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Durvalumab ± tremelimumab combined with particle therapy for advanced hepatocellular carcinoma with macrovascular invasion: a phase Ib trial (DEPARTURE) study protocol

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Durvalumab ± tremelimumab combined with particle therapy for advanced hepatocellular carcinoma with macrovascular invasion: a phase Ib trial (DEPARTURE) study protocol

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ABSTRACT

Introduction: Advanced hepatocellular carcinoma (HCC) with macrovascular invasion (MVI) has the worst prognosis among all phenotypes, owing to the uniqueness of its disease condition. The DEPARTURE trial aimed to evaluate whether treatment with durvalumab, alone or in combination with tremelimumab, plus particle therapy was a safe and synergistically effective treatment in patients with advanced HCC and MVI.

Methods and analysis: This is a phase Ib, multicenter, open label, single arm, investigator-initiated clinical trial to assess the safety of durvalumab monotherapy in combination with particle therapy (cohort A) and that of durvalumab plus tremelimumab in combination with particle therapy (cohort B) for patients with advanced HCC with MVI and who are ineligible for standard systemic therapy and have Child–Pugh A liver disease. Cohort A will receive 1,500 mg durvalumab every four weeks in principle. Cohort B will receive 1,500 mg durvalumab every four weeks in principle and 300 mg tremelimumab only on day 1 of the first cycle. Carbon-ion radiotherapy will be administered after day 8 of the first cycle. The dose is 60 Gy (relative biologic effectiveness) in four fractions per week. The intrahepatic nodule feeding the MVI and the MVI itself will be the target lesion for carbon-ion radiotherapy. The primary endpoints are the rates of all and severe adverse events, including DLTs, whereas the secondary endpoints will include the rates of overall survival, six-month survival, objective response, and six-month progression-free survival, and time to progression.

Ethics and dissemination: This study was approved by the ethics committee of two participating institutions (Chiba University Hospital and National Institute for Quantum and Radiological Science and Technology, QST hospital). The results of the DEPARTURE trial could help provide the basis for development of durvalumab ± tremelimumab combined with particle therapy for advanced HCC with MVI.

Trial registration number: jRCT2031210046

Strengths and limitations of this study

- The DEPARTURE trial is a phase Ib multicenter, open label, single arm, investigator-initiated clinical trial to assess the safety of durvalumab monotherapy in combination with particle therapy (cohort A) and that of durvalumab plus tremelimumab in combination with particle therapy (cohort B) for patients with advanced hepatocellular carcinoma (HCC) with macrovascular invasion (MVI).
- Durvalumab plus tremelimumab showed tolerability and promising clinical activity in a global phase II trial on patients with advanced hepatocellular carcinoma.
- Particle therapy, including carbon-ion radiotherapy, is already known for both its tumor control effect on MVI and tumor microenvironment modification; this increases the effectiveness of immune checkpoint inhibitors.
- The results of the DEPARTURE trial could help provide the basis for development of breakthrough therapy for advanced HCC with MVI, which is the phenotype with the worst prognosis.

INTRODUCTION

Hepatocellular carcinoma (HCC) accounts for the majority of liver cancer cases and remains to have a poor prognosis because most cases are diagnosed at the advanced stage [1, 2]. Recently, liver cancer ranks as the fourth most common cause of cancer-related death and as the sixth most frequently diagnosed cancer. Systemic therapies for advanced HCC have improved dramatically in the last decade. Previously, molecular target agents were the major treatment options for advanced HCC, but the impact on prognosis was limited [3-7]. Nowadays, combination immunotherapy is becoming the mainstream of systemic therapy for advanced HCC. In fact, in a global randomized phase III trial, atezolizumab plus bevacizumab was shown to significantly improve both overall survival (OS) and progression-free survival (PFS), compared with the effects of sorafenib [8]. Several clinical trials on combination immunotherapy are underway, and further improvement of prognosis is strongly expected [9].

Durvalumab is a selective and high-affinity human immunoglobulin G1 monoclonal antibody that blocks PD-L1 binding to PD-1 and CD80 [10]. Tremelimumab, which is a monoclonal immunoglobulin G2 antibody targeting cytotoxic T lymphocyte-associated antigen 4 (CTLA4), prevents the normal downregulation of T cells and prolongs T cell action, thereby, enhancing immune function [11]. Combining anti-PD-1/PD-L1 with anti-CTLA4 therapies was shown to provide additive antitumor activity through its action on the antitumor T cell response by multiple immune checkpoint blockade [12]. The combination of two immune checkpoint inhibitors has already been demonstrated to have clinical efficacy in several malignancies [13-17]. For advanced HCC, durvalumab plus tremelimumab showed tolerability and promising clinical activity, based on the results of a global phase II trial (Study 22) [18]. Patients treated with a single priming dose of tremelimumab 300 mg added to durvalumab every four weeks (i.e., T300 D regimen) achieved a median OS of 18.7 months. Including the other arms, such as

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6 durvalumab alone, tremelimumab alone, and 75 mg of tremelimumab for four doses with
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8 durvalumab every four weeks (T75 + D), this phase II study demonstrated acceptable
9
10 safety profiles and no new adverse events. A very recent press release from AstraZeneca
11
12 on the results of a phase III trial (HIMALAYA trial) reported durvalumab plus
13
14 tremelimumab significantly prolonged OS compared with sorafenib [19].
15

16 Focusing on the disease state of advanced HCC, variations of disease progression
17
18 can be divided into macrovascular invasion (MVI), which is unique to HCC, and
19
20 extrahepatic metastasis, as in other malignant tumors [20]. The presence of MVI is known
21
22 to be an extremely poor prognostic factor that leads not only to progressive malignant
23
24 disease severity but also to deterioration of liver function. Surgical resection of tumors
25
26 that include MVI and local control of MVI by transarterial chemoembolization, hepatic
27
28 arterial infusion chemotherapy, or radiation therapy had been previously reported to
29
30 improve the prognosis of patients with advanced HCC with MVI [20-26]. However, these
31
32 treatment strategies have not become common because of several reasons. First, in the
33
34 majority of cases in which MVI is present, the tumor is not localized and metastatic
35
36 lesions have often spread to both the liver and extrahepatic organs. Second, the
37
38 procedures to remove or control MVI require sufficient skill and experience. In addition,
39
40 all treatments that attempt to remove or control MVI are highly invasive and require
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42 extremely well maintained liver function and general performance status. Development
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44 of innovative treatments that target this specific phenotype of advanced HCC is
45
46 imperative.
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50 While radiotherapy for HCC has been mostly used in a palliative intent, with the
51
52 emergence of particle therapy followed by stereotactic body radiotherapy (SBRT), it has
53
54 become a viable treatment option for those not eligible for resection, transplant or radio
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56 frequency ablation but still with a localized disease [27-29]. Compared to conventional
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58 photon radiotherapy and SBRT, particle radiation therapy, which includes both proton
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6 beam therapy and carbon ion radiation therapy (C-ion RT), has been demonstrated to
7
8 confer a unique dose distribution; its physical characteristics enable delivery of high
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10 radiation doses to the tumor and low doses to normal tissues [30]. Compared with photons,
11
12 charged particles have different depth–dose distributions and deposit majority of the dose
13
14 at the Bragg peak, with little to no exit dose, thereby, resulting in superior sparing of
15
16 normal tissue. One particular advantage of particle radiation therapy for HCC is that
17
18 irradiation can be confined to a localized area of tumor; this results in both high local
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20 control and minimal impact on liver function [31]. Several reports have already confirmed
21
22 the high local control rates and safety profile of both proton beam therapy and C-ion RT
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24 for HCC [29, 32]. Moreover, the possibility of local control of MVI in advanced HCC by
25
26 particle radiation therapy has been suggested [33].
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30 Radiation therapy, especially C-ion RT, is well known to mediate localized tumor
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32 killing and tumor microenvironment modification, thereby, potentiating the effectiveness
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34 of immune checkpoint inhibitors [34-36]. Because the combination of radiation and
35
36 immune checkpoint inhibitors is expected to be a promising treatment, its impact on
37
38 several advanced cancers is still being tested. With its powerful potential of local tumor
39
40 control, immunosuppression, and immunogenicity, C-ion RT in combination with
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42 immune checkpoint inhibitors may lead to further breakthroughs for patients with
43
44 advanced HCC and MVI (Figure 1).
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48 **METHODS AND ANALYSIS**

49 **Study design**

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52 Protocol version 1.2, modified April 20, 2021
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56 **Objective of the potential trial**

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58 The aim of this study is to investigate the safety and synergistic effect of durvalumab with
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particle therapy and durvalumab plus tremelimumab combined with particle therapy in patients with advanced HCC and MVI (Table 1).

Table 1. Study endpoints

Primary Endpoint:

AEs/SAEs including DLTs

Secondary Endpoints:

Overall survival

6-month survival rate

Objective response rate

6-month progression-free survival rate

Time to progression

Study setting of the potential trial

This study is a non-blinded, single arm, phase Ib trial that will be conducted at two institutions (Chiba University Hospital and National Institute for Quantum and Radiological Science and Technology, QST hospital) to assess the safety of durvalumab combined with particle therapy (cohort A) and durvalumab plus tremelimumab combined with particle therapy (cohort B) in patients with advanced HCC and MVI (Figure 2). After providing consent, patients will undergo screening and assessment for study enrollment eligibility. Assessment of Dose-limiting toxicity (DLT) will be for 42 days starting from the administration of durvalumab or durvalumab plus tremelimumab on day 1 of cycle 1. In both cohorts, if the investigators determined any potential clinical benefit, patients will continue to receive durvalumab every four weeks until clinical progression (i.e., durvalumab q4W dosing period). In subjects who will provide additional written informed consent, biopsy specimens will be obtained from the same liver tumor that is not irradiated with C-ion RT before and 42 days after the start of durvalumab or

durvalumab plus tremelimumab administration on day 1 of cycle 1.

Trial resources

This study is funded by AstraZeneca. However, the sponsors are not involved in patient aggregation or analysis.

Eligibility and screening

Potential participants are screened by the principal investigator or one of the associate investigators, according to the eligibility criteria shown in Table 2.

Table 2. Key eligibility criteria

Inclusion criteria

1. Age ≥ 20 years at the time of study entry
2. Eastern Cooperative Oncology Group performance status of 0 or 1
3. Body weight >30 kg
4. Adequately normal organ and marrow functions
5. Life expectancy of at least 12 weeks
6. Advanced HCC confirmed histologically or by the typical findings of a hypervascular tumor on computed tomography or angiography
7. Must not be eligible for locoregional therapy for unresectable HCC
8. Child–Pugh A
9. Patients who have been diagnosed as HCC with macrovascular invasion
10. Patients with history of at least one prior systemic chemotherapy regimen, including atezolizumab/ bevacizumab combination, sorafenib, or lenvatinib, and were judged to be refractory or intolerant to standard therapy (excluded from the inclusion criteria in the expansion cohort)

Exclusion criteria

1. Any unresolved NCI CTCAE grade ≥ 2 toxicity from previous anticancer therapy, with the exception of alopecia, vitiligo, and the laboratory values defined in the inclusion criteria
2. Radiotherapy treatment to more than 30% of the bone marrow or with a wide field of radiation within four weeks of the first dose of the study drug

3. Major surgical procedure, as defined by the investigator, within 28 days prior to the first dose of IP
4. History of allogenic organ transplantation
5. Active or prior documented autoimmune or inflammatory disorders
6. History of another primary malignancy
7. Prior or current brain metastases or spinal cord compression
8. History of active primary immunodeficiency
9. Patients coinfecting with hepatitis B and C viruses or with hepatitis B and D viruses
10. Current or prior use of immunosuppressive medication within 14 days before the first dose of durvalumab or tremelimumab
11. Known allergy or hypersensitivity to any of the study drugs or any of the study drug excipients
12. Prior radiotherapy involving the liver
13. Renal failure requiring hemodialysis or peritoneal dialysis
14. Presence of any severe cardiac disease
15. Poorly controlled hypertension
16. Serious and active infection, excluding hepatitis virus infection
17. Persistent proteinuria of NCI-CTCAE version 5.0 grade ≥ 3 ; urine dipstick result of 3+ is allowed if protein excretion is < 3.5 g/ 24 hours
18. Arterial or venous thrombotic or embolic events, such as cerebrovascular accident, deep vein thrombosis, or pulmonary embolism within six months before the start of the study medication
19. Refractory pleural effusion or ascites
20. History of hepatic encephalopathy within the past 12 months

HCC, hepatocellular carcinoma; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events

Treatment regimen

In cohort A, durvalumab 1,500 mg will be administered every four weeks in principle. Particle therapy in the form of C-ion RT will be administered after day 8 of cycle 1 following the first dose of durvalumab on day 1. In cohort B, durvalumab 1,500 mg will be administered every four weeks in principle, and tremelimumab 300 mg will be administered only on day 1 of cycle 1. Particle therapy in the form of C-ion RT will be administered after day 8 of cycle 1 following the first cycle of durvalumab plus

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6 tremelimumab. C-ion RT will be given after day 8 of cycle 1 following the first dose of
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8 durvalumab plus tremelimumab on day 1. The dose is 60 Gy (relative biologic
9
10 effectiveness) in four fractions per week. The target lesion of the particle therapy will be
11
12 focused on an intrahepatic nodule with MVI. The clinical target volume margin will be 1
13
14 cm for the feeding nodule and 2 cm alongside the vessel for the MVI lesion. Internal
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16 motion will be compensated according to 4D-CT movement assessment. Interfractional
17
18 margin will be set at 3 mm and combined with internal motion compensation to form a
19
20 field-specific planning treatment volume. Study treatments will continue until disease
21
22 progression, according to RECIST ver. 1.1.
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27 **Patient registration rules**

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29 In this modified 3 + 3 design, three patients are initially enrolled into cohort A (Figure
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31 3). If there is no DLT observed in any of the subjects, the trial proceeds to enrol additional
32
33 subjects into cohort B. If one subject in either cohort develops a DLT, three additional
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35 subjects are enrolled into that same cohort. If cohort B treatment is confirmed to be
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37 tolerated (i.e., no DLT in three patients or one DLT in six patients), enrollment of up to a
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39 total of 15 subjects to cohort B is continued. Development of DLTs in at least two subjects
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41 in cohort A will mean that the entire trial will be terminated. Occurrence of DLTs in at
42
43 least two subjects in cohort B would suggest that tolerability is not confirmed, and the
44
45 regimen of cohort B will be discontinued. In this case, additional patients up to a total of
46
47 15 will be enrolled in cohort A.
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52 **Definition of dose-limiting toxicity**

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54 DLT will be evaluated during the assessment period of the trial (i.e., for 42 days starting
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56 from the administration of durvalumab on day 1 of cycle 1). Patients who do not remain
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58 in the study up to this time for reasons other than DLT will be replaced with another
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6 patient who will receive the same dose level. Grading of DLTs will follow the guidelines
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8 provided in the Common Terminology Criteria for Adverse Events version 5.0. A DLT
9
10 is defined as the occurrence of an adverse event (AE) that is at least possibly related with
11
12 the treatment regimen. AEs that are at least possibly related with the treatment regimen
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14 will be designated as DLTs if they meet any of the criteria listed in Supplementary Table
15
16 1. Any treatment-related toxicity that first occurs during the DLT assessment period must
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18 be followed-up for resolution to determine if the event qualifies as a DLT, as specified in
19
20 the DLT criteria (Suppl. Table 1).
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23 24 25 **Statistical methods and sample size determination**

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27 This study will employ a modified 3 + 3 design, and the number of subjects that will
28
29 enable us to assess the safety and tolerability of the investigational regimen in the DLT
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31 population will be defined. The DLT analysis set will comprise all patients who will
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33 undergo DLT assessment or safety analyses. The frequencies of DLTs will be calculated
34
35 for each cohort. For efficacy analyses, OS, six-month survival rate, objective response
36
37 rate, six-month PFS rate, and time to progression will be reported.
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40 41 42 **Patient and Public Involvement statement**

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44 Patients and/or the public were not involved in the design, or conduct, or reporting or
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46 dissemination plans of this research.
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49 50 **ETHICS AND DISSEMINATION**

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52 This study was approved by the ethics committees of the two participating institutions
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54 mentioned above. All patients are required to give written informed consent to a member
55
56 of the study team before inclusion to the DEPARTURE trial.
57

58 The results of the DEPARTURE trial may help provide the basis for
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6 development of durvalumab ± tremelimumab combined with particle therapy in patients
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8 with advanced HCC and MVI. This new innovative treatment based on the synergistic
9
10 effect of combined immunotherapy and particle therapy can be a breakthrough for
11
12 advanced HCC with MVI, which is the phenotype with the worst prognosis.
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22
23

24 **Authors' contributions**

25
26 SO drafted the manuscript. SO, KK, HM, MW, and AT designed the protocol. YO and
27
28 YK preformed the statistical analysis. SY, MN, TI, KO, KF, TI, TS, NF, RK, HK, KK,
29
30 SK, MN, NK, TS, TK, RN, SN, RM, RM, TC, TK, HH, HT, and NK further aided in the
31
32 assessment and revisions of the protocol and manuscript.
33
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35

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40 20168].
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46 **Competing interests**

47
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6 **Figure Legends**
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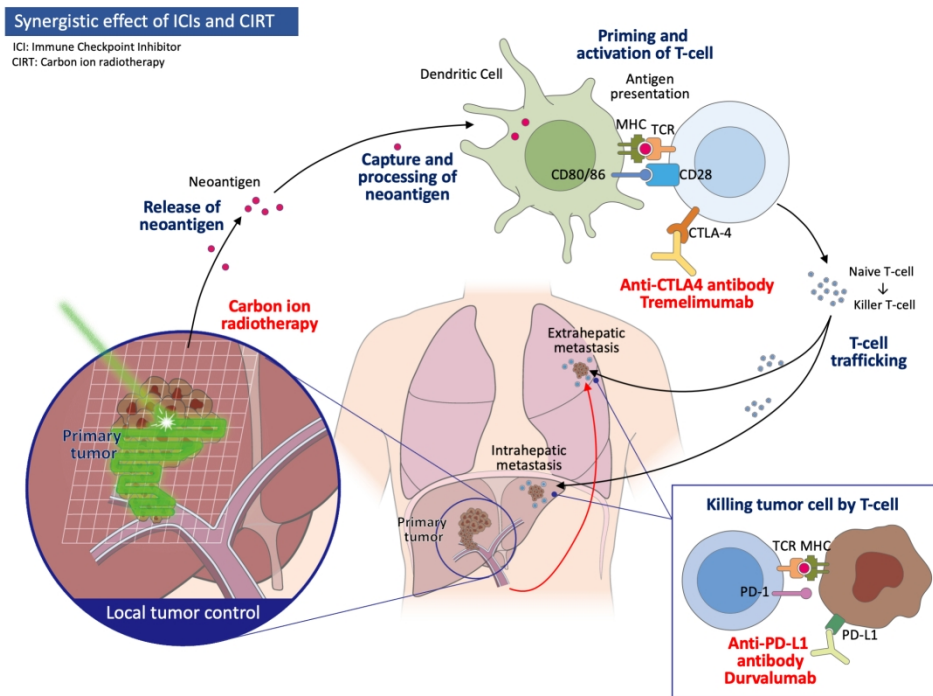
10 **Figure 1. The concept of the study.**
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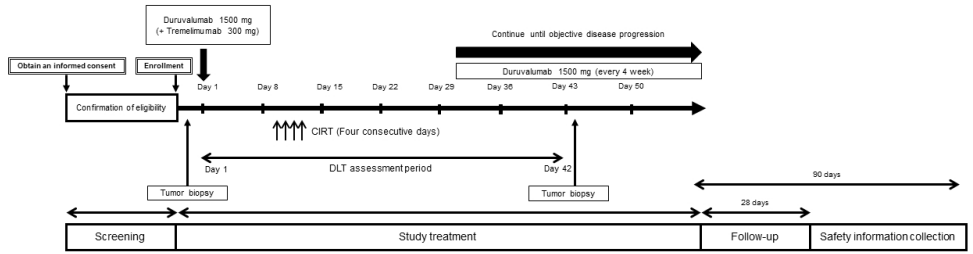
Figure 1. Ogasawara et al.



The concept of the study.

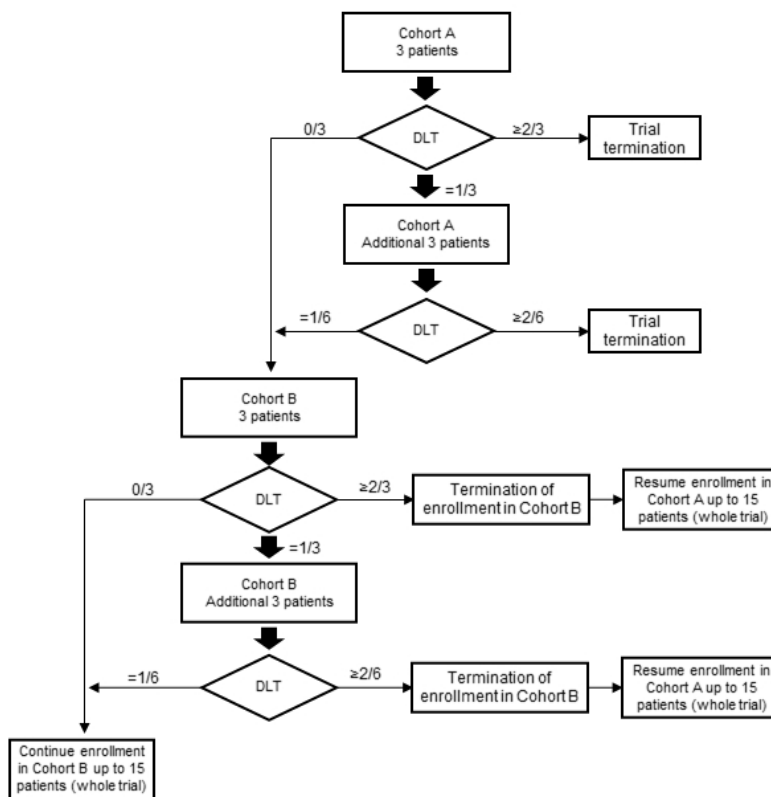
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Figure 2. Ogasawara et al.



Dosing schedule of the study.
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Figure 3. Ogasawara et al.



Schematic depiction of modified 3+3 design

200x229mm (96 x 96 DPI)

Supplementary Table 1. Criteria for DLT

A DLT will be defined as the occurrence of an adverse event (AE) that is at least possibly related with the investigational product (IP) or investigational regimen (IR), with the two following exceptions: any grade of vitiligo or alopecia. AEs that are at least possibly related with durvalumab- and/ or tremelimumab-containing regimens will be defined as DLTs if the following criteria are met:

If a patient initiated on C-ion RT is unable to complete the C-ion RT within the allowable time period because of AEs that cannot be ruled out as causally related with durvalumab, tremelimumab, or C-ion RT, the AEs will be considered as DLT.

Hematologic toxicity:

- Grade ≥ 3 neutropenia complicated by fever of >38.3 °C
- Grade 4 neutropenia lasting more than seven days
- Grade ≥ 3 thrombocytopenia with significant bleeding
- Grade 4 thrombocytopenia, regardless of duration
- Grade 4 anemia, regardless of duration

Nonhematologic toxicity:

- Any grade 4 nonimmune-mediated AE
- Any grade 4 immune-mediated AE, excluding endocrinopathies
- Any grade 3 nonimmune-mediated AE that does not resolve to grade ≤ 1 or baseline within 30 days of optimal medical management
- Any grade 3 immune-mediated AE, excluding diarrhea/ colitis, pneumonitis, hepatitis, rash, neurotoxicity, myocarditis, myositis/ polymyositis, endocrinopathies and nephritis, which does not resolve to grade ≤ 1 or baseline within 30 days after onset of the event despite optimal medical management, including systemic corticosteroids
- Grade 3 diarrhea or colitis that does not resolve to grade ≤ 1 within 14 days (both immune- and nonimmune-mediated; the same applies if not specified in the remaining bullet points below]
- Grade 3 noninfectious pneumonitis
- Grade 2 noninfectious pneumonitis that does not resolve to grade ≤ 1 within three days of initiation of maximal supportive care
- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) $\geq 5 \times$ ULN or $5 \times$ the baseline, if the baseline is abnormal, with concurrent increase in total bilirubin (TBL) $\geq 3 \times$ ULN or $3 \times$ the baseline, if the baseline is abnormal without evidence of cholestasis or alternative explanations, such as viral hepatitis, disease progression in the liver (i.e., Hy's Law)
- ALT or AST $> 8 \times$ ULN or $8 \times$ the baseline, if the baseline is abnormal, or TBL $> 5 \times$ ULN or $5 \times$ the baseline, if the baseline is abnormal
- Grade 3 immune-mediated rash that does not resolve to grade ≤ 1 or baseline within 30 days

- Grade 2 rash covering >30% BSA that does not resolve to grade ≤ 1 or baseline within 30 days
- Any grade of immune-mediated rash with bullous formation
- Grade 3 immune-mediated neurotoxicity, excluding Guillain–Barre and myasthenia gravis, that does not resolve to grade ≤ 1 within 30 days
- Grade 2 or 3 immune-mediated peripheral neuromotor syndrome, such as Guillain–Barre and myasthenia gravis, that does not resolve to grade ≤ 1 within 30 days or that exhibits signs of respiratory insufficiency or autonomic instability
- Grade 3 immune-mediated myocarditis
- Any symptomatic immune-mediated myocarditis that does not become asymptomatic within three days of initiating optimal medical management, including systemic corticosteroids
- Grade 2 or 3 immune-mediated myositis/ polymyositis that does not resolve to grade ≤ 1 within 30 days of initiating optimal medical management, including systemic corticosteroids, or that exhibits signs of respiratory insufficiency, regardless of optimal medical management
- Immune-mediated increase in creatinine $>3 \times$ ULN or $>3 \times$ the baseline for patients with baseline creatinine that is above the ULN
- Transfusion of red cell concentrate or platelet or use of G-CSF during the DLT period

BMJ Open

Durvalumab with or without tremelimumab combined with particle therapy for advanced hepatocellular carcinoma with macrovascular invasion: protocol for the DEPARTURE phase Ib trial

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Keywords:	Hepatobiliary tumours < ONCOLOGY, Radiation oncology < RADIOLOGY & IMAGING, Hepatology < INTERNAL MEDICINE

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Durvalumab with or without tremelimumab combined with particle therapy for advanced hepatocellular carcinoma with macrovascular invasion: protocol for the DEPARTURE phase Ib trial

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12 ¶The authors contributed equally to this work.
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16 Word count: 4390 words
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18 19 20 21 **ABSTRACT**

22
23 **Introduction:** Advanced hepatocellular carcinoma (HCC) with macrovascular invasion
24 (MVI) has the worst prognosis among all phenotypes. The DEPARTURE trial aims to
25 evaluate whether treatment with durvalumab, alone or in combination with tremelimumab,
26 plus particle therapy is a safe and synergistically effective treatment in patients with
27 advanced HCC and MVI.
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33 **Methods and analysis:** This phase Ib, multicenter (two sites in Japan), open-label,
34 single-arm, investigator-initiated clinical trial will assess durvalumab monotherapy in
35 combination with particle therapy (cohort A) and that of durvalumab plus tremelimumab
36 in combination with particle therapy (cohort B) for patients with advanced HCC with
37 MVI. Cohort A will receive 1,500 mg durvalumab every four weeks. Cohort B will
38 receive 1,500 mg durvalumab every four weeks in principle and 300 mg tremelimumab
39 only on day 1 of the first cycle. Carbon-ion radiotherapy (C-ion RT) will be administered
40 after day 8 of the first cycle. The primary endpoints are rates of any and severe adverse
41 events, including DLTs; secondary endpoints are overall survival, six-month survival,
42 objective response, six-month progression-free survival, and time to progression. Patients
43 are initially enrolled into cohort A. If cohort A treatment is confirmed to be tolerated (i.e.,
44 no DLT in three patients or one DLT in six patients), the trial proceeds to enroll more
45 patients into cohort B. Similarly, if cohort B treatment is confirmed to be tolerated (i.e.,
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no DLT in three patients or one DLT in six patients), a total of 15 patients will be enrolled into cohort B.

Ethics and dissemination: This study was approved by the ethics committees of the two participating institutions (Chiba University Hospital and National Institute for Quantum [approval No. 2020040] and Radiological Science and Technology, QST hospital [approval No. C20-001]). Participants will be required to provide written informed consent. Trial results will be reported in a peer-reviewed journal publication.

Trial registration number: Japan Registry of Clinical Trials, jRCT2031210046.

Strengths and limitations of this study

- The DEPARTURE trial is a multicentre, investigator-initiated study assessing a promising combination treatment in patients with advanced hepatocellular carcinoma with macrovascular invasion.
- The trial is designed to investigate both safety (primary endpoints) and synergistic efficacy (secondary endpoints).
- Although this study is designed to assess the performance of immune checkpoint inhibitors (ICIs) followed by carbon-ion radiotherapy (C-ion RT), the order of ICI and C-ion RT treatment requires further investigation.

INTRODUCTION

Hepatocellular carcinoma (HCC) accounts for the majority of liver cancer cases and remains to have a poor prognosis because most cases are diagnosed at the advanced stage [1, 2]. Recently, liver cancer ranks as the fourth most common cause of cancer-related death and as the sixth most frequently diagnosed cancer. Systemic therapies for advanced HCC have improved dramatically in the last decade. Previously, molecular target agents were the major treatment options for advanced HCC, but the impact on prognosis was limited [3-7]. Nowadays, combination immunotherapy is becoming the mainstream of systemic therapy for advanced HCC. In fact, in a global randomized phase III trial, atezolizumab plus bevacizumab was shown to significantly improve both overall survival (OS) and progression-free survival (PFS), compared with the effects of sorafenib [8]. Several clinical trials on combination immunotherapy are underway, and further improvement of prognosis is strongly expected [9].

Durvalumab is a selective and high-affinity human immunoglobulin G1 monoclonal antibody that blocks PD-L1 binding to PD-1 and CD80 [10]. Tremelimumab, which is a monoclonal immunoglobulin G2 antibody targeting cytotoxic T lymphocyte-associated antigen 4 (CTLA4), prevents the normal downregulation of T cells and prolongs T cell action, thereby, enhancing immune function [11]. Combining anti-PD-1/PD-L1 with anti-CTLA4 therapies was shown to provide additive antitumor activity through its action on the antitumor T cell response by multiple immune checkpoint blockade [12]. The combination of two immune checkpoint inhibitors (ICIs) has already been demonstrated to have clinical efficacy in several malignancies [13-17]. For advanced HCC, durvalumab plus tremelimumab showed tolerability and promising clinical activity, based on the results of a global phase II trial (Study 22) [18]. Patients treated with a single priming dose of tremelimumab 300 mg added to durvalumab every four weeks (i.e., T300 D regimen) achieved a median OS of 18.7 months. Including the

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6 other arms, such as durvalumab alone, tremelimumab alone, and 75 mg of tremelimumab
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8 for four doses with durvalumab every four weeks (T75 + D), this phase II study
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10 demonstrated acceptable safety profiles and no new adverse events. Very recently, the
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12 results of a phase III trial (HIMALAYA trial) reported durvalumab plus tremelimumab
13
14 significantly prolonged OS compared with sorafenib [19].
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16 Focusing on the disease state of advanced HCC, variations of disease progression
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18 can be divided into macrovascular invasion (MVI), which is unique to HCC, and
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20 extrahepatic metastasis, as in other malignant tumors [20]. The presence of MVI is known
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22 to be an extremely poor prognostic factor that leads not only to progressive malignant
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24 disease severity but also to deterioration of liver function. Surgical resection of tumors
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26 that include MVI and local control of MVI by transarterial chemoembolization, hepatic
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28 arterial infusion chemotherapy, or radiation therapy had been previously reported to
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30 improve the prognosis of patients with advanced HCC with MVI [20-26]. However, these
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32 treatment strategies have not become common because of several reasons. First, in the
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34 majority of cases in which MVI is present, the tumor is not localized and metastatic
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36 lesions have often spread to both the liver and extrahepatic organs. Second, the
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38 procedures to remove or control MVI require sufficient skill and experience. In addition,
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40 all treatments that attempt to remove or control MVI are highly invasive and require
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42 extremely well maintained liver function and general performance status. Development
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44 of innovative treatments that target this specific phenotype of advanced HCC is
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46 imperative.
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50 While radiotherapy for HCC has been mostly used in a palliative intent, with the
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52 emergence of particle therapy followed by stereotactic body radiotherapy (SBRT), it has
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54 become a viable treatment option for those not eligible for resection, transplant or radio
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56 frequency ablation but still with a localized disease [27-29]. Compared to conventional
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58 photon radiotherapy and SBRT, particle radiation therapy, which includes both proton
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6 beam therapy and carbon-ion radiation therapy (C-ion RT), has been demonstrated to
7 confer a unique dose distribution; its physical characteristics enable delivery of high
8 radiation doses to the tumor and low doses to normal tissues [30]. Compared with photons,
9 charged particles have different depth–dose distributions and deposit majority of the dose
10 at the Bragg peak, with little to no exit dose, thereby, resulting in superior sparing of
11 normal tissue. One particular advantage of particle radiation therapy for HCC is that
12 irradiation can be confined to a localized area of tumor; this results in both high local
13 control and minimal impact on liver function [31]. Several reports have already confirmed
14 the high local control rates and safety profile of both proton beam therapy and C-ion RT
15 for HCC [29, 32]. Moreover, the possibility of local control of MVI in advanced HCC by
16 particle radiation therapy has been suggested [33].
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29 Radiation therapy, especially C-ion RT, is well known to mediate localized tumor
30 killing and tumor microenvironment modification, thereby, potentiating the effectiveness
31 of ICIs [34-36]. Because the combination of radiation and ICIs is expected to be a
32 promising treatment, its impact on several advanced cancers is still being tested. In
33 advanced HCC, several combination immunotherapies based on ICI are further developed
34 [37]. Among various treatments currently under development, we believe that C-ion RT
35 combined with ICIs may lead to further breakthroughs for patients with advanced HCC
36 and MVI using its powerful potential of local tumor control, immunosuppression, and
37 immunogenicity (Figure 1).
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50 **METHODS AND ANALYSIS**

51 **Objective**

52 The aim of this study is to investigate the safety and synergistic effect of durvalumab with
53 particle therapy and durvalumab plus tremelimumab combined with particle therapy in
54 patients with advanced HCC and MVI (Table 1).
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Table 1. Study endpoints

Primary Endpoint: AEs/SAEs including DLTs
Secondary Endpoints: Overall survival 6-month survival rate Objective response rate 6-month progression-free survival rate Time to progression

Study design and setting

This study is a non-blinded, single arm, phase Ib trial that will be conducted at two institutions (Chiba University Hospital and National Institute for Quantum and Radiological Science and Technology, QST hospital) to assess the safety of durvalumab combined with particle therapy (cohort A) and durvalumab plus tremelimumab combined with particle therapy (cohort B) in patients with advanced HCC and MVI (Figure 2). After providing consent, patients will undergo screening and assessment for study enrollment eligibility. Assessment of Dose-limiting toxicity (DLT) will be for 42 days starting from the administration of durvalumab or durvalumab plus tremelimumab on day 1 of cycle 1. In both cohorts, if the investigators determined any potential clinical benefit, patients will continue to receive durvalumab every four weeks until clinical progression (i.e., durvalumab q4W dosing period). In subjects who provide additional written informed consent, biopsy specimens will be obtained from the same liver tumor that is not irradiated with C-ion RT before and 42 days after the start of durvalumab or durvalumab plus tremelimumab administration on day 1 of cycle 1. Specimens will be stored appropriately and may be used for further studies if consent has been obtained from the

subjects.

Trial resources

This study is funded by AstraZeneca. However, the sponsors are not involved in patient aggregation or analysis.

Eligibility and screening

Potential participants are screened by the principal investigator or one of the associate investigators, according to the eligibility criteria shown in Table 2.

Table 2. Key eligibility criteria

Inclusion criteria

1. Age ≥ 20 years at the time of study entry
2. Eastern Cooperative Oncology Group performance status of 0 or 1
3. Body weight >30 kg
4. Adequately normal organ and marrow functions
5. Life expectancy of at least 12 weeks
6. Advanced HCC confirmed histologically or by the typical findings of a hypervascular tumor on computed tomography or angiography
7. Must not be eligible for locoregional therapy for unresectable HCC
8. Child–Pugh A
9. Patients who have been diagnosed as HCC with macrovascular invasion
10. Patients with history of at least one prior systemic chemotherapy regimen, including atezolizumab/ bevacizumab combination, sorafenib, or lenvatinib, and were judged to be refractory or intolerant to standard therapy (excluded from the inclusion criteria in the expansion cohort)

Exclusion criteria

1. Any unresolved NCI CTCAE grade ≥ 2 toxicity from previous anticancer therapy, with the exception of alopecia, vitiligo, and the laboratory values defined in the inclusion criteria
2. Radiotherapy treatment to more than 30% of the bone marrow or with a wide field of radiation within four weeks of the first dose of the study drug

3. Major surgical procedure, as defined by the investigator, within 28 days prior to the first dose of IP
4. History of allogenic organ transplantation
5. Active or prior documented autoimmune or inflammatory disorders
6. History of another primary malignancy
7. Prior or current brain metastases or spinal cord compression
8. History of active primary immunodeficiency
9. Patients coinfecting with hepatitis B and C viruses or with hepatitis B and D viruses
10. Current or prior use of immunosuppressive medication within 14 days before the first dose of durvalumab or tremelimumab
11. Known allergy or hypersensitivity to any of the study drugs or any of the study drug excipients
12. Prior radiotherapy involving the liver
13. Renal failure requiring hemodialysis or peritoneal dialysis
14. Presence of any severe cardiac disease
15. Poorly controlled hypertension
16. Serious and active infection, excluding hepatitis virus infection
17. Persistent proteinuria of NCI-CTCAE version 5.0 grade ≥ 3 ; urine dipstick result of 3+ is allowed if protein excretion is < 3.5 g/ 24 hours
18. Arterial or venous thrombotic or embolic events, such as cerebrovascular accident, deep vein thrombosis, or pulmonary embolism within six months before the start of the study medication
19. Refractory pleural effusion or ascites
20. History of hepatic encephalopathy within the past 12 months

HCC, hepatocellular carcinoma; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events

Treatment regimen

In cohort A, durvalumab 1,500 mg will be administered every four weeks in principle. Particle therapy in the form of C-ion RT will be administered after day 8 of cycle 1 following the first dose of durvalumab on day 1. In cohort B, durvalumab 1,500 mg will be administered every four weeks in principle, and tremelimumab 300 mg will be administered only on day 1 of cycle 1. Particle therapy in the form of C-ion RT will be administered after day 8 of cycle 1 following the first cycle of durvalumab plus tremelimumab. C-ion RT will be given after day 8 of cycle 1 following the first dose of

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6 durvalumab plus tremelimumab on day 1. The dose is 60 Gy (relative biologic
7 effectiveness) in four fractions per week. The target lesion of the particle therapy will be
8 focused on an intrahepatic nodule with MVI. The clinical target volume margin will be 1
9 cm for the feeding nodule and 2 cm alongside the vessel for the MVI lesion. Internal
10 motion will be compensated according to 4D-CT movement assessment. Interfractional
11 margin will be set at 3 mm and combined with internal motion compensation to form a
12 field-specific planning treatment volume. Study treatments will continue until disease
13 progression, according to RECIST ver. 1.1. Prohibited concomitant treatments are
14 described in the Supplementary Table 1. Information on adverse events occurring in the
15 trial or obtained from other trials will be collected and responded to appropriately
16 following the Good Clinical Practice in Japan (J-GCP). The trial team will provide
17 treatment for the patients' recovery and provide appropriate medical care.
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33 **Patient registration rules**

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35 In this modified 3+3 design (Figure 3), three patients are initially enrolled into cohort A.
36 If no DLT is observed in any of these subjects, the trial proceeds to enroll more subjects
37 into cohort B, which regimen contains an additional drug, tremelimumab. If one subject
38 develops a DLT in cohort A or B, three more subjects are enrolled into the same cohort.
39 DLT occurrence in >1 of 6 subjects in either cohort suggests that the regimen is not
40 tolerable. If cohort A turns out to be intolerable, then cohort B regimen will not be pursued.
41 If cohort B treatment is confirmed to be tolerated (i.e., no DLT in three patients or one
42 DLT in six patients), enrollment of up to a total of 15 subjects to cohort B is continued.
43 Development of DLTs in at least two subjects in cohort A will mean that the entire trial
44 will be terminated. Occurrence of DLTs in at least two subjects in cohort B would suggest
45 that tolerability is not confirmed, and the regimen of cohort B will be discontinued. In
46 this case, additional patients up to a total of 15 will be enrolled in cohort A. Criteria for
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discontinuation of the trial treatment are described in Supplementary Table 2.

Definition of dose-limiting toxicity

DLT will be evaluated during the assessment period of the trial (i.e., for 42 days starting from the administration of durvalumab on day 1 of cycle 1). Subjects who do not remain in the study up to this time for reasons other than DLT will be replaced with another subject who will receive the same dose level. Grading of DLTs will follow the guidelines provided in the Common Terminology Criteria for Adverse Events version 5.0. A DLT is defined as the occurrence of an adverse event (AE) that is at least possibly related with the treatment regimen. AEs that are at least possibly related with the treatment regimen will be designated as DLTs if they meet any of the criteria listed in Supplementary Table 3. Any treatment-related toxicity that first occurs during the DLT assessment period must be followed-up for resolution to determine if the event qualifies as a DLT, as specified in the DLT criteria.

Statistical methods and sample size determination

This study will employ a modified 3+3 design, and the number of subjects that will enable us to assess the safety and tolerability of the investigational regimen in the DLT population will be defined. We set the total number of subjects in this study, including the expansion cohort, at 15 based on the enrollment feasibility within the study period. The DLT analysis set will comprise all patients who will undergo DLT assessment or safety analyses. The frequencies of DLTs will be calculated for each cohort. For efficacy analyses, OS, six-month survival rate, objective response rate, six-month PFS rate, and time to progression will be reported. No interim analysis will be conducted in this trial.

Data management, monitoring, safety, and auditing

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6 Data are accurately and appropriately recorded in the case report forms and will be
7 managed appropriately following the J-GCP. Monitors ensure that the trial team is
8 conducting the study per the study protocol and J-GCP. An audit will be conducted at the
9 investigational site to confirm that quality control of the trial is appropriately conducted.
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16 **Data monitoring committee**

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18 The data monitoring committee consists of clinical trial experts, including biostatisticians,
19 who are not involved in this study. The committee will check data obtained from the trial
20 and evaluate the treatment cohort.
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27 **Patient and public involvement**

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29 Patients and/or the public were not involved in the design, or conduct, or reporting or
30 dissemination plans of this research.
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35 **ETHICS AND DISSEMINATION**

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37 This study was approved by the ethics committee of two participating institutions (Chiba
38 University Hospital and National Institute for Quantum [approval no. 2020040] and
39 Radiological Science and Technology, QST hospital [approval no. C20-001]). All
40 patients are required to give written informed consent to a member of the study team
41 before inclusion in the DEPARTURE trial (supplementary file).
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50 If the protocol is revised, the primary investigator will inform the trial team and obtain
51 the institutional review board's approval.
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56 We will submit the trial results as the case study report on the Japan Registry of Clinical
57 Trials. Trial results will be reported in a peer-reviewed journal publication. The
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6 authorship will be ascribed following the International Committee of Medical Journal
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8 Editors guidelines.
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10 11 12 **Protocol version**

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14 Protocol version 1.2, modified April 20, 2021.
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17 18 19 **Study status**

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21 The first subject of this study enrolled on 6th July, 2021. The study is ongoing.
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24 25 **Data availability statement**

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27 We have no plans to share individual participant data obtained in this study. The summary
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29 report will be uploaded to the Japan Registry of Clinical Trials immediately after
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31 completion of the trial, in accordance with Japanese regulations.
32
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34 35 **Acknowledgments**

36
37 The authors are grateful to the following people for their contributions to the data
38
39 management: Satomi Nakamura, Ryoko Arai, and Yuka Iwase.
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42 43 44 **Contributors**

45
46 SO drafted the manuscript. SO, KK, HM, MW, and AT designed the protocol. YO and
47
48 YK performed the statistical analysis. SY, MN, TI, KO, KF, TI, TS, NF, RK, HK, KK,
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50 SK, MN, NK, TS, TK, RN, SN, RM, RM, TC, TK, HH, HT, and NK further aided in the
51
52 assessment and revisions of the protocol and manuscript.
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58
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20168).

Competing interests

SO has received honoraria from Bayer, Eisai, Eli Lilly, and Chugai Pharma and research funding from Bayer, Eisai, Eli Lilly, and AstraZeneca. NK has received honoraria from Bayer, Eisai, Eli Lilly, and Chugai Pharma and research funding from Bayer, Eisai, and Eli Lilly. The other authors have no disclosures.

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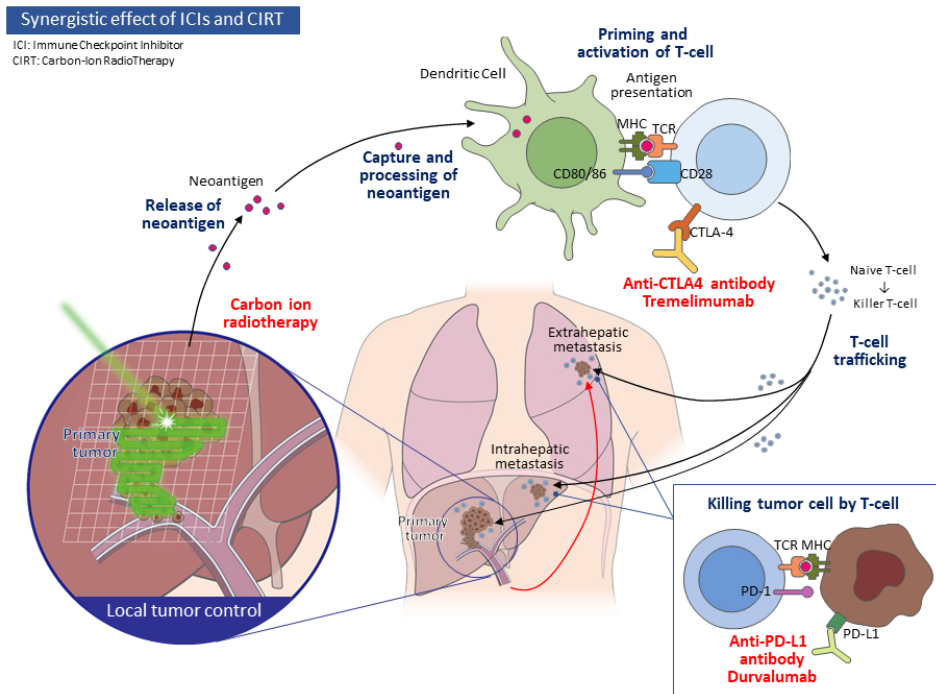
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6 **Figure Titles**
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10 **Figure 1. Study concept**
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14 **Figure 2. Dosing schedule**
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18 **Figure 3. Schematic depiction of modified 3+3 design**
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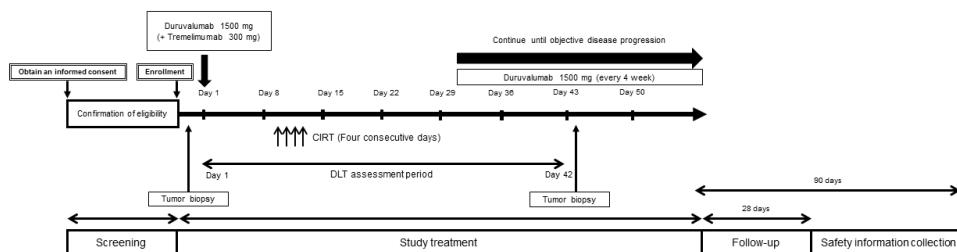
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The concept of the study

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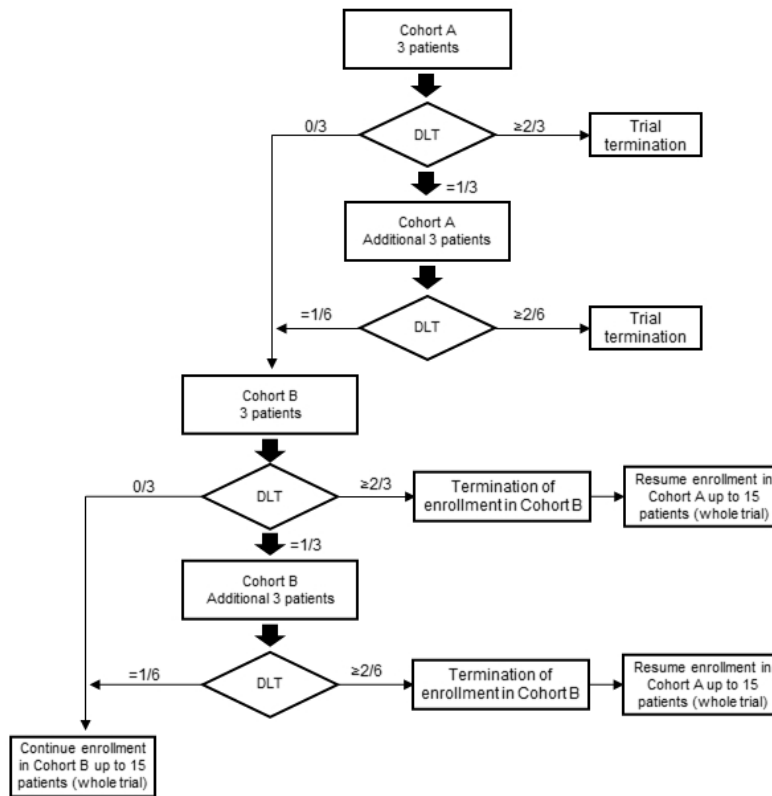
Figure 2. Ogasawara et al.



Dosing schedule of the study.

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Figure 3. Ogasawara et al.



Schematic depiction of modified 3+3 design

200x229mm (96 x 96 DPI)

Supplementary Table 1. Prohibited concomitant treatments

Prohibited medication/class of drug:	Usage:
Any investigational anticancer therapy other than those under investigation in this study	Should not be given concomitantly whilst the patient is on study treatment
mAbs against CTLA-4, PD-1, or PD-L1 other than those under investigation in this study	Should not be given concomitantly whilst the patient is on study treatment
Any concurrent chemotherapy, radiotherapy, immunotherapy, or biologic or hormonal therapy for cancer treatment other than those under investigation in this study	Should not be given concomitantly whilst the patient is on study treatment. (Concurrent use of hormones for non-cancer-related conditions [e.g., insulin for diabetes and hormone replacement therapy] is acceptable. Local treatment of isolated lesions, excluding target lesions, for palliative intent is acceptable [e.g., by local surgery or radiotherapy])
Immunosuppressive medications including, but not limited to, systemic corticosteroids at doses exceeding 10 mg/day of prednisone or equivalent, methotrexate, azathioprine, and tumor necrosis factor- α blockers	Should not be given concomitantly or used for premedication prior to the I-O infusions. The following are allowed exceptions: <ul style="list-style-type: none"> • Use of immunosuppressive medications for the management of IP-related AEs, • Use in patients with contrast allergies. • In addition, use of inhaled, topical, and intranasal corticosteroids is permitted. • A temporary period of steroids will be allowed if clinically indicated and considered to be essential for the management of non-immunotherapy related events experienced by the patient (e.g., chronic obstructive pulmonary disease, radiation, nausea, etc.).

EGFR TKIs	Should not be given concomitantly. Should be used with caution in the 90 days post last dose of durvalumab. Increased incidences of pneumonitis (with third generation EGFR TKIs) and increased incidence of transaminase increases (with 1 st generation EGFR TKIs) has been reported when durvalumab has been given concomitantly.
Live attenuated vaccines	Should not be given through 30 days after the last dose of IP.
Drugs with a laxative effect (ex. magnesium oxide) and herbal and natural remedies which may have immune-modulating effects	Should not be given concomitantly.
Transfusion (Red cell concentrate, Platelet)	Should not be given during DLT period
G-CSF	Should not be given during DLT period

Supplementary Table 2. Criteria for discontinuation of the trial treatment

We discontinue the trial treatment if any of the following defined criteria are met:

- If the objective disease progression is observed
- If the patient requests to withdraw from the study treatment.
- If it is difficult to continue the administration of the investigational drug due to worsening comorbidities.
- When it is difficult to continue the administration of the investigational drug due to adverse events.
- If a subject becomes pregnant.
- In any other cases where, at the discretion of the investigator or co-investigator, it is deemed necessary to discontinue the administration of the investigational drug.

Supplementary Table 3. Criteria for DLT

A DLT will be defined as the occurrence of an adverse event (AE) that is at least possibly related with the investigational product (IP) or investigational regimen (IR), with the two following exceptions: any grade of vitiligo or alopecia. AEs that are at least possibly related with durvalumab- and/ or tremelimumab-containing regimens will be defined as DLTs if the following criteria are met:

If a patient initiated on C-ion RT is unable to complete the C-ion RT within the allowable time period because of AEs that cannot be ruled out as causally related with durvalumab, tremelimumab, or C-ion RT, the AEs will be considered as DLT.

Hematologic toxicity:

- Grade ≥ 3 neutropenia complicated by fever of >38.3 °C
- Grade 4 neutropenia lasting more than seven days
- Grade ≥ 3 thrombocytopenia with significant bleeding
- Grade 4 thrombocytopenia, regardless of duration
- Grade 4 anemia, regardless of duration

Nonhematologic toxicity:

- Any grade 4 nonimmune-mediated AE
- Any grade 4 immune-mediated AE, excluding endocrinopathies
- Any grade 3 nonimmune-mediated AE that does not resolve to grade ≤ 1 or baseline within 30 days of optimal medical management
- Any grade 3 immune-mediated AE, excluding diarrhea/ colitis, pneumonitis, hepatitis, rash, neurotoxicity, myocarditis, myositis/ polymyositis, endocrinopathies and nephritis, which does not resolve to grade ≤ 1 or baseline within 30 days after onset of the event despite optimal medical management, including systemic corticosteroids
- Grade 3 diarrhea or colitis that does not resolve to grade ≤ 1 within 14 days (both immune- and nonimmune-mediated; the same applies if not specified in the remaining bullet points below]
- Grade 3 noninfectious pneumonitis
- Grade 2 noninfectious pneumonitis that does not resolve to grade ≤ 1 within three days of initiation of maximal supportive care
- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) $\geq 5 \times$ ULN or $5 \times$ the baseline, if the baseline is abnormal, with concurrent increase in total bilirubin (TBL) $\geq 3 \times$ ULN or $3 \times$ the baseline, if the baseline is abnormal without evidence of cholestasis or alternative explanations, such as viral hepatitis, disease progression in the liver (i.e., Hy's Law)
- ALT or AST $> 8 \times$ ULN or $8 \times$ the baseline, if the baseline is abnormal, or TBL $> 5 \times$ ULN or $5 \times$ the baseline, if the baseline is abnormal
- Grade 3 immune-mediated rash that does not resolve to grade ≤ 1 or baseline within 30 days

- Grade 2 rash covering >30% BSA that does not resolve to grade ≤ 1 or baseline within 30 days
- Any grade of immune-mediated rash with bullous formation
- Grade 3 immune-mediated neurotoxicity, excluding Guillain–Barre and myasthenia gravis, that does not resolve to grade ≤ 1 within 30 days
- Grade 2 or 3 immune-mediated peripheral neuromotor syndrome, such as Guillain–Barre and myasthenia gravis, that does not resolve to grade ≤ 1 within 30 days or that exhibits signs of respiratory insufficiency or autonomic instability
- Grade 3 immune-mediated myocarditis
- Any symptomatic immune-mediated myocarditis that does not become asymptomatic within three days of initiating optimal medical management, including systemic corticosteroids
- Grade 2 or 3 immune-mediated myositis/ polymyositis that does not resolve to grade ≤ 1 within 30 days of initiating optimal medical management, including systemic corticosteroids, or that exhibits signs of respiratory insufficiency, regardless of optimal medical management
- Immune-mediated increase in creatinine $>3 \times$ ULN or $>3 \times$ the baseline for patients with baseline creatinine that is above the ULN
- Transfusion of red cell concentrate or platelet or use of G-CSF during the DLT period

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5 医師保管用
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同意文書

11 私は、「脈管浸潤を伴う進行肝細胞癌患者を対象としたデュルバルマブ・トレメリムマブと重粒
12 子線治療との併用療法の安全性と有効性を評価する第Ⅰb相臨床試験」に参加するにあたり、以
13 下の内容について説明を受け、十分に理解した上で、自らの自由意思により本治験に参加するこ
14 とに同意します。
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- 治験とは
 - あなたの病気と治療について
 - 治験薬について
 - 重粒子治療について
 - 治験の目的と方法
 - 治験のスケジュール
 - 検体（血液、組織）の保管に関して
 - 治験への参加予定期間と参加いただく人数
 - 試験の参加によって受ける利益
 - 予測される不利益および副作用について
 - 自由意思による治験の参加といつでも同意の撤回
ことができること
 - 治験に参加しない場合の治療
 - 治験参加後の中止について
 - 新たに重要な情報が得られた場合について
 - 治験に関する健康被害の補償について
 - 治験に参加された場合の費用について
 - 医療記録の閲覧と参加者の秘密の保全について
 - 利益相反について
 - 患者さんに守っていただきたいことについて
 - 治験を審査する委員会
 - 治験に関する相談窓口 連絡先

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35 ● 肝生検・肝腫瘍生検を行うことについて（治療開始前／治療開始 42 日以降）

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37 同意します 同意しません

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39 ● 治験終了後に検体を保管することについて

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41 同意します 同意しません

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45 同意日： _____ 年 _____ 月 _____ 日

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55 担当医師 説明日： _____ 年 _____ 月 _____ 日

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59 説明補助者 説明日： _____ 年 _____ 月 _____ 日

署名： _____

病院保管用

同意文書

私は、「脈管浸潤を伴う進行肝細胞癌患者を対象としたデュルバルマブ・トレメリムマブと重粒子線治療との併用療法の安全性と有効性を評価する第Ⅰb相臨床試験」に参加するにあたり、以下の内容について説明を受け、十分に理解した上で、自らの自由意思により本治験に参加することに同意します。

- 治験とは
- あなたの病気と治療について
- 治験薬について
- 重粒子治療について
- 治験の目的と方法
- 治験のスケジュール
- 検体（血液、組織）の保管に関して
- 治験への参加予定期間と参加いただく人数
- 試験の参加によって受ける利益
- 予測される不利益および副作用について
- 自由意思による治験の参加といつでも同意の撤回ができること
- 治験に参加しない場合の治療
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- 治験を審査する委員会
- 治験に関する相談窓口 連絡先

● 肝生検・肝腫瘍生検を行うことについて（治療開始前／治療開始 42 日以降）

同意します 同意しません

● 治験終了後に検体を保管することについて

同意します 同意しません

同意日： _____ 年 _____ 月 _____ 日

本人（署名または記名捺印）： _____

担当医師 説明日： _____ 年 _____ 月 _____ 日 署名： _____

説明補助者 説明日： _____ 年 _____ 月 _____ 日 署名： _____

患者さん保管用

同意文書

私は、「脈管浸潤を伴う進行肝細胞癌患者を対象としたデュルバルマブ・トレメリムマブと重粒子線治療との併用療法の安全性と有効性を評価する第Ⅰb相臨床試験」に参加するにあたり、以下の内容について説明を受け、十分に理解した上で、自らの自由意思により本治験に参加することに同意します。

- 治験とは
- あなたの病気と治療について
- 治験薬について
- 重粒子治療について
- 治験の目的と方法
- 治験のスケジュール
- 検体（血液、組織）の保管に関して
- 治験への参加予定期間と参加いただく人数
- 試験の参加によって受ける利益
- 予測される不利益および副作用について
- 自由意思による治験の参加といつでも同意の撤回ができること
- 治験に参加しない場合の治療
- 治験参加後の中止について
- 新たに重要な情報が得られた場合について
- 治験に関する健康被害の補償について
- 治験に参加された場合の費用について
- 医療記録の閲覧と参加者の秘密の保全について
- 利益相反について
- 患者さんに守っていただきたいことについて
- 治験を審査する委員会
- 治験に関する相談窓口 連絡先

● 肝生検・肝腫瘍生検を行うことについて（治療開始前／治療開始 42 日以降）

同意します 同意しません

● 治験終了後に検体を保管することについて

同意します 同意しません

同意日： _____ 年 _____ 月 _____ 日

本人（署名または記名捺印）： _____

担当医師 説明日： _____ 年 _____ 月 _____ 日 署名： _____

説明補助者 説明日： _____ 年 _____ 月 _____ 日 署名： _____



SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	<u>Page 1, Lines 1–3</u>
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	<u>Page 4, Line 1</u>
	2b	All items from the World Health Organization Trial Registration Data Set	<u>Page 1–20 (see Page 4, Line 1, jRCT2031210046)</u>
Protocol version	3	Date and version identifier	<u>Page 7, Line 24</u>
Funding	4	Sources and types of financial, material, and other support	<u>Page 9, Lines 6–8, Page 15, Lines 1–2</u>
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	<u>Page 1, Page 14, Lines 16–20</u>
	5b	Name and contact information for the trial sponsor	<u>Page 2, Lines 1–2</u>
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	<u>Page 9, Lines 6–8, Page 14, Lines 22–24</u>

1		5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	<u>Page 13, Line 5–14</u>
2				
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9	Introduction			
10				
11	Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	<u>Page 5, Line 1–7, Line 20</u>
12				
13		6b	Explanation for choice of comparators	<u>Page 8, Lines 18–22</u>
14				
15				
16	Objectives	7	Specific objectives or hypotheses	<u>Page 7, Line 26, Page 8, Lines 1–3</u>
17				
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20				
21	Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	<u>Page 8, Lines 18–22</u>
22				
23				
24				
25	Methods: Participants, interventions, and outcomes			
26				
27	Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	<u>Page 8, Lines 17–22</u>
28				
29				
30	Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	<u>Page 9, Line 16–Page 10, Line 1–22</u>
31				
32				
33	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	<u>Page 10, Line 24–26, Page 11, Lines 1–19</u>
34				
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38		11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	<u>Page 12, Lines 5–6 (suppl. Table 2)</u>
39				
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1		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	<u>Page 13, Lines 5–9</u>
2				
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4		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	<u>Page 11 Lines</u>
5				<u>13–14 (suppl.</u>
6				<u>Table 1)</u>
7				
8	Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	<u>Page 8, Lines 1–3,</u> <u>Page 12, Lines</u> <u>21–26, Page 13,</u> <u>Lines 1–3</u>
9				
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14	Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	<u>Page 20, Line 5</u> <u>(Figure 2.)</u>
15				
16				
17	Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	<u>Page 12, Lines</u> <u>25–26</u>
18				
19				
20	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	<u>Page 12, Lines</u> <u>24–25</u>
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Methods: Assignment of interventions (for controlled trials)

Allocation:

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28	Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	<u>Page 8, Lines 14–</u> <u>19</u>
29				
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34	Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	<u>Page 8, Lines 14–</u> <u>19</u>
35				
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38	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	<u>Page 8, Lines 14–</u> <u>19</u>
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1	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	<u>Page 8, Lines 14–19</u>
2				
3				
4		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	<u>Page 8, Lines 14–19</u>
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8 **Methods: Data collection, management, and analysis**

9				
10	Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	<u>Page 13, Lines 5–9</u>
11				
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15		18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	<u>Page 13, Lines 5–9</u>
16				
17				
18	Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	<u>Page 13, Lines 5–9</u>
19				
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23	Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	<u>Page 12, Lines 21–26, Page 13, Lines 1–3</u>
24				
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28		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	<u>Page 12, Lines 21–26, Page 13, Lines 1–3</u>
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32		20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	<u>Page 12, Lines 21–26, Page 13, Lines 1–3</u>
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37 **Methods: Monitoring**

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1	Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	Page 13, Line 5–9
2				
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6		21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	Page 13 Line 3
7				
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9	Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	Page 11, Lines 14–17
10				
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13	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Page 13, Lines 5–9
14				
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16				
17	Ethics and dissemination			
18	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	Page 13, Lines 22–25
19				
20				
21	Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	Page 14, Lines 1–2
22				
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26	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	Page 13, Lines 21–22
27				
28				
29		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Page 9, Lines 2–4
30				
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32	Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	Page 13, Lines 5–9
33				
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36	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Page 14, Line 25–26, Page 15, Lines 1–3
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1	Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	<u>Page 14, Lines 6–9</u>
2				
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4	Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	<u>Page 11, Lines 16–17</u>
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7	Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, health care professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	<u>Page 13, Line 26, Page 14, Lines 1–4</u>
8				
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11		31b	Authorship eligibility guidelines and any intended use of professional writers	<u>Page 14, Lines 2–4</u>
12				
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15		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	<u>Page 14, Lines 6–9</u>
16				
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19	Appendices			
20	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	<u>Consent form (uploaded)</u>
21				
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23	Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	<u>Page 9, Lines 2–4</u>
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27 *It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items.
 28 Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons
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