*JIVROSG　(Japan Interventional Radiology in Oncology Study Group)*

**JIVROSG-1302**

**A prospective randomized controlled trial of selective DEB-epiDOX vs. selective conventional TACE for advanced hepatocellular carcinoma focusing on local complete response rate: PRESIDENT study**

**Protocol**

Group Representative and Principal Investigator

Yasuaki Arai

Department of Diagnostic Radiology, National Cancer Center Hospital

5-1-1 Tsukiji, Chuo-ku, Tokyo, 104-0045 Japan

TEL：03-3542-2511，FAX：03-3547-6096

E-mail[：arai-y3111@mvh.biglobe.ne.jp](mailto:%81%46arai-y3111@mvh.biglobe.ne.jp)

Study Secretariat

Masafumi Ikeda

Department of Hepatobiliary and Pancreatic Oncology

National Cancer Center Hospital East

6-5-1 Kashiwanoha, Kashiwa, Chiba, 277-8577 Japan

TEL：04-7133-1111，FAX：04-7133-0335

E-mail：[masikeda@east.ncc.go.jp](mailto:masikeda@east.ncc.go.jp)

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# Protocol Summary

Group B: Selective conventional TACE

Epirubicin + lipiodol + embolization gelatin

Group A: Selective DEB-epiDOX

Drug-eluting beads of epirubicin

Patients with hepatocellular carcinoma scheduled for selective transarterial chemoembolization (TACE)

PS0-1, age 20 years or older

## Schema

Random allocation

Adjustment factors: maximum tumor diameter, number of tumors, institution

## Objectives

The objective of this randomized controlled trial is to compare selective transarterial chemoembolization (TACE) using drug-eluting beads of epirubicin (selective DEB-epiDOX: group A) and selective conventional TACE (cTACE) using epirubicin + lipiodol + embolization gelatin (selective cTACE: group B) in terms of the local complete response (CR) rate at the treatment site in patients with hepatocellular carcinoma (HCC) selected to receive treatment by selective TACE.

Primary endpoint: The local CR rate at 3 months in the treated HCC nodule (Independent review committee: IRC).

Secondary endpoints: The local CR rate at 1 month in the treated HCC nodule (IRC), the incidence rate of adverse events, and the incidence rate of serious adverse events.

Selective TACE refers to segmental or subsegmental TACE performed via hepatic segmental or subsegmental arteries.

## Study population

Inclusion criteria

1. Histologically or clinically diagnosed HCC. \*
2. Not a suitable candidate for hepatectomy, liver transplantation, or local ablative therapy (e.g., radiofrequency ablation). †
3. Hypervascular lesion showing enhancement in the early phase on contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) (intravenous bolus injection) and possible to perform selective TACE.
4. No previous treatment for HCC nodules for which TACE planned. ‡
5. Target HCC nodule measurable. §
6. Maximum diameter of the target HCC nodule is 5 cm or less.
7. Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0-1.
8. Child-Pugh class A or B.
9. Adequately maintained functions of the major organs (bone marrow, heart, kidney, etc.) with the following criteria for laboratory data met within 2 weeks prior to enrollment:
   1. Serum total bilirubin: ≤3.0 mg/dL
   2. Serum aspartate aminotransferase (AST)/alanine aminotransferase (ALT): Not more than 5-fold the upper limit of normal or more than 250 IU/L.
10. Age 20 years or older.
11. Availability of written informed consent.

\*Clinically diagnosed HCC refers to a hepatic tumor measuring at least 10 mm in diameter that shows enhancement in the early phase, followed by washout in the late phase, of contrast-enhanced CT or contrast-enhanced MRI.

†Suitability of the patient for hepatectomy, liver transplantation, or local ablative therapy is determined by the investigators at the institution.

‡Target HCC nodule refers to the lesion enrolled in this clinical study that is to be treated by selective TACE.

§There should be at least one HCC nodule measuring 10 mm or more in maximum diameter that shows enhancement on contrast-enhanced CT/MRI.

Exclusion criteria

1. Portal vein tumor thrombosis.
2. Extrahepatic metastasis present.
3. Formation of the target HCC nodule by rupture of HCC.
4. The target HCC nodule has evident extrahepatic blood supply.
5. History of surgical reconstruction of the biliary tract or endoscopic treatment of the bile duct.
6. Moderate or large amount of ascites or pleural effusion unresponsive to treatment.
7. Severe arterioportal shunt or arteriovenous shunt that may affect the treatment.
8. Difficulty in performing contrast-enhanced CT because of serious allergy to iodinated contrast media.
9. Previously enrolled in this clinical trial.
10. Has the following serious complications:

* Cardiac failure, angina pectoris, or arrhythmia that is difficult to control despite treatment
* Myocardial infarction within 6 months of the study
* Renal failure
* Active infection (excluding viral hepatitis)
* Active gastrointestinal hemorrhage
* Active double cancer requiring treatment
* Hepatic encephalopathy or severe psychiatric disorder

1. Women who are pregnant, breastfeeding, possibly pregnant, or intending to become pregnant, or patients who desire to have children.
2. Patients who are judged by each investigators as being unsuitable for safe participation in this study.

## Treatment modality

Group A (selective DEB-epiDOX): Selective TACE using drug-eluting beads of epirubicin

Group B (selective cTACE): Selective TACE using porous gelatin particles for embolization after administration of epirubicin plus ethyl ester of iodinated poppy-seed oil fatty acid (lipiodol)

Patients with untreated HCC who are selected to receive treatment by selective TACE are enrolled and allocated to group A or group B treatment. Two sessions of TACE for the same site are permitted within 1 month (up to two sessions of split TACE are allowed).

The therapeutic efficacy is confirmed by contrast-enhanced CT or MRI (bolus injection technique) at 1 and 3 months after treatment to assess the CR rate at 3 months. Assessment of the therapeutic efficacy at 3 months is only performed in those patients who show CR on the contrast-enhanced CT or MRI (intravenous bolus injection) performed at 1 month after treatment.

## Planned number of patients and study period

Planned number of enrolled patients: 200 (group A: 100, group B: 100)

Enrollment period: 4.0 years

Follow-up period: 6 months

Total study period: 4.5 years

## Contact information

Inquiries that require clinical judgment, including the eligibility criteria and criteria for treatment change: Study Secretariat

Enrollment procedure, filling in of the Case Report Form (CRF), etc.: Data Center

Report of adverse events: Study Secretariat

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# Objective

The objective of this randomized controlled trial is to compare selective transarterial chemoembolization (TACE) using drug-eluting beads of epirubicin (selective DEB-epiDOX: group A) and selective conventional TACE (cTACE) using epirubicin + lipiodol + embolization gelatin (selective cTACE: group B) in terms of the local complete response (CR) rate at the treatment site in patients with hepatocellular carcinoma (HCC) who are selected to receive treatment by selective TACE.

Primary endpoint: The local CR rate at 3 months in the treated HCC nodule (Independent review committee: IRC).

Secondary endpoints: The local CR rate at 1 month in the treated HCC nodule (IRC), the incidence rate of adverse events, and the incidence rate of serious adverse events.

# Background and Rationale for the Study Design

## Study population

### Epidemiology

In Japan, primary liver cancer, with an estimated 30 175 deaths from this cancer (1) in 2013, ranks as the fifth leading cause of mortality from cancer, after only lung cancer, gastric cancer, colorectal cancer, and pancreatic cancer. According to the World Health Organization (WHO) database of 182 countries in 2008, the number of deaths from hepatic cancer is the second highest in Japan, after China (2). However, the number of deaths in Japan has gradually varied from leveling off to a decreasing trend in recent years, in contrast to the increasing number of deaths from this cancer in Europe and North America (3). This decreasing trend may be explained by a decrease in the number of new patients of hepatitis virus infection owing to the screening of transfusion products and the establishment of treatments for hepatitis B and C (3,4). It is estimated that the number of deaths from liver cancer will decrease to a total of 24 600 in 2025, including 15 000 among men, and 9600 among women.

Primary liver carcinomas are classified into HCC, intrahepatic cholangiocarcinoma, cholangiolocellular carcinoma, bile duct cystadenocarcinoma, combined hepatocellular and cholangiocarcinoma, hepatoblastoma, and undifferentiated carcinoma. Among the primary liver cancers, HCC accounts for 94.7%, and intrahepatic cholangiocarcinoma accounts for 4.4%; the remaining types account for less than 1% (5).

In most patients, HCC arises in a background of chronic hepatitis or cirrhosis resulting from persistent infection with hepatitis C virus (about 65% of patients) or hepatitis B virus (about 15% of patients) (5). The incidence rate of HCC is estimated to be about 500-fold higher in hepatitis C-infected pateints and about 100-fold higher in hepatitis B-infected patients, as compared to that in persons not infected with either of these viruses. Therefore, patients with hepatitis C and hepatitis B are said to represent a group of patints that are at a high risk of developing HCC. Other risk factors for hepatic carcinogenesis include heavy drinking, smoking, exposure to aflatoxin, old age, and male sex (6). In addition, occurrence of carcinoma in a background of nonalcoholic steatohepatitis (NASH) has recently begun to attract attention.

### Staging

Staging of HCC is conducted according to the tumor size, number of tumors, and status of vascular invasion (T factor), status of lymph node metastasis (N factor), and status of distant metastasis (M factor). In Japan, staging of HCCs is often performed in accordance with the General Rules for the Clinical and Pathological Study of Primary Liver Cancer, 5th edition revised (7). However, this staging system, while being known to be correlated with the prognosis, is not the most suitable for selecting the appropriate treatment modality, which requires consideration of the hepatic function and of the characteristics and site of the cancer. Other systems used for staging of HCC include the Union for International Cancer Control (UICC) classification and the Barcelona Clinic Liver Cancer (BCLC) staging classification. In this study, we elected to adopt the BCLC staging classification, considering that this classification system has been generally used widely across the world in recent years, and that it is useful for selecting the appropriate treatment modality and predicting the prognosis in patients with HCC (8) (Fig. 1).

Figure 1. BCLC staging classification and treatment schedule (excerpt from Reference 8)



### Outline of the standard treatment and prognosis by stage

Curative treatment, such as hepatectomy, liver transplantation, and/or local ablative therapy (e.g., radiofrequency ablation) is recommended for patients with stage 0 (very early stage) or stage A (early stage) disease according to the BCLC staging classification, and the reported 5-year survival rates in these patients are in the range of 40%-70% (8). TACE is recommended for patients with stage B disease (intermediate stage) with multiple intrahepatic lesions, and the estimated 2-year survival rate in this patient group is 20%-60%, according to the results of previous randomized controlled trials (9-18). For patients with stage C disease (advanced stage) with vascular invasion or extrahepatic metastasis, systemic therapy is recommended. The standard systemic therapy is sorafenib therapy, and the median survival period of this therapy is 6-12 months (19,20).

### Rationale for selecting the study population

Although hepatectomy and liver transplantation are performed as curative treatments for HCC, actual implementation of these treatments is currently limited by the tumor stage and hepatic reserve. For small HCCs measuring 3 cm or less in diameter, efficacy comparable to that of hepatectomy can be expected from local ablative therapy, as represented by radiofrequency ablation (RFA). However, therapeutic efficacy of RFA cannot be expected in HCC patients with tumors measuring more than 3 cm in diameter and/or multiple tumors. Even in some HCC patients with small tumors measuring 3 cm or less in diameter, the location of the tumor may make RFA difficult to perform. In order to examine the therapeutic efficacy of selective TACE, we select patients with HCC who are not suitable candidates for more effective treatments, i.e., hepatectomy/liver transplantation or radiofrequency ablation, as the subjects for this clinical trial. Therefore, the main target population is patients with BCLC stage B disease. However, some BCLC stage A patients who are not suitable candidates for hepatectomy/liver transplantation or radiofrequency ablation in view of poor hepatic reserve function or inappropriate location of the tumor may also be included. In addition, patients with BCLC stage C with performance status (PS) 1 are also included in this study, because they are a suitable population for assessing the therapeutic efficacy of TACE. However, patients of BCLC stage C with portal vein tumor thrombosis are not suitable candidates for TACE, and are therefore not enrolled for this study, even though TACE is adopted to treat such patients at some institutions.

Therefore, the subjects of this study are mainly patients with multiple lesions or BCLC stage B, along with some BCLC stage A patients who are not suitable candidates for hepatectomy/liver transplantation/radiofrequency ablation despite having a limited number of HCC nodules, and some patients with BCLC stage C disease with PS 1.

The reported CR rate to selective TACE in HCC patients with tumors measuring ≤5 cm in diameter is 30%-60% (21). Because tumors measuring ≤5 cm in diameter account for 75% of patients treated by selective TACE (22), setting the upper limit of the tumor size at 5 cm seems to have no great influence on the accumulation of patients. Therefore, the maximum diameter of the cancer nodules for this study is set at ≤5 cm.

## Standard treatment for the study population

TACE is established as the standard treatment for patients with HCC who are unlikely to be suitable candidates for curative treatments such as hepatectomy, liver transplantation, or radiofrequency ablation. Several previously conducted randomized controlled trials (9-16) (Table 1) and meta-analyses (17,18) have shown that TACE yields significantly prolonged survival as compared to palliative treatment, with the results leading to the international recognition of TACE as the standard treatment for selected patients of HCC.

TACE is a therapeutic procedure that was developed by Yamada et al. in 1978 (22), and had been used for more than 30 years as an effective treatment in Japan, before its efficacy also came to be recognized in Europe and North America (5,6,23). Nonetheless, prospective clinical studies of TACE that could provide a high level of evidence had scarcely been performed. Under such situations, the results of a study (JIVROSG-0604) of TACE using epirubicin or doxorubicin/ethyl ester of iodinated poppy-seed oil fatty acid (ethiodized oil, lipiodol) in patients with unresectable HCC, which was a collaborative study jointly conducted by our study group (JIVROSG) and a South Korean interventional radiology (IVR) study group (KIVROSG), were reported in 2013 (24). In the study, TACE using epirubicin (or doxorubicin)/lipiodol was performed as the initial treatment in 99 patients with unresectable HCC (75 Japanese and 24 Korean patients), and the following results were obtained: 2-year survival rate, 75%; survival period (median), 3.1 years; time to progression, 7.6 months; response rate after the initial treatment, 73% [95% confidence interval (CI): 63%-81%]. These results were better than those of the previously reported randomized controlled trials. Therefore, TACE came to be regarded as the standard treatment for patients with unresectable HCC in both Japan and South Korea.

Table 1. Randomized controlled trials of transcatheter arterial (chemo)embolization vs. palliative treatment

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Reporter | Year | Treatment | No. of patients | Survival rate | | p-value |
| 1-year | 2-year |
| Lin (9) | 1988 | TAE | 21 | 42 | 25 | <0.01 |
|  |  | 5FU | 21 | 13 | 13 |  |
| Pelletier (10) | 1990 | TACE (DOX) | 21 | 24 | - | NS |
|  |  | BSC | 21 | 31 | - |  |
| GETCH(11) | 1995 | TACE (CDDP) | 50 | 62 | 38 | 0.13 |
|  |  | BSC | 46 | 43 | 26 |  |
| Pelletier (12) | 1998 | TACE (CDDP)+TAM | 37 | 51 | 24 | 0.77 |
|  |  | TAM | 36 | 55 | 26 |  |
| Bruix (13) | 1998 | TAE | 40 | 70 | 49 | 0.72 |
|  |  | BSC | 40 | 72 | 50 |  |
| Lo (14) | 2002 | TACE (CDDP) | 40 | 57 | 31 | 0.002 |
|  |  | BSC | 39 | 32 | 11 |  |
| Llovet (15) | 2002 | TACE (DOX) | 40 | 82 | 63 | 0.009 |
|  |  | BSC | 35 | 63 | 27 |  |
| Doffoel (16) | 2008 | TACE (epiDOX) | 62 | 51 | 25 | 0.68 |
|  |  | TAM | 61 | 46 | 22 |  |

GETCH: Groupe d’Etude et de Traitement du Carcinoma Hepatocellulaire; TAE: transcatheter arterial embolization; TACE: transcatheter arterial chemoembolization; BSC: best supportive care; DOX: doxorubicin; CDDP: cisplatin; epiDOX: epirubicin; TAM: tamoxifen; NS: not significant.

### Conventional TACE

In this study, cTACE refers to the classical TACE procedure performed in Japan using epirubicin, lipiodol, and a gelatin embolization material.

Anticancer agents

TACE is performed using various anticancer agents, including epirubicin, doxorubicin, cisplatin, mitomycin C, mitoxantrone, zinostatin stimalamer, and miriplatin. Kawai et al. compared epirubicin and doxorubicin (25), and Kasugai et al. compared cisplatin and doxorubicin (26), but no superiority of any of the agents over the others was demonstrated in their studies. Therefore, no one agent has been shown to be particularly useful over other agents as yet. Although even the value of combined use of anticancer chemotherapy has not been established, anticancer chemotherapy is used concomitantly with cTACE as the de-facto standard. Therefore, in this study, anticancer chemotherapy is combined with TACE in the study subjects.

Epirubicin is an anthracycline anticancer agent that inhibits DNA polymerasesand RNA polymerasesby intercalating with the tumor cell DNA, exerting its anticancer effect through inhibiting the biosynthesis of both DNA and RNA (27). The agent is a stereoisomer of doxorubicin, in which the hydroxyl group of doxorubicin is inverted at position 4'. It exerts less cardiotoxicity than doxorubicin, and hepatic arterial administration of this agent in patients with HCC is covered by National Health Insurance in Japan (28). The response rate to arterial infusion of epirubicin alone is reported to be 15.1% (8/53) in patients with unresectable HCC (29). In this study, we use epirubicin as the most commonly used agent for cTACE in Japan.

Ethyl ester of iodinated poppy-seed oil fatty acid (ethiodized oil, lipiodol)

Since selective tumor accumulation of lipiodol, an oil-based contrast medium, at a high concentration has been reported following hepatic arterial administration, lipiodol is often used as a carrier of the anticancer agent combined with TACE (30-33). It has been reported that hepatic arterial infusion of an anticancer agent emulsified in lipiodol elicits a stronger therapeutic effect than hepatic arterial infusion of an anticancer agent alone (32). Lipiodol was used in the aforementioned collaborative study performed by Japanese and South Korean study groups (24), and we have also adopted use of lipiodol in this study.

Gelatin sponge

Fragmented gelatin sponge, prepared from surgical hemostatic gelatin sponge, has been utilized as an embolization material for TACE since the 1970s, and its safety and efficacy are well established (6,23,24). In Japan, porous gelatin particles are used predominantly as the embolization material, ever since hepatic arterial administration of this material received approval for National Health Insurance coverage in January 2005. We selected porous gelatin particles as the embolization agent in this study.

TACE sessions

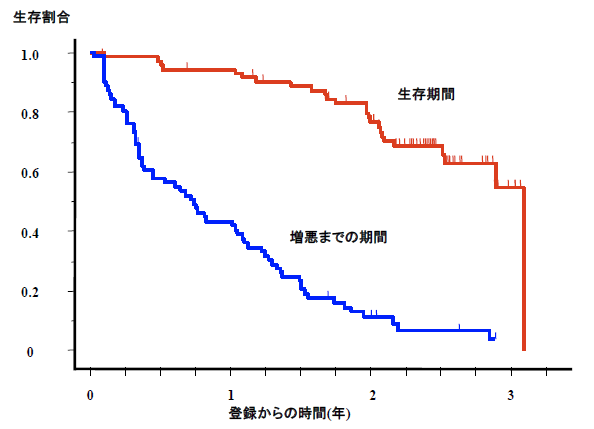
In Europe and North America, TACE is often repeated periodically, e.g., at intervals of 2 months, whereas in Japan, on-demand repetition for progression/persistence of cancer is the more common practice. Therefore, in Japan, patients showing CR are usually followed up without repeat TACE.

Treatment outcome of cTACE

TACE using an emulsion of epirubicin in lipiodol and gelatin embolization material was used in the aforementioned prospective collaborative study between Japanese and South Korean study groups, and the results of subgroup analyses conducted in the Japanese subjects of that study have been reported (33).

A total of 73 Japanese HCC patients with no history of prior treatment received TACE using an emulsion of epirubicin in lipiodol and gelatin embolization material. In response to the initial TACE, CR was achieved in 33 (45%) patients, and partial response (PR) in 27 (37%) patients, corresponding to a response rate (CR + PR) of 82% (95% CI: 71%-90%). Among the 25 patients with elevation of the serum α-fetoprotein (AFP) level to ≥100 ng/mL, 20 (80%) patients showed a ≥50% reduction in the level of this protein after treatment. Among the 41 patients with elevation of the serum protein induced by vitamin K absence or antagonist (PIVKA) II level to 100 mAU/mL or more, 37 (90%) patients showed a ≥50% decrease in the level of this protein after treatment. Among the 73 patients, the median time to progression was 8.8 months, the 1-year progression-free survival rate was 43.2%, and the 2-year progression-free survival rate was 11.0%. The median overall survival period was 36.9 months, and the 1-year and 2-year overall survival rates were 94.5% and 76.7%, respectively. Thus, favorable results were obtained in the Japanese subgroup (Fig. 2).

Figure 2. Survival period and time to progression in the Japanese subgroup of patients with HCC after cTACE



The long-term results of a prospective observational study of 8510 patients who underwent cTACE in Japan have also been reported (23). The results were favorable; the median survival period was 34 months, and the 1-year, 2-year, 3-year, 5-year, and 7-year survival rates were 82%, 63%, 47%, 26%, and 16%, respectively.

### DEB-epi DOX

TACE performed using drug-eluting beads (DEBs) is referred to as DEB-TACE in this study. DEB-TACE using doxorubicin is referred to as DEB-DOX, and DEB-TACE using epirubicin is referred to as DEB-epiDOX.

Beads

Beads are spherical particles or microspheres that are homogeneous in size, which makes them less likely to aggregate. Different sizes of beads are available, so that a suitable size can be selected according to the diameter of the target vessel and the tumor size, making it easier to predict the degree of embolization in individual patients, and the beads potentially have a persistent embolization effect. Beads, rather than polyvinyl alcohol particles, began to be used widely about 10 years ago in Europe and North America, and have been widely applied to TACE in recent years (34). In Japan, three types of beads, namely, DC Bead®, HepaSphere®, and Embosphere® are approved for coverage by National Health Insurance.

1. DC Bead®

The DC Bead® (hereinafter simply, DC Bead) microspheres consist of hydrophilic microspherical particles made of a cross-linked polyvinyl alcohol polymer. DC Bead particles are embolic beads that are injected through a catheter to selectively embolize the targeted blood vessels. The product is available in three particle sizes (100-300 μm, 300-500 μm, and 500-700 μm), so that the size best suited to an individual patient according to the vessel diameter, tumor size, and intended degree of embolization of the targeted blood vessel can be selected.

1. HepaSphere

HepaSphere microspheres consist of hydrophilic and swellable particles made of a polyvinyl alcohol-acrylic acid copolymer. Taking advantage of its characteristics, it is used for the treatment of hypervascular tumors, such as HCC and metastatic liver cancer, and is commercially available in more than 40 countries, mainly in Europe and North America. This type of embolic beads was developed in Japan, and is available in three particle sizes, ranging from 50 μm to 200 μm. HepaSphere beads can be loaded with anticancer agents for administration.

1. Embosphere

Embosphere microspheres consist of nonhydrophilic particles made of a swine gelatin-impregnated and coated acrylic copolymer. It is commercially available in more than 50 countries for use in the treatment of uterine myomas, hypervascular tumors, and arteriovenous malformations. This product is widely used, in particular, for uterine artery embolization in patients with uterine myomas in the US. It is available in five particle sizes, ranging from 100 μm to 1000 μm, and is used widely in Europe and North America. Embosphere beads cannot be loaded with anticancer agents.

From among the three products described above, mainly **DC Bead** microspheres, the product most commonly used in Japan, are used in the present study. After the initial embolization with epirubicin-loaded beads, the protocol allows for additional embolization using non-drug-loaded beads, if necessary. Embosphere or HepaSphere beads may also be used for additional embolization.

Anticancer agents

The anticancer agents that can be used for DEB-TACE include doxorubicin, epirubicin, and irinotecan, although it remains unclear which of the three agents would be optimal. Among these anticancer agents, predominantly doxorubicin is used overseas for DEB-TACE (DEB-DOX), and favorable results have been reported (35-40). For this study, we selected TACE using epirubicin-eluting beads (DEB-epiDOX) rather than doxorubicin-eluting beads. Both doxorubicin and epirubicin are anthracycline anticancer agents that are similar to each other in structure and efficacy. Epirubicin is a stereoisomer with the hydroxyl group of doxorubicin inverted at position 4', and exerts less cardiotoxicity than doxorubicin (27,28). On the other hand, the antitumor activity of doxorubicin is reported to be 1.5-fold that of epirubicin. In Japan, hepatic arterial administration of epirubicin in patients with HCC is approved for coverage by National Health Insurance, and is used in both patients allocated to the cTACE arm and those allocated to the DEB-TACE arm in this study. Because DEB-epiDOX therapy using DC Bead particles and epirubicin has been reported previously (41), it has been confirmed that DC Bead microspheres can be successfully impregnated with epirubicin particles. A feasibility assessment study of DEB-epiDOX in patients with HCC (JIVROSG-1301) was performed, and 8 patients were enrolled (unpublished data). The patients received DC Bead microspheres containing 75 mg of epirubicin/vial. Evaluation of the response at 4 weeks after treatment revealed CR in none of the patients, PR in 4 patients, stable disease (SD) in 2 patients, and progressive disease (PD) in 2 patients. Although the CR rate was 0%, the response rate was 50%. There were no serious adverse events, and the tolerability was favorable, and we concluded that this therapy is feasible.

TACE sessions

As a matter of general rule, in Europe and North America, TACE is repeated periodically at regular intervals. In a randomized controlled trial conducted to compare DEB-DOX and cTACE (Prospective Randomized Study of Doxorubicin in the Treatment of Hepatocellular Carcinoma by Drug-Eluting Bead Embolization: PRECISION V) (35), after the initial session, DEB-DOX was repeated at 2 months and 4 months. However, in Japan, it is more common practice to repeat TACE only in an on-demand manner, when it is judged to be necessary on account of progression/persistence of cancer. Therefore, in this study also, the on-demand method is adopted in both the DEB-epiDOX group and the cTACE group.

Therapeutic outcomes of DEB-DOX vs. cTACE

Lammer et al. reported the results of a randomized controlled trial conducted to compare DEB-DOX and cTACE (PRECISION V) (35). The response rate at 6 months, which was the primary endpoint, was 51.6% in the DEB-DOX group and 43.5% in the cTACE group, the difference not being statistically significant (p = 0.11) (Fig. 3). However, subgroup analyses revealed significantly better response rates to DEB-DOX in the subgroups with Child-Pugh class B, Eastern Cooperative Clinical Oncology Group performance status (ECOG PS) 1, bilateral lobe involvement, and recurrence (Fig. 4). Furthermore, the post-treatment hepatic impairment, in terms of elevation of the serum aspartate aminotransferase (AST)/alanine aminotransferase (ALT), etc., was also lower in the DEB-DOX group. The frequency of hepatic function impairment and frequency of doxorubicin-related adverse events were lower in the DEB-DOX group, suggesting the usefulness of this therapy in patients with advanced HCC selected to receive TACE.

In the above study, although there was no significant difference in the response rate between the two treatment arms at 6 months, i.e., in the primary endpoint, the outcomes of DEB-DOX were better in the subgroups with Child-Pugh class B, ECOG PS 1, bilateral lobe involvement, and recurrence, which led to DEB-DOX becoming adopted as the de-facto standard in place of cTACE in many countries overseas.

Figure 3. Response rates at 6 months, disease control rates, and CR rates among all patients and patients with advanced disease in the DEB-DOX group vs. the cTACE group



Figure 4. Disease control rates at 6 months in the patient subgroups with Child-Pugh class B, ECOG PS1, bilateral lobe involvement, and recurrence assigned to the DEB-DOX vs. cTACE arm



Nicolini et al. reported the results of a randomized controlled trial performed to compare DEB-DOX with cTACE in patients with HCC priorto liver transplantation. This was a small-scale study with 22 patients assigned to the DEB-DOX arm and 16 patients assigned to the cTACE arm. Although there was no significant difference in the direct therapeutic efficacy in terms of the degree of histologic necrosis or the CR rate, the recurrence-free survival period after liver transplantation was reported to be significantly longer in the DEB-DOX group (37).

In 2014, Golfieri et al. reported the results of a randomized controlled trial conducted to compare DEB-DOX (n = 89) and cTACE (n = 88) (40). The on-demand policy was used for repeating TACE, as in Japan, wherein TACE was repeated only when there was progression of HCC. The results revealed that the frequency of pain after TACE was lower in the DEB-DOX group. There was no significant difference in the time-to-progression (median: DEB-DOX, 9 months; cTACE, 9 months; p = 0.766) or survival (1-year/2-year survival rates: DEB-DOX 83.5%/55.4%; cTACE: 86.2%/56.8%; p = 0.949) between the two groups, suggesting that DEB-DOX and cTACE are approximately equivalent in efficacy. This report also described the local response rates at the TACE treatment site, which were approximately equal in the two groups (Fig. 5).

Figure 5. Comparison of the local response rates in the DEB-DOX vs. cTACE arm

Local CR rates at 1, 3, 6, 9, and 12 months



Local overall response (OR, CR + PR) rates at 1, 3, 6, 9, and 12 months



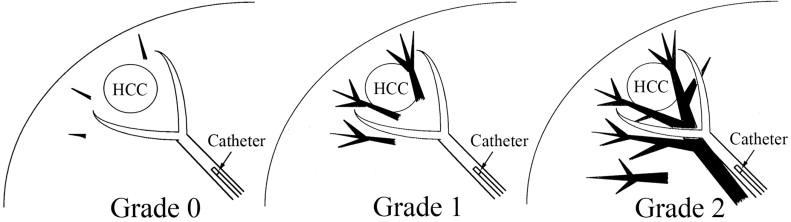
In summary, while recent studies have shown that DEB-TACE and cTACE are approximately equivalent in terms of their efficacy, DEB-TACE has come to be used widely as the de-facto standard overseas, based on the results of the PRECISION V study.

### Selective TACE

Selective TACE refers to segmental or subsegmental TACE performed via hepatic segmental or subsegmental arteries. Selective TACE, in which a catheter is selectively inserted into a tumor feeding vessel to enhance the therapeutic efficacy of TACE, is often performed in Japan. In 1993, Matsui et al. reported the usefulness of selective TACE performed via subsegmental arteries for small HCC (42). Ever since, this technique has come to be employed widely in Japan. According to the Report of the 19th Nationwide Follow-up Survey of Primary Liver Cancer in Japan (5), TACE in less than one segment was performed in as many as 2596 (36.9%) of all 7035 patients.

Miyayama et al. classified 123 small HCC nodules measuring ≤5 cm in diameter into three groups according to the degree of visualization of the portal vein branches during cTACE (Grade 0, no visualization; Grade 1, peritumoral visualization; Grade 2, visualization in the entire embolization area or exceeding it) (Fig. 6), and reported the local recurrence rates in relation to this classification (43).

Figure 6. Degree of visualization of the portal vein branches during cTACE



The 2-year recurrence rates in the Grade 0, 1, and 2 cases were 85.7%, 38.9%, and 17.7%, respectively. It has been reported that adequate infusion of lipiodol to the portal vein side yields favorable therapeutic results, and the therapeutic usefulness of cTACE was also suggested.

Matsui et al. have also reported that CR rates of 30%-60% can be expected from selective TACE when the tumor size is ≤5 cm. On the other hand, randomized controlled trials performed in Europe and North America have shown CR + PR rates in the range of 15%-55%, indicating evident differences between Japanese studies and those conducted in Europe and North America (22).

Thus, although data suggesting the usefulness of cTACE in patients undergoing selective TACE have been predominantly obtained from Japanese studies, it has not been clearly elucidated whether DEB-TACE or cTACE might be the more effective in terms of the local response.

### Reason for planning this clinical study

As mentioned above, DEB-TACE is the predominantly used TACE technique, as the de-facto standard, in many countries overseas. Previous reports of randomized controlled trials mostly indicate that DEB-TACE and cTACE are equivalent in terms of the survival period of the patients (35,40). However, in regard to the local response in the treated HCC nodule, their equivalence is controversial, with some studies indicating equivalent responses to the two techniques (40) and others indicating the superiority of DEB-TACE in some subgroups of patients (35). DEBs have also been approved in Japan, and it is now feasible to use them in actual clinical settings in this country. However, there is the impression that the embolization effect of DEBs is difficult to judge because of their poor visibility. There is also the view that the selective TACE technique commonly used in Japan may fail to deliver the beads into the tumor, and hence not yield the expected therapeutic efficacy. On the other hand, cTACE using lipiodol is better visualizable, and the embolization material can be infused via the hepatic artery into the portal vein side, as shown in section 2.2.3; thus, it is reported that a higher efficacy can be expected with this technique. In Japan, the size and extent of HCC is often limited, even in patients with BCLC stage B, and therefore, the use of selective TACE is more common here than overseas, because TACE is performed with the aim of achieving local cure at the site of treatment (44). Under these situations in Japan, there is confusion about the optimal technique of TACE in the clinical setting. Namely, it is currently unclear whether cTACE or DEB-TACE should be employed in patients with HCC who are selected to receive treatment by selective TACE. In addition, when performing selective TACE, which is common in Japan, there is a clinical question as to whether the cTACE technique that is widely employed in Japan can yield better therapeutic results. As it is important to answer this question, we planned this randomized controlled trial to compare the local response rates of the treated HCC nodules to selective cTACE and selective DEB-epiDOX.

## Rationale for setting the treatment plan

### Treatment regimens in this study

Rationale for setting the selective DEB-epiDOX therapy

DEB-DOX is a widely used treatment in many countries overseas. The aforementioned randomized controlled trial, the PRECISION V study (35), also used DEB-DOX. Because epirubicin, rather than doxorubicin, is commonly used in combination with TACE in Japan, in this present study, we elected to use epirubicin-eluting beads for selective TACE, the technique being referred to as selective DEB-epiDOX.

Rationale for setting the selective cTACE technique

TACE using epirubicin, lipiodol, and gelatin embolization material is used commonly in Japan, and was also used in the aforementioned prospective collaborative study conducted in Japan and South Korea (23). Therefore, in this study, we adopted TACE using epirubicin, lipiodol, and gelatin embolization material as the selective cTACE technique.

## Study design

### Study design

A multicenter collaborative open-label randomized controlled trial in Japan.

### Rationale for setting endpoints

The endpoints of this study are as follows.

Primary endpoint: The local CR rate at 3 months in the treated HCC nodule (IRC).

Secondary endpoints: The local CR rate at 1 month in the treated HCC nodule (IRC), incidence rate of adverse events, and incidence rate of serious adverse events.

In this study, the local CR rate at 3 months in the treated HCC nodule is adopted as the primary endpoint. In general, phase-III randomized controlled trials conducted to verify the superiority/inferiority of treatments for HCC often use the overall survival period as the endpoint. However, investigators engaged in IVR mostly aim to achieve CR at the treatment site when performing TACE. In addition, the policy of the subsequent treatment is usually decided based on the direct therapeutic efficacy of the TACE procedure employed. Therefore, a high value is attached to achieving a direct therapeutic effect in the target lesions, particularly CR.

In actuality, the direct therapeutic efficacy at the treatment site has a large influence on the subsequent treatment policy. The aforementioned randomized controlled trial, the PRECISION V study (34), which compared DEB-DOX and cTACE also adopted the response rate as the primary endpoint. Although there was no significant difference in the response rate between the two treatments, the response rate to DEB-DOX was significantly better among patients with Child-Pugh class B, ECOG PS1, bilateral lobe involvement, and recurrence, and the degree of hepatic function impairment in terms of elevation of the serum AST/ALT, etc., was also lower after DEB-DOX. Although there were no data on the overall survival period, these findings led to the current situation that DEB-DOX is regarded as the de-facto standard for the treatment of more advanced patients of HCC in many countries overseas. Therefore, the superiority/inferiority of the direct therapeutic efficacy is important for determination of the standard treatment. The definitions of nonresponse of intrahepatic lesions to TACE (45) include the following: two consecutive findings of a persistent contrast effect (50% or more) in the treated HCC nodule on CT or MRI performed for efficacy assessment at 1-3 months after TACE, and two consecutive findings of an increase in the number of intrahepatic tumors in comparison with the previous TACE on CT or MRI performed for efficacy assessment at 1-3 months after TACE. The subsequent treatment policy depends on the direct therapeutic efficacy of TACE. An analysis of randomized controlled trials by Llovet et al. revealed a relationship between the response rate and the survival period (15), suggesting that treatment with a high direct therapeutic efficacy is also associated with a prolonged overall survival period. Similarly, several reports of retrospective investigations of patients who underwent TACE for HCC have shown that the prognosis was favorable in patients where the direct therapeutic efficacy, including CR, was achieved (46-50).

Although the direct therapeutic efficacy including CR at the treatment site by TACE is not necessarily a surrogate endpoint alternative to the true endpoint of survival period, subsequent treatment strategy may vary according to whether or not direct therapeutic efficacy is achieved. The clinical question as to whether DEB-TACE or cTACE is more likely to yield CR at the treatment site of TACE is very important for investigators who are engaged in IVR. Therefore, in this study, we adopted the local CR rate at 3 months in the treated cancer nodule as the primary endpoint. The secondary endpoints are the direct therapeutic efficacy at 1 month in the treated HCC nodule, incidence rate of adverse events, and incidence rate of serious adverse events.

### Rationale for setting the number of patients

This study is aimed at obtaining an answer to the interesting question as to which of cTACE and DEB-TACE might exert better direct therapeutic efficacy in patients scheduled to receive selective TACE as treatment. In general, an about 10% difference in the local CR rate may be regarded as being of no consequence. A 20% difference would, however, seem to have a significant influence on selection of the treatment modality. Therefore, we set the minimum important clinical difference (MID) in the local CR rate between the two techniques of TACE at 20%, and consider that the technique that provides higher local CR rates by 20% or more could be deemed as the superior treatment technique.

A subgroup analysis of Japanese patients examined in the prospective study jointly performed by Japan and South Korea (33) revealed that the CR rate at 1-2 months after the initial session of cTACE using epirubicin, lipiodol, and gelatin embolization material was 45%. The primary endpoint of the present study is the CR rate at 3 months. It is assumed that the longer time may result in a slight decrease of the CR rate. On the other hand, the slightly better results may be obtained considering that the subjects of this clinical study are restricted to patients who are suitable candidates for selective TACE. Therefore, the CR rate that would be obtained at 3 months after selective cTACE is assumed to be 45%, being consistent with the previous findings. On the other hand, the CR rate after DEB-TACE was found to be 26.9% in the PRECISION V study (35) reported by Lammer et al. The complete response was 0% in the JIVROSG-1301 study which was performed to assess the feasibility of DEB-epiDOX; PR was obtained in 4 (50%) patients. Thus, although data on the CR rate associated with DEB-epiDOX remain insufficient, it is hypothesized, based on the results of the PRECISION V study, that the response rate to DEB-epiDOX in this study would be 25%. On the basis of this hypothesis, a power of 75% or more can be secured by analysis of 192 patients divided into two groups, i.e., 96 patients in each group, at a two-sided significance level of 5% (Table 2). However, the planned number of enrollments is 200 in total, that is, 100 patients in each group, to allow for a few patients who may not receive the protocol treatment or who may be found to be ineligible after enrollment.

Table 2. Required number of patients calculated from the expected CR rate

cTACE 45% vs. DEB-epiDOX 25%

|  |  |  |  |
| --- | --- | --- | --- |
|  |  | Required No. of patients at two-sided 5% | Percent difference required for *p*<0.05 by point estimation |
|  | Power 90% | 278 | 12.5% |
| One-sided 0.025 | Power 80% | 214 | 14.3% |
| (Two-sided 5%) | **Power 75%** | **192** | **15.1%** |
|  | Power 70% | 173 | 15.9% |

### Expected patient enrollment

In the aforementioned clinical study conducted in Japan and South Korea (JIVROSG-0604), the number of Japanese patients enrolled annually was 75 (24). This study covered patients with HCC undergoing their initial treatment. In contrast, in the present study, inclusion of not only patients with recurrence after resection/local ablative therapy, but also cases of TACE combined with selective TACE for tumors at another site is permitted, presumably allowing accumulation of a greater number of patients, i.e., about 150 patients per year. However, this is a randomized controlled study, and patients’ consent to participate in the study may be difficult to obtain. Considering that the success rate of informed consent acquisition is approximately 70%, about 100 patients can be enrolled per year. Therefore, allowing for some margin, the enrollment period was initially set at 2.5 years. However, as of July 18, 2018, the number of enrolled patients was 149, showing an increase by about 3 patients per month in the enrollment status. Because it is estimated that it would take another 1.5 years to reach the target number of patients, that is, 200, the enrollment period has been extended by 1.5 years. As the primary endpoint is the CR rate at 3 months, the follow-up period is set at 6 months, and the total study period is set at 4.5 years, giving some margin for the time to data fixation, etc.

### Allocation stratification factors

In this study, the factors that may affect the therapeutic efficacy of selective TACE are the maximum diameter and the number of treated HCC nodules. The TACE procedures require skill, and there could be variations among different institutions. Therefore, in this clinical study, three factors, i.e., the maximum diameters of the target tumor, number of target tumors, and the institution, are regarded as allocation stratification factors. Patients are randomly allocated to two groups by the minimization method to eliminate any large bias during the grouping.

1) Maximum tumor diameter

In general, tumors measuring ≤3 cm in diameter are considered to be suitable candidates for, and to show favorable therapeutic outcomes, to local ablative therapy. Therefore, the enrolled patients are stratified according to whether the target tumor measures ≤3 cm or >3 cm in maximum tumor diameter.

2) Number of tumors

It is predicted that the therapeutic efficacy varies between patients with single tumors and those with multiple tumors. Therefore, the enrolled patients are stratified according to whether they have single or multiple tumors.

3) Institution

It is widely known that there are differences among institutions in regard to the backgrounds of enrolled patients, treatment, efficacy assessment, and safety assessment.

## Outline of the expected advantages and disadvantages associated with participation in the study

### Expected advantages

The agent used in this study have been approved for the indications that were targeted in this study and their use is covered by the National Health Insurance in Japan. The treatments in both groups are those that are used in daily healthcare services and are covered by health insurance. All medical expenses for the participating patients, including the drug costs during the study period, are paid by the National Health Insurance or self-paid by the patients. Therefore, there is no particular advantage in terms of either healthcare or finance that accrues to patients who chose to participate in this study as compared to daily healthcare services. Patients cancontribute to judgment on which treatment can provide better direct therapeutic efficacy.

### Expected risks and disadvantages

If either cTACE or DEB-epiDOX is distinctly inferior in efficacy to the other, patients who are assigned to the inferior treatment arm would risk losing the opportunity to obtain a sufficient beneficial effect owing to their participation in the study. If the toxicity of either cTACE or DEB-epiDOX is higher than that of the other, patients who are assigned to the more toxic treatment arm may suffer more frequent (more severe) adverse events. However, as far as adverse events are concerned, we consider such a risk as being unlikely, judging from the results of randomized controlled trials conducted in Europe and North America (37,42).

To minimize the risk of adverse events and other disadvantages, “4. Criteria for Patient Selection,” “6. Treatment Planning and Criteria for Treatment Change,” and other issues are discussed carefully by the members of the Study Group. Periodic monitoring is scheduled after the beginning of the study, and the frequency of adverse events is monitored by the Data Center and the Efficacy and Safety Assessment Committee. If serious or unexpected adverse events occur, careful discussion and review is held with the Efficacy and Safety Assessment Committee to take necessary measures.

### Clinical implicationof this study

This study is a randomized controlled trial that is aimed at elucidating which of DEB-epiDOX (the mainstay technique in Europe and North America) or cTACE, used as the standard technique in Japan, might be more beneficial, by determining the CR rate to the selective TACE. If this study shows significantly better results of cTACE thanof DEB-epiDOX, the data can serve as an important reference for judging which treatment is more likely to yield a better CR rate in patients scheduled for treatment by selective TACE in Japan.

### Associated research

No associated research related to this study is planned currently.

# Criteria and Definitions Used in This Study

Clinical diagnosis and histological diagnosis of liver cancer are based on the General Rules for the Clinical and Pathological Study of Primary Liver Cancer (5th edition revised). Staging of liver cancer is in accordance with the BCLC staging classification, as shown in section 2.1.2. In addition, data based on the General Rules for the Clinical and Pathological Study of Primary Liver Cancer (5th edition revised) (Table 3) and UICC TNM classification (7th edition) (Table 4) are also collected. Hepatic function is assessed according to the Child-Pugh classification (Table 5).

## Histological classification:

### General Rules for the Clinical and Pathological Study of Primary Liver Cancer (5th edition revised)

The targets of this study are shown by screen and underline.

In this study, a lesion satisfying the following conditions is clinically diagnosed as a HCC, and a histological diagnosis is not necessary.

Clinically diagnosed HCC should satisfy the following conditions:

* Tumor enhancement is observed on contrast-enhanced CT or contrast-enhanced MRI.
* The serum AFP level is ≥10 ng/mL, and/or the serum PIVKA-II level is ≥40 mAU/mL.

Clinical Practice Guidelines for Hepatocellular Carcinoma 2013 also specify that a diagnosis of HCC can be made without performing biopsy when typical findings are obtained on contrast-enhanced CT or contrast-enhanced MRI.

Classification of primary liver cancer by clinical diagnosis or histological diagnosis

HCC

Intrahepatic bile duct carcinoma (cholangiocarcinoma)

Cholangiolocellularcarcinoma (cholangiolocarcinoma)

Bile duct cystadenocarcinoma

Combined hepatocellular cholangiocarcinoma

Hepatoblastoma

Sarcoma

Undifferentiated carcinoma

Others

## Staging

### 

### BCLC classification: See section 2.1.2. Staging.

### General Rules for the Clinical and Pathological Study of Primary Liver Cancer (5th edition revised) (Table 3)

|  |  |  |  |
| --- | --- | --- | --- |
| Stage | T factor | N factor | M factor |
| I | T1 | N0 | M0 |
| II | T2 | N0 | M0 |
| III | T3 | N0 | M0 |
| IV-A | T4  T1-4 | N0  N1 | M0  M0 |
| IV-B | T1-4 | N0-1 | M1 |

T factor: Determined by three items, i.e., number of tumors, tumor size, and presence/absence of vascular invasion (portal veins, hepatic veins and bile ducts). In cases of multiple tumors, the tumors may be multicentric tumors or intrahepatic metastases. Ruptured HCC S3 is dealt with as T4.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | T1 | T2 | T3 | T4 |
| 1. Number of tumors, single tumor 2. Tumor diameter ≤2 cm 3. No vascular invasion   (Vp0, Vv0, B0) | Meets all items (1) (2) (3). | Meets 2 items. | Meets 1 item. | Meets none of the 3 items. |

N factor

N0: Lymph node metastasis absent.

N1: Lymph node metastasis present.

M factor

M0: Distant metastasis absent.

M1: Distant metastasis present.

### UICC TNM classification (7th edition) (Table 4)

**HCC**

|  |  |  |  |
| --- | --- | --- | --- |
| Stage | T factor | N factor | M factor |
| I | T1 | N0 | M0 |
| II | T2 | N0 | M0 |
| IIIA | T3a | N0 | M0 |
| IIIB | T3b | N0 | M0 |
| IIIC | T4 | N0 | M0 |
| IVA | Any T | N1 | M0 |
| IVB | Any T | Any N | M1 |

T-Primary tumor status

T1 Single nodule, no vascular invasion.

T2 Single nodule, vascular invasion present. Or multiple tumors, with the maximum diameter not exceeding 5 cm.

T3 Multiple tumors, including tumors exceeding 5 cm in maximum diameter, or with invasion into the first branch of the portal vein or hepatic vein.

T3a Multiple tumors, including tumors exceeding 5 cm in maximum diameter.

T3b Invasion of the first branch of portal vein or hepatic vein present.

T4 Direct invasion of adjacent organs (excluding the gallbladder) or rupture of the visceral peritoneum.

N-Lymph node status

NX Regional lymph node metastasis is not evaluable.

N0 Regional lymph node metastasis absent.

N1 Regional lymph node metastasis present.

M-Distant metastasis status

M0 Distant metastasis absent.

M1 Distant metastasis present.

## Evaluation of hepatic function

### Child-Pugh classification (7) (Table 5)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | | Score | | |
| 1 point | 2 points | 3 points |
| Items | Encephalopathy | Absent | Minimal | Occasionally coma |
| Ascites | Absent | Slight | Moderate |
| Serum bilirubin (mg/dL) | <2.0 | 2.0-3.0 | >3.0 |
| Serum albumin (g/dL) | >3.5 | 2.8-3.5 | <2.8 |
| Prothrombin time (INR) | <1.7 | 1.7-2.3 | >2.3 |

Add the score for each item, and classify by the total score.

Child-Pugh class A 5-6 points

B 7-9 points

C 10-15 points

# Criteria for Patient Selection

Eligible patients are those who satisfy all of the inclusion criteria and meet none of the exclusion criteria listed below.

## Inclusion criteria

Inclusion criteria

1. Histologically or clinically diagnosed HCC. \*
2. Not a suitable candidate for hepatectomy, liver transplantation, or local ablative therapy (e.g., radiofrequency ablation). †
3. Hypervascular lesion showing enhancement in the early phase on CT or MRI with bolus contrast injection and possible to perform selective TACE
4. No prior treatment for the target HCC nodule for which TACE planned. ‡
5. Target HCC nodule measurable. §
6. Maximum diameter of the target HCC nodule is 5 cm or less.
7. ECOG PS 0-1.
8. Child-Pugh class A or B.
9. Adequately maintained functions of the major organs (bone marrow, heart, kidney, etc.) with the following criteria for laboratory data met within 2 weeks prior to enrollment:
10. Serum total bilirubin: ≤3.0 mg/dL
11. Serum AST/ALT: Not more than 5-fold the upper limit of normal or more than 250 IU/L.
12. Age 20 years or older.
13. Availability of written informed consent.

\*Clinically diagnosed HCC refers to a hepatic tumor measuring at least 10 mm in diameter that shows enhancement in the early phase, followed by washout in the late phase, of contrast-enhanced CT or contrast-enhanced MRI.

†Suitability of the patient for hepatectomy, liver transplantation, or local ablative therapy is determined by the investigators at the institution.

‡Target HCC nodule refers to the lesion enrolled in this clinical study that is to be treated by selective TACE.

§There should be at least one HCC nodule measuring 10 mm or more in maximum diameter that shows enhancement on contrast-enhanced CT/MRI.

Exclusion criteria

1. Portal vein tumor thrombosis.
2. Extrahepatic metastasis present.
3. Formation of the target HCC nodule by rupture of HCC.
4. The target HCC nodule has evident extrahepatic blood supply.
5. History of surgical reconstruction of the biliary tract or endoscopic treatment of the bile duct.
6. Moderate or large amount of ascites or pleural effusion unresponsive to treatment.
7. Severe arterioportal shunt or arteriovenous shunt that may affect the treatment.
8. Difficulty in performing contrast-enhanced CT because of serious allergy to iodinated contrast media.
9. Previously enrolled in this clinical trial.
10. Has the following serious complications:

* Cardiac failure, angina pectoris, or arrhythmia that is difficult to control despite treatment
* Myocardial infarction within 6 months of the study
* Renal failure
* Active infection (excluding viral hepatitis)
* Active gastrointestinal hemorrhage
* Active double cancer requiring treatment
* Hepatic encephalopathy or severe psychiatric disorder

1. Women who are pregnant, breastfeeding, possibly pregnant, or intending to become pregnant, or patients who desire to have children.
2. Patients who are judged by doctors as being unsuitable for safe participation in this study.

# Enrollment

In this study, patients are enrolled through a web enrollment system.

## Enrollment procedure

### Web enrollment procedure

The investigator accesses the web enrollment system via the Internet to enroll the patient after he/she is confirmed as satisfying all the inclusion criteria and meeting none of the exclusion criteria, and has given written consent to participate in the study. Patient enrollment is feasible 24 hours a day, except during maintenance hours for system check and troubleshooting. The investigator should choose the appropriate study and fill in the necessary items on the enrollment screen to enroll the patient.

Web enrollment Possible 24 hours a day on weekdays, Saturdays, Sundays, and holidays.

https://edmsweb16.eps.co.jp/edmsweb/

### Issuance of enrollment completion notification

When entry about inclusion criteria, exclusion criteria, and necessary items is confirmed by the system on the enrollment screen, the assigned treatment group and the enrollment number are issued. Screen display of the assigned treatment group and the enrollment number denote completion of enrollment. The investigator who performs the enrollment procedure prints out this notification, and store it in the patient’s chart. Enrollment is not considered as complete when there is conflict with the inclusion criteria or exclusion criteria or when there is data entry omission.

### Notice of enrollment completion

When allocation and enrollment are complete, an e-mail is sent to the investigator, the Study Secretariat, the Principal Investigator/Group Representative, and the person in charge at the Data Center.

### Delivery of the Case Report Form (CRF)

When the e-mail for notice of enrollment completion is received, the Data Center prepares a CRF on which the enrollment number of the patient is specified, and send it by mail to the concerned institution. Patient enrollment alone is performed via the Internet. Subsequent data collection is conducted by sending the CRF by fax to the Data Center.

### Contact information

For inquiries about system troubles during enrollment and criteria for patient selection, you may contact the following departments.

[Concerning criteria for patient selection]

Study Secretariat:

Masafumi Ikeda, Department of Hepatobiliary and Pancreatic Oncology, National Cancer Center Hospital East

TEL: 04-7133-1111 (PHS: 91230)

FAX: 04-7133-0335

E-mail：masikeda@east.ncc.go.jp

[Contact address and office hours concerning web enrollment]

JIVROSG1302 Data Center

Data Center 1, Clinical Research Operational Headquarters, EP-CRSU Co., Ltd.

TEL：03-5946-8262

E-mail：[JIVROSG@j-crsu.co.jp](mailto:JIVROSG@j-crsu.co.jp)

Telephone reception hours: 10:00-17:00 on weekdays (except for Saturdays, Sundays, holidays, and 12/29-1/4)

[Delivery of CRF]

JIVROSG1302 Data Center

Data Center 1, Clinical Research Operational Headquarters, EP-CRSU Co., Ltd.

TEL：03-5946-8262

FAX：03-5946-8276

E-mail：[JIVROSG@j-crsu.co.jp](mailto:JIVROSG@j-crsu.co.jp)

### Security of data in web enrollment

Leakage of patient data to a third party

The web enrollment system protects the patient data by means of cipher communication. In addition, the computer network of the web enrollment system is placed in a firewall, and measures are taken to protect the network from unauthorized access.

Enrollment data loss

Enrollment data are backed up every day. It is extremely unlikely for all data to be lost.

## Precautions for enrollment

1) Strictly no enrollment is permitted after the initiation of the protocol treatment.

2) Enrollment is not complete when there is conflict with the inclusion criteria or exclusion criteria or when there is data entry omission.

3) Enrollment of patients once completed cannot be cancelled (deleted from the database). In cases of overlapping enrollment, the initial enrollment information (enrollment number) is adopted.

4) This clinical study is aimed at examining the local CR rate of the treated HCC nodules. Patients may meet the inclusion criteria for HCC nodules present at sites other than the target treatment site. However, additional enrollment of the same patients for the treatment of nodules at a different site is not permitted.

## Random allocation and allocation stratification factors

At the time of enrollment, patients are randomly allocated to either of the two treatment groups by the web enrollment system. The minimization method is used for the random allocation, using “maximum tumor diameter of the target HCC nodule (≤ 3 cm/> 3 cm),” “number of tumors (single tumor/multiple tumors),” and “the institution” as the allocation stratification factors. Details of the allocation method are stated in the allocation specification document, which is kept in the custody of the person responsible for the data management and will not be disclosed to the investigators until the end of this study.

# Treatment Planning and Criteria for Treatment Change

With the patient safety secured, treatment and treatment change are implemented according to the description given in this section. If treatment per protocol is deemed to be medically dangerous, treatment change is implemented based on the medical judgment of the investigators. Such case is labelled as “protocol deviation.” Protocol deviation is regarded as “clinically reasonable deviation” if it is judged to be medically appropriate. Protocol deviation for purposes other than safety, such as with the intent to enhance the efficacy, is not regarded as “clinically reasonable deviation.”

## Protocol treatment

Group A: Selective DEB-epiDOX (epirubicin-loaded beads): Embolization is performed by infusing epirubicin-loaded beads into the segmental or subsegmental hepatic artery supplying the target HCC nodule. After embolization with epirubicin-loaded beads, additional embolization, if necessary, is permitted, but only with non-drug-loaded beads.

Group B: Selective cTACE (epirubicin + lipiodol + gelatin embolization material):

After administration of an emulsion of epirubicin and ethyl ester of iodinated poppy-seed oil fatty acid (ethiodized-oil, lipiodol), embolization is performed using porous gelatin particles via the segmental or subsegmental hepatic artery supplying the target HCC nodule.

In both groups A and B, the protocol treatment is started within 14 days after the patient is enrolled. If the treatment is started on day 15 or later for some reason, the reason is described in the treatment process record form. If it is judged that the treatment cannot be started, the patient is labelled as “discontinued protocol treatment,” and the details are described in the “treatment completion report.” If a patient no longer meets the inclusion criteria after enrollment because the clinical laboratory values became worse even prior to the initiation of the protocol treatment, it is left to the discretion of the investigator as to whether to start the protocol treatment or withdraw the patient from the study.

### Drugs used in this study

Anticancer agent

Agent name: epirubicin

Trade name: Farmorubicin® (Kyowa Hakko Kogyo Co., Ltd., Pfizer Japan Inc.), Epirubicin Hydrochloride® (Mylan Inc.), etc.

Embolization material

Embolization material: beads

Trade name: DC Bead® (Eisai Co., Ltd.)

Trade name: Embosphere® (Nippon Kayaku Co., Ltd.)

Trade name: HepaSphere® (Nippon Kayaku Co., Ltd.)

Embolization material: porous gelatin particles

Trade name: Gelpart® (Astellas Pharma Inc., Nippon Kayaku Co., Ltd.)

Lipiodol

Drug name: ethyl ester of iodinated poppy-seed oil fatty acid injection

Trade name: Lipiodol Ultra-Fluid® (Guerbet Japan KK)

There is no restriction on the use of generic drugs.

### Definition of protocol treatment

The protocol treatment in this study is defined as “one session of the assigned DEB-epiDOX or cTACE via the segmental or subsegmental hepatic artery supplying the target HCC nodule in patients with HCC not amenable to hepatectomy, liver transplantation, and local ablative therapy.” It is allowed to provide the protocol treatment in at most two sessions within 1 month (up to two sessions of split TACE are allowed), assuming that the treatment may not be completed in one session.

### Protocol treatment technique

In principle, in both groups A and B, TACE is performed via a segmental or subsegmental hepatic artery supplying the target HCC nodule. If assessment of the therapeutic efficacy at 1 month after the TACE does not show CR, use of other anticancer treatments may be considered. There are no particular regulations about the subsequent treatment. When TACE is found to have been sufficiently effective as to allow other useful treatment options such as resection and radiofrequency ablation, such treatments may be performed.

The protocol treatment technique is as follows.

1. Perform abdominal angiography to identify tumor enhancement and the feeding vessel.

If extrahepatic feeding arteries that had not been identified on the pretreatment CT/MRI are identified by angiography, alteration of blood flow may have been induced. Because use of beads is not recommended for altered blood flow cases, coils or porous gelatin particles are used instead. However, porous gelatin particles should also not be used for patients allocated to group A.

1. Insert a catheter into the segmental or subsegmental hepatic artery supplying the HCC.

Group A: Embolization is performed using epirubicin-eluting beads (DC Bead®) in selective DEB-epiDOX. Use of 100- to 300-μm particles is recommended initially. Additional embolization is permitted, as needed, using beads approved for insurance coverage (Embosphere® and HepaSphere® as of April 2015). However, use of lipiodol or porous gelatin particles is not allowed. Also, concomitant use of other anticancer agents such as mitomycin C or cisplatin is not permitted.

When performing DEB-epiDOX, it is recommended that the investigator refer to available technical recommendations (51). It has been reported that a vascular lake (blood sinus or pooling of contrast medium emerging inside the tumor) may form during DEB-epiDOX. Such formation of a vascular lake is associated with the risk of rupture of HCC, and no benefit is obtained by infusion of beads. Therefore, with the patient safety taken into account, use of porous gelatin particles is permitted in the event of formation of a vascular lake (52).

Group B: In the case of selective cTACE, epirubicin mixed with lipiodol injection is administered, and then, embolization is performed using porous gelatin particles. Embolization using beads is not permitted in Group B. Also, concomitant use of other anticancer agents such as mitomycin C or cisplatin is not permitted. When performing cTACE therapy, it is recommended that the treating physician refer to available technical recommendations (53).

1. End the treatment when tumor enhancement in the target area is no longer visualized.
2. Confirm the therapeutic efficacy by contrast-enhanced CT or MIR (bolus injection technique) at 1 and 3 months after the treatment. Assessment of the therapeutic efficacy at 3 months is only performed in patients who show CR, as assessed by contrast-enhanced CT or MRI (intravenous bolus injection) performed at 1 month after the treatment.

### Dosages of agents

Because the agent doses for TACE are determined according to the tumor volume, the maximum dose is prescribed for this study.

Group A: Selective DEB-epiDOX

Dose of epirubicin:  A daily dose of 60 mg/m2. This may be appropriately decreased or increased up to 150 mg/body according to the patient’s condition.

Dose of beads: Up to 2 vials in principle. Additional embolization, as needed, is permitted, using beads approved for insurance coverage (Embosphere® and HepaSphere® as of June 2014) not loaded with epirubicin.

Method of preparation: Beads are loaded with epirubicin (loading of 75 mg epirubicin per vial of beads).

Group B: Selective cTACE

Dose of epirubicin: A daily dose of 60 mg/m2. This may be appropriately decreased or increased up to 150 mg/body according to the patient’s condition.

Dose of lipiodol: Up to 10 mL.

Dose of porous gelatin particles: There are no regulations on the dose.

Method of preparation: Mixture of epirubicin and lipiodol injection may be prepared according to the method adopted at each institution.

## Criteria for discontinuation and completion of protocol treatment

### Criteria for completion of protocol treatment

A patient in which 1 session (or 2 sessions) of selective TACE via the segmental or subsegmental hepatic artery is performed is defined as “completed protocol treatment.” In contrast, a patient in which selective TACE via the segmental or subsegmental hepatic artery cannot be performed is defined as “unattained protocol treatment,” and the reason for the ‘unattainment’ (e.g., when tumor embolism is found in the first branch or the trunk of the portal vein during the protocol treatment, when selective TACE is technically difficult to perform, and when the case is judged to be amenable to other treatments, such as local therapy or systemic therapy) should be investigated.

### Criteria for implementation of the second session of protocol treatment in patients of planned split TACE

In patients where split TACE is planned prior first TACE, the second session of treatment is performed within 1 month after the first session, at the discretion of the investigator. However, the second treatment is the same as the treatment assigned to the patient at the time of enrollment in this study (A or B). The therapeutic efficacy is assessed at 1 month and 3 months after the second treatment.

## Consultation about protocol treatment

In case of any questions, please contact the Study Secretariat.

Study Secretariat:

Masafumi Ikeda, Department of Hepatobiliary and Pancreatic Oncology, National Cancer Center Hospital East

TEL: 04-7133-1111　(PHS:91230)

FAX: 04-7133-0335

E-mail：[masikeda@east.ncc.go.jp](mailto:masikeda@east.ncc.go.jp)

## Combined therapy and supportive therapy

### Recommended supportive therapy

**Examination and supportive therapy for hepatitis B surface antigen (HBsAg)-positive patients**

In HBsAg-positive patients, rapid proliferation (reactivation) of hepatitis B virus (HBV) may occur, leading to the development of severe and fatal hepatitis. Implementation of the following examinations is strongly recommended, with initiation of supportive therapy prior to the initiation of TACE.

**(1) Examination: HBV-DNA quantification**

HBV-DNA quantification is performed before the initiation of TACE.

HBV-DNA quantification is also performed every 4 weeks from the initiation of TACE to 12 months after the end of TACE. However, quantification every 3 months is permitted when the HBV-DNA titer is under the detection sensitivity in patients receiving entecavir or tenofovir.

**(2) Drugs to be used:**

**Entecavir hydrate (Bristol-Myers: Baraclude 0.5 mg tablets)**

Administration of entecavir should be started at least 1 week prior to the TACE according to the following dosage regimen, and continued for at least 12 months after the TACE.

**Dosage regimen:** Taken orally on an empty stomach fasting (at least 2 h after a meal and at least 2 h before the next meal).

**Dose:**

|  |  |
| --- | --- |
| Creatinine clearance (mL/min) | Dose |
| ≥50 | 0.5 mg once a day |
| ≥30 and <50 | 0.5 mg once every 2 days |
| ≥10 and <30 | 0.5 mg once every 3 days |
| <10 | 0.5 mg once a week |

**Adverse reactions (incidence rate of adverse reactions of all grades):** Nucleoside analogue-naïve patients

Diarrhea (6.0%), nausea (4.5%), constipation (3.7%), upper abdominal pain (3.0%), malaise (1.5%), nasopharyngitis (3.0%), muscle stiffness (2.2%), headache (14.2%), dizziness (3.0%), rash (incidence rate unclear), hair loss (incidence rate unclear), laboratory abnormalities: increased AST (3.7%), increased ALT (3.7%), increased blood bilirubin (6.0%), increased blood amylase (10.4%), increased lipase (10.4%), increased blood glucose (6.0%), increased blood lactic acid (23.1%), increased blood urea nitrogen (BUN) (6.7%), urinary occult blood positive (4.5%), white blood cells urine positive (3.0%), decreased white blood cell count (8.2%), and increased eosinophil count (0.7%).

**[Clinically significant adverse reactions (incidence rate unclear)]** Aggravation of hepatitis after the end of administration, anaphylactoid symptoms, lactic acidosis, severe hepatomegaly due to fatty deposition (fatty liver).

**Tenofovir (Glaxo SmithKline: Tenozet 300 mg tablets)**

**Dosage regimen:** This drug is taken orally at the dose of 300 mg once a day.

**Dose:**

|  |  |
| --- | --- |
| Creatinine clearance (mL/min) | Dose |
| ≥50 | 300 mg once a day |
| ≥30 and <50 | 300 mg once every 2 days |
| ≥10 and <30 | 300 mg once every 3-4 days |
| Hemodialysis | 300 mg once a week Note)  Or 300 mg after the end of a cumulative 12- h period of hemodialysis  Note) After implementation of hemodialysis. Pharmacokinetics in non-hemodialysis patients with creatinine clearance values of less than 10 mL/min has not yet been studied. |

**Adverse reactions (incidence rate of adverse reactions of all grades):**

Abnormal liver function tests (e.g., increased AST, ALT, and γ-gamma-glutamyl transpeptidase [γ-GTP]) in 7 (4.9%) patients, increased creatinine clearance in 4 (2.8%), increased amylase, increased lipase, and nausea in 3 each (2.1%), and abdominal pain in 2 (1.4%) patients.

**[Clinically significant adverse reactions (incidence rate unclear)]** Severe impairment of renal function, such as renal insufficiency, renal failure, acute renal failure, proximal renal tubular dysfunction, Fanconi syndrome, acute renal tubular necrosis, nephrogenic diabetes insipidus, or nephritis; lactic acidosis; severe hepatomegaly due to fatty deposition (fatty liver), and pancreatitis.

**Examination and supportive therapy for HBsAg-negative, hepatitis B core (HBc) antibody-positive, and/or HBs antibody-positive patients**

Even if patients are negative for HBsAg, reactivation of HBV may occur when they are positive for HBc antibody or HBs antibody, and occurrence of severe hepatitis in some patients has been reported. Implementation of the following examination is recommended before the initiation of TACE, with provision of the following supportive therapy according to the results of the examination.

**(1) Examinations before the initiation of TACE: HBV-DNA quantification**

HBV-DNA quantification is performed before the initiation of TACE.

**(2) When the HBV-DNA titer is above the detection sensitivity prior to the initiation of TACE**

As to the HBsAg-positive patients, entecavir or tenofovir should be administered, and measures (1) and (2) described under “examination and supportive therapy for HBsAg-positive patients” are taken.

**(3) When the HBV-DNA titer is under the detection sensitivity prior to treatment**

Periodic monitoring by HBV-DNA quantification, at least once every 3 months, is implemented. If the HBV-DNA goes over the detection sensitivity, entecavir or tenofovir is administered as to HBsAg-positive patients, and measures (1) and (2) described under “examination and supportive therapy for HBsAg-positive patients” are taken.

### Permitted concomitant treatments and supportive therapy

Concomitant use of the following treatments for adverse events is permitted because they are not expected to affect the results of efficacy assessment of the protocol treatment.

1) Administration of antiemetics and steroids aimed at alleviating nausea and vomiting

2) Prophylactic administration of antibiotics

3) Administration of nonsteroidal anti-inflammatory drugs and steroids for pain and fever

4) Liver support therapy for transient hepatic disorder and continuation of any pre-study treatments (glycyrrhizin, ursodeoxycholic acid, amino-acid preparations, etc.) for chronic liver disease or complications of chronic liver disease (gastrointestinal disorder, etc.)

5) Administration of G-CSF preparations for neutropenia (grade 3 neutropenia accompanied by fever, or grade 4 neutropenia)

6) Intra-arterial injection of xylocaine for pain prophylaxis

7) Intra-arterial injection of nitroglycerin preparations during vascular spasm

8) TACE using a balloon catheter

### Prohibited concomitant treatments

Resection, liver transplantation, or local necrosis therapy concomitantly with the protocol treatment is not permitted. Combined use of DEB-epiDOX and cTACE techniques is also not permitted (such combined use is judged to be “protocol deviation.” However, treatment for vascular lake and the use of porous gelatin particles is permitted in group A). Implementation of TACE using other anticancer agents such as mitomycin C and cisplatin is also not permitted. The usefulness of other concomitant treatments and supportive therapy remain unclear, and there are no regulations about such treatments in relation to the protocol treatment.

## Subsequent treatment

This study has no particular regulations about subsequent treatment in patients who do not show CR on the efficacy assessment by CT or MRI at 1 month after completion of the protocol treatment. Patients who have achieved CR are followed up without any treatment until the efficacy assessment performed 3 months later. (In the actual clinical setting in Japan, it is common for patients showing CR to be followed up without performing further TACE.)

As subsequent treatment, the assigned treatment may be repeated, or treatment using drugs included in the counterpart treatment regimen (cross-over) may be given. If TACE proves effective enough to allow other useful treatment options, such as resection and radiofrequency ablation, such treatment may be performed.

# Expected Adverse Reactions and Supportive Therapy



## Assessment of adverse events/adverse reactions

Adverse events/adverse reactions are assessed according to the Japan Clinical Oncology Group (JCOG) Japanese translation version of the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events v4.0 (CTCAE v4.0). Adverse events are graded to the closest grade by definition among Grades 0-5. In regard to adverse events, presence/absence of abnormal variations, the worst grade, and causal relationship with the protocol treatment are specified in the “pretreatment and initial treatment course report.” The causal relationship is classified as “present” or “absent.” In patients of “absent,” the reason for the judgment is also described.

## Expected adverse drug reactions for individual agents

As for adverse drug reactions to individual agents, refer to the latest version of the package insert of each drug shown in an appendix. All items specified under the “Warnings” and “Precautions” sections in the package inserts are “expected adverse drug reactions.”

### Overview of adverse reactions to epirubicin

Of 4818 patients surveyed, adverse drug reactions occurred in 2732 (56.7%) patients, and there were a total of 9002 reports of adverse drug reactions. Major adverse reactions included nausea/vomiting in 1767 (36.7%) cases, leukopenia in 1621 (33.6%) cases, anorexia in 1182 (24.5%) cases, and hair loss in 1167 (24.2%) cases.

Clinically significant adverse reactions

Myocardial disorder, myelosuppression, shock, interstitial pneumonia, hepatic/biliary tract disorder, gastric ulcer, duodenal ulcer

Other adverse reactions

Heart: Abnormal electrocardiogram, arrhythmia, tachycardia, chest pain

Hypersensitivity: Rash, erythema, redness, urticaria

Liver: Abnormal hepatic function (e.g., increased AST and ALT)

Kidney: Abnormal renal function (e.g., increased BUN)

Digestive organs: Nausea/vomiting, anorexia, stomatitis, diarrhea, abdominal pain, esophagitis, gastritis, gastrointestinal hemorrhage

Skin: Severe hair loss, pigmentation, pruritus, skin disorders, such as redness or erythema, erosions and ulcer at the time of hepatic arterial administration, skin necrosis

Neuropsychiatric system: Malaise, numbness, pain, headache, ear pain/tinnitus, insomnia, consciousness disturbance, paresthesia (strange sensation in mouth)

Urinary organ: Pollakiuria, pain during urination, cystitis, hematuria

Respiratory organ: Dyspnea, pneumothorax/hemothorax

Others: Fever, chills, facial edema, decreased blood pressure, hot flashes

### Overview of adverse reactions to ethyl ester of iodinated poppy-seed oil fatty acid injection

Clinically significant adverse reactions

Shock, pneumonia, thromboembolism, myocardial disorder, myelosuppression, interstitial pneumonia, hepatic/biliary tract disorder, gastric ulcer, duodenal ulcer, gastrointestinal hemorrhage

Other adverse reactions

Heart: Abnormal electrocardiogram, arrhythmia, tachycardia, chest pain

Hypersensitivity: Rash, erythema, redness, urticaria

Liver: Abnormal hepatic function (e.g., increased AST and ALT)

Kidney: Abnormal renal function (e.g., increased BUN)

Digestive organs: Nausea/vomiting, anorexia, stomatitis, diarrhea, abdominal pain, esophagitis, gastritis

Skin: Severe hair loss, pigmentation, pruritus, skin disorders, such as

redness, erythema, erosions and ulcer, skin necrosis

Neuropsychiatric system: Malaise, numbness, pain, headache, ear pain/tinnitus, insomnia,

consciousness disturbance, paresthesia (strange sensation in

mouth)

Urinary organ: Pollakiuria, hematuria

Respiratory organ: Dyspnea

Others: Fever, chills, facial edema, decreased blood pressure, hot flashes

### Overview of adverse reactions to gelatin sponge materials

In clinical studies conducted prior to approval of the product, adverse events, including abnormal laboratory test values (for which a causal relationship to the product could not be denied), were found in 62 (98.4%) of 63 patients. The major adverse events were as follows: fever 50.8%, abdominal pain 30.2%, nausea 11.1%, increased blood pressure 7.9%, increased AST 68.3%, increased ALT 65.1%, decreased cholinesterase 62.9%, increased lactate dehydrogenase (LDH) 50.8%, increased total bilirubin 50.8%, decreased albumin 49.2%, increased alkaline phosphatase (ALP) 36.5%, decreased total protein 31.7%, thrombocytopenia 29.0%, erythropenia25.4%, leukopenia 19.0%, and leukocytosis 12.7%.

Post-marketing drug use investigations revealed adverse events, including abnormal laboratory test values (for which a causal relationship to the product could not be denied), in 209 (34.7%) of 602 patients. The incidence rate of adverse events, including abnormal laboratory test values (for which a causal relationship to the product could not be denied), during concomitant use with anticancer agents was 34.8% (201/578 patients). The corresponding incidence rates specific to individual anticancer agents were as follows: 29.2% (123/421 patients) for epirubicin hydrochloride, 49.6% (58/117 patients) for intra-arterial cisplatin, 29.2% (28/96 patients) for mitomycin C, and 42.9% (18/42 patients) for doxorubicin hydrochloride. The major adverse events included increased AST, increased ALT, and fever. The incidence rate of adverse events, including abnormal laboratory test values (for which a causal relationship to the product could not be denied), when lipiodol was used concomitantly was 46.8% (109/233 patients), and the major adverse events were fever, increased AST, and increased ALT. (At the end of re-examination)

Clinically significant adverse events

Hepatic encephalopathy, liver abscess, intrahepatic biloma, serious thrombocytopenia

Other adverse events

Hemogram: Erythropenia, thrombocytopenia, leukocytosis, leukopenia,

thrombocytosis

Liver: Increased AST, increased ALT, increased total bilirubin, decreased

albumin, increased LDH, decreased cholinesterase, increased

ALP, decreased total protein, hepatic disorder, right

hypochondrium pain

Digestive organs: Abdominal pain, vomiting, nausea, epigastric pain, anorexia,

hematemesis

Cardiovascular system: Increased blood pressure, decreased blood pressure

Kidney: Increased BUN, increased creatinine, decreased creatinine,

increased urinary sugar, increased urinary protein, increased

urinary urobilinogen

Others: Fever, post-embolization infection, decreased serum sodium,

decreased serum calcium, increased serum potassium, decreased

serum potassium, increased serum chloride, decreased serum

chloride, sensation of pressure on the chest

### Beads: Overview of adverse reactions to DC Bead®

No surveys have been conducted in Japan to clarify the incidence rates of failures and adverse events associated with the use of DC Bead® microspheres in clinical studies. In an overseas clinical trial conducted in patients with HCC, a group of patients was treated with this product loaded with doxorubicin. It was reported that adverse events for which a causal relationship to this treatment could not be denied occurred in 76 (62.8%) of 121 patients included in the safety analysis.

Clinically significant adverse events

Hepatic failure, liver abscess

Other adverse events

Hemogram: Hemorrhage, tumor hemorrhage, thrombosis, leukocytosis, neutrophilia

Liver: Increased AST, increased ALT, increased γ-GTP, increased total bilirubin, jaundice

Digestive organs: Abdominal pain, nausea, vomiting, constipation, ascites, melena, pancreatitis, peritonitis

Cardiovascular system: Tachycardia, increased blood pressure, arterial dissection, pseudoaneurysm

General symptoms: Fever, pain, fatigue, edema, malaise, chest pain

Neuropsychiatric system: Anxiety, headache, insomnia

Musculoskeletal system: Back pain, muscle pain

Others: Increased blood glucose, weight loss, urinary retention, skin infection

### Beads: Overview of adverse reactions to HepaSphere®

Among 26 patients subjected to safety assessment in a domestic clinical trial, 59 reports of adverse events (signs and symptoms) for which a causal relationship to this product could not be denied were found in 24 (92.3%) patients. The major events were as follows: fever 61.5% (16/26 patients), abdominal pain 23.1% (6/26 patients), hypertension 19.2% (5/26 patients), nausea 11.5% (3/26 patients), malaise 11.5% (3/26 patients), decreased appetite 11.5% (3/26 patients), and vomiting 11.5% (3/26 patients). There were 110 reports of abnormal laboratory test values for which a causal relationship to this product could not be denied in 23 (88.5%) patients. Major abnormal variations in laboratory items included the following: increased C-reactive protein (CRP) 69.2% (18/26 patients), decreased lymphocyte count 57.7% (15/26 patients), increased AST 34.6% (9/26 patients), increased neutrophil count 34.6% (9/26 patients), increased ALT 30.8% (8/26 patients), and increased LDH 26.9% (7/26 patients).

Among these adverse events, fever, abdominal pain, vomiting, malaise, decreased lymphocyte count, increased AST, increased ALT, increased CRP, etc., were judged to be “post-embolization syndrome,” and the incidence rate of this syndrome was 69.2% (18/26 patients).

Clinically significant adverse events

Post-embolization syndrome including embolism or ischemia in unintended sites such as cerebral infarction, myocardial infarction, pulmonary embolism, and deep vein thrombosis, blindness, hearing loss, loss of the sense of smell, paralysis, and death

Other adverse events

Digestive organs: Abdominal pain, nausea, vomiting, upper abdominal pain, abdominal distension, diarrhea

Vascular system and tissue surrounding the target site:

Hypertension, decreased blood pressure, capillary bed occlusion

and tissue injury, vasospasm, recanalization, rupture of blood

vessel or lesion, hemorrhage

General/whole body: Fever, malaise, chills, chest pain, pain, sensation of pressure

Catheter insertion site: Application site erythema, application site pain, application site warmth, insertion site hematoma, clot formation at catheter tip and clot release, nerve injury, vascular injury

Musculoskeletal system and connective tissue:

Back pain, muscle weakness

Laboratory test values: Increased CRP, decreased lymphocyte count, increased AST, increased neutrophil count, increased ALT, increased LDH, increased white blood cell count, decreased blood albumin, decreased platelet count, decreased hemoglobin, increased γ-GTP, increased blood bilirubin, decreased blood sodium, decreased white blood cell count, decreased neutrophil count, increased basophil percentage, decreased eosinophil percentage, increased eosinophil percentage, increased monocyte percentage, increased ALP, increased BUN, increased blood creatinine, decreased blood potassium, increased blood potassium, decreased blood calcium, increased blood calcium, increased serum amylase, increased lipase, increased urine amylase

Others: Decreased appetite, bradycardia, coughing, hypoxia, skin tightness, foreign body reaction, infection, allergic reaction to a drug (analgesic, contrast medium, etc.)

### Beads: Overview of adverse reactions to Embosphere®

Among the 25 patients subjected to safety assessment in a domestic clinical trial, 53 reports of adverse events (signs and symptoms) for which a causal relationship to this product could not be denied were found in 18 (72.0%) patients. The major events were as follows: fever 28.0% (7/25 patients), hypertension 28.0% (7/25 patients), vomiting 24.0% (6/25 patients), and pain 20.0% (5/25 patients).

There were 92 reports of abnormal laboratory test values for which a causal relationship to this product could not be denied in 17 (68.0%) patients. Major abnormal variations in the laboratory test items included: increased CRP 64.0% (16/25 patients), increased LDH 52.0% (13/25 patients), increased AST 32.0% (8/25 patients), decreased blood albumin 32.0% (8/25 patients), increased white blood cell count 28.0% (7/25 patients), increased neutrophil count 28.0% (7/25 patients), decreased lymphocyte count 24.0% (6/25 patients), increased ALT 24.0% (6/25 patients), and decreased total protein 20.0% (5/25 patients).

Among these adverse events, vomiting, fever, pain, abdominal pain, nausea, malaise, decreased appetite, abdominal discomfort, epigastric discomfort, pain in the extremities, musculoskeletal discomfort, hypertension, increased CRP, increased LDH, etc., were judged to represent “post-embolization syndrome,” and the incidence rate of this syndrome was 56.0% (14/25 patients).

Clinically significant adverse events

Post-embolization syndrome, including embolism or ischemia in unintended sites such as cerebral infarction, myocardial infarction, pulmonary embolism, and deep vein thrombosis, blindness, hearing loss, loss of the sense of smell, paralysis, and death

Other adverse events

Digestive organs: Abdominal pain, nausea, vomiting, abdominal discomfort, epigastric discomfort, constipation

General/whole body: Malaise, pain, fever, decreased appetite, gait disturbance, dehydration

Vascular system and tissue surrounding the target site:

Hypertension, capillary bed occlusion and tissue injury, rupture of blood vessel or lesion, hemorrhage, vasospasm, recanalization, phlebitis

Catheter insertion site: Insertion-site hematoma, clot formation at catheter tip and clot release, nerve injury, vascular injury

Musculoskeletal system: Back pain, pain in the extremities, musculoskeletal discomfort

Nervous system: Dizziness, vasovagal reflex

Gynecologic system: Uterine hemorrhage, early menopause, amenorrhea, infection in the pelvic area, uterine/ovarian necrosis, vaginal discharge, myoma prolapse/expulsion, extraction of necrotic tissue, hysterectomy

Laboratory test values: Decreased hemoglobin, increased white blood cell count, increased neutrophil count, decreased lymphocyte count, increased AST, increased ALT, increased LDH, increased CRP, decreased total protein, decreased Alb, decreased red blood cell count, decreased hematocrit, decreased white blood cell count, increased monocytes, increased γ-GTP, increased ALP, increased total bilirubin, decreased sodium, decreased potassium, decreased chloride, decreased calcium, positive urinary occult blood

Others: Sinus bradycardia, hypoxia, hepatic infarction, rash, foreign-body reaction, infection, hypersensitivity



## Adverse reactions attributable to the angiographic procedures and TACE

### Overview of adverse reactions attributable to the angiographic procedures and TACE

Allergic reactions: Iodine contrast agent hypersensitivity, gelatin hypersensitivity, vasovagal symptoms

Skin: Skin ulcer, urticaria, others (tape rash, dermatitis)

Gastrointestinal tract: Gastrointestinal necrosis, gastrointestinal ulceration/erosion

Puncture site hematoma/procedure-related hemorrhage

Hepatic dysfunction, hepatic failure, cholecystitis, pancreatitis

Infection: Puncture-site infection, cholangitis, liver abscess

Lung, upper respiratory tract: Hiccups, pleural effusion

Others: Peripheral arterial ischemia, thrombosis, thrombus, embolism, vascular injury, visceral arterial ischemia

## Adverse events expected in the DEB-epiDOX and cTACE arms of the study

The expected adverse reactions in this study are as follows.

### Group A: DEB-epiDOX

All items specified under the “Warnings” and “Precautions” sections in the package inserts of epirubicin and the beads used are labelled as “expected adverse drug reactions.” Table 8 shows the adverse events of DEB-epiDOX reported from an overseas study. Table 6 shows the adverse events found in 8 patients of the DEB-epiDOX arm in the JIVROSG-1301 trial. Expected serious adverse drug reactions comprise all the adverse reactions enumerated as “clinically significant adverse reactions” in the package insert of each of the drug products and all the Grade 3 or 4 non-hematological toxicities listed in Table 7.

**Table 6. Adverse events in the DEB-epiDOX arm (JIVROSG-1301)**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | *No. of patients (n = 8) (%)* | | | |
| *Grade 1* | *Grade 2* | *Grade 3* | *Grade 4* |
| *Hematotoxicity* |  |  |  |  |
| Leukopenia | 1(13) | 1 (13) | 0 (0) | 0 (0) |
| Decreased hemoglobin | 1 (13) | 0 (0) | 0 (0) | 0 (0) |
| Thrombocytopenia | 0 (0) | 0 (0) | 1 (13) | 0 (0) |
| *Non-hematological toxicity* |  |  |  |  |
| Fatigue | 1 (13) | 2 (25) | 0 (0) | 0 (0) |
| Fever | 2 (25) | 0 (0) | 0 (0) | 0 (0) |
| Hair loss | 0 (0) | 0 (0) | - | - |
| Anorexia | 1 (13) | 1 (13) | 0 (0) | 0 (0) |
| Nausea | 1 (13) | 0 (0) | 0 (0) | 0 (0) |
| Vomiting | 3 (38) | 0 (0) | 0 (0) | 0 (0) |
| Abdominal pain | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| Decreased albumin | 3 (38) | 1 (13) | 0 (0) | 0 (0) |
| Increased bilirubin | 1 (13) | 1 (13) | 1 (13) | 0 (0) |
| Increased AST | 4 (50) | 1 (13) | 1 (13) | 0 (0) |
| Increased ALT | 2 (25) | 1 (13) | 1 (13) | 0 (0) |
| Increased ALP | 3 (38) | 0 (0) | 0 (0) | 0 (0) |

### Grape B: cTACE

All items specified under the “Warnings” and “Precautions” sections in the package inserts of epirubicin and gelatin sponge fragments are labelled as “expected adverse drug reactions.” Table 7 shows the adverse events of cTACE performed by our trial group (23). Table 8 shows the adverse events reported from an overseas study (PRECISION V) (35). Expected serious adverse drug reactions comprise all the adverse reactions enumerated as “clinically significant adverse reactions” in the package insert of each of the drug products and all the Grade 3 or 4 non-hematological toxicities listed in Tables 7 and 8.

**Table 7. Adverse events in the cTACE arm (JIVROSG-0604)**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | *No. of patients (n = 99) (%)* | | | |
| *Grade 1* | *Grade 2* | *Grade 3* | *Grade 4* |
| *Hematotoxicity* |  |  |  |  |
| Leukopenia | 30 (30) | 12 (12) | 0 (0) | 0 (0) |
| Neutropenia | 11 (11) | 14 (14) | 1 (1) | 0 (0) |
| Decreased hemoglobin | 53 (54) | 14 (14) | 1 (1) | 0 (0) |
| Thrombocytopenia | 45 (45) | 25 (25) | 11 (11) | 1 (1) |
| *Non-hematological toxicity* |  |  |  |  |
| Malaise | 42 (42) | 10 (10) | 0 (0) | 0 (0) |
| Anorexia | 37 (37) | 4 (4) | 0 (0) | 0 (0) |
| Nausea | 22 (22) | 4 (4) | 0 (0) | 0 (0) |
| Vomiting | 10 (10) | 1 (1) | 0 (0) | 0 (0) |
| Fever | 55 (56) | 9 (9) | 0 (0) | 0 (0) |
| Abdominal pain | 24 (24) | 12 (12) | 4 (4) | 0 (0) |
| Hair loss | 1 (1) | 0 (0) | - | - |
| Gastrointestinal hemorrhage | 0 (0) | 0 (0) | 1 (1) | 0 (0) |
| Liver abscess | 0 (0) | 0 (0) | 1 (1) | 0 (0) |
| Increased bilirubin | 28 (28) | 36 (36) | 2 (2) | 0 (0) |
| Increased AST | 28 (28) | 32 (32) | 30 (30) | 5 (5) |
| Increased ALT | 26 (26) | 31 (31) | 31 (31) | 5 (5) |
| Increased ALP | 57 (58) | 4 (4) | 1 (1) | 0 (0) |
| Decreased albumin | 49 (49) | 35 (35) | 0 (0) | - |
| Increased creatinine | 12 (12) | 3 (3) | 0 (0) | 0 (0) |

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Table 8. Adverse events in the DEB-DOX arm vs. cTACE arm (PRECISION V)** | | | | |
|  | DEB-DOX (n = 93) | | cTACE (n = 108) | | |
|  | Events | Patients | Events | Patients | |
| All adverse events | 417 (100) | 79 (84.9) | 491 (100) | 88 (81.5) | |
| Post-embolization syndrome | 35 (37.6) | 23 (24.7) | 43 (39.8) | 28 (25.9) | |
| Post-embolization syndrome and symptoms | 67 (72.0) | 34 (36.6) | 78 (72.2) | 41 (38.0) | |
| Adverse events found in at least 10% of patients | | |  |  | |
| Abdominal pain | 24 (5.8) | 20 (21.5) | 24 (4.9) | 19 (17.6) | |
| Nausea | 19 (4.6) | 15 (16.1) | 20 (4.1) | 15 (13.9) | |
| Vomiting | 13 (3.1) | 10 (10.8) | 16 (3.3) | 10 (10.8) | |
| Upper abdominal pain | 12 (2.9) | 12 (12.9) | 5 (1.0) | 12 (12.9) | |
| Fever | 20 (4.8) | 16 (17.2) | 42 (8.6) | 16 (17.2) | |
| Fatigue | 15 (3.6) | 13 (14.0) | 6 (1.2) | 13 (14.0) | |
| Other than post-embolization syndrome | 35 (8.4) | 23 (24.7) | 44 (9.0) | 23 (24.7) | |

cTACE, conventional TACE.

# Assessment Items, Laboratory Tests, and Assessment Schedule



## Pre-enrollment assessment items

### Items to be assessed before the initiation of treatment (any time before enrollment is acceptable)

HBs antigen, HBc antibody, HBs antibody, hepatitis C virus (HCV) antibody

### Items to be assessed within 28 days prior to the date of enrollment

1. Patient characteristics:

Age, gender, presence/absence of complications, presence/absence of ascites, Child-Pugh class

1. Diagnosis of HCC: method of definitive diagnosis, presence/absence of vascular invasion, number of tumors, tumor location, percent area of tumor involvement, maximum tumor diameter, presence/absence of invasion of adjacent organs, etc.
2. Contrast-enhanced abdominal CT or MRI (slice width: 5 mm or less) after intravenous bolus injection of contrast
3. Chest radiography or chest CT
4. Electrocardiography

### Items to be assessed within 14 days prior to the date of enrollment

1. ECOG Performance status
2. Signs and symptoms
3. Child-Pugh class
4. Laboratory tests

(1) Blood counts: WBC，Neu，Hb，PLT

(2) Biochemistry: Alb, T-Bil, AST, ALT, ALP, Cr

(3) Coagulation profile: PT(INR)

(4) Tumor markers: AFP, PIVKAII

## Post-treatment assessment (until 3 months after the initial TACE)

Assessment of each item is performed according to the following schedule. Adverse events are judged according to CTCAE v4.0.

[Within 3 ± 2 days after treatment]

1. Adverse events (CTCAE v4.0):

Fever, fatigue, malaise, anorexia, nausea, vomiting, abdominal pain, hair loss, others

1. ECOG Performance status
2. Laboratory tests

(1) Blood counts: WBC，Neu，Hb，PLT

(2) Biochemistry: T-Bil, AST, ALT, Cr

[4 ± 2 weeks after treatment]

1. Adverse events (CTCAE v4.0):

Fever, fatigue, malaise, anorexia, nausea, vomiting, abdominal pain, hair loss, others

1. ECOG Performance status
2. Measurement of the target lesion

Contrast-enhanced abdominal CT after intravenous bolus injection of contrast (CT slice width: 5 mm or less)

Contrast-enhanced MRI is permitted if contrast-enhanced abdominal CT is difficult to perform because of allergy to the CT contrast medium detected after enrollment.

1. Laboratory tests

(1) Blood counts: WBC，Neu，Hb，PLT

(2) Biochemistry: Alb，T-Bil, AST, ALT, ALP, Cr

(3) Tumor markers: AFP, PIVKA-II

[3 months ± 2 weeks after treatment] (Only in cases showing CR at 4 ± 2 weeks. Not necessary for non-CR cases.)

1. Contrast-enhanced abdominal CT after intravenous bolus injection of contrast (CT slide width: 5 mm or less)

Contrast-enhanced MRI is permitted if contrast-enhanced abdominal CT is difficult to perform because of allergy to CT contrast medium detected after enrollment.

1. Laboratory tests

Tumor markers: AFP, PIVKA-II

## Follow-up observation (at 3 months or more after the initial TACE)

Not particularly regulated. Patients will be followed based on routine clinical practice.

## Study calendar

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Examination items | Pre-enrollment | Post-treatment\* | | |
| Within 2 weeks | 3 ± 2 days | 4 ± 2 weeks | 3 months ± 2 weeks |
| Patient characteristics | □ |  |  |  |
| Signs and symptoms | ○ | ○ | ○ |  |
| Performance status | ○ | ○ | ○ |  |
| Blood counts | ○ | ○ | ○ |  |
| Biochemistry | ○ | ○ | ○ |  |
| Coagulation profile | ○ |  | ○ |  |
| Viral markers | △ |  |  |  |
| Tumor markers | ○ |  | ○ | ● |
| Contrast-enhanced CT/MRI | □ |  | ○ | ● |
| Chest radiography | □ |  |  |  |
| Electrocardiography | □ |  |  |  |

○: Should be implemented in all patients.

△: Pretreatment data, if available, are acceptable.

□: Should have been performed within 4 weeks prior to enrollment.

●: Performed only in patients showing CR at 4 ± 2 weeks.

\*In patients who undergo two sessions of split TACE, the therapeutic efficacy is assessed at 1 month and 3 months after the second treatment.

# Data Collection

## Types of CRFs used in this study and the deadlines for their submission

The types of CRFs used in this study and the deadlines for their submission are as follows.

1) Eligibility confirmation form: This form is submitted through the web enrollment system immediately after a case is enrolled.

2) Pretreatment, initial treatment efficacy, and adverse event report form: This form is submitted to the Data Center by fax within 4 weeks after adverse event assessment and therapeutic efficacy assessment performed at 4 weeks ± 2 weeks after the treatment.

3) Report form for therapeutic efficacy at 3 months: Assessment of the therapeutic efficacy at 3 months includes only patients who have shown CR in the efficacy assessment performed at 1 month. Patients who do not show CR at 1 month are not eligible. This form is sent to the Data Center by fax within 4 weeks after the efficacy assessment performed at 3 months ± 2 weeks after the end of treatment.

(Point to consider)

- The “pretreatment, initial treatment efficacy, and adverse event report form” and a “report form for therapeutic efficacy at 3 months” on which the enrollment number of the patient is pre-printed is sent by mail from the Data Center after patient enrollment. If these forms do not arrive within 5 days of the patient enrollment or if the forms are lost or damaged, apply to the Data Center for reissue.

## Method of CRF delivery

Except the eligibility confirmation form, all CRF forms are submitted to the Data Center by fax. To avoid the risk of leakage of the patients’ personal information, the patient enrollment number is used when contacting the Data Center, e.g., to request for the delivery of CRFs.

## Correction of the CRFs

If any flaw, such as missing data on a necessary item or inappropriate categorization, is found after the beginning of the study, correction of the CRF is undertaken based on a consensus between the Principal Investigator and the Study Secretariat, provided that the correction of the CRF does not exceed the extent of data collection prescribed in section “8. Assessment items, laboratory tests, and assessment schedule,” and that the correction of the CRF is judged to cause no increase in the medical or financial burden on the enrolled patient. Correction of the CRF requiring no correction in the text of the protocol is not regarded as protocol revision. With regard to how to report a CRF correction to the head of the institution and whether an application needs to be made for amendment, follow the rules of the institution.

# Reporting of Adverse Events

When a “serious adverse event” occurs, the representative of the institution reports the adverse event to the Study Secretariat or Principal Investigator. Reporting of adverse reactions to the Minister at the Ministry of Health, Labour and Welfare (MHLW) based on the Pharmaceutical Affairs Law, reporting of serious adverse events to the heads of institutions and regulatory authorities based on the “Ethical Guidelines for Medical and Health Research Involving Human Subjects (Ministry of Education, Culture, Sports, Science and Technology (MEXT)/MHLW Notification No. 3, 2014),” and reporting of adverse reactions by the each institutions to companies will be performed, as appropriate, according to the rules of the respective institutions, under the responsibility of the representatives of the institutions.

## Serious adverse events

A serious adverse event is defined as an adverse event that meets at least one of the following conditions, regardless of whether or not there is a causal relationship with the protocol treatment. Serious adverse events are subject to expedited reporting.

(1) Results in death.

(2) Is life-threatening.

(3) Results in hospitalization or prolongation of hospital stay for treatment is necessary.

(4) Results in permanent or prominent impairment/dysfunction.

(5) Causes congenital anomaly.

(6) Results in other events or reactions that are judged as being medically significant conditions.

## Duty of the institution representative to report and reporting procedure

### Expedited reporting

If an adverse event subject to expedited reporting occurs, the investigator reports it promptly to the institution representative. If the institution representative cannot be reached, the investigator assumes the responsibilities of the institution representative. The responsible investigator performs expedited reporting according to the following procedure. When submitting the report, attention is paid so that no personally identifiable information, such as the patient’s name or chart number is included in the report.

Primary reporting:

The institution representative fills the “adverse event report form” as much as possible and submits it to the Study Secretariat by e-mail, fax, or phone within 72 hour of learning about the occurrence of the adverse event.

Secondary reporting:

In addition, the institution representative fills in the “adverse event report form” completely, and prepares a “detailed report of the adverse event” with a more detailed description. He/She submits both the reports to the Study Secretariat by e-mail, fax, snail mail, or hand within 7 days of learning about the occurrence of the adverse event. If autopsy is performed, the autopsy report is attached in principle. When submitting the reports, attention is paid so that no personally identifiable information, such as the patient’s name or chart number is included in the reports (the same hereinafter).

Study Secretariat:

Masafumi Ikeda

Department of Hepatobiliary and Pancreatic Oncology,

National Cancer Center Hospital East

TEL: 04-7133-1111　(PHS:91230)

FAX: 04-7133-0335

E-mail：[masikeda@east.ncc.go.jp](mailto:masikeda@east.ncc.go.jp)

### Action of the head of the institution at which the adverse event has occurred

When a serious adverse event that has a causal relationship with the protocol treatment occurs at a participating institution during implementation of this study, the head of the institution reports it to the Minister at the MHLW according to the provisions of the “Ethical Guidelines for Medical and Health Research Involving Human Subjects,” and announces the review results of the Institutional Review Board.

## Duties of the Principal Investigator/Study Secretariat

### Judgment on whether to suspend enrollment and to urgently notify the participating institutions

Upon receiving the report of the adverse reaction from the institution representative, the Study Secretariat will report it to the Principal Investigator, and consider the urgency, importance, and intensity of influence of the content of the report, in consultation with the Principal Investigator. Then, the Study Secretariat takes measures such as suspension of enrollment (notifying the Data Center and all participating institutions) and urgent notification of the information to the participating institutions, as needed. The information may be delivered to the Data Center or institutions by phone according to the degree of urgency, but it is also promptly followed by communication in writing (by e-mail, fax, snail mail, or hand).

### Reporting to the Efficacy and Safety Assessment Committee

If the Study Secretariat deems that section “10.1. Serious adverse events” is applicable to the adverse event reported from an institution as an expedited report or routine report, the Study Secretariat reports it in writing to the executive office of the Efficacy and Safety Assessment Committee, in consultation with Principal Investigator/Group Representative, within 15 days of learning about the occurrence of the adverse event. The Committee is simultaneously required to review the propriety of the Principal Investigator’s view and action about the adverse event in question.

At such instances, a written opinion of the Study Secretariat/Principal Investigator about considerations and countermeasures (including judgment about continuation/discontinuation of the study) is attached to the “adverse event report” and “detailed report of the adverse event.” Consideration about not only the course of illness in each patient, but also about whether or not the incidence rate is within the expected range is also included.

### Notification to the investigators at each institution

After reporting to the Efficacy and Safety Assessment Committee, Study Secretariat/Principal Investigator notifies the representatives of all the participating institutions about the contents of the review and recommendations of the committee in writing (e-mail is allowed).

Even when no reporting to the Efficacy and Safety Assessment Committee is conducted, the Study Secretariat/Principal Investigator notifies the representative of the reporting institution about the judgment of the Study Secretariat/Principal Investigator in writing (e-mail is allowed).

### Consideration of adverse events by periodic monitoring

When performing periodic monitoring, the Study Secretariat/Principal Investigator carefully checks for adverse events reported in the form of the monitoring report to ensure that all adverse events are reported from the participating institutions. It is verified that there are no unreported adverse events. On the other hand, it is also verified that all the reported adverse events are listed in the periodic monitoring report. Presence/absence of unreported adverse events is specified in the report of the results of the group meeting about periodic monitoring reports.

### Action of the representatives of the participating institutions (including the institution at which the event has occurred)

The representative of each participating institution in this study takes actions in accordance with the instructions of the Study Secretariat/Principal Investigator. The institution representative reports any “serious adverse events related to clinical research” to the head of the institution in question, according to the rules of the institution.

### Review by the Efficacy and Safety Assessment Committee

The Efficacy and Safety Assessment Committee reviews and discusses the contents of the report, and provides recommendations, in writing, about future actions, such as whether to continue enrollment or whether to revise the protocol, to the Study Secretariat/Principal Investigator.

# Criteria for Study Discontinuation and Closure

## Criteria for discontinuation of a part of the study (discontinuation at a participating institution)

When it is considered that appropriate continuation of the study is interfered with by systematic or continuous nonadherence to the study protocol by an institution representative or a investigator, the Principal Investigator can discontinue the study at the concerned institution. In such a case, the Principal Investigator will notify the institution representative and the head of the concerned institution about discontinuation of the study at his/her institution.

## Criteria for discontinuation of the entire study

When the Efficacy and Safety Assessment Committee recommends, or Principal Investigator decides, that the entire study should altogether be discontinued, because there is a prominent threat to the participating patients, such as the possibility of serious adverse events, etc., during the course of the study, the Principal Investigator will promptly notify, in writing, the institution representatives and the heads of the institutions about the discontinuation of the study and the reasons behind it.

# Statistical Considerations

## Definitions of populations for analyses

Populations for analyses in this study are defined as follows. If it is not possible to decide how to handle a certain patient according to the following criteria, handling of the patient will be decided in consultation with the Efficacy and Safety Assessment Committee before the data are locked.

(1) All enrolled patients

All patients enrolled in this study.

(2) Full analysis set (FAS)

Population of all enrolled patients, excluding those who have received no protocol treatment, and those found to be ineligible after enrollment.

(3) Safety analysis set

Population of all enrolled patients, excluding those for whom safety data are not available.

## Items and methods of analyses

### Primary endpoint

The population for this analysis is the FAS. The treatment groups will be compared in regard to the CR rate at 3 months in the treated cancer nodule by Fisher’s exact test at a two-sided significance level of 5%. The estimated two-sided 95% confidence intervals for the response rate in each treatment group, the difference in the response rates, and the odds ratio will also be determined. The anticancer effects of the protocol treatments will be assessed according to the modified Response Evaluation Criteria in Solid Tumors (RECIST) (54). The therapeutic efficacy will be assessed at 3 months ± 2 weeks after the treatment by the findings on contrast-enhanced CT or MRI (intravenous bolus injection), the same modality as that used before the treatment. If contrast-enhanced CT or MRI is performed twice within 1 month ± 2 weeks after the treatment, the results of the contrast-enhanced CT or MRI performed on the date closer to 3 months (90 days) after the treatment will be used. The efficacy assessment will focus only on the treated site, and will not include the effects in untreated sites. Assessment of efficacy at 3 months will only include patients who have achieved CR on contrast-enhanced CT or MRI (intravenous bolus injection) at 1 month after the treatment. However, patients without CR at 1 month after treatment will nevertheless be included in the denominator for calculation of the CR rate and the response rate at 3 months.

Assessment by the modified RECIST will be performed in the form of a central judgement by independent review committee. The final analysis results will be the results of the central judgment, while the results of judgment of each of the investigators will be adopted as reference data. Each investigator sends the CT or MRI data obtained at the baseline and at 1 and 3 months after the treatment of eligible patients with measurable lesions to the Study Secretariat, if requested by the Study Secretariat. Details of the central judgement will be specified in the central judgment protocol prepared before implementation of the central judgment.

### Secondary endpoints

* 1. The local CR rate at 1 month in the treated cancer nodule

The population for this analysis is the FAS. The CR in the treatment groups will be compared by Fisher’s exact test at a two-sided significance level of 5%. The estimated two-sided 95% confidence intervals for the response rate in each treatment group, the difference in the response rates, and the odds ratio will also be determined. The anticancer effect of the protocol treatment will be assessed according to the modified RECIST (54). The therapeutic efficacy will be assessed at 1 month ± 2 weeks after the treatment by the findings on contrast-enhanced CT or MRI (intravenous bolus injection), the same modality as that used before the treatment. If contrast-enhanced CT or MRI is performed twice within 1 month ± 2 weeks after the treatment, the results of the contrast-enhanced CT or MRI performed on the date closer to 30 days after treatment will be used.

* 1. Incidence rate of adverse events

The incidence rate will be calculated for each type of adverse event and for each treatment group. The population for this analysis is the safety analysis set. Adverse events will be assessed according to the “JCOG Japanese version of the NCI CTCAE v4.0.”

* 1. Incidence rate of serious adverse events

The incidence rate of serious adverse events and its 95% confidence interval will be determined for each treatment group. The population for this analysis is the safety analysis set.

### Method of assessment of the efficacy

**Modified RECIST**

This study uses the modified RECIST (54) for assessment of the tumor response to the protocol treatment. The results of a number of previous studies on HCC have shown that the RECIST criteria do not appropriately reflect the tumor necrosis caused by TACE. Only viable tumors assessed by properly performed CT or MRI should be regarded as representing the amount of tumor tissue, and a viable tumor should be defined as a mass that enhances in the arterial phase of contrast imaging. Therefore, the modified RECIST has spread widely since it was first proposed by an expert panel. According to it, the diameter of the target lesion having viable tumor tissue should be based on measurement of the intrahepatic lesion.

The modified RECIST is RECIST modified for efficacy assessment in patients of HCC. According to it, efficacy assessment should be based on use of the same conditions (slice width, use of contrast medium, etc.) as those at baseline. Only when allergy to contrast medium is found midway as to make it difficult to use the same imaging modality again, use of plain CT or contrast imaging using a different modality is permitted. In this situation, comprehensive judgment will be made in reference to the modified RECIST in patients where contrast imaging is performed using a different modality, or evaluation is performed based on the tumor size in patients of plain CT or plain imaging using a different modality.

The CR rate will be calculated as the number of patients in whom the best overall response is CR as a proportion of eligible patients who have measurable lesions and who have received the protocol treatment.

1. Definition of measurable lesions

A lesion that satisfies the following two conditions is defined as a measurable lesion.

* Size: maximum diameter 10 mm or more.
* Contrast-enhanced images of the intrahepatic lesion should essentially be obtained in the arterial phase of dynamic CT or dynamic MRI.

1. Selection and recording of the target lesion

Among the measurable lesions to be treated, lesions with the five greatest diameters are chosen as the target lesions. The location, method of examination, date of examination, longest diameter, and sum of the longest diameters of all five lesions are recorded in the record form.

1. Criteria for efficacy assessment in target lesions (baseline)

The sum of the longest diameters of all the five target lesions is calculated and recorded as the baseline sum of the longest diameter (BSLD). The BSLD of the target lesions is used as the reference for determining the tumor-reducing effect of the protocol treatment. The minimum sum recorded after observation of the initial tumor-reducing effect is used as the reference for determining disease progression.

1. Definition of the anticancer effect on the target lesions

The best overall response during the course of the study is determined in each participating patient. An outline is given below. The area of the intrahepatic measurable lesion that shows contrast enhancement in the arterial phase of dynamic CT or dynamic MRI is assessed as a viable tumor.

* CR: Complete Response

Disappearance of all the target lesions.

* PR: Partial Response

A reduction by 30% or more of the sum of the longest diameters of the target lesions as compared to the BSLD.

* SD: Stable Disease

Not meeting the criteria of CR or PR and showing no PD.

* PD: Progressive Disease

An increase by 20% or more of the sum of the longest diameters of the target lesions as compared to the previously obtained minimum sum.

* NE: Not Evaluable

When examination cannot be performed for some reason, or when the therapeutic effect cannot be not judged as CR, PR, SD, or PD.

Efficacy assessment is performed at 1 month ± 2 weeks and 3 months ± 2 weeks after TACE. When assessment of the images is not possible because of evident progression of the patient’s condition or death of the patient due to disease progression prior to the assessment at 1 month ± 2 weeks after TACE, the patient is regarded as showing PD. When assessment of the images is not possible because of treatment discontinuation as a result of toxicity, patient refusal, or death due to causes other than disease progression (e.g., ruptured varices), the patient is regarded as NE.

## Allocation stratification factors

“Maximum tumor diameter of the target cancer nodule (≤ 3 cm/> 3 cm),” “number of tumors (single tumor/multiple tumors),” and “the institution” are used as allocation stratification factors. Random allocation is performed by the minimization method. See section 2.4.3 for the rationale for setting the number of cases.

## Interim analysis

No interim analysis is planned for this study.

## Final analysis

The final analysis of this study will be performed promptly after assessment of the therapeutic efficacy at 3 months after the treatment in the last enrolled patient, as described in section “12.2. Items and methods of analyses.” The Principal Investigator/Study Secretariat will provide anoverview of the contents of the final analysis report, prepare a “Clinical Study Report” containing the conclusion of the study as a whole, the problems encountered, interpretation of the results, results of discussion of the results, future policies, etc., formulated mainly from the clinical standpoint, and submit it to the Efficacy and Safety Assessment Committee after obtaining the approval of the Group Representative. The study will be considered as “completed” after the Clinical Study Report is approved by the Efficacy and Safety Assessment Committee.

# Target Number of Patients and Study Period

## Target number of patients

200 patients (100 patients per group)

See section 2.4.3 for the rationale for setting the number of patients.

## Expected patient enrollment

See section 2.4.4 for expected patient enrollment.

## Study period

Enrollment period 4.0 years

Follow-up period 6 months

Total study period 4.5 years

The protocol revision procedure need not be followed for extension of the enrollment period by up to 6 months.

# Ethical Considerations

## Protection of patients

All investigators involved in this study should implement the study in accordance with the “Declaration of Helsinki” and the “Ethical Guidelines for Medical and Health Research Involving Human Subjects (MEXT/MHLW Notification No. 3, 2014).” If these guidelines are revised or amended, the updated guidelines should be followed, as needed.

## Informed consent

### Explanation to patients

Prior to enrollment, the investigator should provide the patient with an explanatory document (the explanatory document in the Appendix or an explanatory document modified by the institution) approved by the Institutional Review Board (IRB) at each participating institution, and provide a detailed verbal explanation to the patient about the following issues.

“Approval of the institution” in this protocol applies to one of the following.

1. When the certificate of approval addressed to the applying investigator is issued by the head of the institution, after discussion with the IRB, in response to the request of the head of the institution.

2. When the certificate of approval addressed to the applying investigator is issued by the IRB, after discussion by the IRB, in response to the request of the head of the institution.

1) Disease, stage, and expected prognosis

2) That this study is a clinical trial.

3) The design and rationale of this study (importance, number of enrollments, necessity, purpose, allocation, etc.)

4) The contents of the protocol treatment

Drug names, dosage, details of protocol treatments, etc.

5) Expected effects of the protocol treatment

Tumor reduction, life prolongation, etc.

6) Expected adverse events, complications, sequelae, and how to manage them

The severity and frequency of the expected adverse events, including complications, sequelae, and treatment-related death, and how to manage them when they occur.

7) Cost burden and compensation

Treatment will be provided in the same manner as in general practice. More specifically, the cost of treatment will be covered by the National Health Insurance system in Japan, and compensation for health hazards, if any, will be dealt with in the same manner as in general practice.

8) Alternative treatment

Alternative treatment will be provided to the patient if he/she will not participate in the study.

9) Expected advantages and possible disadvantages

Advantages and disadvantage that may result from participating in the study

10) Direct access to medical records

Audit should be accepted, with the understanding that “healthcare professionals in other institutions will have direct access to the patients’ medical records by permission of the head of each institution.”

11) Refusal and withdrawal of consent

Patients can freely refuse consent for participation prior to the start of the study, and can withdraw consent for participation at any time, without any disadvantages accruing to them in terms of treatment.

\*Withdrawal of consent means withdrawal of consent for participation in the study (the following items (2) and (3)). If withdrawal of consent is pronounced by the patient, the withdrawal should be clarified to be (2) or (3), and promptly notified to the Data Center. If it corresponds to (3), the data of the patient in question should be deleted from the database.

(1) Patient refusal: refusal of protocol treatment (follow-up is continued).

(2) Withdrawal of consent: The patient withdraws consent for participation in the study, and all subsequent follow-up procedures according to the protocol will be disapproved. Data obtained before withdrawal of consent may be used for the study.

(3) Total withdrawal of consent: The patient withdraws consent to participate in the study, and none of the data obtained, that is, from the initial participation in the study, including information provided at the time of enrollment, can be used.

12) Protection of human rights

Maximum effort will be made to protect patient confidentiality (name and personal information).

13) Secondary use of data

Secondary use of the data (e.g., in meta-analysis) will be permitted only if approval is obtained from the IRB, in a form not linked to personally identifiable information.

14) Freedom to ask questions

The patient is given written contact information of not only the investigator, but also the representative of the institution, the Principal Investigator (or the Study Secretariat), and is free to ask any questions about the contents of the study and the treatment.

### Informed consent

After ensuring that the patient has obtained a good understanding of the contents of the study based on the explanation given, the patient is asked about his/her willingness to participate in the study. If the patient him- or herself gives consent to participate in the study, the informed consent document will be prepared using the informed consent form in Appendix or the informed consent form available at the institution. The informed consent document, containing the name of the investigator who gave the explanation, name of the patient who received the explanation and whose consent is being sought, date of provision of the explanation, and date of obtaining the informed consent, is signed by the investigator and the patient.

A copy of the informed consent document is given to the patient by hand, and another copy is kept in the patient’s chart. If electronic charts are used at the concerned institution, the document is stored according to the rules of the institution.

## Laws and norms to follow

In principle, implementation of this study is in accordance with the following laws or norms. If laws, norms, policies other than the following become applicable, the study should also follow such rules.

・ Act on the Protection of Personal Information (Act No. 57 of May 30, 2003, Final revision: Act No. 119 of July 16, 2003)

・ Declaration of Helsinki (Japanese translation by Japan Medical Association)

・ Ethical Guidelines for Medical and Health Research Involving Human Subjects (MEXT/MHLW Notification No. 3 of December 22, 2014)

## Protection of personal information

In this study, the patient’s initials, date of birth, age, chart number, name of the institution, and name of the investigator are used for web enrollment (5.1. Enrollment procedure), to maintain the scientific reliability. However, only the study number and patient enrollment number are used for operation of the CRFs, and there is no risk of leakage of the patients’ personal information through transmission of patient data via the CRFs. If the name of the patient is transmitted by error, the CRF is stored only after it is appropriately processed to make the name illegible.

Personal information about the patients used for web enrollment is stored in a database server protected by measures against unauthorized access (5.1.6. Security of data in web enrollment). Only specific users at the concerned institution, the Study Secretariat, the Principal Investigator, the Group Representative, and the person in charge at the Data Center are authorized access to this database. The patient enrollment number and/or patient personal information is accessed only when persons authorized to access the data deem the information as being necessary for implementation of the study, and such access is recorded to allow verification. Secondary use of the data from this study for another purpose is allowed only if the IRB approves of such use. In such a case, none of the patient personal information used for web enrollment will be used.

## Adherence to the protocol

Investigators participating in this study should adhere to the protocol of this study as far as the safety and human rights of the patients are secured.

## Approval by the Institutional Review Board

For participation in this study, it is necessary for the protocol and the explanatory document for the patient to be approved by the IRB of the concerned institution. After obtaining the approval of the IRB, the representative of the institution should send a copy of the IRB approval document to the Study Secretariat. The original IRB approval document will be kept by the institution representative, and a copy of the approval document will be kept by the Study Secretariat.

It is permitted for the explanatory document to be modified by each institution after obtaining approval from the institution, as long as it does not result in significant deviations from the point of view of the clinical research. However, no modification of the content of the protocol is permitted by any participating institution. The protocol is common to all participating institutions. Any alteration, revision or amendment of the protocol will be common for all institutions. Therefore, if there is a request from a institution for modifying the text of the protocol, the institution representative should contact the Study Secretariat.

## Alterations to the protocol content

### Classification of alterations to the protocol content

When making any alterations to the protocol content, an “application for protocol revision” should be submitted to the Efficacy and Safety Assessment Committee (hereinafter simply, Committee) to obtain the approval of this Committee prior to activation of the altered content. However, this protocol revision procedure need not be followed for extension of the enrollment period by up to 6 months.

Alteration of the protocol content after obtaining the approval of the Committee falls under 2 classes (amendment and revision). Distinction between amendment and revision is made by the Committee. Addition of supplementary explanation, which does not correspond to alteration of the protocol content, is handled separately as a memorandum. The definitions of these terms and handling of the classes are as follows.

1. Amendment

Amendment is a partial alteration of the protocol which may increase the risk to the participating patients or which is related to the primary endpoint of the study. This requires approval of the Committee and of each institution. Before an application is made to the Committee, approval by the Principal Investigator is required. Date of approval from the Committee should be specified on the cover page. If enrollment is ongoing at the time that the Committee has judged that the alteration of the protocol content corresponds to “amendment,” patient enrollment should be suspended temporarily, and approval for the alteration should be obtained from each institution. After approval is obtained, the representative from each institution should send a copy of the approval document of the institution to the Study Secretariat. Enrollment shall be resumed in the order of precedence of institutions for which the approval document is confirmed.

1. Revision

Revision is an alteration of the protocol content that has no potential to increase the risk to the participating patients and that is not related to the primary endpoint of the study. This also requires approval of the Efficacy and Safety Assessment Committee. Whether the revision is handled by ordinary review or by prompt review at the concerned institution is left to the judgment of the institution. In principle, patient enrollment is not suspended during “revision” of the protocol.

Approval of the Principal Investigator is necessary before application is made to the Committee. Review and approval by the IRB are implemented according to the agreement at each institution. Date of approval from the Committee should be specified on the cover page.

1. Memorandum

Memorandum is not an alteration of the protocol content, but supplementary explanation of the protocol. A memorandum is distributed by the Principal Investigator/Study Secretariat to the persons involved in the study for the purpose of reducing variations of interpretation of the protocol and promoting their awareness. There are no restrictions in its format. Approval of the Principal Investigator is necessary before it is distributed. A report should be made to the Committee before or immediately after it is distributed. No statement about a memorandum is required on the cover page of the protocol.

### Approval of the institution for protocol amendment/revision

When the protocol of the study or the explanatory document for patients is amended or revised during the study with the approval of the Efficacy and Safety Assessment Committee, the amended/revised protocol or explanatory document should be approved by the IRB of each institution. When approval of the amendment/revision is obtained from the IRB, the representative of each institution will send a copy of the IRB approval document to the Study Secretariat. The original IRB approval document will be kept by the institution representative, and a copy of the approval document will be kept by the Study Secretariat.

### Report of the study implementation status to the head of the institution

The implementation status of the study, including the patient accumulation status and frequency of adverse events, should be reported to the head of the institution at least once a year.

### Correction of a CRF

If any flaw, such as missing data on a necessary item or inappropriate categorization, is found after the beginning of the study, the CRF is corrected based on a consensus between the Principal Investigator and the Study Secretariat, provided that the correction of the CRF does not exceed the extent of data collection prescribed in section “8. Assessment items, laboratory tests, and assessment schedule,” and that it is judged that the correction of the CRF would cause no increase in the medical or financial burden of the enrolled patient. Correction of a CRF requiring no correction in the text of the protocol is not regarded as protocol revision. How to report correction of a CRF to the head of the institution and whether an application needs to be made for amendment are in accordance with the rules of the participating institution.

## Secondary use of data

Secondary use of data obtained from this study will be allowed only with the approval of the IRB, (e.g. in meta-analysis), in a form not linked to personally identifiable information.

## Storage and disposal of data

Data related to this study will be stored at least until the end of 5 years after the date of reporting completion/termination of this study or until 3 years after the date of final publication of the results of this study, whichever is later, and the Principal Investigator or Study Secretariat will assume responsibility for disposing off the data after that period.

## Compensation and entry in insurance

There is no entry in liability insurance to compensate for health hazards that may occur in patients. If a health hazard related to this study occurs in a patient, the concerned institution will provide appropriate treatment to the patient in the same manner as in usual clinical practice. The cost for such treatment will be paid by the patient’s insurance or self-paid by the patient. Compensation in this study is provision of medical care, and no medical expenses, medical allowance, or compensation money will be paid. This compensation rule does not interfere with the participating patients’ right to claim compensation for damage.

## Management of conflict of interest (COI)

Because this clinical study is not financed by any particular organization and was not conducted with free drugs or other materials, there is no possible COI in the overall study organization. Therefore, we declare that, during planning, implementing, and reporting of this study, there is no “potential COI” that could affect the results or the interpretation of the results of the study, and that implementation of the study will not compromise patients’ rights of benefits. The COIs of the Principal Investigator, Study Secretariat, and others involved in this study are managed appropriately according to the rules at each of the participant institutions.

## Intellectual property rights

The results, data, and intellectual property rights related to this study belong to the Principal Investigator/JIVROSG Group Representative, the Study Secretariat, and institution of affiliation. Specific handling procedures and distribution of the intellectual property rights will be decided by conference among these four parties. Whether intellectual property rights related to the Principal Investigator/JIVROSG Group Representative and Study Secretariat belongs to the investigator or the institution of affiliation will conform to the regulations of the institution of affiliation.

## Disclosure of study-related information

This study is registered in the University hospital Medical Information Network (UMIN) and is disclosed in the network prior to the beginning of the clinical trial. The Principal Investigator and Study Secretariat are in charge of providing responses to inquiries.

# Monitoring and Audit

## Periodic monitoring

Periodic monitoring is performed to confirm that the study is implemented safely according to the protocol, that the data are collected with accuracy, and that there are no obstacles to continuation of the study. Periodic monitoring is performed twice a year, in principle, on the basis of periodic monitoring reports prepared by the Study Secretariat, through discussions at the JIVROSG general meeting that is attended by the Principal Investigator, the Study Secretariat, members of the Committee, and all or some representatives of the participating institutions.

### Items monitored

* Patient accumulation status: Number of enrolled patients - accumulation/by period, all institutions/by institution
* Eligibility: Ineligible patients/possibly ineligible patients (institutions)
* During/after protocol treatment, reason for discontinuation/closure (institutions)
* Pretreatment background factors
* Serious adverse events
* Adverse events
* Protocol deviation
* Other issues related to the progress and safety of the study

### Protocol deviation and violation

Protocol deviation is an act of nonadherence to the protocol in relation to the protocol treatment, laboratory tests, assessment of adverse events, etc. Patients of protocol deviation are classified into one of the following categories after investigation by the Study Secretariat and the Study Group.

1) Violation

In principle, a patient of nonadherence to the protocol that meets at least two of the following items is defined as “violation.”

(1) Affects assessment of the study endpoints

(2) Attributable to the investigator/institution

(3) Intentional or systematic

(4) Dangerous or marked deviation

(5) Clinically inappropriate

In principle, the details of each patient of “violation” will be described when the research paper is published.

2) Deviation

Deviations not defined as 1) Violation or 3) Acceptable deviation.

If there are many deviations of a particular type, they will be described when the research paper is published.

3) Acceptable deviation

Deviations from the protocol that are within the allowable range set ex ante or ex post through discussions by the study group.

## On-site audit

The JIVROSG performs on-site audit, aimed at education as well as improvement of the scientific and ethical quality of research conducted by the group.

The on-site audit group is composed of 1 chief auditor responsible for the on-site audit, and 2 or more member auditors. The chief auditor is selected from among members of the JIVROSG Protocol Committee, and the member auditors are selected from among the investigators at the institutions participating in this study conducted by the JIVROSG, by the JIVROSG group representative. The on-site audit group visits the participating institutions to confirm the IRB approval document and patients’ informed consent documents, and to check the patients’ charts against the data recorded on the forms submitted to the Study Secretariat (direct access to source material) in accordance with the procedure laid out in the JIVROSG on-site audit manual. The chief auditor and member auditors are selected from among members other than the Principal Investigator, Study Secretariat, and the investigators at the target institution of the on-site audit. The results of the audit at each institution will be reported to the representative of the concerned institution and at the JIVROSG general meeting, and used as educational material for improving the quality of the researches conducted by the JIVROSG. If any obvious impropriety or irregularity is found during the on-site audit, the issue, including the propriety of participation of the concerned institution in the study, is discussed separately at the JIVROSG general meeting,

## Spot inspection by the Institutional Review Board, Efficacy and Safety Assessment Committee, and MHLW

This study protocol began to be implementedinto force after the IRB at each of the participating institutions granted approval. Implementation of the protocol during the study period will be monitored by the Committee.

## Supervision of the Data Center service contractor

Rules to follow are prescribed in the outsourcing agreement in writing. Outsourced services are performed according to the standard operating procedure developed based on a consensus between the Principal Investigator and the Study Secretariat. The Principal Investigator and the Study Secretariat conduct checks, as needed, to verify whether or not the contractor is providing the outsourced services according to the standard operating procedure.

# Study Organization

## Organization implementing this study

1) Study group: JIVROSG (Japan Interventional Radiology in Oncology Study Group)

This is a multicenter collaborative clinical study group comprising members from 84 institutions (as of June 2009) who are accredited by the Japanese Society of Interventional Radiology (JSIR). This Study Group, set up in 2002 to establish evidence for IVR in cancer treatment, is fundedby the National Cancer Center Research and Development Fund and competitive public research grants such as the MHLW Scientific Research Grants.

2) Group Representative and Principal Investigator: Yasuaki Arai

Department of Diagnostic Radiology, National Cancer Center Hospital

5-1-1 Tsukiji, Chuo-ku, Tokyo, 104-0045 Japan

TEL: 03-3542-2511, FAX: 03-3547-6096

E-mail: arai-y3111@mvh.biglobe.ne.jp

3) Study Secretariat: Masafumi Ikeda

Department of Hepatobiliary and Pancreatic Oncology,

National Cancer Center Hospital East

6-5-1 Kashiwanoha, Kashiwa-shi, Chiba, 277-8577 Japan

TEL：04-7133-1111，FAX：04-7133-0335

E-mail：[masikeda@east.ncc.go.jp](mailto:masikeda@east.ncc.go.jp)

4) Collaborating institutions

(Listed in Appendix 2)

5) Efficacy and Safety Assessment Committee

Kei Muro Director, Department of Pharmacy, Aichi Cancer Center Hospital

Nobunari Hayashi IVR Consultants

Yukio Takayasu Director, Takayasu Clinic

6) JIVROSG1302 Data Center

Person responsible for data management: Yoshiteru Ishikawa

Contact information: person in charge at JIVROSG1302 Data Center

Data Center 1, Clinical Research Operational Headquarters, EP-CRSU Co., Ltd.

Acropolis Tokyo 3F, 6-29 Shin-ogawamachi, Shinjuku-ku, Tokyo, 162-0814 Japan

TEL：03-5946-8262, FAX：03-5946-8276

E-mail：[JIVROSG@j-crsu.co.jp](mailto:JIVROSG@j-crsu.co.jp)

7) Statistics advisor

Takeharu Yamanaka Professor, Department of Biostatistics, Yokohama City University School of Medicine

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# Publication of Study Results

Publication of the results of this study at academic meetings and in research papers will be in conformity with the policies decided at the JIVROSG general meeting at the time of publication. The main research paper will be submitted to an English-language journal after completion of the final analysis. In principle, the leading author of the main research paper is the Study Secretariat/Principal Investigator, followed by representatives of the participant institutions, in descending order of the number of enrollments. Coauthors will be restricted to those who review the contents of the paper and approve of the contents prior to submission of the paper. Because this study may be presented in whole or in part at several academic meetings, the Group Representative will assign the presenters based on the results of discussions held among members of the Study Group.

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