Evaluation of the Safety and Therapeutic Effect of Multidisciplinary Treatment strategy involving RT after HAIC followed by immunotherapy for Advanced Hepatocellular Carcinoma with Major Vascular Invasion: A Prospective Registry Study

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Abstract

Background: Systemic therapy, including immune checkpoint inhibitors (ICIs), has improved survival in advanced hepatocellular carcinoma (HCC); however, its efficacy remains limited in patients with macroscopic vascular invasion (MVI), a subgroup with an extremely poor prognosis. Although combining immunotherapy with local treatments such as hepatic arterial infusion chemotherapy (HAIC) and radiation therapy (RT) is considered a promising approach, robust supportive evidence from routine clinical practice is lacking.

Objective: This study aims to evaluate the safety and therapeutic effectiveness of a multidisciplinary treatment strategy involving RT after HAIC, followed by immunotherapy, in patients with MVI-positive HCC, using real-world clinical data from Japan.

Methods: This is a prospective, multicenter registry study conducted at three hospitals in Hiroshima Prefecture, Japan. Eligible patients will have unresectable MVI-positive HCC confirmed by dynamic computed tomography. The treatment protocol follows a standardized sequence: one session of HAIC (cisplatin), RT targeting the MVI site (25 Gy in 5 fractions), and subsequent systemic immunotherapy. The primary endpoint is safety, which will be evaluated using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Secondary endpoints include progression-free survival (PFS) at 12 and 24 weeks, tumor response, overall PFS, and overall survival (OS), Objective response rate (ORR) at 12 and 24 weeks, assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST). Data will be collected prospectively and analyzed according to the intention-to-treat principle.

Results: Patient enrollment begun in March 2025, with data collection and analysis ongoing as participants are followed.

Conclusions: This prospective registry study will generate real-world evidence on the safety and effectiveness of a multidisciplinary strategy combining HAIC, RT, and immunotherapy in patients with MVI-positive HCC. Given that all components are covered under Japan's national health insurance, this approach could be readily implemented in clinical practice and may inform future treatment guidelines for MVI-positive HCC.

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Protocol: Evaluation of the Safety and Therapeutic Effect of Multidisciplinary Treatment strategy involving RT after HAIC followed by immunotherapy for Advanced Hepatocellular Carcinoma with Major Vascular Invasion: A Prospective Registry Study

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Abstract

Background:

Systemic therapy, including immune checkpoint inhibitors (ICIs), has improved survival in advanced hepatocellular carcinoma (HCC); however, its efficacy remains limited in patients with macroscopic vascular invasion (MVI), a subgroup with an extremely poor prognosis. Although combining immunotherapy with local treatments such as hepatic arterial infusion chemotherapy (HAIC) and radiation therapy (RT) is considered a promising approach, robust supportive evidence from routine clinical practice is lacking.

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This study aims to evaluate the safety and therapeutic effectiveness of a multidisciplinary treatment strategy involving RT after HAIC, followed by immunotherapy, in patients with MVI-positive HCC, using real-world clinical data from Japan.

Methods:

This is a prospective, multicenter registry study conducted at three hospitals in Hiroshima Prefecture, Japan. Eligible patients will have unresectable MVI-positive HCC confirmed by dynamic computed tomography. The treatment protocol follows a standardized sequence: one session of HAIC (cisplatin), RT targeting the MVI site (25 Gy in 5 fractions), and subsequent systemic immunotherapy. The primary endpoint is safety, which will be evaluated using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Secondary endpoints include progression-free survival (PFS) at 12 and 24 weeks, tumor response, overall PFS, and overall survival (OS), Objective response rate (ORR) at 12 and 24 weeks, assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST). Data will be collected prospectively and analyzed according to the intention-to-treat principle.

Results:

Patient enrollment begun in March 2025, with data collection and analysis ongoing as participants are followed.

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This prospective registry study will generate real-world evidence on the safety and effectiveness of a multidisciplinary strategy combining HAIC, RT, and immunotherapy in patients with MVI-positive HCC. Given that all components are covered under Japan’s national health insurance, this approach could be readily implemented in clinical practice and may inform future treatment guidelines for MVI-positive HCC.

Trial Registration:

Trial registration is not planned for this observational study.

Introduction

In the treatment of unresectable, locally advanced hepatocellular carcinoma (HCC), multikinase inhibitors such as sorafenib and lenvatinib were long regarded as standard first-line therapies, as established by the SHARP and REFLECT trials [1,2]. However, recent landmark phase III trials—IMbrave150 (atezolizumab plus bevacizumab) [3], HIMALAYA (durvalumab plus tremelimumab) [4], and CheckMate 9DW (nivolumab plus ipilimumab) [5]—have demonstrated that immune checkpoint inhibitor (ICI)-based combination regimens significantly improve overall survival (OS), resulting in a paradigm shift in the management of advanced HCC [6,7].

Despite these advances, ICI-based regimens have shown limited benefit in patients with macroscopic vascular invasion (MVI), one of the most prognostically unfavorable subgroups. In IMbrave150, atezolizumab plus bevacizumab significantly improved OS in high-risk patients—including those with main portal vein tumor thrombi, bile duct invasion, or ≥50% liver involvement—yet the median OS in this subgroup was only 7.6 months [8]. Moreover, the HIMALAYA and CheckMate 9DW trials excluded patients with the main portal vein tumor thrombi, leaving a lack of robust clinical evidence for this population.

Before the advent of immunotherapy, several studies demonstrated that combining locoregional therapies—such as hepatic arterial infusion chemotherapy (HAIC), and radiation therapy (RT)—with systemic agents could improve outcomes in MVI-positive HCC [9–13]. In phase III trial, He et al. showed that HAIC using the FOLFOX regimen (folinic acid, fluorouracil, and oxaliplatin) plus sorafenib yielded a markedly higher overall response rate (ORR) (40.8% vs. 2.46%; $P < .001$) and longer PFS (7.03 vs. 2.6 months; $P < .001$) than sorafenib monotherapy for HCC with portal vein invasion [9]. A Japanese prospective study also demonstrated improved survival with HAIC using the cisplatin regimen plus sorafenib versus sorafenib alone in patients with major portal vein tumor thrombus (median OS: 11.4 vs. 6.5 months) [10]. Furthermore, in a large-scale multicenter

retrospective study conducted in Japan using propensity score matching, HAIC using the cisplatin was associated with better survival outcomes than sorafenib monotherapy in MVI-positive patients without extrahepatic lesions (median OS: 11.4 vs. 6.5 months, $p = 0.018$) [11]. In particular, Kosaka et al. reported an ORR of 19.6%, a thrombus response rate of 51.0%, and a median OS of 19.8 months for the combination therapy of HAIC using the cisplatin and RT in cases of MVI-positive liver cancer with main portal vein tumor thrombi [12].

Since the advent of immunotherapy, combination treatments of HAIC with immunotherapy [13-15] or RT with immunotherapy [16] have been increasingly implemented for MVI-positive HCC, particularly in Asia. In both approaches, the addition of immunotherapy has tended to enhance therapeutic efficacy. This may be attributable to the induction of immunogenic cell death by HAIC or radiotherapy through tumor necrosis, thereby potentiating the effects of immunotherapy [17.18]. Furthermore, combining all three modalities—HAIC, RT, and immunotherapy—may also offer promising therapeutic potential. A case series by Yamaoka et al. described six patients treated with atezolizumab plus bevacizumab following HAIC and RT, with four achieving survivals exceeding the previously reported median OS [19]. These findings suggest that multimodal strategies targeting both intrahepatic tumor burden and vascular invasion may offer meaningful clinical benefits for this challenging patient population.

Methods

Objective

The objective of this study is to evaluate the safety and therapeutic effectiveness of a multidisciplinary treatment approach combining local therapies (HAIC and RT) and immunotherapy in patients with MVI-positive HCC, using real-world data from routine clinical practice in Japan.

Study Design and Setting

This is a prospective, multicenter, observational registry study conducted at three institutions in Hiroshima Prefecture, Japan: Hiroshima Prefectural Hospital, Hiroshima University Hospital, and Hiroshima Red Cross Hospital & Atomic-bomb Survivors Hospital. Patient enrollment began in March 2025. Based on sample size estimation, 38 patients will be enrolled consecutively if they meet the eligibility criteria, with longitudinal data collection until treatment discontinuation or death. No randomization or intervention assignment will be performed, and treatment decisions will follow routine clinical practice.

Patient Population

Eligible participants are patients with unresectable, locally advanced HCC with MVI who are scheduled to receive multidisciplinary treatment consisting of HAIC, RT, and subsequent immunotherapy. MVI is defined radiologically as tumor thrombus in the first-order branch or main trunk of the portal vein (Vp3/4) or in the inferior vena cava or hepatic veins (Vv2/3), based on dynamic contrast-enhanced computed tomography (CT). Key inclusion and exclusion criteria are summarized in Table 1.

Table.1 Key inclusion and exclusion criteria

Inclusion criteria:
• HCC with macroscopic vascular invasion diagnosed by dynamic computed tomography (CT) Vp3/Vp4: portal vein (first-order branches or main trunk) Vv2/Vv3: tumor thrombus in IVC or hepatic veins (left/middle/right)

- Age ≥ 18 years
- ECOG Performance Status 0–2
- Chronic hepatitis or liver cirrhosis (Child–Pugh class A, or B with score ≤ 7)
- Written informed consent obtained

Exclusion Criteria

- History of prior radiotherapy overlapping the planned field
- Unsuitable for immunotherapy
- Uncontrolled ascites or hepatic encephalopathy
- Active gastric/duodenal ulcers or untreated esophageal/gastric varices or hemorrhagic ulcers
- Severe infections or comorbidities (excluding chronic hepatitis/liver cirrhosis)
- Psychiatric disorders interfering with study participation (per investigator judgment)
- Active double cancers (concurrent malignancies)
- Contraindication to CT imaging (e.g., allergy to iodinated contrast)
- No informed consent provided
- Any other reason deemed inappropriate by the attending physician

Treatment Protocol

Overview

A schematic of the treatment protocol is shown in Figure 1. All eligible patients will receive one session of HAIC followed by RT targeting the MVI site, and then systemic immunotherapy. The interval between treatments will generally be 1–2 weeks. Modifications to the sequence or addition of other therapies may be made at the treating physician's discretion based on therapeutic response and clinical condition.

HAIC Procedure

HAIC will be performed promptly after diagnosis in clinically appropriate patients with adequate liver function (Child–Pugh class A or B7), acceptable renal function, and no contraindications to cisplatin (CDDP)-based chemotherapy. In this study, single-dose HAIC (single intra-arterial administration of CDDP) is the main treatment and is covered by insurance in Japan.

Catheter insertion will generally be performed via the femoral artery using the Seldinger technique. Abdominal angiography will confirm tumor staining and feeding arteries. A catheter will then be inserted into the feeding artery, and CDDP (65 mg/m²) will be infused over 20–40 minutes, with

earlier termination permitted if sufficient tumor perfusion is achieved. If the estimated glomerular filtration rate is <60 mL/min/1.73 m², the CDDP dose will be reduced by 75%. When CDDP is infused into only part of the liver, the dose will be adjusted according to the proportion of tumor volume in the liver based on CT imaging.

To prevent CDDP-induced nephrotoxicity, patients will receive adequate intravenous hydration before and after infusion. Patients will be hospitalized for observation for at least 24 hours post-infusion, with monitoring of vital signs, urine output, and laboratory tests to assess renal and hepatic function. Prophylactic antibiotics will be administered according to institutional protocols.

Radiotherapy

RT will be initiated preferably within two weeks after completion of HAIC. While specific technical approaches will be left to each institution’s policy, two points will be standardized across all sites: (1) the irradiated target volume should primarily encompass the intravascular portion of the tumor while including, whenever feasible, the adjacent intrahepatic lesion; and (2) the prescribed dose should be 25 Gy in 5 fractions.

Under the supervision of a radiation oncologist at each institution, an appropriate margin of 5–20 mm will be added to the target volume to account for respiratory motion and setup error, aiming for a homogeneous dose distribution within the target while minimizing exposure to surrounding organs at risk (OARs). Dose constraints for OARs will follow institutional protocols, with typical limits including a mean dose to the normal liver (whole liver excluding the tumor) of <13 Gy, a maximum dose to the stomach/duodenum of <30 Gy, and a maximum spinal cord dose of <25 Gy.

Patients will be immobilized using customized vacuum cushions or equivalent devices to ensure reproducibility, with respiratory motion management (e.g., breath-hold) employed throughout treatment with each facility's policies. Either three-dimensional conformal radiotherapy (3DCRT) or

intensity-modulated radiotherapy (IMRT) may be used. Image-guided radiotherapy (IGRT), typically with daily cone-beam CT, is recommended for treatment delivery.

All treatment plans will be generated using a treatment planning system capable of Monte Carlo-equivalent dose calculation. Pre-treatment plan quality assurance (QA) will be performed according to institutional standards, and daily machine QA will be conducted in accordance with international recommendations. Adaptive replanning will be considered if significant anatomical changes or tumor regression are observed during treatment.

Immunotherapy

Systemic immunotherapy will be initiated preferably within two weeks after the completion of RT, provided that adequate hematologic, hepatic, and renal function is confirmed. Regimens may include:

- Atezolizumab (1,200 mg IV) plus bevacizumab (15 mg/kg IV) every 3 weeks
- Durvalumab (1,500 mg IV) plus tremelimumab (300 mg IV once), followed by durvalumab monotherapy every 4 weeks (STRIDE regimen)
- Nivolumab (80 mg IV) plus ipilimumab (3 mg/kg IV) plus every 3 weeks, followed by nivolumab (240 mg IV) every 2 weeks or nivolumab (480 mg IV) every 4 weeks

The choice of regimen will be determined at the discretion of the treating physician, taking into account patient comorbidities, prior treatment history, baseline organ function, and potential contraindications. All regimens will adhere to recommendations outlined in established guidelines for systemic therapy in HCC, including the American Society of Clinical Oncology (ASCO) guideline for advanced HCC [20]and the Japan Society of Hepatology's 2021 clinical practice guidelines [21], as well as the European Society for Medical Oncology (ESMO) Clinical Practice Guideline [22].

Treatment will continue until radiologically confirmed disease progression, unacceptable toxicity, or loss of clinical benefit, whichever occurs first. Temporary dose delays, reductions, or regimen modifications will be permitted according to protocol-specific criteria and clinical judgment. All modifications, interruptions, or discontinuations will be documented in detail, including the reason and subsequent management.

Patients will undergo routine laboratory monitoring, including complete blood count, liver and renal function tests, and coagulation parameters, at each treatment cycle. Imaging assessments (dynamic contrast-enhanced CT or magnetic resonance imaging (MRI)) will be performed in accordance with the study's assessment schedule to evaluate tumor response and detect potential treatment-related complications, such as immune-related adverse events (irAEs). Prompt initiation of appropriate management strategies (e.g., corticosteroids or immunosuppressants) will be undertaken for clinically significant irAEs, following current consensus recommendations [23-25].

Data Collection

Collected data will include:

A) Patient background: age, sex, Eastern Cooperative Oncology Group performance status, comorbidities, prior cancer history, and prior HCC treatments.

B) Baseline liver function: etiology of liver disease, presence of ascites or hepatic encephalopathy, Child–Pugh class, and relevant laboratory values.

C) HAIC: procedure date, infusion duration, and cisplatin dose.

D) RT: start and completion dates, technique, treatment planning system, dose calculation algorithm, respiratory motion management, dose parameters, and dose–volume histogram metrics.

E) Immunotherapy: regimen, dosage, initiation date, and treatment duration.

F) Laboratory trends: serial laboratory test results during the treatment course.

G) Additional therapies: details of any subsequent locoregional or systemic treatments administered

during follow-up.

Assessment Schedule

Clinical and laboratory assessments will be performed at baseline, at HAIC administration, at the start of RT, at the initiation of immunotherapy. Adverse events will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 and assessed at each visit or whenever clinically indicated. Specific laboratory monitoring for immune-related adverse events, including liver function, renal function, thyroid function, and blood glucose, will be conducted regularly. Imaging (contrast-enhanced CT, MRI, or ultrasound) will be performed at baseline, at 6 weeks and 12 weeks after starting immunotherapy, and every 2 months thereafter (±1 week), with tumor response evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 and/or modified RECIST (mRECIST) criteria.

Endpoints

Primary Endpoint

The primary endpoint is safety, defined as the incidence of treatment-related AEs graded according to the CTCAE v5.0, occurring during the treatment period after the last dose of any study treatment. Treatment-related AEs are those considered by the investigator to be possibly, probably, or definitely related to any component of the study regimen.

Secondary Endpoints

The secondary endpoint is PFS at 12 and 24 weeks, Overall PFS, OS, ORR at 12 and 24 weeks. The ORR will be defined as the proportion of patients achieving a complete response (CR) or partial response (PR) as their best overall response, assessed according to the RECIST 1.1 and/or mRECIST for HCC, in which viable tumor is defined as uptake in the arterial phase of dynamic imaging. Tumor response will be evaluated by dynamic contrast-enhanced CT or MRI at baseline, at 6 and 12 weeks

after initiation of immunotherapy, and every 2 months thereafter. In patients with measurable lesions at baseline, all target and non-target lesions will be assessed, and any unmeasurable but evaluable lesions (e.g., tumor thrombus) will be included in accordance with the RECIST 1.1 and/or mRECIST guidelines. PFS is defined as the time from initiation of treatment to the first documented disease progression per the RECIST 1.1 and/or mRECIST or death from any cause, whichever occurs first. OS is defined as the time from initiation of treatment to death from any cause. Patients without an event at the time of analysis will be censored at the date of the last disease assessment. Patients lost to follow-up will be censored at the date they were last known to be alive.

Statistical Analysis

All analyses will be performed using descriptive statistics to summarize patient characteristics, treatment delivery, and outcomes. Continuous variables will be presented as medians with interquartile ranges (IQRs) or means with standard deviations, as appropriate. Categorical variables will be expressed as counts and percentages.

Time-to-event endpoints (PFS and OS) will be estimated using the Kaplan–Meier method, with median survival times and 95% confidence intervals (CIs) reported. Exploratory subgroup analyses may be performed using the log-rank test and Cox proportional hazards regression models, adjusting for baseline covariates such as liver function, tumor burden, and treatment regimen. Hazard ratios (HRs) with 95% CIs will be calculated. In multicenter analyses, participating institutions may be included as stratification factors.

ORR will be calculated with exact binomial 95% CIs. Safety will be summarized by incidence, severity (CTCAE v5.0), and relationship to study treatment, with results presented overall and stratified by treatment phase (HAIC, RT, immunotherapy). The timing of onset, resolution, and reasons for treatment discontinuation due to adverse events will also be reported.

Missing data will not be imputed; patients without an event at data cutoff will be censored at the date of last contact. Reasons for missing data will be recorded, and sensitivity analyses may be conducted under different missing-data assumptions (e.g., worst-case imputation for progression events).

Given the observational nature of the study, all analyses will be exploratory and hypothesis-generating. No formal sample size calculation has been performed, and p-values from statistical tests will be interpreted descriptively without adjustment for multiplicity. Statistical analyses will be conducted using the EZR (Saitama Medical Center, Jichi Medical University), a graphical user interface for R (The R Foundation Computing, version 3.4.1).

Sample Size Estimation

Although the primary objective of this study is to evaluate safety, the planned sample size was determined to ensure adequate statistical precision for descriptive analyses and to permit exploratory evaluation of efficacy outcomes. For reference, if superiority in the ORR over a historical benchmark of 30% were to be assessed—based on prior studies reporting ORRs ranging from 20% to 40% in similar patient populations [3-5,8,9,12]—assuming a true ORR of 50%, a one-sided α of 0.10, and 80% power (normal approximation, one-sample Z test), 26 evaluable patients would be required. Allowing for an anticipated 30% unevaluable rate, the planned enrollment is 38 patients. These calculations are provided solely for context; all efficacy analyses will remain exploratory, and the study is not powered primarily for formal hypothesis testing.

Data Management and Confidentiality

All study data will be anonymized before sharing, with all personal identifiers removed to protect patient privacy. Data transfer between participating investigators will be conducted via encrypted

electronic mail, and each investigator will store the received data on a password-protected personal computer under their direct control.

Investigators will be responsible for implementing adequate safeguards to prevent unauthorized access, including the use of secure passwords, regularly updated antivirus software, and physical access restrictions to devices storing study data. Backup copies will be maintained by each investigator to prevent data loss.

All data will be retained for a minimum of five years after study completion, in accordance with institutional policies and applicable regulations. Access to study data will be restricted to authorized investigators only. Monitoring or audits by the institutional review board (IRB) or regulatory authorities may be conducted using anonymized data. All procedures will comply with the Act on the Protection of Personal Information in Japan, relevant local regulations, and international research ethics standards conducted in accordance with the ethical standards of the Declaration of Helsinki and the International Council for Harmonisation Good Clinical Practice (ICH-GCP).

Monitoring and Quality Assurance

No formal coordinating center has been established for this study. Instead, the principal investigator and participating investigators will jointly oversee all aspects of study conduct. Regular meetings (either in person or via teleconference) will be held to review study progress, verify the accuracy and completeness of collected data, and ensure adherence to the study protocol.

Any protocol deviations, data inconsistencies, or other study-related issues identified during these reviews will be documented in meeting minutes. Corrective actions will be determined through consensus among the investigators, and follow-up will be performed to confirm resolution.

All monitoring activities will be conducted in compliance with institutional policies, relevant regulations, and the principles of Good Clinical Practice, ensuring that participant safety and data integrity are maintained throughout the study period.

Protocol Deviations

All deviations from the approved protocol will be documented by the responsible investigator at each participating site, including the date, details, and reason for the deviation. Given the investigator-driven nature of this study, no formal deviation classification system will be applied; however, any deviations judged by the investigators to potentially impact patient safety or data reliability will be discussed collectively among the study team.

Corrective actions will be decided through investigator consensus and implemented promptly. Records of all deviations and their resolution will be maintained securely by each investigator and shared within the study group as necessary. As this is not a formally regulated clinical trial, deviations will not be reported to regulatory authorities, but will be transparently described in the final study report or publication when relevant.

Trial Status

At the time of manuscript submission, patient enrollment had already commenced, and data collection was actively ongoing. Participating investigators continue to recruit eligible patients and record study data in accordance with the protocol schedule.

Dissemination Plan

The findings from this study will be disseminated through publication in peer-reviewed journals and presentation at national and international scientific meetings. While the raw dataset will not be made publicly available, anonymized summary data may be shared upon reasonable request and with investigator approval.

Funding and Competing Interests

This study is supported by the Research Support Program of Hiroshima Prefectural Hospital (April 2025 to March 2026). The authors declare no competing interests relevant to this study.

Discussion

The primary objective of this prospective registry study is to evaluate the safety and therapeutic effectiveness of a multidisciplinary treatment approach that combines locoregional therapies and immunotherapy in patients with MVI-positive HCC.

In Japan, both the incidence and mortality rates of HCC have declined over recent decades, largely owing to the decreasing prevalence of viral hepatitis. According to the 24th Nationwide Follow-up Survey Report on Primary Liver Cancer, the numbers of patients with Vp3/4 and Vv2/3 tumor thrombi in 2016–2017 were approximately 980 and 570, respectively, underscoring the relative rarity of these high-risk cases. Furthermore, the prevalence of MVI-positive HCC has continued to decrease since that period, making such cases even less common in current clinical practice. Because of this low and declining incidence, conducting adequately powered prospective randomized controlled trials in this population is challenging, and a real-world, prospective registry design was therefore considered the most feasible and appropriate approach to capture treatment patterns and outcomes in a sufficiently large cohort.

A critical consideration is that MVI-positive HCC is associated with extremely poor prognosis, making the prompt initiation of aggressive treatment after diagnosis essential to maximize the potential for improved outcomes. Consequently, treatment strategies should prioritize modalities that are widely applicable and readily implementable in routine clinical settings. All components of the present protocol—HAIC, RT, and immunotherapy—are established treatment methods in daily clinical practice in Japan, with minimal variation in availability or technical feasibility across institutions. Therefore, if this protocol demonstrates both safety and favorable efficacy, it could be rapidly adopted across many treatment centers, providing substantial clinical benefit for this difficult-to-treat MVI-positive HCC patients in Japan.

Recent reports suggest that multidisciplinary, team-based treatment may facilitate conversion to resectable status and improve long-term survival rates in patients with unresectable, MVI-positive hepatocellular carcinoma [26]. The sequential multidisciplinary collaboration strategy employed in this study seeks to enhance therapeutic efficacy by leveraging the synergistic effects of each treatment modality. Furthermore, we anticipate that this approach will increase resectability and ultimately lead to better long-term outcomes.

In conclusion, this prospective registry study aims to generate valuable real-world evidence to inform treatment decisions for MVI-positive HCC and to contribute to the development of more effective therapeutic strategies in clinical practice.

Abbreviations

AE	Adverse events
irAE	Immune-related adverse events
ASCO	American Society of Clinical Oncology
CDDP	Cisplatin
CI	Confidence interval
CR	Complete response
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events from
EQD2	Equivalent dose in 2-Gy fractions
ESMO	European Society for Medical Oncology
FOLFOX	Folinic acid, fluorouracil, and oxaliplatin
HAIC	Hepatic arterial infusion chemotherapy
HCC	Hepatocellular carcinoma
HR	Hazard ratio
IQRs	interquartile ranges
ICI	Immune checkpoint inhibitor
ICH-GCP	International Council for Harmonisation Good Clinical Practice
IGRT	Image-guided radiotherapy
IMRT	intensity-modulated radiotherapy
IRB	institutional review board
MRI	Magnetic resonance imaging
MVI	Macroscopic vascular invasion
OAR	Organs at risk
ORR	Objective response rate
OS	Overall survival
PFS	Progression-free survival
PR	Partial response
QA	Quality assurance
(m)RECIST	(Modified) Response Evaluation Criteria in Solid Tumors
RT	Radiation therapy
3DCRT	Three-dimensional conformal radiotherapy
Vp3/4	Presence of a tumor thrombus in the first-order branch or main trunk of the portal vein
Vv2/3	Presence of a tumor thrombus in the inferior vena cava or hepatic veins

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Conflicts of Interest

Dr. Aikata has received lecture fees from Eisai Co., Ltd. and Chugai Pharmaceutical Co., Ltd. Dr. Kawaoka has received lecture fees from Eisai Co., Ltd., AstraZeneca, and Chugai Pharmaceutical Co., Ltd. Dr. Tsuge has received lecture fees from Gilead Sciences and AbbVie. The other authors declare no conflicts of interest related to this study.

Data Availability Statement

The datasets generated and/or analyzed during the current study are not publicly available due to patient privacy restrictions but are available from the corresponding author on reasonable request.

Authors' Contributions

Concept and design: HA; Funding acquisition: HA (lead), YD (supporting); Investigation: HA (lead); Writing – original draft: YD (lead), HA (equal); Writing – review & editing: all authors; Approval of final manuscript: all authors.

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Figure legends

Figure1

Treatment sequence of the study protocol. Patients with MVI-positive HCC receive hepatic arterial infusion chemotherapy (HAIC), followed within 1–2 weeks by radiotherapy (RT), and subsequently by immunotherapy initiated within 1–2 weeks after RT, using one of the following regimens: atezolizumab plus bevacizumab, nivolumab plus ipilimumab, or durvalumab plus tremelimumab. The dosing interval of immunotherapy follows the respective regimen.

Supplementary Files

Figures

Treatment sequence of the study protocol. Patients with MVI-positive HCC receive hepatic arterial infusion chemotherapy (HAIC), followed within 1–2 weeks by radiotherapy (RT), and subsequently by immunotherapy initiated within 1–2 weeks after RT, using one of the following regimens: atezolizumab plus bevacizumab, nivolumab plus ipilimumab, or durvalumab plus tremelimumab. The dosing interval of immunotherapy follows the respective regimen.