget 2015;6:24550–9.

[33] Marinelli S, Salvatore V, Baron Toaldo M, et al. Evaluation of the impact of transient interruption of antiangiogenic treatment using ultrasound-based techniques in a murine model of hepatocellular carcinoma. BMC Cancer 2014;14:403.