Phase Ib study of durvalumab (MEDI4736) in combination with carbon-ion radiotherapy and weekly cisplatin for patients with locally advanced cervical cancer (DECISION study): study protocol for a prospective open-label single-arm study

Noriyuki Okonogi, Hirokazu Usui, Kazutoshi Murata, Makoto Hori, Tomoya Kurokawa, Tadami Fujiwara, Yasuhsa Fuji, Michiko Hanawa, Yohei Kawasaki, Yoko Hattori, Kazuko Suzuki, Kyoko Tsuyuki, Masaru Wakatsuki, Sumitaka Hasegawa, Shigeru Yamada, Hideki Hanaoka, Makio Shozu, Hiroshi Tsuji

ABSTRACT

Introduction Concurrent chemoradiotherapy is considered the standard treatment strategy for locally advanced cervical cancer. Most recent reports indicate that patients with bulky tumours or adenocarcinoma subtypes have poorer local control. Carbon-ion radiotherapy (CIRT) with the concurrent use of chemotherapy has shown promising results in such cases of difficult-to-treat uterine cervical cancer. Programmed death-ligand 1 (PD-L1) upregulation was observed in tumour tissue samples from patients who had undergone CIRT. Thus, a combination of CIRT and anti-PD-L1 antibody may suppress metastasis by activating antitumour immune response, in addition to exhibiting strong local effects.

Objective We will assess the safety and tolerability (primary endpoint) of the concomitant use of durvalumab, an anti-PD-L1 antibody, with CIRT and weekly cisplatin for locally advanced cervical cancer.

Methods and analysis This study is a non-randomised, open-label, prospective phase Ib study. Up to 10 patients with histologically proven uterine cervical cancer at stage IIB, IIIA, IIIB, IIIC1 or IVA as per International Federation of Gynecology and Obstetrics (2018) staging will be enrolled. All patients will receive CIRT of 74.4 Gy relative biological effectiveness in 20 fractions over 5 weeks (four fractions per week). Weekly cisplatin at a dose of 40 mg/m² will be administered up to five times. Durvalumab at a dose of 1500 mg/bod will be administered at weeks 2 and 6. Safety and tolerability will be evaluated based on the frequency of dose-limiting toxicities until 92 days after CIRT starts. Patients will be followed-up strictly as per the scheduled protocol for 1 year after CIRT initiation.

Ethics and dissemination The Human Research Ethics Committees of QST Hospital (#2021-002) and Chiba University (#2021006) have approved this study protocol.

Strengths and limitations of this study

- The strength of this study is the concurrent use of carbon-ion radiotherapy, weekly cisplatin and durvalumab.
- Biopsies of the tumour tissue and blood samples will be collected and correlated with the clinical results to identify useful biomarkers.
- A primary limitation of this study is the small number of patients.
- Other limitations include possible bias on the basis of good performance status and that study will be performed in a single country.

The findings will be published in peer-reviewed journals and presented at scientific conferences.

Trial registration number Japan Registry of Clinical Trials (jRCT2031210083), registered on 12 May 2021.

INTRODUCTION

Standard care for cervical cancer

Cervical cancer continues to be one of the most common cancers among women. It is estimated that annually approximately 604,000 new cases of cervical cancer are reported, and 341,000 people die from this disease annually worldwide. Radiation therapy (RT) plays a critical role in the treatment of cervical cancer. According to National Comprehensive Cancer Network guidelines, RT/concurrent chemo-RT (CCRT) is the standard of care, except for stage IA disease.
size is thought to be a significant prognostic factor in RT/CCRT for cervical cancer. Toita et al reported a decrease in local control (LC) and survival in patients with larger tumour diameters following CCRT. In this clinical trial, the 2-year pelvic control rates at tumour diameters 5–7 cm and ≥7 cm were 72% and 54%, respectively. A similar tendency was found in a study by Parker et al; the 5-year LC rate for patients with a tumour >6 cm was 47.7%. Therefore, improving the LC rates for cervical squamous cell carcinomas with large tumour sizes is an unsolved issue. In addition, a large tumour size is known to be a significant predictive factor for distant metastases. Adenocarcinoma of the uterine cervix is known to be less radiosensitive than cervical squamous cell carcinomas. Previous studies have shown that 5-fluorouracil (5-FU) is effective in treating cervical squamous cell carcinomas with large tumour sizes.4,6 Adenocarcinoma of the uterine cervix is known to be a significant predictive factor for distant metastases. In addition, a large tumour size is known to be a significant predictive factor for distant metastases.

Adenocarcinoma of the uterine cervix is known to be less radiosensitive than cervical squamous cell carcinoma. Previous studies have shown that 5-year LC rates of patients who received CCRT for adenocarcinoma of the uterine cervix were 36%–58%, and distant metastases were frequently observed.7-9 With recent advancements in RT, RT including three-dimensional image-guided brachytherapy (3D-IGBT) has become an essential strategy for cervical cancer treatment.10-11 Recent studies on 3D-IGBT have shown favourable clinical outcomes in cervical cancer.12,13 However, more recent reports indicate that patients with bulky tumours or adenocarcinomas have poorer LC even if 3D-IGBT is applied.14-17 Therefore, new therapeutic strategies are required for bulky adenocarcinoma of the uterine cervix.

**Carbon-ion radiotherapy for cervical cancer**

Carbon-ion RT (CIRT) possesses biological advantages over standard photon beam therapy,18,19 and has become the first-line treatment for several types of malignant diseases in recent years in Japan. In the previous decades, we have investigated the significance of CIRT for cervical cancer without the use of brachytherapy and have reported a 5-year LC of 70.0% for cervical squamous cell carcinoma even in patients with a tumour diameter >6 cm.20 Regarding adenocarcinoma of the uterine cervix, Wakatsuki et al reported that CIRT was associated with a 5-year LC of 55%.21 Recently, we reported the significance of the concurrent use of cisplatin in CIRT for locally advanced adenocarcinoma of the uterine cervix by propensity score-matched analysis.22 In that study, the administration of 74.4 Gy (relative biological effectiveness (RBE)) in 20 fractions of CIRT and the concurrent use of weekly cisplatin at a dose of 40 mg/m2 resulted in improved overall survival (OS) and distant metastasis-free rates compared with CIRT alone. The results of CIRT for cervical cancer were assessed in a systematic review, and CIRT for uterine cervical cancer was evaluated as safe, effective and feasible.23 However, distant metastasis was observed even when concurrent chemo-CIRT was administered. Thus, to improve the clinical outcomes of difficult-to-treat uterine cervical cancer such as bulky tumours or adenocarcinomas, a new strategy to prevent distant metastasis is required.

**The role of PD-1/PD-L1 and its inhibition**

Cancers are recognised by the immune system and are thought that the immune system may control or even eliminate tumours.24 Programmed death-ligand 1 (PD-L1) is part of a complex system of receptors and ligands that are involved in controlling T-cell activation. The programmed death-1 (PD-1) receptor is expressed on the surface of activated T cells.25 It has two known ligands, PD-L1 and PD-L2.26 PD-1 and PD-L1/PD-L2 belong to a family of immune checkpoint proteins that act as coinhibitory factors which can halt or limit the development of T-cell responses. When PD-L1 binds to PD-1, an inhibitory signal is transmitted into the T cell, and leads to reduced cytokine production and suppressed T-cell proliferation. Tumour cells exploit this immune checkpoint pathway as a mechanism to evade detection and inhibit immune responses.

The blockade of PD-L1/PD-1 and PD-L1/CD80 interactions releases the inhibition of immune responses, including those that may result in tumour elimination. In vitro studies have demonstrated that durvalumab (an anti-PD-L1 antibody) antagonises the inhibitory effect of PD-L1 on primary human T cells, restoring the production of IFN-γ.27 In vivo studies have shown that durvalumab inhibits tumour growth in xenograft models via a T-cell-dependent mechanism.27 These data imply that durvalumab can stimulate the patient's antitumour responses.

**Figure 1** The design of the present study. An overall outline of this clinical trial is presented. Written informed consent was obtained from patients at both hospitals. C-ion RT, carbon-ion radiotherapy; DLT, dose-limiting toxicity; RBE, relative biological effectiveness.
immune response by binding to PD-L1 and shifting the balance toward an antitumour response. Durvalumab was engineered to reduce antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity.

**Box 1 List of dose-limiting toxicities**

**Haematologic toxicity:**
- Grade ≥3 neutropenia complicated by fever ≥38.3°C.
- Grade 4 neutropenia (≥7 days).
- Grade ≥3 thrombocytopenia with significant bleeding.
- Grade 4 thrombocytopenia (regardless of duration).
- Grade 4 anaemia (regardless of duration).

**Non-haematologic toxicity:**
- Any Grade 4 non-immune-mediated adverse event (AE).
- Any Grade 4 immune-mediated AE, excluding endocrinopathies.
- Any Grade 3 non-immune-mediated AE that does not resolve to ≤Grade 1 one or baseline within 30 days with optimal medical management.
- Any Grade 3 immune-mediated AE – excluding diarrhoea/colitis, pneumonitis, hepatitis, rash, neurotoxicity, myocarditis, myositis/polymyositis, endocrinopathies and nephritis – that 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 diarrhoea or colitis that does not resolve to ≤Grade 1 within 14 days.
- (both immune-mediated and non-immune-mediated indicated here; the same is the case if not specified in remaining bullet points below)
- Grade 3 non-infectious pneumonitis.
- Grade 2 non-infectious pneumonitis that does not resolve to ≤Grade 1 within 3 days days of the initiation of maximal supportive care.
- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥3×upper limit of normal (ULN) with concurrent increase in total bilirubin (TBL) ≥2×ULN without evidence of cholestasis or alternative explanations (eg, viral hepatitis, disease progression in the liver, ie, ‘Hy’s Law’).
- ALT or AST >8×ULN or TBL >5×ULN.
- Grade 3 immune-mediated rash that does not resolve to ≤Grade 1 or baseline within 30 days.
- Grade 2 rash covering >30% body surface area 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 or myasthenia gravis) that does not resolve to ≤Grade 1 within 30 days or is associated with signs of respiratory insufficiency or autonomic instability.
- Grade 3 immune-mediated myocarditis.
- Any symptomatic immune-mediated myocarditis that does not become asymptomatic within 3 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 is associated with signs of respiratory insufficiency regardless of optimal medical management.
- Immune-mediated increase in creatinine >3×ULN, or >3×baseline for patients with a baseline creatinine elevated above ULN.

**Rationale for combining CIRT and durvalumab**

To date, durvalumab has been tested in numerous clinical trials as either monotherapy or in combination with other anticancer therapies. Among these clinical trials, durvalumab after CCRT for non-small-cell lung cancer (NSCLC) has had significant impact in clinical practice. The ‘PACIFIC Trial’ reported significantly longer OS compared with placebo in patients with stage III, unresectable NSCLC. The results of the abovementioned study suggest that durvalumab is efficacious in the treatment of lung cancer, and that combining it with CCRT is a promising treatment strategy. The CALLA trial is an ongoing phase III randomised trial which assesses the efficacy and safety of concurrent and adjuvant durvalumab with CCRT for locally advanced cervical cancer.

Recently, we found that PD-L1 upregulation was observed in the tumour tissue samples of patients who had undergone CIRT. This may imply that the antitumour effect of CIRT may be suppressed by the upregulation of PD-L1. Thus, a combination of CIRT and an anti-PD-L1 antibody such as durvalumab may effectively suppress metastasis by activating antitumour immune responses in addition to exhibiting strong local effects. This combination has potential as a new therapeutic strategy for cervical cancer.

**Objectives of this study**

The primary objective of this study (the DECISION study) is to assess the safety and tolerability of the concomitant use of durvalumab with CIRT and weekly cisplatin for locally advanced cervical cancer. The secondary objective is to assess the efficacy of this strategy. In addition, we aim to assess the correlations between clinical outcomes and biomarkers using blood samples and biopsy specimens obtained in this study.

**METHODS**

**Overview of study design**

This DECISION study (Japan Registry of Clinical Trials: jRCT2031210083) is a phase 1b, interventional, open-label, single-arm study. The study design is depicted in figure 1. Ten Japanese patients will be enrolled according to a modified 3+3 design; we will assess the safety in the first three patients. Non-Japanese patients who can fully understand Japanese will also be allowed. No randomisation is planned for patient enrolment. To conform to the 3+3 design to evaluate the safety of this study, and to simultaneously evaluate the relationship between each individual’s immune response and prognosis by using tumour and blood samples as an exploratory objective, this study plans to have a maximum of 10 patients. The details of dose-limiting toxicity (DLT) are described in box 1. The period for evaluating DLTs will be from the start of treatment until 92 days thereafter. If DLTs do not occur in the three patients, the seven additional patients will be enrolled. If one of the first three develops DLT, an additional three patients will be enrolled. If two or all...
of the first/additional three develop DLTs, this study will be terminated (figure 2). The patient registration process began in August 2021. The last patient’s enrolment is expected to be completed by May 2022. One year of follow-up is designed for all patients, and the final study report will be prepared within 6 months. Therefore, this study is scheduled to end in November 2023.

**Patient eligibility**

This study will include patients with locally advanced cervical cancer, as follows: histologically proven uterine cervical cancer of Stages IIB, IIIA, IIIB, IIIC1 or IVA in International Federation of Gynecology and Obstetrics (2018) staging. The staging in this study will be classified by physical examination and diagnostic imaging but does not include a surgical diagnosis. The inclusion and exclusion criteria are listed in table 1.

**Protocol treatment**

All patients will receive 74.4 Gy (RBE) of CIRT in 20 fractions and concurrent weekly cisplatin at a dose of 40 mg/m²; durvalumab will be administered (1500 mg/body) at weeks 2 and 6. CIRT and cisplatin will be administered at QST Hospital, based on the method which is approved by the responsible ministry and relevant radiotherapy society. Durvalumab will be administered at Chiba University Hospital. The dosage of durvalumab is based on the CALLA trial. This is the first study in which durvalumab is administered concurrently with CIRT, and unless the safety of the concurrent administration itself could be ensured, a study design including durvalumab administration as concurrent and adjuvant therapy would not be feasible. Thus, we plan to administer durvalumab only twice to verify whether the concurrent use of durvalumab with CIRT and weekly cisplatin is safe. The safety and tolerability will be evaluated based on the frequency of DLTs until 92 days after CIRT initiation. Patients will be followed-up strictly as per the scheduled protocol for 1 year after CIRT initiation (see figure 1).

**Endpoints of this study**

The tolerability of concurrent chemo CIRT in combination with durvalumab is unknown. Thus, this phase I study will be conducted to determine the safety and tolerability of this approach. The primary endpoint is the incidence rate of adverse events (AEs) and serious adverse events (SAEs), including DLTs. All AEs will be evaluated using Common Terminology Criteria for Adverse Events (CTCAE) V.5.0. We will assess OS, progression-free survival and distant metastasis rate at 1 year after treatment as secondary endpoints. In addition, objective and complete response rates based on Response Evaluation Criteria in Solid Tumours (RECIST) V.1.1 will be evaluated as secondary endpoints. Furthermore, tumour tissue and blood will be sampled before and at 1 week after starting the treatment. As an exploratory objective, these samples will be evaluated to determine the relationship between each individual’s immune response and prognosis.

**Statistical methods**

All data analyses will be carried out according to a pre-established statistical analysis plan. Regarding the safety analyses, the frequencies of DLT will be calculated in all patients who received at least one dose of durvalumab. The period for evaluating DLTs will be from the start of treatment until 92 days thereafter. DLTs will be summarised at 30 and 92 days after the start of the CIRT treatment. The AE/SAEs will also be summarised and listed according to severity and frequency. Regarding the efficacy analyses, OS, progression-free survival and distant metastasis rate 1 year after treatment will be calculated using the Kaplan-Meier method. The objective response rate is the percentage of evaluable patients with an investigator-assessed complete response rate...
### Table 1  Inclusion and exclusion criteria

**Inclusion criteria**

- Patients must fulfill all the following criteria
- Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the ICF and in this protocol. Written informed consent and any locally required authorization obtained from the patient/legal representative prior to performing any protocol-related procedures, including screening evaluations.
- Aged 20–75 years at time of study entry.
- Japanese nationality.
- Histologically proven uterine cervical cancer; Stage IIB, IIIA, IIB, IIIC1 and IVA in FIGO (2018) staging.
- ECOG performance status of 0 or 1.
- Body weight >30 kg.
- Adequate normal organ and marrow function as defined below:
  - Haemoglobin >9.0 g/dL
  - Absolute neutrophil count (ANC) ≥1000 per mm$^3$
  - Platelet count ≥75 × 10$^5$/L (≥75,000 per mm$^3$)
  - Serum bilirubin ≤1.5 x institutional upper limit of normal (ULN). This will not apply to patients with confirmed Gilbert’s syndrome (persistent or recurrent hyperbilirubinemia that is primarily unconjugated in the absence of haemolysis or hepatic pathology), who will be allowed only in consultation with their physician.
  - Aspartate aminotransferase (AST) glutamic oxaloacetic transaminase (SGOT)/alanine aminotransferase (ALT) glutamic pyruvic transaminase (SGPT) ≤2.5x institutional ULN unless liver metastases are present, in which case it must be ≤5x ULN
  - Measured creatinine clearance (CL) ≥40 mL/min or calculated creatinine CL ≥40 mL/min by the Cockcroft-Gault formula (Cockcroft and Gault 1976) or by 24-hour urine collection for the determination of creatinine clearance:
    - **Women:** 
      \[
      \text{Creatinine CL (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{Age})}{72 \times \text{serum creatinine (mg/dL)}} \times 0.85
      \]
    - **Men:** 
      \[
      \text{Creatinine CL (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{Age})}{72 \times \text{serum creatinine (mg/dL)}}
      \]
- Patient is willing and able to comply with the protocol for the duration of the study including receiving treatment, undergoing examinations (including follow-up), and making scheduled visits.
- Must have a life expectancy of at least 12 weeks.
- No prior chemotherapy or radiotherapy for cervical cancer.
- Tumour assessment by CT scan or MRI must be performed within 28 days prior to the start of the study.

**Exclusion criteria**

- Participation in another clinical study with an investigational product during the last 3 months.
- Concurrent enrolment in another clinical study unless it is an observational (non-interventional) clinical study or during the follow-up period of an interventional study.
- Receipt of the last dose of anticancer therapy (chemotherapy, immunotherapy, endocrine therapy, targeted therapy, biologic therapy, tumour embolisation, monoclonal antibodies) ≤1 year prior to the first dose of study drug.
- Any unresolved toxicity NCI CTCAE Grade ≥2* from previous anticancer therapy with the exception of alopecia, vitiligo and the laboratory values defined in the inclusion criteria.
- Any concurrent chemotherapy, biologic or hormonal therapy for cancer treatment. Concurrent use of hormonal therapy for non-cancer-related conditions (e.g., hormone replacement therapy) is acceptable.
- 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 durvalumab. Note: Local surgery of isolated lesions for palliative intent is acceptable.
- History of allogenic organ transplantation.
- Active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease [e.g., colitis or Crohn’s disease], diverticulitis [with the exception of diverticulosis], systemic lupus erythematosus, sarcoidosis syndrome or Wegener syndrome [granulomatosis with polyangiitis, Graves’ disease, rheumatoid arthritis, hypophysitis, uveitis, etc]. The following are exceptions to this criterion:
  - Malignancy treated with curative intent and with no known active disease ≥5 years before the first dose of durvalumab and of low potential risk for recurrence.
  - Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease.
  - Adequately treated carcinoma in situ without evidence of disease.
- History of another primary malignancy except for the following:
  - Malignancy treated with curative intent and with no known active disease ≥5 years before the first dose of durvalumab and of low potential risk for recurrence.
  - Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease.
  - Adequately treated carcinoma in situ without evidence of disease.

**Continued**
| Inclusion criteria | Exclusion criteria |
|--------------------|-------------------|
| Patients must fulfil all the following criteria | Patients should not be included if any of the following exclusion criteria are fulfilled |
| History of leptomeningeal carcinomatosis. | ► History of leptomeningeal carcinomatosis. |
| History of active primary immunodeficiency. | ► History of active primary immunodeficiency. |
| Active infection including tuberculosis (TB) (clinical evaluation that includes clinical history, physical examination and radiographic findings, and TB testing in line with local practice); hepatitis B (known positive hepatitis B virus (HBV) surface antigen (HBsAg) result). Patients with a past or resolved HBV infection (defined as the presence of hepatitis B core antibody (anti-HBc) and absence of HBsAg are eligible; hepatitis C: Patients positive for hepatitis C (HCV) antibody are eligible only if PCR is negative for HCV RNA. |
| Active infection including tuberculosis (TB) (clinical evaluation that includes clinical history, physical examination and radiographic findings, and TB testing in line with local practice); hepatitis B (known positive hepatitis B virus (HBV) surface antigen (HBsAg) result). Patients with a past or resolved HBV infection (defined as the presence of hepatitis B core antibody (anti-HBc) and absence of HBsAg are eligible; hepatitis C: Patients positive for hepatitis C (HCV) antibody are eligible only if PCR is negative for HCV RNA. |
| Current or prior use of immunosuppressive medication within 14 days before the first dose of durvalumab. The following are exceptions to this criterion: | ► Current or prior use of immunosuppressive medication within 14 days before the first dose of durvalumab. The following are exceptions to this criterion: |
| – Intranasal, inhaled, topical steroids or local steroid injections (e.g., intra-articular injection). | – Intranasal, inhaled, topical steroids or local steroid injections (e.g., intra-articular injection). |
| – Systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or its equivalent. | – Systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or its equivalent. |
| – Steroids as premedication for hypersensitivity reactions (e.g., CT scan premedication). | – Steroids as premedication for hypersensitivity reactions (e.g., CT scan premedication). |
| Receipt of live attenuated vaccine within 30 days prior to the first dose of durvalumab. Note: | ► Receipt of live attenuated vaccine within 30 days prior to the first dose of durvalumab. Note: |
| Patients, if enrolled, should not receive live vaccine while receiving durvalumab and up to 30 days after the last dose of durvalumab. | Patients, if enrolled, should not receive live vaccine while receiving durvalumab and up to 30 days after the last dose of durvalumab. |
| Female patients who are pregnant or breastfeeding or female patients of reproductive potential who are not willing to employ effective birth control from screening to 90 days after the last dose of durvalumab monotherapy. | ► Female patients who are pregnant or breastfeeding or female patients of reproductive potential who are not willing to employ effective birth control from screening to 90 days after the last dose of durvalumab monotherapy. |
| Known allergy or hypersensitivity to any of the study drugs or any of the study drug excipients. | ► Known allergy or hypersensitivity to any of the study drugs or any of the study drug excipients. |
| Prior randomisation or treatment in a previous durvalumab clinical study regardless of treatment arm assignment. | ► Prior randomisation or treatment in a previous durvalumab clinical study regardless of treatment arm assignment. |
| Patients who have received prior anti-PD-1, anti PD-L1, or anti CTLA-4 therapy. | ► Patients who have received prior anti-PD-1, anti PD-L1, or anti CTLA-4 therapy. |
| Resectable uterine cervical cancer. | ► Resectable uterine cervical cancer. |
| Recurrence of uterine cervical cancer. | ► Recurrence of uterine cervical cancer. |
| Patients with intestinal invasion of cervical cancer. | ► Patients with intestinal invasion of cervical cancer. |
| Uncontrollable pain due to cervical cancer. | ► Uncontrollable pain due to cervical cancer. |
| Patients who have a history of or have active severe interstitial pneumonia or pulmonary fibrosis. | ► Patients who have a history of or have active severe interstitial pneumonia or pulmonary fibrosis. |
| Patients with ileus. | ► Patients with ileus. |
| Patients with systemic infection which required intensive treatment. | ► Patients with systemic infection which required intensive treatment. |
| Patients with a history of transient ischaemic stroke, cerebrovascular accident, thrombosis or thromboembolism within 180 days before the enrolment of this study. | ► Patients with a history of transient ischaemic stroke, cerebrovascular accident, thrombosis or thromboembolism within 180 days before the enrolment of this study. |
| Patients with uncontrolled diabetes or bleeding tendency. | ► Patients with uncontrolled diabetes or bleeding tendency. |
| Judgement by the investigator that the patient is unsuitable to participate in the study and the patient is unlikely to comply with study procedures, restrictions and requirements. | ► Judgement by the investigator that the patient is unsuitable to participate in the study and the patient is unlikely to comply with study procedures, restrictions and requirements. |

*Patients with Grade ≥2 neuropathy will be evaluated on a case-by-case basis after consultation with the study physician. Patients with irreversible toxicity not reasonably expected to be exacerbated by treatment with durvalumab may be included only after consultation with the study physician.*

AEs, adverse events; CTCAE, Common Terminology Criteria for Adverse Events; ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynecology and Obstetrics; ICF, informed consent form; NCI, National Cancer Institute; PD-1, programmed death-1; PD-L1, programmed death-ligand 1.
or partial response, as confirmed by investigator assessment per RECIST V.1.1. The complete response rate indicates the disappearance of all target and non-target lesions, as determined at the 28-week assessment. Interim analysis is not scheduled.

ETHICS AND DISSEMINATION
The Human Research Ethics Committees of QST Hospital (C21-002, 26 April 2021) and Chiba University (2021006, 21 April 2021) have approved this study protocol. This study will be conducted in compliance with the Declaration of Helsinki. The findings will be published in peer-reviewed journals and presented at scientific conferences.

Patient and public involvement statement
No patient involved yet.

DISCUSSION
To the best of our knowledge, this is the first clinical trial worldwide to combine CIRT with immune checkpoint inhibitors (ICIs). We previously found that PD-L1 upregulation in tumour tissue was observed in tumour tissue samples of patients with cervical cancer who had undergone CIRT. Thus, the use of anti-PD-L1 antibodies such as durvalumab in conjunction with CIRT would be a logical approach. Notably, PD-L1 upregulation would be observed even in photon beam. Sato et al demonstrated that the DNA double-strand break repair pathway regulates PD-L1 expression in cancer cells. The repair of DNA double-strand breaks in cancer cells is central to the efficacy of RT for cancers. Therefore, a combination of anti-PD-L1 antibodies and RT including CIRT would be a reasonable strategy for cancer therapy. In particular, for tumours that are difficult to control with conventional RT, a combination of CIRT and anti-PD-L1 antibodies may be an ideal treatment method.

A recent systematic review showed that CIRT for uterine cervical cancer was evaluated as safe, effective and feasible. In addition, concurrent chemo-CIRT for uterine cervical cancer showed acceptable toxicity. However, the safety of the combination of chemo-CIRT and anti-PD-L1 antibodies is unclear. A recent systematic review and meta-analysis of toxicity in a regimen with a combination of ICIs and conventional RT showed grade 3–4 toxicity comparable to that with an ICI-alone regimen in metastatic melanoma, NSCLC and prostate cancer. Cion beams have better localisation properties than photon beams, so that the irradiation dose to normal organs would be minimised. However, AE will not need to be carefully monitored during this trial.

A primary limitation of this study is the small number of patients. However, this may be a reasonable number for a phase Ib study. After the safety of the strategy is confirmed by this study, a phase II study with a larger number of patients will be conducted in the future. It is expected that the safety and efficacy of the strategy will be evaluated over a more extended period in that study. Other limitations include possible bias on the basis of good performance status and that this study will be conducted in a single country. Although currently limited, the number of facilities providing CIRT is gradually increasing. Hence, chemo-CIRT with ICIs will be available in many institutions in the future.

Author affiliations
1 QST Hospital, National Institutes for Quantum Science and Technology, Chiba, Japan
2 Reproductive Medicine, Chiba University Graduate School of Medicine, Chiba, Japan
3 Clinical Research Center, Chiba University Hospital, Chiba, Japan
4 Radiation and Cancer Biology Group, National Institutes for Quantum Science and Technology, Chiba, Japan

Acknowledgements The authors thank to Ms Miwa Saito, Ms Yoko Kaneko, Ms Emi Kabasawa, Ms Kokoro Someya, Mr Tamiki Hikake, Mr Yosuke Inaba, Ms Eri Imanishi, Ms Emiko Miyahara and Ms Eri Matsuura for helpful discussions in protocol and database construction.

Contributors NO, HU, KM, SY, HH and MS conceptualised the study and participated in the initial study design, with assistance from MHO, TK, TF, YF, MHa, YK, YH, KS, KT, MW, SH, HT, NO, KM and HU drafted the manuscript. NO and MHO prepared visual content and coordinated manuscript revisions. NO and SY obtained the research funding. All other authors contributed to the study design and revisions of the manuscript.

Funding This study was supported by AstraZeneca (ESR-19-20362). This study was also supported by the management expenses grants for national universities and institutes.

Competing interests None declared.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

ORCID iD
Noriyuki Okonogi http://orcid.org/0000-0002-9486-1922

REFERENCES
1 Bosch FX, Lorincz A, Muñoz N, et al. The causal relation between human papillomavirus and cervical cancer. J Clin Pathol 2002;55:244–5.
2 International agency for research on cancer, world Health organization, cervical cancer: estimated incidence, mortality and prevalence worldwide in 2020. Available: http://gco.iarc.fr/today/ data/factsheets/cancers/23-Cervix-uteri-fact-sheet.pdf [Accessed 8 Jun 2021].
3 NCCN. Available: https://www.nccn.org/professionals/physician_gls/pdf/cervical.pdf [Accessed 16 Jun 2021].
4 Toita T, Kitagawa R, Hamano T, et al. Phase II study of concurrent chemoradiotherapy with high-dose-rate intracavitary brachytherapy in patients with locally advanced uterine cervical cancer: efficacy and toxicity of a low cumulative radiation dose schedule. Gynecol Oncol 2012;126:211–6.
5 Parker K, Gallop-Evans E, Hanna L, et al. Five years’ experience treating locally advanced cervical cancer with concurrent chemoradiotherapy and high-dose-rate brachytherapy: results from a single institution. Int J Radiat Oncol Biol Phys 2009;74:140–6.
6 Kodaira T, Fuwa N, Toita T, et al. Clinical evaluation using magnetic resonance imaging for patients with stage III cervical carcinoma treated by radiation alone in multicenter analysis: its usefulness and limitations in clinical practice. Am J Clin Oncol 2003;26:574–83.
7 Eifel PJ, Morris M, Oswald NJ, et al. Adenocarcinoma of the uterine cervix, prognosis and patterns of failure in 367 cases. Cancer 1990;65:2507–14.
8 Huang Y-T, Wang C-C, Tsai C-S, et al. Long-Term outcome and prognostic factors for adenocarcinoma/adenosquamous carcinoma of cervix after definitive radiotherapy. Int J Radiat Oncol Biol Phys 2011;80:423–36.
9 Niibe Y, Kenjo M, Onishi H, et al. High-dose-rate intracavitary brachytherapy combined with external beam radiotherapy for stage IIIB adenocarcinoma of the uterine cervix in Japan: a multi-institutional study of Japanese Society of therapeutic radiology and oncology. Jpn J Clin Oncol 2010;40:795–9.

10 Haie-Meder C, Pötter R, Van Limbergen E, et al. Recommendations from gynaecological (GYN) GEC-ESTRO Working Group (II): concepts and terms in 3D image based 3D treatment planning in cervix cancer brachytherapy with emphasis on MRI assessment of GTV and CTV. Radiother Oncol 2005;74:235–45.

11 Pötter R, Haie-Meder C, Van Limbergen E, et al. Recommendations from gynaecological (GYN) GEC ESTRO Working Group (II): concepts and terms in 3D image-based treatment planning in cervix cancer brachytherapy-3D dose volume parameters and aspects of 3D image-based anatomy, radiation physics, radiobiology. Radiother Oncol 2006;78:67–77.

12 Sturdza A, Pötter R, Fokdal LU, et al. Image guided brachytherapy in locally advanced cervical cancer: improved pelvic control and survival in RetrOEMRACE, a multicenter cohort study. Radiother Oncol 2016;120:428–33.

13 Ohno T, Noda S-E, Okonogi N, et al. In-room computed tomography-based brachytherapy for uterine cervical cancer: results of a 5-year retrospective study. J Radiat Res 2017;58:543–51.

14 Minkoff D, Gill BS, Kang J, et al. Cervical cancer outcome prediction to high-dose rate brachytherapy using quantitative magnetic resonance imaging analysis of tumor response to external beam radiotherapy. Radiother Oncol 2015;115:78–83.

15 Kusada T, Toi T, Ariga T, et al. Computed tomography-based image-guided brachytherapy for cervical cancer: correlations between dose-volume parameters and clinical outcomes. J Radiat Res 2018;59:67–76.

16 Yokoi E, Mabuchi S, Takahashi R, et al. Impact of histological subtype on survival in patients with locally advanced cervical cancer that were treated with definitive radiotherapy: adenocarcinoma/adeno squamous carcinoma versus squamous cell carcinoma. J Gynecol Cancer 2017;28:e19.

17 Miyasaka Y, Yoshimoto Y, Murata K, et al. Treatment outcomes of patients with adenocarcinoma of the uterine cervix after definitive radiotherapy and the prognostic impact of tumor-infiltrating CD8+ lymphocytes in pre-treatment biopsy specimens: a multi-institutional retrospective study. J Radiat Res 2020;61:275–84.

18 Kanai T, Furusawa Y, Fukutsu K, et al. Irradiation of mixed beam and design of spread-out Bragg peak for heavy-ion radiotherapy. Radiat Res 1997;147:78–85.

19 Kanai T, Endo M, Minohara S, et al. Biophysical characteristics of HIMAC clinical irradiation system for heavy-ion radiotherapy. Int J Radiat Oncol Biol Phys 1999;44:201–10.

20 Okonogi N, Wakatsuki M, Kato S, et al. Long-term outcomes of carbon-ion radiotherapy for locally advanced adenocarcinoma of the uterine cervix in phase 1/2 clinical trial (protocol 9704). Cancer 2014;120:1663–9.

21 Okonogi N, Fukuda T, Kato S, et al. Significance of concurrent use of weekly cisplatin in carbon-ion radiotherapy for locally advanced adenocarcinoma of the uterine cervix: a propensity score-matched analysis. Cancer Med 2020;9:1400–8.

22 Wang L, Wang X, Zhang Q, et al. Is there a role for carbon therapy in the treatment of gynecological carcinomas? A systematic review. Future Oncol 2019;15:3081–95.

23 Dunn GP, Old LJ, Servais TR. The three ES of cancer immunotherapy. Annu Rev Immunol 2004;22:329–60.

24 Keir ME, Butte MJ, Freeman GJ, et al. Pd-1 and its ligands in tolerance and immunity. Annu Rev Immunol 2008;26:677–704.

25 Okazaki T, Honjo T. Pd-1 and PD-1 ligands: from discovery to clinical application. Int Immunol 2007;19:813–24.

26 Stewart R, Morrow M, Hammond SA, et al. Identification and characterization of MEDI4736, an antagonistic anti-PD-L1 monoclonal antibody. Cancer Immunol Immunother 2015;3:1052–62.

27 Antonia SJ, Villegas A, Daniel D, et al. Durvalumab after chemoradiotherapy in stage III non-small-cell lung cancer. N Engl J Med 2017;377:1919–29.

28 Antonia SJ, Villegas A, Daniel D, et al. Overall survival with Durvalumab after chemoradiotherapy in stage III NSCLC. N Engl J Med 2018;379:2342–50.

29 Mayadve J, Nunes AT, Li M, et al. Calla: efficacy and safety of concurrent and adjuvant durvalumab with chemoradiotherapy versus chemoradiotherapy alone in women with locally advanced cervical cancer: a phase III, randomized, double-blind, multicenter study. Int J Gynecol Cancer 2020;30:1049–57.

30 Iijima M, Okonogi N, Nakajima NL, et al. Significance of PD-L1 expression in carbon-ion radiotherapy for uterine cervical adenocarcinoma. J Gynecol Oncol 2020;31:e19.

31 Merino M, Vidal C, Pals C, et al. The three ES of cancer immunotherapy. Annu Rev Immunol 2020;38:117–47.

32 Shimizu H, Nakajima NL, et al. Durvalumab after chemoradiotherapy in stage III non-small-cell lung cancer. N Engl J Med 2017;377:1919–29.

33 Common terminology criteria for adverse events (CTCAE) version 5.0. Available: https://ctep.cancer.gov/protocoldevelopment/ electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf [Accessed 21 Jun 2021].

34 RECIST guidelines. Available: https://recist.eortc.org/recist-1-1-2/ [Accessed 21 Jun 2021].

35 Sato H, Nishimura A, Yasuhara T, et al. Dna double-strand break repair pathway regulates PD-L1 expression in cancer cells. Nat Commun 2017;8:8.

36 Okonogi N, Nakajima N, et al. A phase 1/2 study of carbon ion radiotherapy with concurrent chemotherapy for locally advanced uterine cervical adenosquamous cell carcinoma (protocol 1302). Int J Radiat Oncol Biol Phys 2019;104:631–9.

37 Sha CM, Lehrer EJ, Hwang C, et al. Toxicity in combination immune checkpoint inhibitor and radiation therapy: a systematic review and meta-analysis. Radiother Oncol 2020;151:141–8.