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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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ABSTRACT

Introduction Advanced hepatocellular carcinoma (HCC) with macrovascular invasion (MVI) has the worst prognosis among all phenotypes. This 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, multicentre (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 1500 mg durvalumab every 4 weeks. Cohort B will receive 1500 mg durvalumab every 4 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 primary endpoints are rates of any and severe adverse events, including dose-limiting toxicities (DLTs); secondary endpoints are overall survival, 6-month survival, objective response, 6-month progression-free survival and time to progression. Patients are initially enrolled into cohort A. If cohort A treatment is confirmed to be tolerated (ie, no DLT in three patients or one DLT in six patients), the trial proceeds to enrol more patients into cohort B. Similarly, if cohort B treatment is confirmed to be tolerated (ie, 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 Institutes for Quantum (approval number: 2020040) and Radiological Science and Technology, QST Hospital (approval number: 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 jRCT2031210046.

Strengths and limitations of this study

- This 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

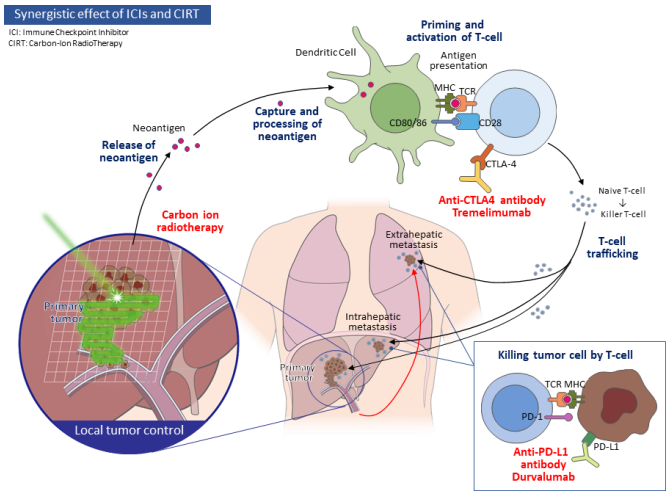

Figure 1 Study concept.

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 randomised 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 antitumour activity through its action on the antitumour 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 4 weeks (ie, 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 4 weeks (T75+D), this phase II study demonstrated acceptable safety profiles and no new adverse events (AE). Very recently, the results of a phase III trial (A Randomized, Open-label, Multi-center Phase III Study of Durvalumab and Tremelimumab as First-line Treatment in Patients with advanced Hepatocellular Carcinoma [HIMALAYA]) reported durvalumab plus tremelimumab significantly prolonged OS compared with sorafenib.[19]

Box 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.

AE, adverse event; SAE, severe adverse event; DLT, dose-limiting toxicity.

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 tumours.[20] The presence of MVI is known to be an extremely poor prognostic factor that leads to progressive malignant disease severity and to deterioration of liver function. Surgical resection of tumours that include MVI and local control of MVI by transarterial chemoembolisation, 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 tumour is not localised 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 localised disease.[27–29] Compared with conventional photon radiotherapy and SBRT, particle radiation therapy, which includes both proton beam therapy and carbon-ion radiotherapy (C-ion RT), has been demonstrated to confer a unique dose distribution; its physical characteristics enable delivery of high radiation doses to the tumour 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 localised area of tumour; 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

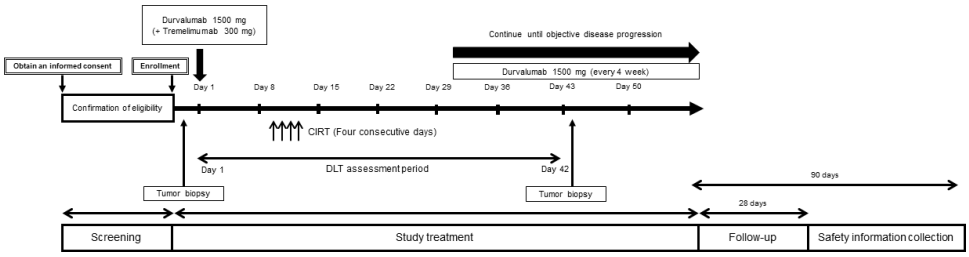

Figure 2 Dosing schedule. DLT, dose-limiting toxicity. CIRT, carbon-ion radiotherapy

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 localised tumour killing and tumour 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 tumour 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 (box 1).

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 Institutes 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 enrolment 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 4 weeks until clinical progression (ie, durvalumab q4W dosing period). In subjects who provide additional written informed consent, biopsy specimens will be obtained from the same liver tumour 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 box 2.

Treatment regimen

In cohort A, durvalumab 1500 mg will be administered every 4 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 1500 mg will be administered every 4 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 biological 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 Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Prohibited concomitant treatments are described in the online supplemental table 1. Information on AEs 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 enrol more

Box 2 Key eligibility criteria

Inclusion criteria

- Age ≥20 years at the time of study entry.
- Eastern Cooperative Oncology Group performance status of 0 or 1.
- Body weight >30 kg.
- Adequately normal organ and marrow functions.
- Life expectancy of at least 12 weeks.
- Advanced HCC confirmed histologically or by the typical findings of a hypervascular tumour on CT or angiography.
- Must not be eligible for locoregional therapy for unresectable HCC.
- Child-Pugh A.
- Patients who have been diagnosed with HCC with macrovascular invasion.
- 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

- 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.
- Radiotherapy treatment to more than 30% of the bone marrow or with a wide field of radiation within 4 weeks of the first dose of the study drug.
- Major surgical procedure, as defined by the investigator, within 28 days prior to the first dose of IP.
- History of allogenic organ transplantation.
- Active or prior documented autoimmune or inflammatory disorders.
- History of another primary malignancy.
- Prior or current brain metastases or spinal cord compression.
- History of active primary immunodeficiency.
- Patients coinfected with hepatitis B and C viruses or with hepatitis B and D viruses.
- Current or prior use of immunosuppressive medication within 14 days before the first dose of durvalumab or tremelimumab.
- Known allergy or hypersensitivity to any of the study drugs or any of the study drug excipients.
- Prior radiotherapy involving the liver.
- Renal failure requiring haemodialysis or peritoneal dialysis.
- Presence of any severe cardiac disease.
- Poorly controlled hypertension.
- Serious and active infection, excluding hepatitis virus infection.
- 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.
- Arterial or venous thrombotic or embolic events, such as cerebrovascular accident, deep vein thrombosis or pulmonary embolism within 6 months before the start of the study medication.
- Refractory pleural effusion or ascites.
- History of hepatic encephalopathy within the past 12 months.

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

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 six subjects in either cohort suggests that the regimen is not tolerable. If cohort A turns out to be intolerable, then cohort

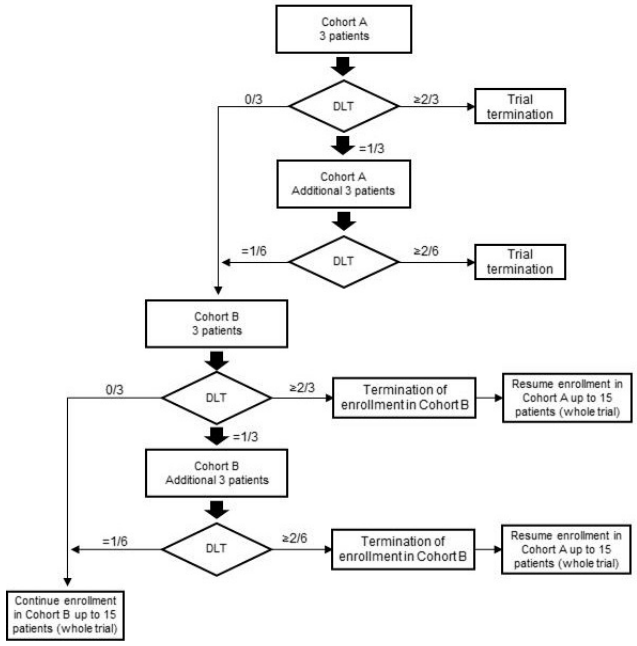

Figure 3 Schematic depiction of modified 3+3 design. DLT, dose-limiting toxicity.

B regimen will not be pursued. If cohort B treatment is confirmed to be tolerated (ie, no DLT in three patients or one DLT in six patients), enrolment 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 online supplemental table 2.

Definition of DLT

DLT will be evaluated during the assessment period of the trial (ie, 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 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 online supplemental 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 enrolment 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, 6-month survival rate, objective response rate, 6-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 the 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 the 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 Institutes for Quantum (approval number: 2020040) and Radiological Science and Technology, QST Hospital (approval number: C20-001)). All patients are required to give written informed consent to a member of the study team before inclusion in a phase Ib study of durvalumab with or without tremelimumab combined with particle therapy in advanced hepatocellular carcinoma patients with macrovascular invasion (DEPARTURE trial) (online supplemental 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 2021.

Study status

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

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

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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.

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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

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医師保管用

同 意 文 書

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□　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

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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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