an increase in arterial blood flow or a decrease in portal blood flow, even though such a case is rare, nodules are regarded as malignant. However, in nodules in which arterial blood flow is low, and portal blood flow is preserved, follow-up may be continued when biopsy suggests benign nodules. However, when biopsy leads to a diagnosis of typical well-differentiated HCC, the treatment of early HCC may be considered.

When EOB-MRI shows uptake, nodules in which biopsy suggests a borderline lesion may be followed up. In conclusion, currently, EOB-MRI is the most useful tool for diagnosing early HCC in hypovascular hepatocellular nodes (fig. 1, 7).

**Consensus Statements**

18 It is essentially difficult to differentiate a histopathological diagnosis of early HCC from a dysplastic nodule by imaging.
19 Gd-EOB-MRI is the most sensitive tool for detection of any initial change of hepatocarcinogenesis, i.e. low intense mass on hepatocyte image of Gd-EOB-MRI. Therefore, it is recommended that Gd-EOB-MRI be performed as much as is possible.
20 Sonazoid-enhanced contrast US is more sensitive for detection of intranodular hypervascularity than MDCT (dynamic CT) or dynamic MRI. Therefore, to confirm true hypovascularity, Sonazoid-enhanced CEUS is recommended.
21 Decreased intranodular portal flow on CTAP suggests a high malignant potential of a nodule. Therefore, such nodules should be treated as malignant.
22 Nodules with a low uptake of EOB-MRI and a size >1.5 cm should be treated as malignant after confirmation by biopsy.
23 Nodules with hypovascularity and negative findings on EOB-MRI and Kupffer phase imaging of Sonazoid CEUS are likely to be benign. Thus, they can be followed up without treatment when the nodule size is <1.5 cm.
24 Biopsy-proven early HCC should be treated.

## Staging for Hepatocellular Carcinoma

### *Classification of Staging Systems*

TNM stages representing the degree of cancer spreading are clinically used for various cancers, not only for HCC. It is well recognized that for HCC stages of not only tumors but also the liver functional reserve are very important for deciding a treatment strategy and prognosis prediction. Thus, HCCs should be treated with an understanding of the importance of the liver cancer staging systems.

**Table 11.** TNM stage by the Liver Cancer Study Group of Japan [cited from 54, with permission]

| Stage | T category | N category | M category |
|---|---|---|---|
| Stage I | T1 | N0 | M0 |
| Stage II | T1 | N0 | M0 |
| Stage III | T3 | N0 | M0 |
| Stage IVA | T4 | N0 | M0 |
| | T1, T2, T3, T4 | N1 | M0 |
| Stage IVB | T1, T2, T3, T4 | N0, N1 | M1 |

Currently there are three staging systems for HCC: (1) TNM staging as tumor spreading staging, (2) liver function staging, and (3) systems integrating (1) and (2).

### *TNM Stage*

For TNM staging, UICC or AJCC classification is used internationally, but these are thought inappropriate because the cut-off tumor size is set to 5 cm. Since portal microinvasion and intrahepatic metastasis occurs in 27 and 10% of tumors with a tumor size of ≥2 cm, respectively, a TNM staging classification setting the cut-off size to 2 cm is necessary. TNM stages should be specified by three factors: 2-cm tumor size, solitary or multiple lesions, and the presence or absence of vascular invasion, as used by the Liver Cancer Study Group of Japan (LCSGJ), may be the most appropriate for countries, including Japan, where the early detection of HCC is possible [26] (tables 11, 12).

### *Liver Damage Stage*

There are two liver function staging systems: Child-Pugh staging that is used internationally for a long time, and the liver damage staging established by LCSGJ (table 13). Liver damage staging [26] established by LCSGJ is different from Child-Pugh staging in that the ICG retention rate at 15-min ($ICGR_{15}$) value is incorporated instead of hepatic encephalopathy, and specifications of the prothrombin time and albumin level are more strict. Also, Child-Pugh staging employs scoring in which grades are determined based on the total score, whereas a higher stage with consistency of two items is regarded as

**Table 12.** T category of TNM stage by the Liver Cancer Study Group of Japan [cited from 26, with permission]

| Criteria | T1 | T2 | T3 | T4 |
|---|---|---|---|---|
| (1) Number of tumors: solitary | (2) All three criteria are fulfilled | (3) Two of the three criteria are fulfilled | (4) One of the three criteria is fulfilled | (5) None of the three criteria are fulfilled |
| (2) Tumor diameter: no more than 2 cm | |  |  | |
| (3) No vascular or bile duct invasion: Vp0, Vv0, B0 |  |   |   |  |

**Table 13.** Degree of liver damage by the Liver Cancer Study Group of Japan [cited from 26, with permission]

| Clinical and laboratory findings | Grade[1] | | |
|---|---|---|---|
| | A | B | C |
| Ascites | none | controllable | uncontrollable |
| Serum bilirubin, mg/dl | <2.0 | 2.0–3.0 | >3.0 |
| Serum albumin, g/dl | >3.5 | 3.0–3.5 | <3.5 |
| $ICGR_{15}$, % | <15 | 15–40 | >40 |
| Prothrombin activity, % | >80 | 50–80 | <50 |

[1] Degree of liver damage is designated as class A, B, or C, based on the highest grade containing at least two findings.

**Table 14.** Definition of the Japan Integrated Staging Score

| | Variable | | | |
|---|---|---|---|---|
| | 0 | 1 | 2 | 3 |
| Child-Pugh stage | A | B | C | |
| TNM stage[1] | I | II | III | IV |

[1] By the Liver Cancer Study Group of Japan.

the grade in LCSGJ liver damage staging. Since LCSGJ liver damage staging was originally designed for cases indicated for hepatectomy, $ICGR_{15}$ is specified as an essential factor. By contrast, Child-Pugh staging was originally widely used for diagnosis of liver functional reserve in cirrhotic patients, including terminal liver cirrhosis cases such as those with hepatic encephalopathy or ascites. However, differential use of the two staging systems is probably what is important. In the surgical field, LCSGJ liver damage staging is used for consideration of hepatectomy, and Child-Pugh staging is widely used for consideration of liver transplantation. The two systems are differentially used corresponding to the clinical objectives.

*Integrated Staging System*

The third type of staging system actually sees several systems integrating the TNM and liver damage stages. Various staging systems such as: (1) Okuda stage [56], (2) BCLC stage [1], (3) CLIP score, (4) JIS score [58, 59] (table 14), and (5) Tokyo Score [61], have all seen long-time use. The JIS score utilizing both the LCSGJ TNM and Child-Pugh stages is considered the most useful for overall staging of HCC in Japan [59, 60]. The CLIP score has disadvantages: specification of the tumor spreading degree is rough, only AFP is used as a biological malignancy marker, and stratification ability is also poor in advanced cases (many cases cluster to a score of 0–2). By contrast, the JIS score is superior for stratification of scores. The original JIS score employs Child-Pugh staging, but the modified JIS score employing liver damage staging in-

stead of Child-Pugh staging is frequently used in the surgical field [62]. The modified JIS score may be useful for hepatectomy cases because LCSGJ liver damage is more strictly classified. The original and modified JIS scores may be differentially used in accord with the clinical objectives, as with Child-Pugh and liver damage staging. Recently, biomarker combined JIS scores, which better stratify HCC patients than conventional JIS scores [63].

*Importance of Integrated Staging Systems*

There are several reasons why integrated staging systems are clinically important:

(1) For HCC, TNM staging is insufficient for predicting the prognosis, and a staging system integrating TNM and liver function stages is necessary to accurately predict the prognosis.

(2) Prediction of an accurate prognosis for individual patients.

(3) Establishment of a common scale for selection of the optimum treatment for individual patients.

(4) Identification of the patient population to be treated with the most curative therapy.

(5) Identification of the patient population in which the prognosis is worsened by overtreatment.

(6) Establishment of a fairly common scale for the comparison of outcomes among treatment methods and institutions. Although simple comparisons among treatment methods are difficult, it is useful for comparisons of a modality (resection, local treatment, or TACE) with identical scores among institutions.

(7) Evaluation of therapeutic effects of new treatment methods, for example comparison of therapeutic effects of liver transplantation and a new drug in homogenous populations, i.e. comparison of therapeutic effects between current and novel treatment methods.

(8) A graph contrasting outcomes of transplantation of individual JIS scores to long-term outcomes of preexisting treatment methods of individual JIS scores is useful for deciding indication of liver transplantation and for obtaining informed consent from patients indicated for this treatment.

*Current State and Future Perspectives*

Globally, CLIP scores or BCLC stage are used in Europe and North America as staging systems. However, these have different bases: the BCLC stage is basically a treatment selection system for deciding on a therapeutic strategy, whereas the CLIP and JIS scores are prognostic prediction stagings. The CLIP score and BCLC stage are useful for use in European and North American systems that tend to detect only large HCCs, but the JIS score is most useful for countries, such as Japan, where many small liver cancers are detected. At present, the JIS score is appropriate for Japan, while CLIP or BCLC score suits Europe and North America.

Attention needs to be paid to the fact that the BCLC stage corresponds to the Japanese treatment algorithm, but is not a prognostic prediction staging system. For countries incapable of the early detection of HCC or developing countries with insufficient screening systems and diagnostic instruments, the CLIP score may provide good stratification as a prognostic prediction system. The JIS score may be used worldwide when surveillance systems for early detection of HCC become more common and early detection of HCC reaches the same level as found in Japan.

*Summary*

Various liver cancer staging systems have been proposed. However, for practical purposes the following conditions are essential for comprehensive discussions of all liver cancer cases: (1) the system should be simple, (2) no data lacking, (3) can be applied by anyone anywhere, (4) the system is easy to memorize, and (5) the system is superior for stratifying early, advanced, and terminal groups. Considering these conditions, the JIS score may be the most appropriate staging system for the overall distribution of liver cancer cases in Japan.

**Consensus Statements**

25 The TNM stage proposed by the Liver Cancer Study Group of Japan is ideal for use in countries like Japan, where many small HCCs <2 cm in diameter are found based on an established nationwide surveillance system. Similarly, the JIS score, biomarker combined JIS score or a modified JIS score appears the best prognostic staging system for use in countries where small HCCs can be detected.

26 BCLC staging proposed by AASLD is a treatment selection staging not a prognostic predictive staging. Therefore, comparisons between treatment selection staging (BCLC) and prognostic predictive staging (CLIP or JIS score) are inappropriate. This issue is really important and should be kept in mind.

## Treatment Algorithm of Hepatocellular Carcinoma

### *Evidence-Based Guidelines in Japan*

In a 2005 version of the guidelines, a treatment algorithm was prepared by the Makuuchi Group, Ministry of Health, Labour and Welfare. In 2009, a revision was published [5, 64]. Concretely, treatment is recommended in accordance with the severity of liver disease, number of tumors, and tumor diameter. Initially, it is described that resection or local ablation be performed in solitary tumor patients with liver damage grade A/B. However, local ablation should be selected only in liver damage grade B patients with tumors measuring ≤2 cm in tumor diameter. In liver damage grade A/B patients with 2 or 3 tumors measuring ≤3 cm in tumor diameter, resection or ablation should be conducted. Resection or TACE is selected in those with 2–3 tumors measuring >3 cm. TACE or arterial infusion chemotherapy is recommended in those with multiple (four or more) tumors. In liver damage grade C patients with three or less tumors measuring ≤3 cm, or a solitary tumor measuring ≤5 cm, liver transplantation is recommended if a donor is available. In those with four or more tumors, best supportive care should be performed (fig. 8).

When establishing the 2009 revision, only articles based on high-level evidence were selected from the literature published between 2002 and June 2007. Therefore, a high-level evidence-based molecule-targeting agent reported in 2008 [65] and 2009 [66], sorafenib, was not included. This is somewhat controversial. However, in the footnotes, it was stated that 'chemotherapy is selected in some patients with extrahepatic metastasis'. This was noted considering sorafenib. The other revision point is 'liver transplantation should be performed in patients aged 65 years or younger', which is described in the footnotes. This algorithm consists of evidence described in high-level quality articles. Low-level evidence-based articles are omitted; therefore, this algorithm can be objectively understood, but seems to be a bit conservative. In the future, a practical algorithm involving the new evidence created worldwide should be included in this algorithm.

### *Treatment Algorithm in the West*

The treatment algorithms in Europe and North America were published in the *Journal of Hepatology* as the EASL consensus in 2001, and then as the AASLD Clinical

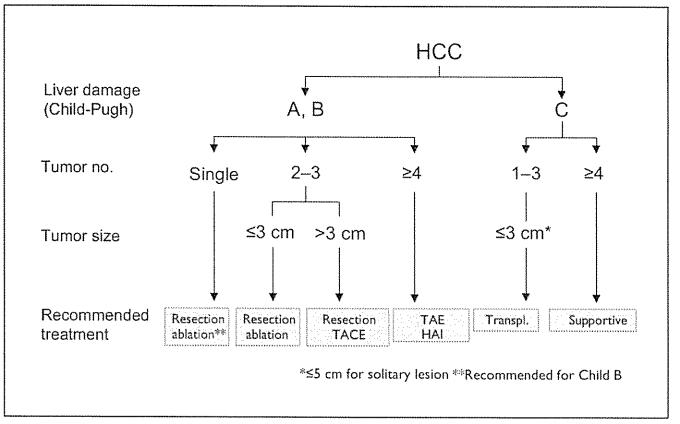


**Fig. 8.** Evidenced-based algorithm for HCC. Resection or TACE may be selected for liver damage A patients with vascular invasion. Chemotherapy may be selected for extrahepatic HCC. Liver transplantation is only for ≤65-year-olds [cited from 5, with permission].

Practice Guidelines in Hepatology in 2005 [2] followed by an updated version in 2010 [3]. Both these were prepared based on BCLC staging [1, 57]. The BCLC staging classification consists of stages 0 to D. Only palliative treatment is specified for stage D, while stage 0 is defined as a very early stage, specifying 2-cm or smaller solitary liver cancers with carcinoma in situ and corresponds to early HCC in Japan. These are solitary, and resection is desirable when portal pressure and the bilirubin levels are normal. When portal hypertension is present, other potentially curative treatments, such as liver transplantation and local treatment, are selected. For solitary HCC for three or fewer 3-cm lesions with mild portal hypertension, liver transplantation or local ablation is recommended. These are very strict criteria, and only stages 0 and A are indicated for curative treatments, i.e. resection, local ablation, and liver transplantation. The moderate stage B specifies multinodular lesions, and the advanced stage C specifies cases with portal invasion or extrahepatic spread. For stage B, TACE is selected. For stage C HCCs with vascular invasion and/or extrahepatic spread, sorafenib is a choice of treatment.

These selection criteria do not meet the current conditions performed in Japan. Application of these staging methods is difficult because many parameters and stage classifications (performance status, Child-Pugh, and portal hypertension) are used, and their application in Japan is inappropriate and so unlikely. However, BCLC is basically identical to the simplified evidence-based treatment algorithm established by Makuuchi's group, except for the application of liver transplantation.

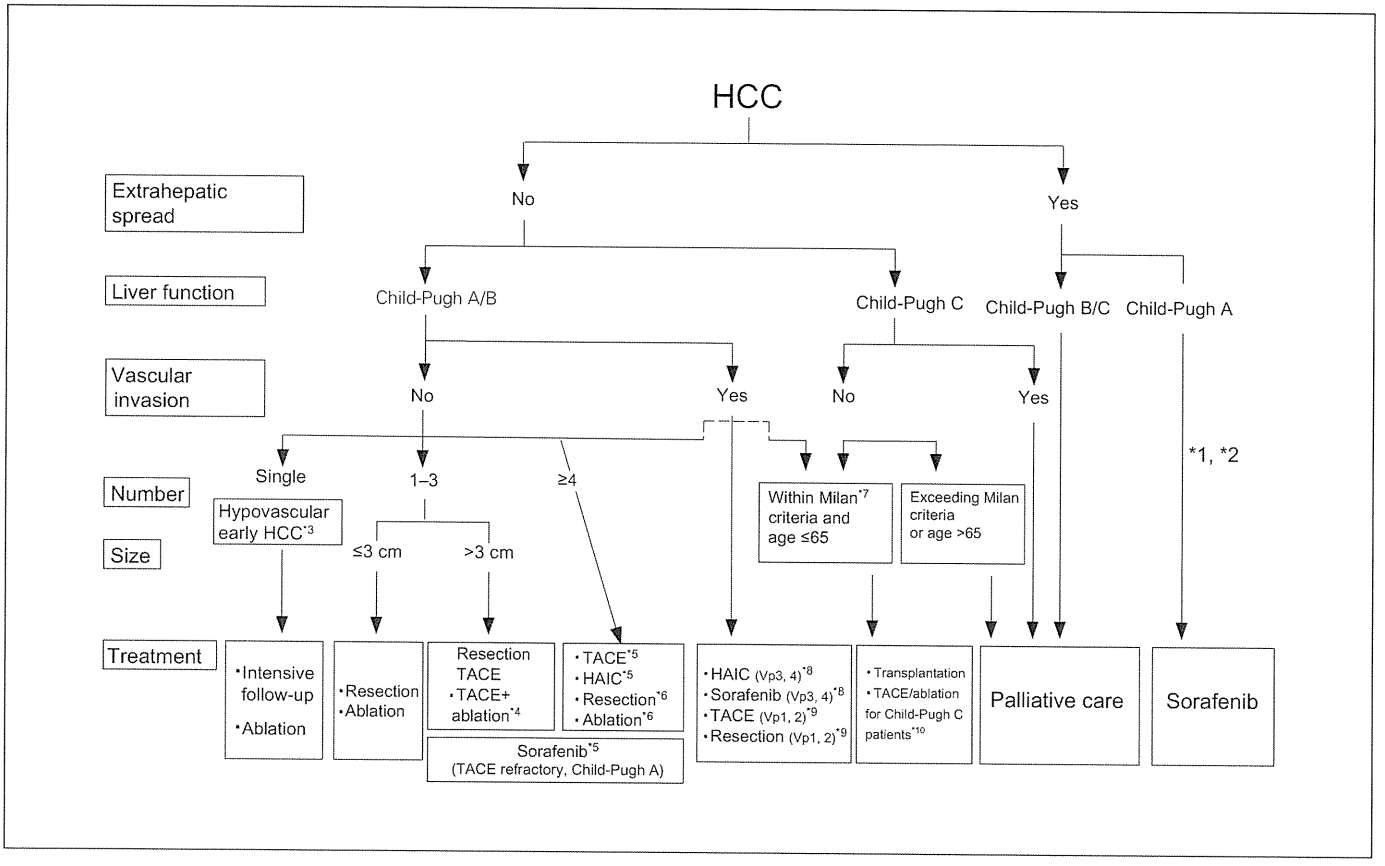


**Fig. 9.** Consensus-based treatment algorithm for HCC proposed by JSH revised in 2010. Footnotes: *1 = Treatment should be performed as if extrahepatic speed is negative, when extrahepatic spread is not regarded as a prognostic factor. *2 = Sorafenib is the first choice of treatment in this setting as a standard of care. *3 = Intensive follow-up observation is recommended for hypovascular nodules by the Japanese Evidence-Based Clinical Practice Guidelines. However, local ablation therapy is frequently performed in the following cases: (1) when the nodule is diagnosed pathologically as early HCC, (2) when the nodules show decreased uptake on Gd-EOB-MRI, or (3) when the nodules show decreased portal flow by CTAP, since these nodules are known to frequently progress to the typical advanced HCC. *4 = Even for HCC nodules exceeding 3 cm in diameter, combination therapy of TACE and ablation is frequently performed when resection is not indicated. *5 = TACE is the first choice of treatment in this setting. HAIC (hepatic arterial infusion chemotherapy) using an implanted port is also recommended for TACE refractory patients. The regimen for this treatment is usually low-dose FP (5-FU + CDDP) or intra-arterial 5-FU infusion combined with systemic IFN therapy. Sorafenib is also a treatment of choice for TACE refractory patients with Child-Pugh A liver function. *6 = Resection is sometimes performed even when numbers of nodules are over 4. Furthermore, ablation is sometimes performed in combination with TACE. *7 = Milan criteria: tumor size ≤3 cm and tumor number ≤3; or solitary tumor ≤5 cm. Even when liver function is good (Child-Pugh A/B), transplantation is sometimes considered for frequently recurring HCC patients. *8 = Sorafenib and HAIC are recommended for HCC patients with Vp3 (portal venous invasion at the first portal branch) or Vp4 (portal invasion at the main portal trunk). *9 = Resection and TACE is frequently performed when portal invasion is minimum such as Vp1 (portal invasion at the third or more peripheral portal branch) or Vp2 (portal invasion at the second portal branch). *10 = Local ablation therapy or subsegmental TACE is performed even for Child-Pugh C patients when transplantation is not indicated when there is no hepatic encephalopathy, no uncontrollable ascites, and a low bilirubin level (<3.0 mg/dl). However, it is regarded as an experimental treatment since there is no evidence of its survival benefit in Child-Pugh C patients. A prospective study is necessary to clarify this issue. Even in Child-Pugh A/B patients, transplantation is sometimes performed for relatively younger patients with frequently or early recurring HCC after curative treatments [cited from 10, 49, with permission].

*A Consensus-Based Treatment Algorithm for HCC Proposed by the JSH*

For HCC treatment, practice patterns markedly differ between Europe/USA and Japan. For this reason, a unique Japanese algorithm (JSH Consensus 2007) was proposed in 2007 [67]. Consequently, a revised draft was presented at the 45th Meeting of the Japanese Liver Society in 2009 (Congress Chair: Masatoshi Kudo), and an article was published in 2010 [10] (fig. 9). The consensus-based treatment algorithm recommended by this society consists of extrahepatic lesions, hepatic functional reserve, vascular invasion, number of tumors, and tumor diameter. Treatment is classified into curative treatment (resection, local ablation), TACE, arterial infusion chemotherapy, liver transplantation, and best supportive care. Basically, the contents are consistent with the evidence-based treatment algorithm established by the Makuuchi group. However, a consensus-based algorithm is not always based on evidence, but involves routinely employed treatment for which a consensus has been reached in Japan. For example, concerning the item of early HCC, local ablation is performed for the lesions in which biopsy diagnosis, CTHA/CTAP, or gadolinium-DTPA ethoxybenzyl (EOB)-MRI suggests malignancy. In evidence-based guidelines, hypovascular tumors are categorized as 'non-typical for HCC', reflecting lesions without an arterial enhancement. Evidence-based guidelines recommend that these lesions should be followed up. However, among hypovascular tumors, 'early liver cancer' definitively diagnosed based on CTAP, EOB-MRI, or biopsy findings, is known to frequently progress to typical HCC. Based on this fact, treatment is performed in many cases in a routine clinical setting; less invasive ablation therapy is performed rather than resection, which is more invasive. With respect to hypovascular lesions without malignant findings, intensive follow-up is recommended. For management, early hypovascular HCC should be separated from other types of hypervascular liver cancer.

Initially, resection or local ablation therapy should be performed to treat three or less tumors measuring ≤3 cm in diameter without extrahepatic lesions/vascular invasion in which the liver function is good. In this group, the prognosis of curative treatment may be favorable. In three or less lesions measuring >3 cm in diameter, resection or TACE is recommended. Curability may be improved by adding ablation therapy to previous transarterial treatment (TACE or lipiodol TACE). Secondly, TACE and arterial infusion chemotherapy are recommended to treat four or more lesions. However, arterial infusion chemotherapy is performed based on expert experience, but there is no solid evidence because there is no randomized controlled trial (RCT). The combination of local ablation therapy and TACE/arterial infusion chemotherapy for five to six or less lesions is beneficial in some cases. Furthermore, resection may be considered for such lesions if possible. In young Child-Pugh A/B hepatic functional reserve patients with early recurrence, liver transplantation is sometimes the choice of treatment when they meet the Milan criteria. In the presence of vascular invasion, resection is performed for patients with third or fourth branch of portal venous invasion if possible. In such patients, TACE can be a choice of treatment. In patients with main trunk or first branch of portal vein, arterial infusion chemotherapy, in addition to hepatic arterial infusion chemotherapy with implanted port, is a choice of treatment.

In Child-Pugh C hepatic functional reserve patients aged 65 years or younger, with an unfavorable liver function in the absence of vascular invasion, meeting the Milan criteria, liver transplantation is recommended. Furthermore, as test therapy, local ablation or subsegmental TACE is conducted in Child-Pugh C hepatic functional reserve patients without hepatic encephalopathy or refractory ascites, showing a bilirubin level of ≤3 mg.

However, there is no evidence regarding the survival benefits. In the future, a prospective clinical trial should be conducted. In Child-Pugh C hepatic functional reserve patients with vascular invasion or extrahepatic lesions, the best supportive care is basically selected. In this case, palliative radiotherapy to resolve pain is included. However, when extrahepatic lesions are not a prognostic factor, treatment in accordance with the standard treatment algorithm may improve the prognosis.

In Child-Pugh A hepatic functional reserve patients with extrahepatic lesions, sorafenib should be recommended as a first choice of treatment. This agent is recommended for patients with vascular invasion, especially patients with macrovascular invasion, in addition to arterial injection chemotherapy. In non-responders to TACE/arterial injection chemotherapy, sorafenib may become a treatment option when the hepatic functional reserve is preserved as Child-Pugh A.

The consensus-based treatment algorithm is not always based on scientific evidence. However, it is significant because a consensus has been reached among specialists belonging to the JSH, as demonstrated in BCLC, and therefore their own treatment algorithm is introduced. In the future, evidence-lacking parts must be re-

vised through a prospective study. The treatment algorithm for liver cancer reflects a primary concept for treatment strategies. Basically, it is important to perform individualized treatment in individual patients, considering various conditions.

### *Definition of TACE Failure*

In Japan, repeated TACE is commonly performed for multiple nodules without major vascular invasion or extrahepatic spread in Child-Pugh A or B patients. Even though recurrence becomes very rapid, TACE has been repeatedly performed (sometimes over 10 times). The reason why this is that there was no further treatment option after TACE failure/refractory patients before sorafenib was introduced. Since hepatic arterial infusion chemotherapy is not effective for TACE failure patients, sorafenib is regarded as a first choice of treatment for TACE failure patients. Since up to now there was no clear definition of TACE failure JSH expert panel all agrees that the definition of TACE is mandatory to change the treatment strategy to sorafenib if TACE failure is confirmed.

In this regard, the definition of TACE failure has been proposed for the first time in the world as shown in table 15.

**Consensus Statements**

27 The following situation should be regarded as TACE failure or refractory:
(a) Intrahepatic lesion.
(i) More than two consecutive incomplete necrosis (depositions (<50%) of lipiodol) are seen by response evaluation CT within the treated tumors at the 4 weeks after adequately performed TACE.
(ii) More than two consecutive appearances of a new lesion (recurrence) are seen in the liver by response evaluation CT at the 4 weeks after adequately performed TACE.
(b) Appearance of vascular invasion.
(c) Appearance of extrahepatic spread – continuous elevation of tumor markers even though right after TACE.
(d) Tumor marker – continuous elevation of tumor markers even though right after TACE.
28 Since hepatic arterial infusion chemotherapy (HAIC) is not effective for TACE failure patients, molecular-targeted therapy is the first choice of treatment.

**Table 15.** Definition of TACE failure [cited and modified from 9, with permission]

| |
|---|
| Intrahepatic lesion |
| – More than two consecutive incomplete necrosis (depositions (<50%) of lipiodol) are seen by response evaluation CT within the treated tumors 4 weeks after adequately performed TACE |
| – More than two consecutive appearances of a new lesion (recurrence) are seen in the liver by response evaluation CT 4 weeks after adequately performed TACE |
| Appearance of vascular invasion |
| Appearance of extrahepatic spread |
| Tumor marker |
| – Continuous elevation of tumor markers even though right after TACE |

### *Summary*

Establishment of an original consensus-based Japanese treatment algorithm was necessary because the situation in Japan, including the availability of transplantation, is different from that found in Western countries. The algorithm established by the JSH is not necessarily based on scientific evidence; indeed consensus-based practices were combined with an evidence-based algorithm. Since it is equally hard to determine if the European or North American algorithm is always based on evidence, the newly established consensus-based treatment algorithm may be a valid guideline. Thus, a treatment algorithm widely agreed on and performed in Japan was presented. However, this algorithm should be revised step by step through prospective investigations of low-evidenced issues. The treatment algorithm for HCC presents the general concept for a therapeutic strategy. It is important to undertake accurate treatments after considering the various conditions found in individual cases.

**Consensus Statements**

29 The treatment algorithm proposed by the Consensus-Based Clinical Practice Guideline was established based on an evidence-based treatment algorithm and consensus among an expert panel of the JSH. More details are described in the treatment algorithm proposed by the Consensus-Based Clinical Practice Manual.
30 The treatment algorithm proposed by the AASLD is not suitable for application in Japan.
31 Definition of TACE failure is important as described earlier.

## Conclusion

Management of HCC in Japan has been described by citing the recently published 'Clinical Practice Manual for HCC' authored by an expert panel of the JSH [9]. This is a consensus-based practice manual, not an evidence-based practice guideline. This manual was established after extensive consideration by combining evidence-based guidelines and the consensus opinions on HCCs of an expert panel. Therefore, no conflict exists between these two documents.

The consensus-based manual presented here includes much detail on the diagnosis and treatment of HCC. However, there are several issues that have no scientific evidence-based support in the diagnostic and treatment algorithm in this manual. In that sense, further extensive efforts involving prospective studies are essential to confirm the validity of this manual and consequently to improve the Evidence-Based Clinical Practice Guidelines for HCC.

## Disclosure Statement

The authors have no conflict of interest to declare.

## References


1 Bruix J, Sherman M, Llovet JM, Beaugrand M, Lencioni R, Burroughs AK, Christensen E, Pagliaro L, Colombo M, Rodes J: Clinical management of hepatocellular carcinoma. Conclusions of the Barcelona 2000 EASL Conference. European Association for the Study of the Liver. J Hepatol 2001;35:421–430.

2 Bruix J, Sherman M: Management of hepatocellular carcinoma. Hepatology 2005;42:1208–1236.

3 Bruix J, Sherman M: Management of hepatocellular carcinoma: an update. Hepatology 2011;53:1020–1022.

4 Group formed to establish 'Guidelines for Evidence-Based Clinical Practice for the Treatment of Liver Cancer': Clinical Practice Guidelines for Hepatocellular Carcinoma (in Japanese). Tokyo, Kanehara, 2005.

5 Makuuchi M, Kokudo N, Arii S, Igaki H, Ikai I, Kaneko S, Kawasaki S, Kudo M, Matsuyama Y, Ohtomo K, et al: Surveillance algorithm and diagnostic algorithm for hepatocellular carcinoma. Hepatol Res 2010;40 (suppl 1):1–144.

6 Makuuchi M, Kokudo N: Clinical practice guidelines for hepatocellular carcinoma: the first evidence-based guidelines from Japan. World J Gastroenterol 2006;12:828–829.

7 Kokudo N, Sasaki Y, Nakayama T, Makuuchi M: Dissemination of evidence-based clinical practice guidelines for hepatocellular carcinoma among Japanese hepatologists, liver surgeons and primary care physicians. Gut 2007;56:1020–1021.

8 Expert Panel of Japan Society of Hepatology: Clinical Practice Manual for Hepatocellular Carcinoma (in Japanese). Tokyo, Igaku-Shoin, 2007.

9 Japan Society of Hepatology: Consensus-Based Clinical Practice Manual of Hepatocellular Carcinoma, ed 2 (in Japanese). Tokyo, Igaku-Shoin, 2010.

10 Arii S, Sata M, Sakamoto M, Shimada M, Kumada T, Shiina S, Yamashita T, Kokudo N, Tanaka M, Takayama T, et al: Management of Hepatocellular Carcinoma: Report of Consensus Meeting in the 45th Annual Meeting of the Japan Society of Hepatology 2009. Hepatol Res 2010;40:667–685.

11 Lin SM, Sheen IS, Chien RN, Chu CM, Liaw YF: Long-term beneficial effect of interferon therapy in patients with chronic hepatitis B virus infection. Hepatology 1999;29:971–975.

12 Lin SM, Yu ML, Lee CM, Chien RN, Sheen IS, Chu CM, Liaw YF: Interferon therapy in HBeAg-positive chronic hepatitis reduces progression to cirrhosis and hepatocellular carcinoma. J Hepatol 2007;46:45–52.

13 Camma C, Giunta M, Andreone P, Craxi A: Interferon and prevention of hepatocellular carcinoma in viral cirrhosis: an evidence-based approach. J Hepatol 2001;34:593–602.

14 Liaw YF, Sung JJ, Chow WC, Farrell G, Lee CZ, Yuen H, Tanwandee T, Tao QM, Shue K, Keene ON, et al: Lamivudine for patients with chronic hepatitis B and advanced liver disease. N Engl J Med 2004;351:1521–1531.

15 Yuen MF, Seto WK, Chow DH, Tsui K, Wong DK, Ngai VW, Wong BC, Fung J, Yuen JC, Lai CL: Long-term lamivudine therapy reduces the risk of long-term complications of chronic hepatitis B infection even in patients without advanced disease. Antivir Ther 2007;12:1295–1303.

16 Papatheodoridis GV, Dimou E, Dimakopoulos K, Manolakopoulos S, Rapti I, Kitis G, Tzourmakliotis D, Manesis E, Hadziyannis SJ: Outcome of hepatitis B e antigen-negative chronic hepatitis B on long-term nucleos(t)ide analog therapy starting with lamivudine. Hepatology 2005;42:121–129.

17 Kasahara A, Hayashi N, Mochizuki K, Takayanagi M, Yoshioka K, Kakumu S, Iijima A, Urushihara A, Kiyosawa K, Okuda M, et al: Risk factors for hepatocellular carcinoma and its incidence after interferon treatment in patients with chronic hepatitis C. Osaka Liver Disease Study Group. Hepatology 1998;27:1394–1402.

18 Yang HI, Lu SN, Liaw YF, You SL, Sun CA, Wang LY, Hsiao CK, Chen PJ, Chen DS, Chen CJ: Hepatitis B e antigen and the risk of hepatocellular carcinoma. N Engl J Med 2002;347:168–174.

19 Kurokawa M, Hiramatsu N, Oze T, Mochizuki K, Yakushijin T, Kurashige N, Inoue Y, Igura T, Imanaka K, Yamada A, et al: Effect of interferon-$\alpha_{2b}$ plus ribavirin therapy on incidence of hepatocellular carcinoma in patients with chronic hepatitis. Hepatol Res 2009;39:432–438.

20 Lok AS, Everhart JE, Wright EC, et al: Maintenance peginterferon therapy and other factors associated with hepatocellular carcinoma in patients with advanced hepatitis C. Gastroenterology 2011;140:840–849.

21 Arase Y, Ikeda K, Tsubota A, Suzuki F, Suzuki Y, Saitoh S, Kobayashi M, Akuta N, Someya T, Hosaka T, et al: Interferon therapy for two years or longer reduces the incidence of hepatocarcinogenesis in patients with chronic hepatitis C viral infection. Intervirology 2004;47:355–361.

22 Omata M, Yoshida H, Toyota J, Tomita E, Nishiguchi S, et al: A large-scale, multicentre, double-blind trial of ursodeoxycholic acid in patients with chronic hepatitis C. Gut 2007;56:1747–1753.

23 Kato J, Miyanishi K, Kobune M, Nakamura T, Takada K, Takimoto R, Kawano Y, Takahashi S, Takahashi M, Sato Y, et al: Long-term phlebotomy with low-iron diet therapy lowers risk of development of hepatocellular carcinoma from chronic hepatitis C. J Gastroenterol 2007;42:830–836.
24 Sakamoto M, Hirohashi S, Shimosato Y: Early stages of multistep hepatocarcinogenesis: adenomatous hyperplasia and early hepatocellular carcinoma. Hum Pathol 1991;22:172–178.
25 Nakashima O, Sugihara S, Kage M, Kojiro M: Pathomorphologic characteristics of small hepatocellular carcinoma: a special reference to small hepatocellular carcinoma with indistinct margins. Hepatology 1995;22:101–105.
26 Liver Cancer Study Group of Japan: General Rules for the Clinical and Pathological Study of Primary Liver Cancer, Engl ed 3. Tokyo, Kanehara, 2010.
27 Kondo F, Kondo Y, Nagato Y, Tomizawa M, Wada K: Interstitial tumour cell invasion in small hepatocellular carcinoma. Evaluation in microscopic and low magnification views. J Gastroenterol Hepatol 1994;9:604–612.
28 International Consensus Group for Hepatocellular Neoplasia: Pathologic diagnosis of early hepatocellular carcinoma: a report of the International Consensus Group for Hepatocellular Neoplasia. Hepatology 2009;49:658–664.
29 Kutami R, Nakashima Y, Nakashima O, Shiota K, Kojiro M: Pathomorphologic study on the mechanism of fatty change in small hepatocellular carcinoma of humans. J Hepatol 2000;33:282–289.
30 Kudo M: Will Gd-EOB-MRI change the diagnostic algorithm in hepatocellular carcinoma? Oncology 2010;78:S87–S93.
31 Nakashima Y, Nakashima O, Tanaka M, Okuda K, Nakashima M, Kojiro M: Portal vein invasion and intrahepatic micrometastasis in small hepatocellular carcinoma by gross type. Hepatol Res 2003;26:142–147.
32 Kudo M: Atypical large well-differentiated hepatocellular carcinoma with benign nature: a new clinical entity. Intervirology 2004;47:227–237.
33 Kumano S, Uemura M, Haraikawa T, Hirata M, Kikuchi K, Kim T, Okada M, Mochizuki T, Murakami T: Efficacy of double arterial phase dynamic magnetic resonance imaging with the sensitivity encoding technique versus dynamic multidetector-row helical computed tomography for detecting hypervascular hepatocellular carcinoma. Jpn J Radiol 2009;27:229–236.
34 Ueda K, Matsui O, Kawamori Y, Nakanuma Y, Kadoya M, Yoshikawa J, Gabata T, Nonomura A, Takashima T: Hypervascular hepatocellular carcinoma: evaluation of hemodynamics with dynamic CT during hepatic arteriography. Radiology 1998;206:161–166.
35 Shapiro RS, Katz R, Mendelson DS, Halton KP, Schwartz ME, Miller CM: Detection of hepatocellular carcinoma in cirrhotic patients: sensitivity of CT and ultrasonography. J Ultrasound Med 1996;15:497–502.
36 Lim JH, Kim CK, Lee WJ, Park CK, Koh KC, Paik SW, Joh JW: Detection of hepatocellular carcinomas and dysplastic nodules in cirrhotic livers: accuracy of helical CT in transplant patients. AJR Am J Roentgenol 2000;175:693–698.
37 Peterson MS, Baron RL, Marsh JW Jr, Oliver JH 3rd, Confer SR, Hunt LE: Pretransplantation surveillance for possible hepatocellular carcinoma in patients with cirrhosis: epidemiology and CT-based tumor detection rate in 430 cases with surgical pathologic correlation. Radiology 2000;217:743–749.
38 Hatanaka K, Kudo M, Minami Y, Ueda T, Tatsumi C, Kitai S, Takahashi S, Inoue T, Hagiwara S, Chung H, et al: Differential diagnosis of hepatic tumors: value of contrast-enhanced harmonic sonography using the newly developed contrast agent, Sonazoid. Intervirology 2008;51:S61–S69.
39 Kudo M, Hatanaka K, Maekawa K: Newly developed novel ultrasound technique, defect reperfusion ultrasound imaging, using Sonazoid in the management of hepatocellular carcinoma. Oncology 2010;78(suppl 1):40–45.
40 Kudo M, Hatanaka K, Kumada T, Toyoda H, Tada T: Double contrast ultrasound: a novel surveillance tool for hepatocellular carcinoma. Am J Gastroenterol 2011;106:368–370.
41 Kudo M, Hatanaka.K., Maekawa K: Defect reperfusion imaging, a newly developed novel technology using Sonazoid in the treatment of hepatocellular carcinoma. J Med Ultrasound 2008;16:169–175.
42 Minami Y, Kudo M, Hatanaka K, Kitai S, Inoue T, Hagiwara S, Chung H, Ueshima K: Radiofrequency ablation guided by contrast harmonic sonography using perfluorocarbon microbubbles (Sonazoid) for hepatic malignancies: an initial experience. Liver Int 2010;30:759–764.
43 Rode A, Bancel B, Douek P, Chevallier M, Vilgrain V, Picaud G, Henry L, Berger F, Bizollon T, Gaudin JL, et al: Small nodule detection in cirrhotic livers: evaluation with US, spiral CT, and MRI and correlation with pathologic examination of explanted liver. J Comput Assist Tomogr 2001;25:327–336.
44 Kubota K, Hisa N, Nishikawa T, Fujiwara Y, Murata Y, Itoh S, Yoshida D, Yoshida S: Evaluation of hepatocellular carcinoma after treatment with transcatheter arterial chemoembolization: comparison of lipiodol-CT, power Doppler sonography, and dynamic MRI. Abdom Imaging 2001;26:184–190.
45 Van Montfoort JE, Stieger B, Meijer DK, Weinmann HJ, Meier PJ, Fattinger KE: Hepatic uptake of the magnetic resonance imaging contrast agent gadoxetate by the organic anion transporting polypeptide OATP1. J Pharmacol Exp Ther 1999;290:153–157.
46 Pascolo L, Petrovic S, Cupelli F, Bruschi CV, Anelli PL, Lorusso V, Visigalli M, Uggeri F, Tiribelli C: Abc protein transport of MRI contrast agents in canalicular rat liver plasma vesicles and yeast vacuoles. Biochem Biophys Res Commun 2001;282:60–66.
47 Narita M, Hatano E, Arizono S, Miyagawa-Hayashino A, Isoda H, Kitamura K, Taura K, Yasuchika K, Nitta T, Ikai I, et al: Expression of OATP1B3 determines uptake of Gd-EOB-DTPA in hepatocellular carcinoma. J Gastroenterol 2009;44:793–798.
48 Kitao A, Zen Y, Matsui O, Gabata T, Kobayashi S, Koda W, Kozaka K, Yoneda N, Yamashita T, Kaneko S, et al: Hepatocellular carcinoma: signal intensity at gadoxetic acid-enhanced MR imaging – correlation with molecular transporters and histopathologic features. Radiology 2010;256:817–826.
49 Kudo M: The 2008 Okuda Lecture. Management of hepatocellular carcinoma: from surveillance to molecular targeted therapy. J Gastroenterol Hepatol 2010:439–452.
50 Nakayama A, Imamura H, Matsuyama Y, Kitamura H, Miwa S, Kobayashi A, Miyagawa S, Kawasaki S: Value of lipiodol computed tomography and digital subtraction angiography in the era of helical biphasic computed tomography as preoperative assessment of hepatocellular carcinoma. Ann Surg 2001;234:56–62.
51 Kojiro M: Pathology of hepatocellular carcinoma; in Okuda K, Tabor E (eds): Liver Cancer. New York, Churchill Livingstone, 1997.
52 Sakamoto M, Hirohashi S: Natural history and prognosis of adenomatous hyperplasia and early hepatocellular carcinoma: multi-institutional analysis of 53 nodules followed up for more than 6 months and 141 patients with single early hepatocellular carcinoma treated by surgical resection or percutaneous ethanol injection. Jpn J Clin Oncol 1998;28:604–608.
53 Hayashi M, Matsui O, Ueda K, Kawamori Y, Gabata T, Kadoya M: Progression to hypervascular hepatocellular carcinoma: correlation with intranodular blood supply evaluated with CT during intra-arterial injection of contrast material. Radiology 2002;225:143–149.
54 Tajima T, Honda H, Taguchi K, Asayama Y, Kuroiwa T, Yoshimitsu K, Irie H, Aibe H, Shimada M, Masuda K: Sequential hemodynamic change in hepatocellular carcinoma and dysplastic nodules: CT angiography and pathologic correlation. AJR Am J Roentgenol 2002;178:885–897.
55 Kudo M, Hatanaka K, Maekawa K: Sonazoid-enhanced ultrasound in the diagnosis and treatment of hepatic tumors. J Med Ultrasound 2008;16:130–139.
56 Okuda K, Ohtsuki T, Obata H, Tomimatsu M, Okazaki N, Hasegawa H, Nakajima Y, Ohnishi K: Natural history of hepatocellular carcinoma and prognosis in relation to treatment. Study of 850 patients. Cancer 1985;56:918–928.

57 Llovet JM, Bru C, Bruix J: Prognosis of hepatocellular carcinoma: the BCLC staging classification. Semin Liver Dis 1999;19:329–338.
58 Prospective validation of the CLIP score: a new prognostic system for patients with cirrhosis and hepatocellular carcinoma. The Cancer of the Liver Italian Program (CLIP) Investigators. Hepatology 2000;31:840–845.
59 Kudo M, Chung H, Osaki Y: Prognostic staging system for hepatocellular carcinoma (CLIP score): its value and limitations, and a proposal for a new staging system, the Japan Integrated Staging Score (JIS score). J Gastroenterol 2003;38:207–215.
60 Kudo M, Chung H, Haji S, Osaki Y, Oka H, Seki T, Kasugai H, Sasaki Y, Matsunaga T: Validation of a new prognostic staging system for hepatocellular carcinoma: the JIS score compared with the CLIP score. Hepatology 2004;40:1396–1405.
61 Tateishi R, Yoshida H, Shiina S, Imamura H, Hasegawa K, Teratani T, Obi S, Sato S, Koike Y, Fujishima T, et al: Proposal of a new prognostic model for hepatocellular carcinoma: an analysis of 403 patients. Gut 2005;54:419–425.
62 Ikai I, Takayasu K, Omata M, Okita K, Nakanuma Y, Matsuyama Y, Makuuchi M, Kojiro M, Ichida T, Arii S, et al: Liver Cancer Study Group of Japan: A modified Japan integrated stage score for prognostic assessment in patients with hepatocellular carcinoma. J Gastroenterol 2006;41:884–892.
63 Kitai S, Kudo M, Minami Y, Haji S, Osaki Y, Oka H, Seki T, Kasugai H, Sasaki Y, Matsunaga T: Validation of a new prognostic staging system for hepatocellular carcinoma: a comparison of the biomarker-combined Japan integrated staging score, the conventional Japan integrated staging score and the BALAD score. Oncology 2008;75(suppl 1):83–90.
64 The Japan Society of Hepatology: Evidence-Based Clinical Practice Guidelines for Hepatocellular Carcinoma, revised version (in Japanese). Tokyo, Kanehara, 2009.
65 Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, de Oliveira AC, Santoro A, Raoul JL, Forner A, et al: Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 2008;359:378–390.
66 Cheng AL, Kang YK, Chen Z, Tsao CJ, Qin S, Kim JS, Luo R, Feng J, Ye S, Yang TS, 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.
67 Kudo M, Okanoue T: Management of hepatocellular carcinoma in Japan: consensus-based clinical practice manual proposed by the Japan Society of Hepatology. Oncology 2007;72:S2–S15.

EUROPEAN JOURNAL OF CANCER 47 (2011) 2117–2127

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejconline.com

EJC

# Phase III study of sorafenib after transarterial chemoembolisation in Japanese and Korean patients with unresectable hepatocellular carcinoma ☆

*Masatoshi Kudo* [a,*], *Kazuho Imanaka* [b], *Nobuyuki Chida* [c], *Kohei Nakachi* [d], *Won-Young Tak* [e], *Tadatoshi Takayama* [f], *Jung-Hwan Yoon* [g], *Takeshi Hori* [h], *Hiromitsu Kumada* [i], *Norio Hayashi* [j], *Shuichi Kaneko* [k], *Hirohito Tsubouchi* [l], *Dong Jin Suh* [m], *Junji Furuse* [n], *Takuji Okusaka* [o], *Katsuaki Tanaka* [p], *Osamu Matsui* [k], *Michihiko Wada* [q], *Iku Yamaguchi* [q], *Toshio Ohya* [q], *Gerold Meinhardt* [r], *Kiwamu Okita* [s]

[a] *Kinki University, Osaka-Sayama, Japan*
[b] *Osaka Medical Center for Cancer and Cardiovascular Disease, Osaka, Japan*
[c] *Sendai Medical Center, Sendai, Japan*
[d] *National Cancer Center Hospital East, Kashiwa, Japan*
[e] *Kyungpook National University Hospital, Daegu, South Korea*
[f] *Nihon University, Tokyo, Japan*
[g] *Seoul National University Hospital, Seoul, South Korea*
[h] *Miyazaki Medical Center Hospital, Miyakazi, Japan*
[i] *Toranomon Hospital, Tokyo, Japan*
[j] *Osaka University Hospital, Osaka, Japan*
[k] *Kanazawa University Hospital, Kanazawa, Japan*
[l] *Kagoshima University Hospital, Kagoshima, Japan*
[m] *Asan Medical Center, University of Ulsan, Seoul, South Korea*
[n] *Kyorin University, Mitaka, Japan*
[o] *National Cancer Center Hospital, Tokyo, Japan*
[p] *Yokohama City University Medical Center, Yokohama, Japan*
[q] *Bayer Yakuhin Ltd., Osaka, Japan*
[r] *Bayer HealthCare Pharmaceuticals, Montville, New Jersey, USA*
[s] *Shimonoseki Kohsei Hospital, Shimonoseki, Japan*

ARTICLE INFO

*Article history:*
Available online 12 June 2011

*Keywords:*
Hepatocellular carcinoma
Transarterial chemoembolisation
Sorafenib

ABSTRACT

*Background:* In Japan and South Korea, transarterial chemoembolisation (TACE) is an important locoregional treatment for patients with unresectable hepatocellular carcinoma (HCC). Sorafenib, a multikinase inhibitor, has been shown effective and safe in patients with advanced HCC. This phase III trial assessed the efficacy and safety of sorafenib in Japanese and Korean patients with unresectable HCC who responded to TACE.

*Methods:* Patients ($n = 458$) with unresectable HCC, Child-Pugh class A cirrhosis and $\geqslant 25\%$ tumour necrosis/shrinkage 1–3 months after 1 or 2 TACE sessions were randomised 1:1 to

☆ Results from this trial were presented at the American Society of Clinical Oncology Gastrointestinal Cancers Symposium, Orlando, Florida, USA, 22–24 January 2010.

* *Corresponding author:* Address: Department of Gastroenterology and Hepatology, Kinki University School of Medicine, 377-2 Ohnohigashi, Osaka-Sayama 589-8511, Japan. Tel.: +81 72 366 0221; fax: +81 72 367 2880.
E-mail address: m-kudo@med.kindai.ac.jp (M. Kudo).

0959-8049/$ - see front matter 
doi:10.1016/j.ejca.2011.05.007

Randomised Controlled trial

sorafenib 400 mg bid or placebo and treated until progression/recurrence or unacceptable toxicity. Primary end-point was time to progression/recurrence (TTP). Secondary end-point was overall survival (OS).

*Findings:* Baseline characteristics in the two groups were similar; >50% of patients started sorafenib >9 weeks after TACE. Median TTP in the sorafenib and placebo groups was 5.4 and 3.7 months, respectively (hazard ratio (HR), 0.87; 95% confidence interval (CI), 0.70–1.09; P = 0.252). HR (sorafenib/placebo) for OS was 1.06 (95% CI, 0.69–1.64; P = 0.790). Median daily dose of sorafenib was 386 mg, with 73% of patients having dose reductions and 91% having dose interruptions. Median administration of sorafenib and placebo was 17.1 and 20.1 weeks, respectively. No unexpected adverse events were observed.

*Interpretation:* This trial, conducted prior to the reporting of registrational phase III trials, found that sorafenib did not significantly prolong TTP in patients who responded to TACE. This may have been due to delays in starting sorafenib after TACE and/or low daily sorafenib doses.



## 1. Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide, the third most common cause of cancer deaths in men and the sixth most common in women.[1] It has been estimated that 650,000 people per year die from HCC, about three-quarters in East Asian countries.[2,3] Aetiologic factors vary by geographic region; ~70% of HCC patients in the Asia-Pacific (AP) region have chronic hepatitis B virus (HBV) infection, except in Japan, where ~75% of HCC patients have chronic hepatitis C virus (HCV) infection.[2,3]

Many patients with HCC are not diagnosed until the disease is unresectable, such that only non-curative treatment options are available.[4,5] The most frequent locoregional treatment for unresectable HCC is transarterial chemoembolisation (TACE), which concentrates chemotherapeutic agents at the tumour site while blocking the primary artery feeding the tumour.[6,7] Compared with symptomatic treatment alone, TACE has been found to enhance survival in patients with unresectable HCC.[8,9] A meta-analysis of seven randomised trials of arterial embolisation in 545 patients showed that chemoembolisation with cisplatin or doxorubicin showed a significant 2-year survival benefit compared with control, whereas embolisation alone showed no benefit.[10] A subsequent meta-analysis of randomised trials showed that TACE improves patient survival compared with untreated patients, but not when compared with patients treated with arterial embolisation alone.[11] Furthermore, no chemotherapeutic agent was found superior to any other, and there was no evidence that lipiodol had any benefit.[11]

Although TACE effectively delays HCC progression or prevents recurrence within 6 months, it is less effective over longer periods,[12] with 2-year survival rates of 24–63%.[13] Recent trials in Asian patients have found that 2-year overall survival (OS) rates following TACE with a suspension of a fine powder formulation of cisplatin in lipiodol, an emulsion of doxorubicin in lipiodol, and epirubicin-loaded superabsorbent polymer microspheres were 76%, 46% and 59%, respectively.[14,15] Although multiple courses of TACE may improve local tumour control,[11] it may also worsen liver function, both because TACE itself damages the hepatic arterial system[16] and because many patients have poor underlying liver function due to cirrhosis.[17] New and effective treatment strategies for patients with unresectable HCC are therefore needed, including the optimisation of TACE and its combination with other treatment modalities.

The high rate of HCC recurrence after TACE may be due to its enhancement of angiogenesis and upregulation of vascular endothelial growth factor (VEGF) expression, resulting in the formation of rich vascular beds in residual tumours.[18–20] Post-TACE treatment with systemic multikinase inhibitors that are both antiproliferative and antiangiogenic may therefore lengthen time to recurrence, improve survival, and target lesions distal to the TACE site.

Sorafenib is a multikinase inhibitor with antiangiogenic and antiproliferative properties, targeting multiple pathways.[21–23] Two large randomised phase III studies, the Sorafenib Health Assessment Randomised Protocol (SHARP)[24] and Sorafenib Asia-Pacific (AP)[25] trials, demonstrated that sorafenib significantly improves OS in patients with advanced HCC, leading to its approval for the treatment of HCC in more than 90 countries. To date, sorafenib remains the only available systemic therapy proven to extend survival in these patients.

In patients with unresectable HCC, sorafenib after TACE may prolong time to recurrence/progression and/or minimise loss of liver function associated with repeated courses of TACE. This double-blind, placebo-controlled, phase III trial, designed before the results of the SHARP and Sorafenib AP trials were reported, assessed the efficacy and safety of sorafenib in patients in Japan and South Korea with unresectable HCC who responded to TACE.

## 2. Patients and methods

We screened patients ⩾18 years of age with unresectable HCC and Child-Pugh A cirrhosis who sustained a response 1–3 months after TACE, defined using the then-prevailing criteria in Japan as ⩾25% tumour necrosis and/or shrinkage.[26,27] Additional inclusion criteria were life expectancy ⩾12 weeks; maximum target lesion size of 70 mm; ⩽10 target lesions; Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0 or 1; and adequate bone marrow (absolute

neutrophil count $\geqslant 1000/mm^3$; platelet count $\geqslant 50 \times 10^9/L$; prothrombin time [PT] – international normalised ratio $\leqslant 2.3$ or PT $\leqslant 6$ s above control), liver (total bilirubin $\leqslant 3$ mg/dL; alanine aminotransferase and aspartate aminotransferase $\leqslant 5 \times$ upper limit of normal [ULN]), and renal (serum creatinine $\leqslant 1.5 \times$ ULN; amylase and lipase $\leqslant 2 \times$ ULN) function.

Patients were excluded if they had macroscopic vascular invasion, renal failure, history of cardiac disease, active clinically serious infection, history of human immunodeficiency virus infection, symptomatic metastatic brain or meningeal tumour, extrahepatic metastasis, seizure disorder requiring medication, prior use of systemic agents for advanced HCC (although prior use of interferon, retinoid and/or vitamin $K_2$ as adjuvant treatment after curative local treatment was allowed), use of hematopoietic growth factors within 3 weeks before start of study drug, concomitant treatment with cytokines after the last course of TACE, history of organ allograft, documented history of substance abuse, or were pregnant or breast-feeding.

All patients provided written informed consent. The study was approved by the appropriate ethics committees and institutional review boards at each centre, and complied with Good Clinical Practice Guidelines, the Declaration of Helsinki, and local laws and regulations. Ongoing safety and efficacy were assessed independently by the Data Monitoring Committee. This study was registered at Clinicaltrials.gov as trial number NCT00494299.

### 2.1. Procedures

TACE was performed by injecting gelatin foam plus lipiodol in all cases. The chemotherapeutic agents used concurrently were epirubicin, cisplatin, doxorubicin and mitomycin. Eligible patients were stratified by response to TACE (complete response [CR], defined as 100% tumour necrosis or shrinkage versus non-complete response [non-CR], defined as $\geqslant 25\%$ but <100% tumour necrosis or shrinkage),[26] by ECOG PS (0 versus 1), and by number of courses of TACE (one versus two). Patients were blindly randomised 1:1 to 400 mg (two 200-mg tablets) sorafenib (Bayer Schering Pharma; Leverkusen, Germany) or matching placebo twice daily.

Treatment interruptions and dose reductions (first 400 mg qd, then 400 mg qod) were allowed for drug-related toxicity. Patients were monitored for adverse events (AEs) using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 3.0, except that the hand-foot skin reaction (HFSR) was classified and managed by a protocol-defined scale. Treatment continued until radiologic progression or recurrence of HCC, unacceptable toxicity associated with study drug, or withdrawal of consent.

The trial was divided into 28-day cycles. Patients were evaluated for safety and compliance every 2 weeks during cycles 1–3, and every 4 weeks thereafter. Tumours were evaluated, centrally at an image registration centre, $\leqslant 28$ days before the first dose of study drug and every 8 weeks thereafter, or when evaluating recurrence or progression. Throughout treatment, lesions were evaluated by dynamic computed tomography (CT), preferably by the same investigator or radiologist as at screening.

The primary study end-point was time to progression (TTP) by central review, defined as time to recurrence in patients with CR and TTP in those with non-CR at study entry. Progression was defined as a $\geqslant 25\%$ increase in tumour size or development of a new lesion. The secondary end-point was OS, defined as time from randomisation to death from any cause. Exploratory analyses included TTP by investigator assessment and subgroup analyses of TTP by central review, based on aetiology (HBV versus HCV), response to TACE (CR versus non-CR), number of lesions ($\leqslant 3$ versus >3), number of prior courses of TACE (1 versus 2), age (<65 versus $\geqslant 65$ years), sex, treatment lag ($\leqslant 9$ versus >9 weeks), country of enrolment (Japan versus South Korea), and ECOG PS (0 versus 1).

### 2.2. Statistical analysis

Patient sample size was estimated based on TTP. If 30% and 70% of patients achieved CR and non-CR, respectively, in response to TACE, the median TTP for the placebo group in the mixed population would be 5.7 months. Clinically meaningful improvement was defined as median TTP 50% higher in the sorafenib than in the placebo group. Assuming one formal interim and one final analysis performed using an O'Brien-Fleming-type alpha spending function with a two-sided alpha of 0.05, 318 events would be required to achieve a statistical power of 95%. Accrual of 372 patients (186 in each group) within 18 months would be expected to result in 318 events after 30 months; if 10% of patients were lost to follow-up, 414 patients would have to be randomised to observe 318 events.

Efficacy was assessed in the intention-to-treat (ITT) population, defined as all randomised patients. The safety population included all patients who received at least one dose of study medication. TTP and OS in the two treatment arms were calculated by the Kaplan–Meier method and compared by the log-rank test, as were subgroups stratified by response to TACE (CR versus non-CR), ECOG PS (0 versus 1) and number of prior courses of TACE (1 versus 2). Hazard ratios (HRs) for sorafenib versus placebo and 95% confidence intervals (CI) were estimated by Cox proportional hazards models.

### 2.3. Role of the funding source

The study sponsors were involved in the design of the study; the collection, analysis and interpretation of data; the writing of the report; and the decision to submit the paper for publication.

## 3. Results

### 3.1. Patients

From 27th April 2006 to 10th July 2009, 552 patients were screened at 69 centres in Japan and seven centres in South Korea. Of these, 458 patients (387 at 67 centres in Japan and 71 at six centres in South Korea) met the eligibility criteria and were randomised, 229 each to the sorafenib and placebo groups. All were included in the ITT analysis (Fig. 1), whereas

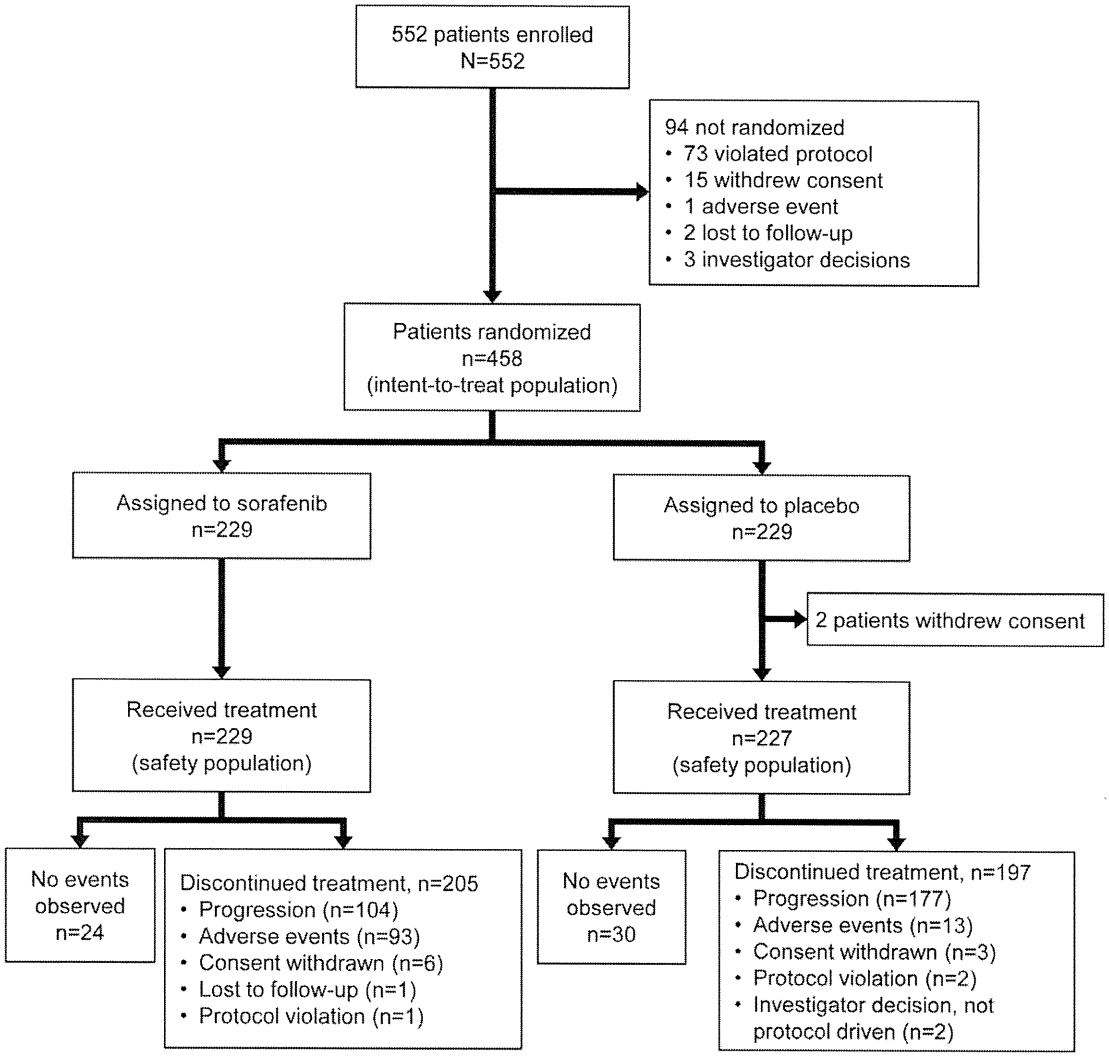


**Fig. 1 – Enrolment and outcomes.**

the 456 who received at least one dose of study drug were included in the safety analysis.

Demographic and baseline disease characteristics were similar in the sorafenib and placebo groups (Table 1). Of the 458 patients, 342 (74.7%) were male and 306 (66.8%) were ⩾65 years. Median age was 69 years (range, 29–86 years). At baseline, 403 patients (88.0%) had an ECOG PS of 0, 287 (62.7%) had HCV infection, and 336 (73.4%) had ⩽3 tumours. TACE consisted of gelatin foam plus lipiodol in all 458 patients, 60 for palliative intent and 398 for curative intent. Of these 458 patients, 355 received TACE monotherapy, including epirubicin ($n = 219$), cisplatin ($n = 89$), doxorubicin ($n = 49$) and mitomycin ($n = 1$); and 103 received combination treatments, including epirubicin + mitomycin ($n = 57$), cisplatin + epirubicin ($n = 16$), cisplatin + doxorubicin + mitomycin ($n = 13$), mitomycin + mitoxantrone ($n = 8$), doxorubicin + mitomycin ($n = 5$) and doxorubicin + iodixanol ($n = 4$). The median time from last TACE to randomisation was 9.3 weeks (range, 5.6–13.3 weeks), and the median time from initial diagnosis to study entry was 9.8 months (range, 1.6–144.3 months). Ten patients (2.2%) had received prior systemic anticancer therapy, consisting of prior adjuvant treatment with interferon, retinoid and/or vitamin K2 treatment after curative local treatment, and 219 (47.8%) had previously undergone some type of locoregional treatment, including radiofrequency ablation alone (10.7%), surgery alone (9.6%), percutaneous ethanol injection alone (5.9%), microwave coagulation therapy alone (0.2%) and other procedures (0.2%), with 21.2% having undergone multiple procedures (Table 1).

### 3.2. *Primary efficacy analysis*

By the cutoff date of 10th July 2009, 324 progression events (137 in the sorafenib and 187 in the placebo group) were confirmed by the Response Evaluation Committee. Median TTP by central review was 5.4 months (95% CI, 3.8–7.2 months) in the sorafenib group and 3.7 months (95% CI, 3.5–4.0 months) in the placebo group (HR [sorafenib/placebo], 0.87; 95% CI, 0.70–1.09; $P = 0.252$; Fig. 2). The 3-month progression-free rates in the sorafenib and placebo groups were 65.0% and 58.7%, respectively, and their 6-month progression-free rates were 45.7% and 33.5%, respectively.

**Table 1 – Demographic and baseline characteristics of randomised patients (ITT population).**

| Variable | All patients | | | Japanese patients | | | Korean patients | | |
|---|---|---|---|---|---|---|---|---|---|
| | Sorafenib + placebo (*n* = 458) | Sorafenib (*n* = 229) | Placebo (*n* = 229) | Sorafenib + placebo (*n* = 387) | Sorafenib (*n* = 196) | Placebo (*n* = 191) | Sorafenib + placebo (*n* = 71) | Sorafenib (*n* = 33) | Placebo (*n* = 38) |
| Median age (years) | 69 | 69 | 70 | 71 | 70 | 71 | 60 | 61 | 59 |
| Male (%) | 74.7 | 76.0 | 73.4 | 72.9 | 74.0 | 71.7 | 84.5 | 87.9 | 81.6 |
| *ECOG PS*[a] *(%)* | | | | | | | | | |
| 0 | 88.0 | 87.8 | 88.2 | 91.5 | 91.3 | 91.6 | 69.0 | 66.7 | 71.1 |
| 1 | 12.0 | 12.2 | 11.8 | 8.5 | 8.7 | 8.4 | 31.0 | 33.3 | 28.9 |
| *Number of lesions (%)* | | | | | | | | | |
| ⩽3 | 73.4 | 72.9 | 73.8 | 70.8 | 69.9 | 71.7 | 87.3 | 90.9 | 84.2 |
| >3 | 26.6 | 27.1 | 26.2 | 29.2 | 30.1 | 28.3 | 12.7 | 9.1 | 15.8 |
| *Aetiology (%)* | | | | | | | | | |
| Alcohol | 6.8 | 8.3 | 5.2 | 6.5 | 7.7 | 5.2 | 8.5 | 12.1 | 5.3 |
| HBV | 21.1 | 20.5 | 22.7 | 12.7 | 12.2 | 13.1 | 70.4 | 69.7 | 71.1 |
| HCV | 62.7 | 60.7 | 64.6 | 71.3 | 68.4 | 74.3 | 15.5 | 15.2 | 15.8 |
| Other | 5.9 | 7.0 | 4.8 | 7.0 | 8.2 | 5.8 | 0 | 0 | 0 |
| Liver cirrhosis[b] (%) | 68.3 | 69.4 | 67.2 | 66.7 | 67.3 | 66.0 | 77.5 | 81.8 | 73.7 |
| *Number of prior TACE*[a] *(%)* | | | | | | | | | |
| 1 | 64.4 | 64.2 | 64.6 | 66.7 | 66.3 | 67.0 | 52.1 | 51.5 | 52.6 |
| 2 | 35.6 | 35.8 | 35.4 | 33.3 | 33.7 | 33.0 | 47.9 | 48.5 | 47.4 |
| *Response to prior TACE*[a,c] *(%)* | | | | | | | | | |
| CR | 62.0 | 62.0 | 62.0 | 58.1 | 58.7 | 57.6 | 83.1 | 81.8 | 84.2 |
| Non-CR | 38.0 | 38.0 | 38.0 | 41.9 | 41.3 | 42.4 | 16.9 | 18.2 | 15.8 |
| *Prior local therapy (%)* | | | | | | | | | |
| RFA | 10.7 | 11.8 | 9.6 | 10.3 | 11.7 | 8.9 | 12.7 | 12.1 | 13.2 |
| Surgery | 9.6 | 7.0 | 12.2 | 10.3 | 8.2 | 12.6 | 5.6 | 0 | 10.5 |
| PEI | 5.9 | 4.8 | 7.0 | 6.5 | 5.1 | 7.9 | 2.8 | 3.0 | 2.6 |
| MCT | 0.2 | 0.4 | 0 | 0.3 | 0.5 | 0 | 0 | 0 | 0 |
| Others | 0.2 | 0.4 | 0 | 0 | 0 | 0 | 1.4 | 3.0 | 0 |
| Multiple | 21.2 | 20.5 | 21.8 | 24.0 | 23.0 | 25.1 | 5.6 | 6.1 | 5.3 |
| Prior systemic therapy (%) | 2.2 | 3.1 | 1.3 | 2.6 | 3.6 | 1.6 | 0 | 0 | 0 |

ITT = intention-to-treat; ECOG PS = Eastern Cooperative Oncology Group performance status; HBV = hepatitis B virus; HCV = hepatitis C virus; TACE = transarterial chemoembolisation; CR = complete response; non-CR = non-complete response; RFA = radiofrequency ablation; PEI = percutaneous ethanol injection; MCT = microwave coagulation therapy.

[a] Protocol-defined stratification factor.

[b] Clinically and/or histologically confirmed liver cirrhosis.

[c] Complete response was defined in the study protocol as 100% tumour shrinkage or necrosis.

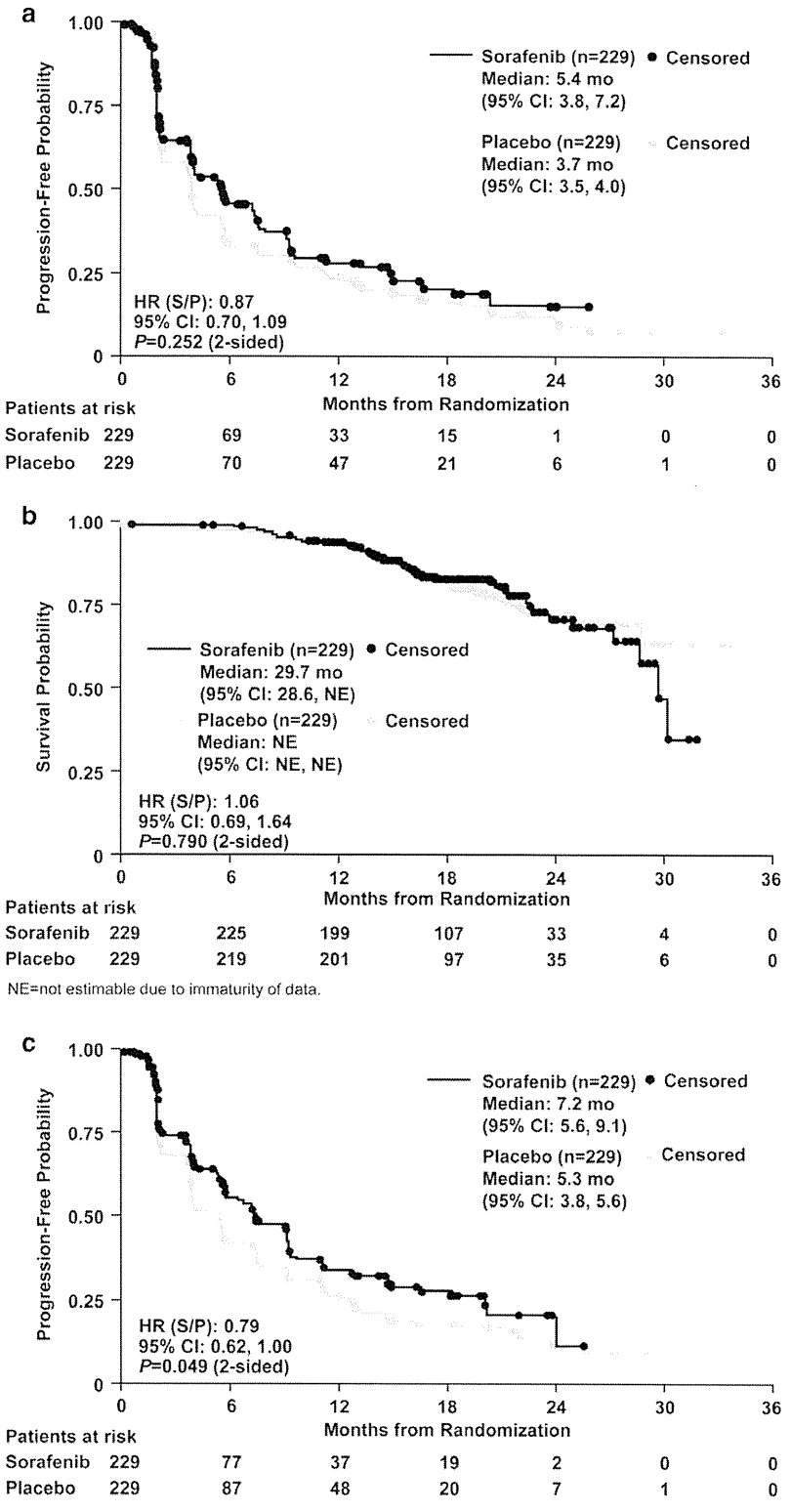


**Fig. 2 – Kaplan–Meier analysis of time to progression (TTP) and overall survival (OS). (a) TTP by central review (primary intention-to-treat (ITT) analysis); (b) OS (secondary ITT analysis) and (c) TTP by investigator assessment (exploratory ITT analysis).**

### 3.3. *Secondary efficacy analysis*

At the same cutoff date, there were 84 deaths, 43 in the sorafenib and 41 in the placebo group; the remaining patients were censored on that date. Median OS was 29.7 months in the sorafenib group (95% CI, 28.6 months – not yet reached) but had not yet been reached in the placebo group (HR [sorafenib/placebo], 1.06; 95% CI, 0.69–1.64; $P = 0.790$). The

**Table 2 – Exploratory subgroup analyses of TTP by central review based on demographic, baseline and prognostic characteristics (ITT population; subgroups that included at least 10% of patients).**

| Variable | Subgroup | *n* | Number of events | Number of patients censored | Median TTP (95% confidence interval [CI]) (months) | | Hazard ratio [HR] (95% CI) for Sorafenib/placebo |
|---|---|---|---|---|---|---|---|
| | | | | | Sorafenib | Placebo | |
| Aetiology | HBV | 99 | 56 | 43 | 9.1 (5.6–20.3) | 5.6 (3.7–10.9) | 0.84 (0.49–1.44) |
| | HCV | 287 | 217 | 70 | 5.3 (3.7–7.1) | 3.6 (2.0–3.7) | 0.81 (0.62–1.07) |
| Response to TACE | CR | 284 | 179 | 105 | 7.4 (5.6–9.2) | 5.3 (3.7–7.4) | 0.84 (0.63–1.14) |
| | Non-CR | 174 | 145 | 29 | 2.1 (1.8–3.9) | 1.9 (1.8–3.6) | 0.85 (0.61–1.18) |
| Number of lesions | ⩽3 | 336 | 219 | 117 | 7.1 (5.3–7.8) | 3.8 (3.7–5.5) | 0.83 (0.64–1.09) |
| | >3 | 122 | 105 | 17 | 3.7 (2.0–5.3) | 2.0 (1.9–3.7) | 0.87 (0.59–1.29) |
| Number of prior TACE | 1 | 295 | 212 | 83 | 5.4 (3.8–7.4) | 3.7 (3.5–5.5) | 0.91 (0.70–1.20) |
| | 2 | 163 | 112 | 51 | 5.3 (3.7–7.8) | 3.7 (2.1–3.8) | 0.76 (0.52–1.11) |
| Age group | <65 years | 152 | 90 | 62 | 9.1 (5.6–18.2) | 3.7 (3.5–7.2) | 0.68 (0.44–1.03) |
| | ⩾65 years | 306 | 234 | 72 | 3.8 (3.5–5.4) | 3.7 (2.1–3.9) | 0.99 (0.76–1.28) |
| Sex | Male | 342 | 241 | 101 | 5.4 (3.8–7.4) | 3.7 (3.5–5.3) | 0.78 (0.60–1.00) |
| | Female | 116 | 83 | 33 | 5.3 (3.6–7.4) | 3.7 (2.1–5.3) | 1.16 (0.75–1.79) |
| Treatment lag[a] | ⩽9 weeks | 205 | 150 | 55 | 5.5 (3.9–9.1) | 3.7 (3.5–5.3) | 0.74 (0.53–1.03) |
| | >9 weeks | 253 | 174 | 79 | 5.1 (3.7–7.2) | 3.7 (2.0–5.3) | 0.95 (0.71–1.29) |
| Country of enrolment | Japan | 387 | 289 | 98 | 3.9 (3.7–5.5) | 3.7 (2.1–3.8) | 0.94 (0.75–1.19) |
| | South Korea | 71 | 35 | 36 | NE[b] (9.0–NE) | 5.5 (3.7–11.0) | 0.38 (0.18–0.81) |
| ECOG PS | 0 | 403 | 286 | 117 | 5.4 (3.8–7.2) | 3.7 (3.6–5.3) | 0.88 (0.69–1.11) |
| | 1 | 55 | 38 | 17 | 5.4 (1.8–16.6) | 3.5 (1.8–5.5) | 0.78 (0.40–1.51) |

[a] Treatment lag was defined as time from the most recent TACE to randomisation.
[b] NE = not estimable due to censored data.

1-year survival rates in the sorafenib and placebo groups were 94.6% and 94.1%, respectively, and their 2-year survival rates were 72.1% and 73.8%, respectively.

### 3.4. *Exploratory analyses*

At the cutoff date, investigators had reported 304 progression events, 120 in the sorafenib and 184 in the placebo group. Median TTP by investigator assessment in the sorafenib and placebo groups were 7.2 months (95% CI, 5.6–9.1 months) and 5.3 months (95% CI, 3.8–5.6 months), respectively (HR [sorafenib/placebo], 0.79; 95% CI, 0.62–1.00; P = 0.049). Their 3-month progression-free rates were 74.1% and 67.9%, respectively, and their 6-month progression-free rates were 54.9% and 41.4%, respectively.

Exploratory analyses of TTP by central review were performed in subgroups containing ⩾10% of patients, including by aetiology (HBV versus HCV), response to TACE (CR versus non-CR), number of lesions (⩽3 versus >3), number of prior courses of TACE (1 versus 2), age (<65 versus ⩾65 years), sex, treatment lag (⩽9 versus >9 weeks), ECOG PS (0 versus 1) and country of enrolment. These analyses were performed to provide descriptive information only; the study was not powered to compare subgroup response to treatment, and no adjustments were made for multiple comparisons. Median TTP and the HR for TTP (sorafenib/placebo) in each subgroup are shown in Table 2, and Forest plots of HRs for TTP are shown in Fig. 3. Most HRs favored sorafenib. Differences were observed, however, between Japanese and Korean patients. The HR for TTP was 0.94 (95% CI, 0.75–1.19) for Japanese patients and 0.38 (95% CI, 0.18–0.81) for Korean patients (Fig. 4). Median TTP in sorafenib-treated patients in the

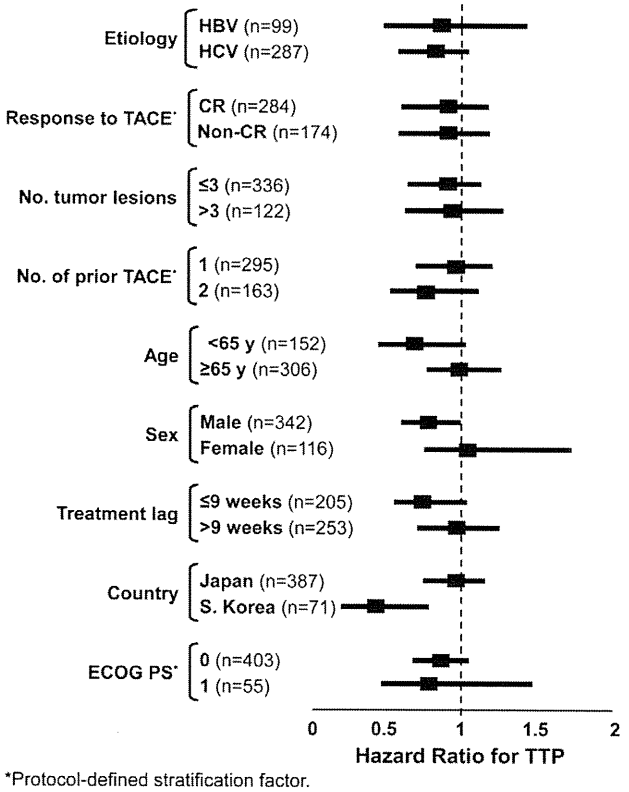


**Fig. 3 – Subgroup analyses of TTP by central review (exploratory ITT analyses in subgroups that include at least 10% of patients): forest plot depicting hazard ratio (HR) for TTP (sorafenib over placebo) for each subgroup.**

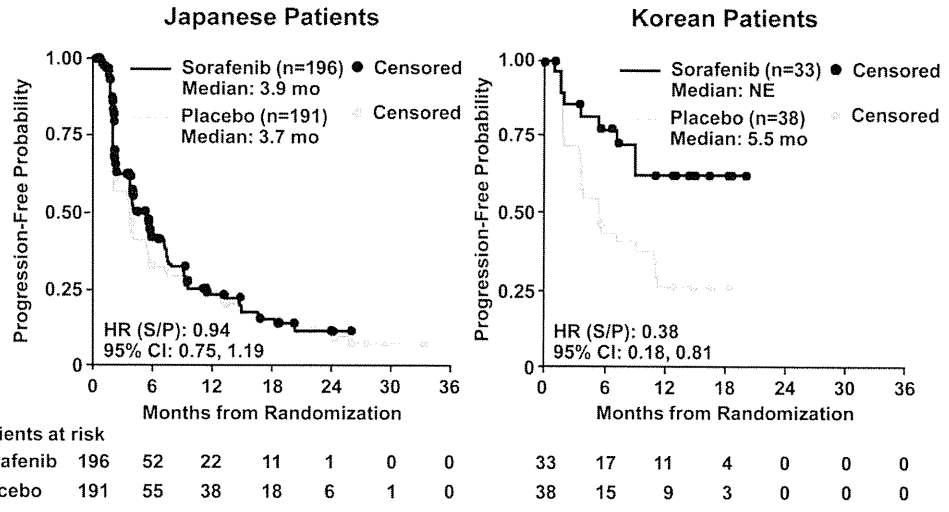


**Fig. 4 – Kaplan–Meier analysis of TTP by central review, by country of enrolment (exploratory ITT analysis).**

Korean subgroup could not be estimated since it was not attained by the study cutoff date.

### 3.5. *Safety*

The safety analysis included 229 sorafenib-treated and 227 placebo-treated patients; their incidence of drug-related AEs (DRAEs) were 100% and 61%, respectively. Most DRAEs were mild to moderate (Table 3), with the most frequent in the sorafenib and placebo groups being HFSR (82% versus 7%), elevated lipase (44% versus 8%), alopecia (41% versus 3%) and rash/desquamation (40% versus 11%). In the sorafenib group, 24% and 4% of patients experienced grades 3 and 4 elevated lipase, respectively, compared with 3% and <1%, respectively, in the placebo group. There was no radiographic or clinical evidence of pancreatitis in either group. The overall incidences of grade 3 HFSR (protocol-defined scale) in the sorafenib and placebo groups were 35% and 0%, respectively, and the overall incidence of serious DRAEs was 18% and 9%, respectively. There were no drug-related deaths.

The median durations of treatment in the sorafenib and placebo groups were 17.1 weeks (range, 1.0–112.1 weeks) and 20.1 weeks (range, 2.1–144.1 weeks), respectively (Table 4), and the median daily doses of sorafenib and placebo were 386.0 mg (range, 112.0–794.5 mg) and 785.8 mg (range, 276.1–810.3 mg), respectively. In the sorafenib group, 40 patients (17.5%) received >80% of the planned dose, compared with 206 (90.7%) in the placebo group. The most common reasons for discontinuing treatment in the sorafenib and placebo groups were disease progression (104/229 [45%] versus 177/229 [77%]) and adverse events (93/229 [41%] versus13/229 [6%]).

Doses were reduced in 166 of the 229 sorafenib-treated (72.5%) and in 33 of the 227 placebo-treated (14.5%) patients,

**Table 3 – Treatment-emergent, drug-related adverse events occurring in ⩾20% of patients in either group.[a]**

| Adverse event | Sorafenib ($n = 229$) Grade (%) | | | Placebo ($n = 227$) Grade (%) | | |
|---|---|---|---|---|---|---|
| | Any | 3 | 4 | Any | 3 | 4 |
| HFSR | 82 | 35 | – | 7 | 0 | – |
| Elevated lipase[b] | 44 | 24 | 4 | 8 | 3 | <1 |
| Alopecia | 41 | – | – | 3 | – | – |
| Rash/desquamation | 40 | 4 | 0 | 11 | 0 | 0 |
| Other metabolic abnormality | 32 | 8 | 1 | 4 | 2 | <1 |
| Diarrhoea | 31 | 6 | 0 | 5 | 1 | 0 |
| Hypertension | 31 | 15 | 0 | 7 | 1 | 0 |
| Hypophosphatemia | 28 | 16 | 0 | 6 | 3 | 0 |
| Thrombocytopenia | 25 | 11 | 1 | 2 | <1 | 0 |
| Elevated AST | 25 | 12 | <1 | 5 | 3 | 0 |
| Elevated ALT | 21 | 8 | <1 | 5 | 2 | 0 |
| Elevated amylase | 21 | 6 | 1 | 8 | 2 | <1 |

HFSR = hand–foot skin reaction; AST = aspartate aminotransferase; ALT = alanine aminotransferase; NCI-CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

[a] Patients were monitored for adverse events using NCI-CTCAE v3.0, except for HFSR, which was classified according to a 3-grade, protocol-defined scale (grade 1, HFSR does not disrupt normal activities; grade 2, HFSR affects the activities of the patient; and grade 3, patient is unable to work or perform activities of daily living because of HFSR).

[b] There was no radiographic or clinical evidence of pancreatitis in either arm.

**Table 4 – Summary of study drug administration.**

| Assessment | All patients | | Japan | | South Korea | |
|---|---|---|---|---|---|---|
| | Sorafenib (*n* = 229) | Placebo (*n* = 227) | Sorafenib (*n* = 196) | Placebo (*n* = 190) | Sorafenib (*n* = 33) | Placebo (*n* = 37) |
| Median duration of treatment (weeks) | 17 | 20 | 16 | 20 | 31 | 33 |
| Median daily dose (mg) | 386 | 786 | 382 | 786 | 403 | 766 |
| Patients with dose reduction (%) | 73 | 14 | 71 | 11 | 82 | 32 |
| Patients with dose interruption (%) | 91 | 18 | 92 | 17 | 85 | 24 |
| Patients with discontinuation (%) | 90 | 87 | 93 | 88 | 70 | 78 |
| Due to progression (%) | 51 | 90 | 52 | 90 | 39 | 90 |
| Due to adverse events (%) | 45 | 7 | 44 | 7 | 57 | 3 |
| HFSR | 11 | 0 | 10 | 0 | 18 | 0 |
| Thrombocytopenia | 4 | 0 | 5 | 0 | 3 | 0 |
| Hypophosphatemia | 4 | <1 | 4 | 1 | 3 | 0 |
| Hypertension | 4 | 0 | 5 | 0 | 0 | 0 |
| Neutropenia | 4 | <1 | 4 | 1 | 0 | 0 |
| Elevated AST | 2 | <1 | 2 | 1 | 3 | 0 |
| Rash/desquamation | 2 | 0 | 2 | 0 | 3 | 0 |
| Elevated ALT | 2 | 1 | 1 | 1 | 6 | 0 |
| Diarrhoea | 1 | 0 | 1 | 0 | 3 | 0 |
| Other | 11 | 4 | 19 | 3 | 18 | 3 |

HFSR = hand–foot skin reaction; AST = aspartate aminotransferase; and ALT = alanine aminotransferase.

due primarily to AEs (163 versus 27). Forest doses were interrupted temporarily in 208 of the 229 sorafenib-treated (90.8%) and 41 of the 227 placebo-treated (18.1%) patients, again due primarily to AEs (206 versus 38).

A total of 107 patients – 94 of the 229 (41.0%) in the sorafenib group and 13 of the 227 (5.7%) in the placebo group – permanently discontinued study drug due to AEs. The most common AEs leading to discontinuation of sorafenib were HFSR (11.4%), thrombocytopenia (4.4%), hypertension (3.9%), hypophosphatemia (3.9%) and neutropenia (3.5%); the most common AE leading to discontinuation of placebo was increased ALT (0.9%).

Death within 30 days of receiving study drug occurred in one patient (0.4%) in each group; neither was deemed drug-related.

## 4. Discussion

This phase III randomised, controlled trial, assessing the efficacy and safety of sorafenib after response to TACE in Japanese and Korean patients with unresectable HCC, employed a protocol consistent with the practice of TACE in these countries at that time.[28,29] Moreover, the protocol was designed before the combination or sequential use of TACE and sorafenib or their optimal timing had been adequately studied, and before the effect of TACE on susceptibility to sorafenib had been characterised. In this setting, sorafenib did not significantly prolong TTP or OS by central review in patients with unresectable HCC who responded to TACE. Exploratory secondary and subgroup analyses suggested, however, that post-TACE sorafenib had a positive impact on these patients. Median TTP by investigator review was approximately 2 months longer in the sorafenib than in the placebo group, and exploratory subgroup analyses suggested that TTP may have been affected by several factors, including age, number of prior TACE courses, treatment lag, treatment duration, total exposed dose and nationality.

Several factors may have contributed to these results. For example, unusually high percentages of sorafenib-treated patients required dose reductions (73%) and/or interruptions (91%), resulting in a much lower than planned median daily dose of sorafenib (386 mg). In comparison, 26% and 44% of sorafenib-treated patients in the SHARP trial, and 31% and 43% of those in the Sorafenib AP trial, required dose reductions and interruptions, respectively, due to AEs,[24,25] and median daily doses of sorafenib were higher in the SHARP (797 mg) and Sorafenib AP (795 mg) trials.

The better outcomes observed in Korean patients may have been due to their substantially longer median treatment duration (31 versus 16 weeks), resulting in a favourable HR in Koreans (0.38; 95% CI, 0.18–0.81). Moreover, the Korean and Japanese subgroups differed in baseline characteristics. Japanese patients were older and a higher percentage had ⩾3 lesions on enrolment. Moreover, Japanese patients were less likely to have received >1 TACE to achieve CR prior to sorafenib. Finally, these subgroups differed in principal aetiology of HCC, in that ~70% of Japanese patients had HCV and ~70% of Korean patients had HBV.

We found that the incidence of treatment-emergent adverse events in the sorafenib-treated patients in this trial was generally higher than that observed in previous trials of sorafenib in patients with HCC. We found that the rates of all grade HFSR, Grade 3 HFSR and discontinuation due to HFSR were higher in this trial than in the SHARP[24] and Sorafenib AP[25] trials. We also found that the rates of all grade alopecia; rash/desquamation; hypertension, including grade 3 hypertension; thrombocytopenia and elevated liver function enzymes were higher in this trial than in the two previous phase III trials of sorafenib in patients with HCC. These results were unexpected and may have been due to the combination of TACE with sorafenib treatment in this trial. These findings suggest that adjustments in sorafenib dose (e.g. starting at a lower dose after TACE) or the timing of sorafenib treatment with respect to TACE may be required for these two

modalities to be tolerated in combination and also have synergistic effects.

The timing of post-TACE sorafenib may also have contributed to the absence of a positive effect of sorafenib observed in this study. Local hypoxia resulting from TACE can induce angiogenesis[18] and enhance serum concentrations of VEGF,[19,20] suggesting that sorafenib may exert its greatest antiangiogenic effects when administered immediately after or even before TACE. Serum VEGF concentrations have also been found to correlate with impaired liver function, tumour size, tumour number, macroscopic vascular invasion,[30] and poor OS.[31] Of our sorafenib-treatment patients, 60% had a treatment lag >9 weeks prior to randomisation, due primarily to the need for central review of CT scans, and shorter lag time has been found associated with better outcomes.

Several ongoing phase II/III trials in patients with unresectable HCC may provide insight into the optimal combination treatment and the optimal timing of sorafenib relative to TACE. These include trials testing TACE with doxorubicin-eluting beads and sorafenib or placebo and alterations in timing of conventional TACE relative to sorafenib or placebo.[32–35]

## 5. Conclusion

Sorafenib did not significantly improve median TTP by central review in Japanese and Korean patients with unresectable HCC who responded to TACE, although exploratory analyses suggested that sorafenib may have clinical benefits in certain patient subsets, including males, patients <65 years of age, and those with a shorter treatment lag between TACE and sorafenib; and that longer treatment duration and greater total daily dose may be associated with clinical improvements. No new or unexpected AEs were observed. The results of these and other clinical investigations may help refine the use of sorafenib and TACE, and define their optimal combination, in patients with unresectable HCC.

## Author contributions

Drs. Masatoshi Kudo and Kiwamu Okita were involved with the study concept and design; acquisition of data; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content; statistical analysis; and study supervision.

Drs. Kazuho Imanaka, Nobuyuki Chida, Kohei Nakachi, Won-Young Tak, Tadatoshi Takayama, Jung-Hwan Yoon, Takeshi Hori, Hiromitsu Kumada, Norio Hayashi, Shuichi Kaneko, Hirohito Tsubouchi, Dong Jin Suh, Junji Furuse, Takuji Okusaka, Katsuaki Tanaka and Osamu Matsui were involved with the acquisition of data; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content; statistical analysis; and study supervision.

Drs. Michihiko Wada, Iku Yamaguchi, Toshio Ohya and Gerold Meinhardt were involved with the study concept and design; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content; statistical analysis; administrative and technical support; and study supervision.

## Clinical trials

Clinicaltrials.gov Identifier NCT00494299.

## Conflict of interest statement

Masatoshi Kudo received advisory and speaker fees and research and travel grants from Bayer. Won-Young Tak received advisory and speaker fees from Bayer, Junji Furuse received advisory fees from Bayer, Takuji Okusaka received advisory and speaker fees, research and travel grants from Bayer. Osamu Matsui received consulting and advisory fees and research grants from Bayer. Michihiko Wada, Iku Yamaguchi, Toshio Ohya and Gerold Meinhardt are employees of Bayer. Kiwamu Okita received consulting fees from Bayer. All other authors declared no conflicts of interest.

## Acknowledgements

This study was supported by Bayer HealthCare Pharmaceuticals and Onyx Pharmaceuticals. Editorial and writing support was provided by John D. Zoidis, MD, Bayer HealthCare Pharmaceuticals, Montville, New Jersey, USA.

REFERENCES

1. Kudo M. The 2008 Okuda lecture management of hepatocellular carcinoma: from surveillance to molecular targeted therapy. *J Gastroenterol Hepatol* 2010;**25**:439–52.
2. Yuen MF, Hou JL, Chutaputti A. Hepatocellular carcinoma in the Asia-Pacific region. *J Gastroenterol Hepatol* 2009;**24**:346–53.
3. Asia-Pacific working party on prevention of hepatocellular carcinoma. Prevention of hepatocellular carcinoma in the Asia-Pacific region: consensus statements. *J Gastroenterol Hepatol* 2010;**25**:657–63.
4. Llovet JM, Burroughs A, Bruix J. Hepatocellular carcinoma. *Lancet* 2003;**362**:1907–17.
5. Makuuchi M, Kokudo N. Clinical practice guidelines for hepatocellular carcinoma: the first evidence based guidelines from Japan. *World J Gastroenterol* 2006;**12**:828–9.
6. Bruix J, Sherman M. Management of hepatocellular carcinoma: an update. *Hepatology* 2011;**53**:1020–2.
7. Trevisani F, De Notariis S, Rossi C, Bernardi M. Randomized control trials on chemoembolization for hepatocellular carcinoma: is there room for new studies? *J Clin Gastroenterol* 2001;**32**:383–9.
8. Lo CM, Ngan H, Tso WK, et al. Randomized control trial of transarterial lipiodol chemoembolization for unresectable hepatocellular carcinoma. *Hepatology* 2002;**35**:1164–71.
9. Llovet JM, Real MI, Montaña X, et al. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. *Lancet* 2002;**359**:1734–9.
10. Llovet JM, Bruix J. Systematic review of randomized trials for unresectable hepatocellular carcinoma: chemoembolization improves survival. *Hepatology* 2003;**37**:429–42.
11. Marelli L, Stigliano R, Triantos C, et al. Transarterial therapy for hepatocellular carcinoma: which technique is more effective? A systematic review of cohort and randomized studies. *Cardiovasc Intervent Radiol* 2007;**30**:6–25.