BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-059779
Article Type:	Protocol
Date Submitted by the Author:	01-Dec-2021
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Keywords:	Hepatobiliary tumours < ONCOLOGY, Radiation oncology < RADIOLOGY & IMAGING, Hepatology < INTERNAL MEDICINE

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

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Word count: 3982 words

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

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

Focusing on the disease state of advanced HCC, variations of disease progression can be divided into macrovascular invasion (MVI), which is unique to HCC, and extrahepatic metastasis, as in other malignant tumors [20]. The presence of MVI is known to be an extremely poor prognostic factor that leads not only to progressive malignant disease severity but also to deterioration of liver function. Surgical resection of tumors that include MVI and local control of MVI by transarterial chemoembolization, hepatic arterial infusion chemotherapy, or radiation therapy had been previously reported to improve the prognosis of patients with advanced HCC with MVI [20-26]. However, these treatment strategies have not become common because of several reasons. First, in the majority of cases in which MVI is present, the tumor is not localized and metastatic lesions have often spread to both the liver and extrahepatic organs. Second, the procedures to remove or control MVI require sufficient skill and experience. In addition, all treatments that attempt to remove or control MVI are highly invasive and require extremely well maintained liver function and general performance status. Development of innovative treatments that target this specific phenotype of advanced HCC is imperative.

While radiotherapy for HCC has been mostly used in a palliative intent, with the emergence of particle therapy followed by stereotactic body radiotherapy (SBRT), it has become a viable treatment option for those not eligible for resection, transplant or radio frequency ablation but still with a localized disease [27-29]. Compared to conventional photon radiotherapy and SBRT, particle radiation therapy, which includes both proton

beam therapy and carbon ion radiation therapy (C-ion RT), has been demonstrated to confer a unique dose distribution; its physical characteristics enable delivery of high radiation doses to the tumor and low doses to normal tissues [30]. Compared with photons, charged particles have different depth–dose distributions and deposit majority of the dose at the Bragg peak, with little to no exit dose, thereby, resulting in superior sparing of normal tissue. One particular advantage of particle radiation therapy for HCC is that irradiation can be confined to a localized area of tumor; this results in both high local control and minimal impact on liver function [31]. Several reports have already confirmed the high local control rates and safety profile of both proton beam therapy and C-ion RT for HCC [29, 32]. Moreover, the possibility of local control of MVI in advanced HCC by particle radiation therapy has been suggested [33].

Radiation therapy, especially C-ion RT, is well known to mediate localized tumor killing and tumor microenvironment modification, thereby, potentiating the effectiveness of immune checkpoint inhibitors [34-36]. Because the combination of radiation and immune checkpoint inhibitors is expected to be a promising treatment, its impact on several advanced cancers is still being tested. With its powerful potential of local tumor control, immunosuppression, and immunogenicity, C-ion RT in combination with immune checkpoint inhibitors may lead to further breakthroughs for patients with advanced HCC and MVI (Figure 1).

METHODS AND ANALYSIS

Study design

Protocol version 1.2, modified April 20, 2021

Objective of the potential trial

The aim of this study is to investigate the safety and synergistic effect of durvalumab with

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 coinfected 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 durvalumab plus tremelimumab on day 1. The dose is 60 Gy (relative biologic effectiveness) in four fractions per week. The target lesion of the particle therapy will be focused on an intrahepatic nodule with MVI. The clinical target volume margin will be 1 cm for the feeding nodule and 2 cm alongside the vessel for the MVI lesion. Internal motion will be compensated according to 4D-CT movement assessment. Interfractional margin will be set at 3 mm and combined with internal motion compensation to form a field-specific planning treatment volume. Study treatments will continue until disease progression, according to RECIST ver. 1.1.

Patient registration rules

In this modified 3 + 3 design, three patients are initially enrolled into cohort A (Figure 3). If there is no DLT observed in any of the subjects, the trial proceeds to enrol additional subjects into cohort B. If one subject in either cohort develops a DLT, three additional subjects are enrolled into that same cohort. If cohort B treatment is confirmed to be tolerated (i.e., no DLT in three patients or one DLT in six patients), enrollment of up to a total of 15 subjects to cohort B is continued. Development of DLTs in at least two subjects in cohort A will mean that the entire trial will be terminated. Occurrence of DLTs in at least two subjects in cohort B would suggest that tolerability is not confirmed, and the regimen of cohort B will be discontinued. In this case, additional patients up to a total of 15 will be enrolled in cohort A.

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). Patients who do not remain in the study up to this time for reasons other than DLT will be replaced with another

patient 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 1. 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 (Suppl. Table 1).

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. 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.

Patient and Public Involvement statement

Patients and/or the public were not involved in the design, or conduct, or reporting or dissemination plans of this research.

ETHICS AND DISSEMINATION

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

The results of the DEPARTURE trial may help provide the basis for

development of durvalumab ± tremelimumab combined with particle therapy in patients with advanced HCC and MVI. This new innovative treatment based on the synergistic effect of combined immunotherapy and particle therapy can be a breakthrough for advanced HCC with MVI, which is the phenotype with the worst prognosis.

Acknowledgments

The authors are grateful to the following people for their contributions to the data management: Satomi Nakamura, Ryoko Arai, and Yuka Iwase.

Authors' contributions

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

Funding statement

This work was supported by Astra Zeneca K.K. (Osaka, Japan) grant number [ESR-19-20168].

Competing interests

SO received honoraria from Bayer, Eisai, Eli Lilly, and Chugai Pharma and research funding from Bayer, Eisai, Eli Lilly, and Astra Zeneca. NK 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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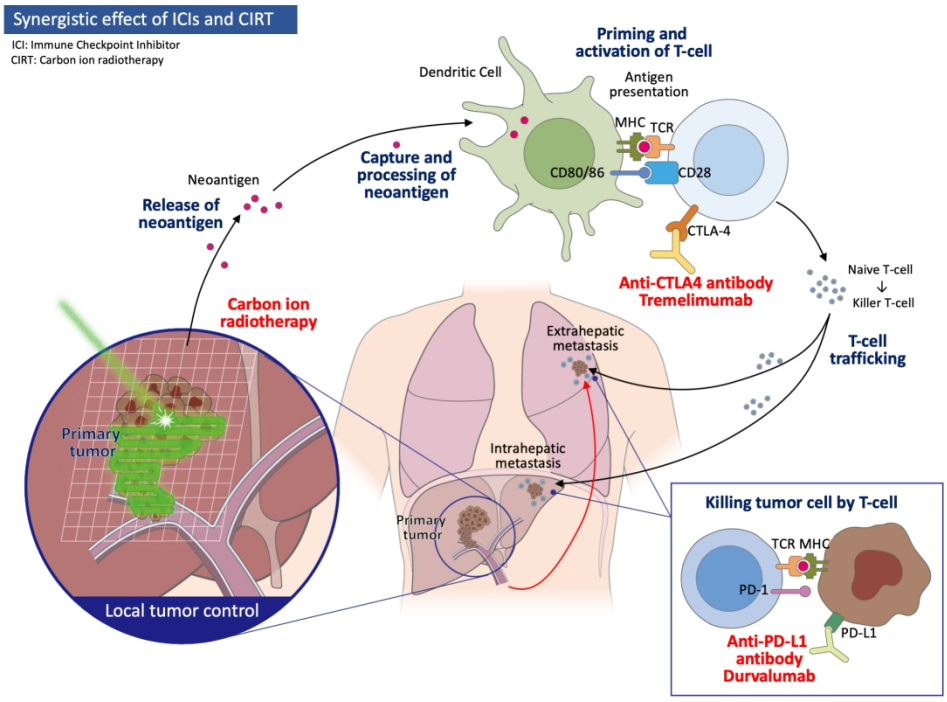
Figure Legends

Figure 1. The concept of the study.

Figure 2. Dosing schedule of the study.

Figure 3. Schematic depiction of modified 3+3 design

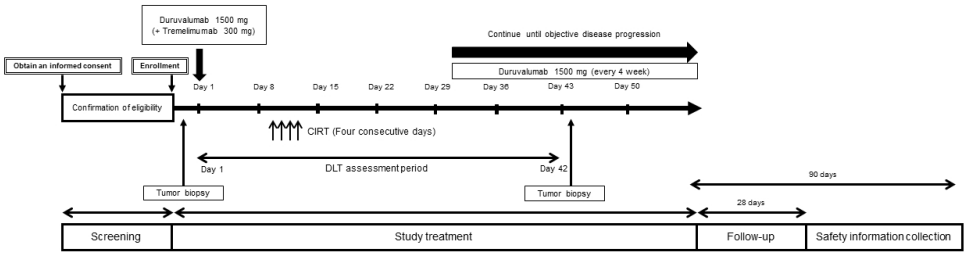
Figure 1. Ogasawara et al.



The concept of the study.

793x677mm (72 x 72 DPI)

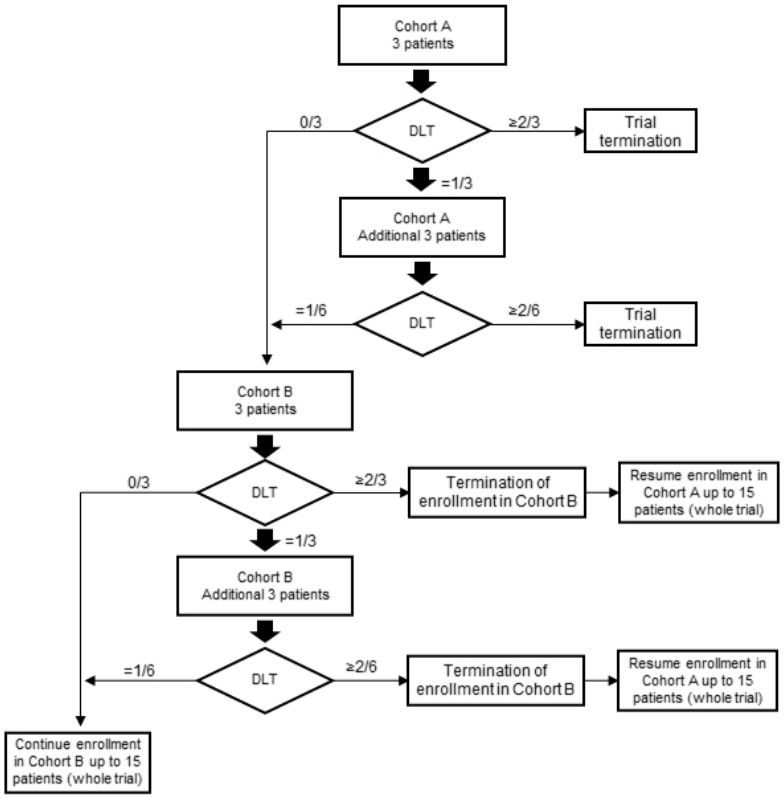
Figure 2. Ogasawara et al.



Dosing schedule of the study.

338x190mm (96 x 96 DPI)

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) ≥5 × ULN or 5× the baseline, if the baseline is abnormal, with concurrent increase in total bilirubin (TBL) ≥3 × ULN or 3× 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 × ULN or 8× the baseline, if the baseline is abnormal, or TBL >5 × ULN or 5× 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 × ULN or >3 × 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

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-059779.R1
Article Type:	Protocol
Date Submitted by the Author:	10-Mar-2022
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Primary Subject Heading:	Oncology
Secondary Subject Heading:	Immunology (including allergy)
Keywords:	Hepatobiliary tumours < ONCOLOGY, Radiation oncology < RADIOLOGY & IMAGING, Hepatology < INTERNAL MEDICINE

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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Word count: 4390 words

ABSTRACT

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

Methods and analysis: This phase Ib, multicenter (two sites in Japan), open-label, single-arm, investigator-initiated clinical trial will assess 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. Cohort A will receive 1,500 mg durvalumab every four weeks. 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 (C-ion RT) will be administered after day 8 of the first cycle. The primary endpoints are rates of any and severe adverse events, including DLTs; secondary endpoints are overall survival, six-month survival, objective response, six-month progression-free survival, and time to progression. Patients are initially enrolled into cohort A. If cohort A treatment is confirmed to be tolerated (i.e., no DLT in three patients or one DLT in six patients), the trial proceeds to enroll more patients into cohort B. Similarly, if cohort B treatment is confirmed to be tolerated (i.e.,

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 multicenre, investigator-initated 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

other arms, such as durvalumab alone, tremelimumab alone, and 75 mg of tremelimumab for four doses with durvalumab every four weeks (T75 + D), this phase II study demonstrated acceptable safety profiles and no new adverse events. Very recently, the results of a phase III trial (HIMALAYA trial) reported durvalumab plus tremelimumab significantly prolonged OS compared with sorafenib [19].

Focusing on the disease state of advanced HCC, variations of disease progression can be divided into macrovascular invasion (MVI), which is unique to HCC, and extrahepatic metastasis, as in other malignant tumors [20]. The presence of MVI is known to be an extremely poor prognostic factor that leads not only to progressive malignant disease severity but also to deterioration of liver function. Surgical resection of tumors that include MVI and local control of MVI by transarterial chemoembolization, hepatic arterial infusion chemotherapy, or radiation therapy had been previously reported to improve the prognosis of patients with advanced HCC with MVI [20-26]. However, these treatment strategies have not become common because of several reasons. First, in the majority of cases in which MVI is present, the tumor is not localized and metastatic lesions have often spread to both the liver and extrahepatic organs. Second, the procedures to remove or control MVI require sufficient skill and experience. In addition, all treatments that attempt to remove or control MVI are highly invasive and require extremely well maintained liver function and general performance status. Development of innovative treatments that target this specific phenotype of advanced HCC is imperative.

While radiotherapy for HCC has been mostly used in a palliative intent, with the emergence of particle therapy followed by stereotactic body radiotherapy (SBRT), it has become a viable treatment option for those not eligible for resection, transplant or radio frequency ablation but still with a localized disease [27-29]. Compared to conventional photon radiotherapy and SBRT, particle radiation therapy, which includes both proton

beam therapy and carbon-ion radiation therapy (C-ion RT), has been demonstrated to confer a unique dose distribution; its physical characteristics enable delivery of high radiation doses to the tumor and low doses to normal tissues [30]. Compared with photons, charged particles have different depth–dose distributions and deposit majority of the dose at the Bragg peak, with little to no exit dose, thereby, resulting in superior sparing of normal tissue. One particular advantage of particle radiation therapy for HCC is that irradiation can be confined to a localized area of tumor; this results in both high local control and minimal impact on liver function [31]. Several reports have already confirmed the high local control rates and safety profile of both proton beam therapy and C-ion RT for HCC [29, 32]. Moreover, the possibility of local control of MVI in advanced HCC by particle radiation therapy has been suggested [33].

Radiation therapy, especially C-ion RT, is well known to mediate localized tumor killing and tumor microenvironment modification, thereby, potentiating the effectiveness of ICIs [34-36]. Because the combination of radiation and ICIs is expected to be a promising treatment, its impact on several advanced cancers is still being tested. In advanced HCC, several combination immunotherapies based on ICI are further developed [37]. Among various treatments currently under development, we believe that C-ion RT combined with ICIs may lead to further breakthroughs for patients with advanced HCC and MVI using its powerful potential of local tumor control, immunosuppression, and immunogenicity (Figure 1).

METHODS AND ANALYSIS

Objective

The aim of this study is to investigate the safety and synergistic effect of durvalumab with 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 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 additonal 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 coinfected 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

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

Patient registration rules

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

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

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

Data monitoring committee

The data monitoring committee consists of clinical trial experts, including biostatisticians, who are not involved in this study. The committee will check data obtained from the trial and evaluate the treatment cohort.

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting or dissemination plans of this research.

ETHICS AND DISSEMINATION

This study was approved by the ethics committee of 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]). All patients are required to give written informed consent to a member of the study team before inclusion in the DEPARTURE trial (supplementary file).

If the protocol is revised, the primary investigator will inform the trial team and obtain the institutional review board's approval.

We will submit the trial results as the case study report on the Japan Registry of Clinical Trials. Trial results will be reported in a peer-reviewed journal publication. The

authorship will be ascribed following the International Committee of Medical Journal Editors guidelines.

Protocol version

Protocol version 1.2, modified April 20, 2021.

Study status

The first subject of this study enrolled on 6th July, 2021. The study is ongoing.

Data availability statement

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

Acknowledgments

The authors are grateful to the following people for their contributions to the data management: Satomi Nakamura, Ryoko Arai, and Yuka Iwase.

Contributors

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

Funding

This work was supported by AstraZeneca K.K. (Osaka, Japan; grant number ESR-19-

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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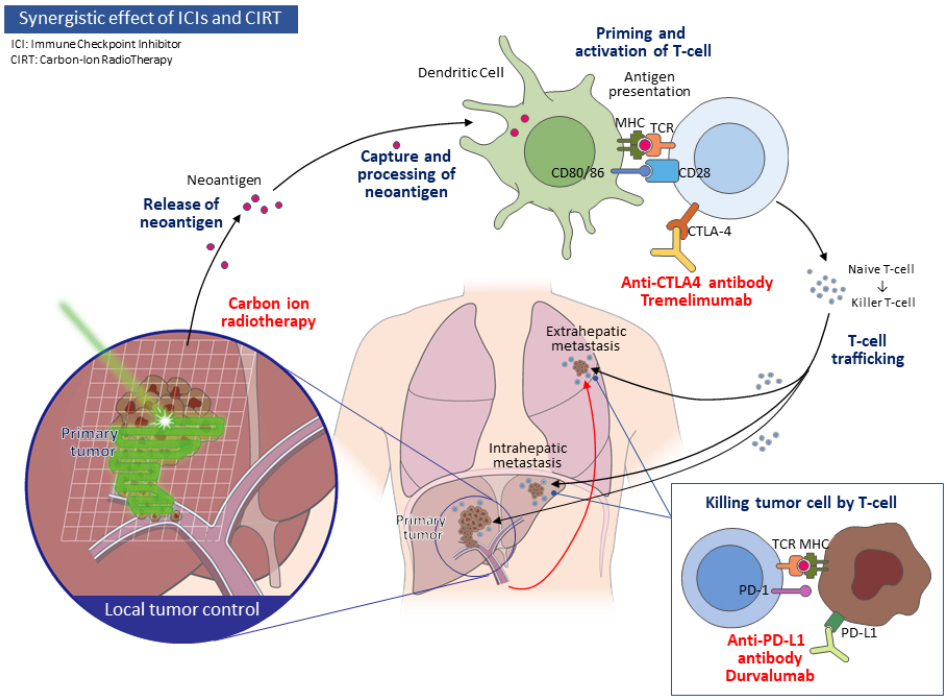
Figure Titles

Figure 1. Study concept

Figure 2. Dosing schedule

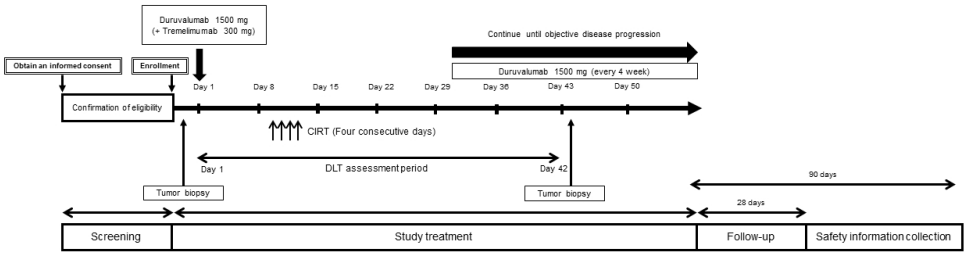
Figure 3. Schematic depiction of modified 3+3 design



The concept of the study

254x190mm (96 x 96 DPI)

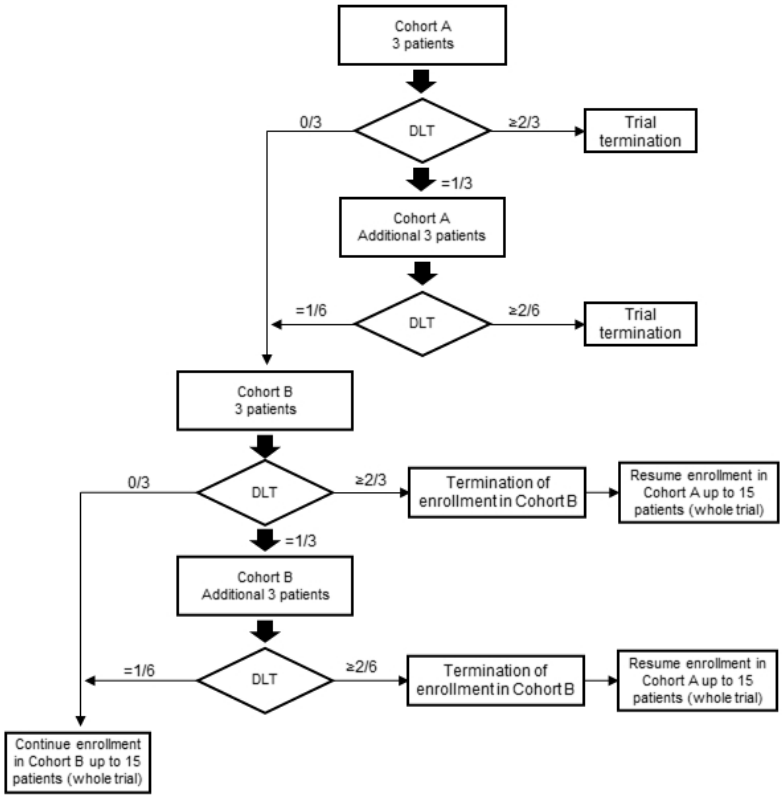
Figure 2. Ogasawara et al.



Dosing schedule of the study.

338x190mm (96 x 96 DPI)

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: • 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 1st 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) ≥5 × ULN or 5× the baseline, if the baseline is abnormal, with concurrent increase in total bilirubin (TBL) ≥3 × ULN or 3× 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 × ULN or 8× the baseline, if the baseline is abnormal, or TBL >5 × ULN or 5× 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 × ULN or >3 × 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

治験実施計画書番号：CCRC2002
作成日：2021 年 5 月 6 日第 1.1 版

医師保管用

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
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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：

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患者さん保管用

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SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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	Page 1, Lines1–3
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	Page 4, Line 1
	2b	All items from the World Health Organization Trial Registration Data Set	Page 1–20 (see Page 4, Line 1, jRCT2031210046)
Protocol version	3	Date and version identifier	Page 7, Line 24
Funding	4	Sources and types of financial, material, and other support	Page 9, Lines6–8, Page 15, Lines 1–2
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Page 1, Page 14, Lines 16–20
	5b	Name and contact information for the trial sponsor	Page 2, Lines 1–2
	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	Page 9, Lines 6–8, Page 14, Lines 22–24

	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)	Page 13, Line 5–14
Introduction			
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	Page 5, Line 1–Page7, Line 20
	6b	Explanation for choice of comparators	Page 8, Lines 18–22
Objectives	7	Specific objectives or hypotheses	Page 7, Line26, Page8, Lines 1–3
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)	Page 8, Lines 18–22
Methods: Participants, interventions, and outcomes			
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	Page 8, Lines 17–22
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)	Page 9, Line 16–Page10, Line 1–22
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Page 10, Line 24–26, Page 11, Lines 1–19
	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)	Page 12, Lines 5–6 (suppl. Table 2)

	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	Page13, Lines 5–9
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Page 11_Lines 13–14 (suppl. Table 1)
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	Page 8, Lines 1–3, Page 12, Lines 21–26, Page 13, Lines 1–3
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)	Page 20, Line 5 (Figure 2.)
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	Page 12, Lines 25–26
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	Page 12, Lines 24–25
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
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	Page 8, Lines 14–19
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	Page 8, Lines 14–19
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Page 8, Lines 14–19

Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	Page 8, Lines 14–19
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	Page 8, Lines 14–19
Methods: Data collection, management, and analysis			
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	Page 13, Lines 5–9
	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	Page 13, Lines 5–9
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	Page 13, Lines 5–9
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	Page 12, Lines 21–26, Page 13, Lines 1–3
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	Page 12, Lines 21–26, Page 13, Lines 1–3
	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)	Page 12, Lines 21–26, Page 13, Lines 1–3
Methods: Monitoring			

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
	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
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
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
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	Page 13, Lines 22–25
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, Lines1–2
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
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Page 9, Lines 2–4
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
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, Page15, Lines 1–3

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	Page 14, Lines 6–9
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	Page 11, Lines 16–17
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	Page 13, Line 26, Page 14, Lines 1–4
	31b	Authorship eligibility guidelines and any intended use of professional writers	Page 14, Lines 2–4
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Page 14, Lines 6–9
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Consent form (uploaded)
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	Page 9, Lines 2–4

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.