BMJ Open

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

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To cite: Okonogi N, Usui H, Murata K, *et al*. 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. *BMJ Open* 2022;**12**:e056424. doi:10.1136/bmjopen-2021-056424

► Prepublication history for this paper is available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2021-056424).

Received 13 August 2021
Accepted 31 January 2022

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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 1b 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/m^2 will be administrated up to five times. Durvalumab at a dose of 1500 mg/body will be administrated 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 (#C21-002) and Chiba University (#2021006) have approved this study protocol. 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.

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.

INTRODUCTION

Standard care for cervical cancer

Cervical cancer continues to be one of the most common cancers among women.[1] 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.[2] 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.[3] Tumour

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.[4] 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%.[5] 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.[4 6] 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/m^2 resulted in improved overall survival (OS) and distant metastatic-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

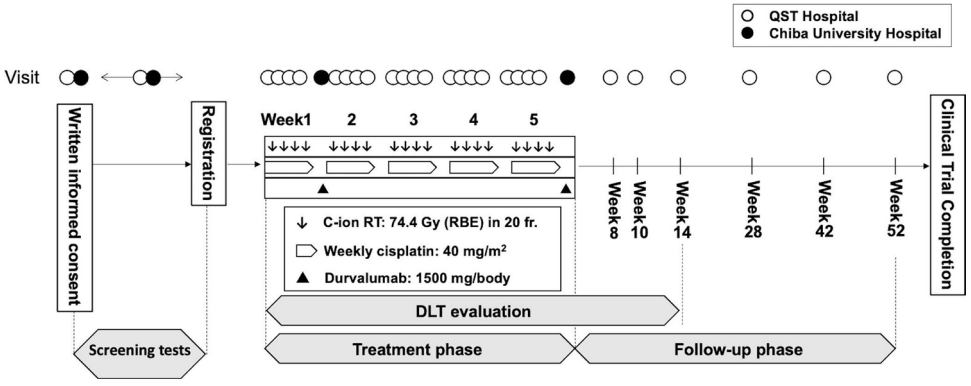

Figure 1 The design of the present study. An overall outline of this clinical trial is presented. Written informed consent was obtained from patients at both hospitals. C-ion RT, carbon-ion radiotherapy; DLT, dose-limiting toxicity; RBE, relative biological effectiveness.

Box 1 List of dose-limiting toxicities

Haematologic toxicity:
- Grade ≥3 neutropaenia complicated by fever ≥38.3°C.
- Grade 4 neutropaenia (≥7 days).
- Grade ≥3 thrombocytopaenia with significant bleeding.
- Grade 4 thrombocytopaenia (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 1one 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.

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.

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.[28 29] 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.[30]

Recently, we found that PD-L1 upregulation was observed in the tumour tissue samples of patients who had undergone CIRT.[31] 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

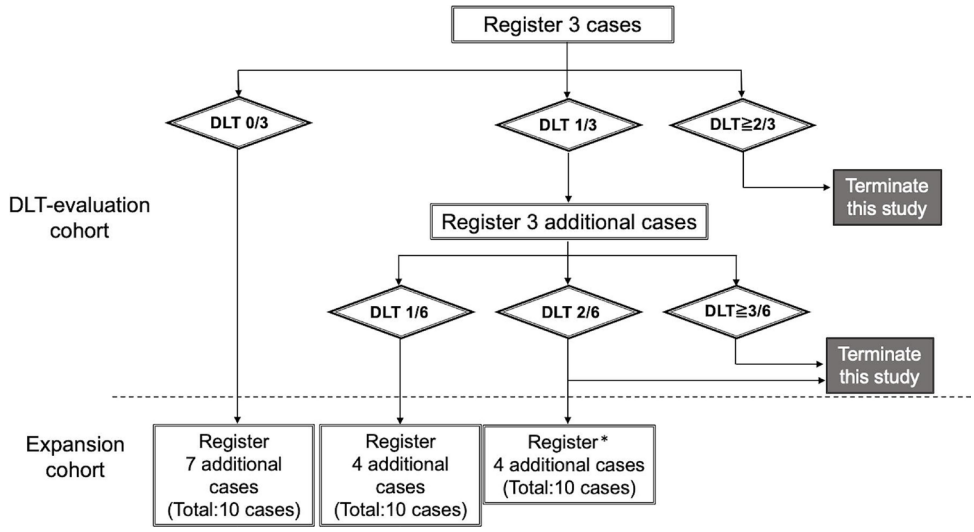

Figure 2 Registration algorithm for the present study. This study will be conducted using a modified 3+3 design. Patient registries are classified as DLT evaluation cohort and expansion cohort. *If two among the six enrolled patients develop DLTs, the independent data monitoring Committee will review the tolerability of this study regimen and determine whether additional patients can be included. DLT, dose-limiting toxicity.

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/m^2; 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.[32] Durvalumab will be administered at Chiba University Hospital. The dosage of durvalumab is based on the CALLA trial.[30] 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.[33] 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[34] 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 fulfil all the following criteria	Exclusion criteria Patients should not be included if any of the following exclusion criteria are fulfilled
► 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 authorisation 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, IIIB, 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 × 10^9/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 predominantly 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: $\text{Women: Creatinine CL}\ (\text{mL/min}) = \frac{\text{Weight}\ (\text{kg}) \times (140 - \text{Age}) \times 0.85}{72 \times \text{serum creatinine}\ (\text{mg/dL})}$ ► 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.	► 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. – 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. ► Any concurrent chemotherapy, biologic or hormonal therapy for cancer treatment. Concurrent use of hormonal therapy for non-cancer-related conditions (eg, 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(eg, 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: – Patients with vitiligo or alopecia. – Patients with hypothyroidism (eg, following Hashimoto syndrome) stable on hormone replacement. – Any chronic skin condition that does not require systemic therapy. – Patients without active disease in the last 5 years may be included but only after consultation with the study physician. – Patients with coeliac disease controlled by diet alone. ► Uncontrolled intercurrent illness including but not limited to ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, interstitial lung disease, serious chronic gastrointestinal conditions associated with diarrhoea or psychiatric illness/social situations that would limit compliance with study requirement, substantially increase risk of incurring AEs, or compromise the ability of the patient to give written informed consent. ► 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

Table 1 Continued

Inclusion criteria Patients must fulfil all the following criteria	Exclusion criteria Patients should not be included if any of the following exclusion criteria are fulfilled
	► History of leptomeningeal carcinomatosis. ► 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. ► 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 (eg, intra-articular injection). – Systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or its equivalent. – Steroids as premedication for hypersensitivity reactions (eg, CT scan premedication). ► 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. ► 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. ► 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. ► Resectable uterine cervical cancer. ► Recurrence of uterine cervical cancer. ► Patients with intestinal invasion of cervical cancer. ► Uncontrollable pain due to cervical cancer. ► Patients who have a history of or have active severe interstitial pneumonia or pulmonary fibrosis. ► Patients with ileus. ► 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 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.

*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.[31] 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.[35] 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.[23] In addition, concurrent chemo-CIRT for uterine cervical cancer showed acceptable toxicity.[22 36] 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.[37] C-ion beams have better localisation properties than photon beams, so that the irradiation dose to normal organs would be minimised. However, AEs will 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.

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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.

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