Clinical Study Protocol	
Drug Substance	Durvalumab
Study Code	D9100C00001
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A Phase III, Randomized, Multi-Center, Double-Blind, Global Study to Determine the Efficacy and Safety of Durvalumab in Combination With and following Chemoradiotherapy Compared to Chemoradiotherapy Alone for Treatment in Women With Locally Advanced Cervical Cancer (CALLA)

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden

Regulatory Agency Identifying Number(s): 2018-002872-42

VERSION HISTORY

Version 4.0, 11 March 2021
Section 2.3.1 Updated identified risk section to align with IB Edition 16. **Section 8.3.12** AESI Updated to align with IB Edition 16. **Section 1.2 Synopsis, Section 3 Objectives and Endpoints, Section 9 Statistical considerations:** Removal of interim analyses for PFS and removal of first two interim analyses for OS **Section 9.4.1.9, Section 9.5.1.7** Changes in relation to CR obtained at 20 week assessment to align with standard duration of response definitions **Section 9.7 China Cohort** Clarification of analysis of China patients **Appendix E Actions Required in Cases of Increases in Liver Biochemistryand Evaluation of Hy's law** Updated to align with standard guidance **J 3 Radiation Therapy Toxicity Management, J 3.1 Radiation Associated Gastrointestinal Colitis:** Deleted link to TMGs as no longer available **Header, SoA, 6.1.1.2 Standard of care, 2.2.4 Treatment of cervical cancer** Administrative changes
Version 3.0, 29 May 2020
Section 1.1 Schedule of activities, Section 1.2 Synopsis, Section 2.2.4 Treatment of cervical cancer Section 4.2.3 Choice of standard of care regimen, Section 6.1.1 Investigational products, Section 6.1.2 Dose and treatment regimens, Section 6.4 Concomitant therapy

Removal of Carboplatin. To ensure appropriate balance between patients treated with cisplatin and carboplatin as the radiosensitizer across regions in the ongoing study, no further use of carboplatin as the radiosensitizer will be allowed in this study.

Section 1.1 Schedule of activities, Section 5.2 Exclusion Criteria
Clarified requirement to perform ECG once during screening unless clinical abnormalities are present.

Section 6.1.1.2 Standard of care

Separated sections for cisplatin and carboplatin as carboplatin is not a treatment option in this version

Section 1.2 Synopsis, Section 3 Objectives and Endpoints, Section 6.1.1 Investigational products, Section 6.1.2 Dose and treatment regimens, Section 6.4 Concomitant therapy, Section 9.3 Populations for analyses, 9.3.3 PK analysis set; Section 9.4.1.6 Overall survival in PD-L1 positive patients, Section 9.5.1 Efficacy analyses

Added OS PD-L1 positive patients to secondary objective and analysis to determine consistency of effect between PFS and OS in this cohort

Section 1.2 Synopsis, Section 1.1 Schedule of activities, Section 4.1 Overall design, 9.7 China cohort

Added details of China cohort, including number of patients required and potential to recruit beyond global LSI

Section 8.4.5.1 Specific toxicity management and dose modification information – durvalumab

Added information that toxicity management guidelines (TMG) have been developed to assist investigators with the recognition and management of toxicities associated with the use of the immune-checkpoint inhibitor durvalumab.

Section 9.2 Sample size determination

Change of the expression of the statistical power to be consistent with the rest of the protocol.

Section 1.1. Schedule of activities, Appendix A7 Study and Site start and closure, Appendix B2 Definitions of serious adverse event, Appendix E Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's law, Appendix G12.1 General Principals

Administrative changes based on updated information.

Version 2.0, 09 September 2019

Section 1.1 Schedule of activities

This section updated with several changes as below

- Clarified requirement to perform ECG's in triplicate at Screening in line with eligibility criteria.
- Added a footnote to clarify that ECOG performance is checked for eligibility at both enrolment and randomization
- Clarification provided stating that ctDNA sample will be taken at last dose of platinum administration.
- Change to ePRO administration schedule to align with expected visits for RECIST /Scan assessment to minimize the required number of patient visits.
- Clarified when tumour assessments are no longer required
- Clarification that a scan is required within 28 days of progressive disease if determined through histopathologic progression on biopsy.
- Footnote added on utilization of targeted physical examination by Investigators

Section 1.2 Synopsis and Section 3 Objectives and endpoints and Section 9.0 Statistical Considerations (subsections)

- PFS analysis at 3 years has been moved from exploratory objective to secondary objective.
- Clarified that duration of response in patients with a complete response endpoint is measured from the date of first detection of CR as determined at the 20-week assessment.
- Clarified that ADA will be analysed for both treatment arms.

Section 1.2 Synopsis, Section 2.1.1 Rationale for combining checkpoint inhibitor therapy with chemoradiotherapy, 2.2.4 Treatment of cervical cancer, 4.1 Overall Design, Section 4.2.4 Rationale of administering durvalumab concurrent with CCRT

Word “maintenance” changed to “adjuvant” in these sections, as this is a more accurate description of the intent of the Durvalumab/Placebo treatment post CCRT for this patient population.

Section 2.2.4 Treatment of cervical cancer

Rationale for the completion of CCRT within 56 days has been added

Section 2.2.4 Treatment of cervical cancer

Background information for the treatment of cervical cancer has been updated

Table 1 Schedule of assessments for durvalumab/placebo ± chemoradiation therapy screening and treatment and retreatment periods (up to total of 24 doses), Section 4.1 Overall Design, Section 7.1.1 Procedures for discontinuation of study treatment, Section 8.1 Efficacy assessments

Clarified the role of pelvic examination in the assessment of progressive disease.

Table 1 Schedule of assessments for durvalumab/placebo ± chemoradiation therapy screening and treatment and retreatment periods (up to total of 24 doses), Table 6 Treatment regimen

Clarified SoC platinum chemotherapy dosing window.

Section 4.2.4 Rationale of administering durvalumab concurrent with CCRT

Duplicate information that was already covered in section 2.1.1 Rationale for combining checkpoint inhibitor therapy with chemoradiotherapy, has been removed from this section

Section 4.2.5 Rationale for treatment duration

Duration of treatment clarified to include histopathologic confirmation of local tumor progression in addition to PD by RECIST 1.1

Section 4.2.6 Rationale for stratification factors

New section added to provide rationale for stratification factors.

Section 5.1 Inclusion criteria 5.0 & multiple sections

Multiple sections of CSP updated to emphasise that FIGO (2009) is used for this protocol.

Section 5.2 Exclusion criteria

Added mucinous adenocarcinoma into exclusion criteria 1.0.

Section 6.1.1.1 Durvalumab (MEDI4736), Section 6.1.1.3 Placebo

Durvalumab blinding procedure updated to include the use of coloured infusion sleeves.

Section 6.1.1.1 Durvalumab (MEDI4736) - Order of Adminsitration

- Clarified SOC chemotherapy administration timing post durvalumab/placebo administration from 24 hour to 1 calendar day
- Removed "Cisplatin or carboplatin should commence within the first 3 radiation treatments" as inconsistent with other sections."

Section 6.1.3 Duration of treatment and criteria for treatment through progression

This section updated to provide clarity on criteria for treatment through progression

Table 7 Prohibited concomitant medications

Added immunosuppressive, EGFR & TKI as additional prohibited medications

Section 8.1.3.6 Administration of patient reported outcome questionnaires

This section updated to allow

- ePRO assessment can be performed post blood sample collection,
- ePRO can be performed prior to C1D1 as long as first of dose of Durvalumab and CCRT is given within 3 days of ePRO completion
- Added that illiterate patients will not be required to complete the PRO assessments.

Section 8.1.4.1 Administration of health care resource assessment

Clarified that HOSPAD eCRF will be completed when there are hospitalization/hospital visits only.

Section 8.8.1.1 Tumor sample collection

- Clarification provided on the screening tumor sample age requirement

- Additional sentence added requesting to refer specific instructions and guidelines refer to lab manual for tumor sample collection.

Section 8.8.2 Exploratory biomarkers

- Previous section 8.8.1.3 deleted and exploratory tumor markers moved to this section.
- ctDNA sample collection section updated to provide more clarity.
- Added the information about Microsatellite instability and tumor mutation burden and tumor markers.

Section 8.8.4 Storage, re-use, and destruction of biomarker samples

Sample storage requirement for China is updated.

Section 1.2 Synopsis, Section 9.2 Sample size determination, 9.5.7 Methods for Multiplicity Control, Section 9.6 Interim analyses

Updated this section to strengthen the analysis plan for the OS endpoint. OS will be analysed at the time of each PFS analysis, in the event that PFS is positive at the same timepoint.

Section 9.4.1.1 RECIST 1.1-based endpoints, Section 9.4.1.2 Primary endpoint - progression-free survival

This section updated to clarify criteria and relationship between date of progression & physical exam

Section 9.4.1.3 Progression Free Survival (3 years), Section 9.4.1.4 Progression free survival in PD-L1 positive patients, Section 9.5.1.2 Progression Free Survival (3 year), Section 9.5.1.2 Progression free survival in PD-L1 positive patients, Table 14 Pre-planned statistical and sensitivity analyses to be conducted

These sections are re-aligned and updated in line with changes made to study objectives

Section 9.4.3.2 EORTC QLQ CX24

Language for threshold value for clinically meaningful change and analysis plan for this PRO has been updated

Section 9.4.9 Calculation or derivation of pharmacokinetic variables Plan for PK analysis has been updated from standard template language to be more appropriate for the CALLA study design. Non-compartmental analysis has been removed because only sparse PK samples are being collected. **Section 9.5.1.6 Complete response rate, Section 9.5.1.8 Duration of complete response** These sections are updated in line with changes in study objectives and endpoints **Section 9.5.3 Pharmacokinetic data, Section 9.5.4 Immunogenicity data** These sections are updated provide clarity on analysis by treatment arms **Appendix G: Standard of Care Radiation Therapy Guidelines** Radiotherapy Appendix G below subsections sections are updated to provide additional clarity and guidance. • General principals, G 2.1.1 Whole Pelvic 3D conformal RT (4-field pelvis), Table 19, 20 and 22 **Appendix J: Standard of care treatment management** New appendix added to provide SoC toxicity management guidelines. **Appendix K: FIGO (2009) guidelines for Cervical Cancer Staging** New appendix K is added to provide details for FIGO (2009) staging
Version 1.0, 02 October 2018
Initial creation

This Clinical Study Protocol has been subject to a peer review according to AstraZeneca Standard procedures. The Clinical Study Protocol is publicly registered and the results are disclosed and/or published according to the AstraZeneca Global Policy on Bioethics and in compliance with prevailing laws and regulations.

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1. PROTOCOL SUMMARY

1.1 Schedule of activities

The procedures for the screening and treatment periods in this study are presented in Table 1, and the procedures for the follow-up period are presented in Table 2. Patients who continue on the trial beyond Cycle 24 will continue with assessments until termination of the study (Table 2).

Whenever vital signs and blood draws are scheduled for the same nominal time, the assessments should occur in the following order: vital signs and then blood draws. The timing of the vital signs assessments should be such that it allows the blood draw (eg, Pharmacokinetics [PK] blood sample) to occur at the timepoints indicated in the schedule of assessments (SoAs). Whenever electrocardiograms (ECGs), vital signs, and blood draws are scheduled for the same nominal time, the assessments should occur in the following order: ECG, vital signs, and then blood draws. The timing of the first 2 assessments should be such that it allows the blood draw (eg, PK blood sample) to occur at the timepoints indicated in the SoAs.

For durvalumab/placebo + standard of care chemoradiation therapy combination arms

- Patients may delay dosing under certain circumstances.
  - Dosing may be delayed per the Dosing Modification and Toxicity Management Guidelines, due to either an immune or a non-immune-related adverse events (AE).
  - If dosing must be delayed for reasons other than treatment-related toxicity, dosing will resume as soon as feasible.
  - Dosing intervals of subsequent cycles may be shortened as clinically feasible in order to gradually align treatment cycles with the schedule of tumor efficacy (Response Evaluation Criteria in Solid Tumors version 1.1 [RECIST 1.1]) and patient-reported outcome (PRO) assessments. Subsequent time between 2 consecutive doses cannot be less than 21 days, based on the half-life of durvalumab (see current Investigator's Brochure [IB] for durvalumab).

Table 1 Schedule of assessments for durvalumab/placebo ± chemoradiation therapy screening and treatment and retreatment periods (up to total of 24 doses)

	Screening	C1[a]	C2[a]	C3[a]	C4[a]	C5 to PD/C24[a]	For details, see Section
Week	**-4 to -1**	**0**	**q4w ±3 days unless dosing needs to be held for toxicity reasons**				
Day	**-28 to -1**	**1**	**q28d ±3 days unless dosing needs to be held for toxicity reasons**				
Informed consent							
Informed consent: study procedures[b]	X						5.1
Consent: genetic sample and analysis (optional)	X						5.1
Study procedures							
Physical exam (full)	X						8.2.1
Targeted physical exam [c]		X	X	X	X	X	8.2.1
Vital signs[d]	X	X	X	X	X	X	8.2.2
ECG[e]	X[f]	As clinically indicated					8.2.3
Concomitant medications	<----------					---------->	6.4
Demography, including baseline characteristics and tobacco use	X						5.1
Eligibility criteria	X						5.1, 5.2
Radiation plan collection	X						Appendix G
Laboratory assessments							
Clinical chemistry[g]	X	X[h]	X	X	X	X	Table 9
Hematology[h]	X	X[h]	X	X	X	X	Table 10
TSH[i] (reflex free T_3 or free T_4)[j]	X	X	X	X	X	X	Table 9
Urinalysis	X	As clinically indicated					Table 11
Hepatitis B and C and HIV	X						8.2.4
Pregnancy test[k]	X	X	X	X	X	X	8.2.4
HPV genotype, if available	X						8.2.4

	Screening	C1[a]	C2[a]	C3[a]	C4[a]	C5 to PD/C24[a]	For details, see Section
Week	**-4 to -1**	**0**	**q4w ±3 days unless dosing needs to be held for toxicity reasons**				
Day	**-28 to -1**	**1**	**q28d ±3 days unless dosing needs to be held for toxicity reasons**				
Pharmacokinetics							
PK sample (serum)		X[l]	X[m]		X[m]		8.5
Monitoring							
WHO/ECOG performance status[n]	X	X	X	X	X	X	8.2.5
AE/SAE assessment[o]	<----------					---------->	8.3
Patient follow-up contact/Patient review for safety		Days 14 (±24 hours) of C1, C2, and C3					8.2.6
IP administration							
Durvalumab/placebo[p,q]		X[p]	X	X	X	X	6.1.1.1, 6.1.2.1
SoC cisplatin chemotherapy		Weekly for 5 weeks[r] (± 1 day except cycle 1)					6.1.1.2, 6.1.2.2
SoC radiation therapy		Refer to Appendix G					6.1.1.2, 6.1.2.2, Appendix G
Other assessments and assays							
Immunogenicity assessment (ADA sampling to identify ADA responses in patient circulation)		X[m]	X[m]		X[m]		8.5.1.1
Whole blood for gene expression (PAXgene RNA tubes)		X	X				8.8.2
ctDNA (plasma)		X	X [s]	X	X	(at 6 months and PD)	8.8.2
EORTC QLQ-C30 and CX24, PGIS, EQ-5D[t]		0 (C1D1), 2 (mid-cycle 1), 4 (C2D1), 8 (C3D1), 12 (C4D1), 16 (C5D1), 20 (C6D1) weeks from C1D1, then q12 weeks ±1w through 164 weeks (relative to C1D1), and then q24w ±2w thereafter (relative to C1D1) through 260 weeks, then q52w ±2w (relative to C1D1) up to PD and at IP pre-mature discontinuation and PD; if IP discontinuation due to PD, then also at month 2 and month 3 post discontinuation; if PD but continue on treatment, follow treatment period schedule.					8.1.3

	Screening	C1[a]	C2[a]	C3[a]	C4[a]	C5 to PD/C24[a]	For details, see Section
Week	**-4 to -1**	**0**	**q4w ±3 days unless dosing needs to be held for toxicity reasons**				
Day	**-28 to -1**	**1**	**q28d ±3 days unless dosing needs to be held for toxicity reasons**				
PRO-CTCAE		Same as other PROs, but will end at week 104 or first follow-up post IP discontinuation (if no PD), or at month 2 post IP discontinuation (if PD)					8.1.3
PGIC[t]			Same as PRO-CTCAE but starting 4 weeks (C2D1) from C1D1				8.1.3
Healthcare resource use (HOSPAD)[u]	To be completed at each hospitalization						8.1.3
FFPE tumor sample (mandatory; a newly acquired sample is preferred if available per site's routine clinical practice; otherwise, archival sample ≤3 months old can be provided)[v]	X						8.8
Optional newly acquired tumor biopsy collected upon progression[v]			X (at PD only, strongly encouraged)				
Genetics research sample (optional DNA element for long-term storage/future use) [w]		X					8.7
Efficacy evaluations							
Tumor radiological assessments (RECIST 1.1) [y] -AND- Physical exam including a pelvic examination	X[x]	On-study tumor assessments occur 20w ±1w after randomization and continue q12w ±1w through 164 weeks (relative to the date of randomization) and then q24w ±2w thereafter (relative to the date of randomization) until RECIST 1.1-defined radiological progression plus an additional follow-up scan. If progressive disease is determined through histopathologic progression on biopsy, a scan is required within 28 days of biopsy. This on-study imaging schedule MUST be followed regardless of any delays in dosing. -AND- Physical examination including a pelvic examination and (if indicated) biopsy for histopathological determination of tumor progression will be assessed on the same schedule as the imaging assessments.[z,aa]					8.1

[a] These cycles refer to the 28-day cycles of administration of durvalumab/placebo.

[b] Written informed consent and any locally required privacy act document authorization must be obtained prior to performing any protocol-specific procedures, including screening/baseline evaluations. All patients will be required to provide consent to supply a sample of their tumor (archived or newly acquired biopsy) for entry into this study. This consent is included in the main patient ICF. Informed consent of study procedures may be obtained prior to the 28-day screening window, if necessary. The collection of additional biopsies upon progression is OPTIONAL but strongly encouraged. If laboratory or imaging procedures were performed for alternate reasons prior

to signing consent, these can be used for screening purposes with consent of the patient. However, all screening laboratory and imaging results must have been obtained within 28 days of randomization.

[c] Targeted physical examinations are to be utilized by the Investigator on the basis of clinical observations and symptomatology and can include assessments of the head, eyes, ears, nose, and throat and the respiratory, cardiovascular, GI, urogenital, musculoskeletal, neurological, dermatological, hematologic/lymphatic, and endocrine systems

[d] Body weight is recorded at each visit along with vital signs.

[e] Any clinically significant abnormalities detected require triplicate ECG results.

[f] A single ECG at screening should be done. Any clinically significant abnormalities detected require triplicate ECG results.

[g] Serum or plasma clinical chemistry (including LFT monitoring) and hematology may be performed more frequently if clinically indicated or based on the local clinical practice.

[h] If screening clinical chemistry and hematology assessments are performed within 3 days prior to Day 1 (first infusion day), they do not need to be repeated at Day 1.

[i] If TSH is measured within 14 days prior to Day 1 (first infusion day), it does not need to be repeated at Day 1.

[j] Free T3 or free T4 will only be measured if TSH is abnormal or if there is clinical suspicion of an AE related to the endocrine system.

[k] For women of childbearing potential only. A urine or serum pregnancy test is acceptable. Women of childbearing potential are required to have a pregnancy test within 7 days prior to the first dose of study treatment and then q4w. Results must be available and reviewed by the treating physician or Investigator prior to commencing an infusion.

[l] Post infusion within 1 hour of the end of infusion.

[m] Pre-dose same day as infusion (may not exceed 6 hours prior to start of infusion).

[m] ECOG performance status (PS) of 0 or 1 at enrolment and randomization.

[o] For AEs/SAEs reported during screening, additional information such as medical history and concomitant medications may be needed

[p] During the combination portion of treatment, durvalumab or placebo will be administered first. If there is not enough time to administer cisplatin afterward on that day, it should be given the following day and must be administered within 1 calendar day of the durvalumab infusion. Treatment should start no more than 3 working days after being randomized. The day patients begin treatment will be designated C1D1.

[q] Results for LFTs, electrolytes, full blood count (while on chemotherapy), and creatinine must be available before commencing an infusion (within 3 days) and reviewed by the treating physician or Investigator prior to dosing.

[r] A 6th week of platinum agent is optional per investigator discretion.

[s] Sample will be taken at last dose of platinum administration (C2D8 if a 6th week of platinum agent is needed or C2D1 if platinum agent is administered only for 5 weeks)

[t] Will be administered using a site-based, ePRO device. The PRO questionnaires must be administered and completed at the clinic prior to treatment administration performed at the site and ideally before any discussions of health status to avoid biasing the participant's responses to the questions. As feasible, site staff should also ensure PRO questionnaires are completed prior to other study procedures, such as collection of laboratory samples and before discussion of disease progression to avoid biasing the patient's responses to the questions.PRO-CTCAE will only be administered in those countries where a linguistically validated version exists. It is permitted for the baseline ePROs to be completed prior to C1D1 as long as treatment is given within 3 days of ePRO completion.

[u] HOSPAD module should be completed by site staff whenever the patient has attended or been admitted in to the hospital. A reminder will be provided at each clinic visit. Any routine visits for protocol-related requirements do not need to be captured. If the patient discontinues study treatment for reasons other than RECIST progression, the HOSPAD form should continue to be administered during the non-study protocol required hospital visits until progression has been confirmed

[v] Blocks are preferred to slides (except China). Refer to the Laboratory Manual for further details on tissue requirements.

[w] The sample for genetic research will be obtained at Day 1 pre-dose (at or after randomization). If, for any reason, the sample is not drawn at Day 1, it may be taken at any visit until the last study visit. Only 1 sample should be collected per patient for genetics during the study.

[x] Patients will have baseline scans collected no more than 28 days before the date of randomization and, ideally, should be performed as close as possible to the date of randomization.

[y] RECIST 1.1 assessments will be performed on images from CT (preferred) or MRI, each preferably with IV contrast of the chest, abdomen, and pelvis. Additional anatomy should be imaged based on the signs and symptoms of individual patients at baseline and follow-up. The follow-up scan collected after a RECIST 1.1-defined PD should be performed no less than 4 weeks after and no later than 12 weeks after the prior assessment of PD, and this follow-up scan is evaluated using the criteria

outlined in Appendix F. If an unscheduled assessment is performed (eg, to investigate clinical signs/symptoms of progression) and the patient has not progressed, every attempt should be made to resume the subsequent assessments following the original imaging visit schedule (relative to the date of randomization). See Section 6.1.3, Section 8.1 and Appendix F for additional details relevant to imaging assessments.

[z] Pap smear should be done per investigator discretion. If results are concerning for progression, progression must be confirmed by biopsy

[aa] A radiological tumor assessment should be obtained within 28 days of confirmed histopathological progression unless no further radiological tumour assessments are indicated for the patient due to RECIST PD already being recorded and the follow up scan for the RECIST PD being completed

Note: All assessments on treatment days are to be performed prior to infusion, unless otherwise indicated.
Abbreviations: ADA Antidrug antibody; AE Adverse event; C Cycle; CR Complete response; CRT Chemoradiation therapy; CT Computerized tomography; ctDNA Circulating tumor deoxyribonucleic acid; DNA Deoxyribonucleic acid; ECG Electrocardiogram; ECOG Eastern Cooperative Oncology Group; EORTC European Organisation for Research and Treatment of Cancer; EQ-5D-5L EuroQol five-dimensional five-level questionnaire; Gy Grey unit; HIV Human immunodeficiency virus; HOSPAD Hospital Admission; HPV Human papillomavirus; ICF Informed consent form; IP Investigational product; IV Intravenous; LFT Liver function tests; MRI Magnetic resonance imaging; PD Progression of disease; PGIC Patient Global Impression of Change; PGIS Patient Global Impression of Severity; PK Pharmacokinetics; PR Partial response; PRO Patient-reported outcomes; PRO-CTCAE Patient-reported outcomes version of the Common Terminology Criteria for Adverse Events; qxw Every x weeks; q28d Every 28 days; QLQ-C30 30 item core quality of life questionnaire; QLQ-CX24 Cervical cancer module; RECIST Response Evaluation Criteria in Solid Tumors version 1.1; RNA Ribonucleic acid; SAE Serious adverse event; SD Stable disease; SoC Standard of care; T3 Triiodothyronine; T4 Thyroxine; TSH Thyroid stimulating hormone; WHO World Health Organization.
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Table 2 Schedule of assessments for patients who have completed or discontinued treatment

	Time since last dose of IP								
	Day (±3)	Months (±2 week)						21 months and every 6 months (±2 weeks)	For details, see Section
Evaluation	**30**	**2**	**3**	**6**	**9**	**12**	**15**		
Physical examination (full)	X								8.2.1
Vital signs (temperature, respiratory rate, blood pressure, and pulse)	X								8.2.2
Weight	X	X	X						8.2.2
Pregnancy test[a]	X	As clinically indicated							8.2.4
AE/SAE assessment	X	X	X						8.3
Concomitant medications	X	X	X						6.4
WHO/ECOG performance status	At timepoints consistent with tumor assessments; at 30, 60, and 90 days; and then at initiation of subsequent anticancer therapy[b]								8.2.5
Subsequent anticancer therapy[c,d]	<---------- >								8.1
Survival status[e]			X	X	X	X	X	X	8.1
Hematology	X	X	X						Table 10
Clinical chemistry	X	X	X						Table 9
Urinalysis	As clinically indicated								Table 11
TSH (reflex free T_3 or free T_4[f])	X	X	X						Table 9
PK assessment[g]			X						8.5
Immunogenicity assessment (ADA sampling) to identify ADA responses[g]			X	X[h]					8.5.1.1
Whole blood for gene expression (PaxGene-RNA tubes)	X	X							8.8.2
ctDNA (plasma)	X	X		X					8.8, 8.8.2

	Time since last dose of IP								
	Day (±3)	Months (±2 week)						21 months and every 6 months (±2 weeks)	For details, see Section
Evaluation	**30**	**2**	**3**	**6**	**9**	**12**	**15**		
EORTC QLQ-C30 and CX24, PGIS, EQ-5D[i]		0 (C1D1), 2 (mid-cycle 1), 4 (C2D1), 8 (C3D1), 12 (C4D1), 16 (C5D1), 20 (C6D1) weeks from C1D1, then q12 weeks ±1w through 164 weeks (relative to C1D1), and then q24w ±2w thereafter (relative to C1D1) through 260 weeks, then q52w ±2w (relative to C1D1) up to PD and at IP pre-mature discontinuation and PD; if IP discontinuation due to PD, then also at month 2 and month 3 post discontinuation; if PD but continue on treatment, follow treatment period schedule.						8.1.3
PRO-CTCAE	Same as other PROs, but will end at week 104 or first follow-up post IP discontinuation (if no PD), or at month 2 post IP discontinuation (if PD)								8.1.3
PGIC[i]	Same as PRO-CTCAE but starting 4 weeks (C2D1) from C1D1								8.1.3
Healthcare resource use (HOSPAD)[j]	To be completed at each hospitalization.								8.1.3
Tumor radiological assessment (RECIST 1.1)[k] -AND- Physical exam including a pelvic examination	On-study tumor assessments occur 20w ±1w after randomization and continue q12w ±1w through 164 weeks (relative to the date of randomization) and then q24w ±2w thereafter (relative to the date of randomization) until RECIST 1.1-defined radiological progression plus an additional follow-up scan. If progressive disease is determined through histopathologic progression on biopsy, a scan is required within 28 days of biopsy. This on-study imaging schedule MUST be followed regardless of any delays in dosing. -AND- Physical examination including a pelvic examination and (if indicated) biopsy for histopathological determination of tumor progression will be assessed on the same schedule as the imaging assessments.[l, m]								8.1

[a] For women of childbearing potential only. A urine or serum pregnancy test is acceptable.

[b] WHO/ECOG performance status should also be collected at other site visits that the patient attends, if appropriate site staff are available to collect such information. In addition, WHO/ECOG performance status should be provided when information on subsequent anticancer therapy is provided, where possible.

[c] Details of any treatment for cervical cancer (including surgery) after the last dose of IP must be recorded in the eCRF. At minimum, collect the start date and description of the subsequent anticancer therapy.

[d] For patients who discontinue their assigned IP following confirmed progression, available readings of CT/MRI from local practice will be collected from patients' medical charts while information on subsequent anticancer treatment is collected.

[e] Patients may be contacted in the week following data cutoffs to confirm survival status. Details of any treatment for cervical cancer (including surgery) after the last dose of IP must be recorded in the eCRF.

[f] Free T3 or free T4 will only be measured if TSH is abnormal or if there is clinical suspicion of an AE related to the endocrine system.

[g] PK and immunogenicity samples are collected 90 days (3 months) (±7 days) after study treatment ends. In addition, a final immunogenicity sample is taken 6 months (±7 days) after study treatment ends.

[h] Immunogenicity sample and ctDNA sample should be obtained at a scheduled study tumor assessments visit

[i] Will be administered using a site-based, ePRO device. The PRO questionnaires must be administered and completed at the clinic prior to treatment administration performed at the site and ideally before any discussions of health status to avoid biasing the participant's responses to the questions. As feasible, site staff should also

ensure PRO questionnaires are completed prior to other study procedures, such as collection of laboratory samples and before discussion of disease progression to avoid biasing the patient's responses to the questions. PRO-CTCAE will only be administered in those countries where a linguistically validated version exists.

[j] HOSPAD module should be completed by site staff whenever the patient has attended or been admitted in to the hospital. A reminder will be provided at each clinic visit. Any routine visits for protocol-related requirements do not need to be captured. If the patient discontinues study treatment for reasons other than RECIST progression, the HOSPAD form should continue to be administered during the non-study protocol required hospital visits until progression has been confirmed.

[k] Only for patients yet to progress, RECIST 1.1 assessments will be performed on images from CT (preferred) or MRI, each preferably with IV contrast, of the chest, abdomen, and pelvis. Additional anatomy should be imaged based on signs and symptoms of individual patients. The follow-up scan collected after a RECIST 1.1-defined PD should be performed no less than 4 weeks after and no later than 12 weeks after the prior assessment of PD, and this follow-up scan is evaluated also using the criteria outlined in Appendix F. If an unscheduled assessment was performed (eg, to investigate clinical signs/symptoms of progression) and the patient has not progressed, every attempt should be made to resume the subsequent assessments following the original imaging visit schedule (relative to the date of randomization). See Section 6.1.3, Section 8.1, and Appendix F for additional details relevant to imaging assessments.

[l] Pap smear should be done per investigator discretion. If results are concerning for progression, progression must be confirmed by biopsy

[m] Radiological tumor assessments should be obtained on all patients within 28 days of progression confirmed by histopathology

Abbreviations: ADA Antidrug antibody; AE Adverse event; CT Computerized tomography; ctDNA Circulating tumor deoxyribonucleic acid; ECOG Eastern Cooperative Oncology Group; eCRF Electronic case report form; EORTC European Organization for Research and Treatment of Cancer; EQ-5D-5L EuroQol five-dimensional five-level questionnaire; IP Investigational product; IV Intravenous; MRI Magnetic resonance imaging; PD Progression of disease; PFS Progression-free survival; PGIC Patient Global Impression of Change; PGIS Patient Global Impression of Severity; PK Pharmacokinetics; PRO Patient-reported outcome; PRO-CTCAE Patient-reported outcomes version of the Common Terminology Criteria for Adverse Events; qxw Every x weeks; QLQ-C30 30 item core quality of life questionnaire; QLQ-CX24 Cervical cancer module; RECIST Response Evaluation Criteria in Solid Tumors; RNA Ribonucleic acid; SAE Serious adverse event; T3 Triiodothyronine; T4 Thyroxine; TSH Thyroid stimulating hormone; WHO World Health Organization.

1.2 Synopsis

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Protocol Title: A Phase III, Randomized, Multi-Center, Double-Blind, Global Study to Determine the Efficacy and Safety of Durvalumab in Combination With and following Chemoradiotherapy Compared to Chemoradiotherapy Alone for Treatment in Women With Locally Advanced Cervical Cancer (CALLA)

Rationale:

Cervical cancer is the 4th most common cancer in women worldwide despite the introduction of the Papanicolaou test (Pap smear) for early screening and prevention of cervical cancer in the 1950s, and more recently, human papillomavirus (HPV) vaccination. Most women globally do not have access to screening and, thus, the global incidence of cervical cancer at all stages continues to rise throughout the world as the population rises and ages. The use of combination chemoradiotherapy is a mainstay of oncology therapy in multiple tumor types. The goal of combination chemotherapy is to utilize agents that affect cancer cells by different mechanisms, thus improving clinical responses and reducing the risk of developing resistance. Non-clinical and clinical studies have indicated that blockade of immune checkpoints (programmed cell death protein 1 [PD-1]/programmed death-ligand 1 [PD-L1] and cytotoxic T-lymphocyte-associated protein 4 [CTLA-4]) can have a positive effect on anti-tumor immunity. Chemotherapy is thought to synergize with PD-1/PD-L1 blockade by making the tumor “immunogenic” by initiating cell death, promoting phagocytosis of tumor cells, and ultimately leading to reactivation of immune-mediated tumor surveillance. The PACIFIC trial evaluated the efficacy of durvalumab after definitive chemoradiotherapy in Stage III non-small cell lung cancer (NSCLC) compared to placebo after chemoradiotherapy and found a significant improvement with durvalumab with a median progression-free survival (PFS) of 16.8 months (95% confidence interval [CI] 13.0 to 18.1) compared to 5.6 months (95%CI, 4.6 to 7.8) in the placebo controlled group. The study’s hypothesis is that durvalumab, when administered concurrently with chemotherapy and radiotherapy (CCRT) and as adjuvant therapy following CCRT will also improve PFS when compared to standard of care concurrent chemoradiation therapy (SoC CCRT) with placebo in patients with International Federation of Gynaecology and Obstetrics (FIGO 2009) Stage IB2 to IVA cervical cancer.

Objectives and Endpoints

Primary objective:	**Endpoint/variable:**
To assess the efficacy of durvalumab + SoC CCRT compared with placebo + SoC CCRT in terms of PFS	Endpoints based on the investigator assessment according to RECIST 1.1 or histopathologic confirmation of local tumor progression: • PFS: Time from date of randomization until tumor progression or death due to any cause
Secondary objectives:	**Endpoints/variables:**
To further assess the efficacy of durvalumab + SoC CCRT compared with placebo + SoC CCRT in terms of PFS (3 year), PFS in PD-L1 positive patients, overall survival (OS) (key), OS in PD-L1 positive patients, ORR, CR rate, and DoR in Patients with a CR	• OS: Time from date of randomization until the date of death by any cause Endpoints based on the investigator assessment according to RECIST 1.1 or pathologic assessment of local disease progression • PFS (3 year): Proportion of patients alive and progression-free at 3 years • PFS in PD-L1 positive patients: Time from date of randomization until tumor progression or death due to any cause in patients who are PD-L1 positive (>=1%) based on either tumor or immune cell staining • OS in PD-L1 positive patients: Time from date of randomization until the date of death by any cause in patients who are PD-L1 positive (>=1%) based on either tumor or immune cell staining • ORR: The percentage of evaluable patients with an Investigator-assessed visit response of CR or PR • CR rate: Disappearance of all target and non-target lesions DoR in Patients with a CR: Time from date of first detection of CR until the date of objective disease progression according to RECIST 1.1
To assess the effect of durvalumab + SoC CCRT compared with placebo + SoC CCRT on the incidence of local progression, distant disease progression, and secondary malignancy as the first documented progression event	• Incidence of Local Progression, Distant Disease Progression, and Secondary Malignancy: Number and percentage of patients who develop local progression, distant disease recurrence, or secondary malignancy

Objectives and Endpoints

To assess disease-related symptoms and health related quality of life (HRQoL) in patients with cervical cancer treated with durvalumab + SoC CCRT compared with placebo + SoC CCRT using the core quality of life questionnaire (EORTC QLQ-C30) and core quality of life questionnaire cervical cancer module (CX24)	• Change from baseline in EORTC QLQ-C30 and EORTC CX24
To assess the PK of durvalumab when in combination with CCRT	Blood concentration of durvalumab
To investigate the immunogenicity of durvalumab in both arms in combination with CCRT	Presence of ADAs
Safety objective:	**Endpoint/variable:**
To assess the safety and tolerability profile of durvalumab + SoC CCRT compared to placebo + SoC CCRT	AEs, laboratory findings, vital signs, and physical examinations,
Exploratory objective:	**Endpoint/variable:**
To collect blood and tissue samples for defining biological response to durvalumab +SoC CCRT compared to placebo +SoC CCRT for candidate markers that may correlate with likelihood of clinical benefit. **(All countries except China)**	• Analysis of blood/tissue samples to assess exploratory biomarkers, which may include, but is not limited to ctDNA, mRNA signatures, CD8 by IHC, and Tumor Mutational Burden (TMB)
To assess treatment-related symptoms using the patient-reported outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE)	• Specific treatment-related PRO-CTCAE symptoms
To assess how a patient perceives her overall change in cancer symptoms since the start of study treatment using the PGIC and overall severity of cancer symptoms using PGIS.	• PGIC and PGIS
To explore the impact of treatment and disease state on health status assessed by EuroQol five-dimensional five-level questionnaire (EQ-5D-5L) to support health economic analysis and health technology assessment	• EQ-5D-5L
To describe and evaluate resource use associated with durvalumab treatment and underlying disease	• Health resource utilization measures including hospitalization, outpatient visits, or emergency department visits

Abbreviations: ADA Antidrug antibody; AE Adverse event; BICR Blinded independent central review; CCRT Concurrent chemoradiation therapy; CR Complete response; EORTC European Organization for Research and Treatment of Cancer; EQ-5D-5L EuroQol five-dimensional five-level questionnaire; HOSPAD Hospital

Admission; HRQoL Health-related quality-of-life; IHC Immunohistochemistry; ORR Objective response rate; OS Overall survival; PFS Progression-free survival; PFS (3yr) Progression-free survival at 3 years; PGIC Patient Global Impression of Change; PGIS Patient Global Impression of Severity; PK Pharmacokinetics; PR Partial response; PRO-CTCAE Patient-reported oucomes version of the Common Terminology Criteria for Adverse Events; QLQ-C30 30item core quality of life questionnaire; QLQ-CX24 Cervical cancer module; RECIST Response Evaluation Criteria in Solid tumors; SoC CCRT Standard of care concurrent chemoradiation therapy.

Overall design:

This is a randomized, double-blind, placebo controlled, multi-center, global, Phase III study to determine the efficacy and safety of durvalumab when combined with SoC CCRT and administered as adjuvant therapy following SoC CCRT compared to placebo with SoC CCRT as systemic treatment in patients with FIGO (2009) Stage IB2 to IVA cervical cancer.

In order to be eligible for this study, patients must be ≥18 years of age with FIGO (2009) Stage IB2 to IIB N+ and IIIA to IVA with any N. Patients must not have previously received any definitive surgical, radiation, or systemic therapy for cervical cancer and must be immunotherapy-naïve.

Approximately 714 patients from multiple sites will be randomized 1:1 to receive either durvalumab 1500 mg or placebo every 4 weeks (q4w) for 24 doses. In China, recruitment will continue until approximately 105 Chinese patients have been randomised, irrespective of whether or not the overall study enrolment has been reached. It is anticipated that this target may not be met before the global recruitment of approximately 714 is achieved. Patients in both arms will receive SoC CCRT consisting of external beam radiotherapy (EBRT) and brachytherapy (See Appendix G) , and concurrent cisplatin 40 mg/m^2 every 1 week (q1w) × 5 weeks with an optional 6th week (See Section 6.1.2 for descriptions of the dosing regimen.) Randomization will be stratified by disease stage status (FIGO (2009) Stage <III and node positive, FIGO (2009) Stage ≥III and node negative, or FIGO (2009) Stage ≥III and node positive), and region [United States, Canada, European Union, South Korea, and Japan] versus rest of the world. Patients will receive their assigned treatment until completion of planned therapy, clinical progression or RECIST 1.1-defined or histopathologic confirmation of local disease progression, unacceptable toxicity, withdrawal of consent, or another discontinuation criteria is met. (See Section 7.1 for additional details on discontinuation of study treatment.) Following completion of SoC CCRT, patients will be evaluated by clinical and radiological assessment. During the first 3 years (164 weeks) after randomization, this assessment will include an interval history for new signs or symptoms, physical examination including a pelvic examination to evaluate for local cervical cancer progression, and imaging (computed tomography [CT] scan or magnetic resonance imaging [MRI]) per RECIST 1.1 or histopathologic assessment every 12 weeks (q12w). During Years 4, and 5, imaging/histopathologic assessments will be performed every 6 months (24 weeks) and then annually until a PFS endpoint has been met or closure of the study.

Study Period:

Estimated date of first patient enrolled Q1 2019

Estimated date of last patient completed Q2 2024

Number of patients:

Approximately 714 patients from multiple sites will be randomized 1:1 to receive either durvalumab + SoC CCRT or placebo + SoC CCRT. In China, recruitment will continue until approximately 105 Chinese patients have been randomised, irrespective of whether or not the overall study enrolment has been reached. It is anticipated that this target may not be met before the global recruitment of approximately 714 is achieved.

Treatments and treatment duration:

Durvalumab 1500 mg via intravenous (IV) infusion q4w, starting C1D1, until completion of planned treatment or progression of disease (PD). (Please note, if a patient's weight falls to 30 kg or below (≤30 kg), then the patient should receive weight-based dosing equivalent to 20 mg/kg of durvalumab q4w after consultation between Investigator and Study Physician, until the weight improves to above 30 kg (>30 kg), at which point the patient should start receiving the fixed dosing of durvalumab 1500 mg q4w).

Placebo: Sterile solution of 0.9% (weight/volume [w/v]) sodium chloride for injection via IV infusion q4w, starting on C1D1, until completion of planned treatment or PD.

Chemoradiotherapy:

- Cisplatin 40 mg/m^2 IV q1w × 5 weeks. Per investigator discretion, patients can continue with an optional 6th week of platinum agent.
- See Appendix G for details regarding the radiotherapy regimen.

Duration of treatment

Unless specific treatment discontinuation criteria are met, patients will continue therapy until completion of planned therapy or clinical progression or RECIST 1.1-defined or histopathologic confirmation of local disease progression.

Progression during treatment

During the treatment period, patients who are clinically stable at an initial RECIST 1.1-defined PD may continue to receive study treatment at the discretion of the Investigator and

patient. A follow-up scan is to be collected after the initial RECIST 1.1-defined PD, no later than the next scheduled imaging visit, and no less than 4 weeks after the prior assessment of PD; this scan is evaluated using the criteria outlined in Appendix F. If the subsequent scan does not demonstrate radiological PD, then patient should continue IP. Scanning should continue until the next RECIST 1.1-defined PD which in turn will require a subsequent scan (must be evaluated using the criteria outlined in Appendix F).

Alternatively, patients may continue treatment until histopathological determination of tumor progression on biopsy. Patients may not continue on durvalumab/placebo if there is histopathological determination of progression.

Follow-up of patients post-discontinuation of study treatment

Patients who have discontinued treatment due to toxicity or symptomatic deterioration, clinical progression, or who have commenced subsequent anticancer therapy will be followed up with tumor assessments until PD (based on RECIST 1.1) plus an additional follow-up scan or until death (whichever comes first) and followed for survival.

Survival

All patients randomized in the study should be followed for survival.

Independent Data Monitoring Committee:

An independent data monitoring committee (IDMC) composed of independent experts will be convened to confirm the safety and tolerability of the proposed dose and schedule of durvalumab + SoC CCRT. The first safety review will take place when the first 25 patients across both treatment arms have completed SoC CCRT and have had at least 28 days of follow-up. The second safety review will take place when the first 60 patients across both treatment arms have completed SoC CCRT and have had at least 28 days of follow-up. Safety reviews will be carried out by the IDMC in an unblinded manner. After review of the unblinded data, the IDMC will make a recommendation on whether the study should continue recruitment as planned or hold recruitment.

An additional safety review for Japanese patients will take place when the first 9 patients in Japan have completed SoC CCRT and had 28 days of follow-up. This review will be carried out by the IDMC in an unblinded manner. After review of the unblinded data, the IDMC will make a recommendation on whether the study should continue recruitment as planned or hold recruitment in Japan.

In addition, the IDMC will meet approximately every 6 months thereafter to continue safety monitoring.

Full details of the IDMC procedures and processes can be found in the IDMC Charter.

Statistical methods

The primary objective of this study is to assess the efficacy of durvalumab + SoC CCRT compared with placebo + SoC CCRT in terms of PFS as assessed by investigator tumor assessments and histopathologic confirmation of local tumor progression. PFS (per RECIST 1.1 as assessed by investigator tumor assessments or histopathologic confirmation of local tumor progression) will be defined as the time from the date of randomization until the date of objective disease progression or death (by any cause in the absence of progression) regardless of whether the patient withdraws from therapy or receives another anticancer therapy prior to progression (ie, date of event or censoring – date of randomization + 1). A key secondary objective is to assess the efficacy of durvalumab + SoC CCRT compared with placebo + SoC CCRT in terms of OS. In order to provide strong control of the type I error rate α=5% (2-sided), the testing procedure for the primary endpoint and key secondary endpoint is hierarchical.

The analysis of the secondary endpoints of PFS (3 year), PFS and OS in PD-L1 positive patients, ORR, and CR rate will be based on investigator assessments using RECIST 1.1 or histopathologic confirmation of local progression. In addition, the key secondary endpoint (OS) and other secondary endpoints (Incidence of Local Progression, Distant Disease Recurrence, and Secondary Malignancy) will also be analyzed.

Efficacy data will be summarized and analyzed on an intent-to-treat (ITT) basis, and the treatment arms will be compared on the basis of randomized treatment, regardless of the treatment actually received. Patients who were randomized but did not subsequently go on to receive study treatment are included in the full analysis set (FAS) population.

Approximately 714 patients will be randomized 1:1 to durvalumab + SoC CCRT or placebo + SoC CCRT to obtain approximately 227 PFS events in the ITT population. The randomization will be stratified according to disease stage status (FIGO (2009) Stage <III and node positive, FIGO (2009) Stage ≥III and node negative, or FIGO (2009) Stage ≥III and node positive) and region [United States, Canada, European Union, South Korea, and Japan] versus rest of world.

The primary endpoint of PFS will be tested once. The secondary endpoint of OS will be tested at an interim and at a final timepoint. The alpha level allocated to OS will be controlled at the interim and final timepoints using the Lan DeMets (Lan and DeMets 1983) spending function separately for PFS and OS that approximates the O'Brien-Fleming approach, where the alpha allocated at the interim depends upon the proportion of information available.

The analysis of PFS and the interim analysis of OS will occur when approximately 227 PFS events have occurred across the durvalumab + SoC CCRT and placebo + SoC CCRT treatment arms. If the true hazard ratio (HR) for PFS is 0.65 (likely to correspond to an 11% increase in the proportion of patients event-free at 3 years from 65% to 76%), this analysis will have 90% power to demonstrate a statistically significant difference for PFS, assuming a 2-sided 5% significance level. Given the recruitment assumptions for PFS outlined above, the analysis for PFS is anticipated to occur approximately 53 months following the randomization of the first patient. It is anticipated that 86% of the target number of OS events (ie, approximately 195 of 227 OS events) will be available for the OS interim analysis.

The final OS analysis will occur at the earlier of 227 death events or 71 months following recruitment of the first patient. Assuming the same recruitment assumptions for PFS and a 3-year OS rate of 70% for placebo + SoC CCRT (Rose et al 1999), 227 deaths would be expected to occur 61 months following the randomization of the first patient. If the true hazard ratio (HR) is 0.65 (likely to correspond to an 9% increase in the proportion of patients alive at 3 years from 70% to 79%), this analysis will have 89% power to demonstrate a statistically significant difference for OS, assuming a 2-sided 5% significance level.

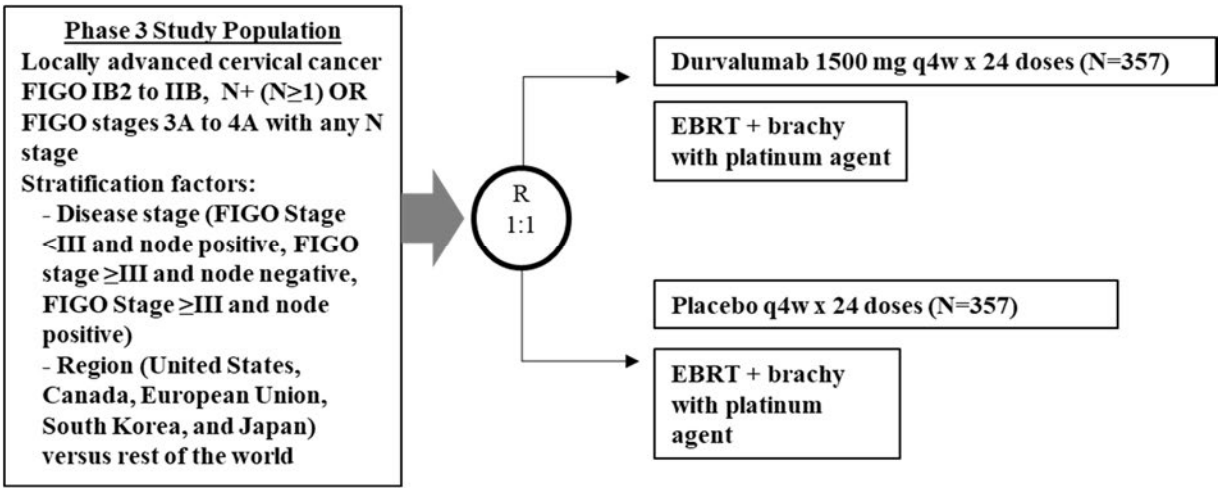
The primary PFS analysis will be based on the programmatically derived RECIST 1.1 using the investigator tumor assessments or histopathologic confirmation of local tumor progression. The effect of durvalumab + SoC CCRT versus placebo + SoC CCRT will be analyzed using a log-rank test stratified by disease stage status (FIGO (2009) Stage <III and node positive, FIGO (2009) Stage ≥III and node negative, or FIGO (2009) Stage ≥III and node positive) and region [United States, Canada, European Union, South Korea, and Japan] versus rest of the world. The HR together with its 95% CI and p-value will be presented (an HR less than 1 will favor durvalumab + SoC CCRT). The HR and CI will be estimated from a stratified Cox proportional hazards model using the same strata as for the primary analysis by stratified log rank test and using the Efron model for ties. The point estimate of the treatment effect, i.e. HR will be obtained by maximizing the Cox partial likelihood functions, which is the product of the likelihood of each stratum (an HR less than 1 will favor durvalumab + SoC CCRT). The 95% CI will be estimated using the profile likelihood approach. The 95% CI and HR from the stratified Cox proportional hazards model will be in support of the p-value from the stratified log rank test, no p-value will be reported from the stratified Cox proportional hazards model.

Safety is a secondary endpoint in this study. All safety analyses will be performed on the safety population. Safety and tolerability data will be presented by treatment arm using the safety population. Safety data will be summarized descriptively and will not be formally analyzed.

1.3 Schema

The general study design is summarized in Figure 1.

Figure 1 Study design



Abbreviations: brachy Brachytherapy; EBRT External Beam Radiotherapy; FIGO (2009) International Federation of Gynaecology and Obstetrics; q4w Every 4 weeks.

2. INTRODUCTION

2.1 Study rationale

Cervical cancer is the 4th most common cancer in women worldwide despite the introduction of the Pap smear for early screening and prevention of cervical cancer in the 1950s, and more recently, HPV vaccination. Many women continue to be diagnosed with and die from this disease, with an estimated 528000 new cases diagnosed in 2012 and 266000 deaths (Ferlay et al 2013). North America has the third lowest rate of cervical cancer; however, in the US there were 12109 women diagnosed with cervical cancer and 4092 deaths in 2011 (Benard et al 2014). In contrast, in China 98900 women were diagnosed with cervical cancer and 30500 women died of the disease in 2015 (Chen et al 2016). Overall, the 5-year OS in this patient population remains poor with survival at Stage IIB 58%, IIIA 35%, and IVA 16% (Ferlay et al 2013).

Rates of cervical cancer vary greatly between the developing world and developed countries due to disparities in access to care and preventive screening. The Pap smear was introduced in the 1950s as a screening method to diagnose atypical, premalignant lesions and early stage cervical cancer. United States Preventive Services Task Force (USPSTF) guidelines recommend screening for cervical cancer in all women aged 21 to 65 years and screening for HPV every 5 years in women aged 30 to 65 years (USPSTF 2016). Where implemented, this preventive care measure has reduced the incidence of advanced stage cervical cancer dramatically. However, most women globally do not have access to screening, and thus the global incidence of cervical cancer at all stages continues to rise throughout the world as the population rises and ages. Additionally, there are barriers to cervical cancer screening. Only 25% of women in Japan are screened for cervical cancer, and the rates of screening in China and India are similarly low with less than 20% of women in China screened and less than 10% in India (De Sanjose 2012). In contrast, the rate of women screened in the US is 88.6% (Benard et al 2014).

2.1.1 Rationale for combining checkpoint inhibitor therapy with chemoradiotherapy

Concurrent chemoradiation therapy (CCRT) have been shown to induce immunogenic cell death. Cell death, from radiation or CCRT, enhances the ability of the immune system to recognize and respond to the tumor through enhanced antigen release and presentation (tumor specific T cell activation; Formenti and Demaria 2013, Weichselbaum et al 2017). In addition, ionizing radiation causes upregulation of various pro-inflammatory signals and cytokines, which play a key role in immune regulatory pathway, leading to improved anti-tumor

immunity. Victor et al also showed that radiation enhanced the diversity of the T cell receptor repertoire of intra-tumoral T cells (Twyman-Saint Victor et al 2015).

Radiotherapy induces double-stranded deoxyribonucleic acid (DNA) breaks that are catastrophic for the rapidly dividing tumor cells, promoting a cascade of cytokine release and mitochondrial disruption and results in apoptosis and activation of both the innate and adaptive immune system. This mechanism promotes neoantigen production, resulting in antigen presentation to dendritic cells, natural killer (NK) cell activation, and cluster of differentiation 8 (CD8) + T cell recruitment to the area of damage (Salama et al 2016).

The PACIFIC trial evaluated the efficacy of durvalumab after definitive chemoradiotherapy in Stage III NSCLC compared to placebo after chemoradiotherapy and found a significant improvement with durvalumab with a median PFS of 16.8 months (95%CI 13.0 to 18.1) compared to 5.6 months (95%CI, 4.6 to 7.8) in the placebo controlled group (Antonia et al 2017). This improvement in PFS in this patient population was thought to be due to multiple variables, with the highly immunogenic tumor microenvironment associated with chemoradiotherapy likely an important contributor.

Concomitant administration of radiotherapy with anti-PD-L1 monoclonal antibodies (mAb) resulted in substantially improved survival benefit in a mouse model. Here, low dose fractionated radiotherapy resulted in an increase in interferon gamma (IFN-y) producing CD8+ T cells and PD-L1 tumor expression during radiotherapy, peaking at 72 hours after the last dose and significantly declining at 7 days after radiotherapy (Dovedi et al 2014). Radiation therapy can additionally induce an abscopal effect, where tumors not directly in the field of radiation therapy also become more immunogenic due to the release of neoantigens from the tumor site, when given sequentially (Postow et al 2012) and also concurrently (Stamell et al 2013).

The use of concurrent durvalumab therapy with chemotherapy and/or radiotherapy is currently being studied in NSCLC [redacted] ([redacted]), colorectal cancer ([redacted]), urothelial bladder cancer [redacted], and hepatocellular carcinoma (NCT02821754).

The use of combination chemoradiotherapy is a mainstay of oncology therapy in multiple tumor types. The goal of combination chemotherapy is to utilize agents that affect cancer cells by different mechanisms, thus improving clinical responses and reducing the risk of developing resistance. Non-clinical and clinical studies have indicated that blockade of immune checkpoints (PD-1/PD-L1 and CTLA-4) can have a positive effect on anti-tumor immunity. Chemotherapy is thought to synergize with PD-1/PD-L1 blockade by making the tumor “immunogenic” by initiating cell death, promoting phagocytosis of tumor cells, and ultimately leading to reactivation of immune-mediated tumor surveillance (Menderes et al

2016). Current studies are now adding immunotherapeutics to chemoradiotherapy to broaden anti-tumor responses through recruitment of the immune system.

The study's hypothesis is that durvalumab, when administered with SoC CCRT and as adjuvant therapy following SoC CCRT, will improve PFS when compared to SoC CCRT combined with placebo.

2.2 Background

A detailed description of the chemistry, pharmacology, efficacy, and safety of durvalumab is provided in the current IB.

2.2.1 Human papilloma virus infection in cervical cancer

Persistent infection with HPV is central to the onset of cervical cancer. There are more than 120 HPV types that have been identified, with 40 types infecting the genital tract and 15 potentially oncogenic. About 50% and 20% of cervical cancer has been linked to HPV 16 and HPV 18 infections, respectively. HPV infection occurs through microtrauma to the suprabasal epidermal cells, allowing the virus access to the basal layer. Viral oncoproteins E6 and E7 promote tumor suppressor p53 degradation and Rb inactivation, respectively, promoting carcinogenesis (Lowy and Schiller 2006). Cell cycle deregulation mediated by deactivation of tumor suppressors and integration of HPV into host genome are key precursors to the invasive disease (Crosbie et al 2013). The most common screening methods for cervical cancer include conventional Papanicolaou (Pap) smear and HPV DNA testing, depending on the geographical region. The Pap smear can identify cellular abnormalities whereas the HPV test can detect suspicious viruses (Jin 2014). For many years, the Pap smear has been the standard method for cervical cancer screening, reducing the incidence by 60% to (Marth et al 2017) and has been shown to provide 60% to 70% greater protection against invasive cancer compared with cytology-based screening (Ronco et al 2014).

To prevent a primary infection with HPV, the quadrivalent vaccine Gardasil was approved by the FDA in 2006 for children and adults between the ages of 11 to 25 years. Currently, there are 3 vaccines in use: the Cervarix bivalent vaccine, which targets HPV 16 and 18, the Gardasil quadrivalet vaccine (HPV 6, 11, 16, and 18) and the Gardasil-9, a 9 valent HPV vaccine (HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58). HPV vaccination is part of the National Immunization Programs (NIP) or pilot demonstration programs in 83 countries (Markowitz et al 2012); however, there are instances where the vaccination program is not being optimally utilized. In Japan, for example, the proactive recommendations for the HPV vaccine were suspended 2 months after its inclusion into the NIP in 2013 after unconfirmed reports of AEs following vaccination (Hanley et al 2015). As a result, current low uptake of the HPV vaccine in Japan (3.5% in 7th to 11th grades in 2013) may potentially lead to a high incidence of cervical cancer in the future (Sekine et al 2016). As of October 2014, about 59.2 million

women have received at least 1 dose of the vaccine, with the majority of women from high-income and upper-middle income countries. With increasing vaccine utilization, it is expected that by 2080 that approximately 440000 cervical cancer cases will be prevented; yet, because many countries have not implemented widespread vaccination or because the cost of vaccine precludes its widespread implementation, an additional 510000 women will develop cervical cancer during this interval (Bruni et al 2016).

2.2.2 Staging of cervical cancer

Cervical tumors are staged using FIGO (2009) classification, which is the most widely used classification (Haie-Meder et al 2010) and is one of the most important prognostic factors (Marth et al 2017). Cervical cancer is the only gynecological cancer that is clinically staged based on tumor size, vaginal or parametrial involvement, bladder/rectum extension, and distant metastases. It requires examination under anaesthesia, radiological imaging such as chest X-ray and IV pyelogram, or other diagnostic tools. CT can detect pathological lymph nodes, MRI can determine tumor size, degree of stromal penetrations, parametrial involvement, vaginal extension, and corpus extension with high accuracy (Wagenaar et al 2001).

2.2.3 Lymph node status in cervical cancer

Lymph node status is not part of the FIGO (2009) staging system for cervical cancer, but provides important information for prognosis and treatment (Gien and Covens 2009). As the FIGO stage increases, the risk of lymph node metastasis and parametrial involvement also increases. In patients who have had a surgical resection, the incidence of pelvic lymph node metastasis in Stage IB cervical cancer ranges from 11.5% to 21.7% (Lee et al 2006). For Stage IIA and IIB cervical cancers, the incidence ranges from 10% to 26.7% and 28.6% to 43.4%, respectively (Benedetti-Panici et al 1996, Havrilesky et al 2004, Inoue et al 1990, Lai et al 1993, Lee et al 2006, Morice et al 1999, Sakuragi et al 1999). In patients with Stage IB cervical cancer, the incidence of para-aortic node involvement is low at 2% to 4%. In the more advanced stages, the incidence increases to 7% to 17% (Benedetti-Panici et al 1996, Berman et al 1984, Morice et al 1999, Sakuragi et al 1999).

Lymph node status is a prognostic predictor of survival (Macdonald et al 2009). The 3 year OS in FIGO (2009) Stage IB to II node-positive patients is lower (55%) compared to node-negative (94%) (Morice et al 1999). Based on data from over 2200 patients in Stage IA1 to IIB, higher number of positive lymph nodes is associated with adverse survival outcomes (Zhou et al 2017), and the extra-pelvic recurrence is higher in patients with ≥3 involved lymph nodes compared to patients with 0 to 2 lymph nodes (data from 141 patients, Stage IB to IIB) (Kasuya et al 2013). Typically, the adjacent obturator nodes will be the first site of lymph node metastasis, and then it will spread in a step-wise fashion to the ipsilateral common iliac lymph nodes and para-aortic lymph nodes (PALN). Patients with PALN metastasis have lower

survival rates and need extended field radiation (EFRT). In a retrospective study looking at 90 patients with Stage IB to IVA cervical cancer and PALN metastasis between 1987 and 2012, it was shown that EFRT was an efficient treatment for uterine cervical cancer with involved PALN, with a 5-year OS of 62.6% and PFS of 43.9% (Yoon et al 2015).

2.2.4 Treatment of cervical cancer

Stage IA1 cervical cancer is typically managed conservatively to preserve fertility, with conization without lymphadenectomy because the risk of nodal metastasis is <1%. Stage IA2 with no lymphovascular space involvement can be treated by conization (if fertility is to be preserved) or extrafascial hysterectomy. In patients with surgical contraindication, brachytherapy may represent an alternative option. Stages IB and IIA cervical carcinoma can be cured by radical surgery including pelvic lymphadenectomy or radiotherapy (Haie-Meder et al 2010). In women with locally advanced cervical cancer (Stages 1B2 to IVA), cisplatin with concurrent radiotherapy has remained the SoC (Colombo et al 2012) and is unchanged since 1999 (Rose et al 1999, Koh et al 2013).

For women who develop locally advanced cervical cancer, the SoC has evolved from EBRT alone, to EBRT plus brachytherapy, to combined EBRT plus brachytherapy with concurrent chemotherapy (Green et al 2001). Brachytherapy involves the application of a radioactive source in close proximity to the tumor, allowing a very high dose of radiation being delivered to the tumor with relative sparing of the surrounding normal structures (Banerjee and Kamrava 2014). Brachytherapy treatments are either interdigitated with EBRT (generally, starting no earlier than Week 3 of treatment) or are given after EBRT is completed. Starting brachytherapy later in the treatment course allows for maximal tumor shrinkage, thus allowing for smaller brachytherapy treatment volumes. Ultimately, the most critical part of deciding when to start brachytherapy is the monitoring of treatment response, through regular pelvic examinations during the course of EBRT (Banerjee and Kamrava 2014). Brachytherapy can be performed using an intracavitary, interstitial, or combination approach. Intracavitary brachytherapy involves placing the radioactive source using an applicator, through the vaginal cavity, and can treat the upper vagina, cervix, and uterus. In interstitial brachytherapy, catheters (small tubes) are placed in and around residual disease, using a transperineal/vaginal approach. The choice of technique depends primarily on disease extent and anatomy (Banerjee and Kamrava 2014).

In the pivotal study, Rose et al 1999 randomized 526 women with Stage IIB, III, or IVA cervical cancer to receive radiation therapy with either cisplatin, cisplatin with 5-fluorouracil (5FU) with hydroxyurea or hydroxyurea alone. For the cisplatin monotherapy cohort when compared to hydroxyurea monotherapy, the PFS risk ratio (RR) of 0.57 (95% CI 0.42 to 0.78) and OS RR of 0.61 (95%CI 0.44 to 0.85) were observed and was similar to- the cisplatin with 5FU group (PFS RR=0.55). Toxicities included cytopenias-, gastrointestinal (GI) effects, renal toxicity, and neurotoxicity **(**Rose et al 1999**).** Additionally, the duration for CCRT administration is critical to patient outcome. Completion of CCRT in 56 days compared to more than 56 days was associated with benefits in reduced pelvic failure rate and improved OS, compared to prolonged CCRT administration (Song et al. 2013, Petereit et al. 1995). In certain clinical scenarios, carboplatin has been substituted for cisplatin as a radiosensitizer,. The potential difference between carboplatin and cisplatin was retrospectively evaluated in 247 women receiving definitive chemoradiotherapy for locally advanced cervical cancer. In this evaluation, cisplatin was superior, with a CR rate of 88.3% compared to 73.9% (p=0.004) (Valdivieso et al 2017). However, in women that are unable to receive cisplatin due to specific pre-existing conditions such as renal insufficiency or peripheral neuropathy, carboplatin is an acceptable alternative. Another study evaluated 51 women who received concurrent carboplatin with radiotherapy in comparison to a historical control of cisplatin with radiotherapy, and there was no appreciable difference in OS and PFS between the 2 groups; there was an increase in the number of cycles administered and a reduction in AEs in the carboplatin group (Nam et al 2013). An additional retrospective study of 148 women treated with carboplatin and concurrent radiotherapy showed that 142 (95.9%) women had a CR and only 6 (4.1%) had persistent disease. The 2-year PFS and OS rates were 75.1% and 81.9%, respectively (Katanyoo et al 2011). In patients that are able to receive cisplatin, both the NCCN guidelines (NCCN 2020) and ESMO guidelines (Marth et al 2017

) for cervical cancer recommend cisplatin to be given with EBRT. To ensure appropriate balance between patients treated with cisplatin and carboplatin as the radiosensitizer across regions in the ongoing study, no further use of carboplatin as the radiosensitizer will be allowed in this study.
Although data are limited, available evidence suggests that concurrent chemoradiotherapy is superior to sequential treatment. An analysis of the trials evaluating systemic chemotherapy after chemoradiotherapy showed that there is limited benefit and instead there may be an increased toxicity in this patient population (Tangjitgamol et al 2014). Currently, the Gynecologic Oncologic Group (GOG) is performing a Phase III randomized multicenter study in 900 women with cervical cancer to evaluate the efficacy of carboplatin with paclitaxel given adjuvantly following definitive chemotherapy/radiotherapy with a primary endpoint of OS (OUTBACK Trial, NCT01414608).

Surgery is not typically indicated in patients with locally advanced cervical cancer. . In a single-center Phase 3 randomized controlled clinical trial, 633 women with locally advanced

cervical cancer were randomly assigned to receive neoadjuvant chemotherapy followed by radical hysterectomy or chemoradiotherapy without surgery; those who received surgery had decreased 5-year disease-free survival (DFS) (69.3% versus 76.7%, p=0.038) (Gupta et al 2018) In a retrospective analysis of 211 patients undergoing definitive chemoradiation and brachytherapy, completion hysterectomy after definitive chemoradiation and brachytherapy was associated with increased morbidity with no change in OS or DFS. Cumulative incidence of severe late morbidity was observed in 22.5% of patients in in the group that received a hysterectomy compared to 6.5% in the non-hysterectomy group (p=0.016) (Mazeron et al 2016).

The relapse rate of cervical cancer ranges between 28 and 64% in FIGO (2009) Stages IIB to IVA (Quinn et al 2006). Although the majority of the recurrences develop in the first 2 to 3 years after treatment, in some patients, cervical cancer recurs after 3 years (Elit et al 2009, Fuglsang et al 2015, Wiebe et al 2012).

2.2.5 Cervical cancer establishes an immunosuppressive environment

HPV is the primary causative agent for the majority of cervical cancer cases, with more than 90% of squamous cervical cancers containing HPV DNA. In the presence of a chronic HPV infection, a natural immune response develops with activation of the adaptive immune system. HPV proteins E6 and E7 also promote neoantigen generation, further stimulating the immune response (Qin et al 2017). However, the viral oncoproteins E5, E6, and E7 play a role in immune evasion, with E5 inhibiting expression of human leukocyte antigens-A (HLA-A) and HLA-B. This results in evasion of CTL and NK cell killing (Menderes et al 2016). HPV16 positive tumors have a unique immune suppressive environment with increasing numbers of tumor-associated macrophages observed, contributing to chronic infection (Lepique et al 2009). From retrospective tissue evaluation of pre-malignant cervical tissue, there is increasing PD-1 expression seen on cervical T cells with increasing levels seen at higher grades of cervical intraepithelial neoplasia (Yang et al 2017). On evaluation of tumor tissue from 115 patients with cervical cancer, PD-L1 was expressed in 19% of samples, and programmed death-ligand 2 (PD-L2) expressed in 29% of tumors (Karim et al 2009).

Histologically, cervical cancer is predominantly squamous cell carcinoma (80% to 90%) with a high tumor mutational burden (TMB). Chronic HPV infection is thought to contribute to continued somatic mutations and therefore the high TMB in cervical cancer. This high mutational load in cervical cancer additionally correlated with increased expression of PD-L1, transforming growth factor beta (TGF-β), and interleukin 10 (IL-10), which supports the role for immunotherapy (Qin et al 2017). Cervical cancer additionally evades the immune response through mutations in the IFN-γ signaling pathway and Janus Kinase 2 (JAK2) (Ojesina et al 2014). The TMB is thought to be directly correlated to response of immune checkpoint inhibitor therapy, which appears to be true for cervical cancer as well (Yarchoan et al 2017).

These nonclinical studies demonstrate that immune suppression is an important factor for PD in cervical cancer. By promoting an immunogenic environment through chemoradiotherapy, there is an opportunity to change the balance in cancer progression through checkpoint inhibitor therapy.

2.2.6 Previous checkpoint inhibitor therapy in cervical cancer

Based on the strong rationale for immunotherapy in this patient population, multiple studies have been done in patients with cervical cancer that were previously treated. In Study CD-ON-MEDI4736-1108 (hereafter referred to as Study 1108), 10 women with cervical cancer were treated with durvalumab monotherapy; an ORR of 20% (2/10) was observed. This is broadly consistent with results seen with other checkpoint inhibitors in previously treated cervical cancer. The KN-158 trial treated 98 women with cervical squamous cell cancer with pembrolizumab. This study demonstrated an ORR of 12% (12/98) with 3 patients with a CR (Schellens et al 2017). The FDA granted accelerated approval to pembrolizumab for the treatment of patients with advanced, PD-L1-positive cervical cancer with disease progression on or after chemotherapy in June 2018. CheckMate 358 treated 19 women with recurrent cervical cancer with nivolumab and found an ORR of 26.3% and median PFS of 5.5 months (Hollebecque et al 2017). These checkpoint inhibitors were well tolerated and had a reasonable toxicity profile. PD-L1 and PD-1 expression positively correlates with HPV-positivity, increase in cervical intraepithelial neoplasia (CIN) grade, and tumor metastasis. In fact, low expression (score 0 or 1) of PD-L1 was found to be a prognostic factor of tumor relapse, highlighting the need for patients with low or negative expression of PD-L1 to use more aggressive treatment other than conventional CRT (Yang et al 2017).

2.2.7 Immunotherapies

It is increasingly understood that cancers are recognized by the immune system, and under some circumstances, the immune system may control or even eliminate tumors (Dunn et al 2004).

PD-L1 is part of a complex system of receptors and ligands that are involved in controlling T-cell activation. The PD-1 receptor (CD279) is expressed on the surface of activated T cells (Keir et al 2008). It has 2 known ligands: PD-L1 (B7-H1; CD274) and PD-L2 (B7-DC; CD273) (Okazaki et al 2007). PD-1 and PD-L1/PD-L2 belong to a family of immune checkpoint proteins that act as co-inhibitory factors, which can halt or limit the development of T cell response. When PD-L1 binds to PD-1, an inhibitory signal is transmitted into the T cell, which reduces cytokine production and suppresses T cell proliferation. Tumor cells exploit this immune checkpoint pathway as a mechanism to evade detection and inhibit immune response.

PD-L1 is constitutively expressed by -B cells-, dendritic cells, and macrophages (Qin et al 2016). Importantly, PD-L1 is commonly overexpressed on tumor cells or on nontransformed cells in the tumor microenvironment (Pardoll 2012). PD-L1 expressed on the tumor cells binds to PD-1 receptors on the activated T cells, leading to the inhibition of cytotoxic T cells. These deactivated T cells remain inhibited in the tumor microenvironment. The PD-1/PD-L1 pathway represents an adaptive immune resistance mechanism that is exerted by tumor cells in response to endogenous anti-tumor activity.

The inhibitory mechanism described above is co-opted by tumors that express PD-L1 as a way of evading immune detection and elimination. The binding of an anti-PD-L1 agent to the PD-L1 receptor inhibits the interaction of PD-L1 with the PD-1 and CD80 receptors expressed on immune cells. This activity overcomes PD-L1-mediated inhibition of anti-tumor immunity. While functional blockade of PD-L1 results in T cell reactivation, this mechanism of action is different from direct agonism of a stimulatory receptor such as CD28.

PD-L1 is expressed in a broad range of cancers. Based on these findings, an anti-PD-L1 antibody could be used therapeutically to enhance anti-tumor immune responses in patients with cancer. Results of pre-clinical and clinical studies of mAbs targeting the PD-L1/PD-1 pathway have shown evidence of clinical activity and a manageable safety profile, supporting the hypothesis that an anti-PD-L1 antibody could be used to therapeutically enhance anti-tumor immune response in cancer patients (Brahmer et al 2012, Hirano et al 2005, Iwai et al 2002, Okudaira et al 2009, Topalian et al 2012, Zhang et al 2008) with responses that tend to be more pronounced in patients with tumors that express PD-L1 (Powles et al 2014, Rizvi et al 2015, Segal et al 2015). In addition, high mutational burden (eg, in bladder carcinoma; Alexandrov et al 2013) may contribute to the responses seen with immune therapy.

Pre-clinical data has now been added to a wealth of clinical data showing that blockade of negative regulatory signals to T cells such as CTLA-4 and PD-L1 has promising clinical activity. Ipilimumab was first granted United States (US) Food and Drug Administration (FDA) approval for the treatment of metastatic melanoma and is currently under investigation for several other malignancies. Nivolumab and pembrolizumab, 2 anti-PD-1 agents, and atezolizumab, an anti-PD-L1 agent, have been granted approvals by agencies for the treatment of a number of malignancies including metastatic melanoma, squamous and non-squamous cell non-small-cell lung cancer, squamous cell carcinoma of the head and neck, and urothelial carcinoma. In addition there are data from agents in the anti-PD-1/PD-L1 class showing clinical activity in a wide range of tumor types.

2.2.8 Durvalumab

Durvalumab (MEDI4736, Imfinzi™) is a human monoclonal antibody (mAb) of the immunoglobulin G 1 kappa subclass that blocks the interaction of PD-L1 (but not PD-L2)

with PD-1 on T cells and CD80 (B7.1) on immune cells. It is being developed by AstraZeneca/MedImmune for use in the treatment of cancer. (MedImmune is a wholly owned subsidiary of AstraZeneca; AstraZeneca/MedImmune will be referred to as AstraZeneca throughout this document.) The proposed mechanism of action (MOA) for durvalumab is interference in the interaction of PD-L1 with PD-1 and CD80 (B7.1). Blockade of PD-L1/PD-1 and PD-L1/CD80 interactions releases the inhibition of immune responses, including those that may result in tumor elimination. In vitro studies demonstrate that durvalumab antagonizes the inhibitory effect of PD-L1 on primary human T cells resulting in the restored proliferation of IFN-γ (Stewart et al 2015). In vivo studies have shown that durvalumab inhibits tumor growth in xenograft models via a T cell-dependent mechanism (Stewart et al 2015). Based on these data, durvalumab is expected to stimulate the patient's anti-tumor immune response by binding to PD-L1 and shifting the balance toward an anti-tumor response. Durvalumab has been engineered to reduce antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity.

To date, durvalumab has been given to more than 6000 patients as part of ongoing studies either as monotherapy or in combination with other anticancer agents. Details on the safety profile of durvalumab monotherapy are summarized in Section 4.3.1 and Section 8.3.12. Refer to the current durvalumab IB for a complete summary of pre-clinical and clinical information including safety, efficacy, and PK.

2.3 Benefit/risk assessment

More detailed information about the known and expected benefits and risks and reasonably expected AEs of durvalumab may be found in the IB.

See Section 9.6.1 and Appendix A for information regarding the IDMC.

2.3.1 Potential benefits

2.3.1.1 Durvalumab as monotherapy in cervical cancer

The majority of the safety and efficacy data currently available for durvalumab are based on the first-in-human, single-agent study, Study 1108, in patients with advanced solid tumors, the study of durvalumab monotherapy in NSCLC (Study D4191C00003 [ATLANTIC]), and the study of durvalumab monotherapy in NSCLC following completion of platinum-based chemotherapy concurrent with radiation therapy (the PACIFIC study). Data from these studies have demonstrated clinical activity of durvalumab therapy in patients with NSCLC. Study 1108 included a 10-patient cohort with cervical cancer that showed 14.3% ORR following durvalumab monotherapy (10 mg/kg every 2 weeks [q2w]). Details pertaining to Study 1108 and ATLANTIC are provided in the durvalumab IB. In a combination study of durvalumab with AXELimogene (HPV vaccine) in recurrent/persistent or metastatic cervical cancer, the durvalumab monotherapy arm showed 8% ORR, and ORR+ stable disease (SD) was 40%.

PACIFIC has shown significant improvements in median PFS with durvalumab treatment compared with placebo for patients with NSCLC (16.8 months [95% CI: 13.0, 18.1] versus 5.6 months [95% CI: 4.6, 7.8]; stratified HR for disease progression or death, 0.52; 95% CI: 0.42, 0.65; p<0.001). Similar findings in favor of durvalumab compared with placebo were found for duration of response (72.8% versus 46.8% of patients had ongoing response at 18 months, respectively) and median time to death or distant metastasis (23.2 months versus 14.6 months, respectively; p<0.001). In addition, CCRT followed by durvalumab monotherapy (10 mg/kg q2w) was well tolerated and had a manageable safety profile relative to the SoC.

2.3.1.2 Concurrent immunotherapy and chemoradiotherapy in cervical cancer

Concurrent immunotherapy and chemotherapy

The efficacy of immunotherapy administered concurrently with chemotherapy agents is supported by recent results from the KEYNOTE021 study (pembrolizumab; PD-1 inhibitor), the CheckMate 012 study (nivolumab; PD-1 inhibitor), and preliminary results from CCI

The anti-tumor activity of pembrolizumab administration concurrent with various chemotherapy regimens versus chemotherapy (carboplatin-pemetrexed) alone as first-line treatment for NSCLC (the KEYNOTE-021 study) demonstrated ORRs of 55% (95% CI: 42, 68) versus 29% (95% CI: 18, 41), respectively (p=0.0016), with durations of response of at least 6 months in 92% (95% CI: 73, 98) and 81% (95% CI: 51, 93), respectively (Langer et al 2016).

The anti-tumor activity of nivolumab administered concurrently with platinum-based doublet chemotherapy as firstline treatment for advanced NSCLC (the CheckMate 012 study) demonstrated ORRs for nivolumab 10 mg/kg plus gemcitabine-cisplatin, nivolumab 10 mg/kg plus pemetrexed-cisplatin, nivolumab 10 mg/kg plus paclitaxel-carboplatin, and nivolumab 5 mg/kg plus paclitaxel-carboplatin of 33%, 47%, 47%, and 43%, respectively, and 24-week PFS rates of 51%, 71%, 38%, and 51%, respectively (Rizvi et al 2016).

The efficacy of durvalumab ± tremelimumab with standard platinum-based chemotherapy in advanced cancers is being generated from 2 ongoing Phase I studies: internal Study CCI and a CCI run by the Canadian Cancer Trials Group (CCTG). Study CCI is evaluating the safety and tolerability of durvalumab + tremelimumab in combination with first line chemotherapy regimens in patients with locally advanced or metastatic solid tumors: ovarian/peritoneal/fallopian tube cancer, squamous cell carcinoma of the head and neck (SCCHN), triple negative breast cancer (TNBC), small cell lung carcinoma (SCLC), and gastric/gastro-esophageal junction (GEJ) cancer, pancreatic ductal adenocarcinoma (PDAC)

and esophageal squamous cell carcinoma (ESCC). Results from this study are expected in 2019. Patients in the CCTG study were treated with durvalumab ± tremelimumab at 1 of 4 dose levels concomitantly with either pemetrexed + carboplatin/cisplatin followed by pemetrexed consolidation for non-squamous histology (45 patients) or gemcitabine + carboplatin/cisplatin for squamous histology (9 patients). Preliminary results from this study indicated that a total of 45 patients (44% male; median age=62 years [range 36 to 78]; 100% Eastern Cooperative Oncology Group [ECOG] PS ≤1) in the pemetrexed-platinum cohort received a total of 346 treatment cycles whereas 9 patients (78% male; median age=64 years [range 57 to 80]; 100% ECOG PS ≤1) in the gemcitabine-platinum group received a total of 55 treatment cycles. The ORR was 57.1% (95% CI: 39.4, 73.7) in 35 evaluable patients receiving pemetrexed-platinum and 37.5% (95% CI: 8.5, 75.5) in 8 evaluable patients receiving gemcitibine-platinum (Juergens et al 2017).

Concurrent immunotherapy and radiation therapy

Currently, over a dozen clinical studies are evaluating anti-PD-1 and anti-PD-L1 antibodies in administration concurrently with (as opposed to after completion of) radiation for cancer treatment, but robust efficacy results are not yet available (Weichselbaum et al 2017). Several non-clinical studies, as described below, suggest that inhibition of the PD-1/PD-L1 checkpoint combined with radiotherapy liberates T cells from immunosuppression, which in turn positively alters the tumor microenvironment owing to killing of suppressive cells via cytokine secretion. Mouse tumor models have been used to demonstrate the synergistic effect of radiotherapy and immunotherapy via checkpoint inhibition in solid tumors (Weichselbaum et al 2017). A preliminary non-clinical report from the Drake laboratory indicates that radiotherapy combined with anti-PD-1 antibody treatment can result in primary tumor control and an abscopal effect (Sharabi et al 2014). More recent data from the same group indicate that this therapy combination results in the induction of endogenous antigen-specific immune responses, leading to improved local control in single tumor models of melanoma or breast carcinoma (Sharabi et al 2015); however, no experiments on the abscopal effect were reported. Dovedi and Illidge (Dovedi and Illidge 2015) subsequently noted that the timing of anti-PD-L1 blockade is crucial; concurrent radiation and anti-PD-L1 treatment, but not sequential treatment, resulted in long-term tumor control, suggesting that concurrent administration of durvalumab and SoC radiotherapy may have improved clinical benefit over sequential therapy.

2.3.2 Overall risks

Monoclonal antibodies directed against immune checkpoint proteins, such as PD-L1 as well as those directed against PD-1 or CTLA-4, aim to boost endogenous immune responses directed against tumor cells. By stimulating the immune system, however, there is the potential for adverse effects on normal tissues.

Most adverse drug reactions seen with the immune checkpoint inhibitor class of agents are thought to be due to the effects of inflammatory cells on specific tissues. These risks are generally events with a potential inflammatory or immune-mediated mechanism and that may require more frequent monitoring and/or unique interventions such as immunosuppressants and/or endocrine therapy. These immune-mediated effects can occur in nearly any organ system, and are most commonly seen as GI AEs such as colitis and diarrhea, pneumonitis/interstitial lung disease (ILD), hepatic AEs such as liver enzyme elevations, skin events such as rash and dermatitis, and endocrinopathies including hypo- and hyper-thyroidism.

2.3.2.1 **Durvalumab**

Risks with durvalumab include, but are not limited to, diarrhea/colitis, pneumonitis/ILD, endocrinopathies (ie, events of hypophysitis/hypopituitarism, adrenal insufficiency, hyper- and hypo-thyroidism, type I diabetes mellitus and diabetes inspidus), hepatitis/increases in transaminases, nephritis/increases in creatinine, pancreatitis/increases in amylase and lipase, rash/dermatitis (including pemphigoid), myocarditis, myositis/polymyositis, immune thrombocytopenia, infusion-related reactions, hypersensitivity reactions, pancreatitis, serious infections, and other rare or less frequent inflammatory events including neuromuscular toxicities (eg, Guillain-Barré syndrome, myasthenia gravis.

For information on all identified and potential risks with durvalumab, please always refer to the current version of the durvalumab IB.

In monotherapy clinical studies, AEs at an incidence of >=20% includes events such as fatigue anddecreased appetite. Approximately 10% of patients discontinued the drug due to an AE. Please see the current version of the IB for a detailed summary of the monotherapy data including AEs, serious adverse events (SAEs), and common terminology criteria (CTC) Grades 3 to 5 events reported across the durvalumab program.

The majority of treatment-related AEs were manageable, with dose delays, symptomatic treatment, and in the case of events suspected to have an immune basis, the use of established treatment guidelines for immune-mediated toxicity (see Section 8.4.5).

A detailed summary of durvalumab monotherapy AE data can be found in the current version of the durvalumab IB.

2.3.3 Overall benefit/risk

The clinical activity associated with potentiating the proinflammatory effects of CCRT suggests that giving durvalumab in combination with CCRT may have clinical benefits, including increasing the response rate to CCRT, improving the CR rate, and decreasing the number of patients who progress on CCRT.

Safety observations to date have demonstrated that concurrent administration of CCRT and immunotherapy has generally been well tolerated, with toxicities comparable to administration of either agent alone. The safety of concurrent administration of durvalumab and CCRT is further supported by results from the PACIFIC study, which showed that durvalumab administered within 42 days of completion of CCRT had a well tolerated and manageable safety profile that was consistent with the established safety profile to date.

Therefore, the overall benefit-risk assessment supports the proposed study to evaluate the efficacy and safety of concurrent administration of durvalumab + SoC CCRT.

3. OBJECTIVES AND ENDPOINTS

Table 3 Study objectives

Primary objective:	**Endpoint/Variable:**
To assess the efficacy of durvalumab + SoC CCRT compared with placebo + SoC CCRT in terms of PFS	Endpoints based on the investigator assessment according to RECIST 1.1 or histopathologic confirmation of local tumor progression: • PFS: Time from date of randomization until tumor progression or death due to any cause
Secondary objectives:	**Endpoint/Variables:**
To further assess the efficacy of durvalumab + SoC CCRT compared with placebo + SoC CCRT in terms of PFS (3 year), PFS in PD-L1 positive patients, overall survival (OS) (key), OS in PD-L1 positive patients, ORR CR rate, and DoR in Patients with a CR	• OS: Time from date of randomization until the date of death by any cause Endpoints based on the investigator assessment according to RECIST 1.1 or pathologic assessment of local disease progression • PFS (3 year): Proportion of patients alive and progression-free at 3 years • PFS in PD-L1 positive patients: Time from date of randomization until tumor progression or death due to any cause in patients who are PD-L1 positive (>=1%) based on either tumor or immune cell staining • OS in PD-L1 positive patients: Time from date of randomization until date of death by any cause in patients who are PD-L1 positive (>=1%) based on either tumor or immune cell staining

	• ORR: The percentage of evaluable patients with an Investigator-assessed visit response of CR or PR • CR rate: Disappearance of all target and non-target lesions DoR in Patients with a CR: Time from date of first detection of CR until the date of objective disease progression according to RECIST 1.1
To assess the effect of durvalumab + SoC CCRT compared with placebo + SoC CCRT on the incidence of local progression, distant disease progression, and secondary malignancy as the first documented progression event	• Incidence of Local Progression, Distant Disease Progression, and Secondary Malignancy: Number and percentage of patients who develop local progression, distant disease recurrence, or secondary malignancy
To assess disease-related symptoms and health-related quality of life (HRQoL) in patients with cervical cancer treated with durvalumab + SoC CCRT compared with placebo + SoC CCRT using the core quality of life questionnaire (EORTC QLQ-C30) and core quality of life questionnaire cervical cancer module (CX24)	• Change from baseline in EORTC QLQ-C30 and EORTC CX24
To assess the PK of durvalumab when in combination with CCRT	• Blood concentration of durvalumab
To investigate the immunogenicity of durvalumab in both arms in combination with CCRT	• Presence of ADAs
Safety objective:	**Endpoint/Variable:**
To assess the safety and tolerability profile of durvalumab + SoC CCRT compared to placebo + SoC CCRT	• AEs, laboratory findings, vital signs, and physical examinations
Exploratory objective:	**Endpoint/Variable:**
To collect blood and tissue samples for defining biological response to durvalumab +SoC CCRT compared to placebo +SoC CCRT for candidate markers that may correlate with likelihood of clinical benefit. **(All countries except China)**	• Analysis of blood/tissue samples to assess exploratory biomarkers, which may include, but is not limited to ctDNA, mRNA signatures, CD8 by IHC, and tumor mutational burden (TMB)
To assess treatment-related symptoms using the Patient-reported outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE)	• Specific treatment-related PRO-CTCAE symptoms

To assess how a patient perceives her overall change in cancer symptoms since the start of study treatment using the PGIC and overall severity of cancer symptoms using the PGIS.	• PGIC and PGIS
To explore the impact of treatment and disease state on health status assessed by EuroQol five-dimensional five-level questionnaire (EQ-5D-5L) to support health economic analysis and health technology assessment	• EQ-5D-5L
To describe and evaluate resource use associated with durvalumab treatment and underlying disease	• Health resource utilisation measures including hospitalization, outpatient visits, or emergency department visits

Abbreviations: ADA Antidrug antibody; AE Adverse event; CR Complete response; ECG Electrocardiogram; EORTC European Organisation for Research and Treatment of Cancer; EQ-5D-5L EuroQol five-dimensional five-level questionnaire; HOSPAD Hospital Admission; HRQoL Health-related quality-of-life; IHC Immunohistochemistry; ORR Objective response rate; OS Overall survival; PFS Progression-free survival; PGIC Patient Global Impression of Change; PGIS Patient Global Impression of Severity; PK Pharmacokinetics; PR Partial response; PRO-CTCAE Patient-reported outcomes version of the Common Terminology Criteria for Adverse Events; QLQ-C30 30-item core quality-of-life questionnaire; QLQ-CX24 Cervical cancer module; RECIST Response Evaluation Criteria in Solid tumors .

4. STUDY DESIGN

4.1 Overall design

This is a randomized, double-blind, placebo controlled, multi-center, global, Phase III study to determine the efficacy and safety of durvalumab when combined with SoC CCRT and administered as adjuvant therapy following SoC CCRT compared to placebo with SoC CCRT as systemic treatment in patients with FIGO (2009) Stages IB2 to IVA cervical cancer.

In order to be eligible for this study, patients must be ≥18 years of age with FIGO (2009) Stages IB2 to IIB N+ and IIIA to IVA with any N. Patients must not have previously received any definitive surgical, radiation, or systemic therapy for cervical cancer and must be immunotherapy-naïve. (Additional details are provided in Sections 5.1 and 5.2.)

Approximately 714 patients from multiple sites will be randomized 1:1 to receive either durvalumab 1500 mg or placebo q4w for 24 doses. In China, recruitment will continue until approximately 105 Chinese patients have been randomised, irrespective of whether or not the overall study enrolment has been reached. It is anticipated that this target may not be met before the global recruitment of approximately 714 is achieved. Patients in both arms will receive SoC CCRT consisting of EBRT + brachytherapy , and concurrent cisplatin 40 mg/m^2 q1w × 5 weeks. A 6th week of platinum agent can be given per investigator discretion (See Section 6.1.2 for descriptions of the dosing regimens.) Randomization will be stratified by

disease stage status (FIGO (2009) Stage <III and node positive, FIGO (2009) Stage ≥III and node negative, or FIGO (2009) Stage ≥III and node positive), and region [United States, Canada, European Union, South Korea, and Japan] versus rest of world. Patients will receive their assigned treatment until completion of planned therapy, clinical progression or RECIST 1.1-defined radiological progression or histopathologic progression on biopsy unless there is unacceptable toxicity, withdrawal of consent, or another discontinuation criteria is met. (See Section 7.1 for additional details on discontinuation of study treatment.) Following completion of SoC CCRT, patients will be evaluated by clinical and radiological assessment. During the first 3 years (164 weeks) after randomization, this assessment will include an interval history for new signs or symptoms, physical examination including a pelvic examination, and imaging (CT or MRI) per RECIST 1.1 or histopathologic assessment q12w. During Years 4, and 5, imaging/histopathologic assessments will be performed q24w and then annually until a PFS endpoint has been met or closure of the study (Section 9.2).

For an overview of the study design see Figure 1, Section 1.3. For details on treatments given during the study, see Section 6.1 Treatments Administered.

For details on what is included in the efficacy and safety endpoints, see Section 3 Objectives and Endpoints.

4.1.1. Study Conduct Mitigation During Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis

The guidance given below supersedes instructions provided elsewhere in this CSP and should be implemented only during cases of civil crisis, natural disaster or public health crisis (eg, during quarantines and resulting site closures, regional travel restrictions and considerations if site personnel or study participants become infected with severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2] or similar pandemic infection), which would prevent the conduct of study-related activities at study sites, thereby compromising the study site staff or the participant's ability to conduct the study. The investigator or designee should contact the study sponsor to discuss whether the mitigation plans below should be implemented.

To ensure continuity of the clinical study during a civil crisis, natural disaster, or public health crisis, changes may be implemented to ensure the safety of study participants, maintain compliance with GCP, and minimise risks to study integrity. Where allowable by local health authorities, ethics committees, health care provider guidelines (eg, hospital policies) or local government, these changes may include the following options:

Obtaining [reconsent] for the mitigation procedures (note, in the case of verbal [reconsent], the informed consent form [ICF] should be signed at the participant's next contact with the study site).

For further details on study conduct during civil crisis, natural disaster, or public health crisis, refer to Appendix L.

4.2 Scientific rationale for study design

The primary aim of this study is to assess the efficacy of durvalumab + SoC CCRT compared with placebo + SoC CCRT in terms of PFS, with a key secondary objective to assess the efficacy of durvalumab + SoC CCRT compared with placebo + SoC CCRT in terms of OS.

4.2.1 Rationale for study endpoints (efficacy)

PFS may serve as a surrogate endpoint for OS when differences between treatment arms are of sufficient magnitude and clinically important (FDA Guidance 2015, Mauguen et al 2013, Pazdur 2008). In particular, a close association of PFS and OS has been observed in Stage III NSCLC.

ORR can be a useful endpoint because it is a direct measure of the drug's anti-tumor activity (Pazdur 2008). The use of ORR in the setting of locally advanced cervical cancer, especially when the responses are sustained and durable (a key feature of immunotherapy), is justified because it is anticipated that it will serve as an early measure of clinical benefit that may be confirmed by the survival endpoints employed in a randomized confirmatory study. Assessing ORR (and CR rate) will help ascertain the benefit of adding durvalumab on top of SoC CCRT versus SoC CCRT alone. Additionally, for patients treated with immunotherapies, including durvalumab, responses appear to be durable, reinforcing the importance of ORR as a likely surrogate for clinical benefit.

The key secondary efficacy endpoints (ie, those included in the multiple testing procedure) of OS, and other secondary endpoints including rate of CR, will be examined to further evaluate the anti-tumor effect of durvalumab + SoC CCRT versus placebo + SoC CCRT.

The patterns of disease relapse of durvalumab + SoC CCRT compared with placebo + SoC CCRT will be described in terms of incidence of local progression, distant disease progression, and secondary malignancy as the first documented progression event.

The secondary symptoms and overall health-related quality of life (HRQoL) endpoints will be assessed using the European Organisation for Research and Treatment of Cancer (EORTC) core cancer instrument (EORTC QLQ-C30) and supplemental cervical cancer module (EORTC CX24). The EuroQol five-dimensional five-level questionnaire (EQ-5D-5L), Patient Global Impression of Change (PGIC), Patient Global Impression of Severity (PGIS) and Patient-Reported Outcome version of the Common Terminology Criteria for Adverse Events

(PRO-CTCAE) questionnaires will be administered as exploratory endpoints. Health resource utilisation measures including hospitalization, outpatient visits, or emergency department visits will be recorded in eCRF. These will show the overall influence of the benefits and toxicity of the treatment from a patient's perspective and will aid in understanding of the benefit/risk evaluation. These PRO questionnaires are well established instruments that have been previously included in clinical cancer studies.

Anti-tumor activity will be assessed according to RECIST 1.1 guidelines in addition to progression seen on physical exam and identified from histopathology. The analysis of PFS and OS will be based on programmatically derived PFS and OS based on investigator assessments; PFS can also be assessed according to histopathologic confirmation of local tumor progression. Sensitivity analyses will also be performed using data from BICR tumor assessments based on RECIST 1.1 and histopathologic confirmation of local tumor progression.

Biological samples will be taken from all patients to allow for research into PK and immunogenicity of durvalumab, and the relationship between durvalumab PK exposure and clinical outcomes, efficacy, AEs, and/or safety parameters.

4.2.2 Rationale for study endpoints (other exploratory endpoints)

Biological samples will be used to explore potential biomarkers in tumor, plasma, and/or serum, which may influence the progression of cancer (and associated clinical characteristics) and/or response.

4.2.3 Choice of standard of care regimen

The study will randomize approximately 714 patients in a 1:1 ratio to the following treatment arms: durvalumab concurrent with and following chemotherapy and radiotherapy and placebo concurrent with or following chemotherapy and radiotherapy. In China, recruitment will continue until approximately 105 Chinese patients have been randomised, irrespective of whether or not the overall study enrolment has been reached. It is anticipated that this target may not be met before the global recruitment of approximately 714 is achieved. Patients will receive SoC CCRT consisting of EBRT and brachytherapy. Pelvic and paraaortic radiation therapy (RT) can be added based on extent of disease at baseline. This regimen will be administered concurrently with cisplatin 40 mg/m^2 q1w for 5 weeks. Both chemotherapy and radiotherapy should be completed within 59 days. Only cisplatin is permitted, and an additional 6th week of therapy can be given per investigator discretion. Following completion of SoC CCRT, patients will be evaluated by clinical and radiological assessment.

In certain clinical scenarios, carboplatin has been substituted for cisplatin as a radiosensitizer. The data directly comparing potential differences between carboplatin and cisplatin in cervical

cancer are limited and inconsistent in findings. Cisplatin and carboplatin were retrospectively evaluated in 247 women receiving definitive CRT for locally advanced cervical cancer. In this evaluation, cisplatin was superior, with a CR rate of 88.3% compared to 73.9% (p=0.004) (Valdivieso et al 2017). However, another study evaluated 51 women who received concurrent carboplatin with radiotherapy in comparison to a historical control of cisplatin with radiotherapy, and there was no appreciable difference in OS and PFS between the 2 groups; there was an increase in the number of cycles administered and a reduction in adverse events in the carboplatin group (Nam et al 2013). An additional retrospective study of 148 women treated with carboplatin and concurrent radiotherapy showed that 142 (95.9%) women had a CR and only 6 (4.1%) had persistent disease. The 2-year PFS and OS rates were 75.1% and 81.9%, respectively (Katanyoo et al 2011). To ensure appropriate balance between patients treated with cisplatin and carboplatin as the radiosensitizer across regions in the ongoing study, no further use of carboplatin as the radiosensitizer will be allowed in this study.

4.2.4 Rationale of administering durvalumab concurrent with CCRT

The use of concurrent durvalumab therapy with chemotherapy and/or radiotherapy is currently being studied in NSCLC CCI colorectal cancer CCI, urothelial bladder cancer CCI, and hepatocellular carcinoma (NCT02821754). As reviewed in Section 2.1.1, there is a strong scientific rationale for combining CCRT with immunotherapy.

The key aspects of the rationale are as follows: Emerging datasets in other solid tumors, most notably NSCLC, suggest that concurrent administration of PD1 or PD-L1 antagonists with chemotherapy substantively improves OS compared to chemotherapy alone, and this benefit extends to patients with low or negative PD-L1 expression. Next, preclinical evidence suggests that concurrent administration of PD-L1 with radiotherapy could have synergistic immunomodulatory effects. Additionally, the PD1 or PD-L1 antibodies have been combined with CCRT in several disease settings with acceptable safety profile. Finally, because brachytherapy is administered after concurrent platinum and EBRT, if a sequential approach was utilized, there could be a long delay between completion of platinum + EBRT and initiation of PD-L1 which could attenuate the potential therapeutic benefit.

The study's hypothesis is that durvalumab, when administered with CCRT and as adjuvant therapy following CCRT, will improve PFS when compared to CCRT combined with placebo.

4.2.5 Rationale for treatment duration

After completion of SoC CCRT, administration of durvalumab/placebo will continue up to 24 cycles (total) or until RECIST 1.1-defined PD or histopathologic confirmation of local tumor progression, or until another discontinuation criterion is met. The rationale for the duration of durvalumab treatment is approximately 80% of progression events occur within

the first 24 cycles of SoC treatment (Elit et al 2009, Fuglsang et al 2015, Wiebe et al 2012). In the PACIFIC study, no new safety signals were observed with durvalumab after 6 months of treatment. Based on these observations, no new safety signals are expected with 24 cycles of durvalumab administration.

4.2.6 Rationale for stratification factors

Stratified randomization prevents imbalance between treatment groups for known factors that influence prognosis or treatment responsiveness. In this study, randomization will be stratified by disease stage status (FIGO (2009) Stage <III and node positive, FIGO (2009) Stage ≥III and node negative, or FIGO (2009) Stage ≥III and node positive), and region (United States, Canada, European Union, South Korea, and Japan) versus rest of world. Cervical cancer disease stage status and nodal status are known prognostic factors in cervical cancer (Pecorelli et al. 2009 and reviewed in sections 2.2.2 and 2.2.3) Region was grouped with the intention to accommodate potential differences in initial imaging approach at diagnosis (including PET/CT) and use of radiation therapy.

4.3 Justification for dose

4.3.1 Durvalumab monotherapy dose rationale

A durvalumab dose of 20 mg/kg q4w is supported by in vitro data, pre-clinical activity, clinical PK/pharmacodynamics, biomarkers, and activity data from Study 1108 in patients with advanced solid tumors and from a Phase I study performed in Japanese patients with advanced solid tumor [redacted]. There were 10 patients with cervical cancer in Study 1108, with an ORR of 20% (2/10).

PK/Pharmacodynamic data

Based on available PK/pharmacodynamic data from ongoing Study 1108 with doses ranging from 0.1 to 10 mg/kg q2w or 15 mg/kg every 3 weeks (q3w), durvalumab exhibited non-linear (dose-dependent) PK consistent with target-mediated drug disposition. The PK approached linearity at ≥3 mg/kg q2w, suggesting near complete target saturation (membrane-bound and sPD-L1), and further shows that the durvalumab dosing frequency can be adapted to a particular regimen given the linearity seen at doses higher than 3 mg/kg. The expected half-life with doses ≥3 mg/kg q2w is approximately 21 days. A dose-dependent suppression in peripheral sPD-L1 was observed over the dose range studied, consistent with engagement of durvalumab with PD-L1. A low level of immunogenicity has been observed. No patients have experienced immune-complex disease following exposure to durvalumab. (For further information on immunogenicity, please see the current durvalumab IB).

A population PK model was developed using the data from Study 1108 (doses=0.1 to 10 mg/kg q2w or 15 mg/kg q3w; Fairman et al 2014). Multiple simulations indicate that a

similar overall exposure is expected following both 10 mg/kg q2w and 20 mg/kg q4w regimens, as represented by AUC_{ss} (4 weeks). Median $C_{max,ss}$ is expected to be higher with 20 mg/kg q4w (~1.5 fold) and median $C_{trough,ss}$ is expected to be higher with 10 mg/kg q2w (~1.25 fold). Clinical activity with the 20 mg/kg q4w dosing regimen is anticipated to be consistent with 10 mg/kg q2w with the proposed similar dose of 20 mg/kg q4w expected to (a) achieve complete target saturation in majority of patients; (b) account for anticipated variability in PK, pharmacodynamics, and clinical activity in diverse cancer populations; (c) maintain sufficient PK exposure in case of antidrug antibody (ADA) impact; and (d) achieve PK exposure that yielded maximal anti-tumor activity in animal models.

Given the similar AUC and modest differences in median peak and trough levels at steady state, the observation that both regimens maintain complete sPD-L1 suppression at trough, and the available clinical data, the 20 mg/kg q4w and 10 mg/kg q2w regimens are expected to have similar efficacy and safety profiles, supporting further development with a dose of 20 mg/kg q4w.

Clinical data

Refer to the current durvalumab IB for a complete summary of clinical information including safety, efficacy, and PK at the 20 mg/kg q4w regimen.

4.3.2 Rationale for fixed dosing

A population PK model was developed for durvalumab using monotherapy data Study 1108 (N=292; doses= 0.1 to 10 mg/kg q2w or 15 mg/kg q3w; solid tumors). Population PK analysis indicated only minor impact of body weight (WT) on the PK of durvalumab (coefficient of ≤0.5). The impact of body weight (WT)-based (10 mg/kg q2w) and fixed dosing (750 mg q2w) of durvalumab was evaluated by comparing predicted steady state PK concentrations (5th, median, and 95th percentiles) using the population PK model. A fixed dose of 750 mg was selected to approximate 10 mg/kg (based on median body WT of ~75 kg). A total of 1000 patients were simulated using body WT distribution of 40 to 120 kg. Simulation results demonstrate that body WT-based and fixed dosing regimens yield similar median steady state PK concentrations with slightly less overall between-patient variability with fixed dosing regimen.

Similar findings have been reported by others (Narwal et al 2013, Ng et al 2006, Wang et al 2009, Zhang et al 2012). Wang and colleagues investigated 12 monoclonal antibodies and found that fixed and body size-based dosing perform similarly, with fixed dosing being better for 7 of 12 antibodies (Wang et al 2009). In addition, they investigated 18 therapeutic proteins and peptides and showed that fixed dosing performed better for 12 of 18 in terms of reducing the between-patient variability in PK/pharmacodynamic parameters (Zhang et al 2012).

A fixed dosing approach is preferred by the prescribing community due to ease of use and reduced dosing errors. Given expectation of similar PK exposure and variability, AstraZeneca considered it feasible to switch to fixed dosing regimens. Based on average body WT of 75 kg, a fixed dose of 1500 mg q4w durvalumab (equivalent to 20 mg/kg q4w) is included in the current study.

4.4 End of study definition

The end of study is defined as the last expected visit/contact of the last patient undergoing the study.

A patient is considered to have completed the study when he/she has completed her last scheduled visit or last scheduled procedure shown in the SoA.

Patients may be withdrawn from the study if the study itself is stopped. The study may be stopped if, in the judgment of AstraZeneca, study patients are placed at undue risk because of clinically significant findings.

In the event that a roll-over or safety extension study is available at the time of the final data cutoff (DCO) and database closure, patients currently receiving treatment with durvalumab may be transitioned to such a study, and the current study would reach its end. The roll-over or safety extension study would ensure treatment continuation with visit assessments per its protocol. Any patient who would be proposed to move to such a study would be given a new Informed Consent.

See Appendix A 6 for guidelines for the dissemination of study results.

5. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

Each patient should meet all of the inclusion criteria and none of the exclusion criteria for this study in order to assigned/randomized to a study intervention. Under no circumstances can there be exceptions to this rule. Patients who do not meet the entry requirements are screen failures; refer to Section 5.4.

In this protocol, “enrolled” patients are defined as those who sign informed consent. “Randomized” patients are defined as those who undergo randomization and receive a randomization number.

For procedures for withdrawal of incorrectly enrolled patients see Section 7.3.

5.1 Inclusion criteria

Patients are eligible to be included in the study only if all of the following inclusion criteria and none of the exclusion criteria apply:

Informed consent

1. Capability of giving signed informed consent, which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol

2. Provision of signed and dated, written informed consent form prior to any mandatory study specific procedures, sampling, and analyses

3. Provision of signed and dated written genetic informed consent prior to collection of sample for genetic analysis

The ICF process is described in Appendix A 3.

Age

4. Females age ≥18 years at the time of screening. For patients aged <20 years and enrolled in Japan, a written informed consent should be obtained from the patient and her legally acceptable representative.

Type of patient and disease characteristics

5. Histologically confirmed cervical adenocarcinoma, cervical squamous carcinoma, or cervical adenosquamous carcinoma and the following requirements:

   - FIGO (2009) Stages IB2 to IIB, node positive (N≥1) -OR- FIGO (2009) Stages IIIA to IVA with any N stage (N≥0) (refer to Appendix K)

   - Nodal staging may be either surgical or by imaging (CT or MRI) with pathological lymph node size defined by a short-axis diameter* of ≥10mm (axial plane)

   - No evidence of metastatic disease (M0)

*Short-axis diameter is the longest diameter perpendicular to the long-axis diameter

6. World Health Organization (WHO)/ECOG performance status (PS) of 0 or 1 at enrollment and randomization

7. At least 1 lesion, not previously irradiated, that qualifies as a RECIST 1.1 TL at baseline. Tumor assessment by CT scan or MRI must be performed within 28 days prior to randomization.

8. Suitability and fitness for CCRT as determined by the Investigator

9. Adequate organ and marrow function as defined below:

   - Hemoglobin ≥9.0 g/dL
   - Absolute neutrophil count ≥1.5 × 10^9 /L
   - Platelet count ≥75 × 10^9/L
   - Serum bilirubin ≤1.5 × the upper limit of normal (ULN). This will not apply to patients with confirmed Gilbert's syndrome, who will be allowed in consultation with their physician and AstraZeneca.
   - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤2.5 × ULN
   - Creatine clearance (CrCl) ≥60 mL/min calculated by Cockcroft-Gault equation (using actual body weight) or by measured 24-hour urine collection

     Females:
     Creatinine CL (mL/min) = $\frac{\text{Weight (kg)} \times (140 - \text{Age})}{72 \times \text{serum creatinine (mg/dL)}} \times 0.85$

10. Life expectancy of at least 12 weeks

Weight

11. Body weight >30 kg

Sex

12. Female

5.2 Exclusion criteria

Medical conditions

1. Diagnosis of small cell (neuroendocrine) histology or mucinous adenocarcinoma cervical cancer

2. Intent to administer a fertility-sparing treatment regimen

3. Evidence of metastatic disease per RECIST 1.1 including lymph nodes ≥15 mm (short axis) above the L1 cephalad body, in the inguinal region or outside the planned radiation field.

4. Patients who have undergone a previous hysterectomy, including a supracervical hysterectomy, or will have a hysterectomy as part of their initial cervical cancer therapy

5. History of allogeneic organ transplantation

6. 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
   - Patients with 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 celiac disease controlled by diet alone

7. Uncontrolled intercurrent illness, including but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, uncontrolled cardiac arrhythmia, active ILD, serious chronic GI conditions associated with diarrhea, 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

8. History of another primary malignancy except for

   - Malignancy treated with curative intent and with no known active disease ≥5 years before the first dose of IP 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

9. History of active primary immunodeficiency

10. Active infection including **tuberculosis** (clinical evaluation that includes clinical history, physical examination and radiographic findings, and tuberculosis testing in line with local practice), **hepatitis B** (known positive HBV HBsAg result), **hepatitis C (HCV)**, or **human immunodeficiency virus** (positive HIV 1/2 antibodies). 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. Patients positive for HCV antibody are eligible only if polymerase chain reaction (PCR) is negative for HCV RNA.

11. Brain metastases or spinal cord compression. Patients with suspected brain metastases at screening should have an MRI (preferred) or CT each preferably with IV contrast of the brain prior to study entry. Brain metastases will not be recorded as RECIST TLs at baseline.

12. QT interval corrected for heart rate using Fridericia's formula (QTcF) ≥470 ms from 1 ECG.

13. Known allergy or hypersensitivity to any of the study drugs or any of the study drug excipients

14. Prior history or presence of vesicovaginal, colovaginal, or rectovaginal fistula.

Prior/concomitant therapy

15. Prior chemotherapy or radiation therapy for the management of cervical cancer

16. Exposure to immune-mediated therapy prior to the study for any indication including, but not limited to, other anti CTLA-4, anti-PD-1, anti-PD-L1, and anti-PD-L2 antibodies, or therapeutic anticancer vaccines

17. Any concurrent chemotherapy, IP, biologic, or hormonal therapy for cancer treatment. Concurrent use of hormonal therapy for non-cancer-related conditions (eg, hormone replacement therapy) is acceptable.

18. Receipt of live attenuated vaccine within 30 days prior to the first dose of IP. Note: Patients, if enrolled, should not receive live vaccine while receiving IP and up to 30 days after the last dose of IP

19. Major surgical procedure (as defined by the Investigator) within 28 days prior to the first dose of IP. Note: Local surgery of isolated lesions for palliative intent is acceptable.

20. 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)

Prior/concurrent clinical study experience

21. Participation in another clinical study with an investigational product (IP) administered in the last 28 days

22. Previous IP assignment in the present study

23. Concurrent enrollment in another clinical study, unless it is an observational (non-interventional) clinical study or during the follow-up period of an interventional study

24. Prior randomization or treatment in a previous durvalumab clinical study regardless of treatment arm assignment

Other exclusions

25. 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 study treatment

26. Judgment by the Investigator that the patient should not participate in the study if the patient is unlikely to comply with study procedures, restrictions, and requirements

27. Genetics research study (optional):

    Exclusion criteria for participation in the optional (DNA) genetics research component of the study include:

    - Previous allogeneic bone marrow transplant
    - Non-leukocyte-depleted whole blood transfusion in 120 days of genetic sample collection

5.3 Lifestyle restrictions

The following restrictions apply while the patient is receiving IP and for the specified times before and after:

1. Female patient of child-bearing potential

   – Female patients of childbearing potential who are not abstinent and intend to be sexually active with a nonsterilized male partner must use at least 1 **highly** effective method of contraception (Table 4) from the time of screening throughout the total duration of the drug treatment and the drug washout period (90 days after the last dose of study treatment). Non-sterilized male partners of a female patient of childbearing potential must use a male condom plus spermicide throughout this period. Cessation of birth control after this point should be discussed with a responsible physician. Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception. Female patients should refrain from breastfeeding throughout this period.

Please note, females of childbearing potential are defined as those who are not surgically sterile (ie, bilateral salpingectomy, bilateral oophorectomy, or complete hysterectomy) or post-menopausal.

Women will be considered post-menopausal if they have been amenorrheic for 12 months without an alternative medical cause. The following age-specific requirements apply:

Women <50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatments and if they have luteinizing hormone and follicle-stimulating hormone levels in the post-menopausal range for the institution.

Women ≥50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatments, had radiation-induced menopause with last menses >1 year ago, had chemotherapy-induced menopause with last menses >1 year ago.

Women who are surgically sterile (ie, bilateral salpingectomy, bilateral oophorectomy) are eligible.

Highly effective methods of contraception, defined as one that results in a low failure rate (ie, less than 1% per year) when used consistently and correctly are described in Table 4. Note that some contraception methods are not considered highly effective (eg, male or female condom with or without spermicide; female cap, diaphragm, or sponge with or without spermicide; non-copper containing intrauterine device; progestogen-only oral hormonal contraceptive pills where inhibition of ovulation is not the primary mode of action [excluding

Cerazette/desogestrel which is considered highly effective]; and triphasic combined oral contraceptive pills).

Patients should follow the local prescribing information for their SoC CCRT relating to the contraception, the time limits for such precautions, and any additional restrictions for agents.

Table 4 Highly effective methods of contraception (<1% failure rate)

Barrier/intrauterine methods	Hormonal methods
• Copper T intrauterine device • Levonorgestrel-releasing intrauterine system (eg, Mirena®)[a]	• Implants: Etonogestrel-releasing implants (eg, Implanon® or Norplant®) • Intravaginal Devices: Ethinylestradiol/etonogestrel-releasing intravaginal devices (eg, NuvaRing®) • Injection: Medroxyprogesterone injection (eg, Depo-Provera®) • Combined Pill: Normal and low dose combined oral contraceptive pill • Patch: Norelgestromin/ethinylestradiol-releasing transdermal system (eg, Ortho Evra®) • Minipill: Progesterone based oral contraceptive pill using desogestrel: Cerazette® is currently the only highly effective progesterone based pill

[a] This is also considered a hormonal method.

2. All patients: Patients should not donate blood or blood components while participating in this study and through 90 days after receipt of the final dose of study treatment or until alternate anticancer therapy is started.

3. Restrictions relating to concomitant medications are described in Section 6.4

5.4 Screen failures

Screen failures are patients who do not fulfill the eligibility criteria for the study, and therefore must not be randomized. These patients should have the reason for study withdrawal recorded as “eligibility criteria not fulfilled” (ie, patient does not meet the required inclusion/exclusion criteria). This reason for study withdrawal is only valid for screen failures (ie, not randomized patients). Patients may be rescreened a single time, but they may not be re-randomized.

A minimal set of screen failure information is required to ensure transparent reporting of screen failure patients to meet the Consolidated Standards of Reporting Trials (CONSORT)

publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

6. STUDY TREATMENTS

Study treatment is defined as any IP(s) (including marketed product comparator and placebo) or medical device(s) intended to be administered to a study participant according to the study protocol. Study treatment in this study refers to durvalumab + SoC CCRT or placebo + SoC CCRT.

6.1 Treatments administered

6.1.1 Investigational products

AstraZeneca will supply durvalumab (MEDI4736). Further details about the study treatments are in Table 5. EBRT + brachytherapy, cisplatin, and the saline solution for the placebo will be supplied locally. Under certain circumstances when local sourcing is not feasible, an SoC treatment may be supplied centrally through AstraZeneca.

Table 5 Study treatments

			Chemoradiotherapy (Standard of care)	
	Durvalumab	***Placebo***	**EBRT + brachytherapy**	**Chemotherapy[f]**
Study treatment name:	Durvalumab (MEDI4736)[a]	Saline solution	External beam radiotherapy and brachytherapy	Cisplatin
Dosage formulation:	500-mg vial solution for infusion after dilution, 50 mg/mL	Sterile solution of 0.9% (w/v) sodium chloride for injection	As sourced locally	As sourced locally
Route of administration	IV	IV	Whole pelvic or pelvic and para-aortic radiation and brachytherapy[b]	IV
Dosing instructions:	1500 mg IV q4w	Dosing to match durvalumab	See Appendix G for treatment details	40 mg/m^2 q1w × 5 weeks Pre- and post-hydration with 1-2 L of IV fluid is recommended with IV supplementation of Mg. Anti-emetics are recommended[c, d]

Table 5 Study treatments

			Chemoradiotherapy (Standard of care)	
	Durvalumab	***Placebo***	**EBRT + brachytherapy**	**Chemotherapy[f]**
Packaging and labeling	Study treatment will be provided in 500-mg vials. Each vial will be labeled in accordance with Good Manufacturing Practice (GMP) Annex 13 and per country regulatory requirement.[a]	Sourced locally by site	n/a	Sourced locally by site
Provider	AstraZeneca	Sourced locally by site	Sourced locally by site[e]	Sourced locally by site[e]

[a] Label text prepared for durvalumab (MEDI4736) will show the product name as "MEDI4736" or "durvalumab (MEDI4736)" depending upon the agreed product name used in the approved study master label document. All naming conventions are correct during this transitional period.
[b] Pelvic and paraaortic radiotherapy is added based on extent of disease at baseline.
[c] Standard antiemetic regimens consist of a steroid and 5HT-antagonist, with or without a substance P antagonist such as aprepitant.
[d] An additional 6th week of platinum agent will be administered per investigator discretion
[e] Under certain circumstances when local sourcing is not feasible, an SoC treatment may be supplied centrally through AstraZeneca.
Abbreviations: EBRT External beam radiotherapy; Gy Grey unit; IV Intravenous; n/a Not applicable; qxw Every x weeks; SoC Standard of care; w/v Weight/volume.
[f] For patients who were treated with carboplatin prior to Protocol Version 3, please see Section 6.1.1.2.2

6.1.1.1 **Durvalumab (MEDI4736)**

Durvalumab (MEDI4736) will be supplied by AstraZeneca as a 500-mg vial solution for infusion after dilution. The solution contains 50 mg/mL durvalumab (MEDI4736), 26 mM histidine/histidine hydrochloride, 275 mM trehalose dihydrate, and 0.02% w/v polysorbate 80; it has a pH of 6.0. The nominal fill volume is 10.0 mL. IP vials are stored at 2°C to 8°C (36°F to 46°F) and must not be frozen. Drug product should be kept in secondary packaging until use to prevent excessive light exposure.

Preparation of durvalumab (MEDI4736) doses for administration with an IV bag

The dose of durvalumab (MEDI4736) for administration must be prepared by the Investigator's or site's designated IP manager using aseptic technique. Total time from needle puncture of the durvalumab (MEDI4736) vial to the start of administration should not exceed:

- 24 hours at 2°C to 8°C (36°F to 46°F)
- 4 hours at room temperature

A dose of 1500 mg (for patients >30 kg in weight) will be administered using an IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose, with a final durvalumab (MEDI4736) concentration ranging from 1 to 15 mg/mL, and delivered through an IV administration set with a 0.2- or 0.22-µm in-line filter. Add 30.0 mL of durvalumab (MEDI4736) (ie, 1500 mg of durvalumab [MEDI4736]) to the IV bag. The IV bag size should be selected such that the final concentration is within 1 to 15 mg/mL. Mix the bag by gently inverting to ensure homogeneity of the dose in the bag. The IV bag should be covered with an opaque or transparent coloured sleeve (e.g. amber) after preparation by the unblinded pharmacist prior to dispensing to other study personnel to maintain double-blind conditions.

If weight falls to ≤30 kg, weight-based dosing at 20 mg/kg will be administered using an IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose, with a final durvalumab (MEDI4736) concentration ranging from 1 to 15 mg/mL, and delivered through an IV administration set with a 0.2- or 0.22-µm in-line filter.

Standard infusion time is 1 hour (± 5min). In the event that there are interruptions during infusion, the total allowed infusion time should not exceed 8 hours at room temperature.

Do not co-administer other drugs through the same infusion line.

The IV line will be flushed with a volume of IV diluent equal to the priming volume of the infusion set used, after the contents of the IV bag are fully administered or complete the infusion according to institutional policy to ensure the full dose is administered and document if the line was not flushed.

If either preparation time or infusion time exceeds the time limits a new dose must be prepared from new vials. Durvalumab (MEDI4736) does not contain preservatives, and any unused portion must be discarded.

Order of administration

After randomisation to receive durvalumab/placebo + SoC CCRT, patients will receive durvalumab/placebo via IV infusion over 1 hour (± 5min). It is recommended that a 60-minute observation period take place after durvalumab/placebo is administered, at least for Cycle 1.

If no issues are observed following durvalumab/placebo administration during the first cycle, reduction of the observation period to 30 minutes is recommended at the Investigator's discretion.

Durvalumab/Placebo administration will be followed by SoC chemotherapy via IV infusion as indicated in Section 6.1.1.1, with radiation therapy given on the same day. If there is not enough time to administer cisplatin it must be administered within 1 calendar day of the durvalumab infusion. This will allow for flexibility in timely administration of the treatment regimen, as radiation therapy and durvalumab/placebo can be given on C1D1, and cisplatin given on C1D2 and similarly for subsequent cycles

Cisplatin should only be given on a day that external-beam radiation is scheduled. Radiation therapy can occur before or after durvalumab and the platinum agent are administered and should be given on the same day if possible. Treatment should preferably be given on a Monday, Tuesday or Wednesday. Cisplatin should not be given on a day of brachytherapy treatment.

All patients should be planned to receive 5 doses of cisplatin regardless of the radiation fractionation schedule planned. An additional 6th dose of platinum chemotherapy can be administered per investigator discretion.

6.1.1.2 Standard of care

The SoC chemotherapy agent for CCRT will either be locally sourced or centrally supplied by AstraZeneca and will be administered according to prescribing information or treatment guidance in general use by the Investigating site. Under certain circumstances when local sourcing is not feasible, AstraZeneca will centrally supply the drug, and it will be labeled with local language translated text in accordance with regulatory guidelines.

6.1.1.2.1 Cisplatin

If a patient develops a toxicity related to cisplatin, the SOC TMGs (Appendix J) should be followed. Patients are not permitted to switch between cisplatin and carboplatin.

6.1.1.2.2 Carboplatin

In prior versions of this protocol carboplatin AUC2 was given for initial treatment or if cisplatin was intolerable. Subjects recruited to the study under this regimen may continue unchanged, as clinically indicated. Carboplatin is to be given AUC 2 q1w × 5 weeks, and an additional 6th week will be administered per investigator discretion. Antiemetics are recommended. Standard antiemetic regimens consist of a steroid and 5HT-antagonist, with or without a substance P antagonist such as aprepitant.

6.1.1.3 Placebo

Placebo will be sourced locally. The placebo should be prepared such that the volume matches that expected for a durvalumab infusion, this requires the addition of 30ml of a sterile solution of 0.9%(w/v) sodium chloride for injection to the IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose The volume of saline solution added will be 30.0 mL or same volume as durvalumab if weight falls to ≤30 kg. The IV bag should be covered with an opaque or transparent coloured sleeve (e.g. amber) after preparation by the unblinded pharmacist prior to dispensing to other study personnel to maintain double-blind conditions. Infusion time is 1 hour (± 5min) and should be delivered through an IV administration set with a 0.2- or 0.22-µm in-line filter.

6.1.2 Dose and treatment regimens

Table 6 shows the dosing regimen for the study.

Table 6 Treatment regimen

	Baseline				
	C1[a]	**C2[a]**	**C3[a]**	**C4[a]**	**C5 to PD[a,b]**
Week	**0**	**q4w ±3 days unless dosing needs to be held for toxicity reasons**			
Day	**1**	**q28d ±3 days unless dosing needs to be held for toxicity reasons**			
Durvalumab/placebo[b]	X	X	X	X	X
SoC cisplatin	40 mg/m^2 q1w × 5 weeks[c](± 1 day except cycle 1)				
SoC EBRT[d,e]	Appendix G				
SoC brachytherapy	Appendix G				

[a] These cycles refer to the 28-day cycles of administration of durvalumab/placebo.
[b] During the combination portion of treatment, durvalumab will be administered first. If there is not enough time to administer cisplatin afterward on that day, it must be administered within 1 calendar day of the durvalumab infusion.
[c] An additional 6th week of platinum agent will be administered per investigator discretion
[d] Chemotherapy, radiotherapy and brachytherapy should ideally be completed within 56 days and up to 59 days.
[e] Radiotherapy should start on C1D1 following Durvalumab/placebo infusion on the same day. Refer to footnote b of this table..

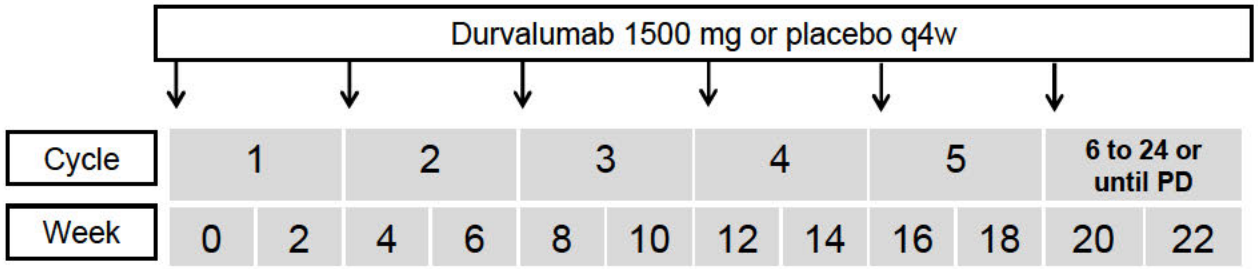
Abbreviations: C Cycle; CR Complete response; EBRT External Beam Radiotherapy; Gy Gray unit; PD Progression of disease; PR Partial response; qxw Every x weeks; q28d Every 28 days; SD Stable disease; SoC Standard of care.

6.1.2.1 Durvalumab (MEDI4736) monotherapy

Patients will receive 1500 mg durvalumab via IV infusion or placebo saline solution q4w until completion of planned therapy or clinical progression or RECIST 1.1-defined radiological progression or histopathologic progression on biopsy unless there is unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met. See Figure 2. (Please note, if a patient's weight falls to 30 kg or below the patient should receive weight-based dosing equivalent to 20 mg/kg of durvalumab or placebo solution q4w after consultation between Investigator and Study Physician, until the weight improves to >30 kg, at which point the patient should start receiving the fixed dosing of durvalumab 1500 mg or placebo saline solution q4w).

The standard infusion time is 1 hour (± 5min). In the event that there are interruptions during infusion, the total allowed time should not exceed 8 hours at room temperature.

Figure 2 Durvalumab dosing schedule



Note: Treatment will continue until completion of planned therapy or clinical progression or RECIST 1.1-defined radiological progression unless there is unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met. Alternatively, patients may continue treatment until histopathological determination of tumor progression on biopsy.
Abbreviations: PD Progression of disease; q4w Every 4 weeks.

6.1.2.2 Standard of care

SoC CCRT agents will be supplied locally where possible. Patients will receive cisplatin in addition to radiation therapy (as described in Table 5). Concurrent radiation therapy will be administered according to the guidelines outlined in Appendix G. Treatment with SoC CCRT will be concurrent with durvalumab/placebo (ie, starting on Cycle 1 Day 1).

In the event that durvalumab/placebo is discontinued or temporarily held due to treatment-related toxicity, SoC CCRT may still be administered as scheduled at the Investigator's discretion.

On days when both durvalumab/placebo and SoC CCRT are administered, durvalumab/placebo will be administered first, followed by SoC chemotherapy.

6.1.3 Duration of treatment and criteria for treatment through progression

All treatment will be administered beginning on Day 1 until completion of planned therapy, clinical progression or RECIST 1.1-defined radiological progression or histopathologic progression on biopsy unless there is unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met.

During the treatment period, patients who are clinically stable at an initial RECIST 1.1-defined PD radiological progression may continue to receive study treatment at the discretion of the Investigator and patient.

A follow-up scan is to be collected no earlier than 4 weeks after and no later than 12 weeks after the RECIST 1.1-defined PD. This follow-up scan is evaluated using the criteria outlined in Appendix F. Patients will not be permitted to continue randomized therapy if progression occurs after response (CR or PR as defined by RECIST 1.1) in the target lesions (regardless of the appearance of new lesions) (ie, the response and progression events both occurred in the target lesions while receiving randomized therapy during the same treatment period). Patients may not continue on durvalumab/placebo if there is histopathological determination of progression.

Patients with rapid tumor progression or with symptomatic progression that requires urgent medical intervention (eg, central nervous system metastasis, respiratory failure due to tumor compression, or spinal cord compression) will not be eligible for continuing IP.

For all patients who are treated through progression, the Investigator should ensure patients do not have any significant, unacceptable, or irreversible toxicities that indicate continuing.

Crossover within the study will not be permitted.

For all patients who are treated through progression, the Investigator should ensure that:

- The patient does not have any significant, unacceptable, or irreversible toxicities that indicate continuing treatment will not further benefit the patient. The patient may not have experienced a toxicity that required permanent discontinuation of study treatment.
- There is absence of clinical symptoms or signs indicating clinically significant disease progression accompanied by a decline in WHO/ECOG PS to >1.
- There is absence of rapid disease progression or threat to vital organs or critical anatomical sites (eg, central nervous system metastasis, respiratory failure due to tumor compression, or spinal cord compression) requiring urgent alternative medical intervention.

- The patient still fulfills the eligibility criteria for this study (see Section 5.1 and 5.2), with the exception of inclusion criteria 7 and 9 and exclusion criteria 16, 17, 18, 22, 23, and 25.

Patients who AstraZeneca and the Investigator determine may not continue treatment after RECIST 1.1-defined PD will be followed up for survival. Patients who have discontinued treatment due to toxicity or symptomatic deterioration, or who have commenced subsequent anticancer therapy, will be followed up with tumor assessments until RECIST 1.1-defined PD plus an additional follow-up scan or until death (whichever comes first) and followed for survival. Alternatively, PD may be determined by histopathological determination of tumor progression on biopsy.

Post final data cut off

Patients who continue to receive benefit from their assigned treatment at the final DCO and database closure may continue to receive their assigned treatment for as long as they and their physician considers they are gaining clinical benefit (total of 24 cycles). For patients continuing to receive durvalumab treatment following the final DCO and database closure, it is recommended that the patients continue the scheduled site visits and Investigators monitor the patients' safety laboratory results prior to and periodically during treatment with durvalumab in order to manage AEs in accordance with the durvalumab Dosing Modification and Toxicity Management Guidelines (see Section 8.4.5).

In the event that a roll-over or safety extension study is available at the time of the final DCO and database closure, patients currently receiving treatment with durvalumab may be transitioned to such a study, and the current study would reach its end. The roll-over or safety extension study would ensure treatment continuation with visit assessments per its protocol. Any patient who would be proposed to move to such a study would be given a new Informed Consent.

6.1.4 Storage

The Investigator, or an approved representative (eg, pharmacist), will ensure that all IP is stored in a secured area, in refrigerated temperatures (2°C to 8°C) and in accordance with applicable regulatory requirements. A temperature log will be used to record the temperature of the storage area. Temperature excursions outside the permissible range listed in the clinical supply packaging are to be reported to the study monitor upon detection. A calibrated temperature monitoring device will be used to record the temperature conditions in the drug storage facility. Storage conditions stated in the IB may be superseded by the label storage. The IP label on the pack/bottle/carton for SoC specifies the appropriate storage for these agents.

6.2 Measures to minimize bias: randomization and blinding

6.2.1 Subject enrollment and randomization

Patients will be randomized in a 1:1 ratio to durvalumab + SoC CCRT or placebo + SoC CCRT. Randomization will be stratified by disease stage status (FIGO (2009) Stage <III and node positive, FIGO (2009) Stage ≥III and node negative, or FIGO (2009) Stage ≥III and node positive), and region [United States, Canada, European Union, South Korea, and Japan] versus rest of the world.

All patients will be centrally assigned to randomized study treatment using an interactive web response system (/IWRS). Before the study is initiated, the telephone number and/or the log-in information and directions for the IWRS will be provided to each site.

If a patient withdraws from the study, then her enrollment/randomization code cannot be reused. Withdrawn patients will not be replaced.

Investigators should keep a record (ie, the patient screening log) of patients who entered screening.

At screening/baseline (Days -28 to -1), the Investigators or suitably trained delegate will:

- Obtain signed informed consent before any study specific procedures are performed. If laboratory or imaging procedures were performed for alternate reasons prior to signing consent, these can be used for screening purposes with consent of the patient. However, all screening laboratory and imaging results must have been obtained within 28 days of randomization. For patients with a single TL, if biopsy ≤3 months old is collected (in place of an archived sample) prior to screening imaging for baseline tumor assessment, allow approximately 2 weeks before imaging scans are acquired.
- Obtain a unique 7-digit enrollment number (E-code), through the IWRS in the following format (ECCNNXXX: CC being the country code, NN being the center number, and XXX being the patient enrollment code at the center). This number is the patient's unique identifier and is used to identify the patient on the electronic case report forms (eCRFs).
- Determine patient eligibility (see Sections 5.1 and 5.2)
- Obtain signed informed consent for genetic research study (optional)

At randomization, once the patient is confirmed to be eligible, the Investigator or suitably trained delegate will:

- Obtain a unique randomization number via the IWRS. Numbers will start at 001 and will be assigned strictly sequentially by IWRS as patients are eligible for entry into the study. The system will randomize the eligible patient to 1 of the 2 treatment arms.

- Obtain tumor sample and send for centralized PD-L1 testing.

If the patient is ineligible and not randomized, the IWRS should be contacted to terminate the patient in the system.

Treatment should start no more than 3 working days after being randomized. The day patients begin treatment will be designated C1D1. Patients must not be randomized and treated unless all eligibility criteria have been met.

6.2.2 Procedures for handling incorrectly enrolled or randomized subjects

Patients who fail to meet the eligibility criteria should not, under any circumstances, be enrolled or receive study medication. There can be no exceptions to this rule. Patients who are enrolled, but subsequently found not to meet all the eligibility criteria must not be randomized or initiated on treatment, and must be withdrawn from the study.

Where a patient does not meet all the eligibility criteria but is randomized in error, or incorrectly started on treatment, the Investigator should inform the AstraZeneca Study Physician immediately, and a discussion should occur between the AstraZeneca Study Physician and the Investigator regarding whether to continue or discontinue the patient from treatment. The AstraZeneca Study Physician must ensure all decisions are appropriately documented and that the potential benefit:risk profile remains positive for the patient.

6.2.3 Methods for assigning treatment arms

The actual treatment given to patients will be determined by the randomization scheme in the IVRS/IWRS. The randomization scheme will be produced by a computer software program that incorporates a standard procedure for generating randomization numbers.
One randomization list will be produced for each of the randomization strata. A blocked randomization will be generated, and all centers will use the same list in order to minimize any imbalance in the number of patients assigned to each treatment arm.

Patients will be identified to the IWRS per country regulations. Randomization codes will be assigned strictly sequentially, within each stratum, as patients become eligible for randomization. The IWRS will provide the kit identification number to be allocated to the patient at the randomization visit and subsequent treatment visits.

6.2.4 Methods for ensuring blinding

The IWRS will provide to the unblinded pharmacists the kit identification number to be allocated to the patient at the dispensing visit. Blinded and unblinded access and notifications will be controlled using the IWRS. Investigators will remain blinded to each patient's assigned study treatment throughout the course of the study. To maintain this blind, an otherwise uninvolved 3rd party will be unblinded and responsible for the reconstitution and dispensation of all study treatment and will endeavour to ensure that there are no differences in time taken to dispense following randomization.

In the event that the treatment allocation for a patient becomes known to the Investigator or other study staff involved in the management of study patients, or needs to be known to treat an individual patient for an AE, the Sponsor must be notified promptly by the Investigator and if possible, before unblinding.

The IWRS will be programmed with blind-breaking instructions. The blind may be broken if, in the opinion of the Investigator, it is in the patient's best interest for the Investigator to know the study treatment assignment. The Sponsor must be notified before the blind is broken unless identification of the study treatment is required for a medical emergency in which the knowledge of the specific blinded study treatment will affect the immediate management of the patient's condition (eg, antidote available). In this case, the Sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and CRF (electronic or paper), as applicable. Study unblinding should not occur until database lock and all decisions on the evaluability of the data from each individual patient have been made and documented.

6.3 Treatment compliance

The administration of all IPs should be recorded in the appropriate sections of the eCRF.

Any change from the dosing schedule, dose delays/interruptions, and dose discontinuations should be recorded in eCRF. Dose reductions are not allowed.

The IP Storage Manager is responsible for managing the IP from receipt by the study site until the destruction or return of all unused IP.

6.4 Concomitant therapy

The Investigator must be informed as soon as possible about any medication taken from the time of screening until the end of the clinical treatment phase of the study including the 90-day follow-up period following the last dose of study treatment.

Any medication or vaccine including over-the-counter or prescription medicines, vitamins, and/or herbal supplements that the patient is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose, unit, and frequency

Patients must be instructed not to take any medications, including over-the-counter products, without first consulting with the Investigator.

Restricted, prohibited, and permitted concomitant medications are described in the following tables. Refer also to the Dosing Modification and Toxicity Management Guidelines (see Section 8.4.5). For SoC agents, please refer to the local prescribing information with regards to warnings, precautions, and contraindications.

General Concomitant Medication and Supportive Care Guidelines for Radiotherapy

Patients should receive full supportive care, including transfusions of blood and blood products, supplemental iron, antibiotics, anti-emetics, etc., when appropriate at the discretion of the treating physician. Because it has been observed that hemoglobin levels below 10-12 g/dL during radiotherapy are associated with decreased local control, blood transfusions should be offered to and used to treat patients at the discretion of treating physicians prior to or during radiotherapy. There should be no radiotherapy treatment delays due to a low hemoglobin levels. Trials evaluating epoeitin alpha (Procrit, Epogen) and radio-chemotherapy in cervical cancer have indicated that epoeitin alpha may be associated with an increased risk for thromboembolism, and thus, may not be used in this study.

In particular, patients should be told of the typical defecation pattern. At the first sign that their stools become softer than usual or they have any increase in stool frequency over what is normal for them, they should begin taking over-the-counter loperamide as directed by their physician(s). Patients should understand that if they do not start taking loperamide at the start of diarrhea, the diarrhea may become severe and last several days. Persistent diarrhea or any evidence of hematochezia should prompt a stool evaluation for fecal leukocytes and/or Clostridium difficile toxin & ova/parasite evaluation. Diphenoxylate/ atropine prescriptions are permitted. Loperamide will be recommended during the study in order to prevent diarrhea that may ultimately lead to intravenous infusion of fluids or hospitalizations. Diarrhea that is suspected to be associated with durvalumab should be treated according to the Toxicity Management Guidelines .

Patients should call their doctor if they have any questions about taking loperamide, if they believe they are not achieving adequate control of diarrhea, or if they are feeling extremely weak, lightheaded, or dizzy (symptoms of dehydration). Side effects of loperamide include tiredness, drowsiness, or dizziness. If they experience these side effects, they should avoid driving a motorized vehicle or operating machinery. Before using any laxative, patients should consult their physician. Patients should make an extra effort to drink lots of fluids (several glasses of water, fruit juices, soda, soup, etc.) every day while they participate in this study

Table 7 Prohibited concomitant medications

Prohibited medication/class of drug:	**Usage:**
Any investigational anticancer therapy other than those under investigation in this study	Should not be given concomitantly while 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 while 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 while the patient is on study treatment. (Concurrent use of hormones for non-cancer-related conditions [eg, insulin for diabetes and hormone replacement therapy] is acceptable. Local treatment of isolated lesions, excluding TLs, for palliative intent is acceptable [eg, by local surgery or radiotherapy])
Live attenuated vaccines	Should not be given through 30 days after the last dose of IP
Herbal and natural remedies which may have immune-modulating effects	Should not be given concomitantly unless agreed by the Sponsor

Prohibited medication/class of drug:	Usage:
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, • short-term premedication for patients receiving cisplatin is permitted • 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 (eg, 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.

Abbreviations: CTLA-4 Cytotoxic T lymphocyte associated protein 4; IP Investigational product; PD-1 Programmed cell death protein 1; PD-L1 Programmed death ligand 1.

Table 8 Supportive medications

Supportive medication/class of drug:	Usage:
Concomitant medications or treatments (eg, acetaminophen or diphenhydramine) deemed necessary to provide adequate prophylactic or supportive care, except for those medications identified as "prohibited," as listed above	To be administered as prescribed by the Investigator
Best supportive care (including antibiotics, nutritional support, correction of metabolic disorders, optimal symptom control, and pain management [including palliative radiotherapy to non-target lesions, etc])	Should be used, when necessary, for all patients

Inactivated viruses, such as those in the influenza vaccine	Permitted

6.4.1 Other concomitant treatment

Other medication other than that described above, which is considered necessary for the patient's safety and wellbeing, may be given at the discretion of the Investigator and recorded in the appropriate sections of the eCRF.

6.4.2 Durvalumab drug-drug interactions

There is no information to date on drug-drug interactions with durvalumab either pre-clinically or in patients. As durvalumab is a monoclonal antibody and therefore a protein, it will be degraded to small peptides and amino acids and will be eliminated by renal and reticuloendothelial clearance. It is therefore not expected that durvalumab will induce or inhibit the major drug metabolizing cytochrome P450 pathways. As a result, there are no expected pharmacokinetic drug-drug interactions. The mechanism of action of durvalumab involves binding to PD-L1 and, therefore, significant pharmacodynamic drug interactions with the commonly administered concomitant medications are not expected. Despite this, appropriate clinical monitoring in all of the planned clinical studies will be conducted to evaluate any potential drug-drug interactions.

6.4.3 Rescue medication

As a result of immune-mediated adverse events (imAEs) that could potentially be experienced by patients on durvalumab, steroids and other immunosuppressant rescue medication has to be made available to this patient population. The 2 products that fall into the category of immunosuppressants are infliximab (eg, for colitis) and mycophenolate (eg, for hepatitis). AstraZeneca supply chain will be responsible for sourcing these 2 rescue medications to the sites if local regulations prevent the use of infliximab and mycophenolate in this indication, as they are considered off-label for the management of immunotherapy related toxicities. These rescue medications must be receipted, controlled, and administered by the unblinded pharmacist and stored according to the labeled storage conditions, with temperature excursions reported accordingly by the unblinded pharmacist. If required for use as a result of an imAE, then the IWRS will provide to the unblinded pharmacists the kit identification number to be allocated to the patient at the time. Blinded and unblinded access and notifications will be controlled using the IWRS.

6.5 Dose modification

Dose delays are permitted for immuno-oncology (IO) therapy (see Dosing Modification and Toxicity Management Guidelines). However, **dose reduction is not permitted**. For Standard of care, please refer to section 8.4.5.2

6.6 Treatment after the end of the study

After the final analysis, AstraZeneca will continue to supply open-label study medication to patients who had not completed 24 doses of study therapy up to the time that they discontinue the treatment for whatever reason (see Section 6.1.2).

7. DISCONTINUATION OF TREATMENT AND SUBJECT WITHDRAWAL

7.1 Discontinuation of study treatment

An individual patient will not receive any further IP (durvalumab + SoC CCRT or placebo + SoC CCRT) if any of the following occur in the patient in question:

Withdrawal of consent from further treatment with IP. The patient is, at any time, free to discontinue treatment, without prejudice to further treatment. A patient who discontinues treatment is normally expected to continue to participate in the study (eg, for safety and survival follow-up) unless they specifically withdraw their consent to all further participation in any study procedures and assessments (see Section 7.3).

- An AE that, in the opinion of the Investigator or AstraZeneca, contraindicates further dosing
- Any AE that meets criteria for discontinuation as defined in the Dosing Modification and Toxicity Management Guidelines (see Section 8.4.5) or as defined in the local prescribing information for the SoC agent
- Pregnancy or intent to become pregnant
- Non-compliance with the study protocol that, in the opinion of the Investigator or AstraZeneca, warrants withdrawal from treatment with IP (eg, refusal to adhere to scheduled visits)
- Initiation of alternative anticancer therapy including another investigational agent
- Clinical progression or RECIST 1.1-defined radiological progression (refer to Appendix F) and Investigator determination that the patient is no longer benefiting from treatment with IP
- Histopathological determination of tumor progression on biopsy
- Completion of planned therapy (24 cycles)

7.1.1 Procedures for discontinuation of study treatment

Discontinuation of study treatment, for any reason, does not impact the patient's participation in the study. A patient who decides to discontinue IP will always be asked about the reason(s) for discontinuation and the presence of any AE. The patient should continue attending subsequent study visits, and data collection should continue according to the study protocol. If the patient does not agree to continue in-person study visits, a modified follow-up must be arranged to ensure the collection of endpoints and safety information. This follow-up could be a telephone contact with the patient, a contact with a relative or treating physician, or information from medical records. The approach taken should be recorded in the medical records. A patient that agrees to modified follow-up is not considered to have withdrawn consent or to have withdrawn from the study.

Patients who are permanently discontinued from further receipt of IP, regardless of the reason, will be identified as having permanently discontinued treatment. Patients who are permanently discontinued will enter follow-up (see the SoAs).

Patients who permanently discontinue drug for reasons other than progression (per RECIST 1.1 as assessed by investigator tumor assessments or histopathologic confirmation of local tumor progression) should continue to have RECIST scans and physical exam including pelvic examination performed q20w ±1w after randomization and continue q12w±1w through 164 weeks and then q24w±2w thereafter until progression (per RECIST 1.1 as assessed by investigator tumor assessments or histopathologic confirmation of local tumor progression) plus an additional follow-up scan or death (whichever comes first) as defined in the SoAs.

If a patient is discontinued for progression, then the patient should have 1 additional follow-up scan performed preferably at the next (and no later than the next) scheduled imaging visit, and no less than 4 weeks after the prior assessment of PD.

All patients will be followed for survival until the end of the study.

Patients who decline to return to the site for evaluations should be contacted by telephone as indicated in the SoAs as an alternative.

Patients who have permanently discontinued from further receipt of IP will need to be discontinued from the IWRS.

7.2 Lost to follow-up

Patients will be considered lost to follow-up only if no contact has been established by the time the study is completed (see Section 4.4), such that there is insufficient information to determine the patient's status at that time. Patients who refuse to continue participation in the study, including telephone contact, should be documented as "withdrawal of consent" rather

than “lost to follow-up”. Investigators should document attempts to re-establish contact with missing patients throughout the study period. If contact with a missing patient is re-established, the patient should not be considered lost to follow-up and evaluations should resume according to the protocol.

In order to support key end points of PFS and OS analyses, the survival status of all patients in the full analysis and the safety analysis sets should be re-checked, this includes those patients who withdrew consent or are classified as “lost to follow-up.”

Lost to follow-up - site personnel should check hospital records, the patient’s current physician, and a publicly available death registry (if available) to obtain a current survival status. (The applicable eCRF modules will be updated.)

In the event that the patient has actively withdrawn consent to the processing of their personal data, the survival status of the patient can be obtained by site personnel from publicly available death registries (if available) where it is possible to do so under applicable local laws to obtain a current survival status. (The applicable eCRF modules will be updated.)

7.3 Withdrawal from the study

Patients are free to withdraw from the study at any time (IP and assessments) without prejudice to further treatment.

Patients who withdraw consent for further participation in the study will not receive any further IP or further study observation, with the exception of follow-up for survival, which will continue until the end of the study unless the patient has expressly withdrawn their consent to survival follow-up. Note that the patient may be offered additional tests or tapering of treatment to withdraw safely.

A patient who withdraws consent will always be asked about the reason(s) for withdrawal and the presence of any AE. The Investigator will follow-up AEs outside of the clinical study.

If a patient withdraws consent, they will be specifically asked if they are withdrawing consent to:

All further participation in the study including any further follow-up (eg, survival contact telephone calls)

Withdrawal to the use of any samples (see Section Appendix C 2)

8. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the SoA.

The Investigator will ensure that data are recorded on the eCRFs. The Web Based Data Capture (WBDC) system will be used for data collection and query handling.

The Investigator ensures the accuracy, completeness, legibility, and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement. The Investigator will sign the completed eCRFs. A copy of the completed eCRFs will be archived at the study site.

Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the patient should continue or discontinue study treatment.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential patients meet all eligibility criteria. The Investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the patient's routine clinical management (eg, blood count and imaging assessments) and obtained before signing of the ICF may be utilized for screening or baseline purposes, provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

The maximum amount of blood collected from each patient over the duration of the study, including any extra assessments that may be required, will be described in the Laboratory Manual. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Efficacy assessments

This study will evaluate the primary endpoint of PFS using either RECIST 1.1 as assessed by investigator tumor assessments or histopathologic confirmation of local tumor progression. Efficacy assessments of ORR, CR rate will be derived (by AstraZeneca) using RECIST 1.1 assessments or histopathologic confirmation of local progression. OS, incidence of local progression, distant disease progression and secondary malignancy will also be evaluated.

The assessment of PFS, incidence of local progression and distant disease recurrence will be performed by periodic clinical and radiological assessment to evaluate for metastatic relapse or loco-regional recurrence. During the first 164 weeks (about 3 years) after randomization, q12w (starting at W20) assessments will include interval history for new signs or symptoms, a

physical examination including pelvic examination, and radiological tumor assessments as per RECIST 1.1 or histopathologic assessment. During Years 4 and 5, patients will be assessed every 24 weeks and then annually until a PFS endpoint has been met or closure of the study. Tumor assessments utilize images from CT (preferred) or MRI, each preferably with IV contrast, of the chest, abdomen, and pelvis collected during screening/baseline and at regular (follow-up) intervals during study treatment. Any other areas of disease involvement should be additionally imaged based on the signs and symptoms of individual patients. It is important to follow the tumor assessment schedule as closely as possible (refer to the SoAs). If an unscheduled assessment is performed (eg, to investigate clinical signs/symptoms of progression) and the patient has not progressed, every attempt should be made to resume the subsequent assessments following the original imaging visit schedule (relative to the date of randomization). Treatment continues until completion of planned therapy, clinical progression or RECIST 1.1-defined radiological progression (refer to Appendix F) or histopathologic progression on biopsy unless there is unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met. Scanning continues throughout treatment until RECIST 1.1-defined radiological progression plus an additional follow-up scan if clinically feasible. If progressive disease is determined through histopathologic progression on biopsy, a scan is required within 28 days of biopsy.

A physical exam can include a pelvic examination with or without speculum, bimanual examination, rectovaginal examination, abdominal examination and optional pap smear and should be performed following the same schedule as tumor assessments by imaging. Any lesion detected on physical exam that is within the radiation field and suspected to be progressive disease will be biopsied. Lesions identified as progressive disease by RECIST on CT or MRI do not require a biopsy. Lesions with histopathologic confirmation of disease will be reported as a response of PD. Radiological assessments should be obtained on all patients within 28 days of progression confirmed by histopathology. If the physical examination and biopsy are performed as unscheduled assessments and there is no evidence of active cervical cancer on histopathology, the patient will not be reported as a PD and will continue with all study procedures according to the Schedule of Assessments (Table 1).

8.1.1 Central reading of scans

Images, including unscheduled visit scans, will be collected on an ongoing basis and sent to an AstraZeneca-appointed Contract Research Organization for QC and storage. Guidelines for image acquisition, de-identification, storage at the investigative site as source data, and transfer to the imaging CRO will be provided in a separate document. A BICR of images will be performed, results of these independent reviews will not be communicated to Investigators, and results of Investigator RECIST 1.1 assessments will not be shared with the central reviewers. The management of patients will be based in part on the results of the RECIST 1.1

assessment conducted by the Investigator. Further details of the BICR will be documented in the Independent Review Charter.

8.1.2 Survival assessments

Assessments for survival must be made every 3 months following treatment discontinuation. Survival information may be obtained via telephone contact with the patient or the patient's family, or by contact with the patient's current physician. The details of first and subsequent therapies for cancer, after discontinuation of study treatment, will be collected.

In addition, patients on treatment or in survival follow-up will be contacted following the DCO for the primary PFS analysis and all subsequent survival analyses to provide complete survival data. These contacts should generally occur within 7 days of the DCO.

8.1.3 Patient-reported Outcomes (PROs)

PROs allow for an understanding of treatment effect from the patients' perspective. In this study, PROs will be used to capture the patient experience of symptoms, functioning and HRQoL and will aid in understanding of the benefit/risk evaluation. The following PRO instruments will be administered in this study: EORTC core quality of life questionnaire (EORTC QLQ-C30 v3) and supplemental cervical cancer module (EORTC QLQ-CX24, Patient-Reported Outcomes-Common Terminology Criteria for Adverse Events (PRO-CTCAE), Patient Global Impression of Change (PGIC), Patient Global Impression of Severity (PGIS) and EuroQol five-dimensional five-level questionnaire (EQ-5D-5L) (see Appendix H). PROs will be administered according to the SoAs.

8.1.3.1 EORTC QLQ-C30 and QLQ-CX24

The EORTC QLQ-C30 was developed by the EORTC Quality of Life Group in 1993. It consists of 30 items and measures symptoms, functioning, and global health status/quality of life (QoL) (Aaronson et al 1993) for all cancer types. Items are grouped into 5 functional scales (physical, role, cognitive, emotional, and social), 3 symptom scales (fatigue, pain, and nausea and vomiting), 5 individual items (dyspnea, insomnia, appetite loss, constipation, and diarrhea), and a 2-item global measure of health status/QoL (see Appendix H).

The EORTC QLQ-CX24 is a 24-item complementary module to the QLQ-C30, designed specifically for use in cervical cancer. Items are grouped into three multi-item scales (symptom experience, body image, and sexual/vaginal functioning) and six single-item scales (lymphedema, peripheral neuropathy, menopausal symptoms, sexual activity, sexual worry, and sexual enjoyment) (Greimel et al 2006).

8.1.3.2 PRO-CTCAE

The PRO-CTCAE is included to address tolerability from the patients' perspective. It was developed by the National Cancer Institute. The PRO-CTCAE will only be administered in those countries where a linguistically validated version exists. It was developed in recognition that collecting treatment-related symptom data directly from patients using PRO tools can improve the accuracy and efficiency of symptomatic AE data collection. This was based on findings from multiple studies demonstrating that physicians and nurses underestimate treatment-related symptom onset, frequency, and severity in comparison with patient ratings (Basch et al 2009, Litwin et al 1998, Sprangers and Aaronson 1992). These treatment-related symptoms have been converted to patient-friendly terms (e.g., the Common Terminology Criteria for Adverse Event [CTCAE] term "myalgia" has been converted to "aching muscles"). Items capture the presence, frequency, severity and/or interference with usual activities, depending upon the AE. The items included in the PRO-CTCAE have undergone extensive qualitative review among experts and patients. Not all items are administered in any clinical study. In this study, only items that are considered relevant for the study, site of cancer, and cancer treatment are selected (see Appendix H).

8.1.3.3 PGIC

The Patient Global Impression of Change (PGIC) is a single item included to assess how a patient perceives her overall change in health status since the start of study treatment. Patients choose from among seven response options ranging from "much better" to "much worse" (see Appendix H).

8.1.3.4 PGIS

The Patient Global Impression of Severity (PGIS) is a single item to assess how a patient perceives her overall severity of symptoms at the time of assessment. Patients choose from among five response options ranging from "no symptoms" to "very severe" (see Appendix H).

8.1.3.5 EuroQol five-dimensional five-level questionnaire (EQ-5D-5L) and visual analogue scale (VAS)

The EQ-5D-5L (Appendix H) is a standardized measure of health status developed by the EuroQol Group to provide a simple, generic measure of health for clinical and economic appraisal (EuroQol Group 1990). Applicable to a wide range of health conditions and treatments, it provides a simple, descriptive profile and a single index value for health status that can be used in the clinical and economic evaluation of health care as well as in population health surveys. The questionnaire assesses 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 response options (no problems, slight problems, moderate problems, severe problems, and extreme problems) that reflect increasing levels of difficulty (EuroQol Group 2013).

The patient will be asked to indicate her current health state by selecting the most appropriate level in each of the 5 dimensions. The questionnaire also includes a visual analog scale, where the patient will be asked to rate current health status on a scale of 0 to 100, with 0 being the worst imaginable health state (Appendix H).

8.1.3.6 Administration of patient reported outcome questionnaires

Patients will perform the PRO assessments using an electronic tablet (ePRO) during clinic visits.

Each site must allocate the responsibility for the administration of the PRO instruments to a specific individual (eg, a research nurse or study coordinator) and, if possible, assign a back up person to cover if that individual is absent. The PRO questionnaires must be administered and completed at the clinic as per the SoAs. If technical or other issues prohibit completion on the device, an appropriate back-up option may be considered with prior approval from AstraZeneca.

It is important that the site staff explains the value and relevance of hearing directly from patients how they feel. The following best practice guidelines should be followed:

The PRO questionnaires must be administered and completed at the clinic prior to treatment administration performed at the site and ideally before any discussions of health status to avoid biasing the participant's responses to the questions. As feasible, site staff should also ensure PRO questionnaires are completed prior to other study procedures, such as collection of laboratory samples and before discussion of disease progression to avoid biasing the patient's responses to the questions.

- It is permitted for the baseline ePROs to be completed prior to C1D1 as long as first of dose of Durvalumab and CCRT is given within 3 days of ePRO completion
- PRO questionnaires must be completed in private by the patient.
- Patients should be given sufficient time to complete the PRO questionnaires at their own speed.
- The research nurse or appointed site staff should stress that the information is confidential and will not be shared with the site staff. Therefore, if the participant has any medical problems, he/she should discuss them with the doctor or research nurse separately from the ePRO assessment.
- The research nurse or appointed site staff must train the patient on how to use the ePRO device using the materials and training provided in the ePRO device.

- The research nurse or appointed site staff must remind patients that there are no right or wrong answers, and the research nurse or appointed site staff should avoid clarifying items to avoid introducing bias.

- Patients must not receive help from relatives, friends, or clinic staff deciding on answers to the PRO questionnaires. The responses are the participant's alone. Site staff must not read or complete the PRO questionnaires on behalf of the patient. If the patient is unable to read the questionnaire (eg, is blind, illiterate or unable to read in the available language), that patient should be exempted from completing PRO questionnaires but may still participate in the study. Patients exempted in this regard should be flagged appropriately by the site staff in the source documents and eCRF.

A key aspect of study success is to have high PRO compliance. Therefore, it is essential to follow the SoAs, and that sites make sure the device is charged and fully functional at all times in order to minimize missing data.

8.1.4 Health care resource use

Health care resource use will be captured including inpatient admissions, ICU, and length of stay in hospital using the HOSPAD eCRF. The module is for all non-study protocol-related hospital admissions; any routine hospital visits for study protocol-related requirements do not need to be captured.

The assessment of health care resource use will increase the understanding regarding the relationship between treatment and tumour related cancer symptoms on resource use, such as the need for palliative procedures to address obstruction and bleeding. This will be captured and analysed to inform submissions to payers.

8.1.4.1 Administration of health care resource assessment

The site should complete the HOSPAD eCRF every time a patient is hospitalized up to and including the post study treatment discontinuation follow up visit. If the patient discontinues study treatment for reasons other than RECIST progression, the "HOSPAD" eCRF should continue to be captured until progression has been confirmed. Study mandated visits should not be included as a hospital admission.

8.2 Safety assessments

Planned timepoints for all safety assessments are provided in the SoA.

8.2.1 Physical examinations

Physical examinations will be performed according to the assessment schedules (see the SoAs). Full physical examinations will include assessments of the head, eyes, ears, nose, and

throat and the respiratory, cardiovascular, GI, urogenital, musculoskeletal, neurological, dermatological, hematologic/lymphatic, and endocrine systems. Height will be measured at screening only. Targeted physical examinations are to be utilized by the Investigator on the basis of clinical observations and symptomatology. Situations in which physical examination results should be reported as AEs are described in Section 8.3.7.

8.2.2 Vital signs

Vital signs (blood pressure [BP], pulse, temperature, and respiration rate) will be evaluated according to the SoAs. Body weight is also recorded at each visit along with vital signs.

First infusion

On the first infusion day, patients will be monitored and vital signs collected/recorded in eCRF prior to, during, and after infusion of IP as presented in the bulleted list below.

BP and pulse will be collected from patients before, during, and after each infusion at the following times (based on a 60-minute infusion):

- Prior to the beginning of the infusion (measured once from approximately 30 minutes before up to 0 minutes [ie, the beginning of the infusion])
- Approximately 30 minutes during the infusion (halfway through infusion)
- At the end of the infusion (approximately 1 hour ±5 minutes)

If the infusion takes longer than 1 hour, then BP and pulse measurements should follow the principles as described above or be taken more frequently if clinically indicated. A 1-hour observation period is recommended after the first infusion of study treatment.

Subsequent infusions

BP, pulse, and other vital signs should be measured, collected/recorded in eCRF prior to the start of the infusion. Patients should be carefully monitored and BP and other vital signs should be measured during and post infusion as per institution standard and as clinically indicated. Any clinically significant changes in vital signs should be entered onto an unscheduled vital signs eCRF page.

Patients receiving SoC will be monitored pre-dose and as clinically indicated with every infusion or administration.

Situations in which vital signs results should be reported as AEs are described in Section 8.3.7. For any AEs of infusion reactions, the vital signs values should be entered into the eCRF.

8.2.3 Electrocardiograms

A resting 12-lead ECG will be recorded at screening and as clinically indicated throughout the study (see the SoAs). ECGs should be obtained after the patient has been in a supine position for 5 minutes and recorded while the patient remains in that position.

At screening Mean QT interval corrected for heart rate using Fridericia's formula (QTcF) should be recorded. For subsequent visits in case of clinically significant ECG abnormalities, including a QTcF value >470 ms, 2 additional 12-lead ECGs should be obtained over a brief period (eg, 30 minutes) to confirm the finding.

Situations in which ECG results should be reported as AEs are described in Section 8.3.7.

8.2.4 Clinical safety laboratory assessments

Blood and urine samples for determination of clinical chemistry, hematology, and urinalysis will be taken at the times indicated in the assessment schedules and as clinically indicated (see the SoAs).

Clinical laboratory safety tests, including serum pregnancy tests, will be performed in a licensed clinical laboratory according to local standard procedures. Sample tubes and sample sizes may vary depending on the laboratory method used and routine practice at the site. Pregnancy tests may be performed at the site using a licensed test (urine or serum pregnancy test). Abnormal clinically significant laboratory results should be repeated as soon as possible (preferably within 24 to 48 hours).

Additional safety samples may be collected if clinically indicated at the discretion of the Investigator. The date, time of collection, and results (values, units, and reference ranges) will be recorded on the appropriate eCRF.

The laboratory variables to be measured are presented in Table 9 (clinical chemistry), Table 10 (hematology), and Table 11 (urinalysis).

Other safety tests to be performed at screening include assessment for HBV surface antigen, HCV antibodies, and HIV antibodies.

HPV status will be recorded at screening, if available.

The following laboratory variables will be measured:

Table 9 Clinical chemistry

Albumin	Lipase[b]
Alkaline phosphatase[a]	Magnesium[c]
ALT[a]	Potassium
Amylase[b]	Sodium
AST[a]	Total bilirubin[a]
Bicarbonate[c]	Total protein
Calcium	TSH[e]
Chloride[c]	T_3 free[f] (reflex)
Creatinine[d]	T_4 free[f] (reflex)
Gamma glutamyltransferase[c]	Urea or blood urea nitrogen, depending on local practice
Glucose	
Lactate dehydrogenase	

[a] Tests for ALT, AST, alkaline phosphatase, and total bilirubin must be conducted and assessed concurrently. If total bilirubin is ≥2 × upper limit of normal (and no evidence of Gilbert's syndrome), then fractionate into direct and indirect bilirubin.
[b] It is preferable that both amylase and lipase parameters are assessed. For sites where only 1 of these parameters is routinely measured, either lipase or amylase is acceptable.
[c] Bicarbonate (where available), chloride, creatinine clearance, gamma glutamyltransferase, magnesium, testing are to be performed at screening, on Day 1 (unless all screening laboratory clinical chemistry assessments are performed within 3 days prior to Day 1), and if clinically indicated.
[d] Creatinine clearance will be calculated using Cockcroft-Gault (using actual body weight).
[e] If TSH is measured within 14 days prior to Day 1 (first infusion day), it does not need to be repeated at Day 1.
[f] Free T_3 or free T_4 will only be measured if TSH is abnormal or if there is a clinical suspicion of an AE related to the endocrine system.

Abbreviations: AE Adverse event; ALT Alanine aminotransferase; AST Aspartate aminotransferase; T_3 Triiodothyronine; T_4 Thyroxine; TSH Thyroid-stimulating hormone.

Table 10 Hematology

Absolute neutrophil count[a]	Absolute lymphocyte count[a]
Hemoglobin	Platelet count
Total white cell count	

Note: For coagulation parameters, activated partial thromboplastin time and international normalized ratio are to be assessed at baseline on Day 1 (unless all screening laboratory hematology assessments are performed within 3 days prior to Day 1), and as clinically indicated.

[a] Can be recorded as absolute counts or as percentages. Absolute counts will be calculated by Data Management if entered as percentage. Total white cell count therefore has to be provided.

Table 11 Urinalysis

Bilirubin	Ketones
Blood	pH
Color and appearance	Protein
Glucose	Specific gravity

Note: Urinalysis should be done at baseline (screening) and then as clinically indicated.
Note: Microscopy should be used as appropriate to investigate white blood cells and use the high power field for red and white blood cells.

If a patient shows an AST or ALT ≥3 × ULN together with total bilirubin ≥2 × ULN, refer to Appendix E for further instructions on cases of increases in liver biochemistry and evaluation of Hy's Law. Cases where a participant shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT ≥ 3 × ULN together with TBL ≥ 2 × ULN may need to be reported as SAEs. Please refer to Appendix E for further instruction on cases of increases in liver biochemistry and evaluation of Hy's Law

All patients should have further chemistry profiles performed at 30 days (±3 days), 2 months (±1 week), and 3 months (±1 week) after permanent discontinuation of study treatment (see the SoAs).

Any clinically significant abnormal laboratory values should be repeated as clinically indicated and recorded on the eCRF. Situations in which laboratory safety results should be reported as AEs are described in Section 8.3.7.

All patients with Grade 3 or 4 laboratory values at the time of completion or discontinuation from IP must have further tests performed until the laboratory values have returned to Grade 1 or 2, unless these values are not likely to improve because of the underlying disease.

8.2.5 WHO/ECOG performance status

WHO/ECOG PS will be assessed at the times specified in the assessment schedules (see the SoAs) based on the following:

0. Fully active; able to carry out all usual activities without restrictions

1. Restricted in strenuous activity, but ambulatory and able to carry out light work or work of a sedentary nature (eg, light housework or office work)

2. Ambulatory and capable of self-care, but unable to carry out any work activities; up and about more than 50% of waking hours.

3. Capable of only limited self-care; confined to bed or chair more than 50% of waking hours

4. Completely disabled; unable to carry out any self-care and totally confined to bed or chair

5. Dead

Any significant change from baseline or screening must be reported as an AE.

8.2.6 Early subject review for safety

It is recommended that patients are contacted 2 weeks after receiving the first 3 cycles of durvalumab (Cycle 1 Day 14 [±24 hours], Cycle 2 Day 14 [±24 hours], and Cycle 3 Day 14 [±24 hours]) to ensure early identification and management of toxicities.

8.2.7 Other safety assessments

If new or worsening pulmonary symptoms (eg, dyspnea) or radiological abnormality suggestive of pneumonitis/ILD are observed, toxicity management as described in detail in the Dosing Modification and Toxicity Management Guidelines (see Section 8.4.5) will be applied. The results of the full diagnostic workup (including high-resolution computed tomography [HRCT], blood and sputum culture, hematological parameters, etc) will be captured in the eCRF. It is strongly recommended to perform a full diagnostic workup, to exclude alternative causes such as lymphangitic carcinomatosis, infection, allergy, cardiogenic edema, or pulmonary hemorrhage. In the presence of confirmatory HRCT scans where other causes of respiratory symptoms have been excluded, a diagnosis of pneumonitis (ILD) should be considered and the Dosing Modification and Toxicity Management Guidelines should be followed.

Pneumonitis investigation

The following assessments, and additional assessments if required, will be performed to enhance the investigation and diagnosis of potential cases of pneumonitis. The results of the assessment will be collected.

Physical examination

- Signs and symptoms (cough, shortness of breath, and pyrexia, etc) including auscultation for lung field will be assessed.

Saturation of peripheral oxygen

Other items

- When pneumonitis (ILD) is suspected during study treatment, the following markers should be measured where possible:

  (i) ILD Markers (KL-6, SP-D) and β-D-glucan

  (ii) Tumor markers: Particular tumor markers, which are related to disease progression.

  (iii) Additional Clinical chemistry: C-reactive protein (CRP), lactate dehydrogenase (LDH)

8.3 Collection of adverse events

The Principal Investigator is responsible for ensuring that all staff involved in the study are familiar with the content of this section

The definitions of an AE or SAE can be found in Appendix B.

AE will be reported by the patient (or, when appropriate, by a caregiver, surrogate, or the patient's legally authorized representative).

The Investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE. For information on how to follow up AEs, see Section 8.3.3.

8.3.1 Method of detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the patient is the preferred method to inquire about AE occurrences.

8.3.2 Time period and frequency for collecting adverse event and serious adverse event information

AEs and SAEs will be collected from the time of the patient signing the informed consent form until the follow-up period is completed (90 days after the last dose of study treatment). If an event that starts post the defined safety follow-up period noted above is considered to be due to a late onset toxicity to study treatment, then it should be reported as an AE or SAE as applicable.

All SAEs will be recorded and reported to the Sponsor or designee within 24 hours, as indicated in Appendix B. The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE in former study patients. However, if the Investigator learns of any SAE, including a death, at any time after a patient's last visit and he/she considers the event to be reasonably related to the Study treatment or study participation, the Investigator should notify the Sponsor.

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix B.

8.3.3 Follow-up of adverse events and serious adverse events

After the initial AE/SAE report, the Investigator is required to proactively follow each patient at subsequent visits/contacts. All AEs and SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the patient is lost to follow-up.

Any AEs that are unresolved at the patient's last AE assessment or other assessment in the study are followed up by the Investigator for as long as medically indicated (this may be beyond the 90 days after the last dose of study treatment), but without further recording in the eCRF. AstraZeneca retains the right to request additional information for any patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

8.3.4 Adverse event data collection

The following variables will be collected for each AE:

- AE (verbatim)
- The date when the AE started and stopped
- The maximum common terminology criteria for adverse events (CTCAE) grade reported
- Changes in CTCAE grade (report only the maximum CTCAE grade for a calendar day)
- Whether the AE is serious or not
- Investigator causality rating against the IPs (yes or no)
- Action taken with regard to IPs
- Administration of treatment for the AE

- Outcome
- In addition, the following variables will be collected for SAEs:
- Date the AE met criteria for SAE
- Date the Investigator became aware of the SAE
- Seriousness criteria
- Date of hospitalization
- Date of discharge
- Probable cause of death
- Date of death
- Whether an autopsy was performed
- Causality assessment in relation to study procedure(s)
- Causality assessment in relation to other medication, as explained in Section 8.3.5
- Description of the SAE

The grading scales found in the revised National Cancer Institute (NCI) CTCAE version 5 will be utilized for all events with an assigned CTCAE grading. For those events without assigned CTCAE grades, the recommendation in the CTCAE criteria that converts mild, moderate, and severe events into CTCAE grades should be used. A copy of the CTCAE version 5 can be downloaded from the Cancer Therapy Evaluation Program website (http://ctep.cancer.gov).

8.3.5 Causality collection

The Investigator will assess causal relationship between IP and each AE, and answer “yes” or “no” to the question “Do you consider that there is a reasonable possibility that the event may have been caused by the IP?”

For SAEs, causal relationship will also be assessed for other medication and study procedures. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as “yes.”

A guide to the interpretation of the causality question is found in Appendix B to the Clinical Study Protocol.

8.3.6 Adverse events based on signs and symptoms

All AEs spontaneously reported by the patient or reported in response to the open question from the study site staff: "Have you had any health problems since the previous visit/you were last asked?" or revealed by observation will be collected and recorded in the eCRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

8.3.7 Adverse events based on examinations and tests

The results from the Clinical Study Protocol (CSP) mandated laboratory tests and vital signs will be summarized in the clinical study report (CSR). Deterioration as compared to baseline in protocol-mandated laboratory values and vital signs should therefore only be reported as AEs if they fulfill any of the SAE criteria or are the reason for discontinuation of study treatment.

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE, and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting Investigator uses the clinical, rather than the laboratory term (eg, anemia versus low hemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Deterioration of a laboratory value, which is unequivocally due to disease progression, should not be reported as an AE/SAE.

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE unless unequivocally related to the disease under study, see Sections 8.3.9and 8.3.10.

8.3.8 Hy's law

Cases where a patient shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT ≥3 × ULN together with total bilirubin ≥2 × ULN may need to be reported as SAEs. Please refer to Appendix E for further instruction on cases of increases in liver biochemistry and evaluation of Hy's Law.

8.3.9 Disease progression

Disease progression can be considered as a worsening of a patient's condition attributable to the disease for which the IP is being studied. It may be an increase in the severity of the disease under study and/or increases in the symptoms of the disease. The development of new

or progression of existing metastasis to the primary cancer under study should be considered as disease progression and not an AE. Events, which are unequivocally due to disease progression, should not be reported as an AE during the study.

8.3.10 New cancers

The development of a new cancer should be regarded as an SAE. New primary cancers are those that are not the primary reason for the administration of the IP and have been identified after the patient's inclusion in this study.

8.3.11 Deaths

All deaths that occur during the study treatment period, or within the protocol-defined follow-up period after the administration of the last dose of study treatment, must be reported as follows:

- Death clearly resulting from disease progression should be reported to the Study Monitor/Physician at the next monitoring visit and should be documented in the eCRF in the Statement of Death page. It should not be reported as an SAE.
- Where death is not due (or not clearly due) to progression of the disease under study, the AE causing the death must be reported to the Study Monitor/Physician as an SAE within 24 hours. It should also be documented in the Statement of Death page in the eCRF. The report should contain a comment regarding the co involvement of PD, if appropriate, and should assign main and contributory causes of death.
- Deaths with an unknown cause should always be reported as an SAE. It should also be documented in the Statement of Death page in the eCRF. A postmortem may be helpful in the assessment of the cause of death, and if performed, a copy of the post-mortem results should be forwarded to AstraZeneca Patient Safety or its representative within the usual time frames.

Deaths occurring after the protocol defined safety follow-up period after the administration of the last dose of study treatment should be documented in the Statement of Death page. If the death occurred as a result of an event that started post the defined safety follow-up period and the event is considered to be due to a late onset toxicity to study drug then it should also be reported as an SAE.

8.3.12 Adverse events of special interest

AESIs are events of scientific and medical interest specific to the further understanding of durvalumab safety profile and require close monitoring and rapid communication by the investigators to AstraZeneca. An AESI can be serious or non-serious. All AESIs will be recorded in the eCRF. Serious AESIs will be recorded and reported as per Section 8.4.1

AESIs for durvalumab include but are not limited to events with a potential inflammatory or immune-mediated mechanism and which may require more frequent monitoring and/or interventions such as steroids, immunosuppressants, and/or hormone replacement therapy. These AESIs are being closely monitored in clinical studies with durvalumab monotherapy and combination therapy. An imAE is defined as an AESI that is associated with drug exposure and is consistent with an immune-mediated mechanism of action and where there is no clear alternate etiology.

If the Investigator has any questions in regards to an event being an imAE, the Investigator should promptly contact the Study Physician.

AESI/imAEs observed with anti PD-L/PD-1 agents such as durvalumab include:

- Diarrhea/colitis and intestinal perforation
- Pneumonitis/ILD
- Endocrinopathies (ie, events of hypophysitis/hypopituitarism, adrenal insufficiency, hyper- and hypo-thyroidism and type I diabetes mellitus)
- Hepatitis/transaminase increases
- Nephritis/blood creatinine increases
- Pancreatitis/serum lipase and amylase increases
- Rash/dermatitis(including pemphigoid)
- Myocarditis
- Myositis/polymyositis
- Immune thrombocytopenia
- Rare/less frequent imAEs including neuromuscular toxicities such as myasthenia gravis and Guillain-Barré syndrome
- Other inflammatory responses that are rare or less frequent with a potential immune-mediated etiology include, but are not limited to, pericarditis, sarcoidosis, uveitis, and other events involving the eye, skin, hematological, and rheumatological events.

In addition, infusion-related reactions and hypersensitivity/anaphylactic reactions with a different underlying pharmacological etiology are also considered AESIs.

Further information on these risks (eg, presenting symptoms) can be found in the current version of the durvalumab IB. More specific guidelines for their evaluation and treatment are described in detail in the Dose Modification and Toxicity Management Guidelines (see Section 8.4.5). These guidelines have been prepared by the Sponsor to assist the Investigator in the exercise of her clinical judgment in treating these types of toxicities. These guidelines apply to AEs considered causally related to the study drug/study regimen by the reporting Investigator.

8.3.13 Safety data to be collected following the final Data Cutoff of the study

For patients continuing to receive durvalumab treatment after final DCO and database closure, it is recommended that the patients continue the scheduled site visits and Investigators monitor the patient's safety laboratory results prior to and periodically during treatment with durvalumab in order to manage AEs in accordance with the durvalumab Dose Modification and Toxicity Management Guidelines (see Section 8.4.5). All data post the final DCO and database closure will be recorded in the patient notes but, with the exception of SAEs, will not otherwise be reported for the purposes of this study.

All SAEs that occur in patients still receiving durvalumab treatment (or within the 90 days following the last dose of durvalumab treatment) post the final DCO and database closure must be reported as detailed in Section 8.4.1.

8.4 Safety reporting and medical management

8.4.1 Reporting of serious adverse events

All SAEs have to be reported, whether or not considered causally related to the IP, or to the study procedure(s). All SAEs will be recorded in the eCRF.

If any SAE occurs in the course of the study, then Investigators or other site personnel inform the appropriate AstraZeneca representatives within 1 day (ie, immediately but **no later than 24 hours** of when he or she becomes aware of it).

The designated AstraZeneca representative works with the Investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within 1 calendar day** of initial receipt for fatal and life-threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform AstraZeneca representatives of any follow-up information on a previously reported SAE within 1 calendar day (ie, immediately but **no later than 24 hours** of when he or she becomes aware of it).

Once the Investigators or other site personnel indicate an AE is serious in the electronic data capture system, an automated email alert is sent to the designated AstraZeneca representative.

If the electronic data capture system is not available, then the Investigator or other study site staff reports an SAE to the appropriate AstraZeneca representative by telephone.

The AstraZeneca representative will advise the Investigator/study site staff how to proceed.

For further guidance on the definition of an SAE, see Appendix B of the Clinical Study Protocol.

8.4.2 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca unless the pregnancy is discovered before the study patient has received any study drug.

If a pregnancy is reported, the Investigator should inform the Sponsor within 24 hours of learning of the pregnancy.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.4.2.1 Maternal exposure

If a patient becomes pregnant during the course of the study, IP should be discontinued immediately.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the IP under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) should be followed up and documented even if the patient was discontinued from the study.

If any pregnancy occurs in the course of the study, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives within 1 day (ie, immediately but **no later than 24 hours** of when he or she becomes aware of it).

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 or 5 calendar days for SAEs (see Section 8.4.1) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

Patients who are permanently discontinued from further receipt of IP, regardless of the reason, will be identified as having permanently discontinued treatment and will enter follow-up (see the SoAs).

8.4.3 Overdose

8.4.3.1 Durvalumab

Use of durvalumab in doses in excess of that specified in the protocol is considered to be an overdose. There is currently no specific treatment in the event of overdose of durvalumab, and possible symptoms of overdose are not established.

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the eCRF and on the Overdose eCRF module.
- An overdose without associated symptoms is only reported on the Overdose eCRF module.

If an overdose on an AstraZeneca study drug occurs in the course of the study, then the Investigator or other site personnel will inform appropriate AstraZeneca representatives immediately, or **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site.

- For overdoses associated with an SAE, the standard reporting timelines apply, see Section 8.3.2. For other overdoses, reporting must occur within 30 days.

8.4.3.2 Standard of Care

Please refer to the local prescribing information for treatment of cases of overdose if any overdose is associated with an AE or SAE please record the AE/SAE diagnosis or symptoms in the relevant AE modules only of the eCRF.

8.4.4 Medication error

If a medication error occurs in the course of the study, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives within 1 day (ie, immediately but no later than 24 hours of when he or she becomes aware of it).

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is completed within 1 (initial fatal/life-threatening or follow-up fatal/life-threatening) or 5 (other serious initial and follow-up) calendar days if there is an SAE associated with the medication error (see Section 8.3.2) and within 30 days for all other medication errors.

The definition of a medication error can be found in Appendix B.

8.4.5 Management of durvalumab-related toxicities

The following general guidance should be followed for management of toxicities.

- Treat each of the toxicities with maximum supportive care (including holding the agent suspected of causing the toxicity if required).
- If the symptoms promptly resolve with supportive care, consideration should be given to continuing the same dose of the assigned IP along with appropriate continuing supportive care. If medically appropriate, dose modifications are permitted
- All dose modifications should be documented with clear reasoning and documentation of the approach taken.

All toxicities will be graded according to NCI CTCAE, version 5.

8.4.5.1 Specific toxicity management and dose modification information - durvalumab

Comprehensive toxicity management guidelines (TMG) have been developed to assist investigators with the recognition and management of toxicities associated with the use of the immune-checkpoint inhibitor durvalumab. These guidelines are applicable when durvalumab is used alone or in combination and is administered concurrently or sequentially with other anti-cancer drugs (i.e. antineoplastic chemotherapy, targeted agents), as part of a protocol specific treatment regimen. Guidelines for the management of immune-mediated reactions, infusion-related reactions, and non-immune-mediated reactions for durvalumab are provided in the Dosing Modification and Toxicity Management Guidelines. The most current version of these guidelines is also maintained within the Site Master File.

Patients should be thoroughly evaluated and appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the imAE. Serologic, immunologic, and histologic (biopsy) data, as appropriate, should be used to support an imAE diagnosis. In the absence of a clear alternative etiology, events should be considered potentially immune related.

In addition, there are certain circumstances in which durvalumab should be permanently discontinued (see Section 7.1 of this protocol and the Dosing Modification and Toxicity Management Guidelines).

Following the first dose of IP, subsequent administration of durvalumab can be modified based on toxicities observed as described in the Dosing Modification and Toxicity Management Guidelines. These guidelines have been prepared by the Sponsor to assist the

Investigator in the exercise of her clinical judgment in treating these types of toxicities. These guidelines apply to AEs considered causally related to durvalumab regimen by the reporting Investigator.

Dose reductions are not permitted. In case of doubt, the Investigator should consult with the Study Physician.

8.4.5.2 Specific toxicity management and dose modification information - chemoradiotherapy

Investigators should follow toxicity management guidelines for chemotherapy and radiation therapy (Appendix J). All effort should be taken to follow the guidelines to ensure optimal and timely medical care for the patients. If the guidelines are not able to be followed, justification should be clearly documented in the electronic database. For specific information regarding the individual agents used in this study, please refer to the local prescribing information for the relevant agent.

Every effort should be made to continue a patient on CCRT definitive SoC therapy. In the case of clinically significant toxicity possibly due to SoC or durvalumab, durvalumab dosing can be delayed one cycle. For further information on durvalumab toxicity management and dose modification see section 8.4.5.1 and the Sponsor study physician may also be contacted.

8.5 Pharmacokinetics

Drug concentration information that may unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

8.5.1 Collection of samples

Blood samples for determination of durvalumab concentration in serum will be obtained according to the SoAs.

Samples for determination of durvalumab concentration in serum will be analyzed by a designated third party on behalf of AstraZeneca. Samples will be collected, labeled, stored, and shipped as detailed in the Laboratory Manual. Full details of the analytical method used will be described in a separate Bioanalytical Validation Report.

8.5.1.1 Collection of samples to measure for the presence of antidrug antibodies

The presence of ADA will be assessed in serum samples taken according to the SoAs.

Samples will be measured for the presence of ADAs and ADA-neutralizing antibodies for durvalumab using validated assays. Tiered analysis will be performed to include screening,

confirmatory, and titer assay components, and positive negative cut points previously statistically determined from drug-naïve validation samples will be employed

8.5.2 Storage and destruction of pharmacokinetic/antidrug antibody samples

Durvalumab PK and ADA samples will be destroyed within 5 years of CSR finalization.

PK and ADA samples may be disposed of or destroyed and anonymized by pooling. Additional analyses may be conducted on the anonymized, pooled PK samples to further evaluate and validate the analytical method. Results from such analyses may be reported separately from the CSR.

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation will not be reported in the CSR but separately in a Bioanalytical Validation Report.

Any residual back-up PK samples may be used for future exploratory biomarker research (in this case, residual back-up PK samples will be shipped to AstraZeneca-assigned Biobank; see details in the Laboratory Manual).

For China: PK and ADA samples collected in China will be stored and disposed according to local laws and regulations. PK and ADA samples collected in China will be destroyed after finalization of bioanalytical report or completion of CSR

8.6 Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7 Genetics

8.7.1 Optional exploratory genetic sample

CCI

[redacted]

This sample will not be collected in China.

8.7.2 Storage and destruction of genetic samples

The processes adopted for the coding and storage of samples for genetic analysis are important to maintain patient confidentiality. Samples may be stored for a maximum of 15 years or as per local regulations from the date of the last patient's last visit (LPLV), after which they will be destroyed. DNA is a finite resource that may be used up during analyses. The results of any further analyses will be reported either in the CSR itself or as an addendum, or separately in a scientific report or publication.

No personal details identifying the individual will be available to AstraZeneca or designated organizations working with the DNA.

8.8 Biomarkers

By participating in this study the patient consents to the mandatory collection and use of donated biological samples as described here.

8.8.1 Tumour samples:

8.8.1.1 Tumor sample collection:

Several tumour biopsy samples are requested for this study as described below:

MANDATORY: A newly acquired sample is preferred if available per site's routine clinical practice; otherwise, archival sample ≤3 months old prior to screening can be provided. Samples should be collected via a core needle (18 gauge or larger) or be collected as an excisional or incisional tumor biopsy sample.

Please refer to the Laboratory Manual for specific instructions and guidelines regarding tumor sample collection.

OPTIONAL: The collection of an additional biopsy sample upon progression is optional but strongly encouraged.

All optional tumour sample will not be collected in China.

Details for collection, storage, and shipment of biologic samples are presented in a separate Laboratory Manual.

8.8.1.2 PD-L1 expression assessment

PD-L1 is a potential biomarker for checkpoint inhibitor therapy in metastatic previously treated cervical cancer. However, it is unknown whether this is true in locally advanced cervical cancer. Previous studies demonstrate about 88% of cases in this population are ≥ 1 %

positive for PD-L1 (Emeka et al 2017). Additionally, the addition of concurrent chemoradiotherapy can result in a shift towards an increase in PD-L1 expression. Therefore, to further evaluate the PD-L1 as a potential biomarker, pretreatment tumor PD-L1 expression will be evaluated in all randomized patients. Data will be compared between arms to determine if baseline PD-L1 status is prognostic and/or predictive of outcomes associated with durvalumab + SoC CCRT versus placebo + SoC CCRT.

8.8.2 Exploratory biomarkers

Blood samples for exploratory biomarker analyses will be obtained according to the schedules presented in the SoAs. Details for collection, volumes, storage, and shipment of biologic samples are presented in a separate Laboratory Manual.

Baseline (preferred to be collected prior to dosing at C1D1) and/or on-treatment measures will be correlated with outcomes. Note that samples will be obtained from patients randomized to each treatment arm. Comparisons will be made between baseline measures to determine if biomarkers (or combination of markers) are prognostic or predictive of outcomes associated with durvalumab + SoC CCRT versus placebo + SoC CCRT therapies, subgrouped by histology.

Additional sample collections and analyses may be completed at select study sites by site-specific amendment. All samples collected for such exploratory analyses will be stored at site, a reference laboratory, or AstraZeneca facilities and may be used for subsequent research relevant to evaluating response to therapy.

The exploratory biomarker plan is described by sample type below.

8.8.2.1 Microsatellite instability and tumor mutation burden

Tumor tissue remaining after PD-L1 testing will be analyzed retrospectively for microsatellite instability (MSI) and tumor mutation burden (TMB) using a Next Generation Sequencing (NGS)-based method such as whole exome sequencing (WES) or a targeted NGS assay. The MSI-H/MSS status and TMB will be determined based on the MSI events or somatic variants detected in the tumor sequence data and correlated with efficacy as an exploratory objective. Blood-based MSI testing may also be performed in cases of insufficient tissue material, unsuccessful tissue-based MSI/TMB testing or for evaluation of blood-based MSI/TMB with clinical outcomes and other biomarkers.

Note: This sample will not be collected in China.

8.8.2.2 Tumor biomarkers

Based on availability of tissue (described in section 8.8.1.1), additional exploratory biomarkers might be analysed by immunohistochemistry (IHC). A primary goal is to measure CD8 and/or CD4/FoxP3 protein expression in an effort to enumerate cytotoxic versus regulatory T cells. Based on availability of tissue, a panel of additional, immune-relevant markers expressed on tumor-infiltrating lymphocytes or on tumor cells may be assessed. Markers of special interest include, but are not limited to, CXCL9 and LAG3.

Other tissue-based approaches may be pursued including messenger ribonucleic acid (mRNA) profiling and in situ hybridization (eg, detection of IFNg signaling genes), molecular profiling, and/or somatic variant detection methodologies.

Note: Above tumor biomarker sample will not be collected in China.

8.8.2.3 Whole blood gene expression (PAXgene RNA)

Whole blood samples will be obtained for RNA analysis. Total RNA will be prepared for quantification of mRNA and/or micro-RNA expression using quantitative reverse transcription PCR, microarray, sequencing, or similar technology. Focus is likely to be given to the expression of immunomodulatory genes. Baseline and/or on-treatment correlations with outcome data will be completed on select candidates, predictive markers with the aim of identifying useful expression thresholds for identifying patients likely to receive benefit.

Note: This sample will not be collected in China.

8.8.2.4 Plasma - ctDNA mutations

Blood samples will be collected for analysis of circulating tumor deoxyribonucleic acid (ctDNA) in plasma. ctDNA samples will be collected at baseline, during treatment, at disease progression, and during follow-up after discontinuation of study treatment, as specified in the Schedule of Assessments (Table 1 & Table 2). Analyses will include, but not be limited to evaluating baseline sensitizing mutations to treatment and correlations with clinical outcomes, changes in levels and variant frequencies of ctDNA and potentially minimal residual disease. Plasma may also be evaluated for relevant cytokines, chemokines and other immune-related biomarkers.

Details for collection, volumes, storage, and shipment of biologic samples are presented in a separate Laboratory Manual.

Note: This sample will not be collected in China.

8.8.3 Management of biomarker data

The results may be pooled with biomarker data from other studies to evaluate biological responses across indications and to compare results in monotherapy versus combination settings.

The biomarker data will have unknown clinical significance. AstraZeneca will not provide biomarker research results to patients, their family members, any insurance company, an employer, clinical study Investigator, general physician, or any other third party, unless required to do so by law. The patient's samples will not be used for any purpose other than those described in the study protocol.

Individual patients will not be identified in any report or publication resulting from this work. The data and results of this research may be reviewed with collaborators and published, but neither the patient's name nor any other personal identifiers will appear in any publication or report.

8.8.4 Storage, re-use, and destruction of biomarker samples

All samples collected for biomarker analyses will be stored at the study site, a reference laboratory, or at AstraZeneca facilities and may be used for subsequent research relevant to evaluating biological and/or clinical response to therapy as described in the exploratory analyses section.

Samples will be stored for a maximum of 15 years from the end of study, after which they will be destroyed. Summaries and analyses for exploratory biomarkers will be documented in a separate analysis plan and will be reported outside the CSR in a separate report. The results of this biomarker research may be pooled with biomarker data from other studies to generate hypotheses to be tested in future research.

For China: The stained tissue slides (PD-L1 and H&E slides) will be retained at Covance as raw data for a minimum of 10 years after study closure and repatriated or discarded at the end of the retention period. Collected tissue slides for PD-L1 testing, if unstained, will be repatriated to the sites or discarded 5 years after study drug approved for marketing in China.

8.8.5 Labeling and shipment of biological samples

The Principal Investigator will ensure that samples are labeled and shipped in accordance with the Laboratory Manual and the Biological Substance, Category B, Regulations (materials containing or suspected to contain infectious substances that do not meet Category A criteria); see Appendix C "IATA 6.2 Guidance Document."

Any samples identified as Infectious Category A materials will not be shipped, and no further samples will be taken from the involved patients unless agreed upon with AstraZeneca and appropriate labeling, shipment, and containment provisions are approved.

8.8.6 Chain of custody of biological samples

A full chain of custody will be maintained for all samples throughout their life cycle.

The Principal Investigator at each center will keep full traceability of collected biological samples from the patients while in storage at the center until shipment or disposal (where appropriate) and will keep documentation of receipt of sample shipments.

The sample receiver will keep full traceability of the samples while in storage and during use until used or disposed of or until further shipment and will keep documentation of receipt of arrival.

AstraZeneca will keep oversight of the entire life cycle through internal procedures, monitoring of study sites, auditing or process checks, and contractual requirements of external laboratory providers.

Samples retained for further use will be stored in the AstraZeneca-assigned biobanks and will be registered with the AstraZeneca Biobank Team during the entire life cycle.

9. STATISTICAL CONSIDERATIONS

The primary aim of the study is to compare the efficacy and safety of durvalumab + SoC CCRT to placebo + SoC CCRT in terms of PFS in patients with FIGO (2009) Stage IB2 to IVA cervical cancer.

- Analyses will be performed by AstraZeneca or its representatives.
- Refer to SAP for details.
- The SAP will be signed off before review of any potential treatment-revealing data is undertaken (this includes blinded delivery reviews and data monitoring committee reviews). For all situations, a full draft of SAP should be available to ensure sufficient time to prepare for any blinded or unblinded data review. A first draft of the SAP will be available before the first patient is enrolled.

Depending on the extent of any impact, summaries of data relating to patients diagnosed with COVID-19, and impact of COVID-19 on study conduct (in particular missed visits, delayed or discontinued IP, and other protocol deviations) may be generated. More detail will be provided in the SAP.

9.1 Statistical hypotheses

The formal statistical analysis will be performed to test the main hypotheses:

- H0: No difference between durvalumab + SoC CCRT and placebo + SoC CCRT
- H1: Difference between durvalumab + SoC CCRT and placebo + SoC CCRT

The primary objective of this study is to assess the efficacy of durvalumab + SoC CCRT compared with placebo + SoC CCRT in terms of PFS as assessed by investigator tumor assessments and histopathologic confirmation of local tumor progression. A key secondary objective is to assess the efficacy in terms of OS.

9.2 Sample size determination

Approximately 714 patients will be randomized 1:1 to durvalumab + SoC CCRT or placebo + SoC CCRT to obtain approximately 227 PFS events in the ITT population. The randomization will be stratified according to disease stage status (FIGO (2009) Stage <III and node positive, FIGO (2009) Stage ≥III and node negative, or FIGO (2009) Stage ≥III and node positive), and region [United States, Canada, European Union, South Korea, and Japan] versus rest of the world.

The PFS analysis will occur when approximately 227 PFS events have occurred across the durvalumab + SoC CCRT and placebo + SoC CCRT treatment arms. If the true HR is 0.65 (likely to correspond to a 11% increase in the proportion of patients progression-free at 3 years from 65% to 76%) (Rose et al 1999), this analysis will have 90% power to demonstrate a statistically significant difference for PFS, assuming a 2-sided 5% significance level. Assuming non-uniform recruitment, a 3-year PFS rate of 65% for placebo + SoC CCRT and an exponential distribution, recruitment of 714 patients in 18 months would be expected to yield 227 PFS events approximately 53 months following recruitment of the first patient. In addition, the sample size has been derived on the assumption that 5% of patients will drop out at an exponential rate within 36 months following the randomization of the first patient.

If the true OS HR is 0.65, the study is also sized to provide 89% power for the OS endpoint in the comparison of durvalumab + Soc CCRT versus placebo + SoC CCRT, assuming a 2-sided 5% significance level allowing for 1 interim analyses conducted at approximately 86% of the target events. The final OS analysis will occur at the earlier of 227 death events or 71 months following recruitment of the first patient. Assuming the same recruitment assumptions for PFS and a 3-year OS rate of 70% for placebo + SoC CCRT (Rose et al 1999), 227 deaths would be expected to occur 61 months following the recruitment of the first patient. The boundaries of

the treatment comparison will be derived based upon the actual number of OS events observed at that time.

9.3 Populations for analyses

Definitions of the analysis sets for each outcome variable are provided in Table 12.

Table 12 Summary of outcome variables and analysis populations

Outcome variable	Populations
Efficacy data	
PFS	Full analysis set (ITT population)
PFS (3 year), OS, ORR, CR rate, DoR in Patients with a CR, Incidence of Local Progression, Distant Disease Progression, and Secondary Malignancy,)	Full analysis set (ITT population)
PFS, OS	PD-L1 positive analysis set
Demography	Full analysis set (ITT population)
PK data	PK analysis set
PROs	Full analysis set (ITT population)
Safety data	
Exposure	Safety analysis set
AEs	Safety analysis set
Laboratory measurements	Safety analysis set
Vital Signs	Safety analysis set

Abbreviations: AE Adverse event; CR rate Complete response rate; ITT Intent-to-treat; ORR Objective response rate; OS Overall survival; PFS Progression-free survival; PK Pharmacokinetics; PRO Patient-reported outcomes;.

9.3.1 Full analysis set

The full analysis set (FAS) will include all randomized patients (ITT population). The FAS will be used for all efficacy analyses (including PROs). Treatment arms will be compared on the basis of randomized study treatment, regardless of the treatment actually received. Patients who were randomized but did not subsequently go on to receive study treatment are included in the analysis in the treatment arm to which they were randomized. The responders analysis set will include the subset of patients the FAS, who achieve an objective response.

9.3.2 Safety analysis set

The safety analysis set (SAS) will consist of all patients who received at least 1 dose of study treatment (durvalumab or placebo). Safety data will not be formally analyzed but summarized using the SAS according to the treatment received; that is, erroneously treated patients (eg,

those randomized to treatment A but actually given treatment B) will be summarized according to the treatment they actually received.

9.3.3 PK analysis set

All patients who receive at least 1 dose of durvalumab per the protocol for whom any post-dose data are available and who do not violate or deviate from the protocol in ways that would significantly affect the PK analyses will be included in the PK analysis set. The population will be defined by the Study Physician, Pharmacokineticist, and Statistician prior to any analyses being performed.

9.3.4 PD-L1 positive analysis set

The PD-L1 positive analysis set will include the subset of patients in the FAS whose PD-L1 status is PD-L1 positive as defined ≥1% based on either tumor or immune cell staining.

9.4 Outcome measures for analyses

9.4.1 Calculation or derivation of efficacy variables

9.4.1.1 RECIST 1.1-based endpoints

The analysis of the secondary endpoints ORR, and CR rate, will be based on investigator assessments using RECIST 1.1 or pathologic assessment of local disease progression. In addition, the key secondary endpoint (OS) and other secondary endpoints (Incidence of Local Progression, Distant Disease Recurrence, and Secondary Malignancy) will also be analyzed.

Investigator RECIST 1.1-based assessments

All RECIST 1.1 assessments, whether scheduled or unscheduled, will be included in the calculations. This is also regardless of whether a patient discontinues study treatment or receives another anticancer therapy.

At each visit, patients will be programmatically assigned a RECIST 1.1 visit response of CR, PR, SD, or PD depending on the status of their disease compared with baseline and previous assessments. Baseline will be assessed within the 28 days prior to enrolment. If a patient has had a tumor assessment that cannot be evaluated, then the patient will be assigned a visit response of NE (unless there is evidence of progression, in which case the response will be assigned as PD).

Blinded independent central review

The BICR of all radiological imaging data will be carried out using RECIST version 1.1. All images will be collected centrally. The imaging scans will be reviewed by 2 independent radiologists using RECIST 1.1 and will be adjudicated, if required. For each patient, the BICR

will define the overall visit response data (CR, PR, SD, PD, or NE) and the relevant scan dates for each timepoint (ie, for visits where response or progression is/is not identified). If a patient has had a tumor assessment that cannot be evaluated, then the patient will be assigned a visit response of not evaluable (NE; unless there is evidence of progression, in which case the response will be assigned as PD). Endpoints (of PFS) will be derived from the overall visit response date and the scan dates.

Further details of the BICR will be documented in the Imaging Charter.

Pathological confirmation of local progression

At response assessment physical exams, patients will be evaluated for local progression. Any lesion detected on physical exam that is not evaluable through RECIST 1.1 and is within the radiation field and suspected to be progressive disease will be biopsied. Lesions with histopathologic confirmation of disease will be reported as a response of PD. If there is no evidence of active cervical cancer on biopsy, the patient will not be reported as PD, and will continue with all study procedures according to the Schedule of Assessments (Table 1). If there is evidence of active cervical cancer on biopsy, the date of progression will be the date of the physical exam that triggered the biopsy.

Please refer to Appendix F for the definitions of CR, PR, SD, and PD.

9.4.1.2 Primary endpoint - progression-free survival

PFS (per RECIST 1.1 as assessed by investigator tumor assessments or histopathologic confirmation of local tumor progression) will be defined as the time from the date of randomization until the date of objective disease progression or death (by any cause in the absence of progression) regardless of whether the patient withdraws from therapy or receives another anticancer therapy prior to progression (ie, date of event or censoring – date of randomization + 1). Progression free survival events will be classified as either local progression, distant recurrence, secondary malignancy, or death. Patients who have not progressed or died at the time of analysis will be censored at the time of the latest date of assessment at which the RECIST 1.1 assessment and response evaluation physical exam were evaluable. However, if the patient progresses or dies after 2 or more missed visits, the patient will be censored at the last date of assessment which the RECIST 1.1 assessment and response evaluation physical exam were evaluable. If the patient has no evaluable visits or does not have baseline data, they will be censored at Day 1 unless they die within 2 visits of baseline, then they will be treated as an event with date of death as the event date. An assessment will be considered non evaluable if, in the absence of progression by RECIST 1.1, a physical exam is not performed, or if a physical exam is performed and progression is suspected and a biopsy result is not reported. Similarly, in the absence of histopathologic confirmation of local tumor

progression, an assessment will be considered non-evaluable if the RECIST visit assessment is not performed.

The PFS time will always be derived based on scan/physical exam dates and not visit dates.

PFS assessments/scans contributing toward a particular visit may be performed on different dates within a 4 week window for the specific timepoint assessment. The following rules will be applied:

- For progression by histopathologic evidence of disease, date of progression will be determined based on the date of the physical exam which showed suggested progression.
- For on-study tumor assessments, the date of progression will be determined based on the earliest date of the scan for RECIST 1.1 defined radiological progression or progression seen on physical exam.
- For BICR sensitivity analysis, date of progression will be determined based on the earliest of the dates of the component that triggered the progression on the first set of scans that indicates progression for the adjudicated reviewer selecting PD, or of either reviewer where both reviewers select PD as a timepoint response, and there is no adjudication for central review (BICR) data.
- When censoring a patient for PFS, the patient will be censored at the latest of the dates contributing to a particular overall visit assessment where both the RECIST 1.1 assessment and response evaluation physical exam were evaluable within a 4 week time frame.

9.4.1.3 **Progression Free Survival (3 years)**

Progression Free Survival (3 years) will be defined as the Kaplan-Meier estimate of PFS at 3 years.

9.4.1.4 **Progression free survival in PD-L1 positive patients**

PFS (per RECIST 1.1 as assessed by investigator tumor assessments or histopathologic confirmation of local tumor progression) in PD-L1 positive patients (≥1% based on either tumor or immune cell staining) will be defined as for the primary endpoint as the time from the date of randomization until the date of objective disease progression or death (by any cause in the absence of progression) regardless of whether the patient withdraws from therapy or receives another anticancer therapy prior to progression (ie, date of event or censoring – date of randomization + 1).

9.4.1.5 **Overall survival**

OS is defined as the time from the date of randomization until death due to any cause. Any patient not known to have died at the time of analysis will be censored based on the last recorded date on which the patient was known to be alive.

Note: Survival calls will be made following the date of DCO for the analysis (these contacts should generally occur within 7 days of the DCO). If patients are confirmed to be alive or if the death date is after the DCO date, these patients will be censored at the date of DCO. Death dates may be found by checking publicly available death registries

9.4.1.6 **Overall survival in PD-L1 postive patients**

OS in PD-L1 positive patients (≥1% based on either tumor or immune cell staining) will be defined as the time from the date of randomization until death due to any cause. Any patient not known to have died at the time of analysis will be censored based on the last recorded date on which the patient was known to be alive.

9.4.1.7 **Objective response rate**

ORR (per RECIST 1.1 using investigator assessments or pathologic assessment of local disease progression) is defined as the number (%) of patients with at least 1 visit response of CR or PR. Data obtained up until progression, or the last evaluable assessment in the absence of progression, will be included in the assessment of ORR. Patients who go off treatment without progression, receive a subsequent therapy, and then respond will not be included as responders in the ORR.

9.4.1.8 **Complete response rate**

CR rate (per RECIST 1.1 using investigator assessments or pathologic assessment of local disease progression) is defined as the disappearance of all TLs and non-target lesions and no evidence of new lesions, which encompasses RECIST 1.1 staging in addition to a physical exam to evaluate for recurrence.

9.4.1.9 **Incidence of Local Progression, Distant Disease Progression, Secondary Malignancy**

The incidence of local progression, distant disease progression, secondary malignancy, and death will each be considered separately and defined as the number and percentage of patients with documented evidence of local progression, distant disease recurrence, secondary malignancies, and death. The time from randomization to the date of first documented local progression, distant disease recurrence/secondary malignancy or death from any cause will also be summarized.

For the summaries, if two recurrence events (local progression and distant disease progression) occur within 2 months of each other, then this is referred to as a simultaneous event and will be considered a single event. In this situation the worst case will be taken as the event 'type', but the date of recurrence will be the earliest of the two events. For example, if local progression and distant recurrence are reported within a 2 month period then for the analysis and reporting of Incidence of Local Progression, Distant Disease, and Secondary Malignancy and time to date of first local progression, distant disease progression, secondary malignancy or death from any cause, the event will be counted as distant disease recurrence but the date will be the earliest date of the two events.

Distant disease progression, secondary malignancy, and deaths are considered to be competing risks for local progression. Local progression and death are considered to be competing risks for distant disease recurrence/secondary malignancy. From the time to event endpoint, distant disease recurrences and secondary malignancies will be summarized together.

Local progressions will be determined by RECIST 1.1 or histopathologic confirmation of disease, more details can be found in Section 9.4.1.1. Distant disease recurrence should be diagnosed by RECIST 1.1 or histopathological confirmation of disease when metastatic lesion is easily accessible for biopsy.

Secondary malignancies must be confirmed by biopsy. If a biopsy is not able to performed then the suspected secondary malignancy will be counted as a distant disease recurrence for the summary.

9.4.1.10 Duration of response for Complete Responders

Duration of response in complete responders (per RECIST 1.1 using Investigator assessments, physical examination, and histopathological confirmation of local disease progression) will be defined as the time from the date of the first documented CR to the first date of documented progression or death in the absence of disease progression. The end of response should coincide with the date of progression or death from any cause used for the PFS endpoint.

The time of the initial response will be defined as the latest of the dates contributing towards the assessment visit. If a patient does not progress following a CR, then their DoR will be censored at the PFS censoring time. Duration of response for complete responders will not be defined for those patients who do not have a documented response of CR.

9.4.2 Calculation or derivation of safety variables

9.4.2.1 Adverse events

Safety and tolerability will be assessed in terms of AEs (including SAEs), physical examinations, laboratory findings, vital signs, and exposure. These will be collected for all

patients. Data from all cycles of treatment will be combined in the presentation of safety data. "On treatment" will be defined as assessments between date of start dose and 90 days following discontinuation of study treatment (ie, the last dose of study treatment). For AEs, on treatment (or treatment-emergent AEs) will be defined as any AEs that started after dosing or prior to dosing and which worsens following exposure to the treatment.

AEs observed up until 90 days following discontinuation of study treatment or until the initiation of the first subsequent therapy following discontinuation of study treatment (whichever occurs first) will be used for the reporting of the AE summary tables. This will more accurately depict AEs attributable to study treatment only as the number of AEs up to 90 days following discontinuation of durvalumab + SoC CCRT or placebo + SoC CCRT are likely to be attributable to subsequent therapy. However, to assess the longer-term toxicity profile, AE summaries will also be produced containing AEs observed up until 90 days following discontinuation of durvalumab + SoC CCRT or placebo + SoC CCRT. Any events in this period that occur after a patient has received further therapy for cancer (following discontinuation of study treatment) will be flagged in the data listings.

The SAS will be used for reporting of safety data.

A separate data listing of AEs occurring more than 90 days after discontinuation of study treatment will be produced. These events will not be included in AE summaries.

9.4.2.2 **Safety assessments**

For the change from baseline summaries for vital signs, laboratory data, hematology, ECGs, and physical examinations, the baseline value will be the latest result obtained prior to the start of study treatment.

QTcF will be derived during creation of the reporting database using the reported ECG values (RR and QT) using the following formula:

QTcF = QT/RR^ (1/3), where RR is in seconds

Corrected calcium product will be derived during creation of the reporting database using the following formula:

Corrected calcium (mmol/L) = Total calcium (mmol/L) + ([40 – albumin (G/L)] × 0.02)

The denominator used in laboratory summaries will only include evaluable patients, ie, those who had sufficient data to have the possibility of an abnormality.

For example:

- If a CTCAE criterion involves a change from baseline, evaluable patients would have both a pre-dose and at least 1 post-dose value recorded.
- If a CTCAE criterion does not consider changes from baseline to be evaluable, the patient need only have 1 post-dose value recorded.

The denominator in vital signs data should include only those patients with recorded data.

9.4.3 Calculation or derivation of patient-reported outcome variables

All items/questionnaires will be scored according to published scoring guidelines.

9.4.3.1 EORTC-QLQ-C30

The EORTC QLQ-C30 consists of 30 questions that can be combined to produce 5 functional scales (physical, role, cognitive, emotional, and social), 3 symptom scales (fatigue, pain, and nausea/vomiting), 5 individual items (dyspnea, insomnia, appetite loss, constipation, and diarrhea), and global health status/QoL scale. The EORTC QLQ-C30 will be scored according to the EORTC QLQ-C30 Scoring Manual (Fayers et al 2001). Briefly, outcome scores are computed by standardizing the average of the items (i.e., a raw score) making up the scale. Outcome scores are computed using a linear transformation of the raw score such that scores range from 0 to 100.

Higher scores on the global measure of health status/QoL and functional scales indicate better health status/function, but higher scores on symptom scales represent greater symptom severity. For each subscale, if <50% of the subscale items are missing, then the subscale score will be divided by the number of non-missing items and multiplied by the total number of items on the subscales (Fayers et al 2001). If at least 50% of the items are missing, then that subscale will be treated as missing. Missing single items are treated as missing. The reason for any missing questionnaire will be identified and recorded. If there is evidence that the missing data are systematic, missing values will be handled to ensure that any possible bias is minimized.

At each post-baseline assessment, the change from baseline in symptom, functional, and global measure of health status/QoL scale scores will be calculated.

Definition of clinically meaningful changes

Changes in score compared with baseline will be evaluated. Change in symptoms, functioning and global health status from baseline will be categorised as improved, stable or worsened as shown in Table 13. A minimum clinically relevant change is defined using the cut off value of 10 points (Osoba et al 1998). Specifically, a clinically meaningful improvement in a symptom is defined as a decrease in the score from baseline of ≥10, while a clinically meaningful

deterioration in a symptom is defined as an increase in the score from baseline of ≥10. In contrast, a clinically meaningful improvement in a functional scale or global heath status is defined as an increase in the score from baseline of ≥10, while a clinically meaningful deterioration in a a functional scale or global heath status is defined as a decrease in the score from baseline of ≥10.

Table 13 Visit responses for EORTC QLQ-C30

Score	Change from baseline	Visit response
Symptom scales/items	≥+10	Worsened
	≤-10	Improved
	Otherwise	Stable
Functional scales and global health status/QoL	≥+10	Improved
	≤-10	Worsened
	Otherwise	Stable

9.4.3.2 EORTC QLQ-CX24

The QLQ-CX24 consists of 24 questions that can be combined to produce three multi-item scales (symptom experience, body image, and sexual/vaginal functioning) and six single-item scales (lymphedema, peripheral neuropathy, menopausal symptoms, sexual activity, sexual worry, and sexual enjoyment). The scales and single item measures are also scored from 0 to 100. In sexual activity and sexual enjoyment, higher scores indicate better functioning, however, in the other scales and single-items, higher scores reflect more problematic functioning or status.

At each post-baseline assessment, the change from baseline in symptom and functional scale scores will be calculated.

The cut-off for a minimum clinically meaningful improvement will be defined in the SAP. Threshold values may also be derived in an exploratory fashion using both distribution-based methods and anchor-based methods, where the anchors are the PGIC and PGIS. Details will be provided in the SAP. At each post-baseline assessment, change in symptoms/functioning from baseline will be categorized as improved, stable, or worsened using the pre-specified clinically meaningful cut-off defined in the SAP.

9.4.4 Patient-reported outcomes version of the Common Terminology Criteria for Adverse Events

The PRO-CTCAE items are not currently scored. The data will be descriptively summarized.

9.4.5 Patient Global Impression of Change and Patient Global Impression of Severity

The response options of the PGIC are scored as follows: Much Better (+3), Moderately Better (+2), A Little Better (+1), No Change (0), A Little Worse (-1), Moderately Worse (-2) and Much Worse (-3).

The response options of the PGIS are scored using a 6-point scale: 1 = None; 2 = Very Mild; 3 = Mild; 4 = Moderate; 5 = Severe; 6 = Very Severe.

9.4.6 EuroQol five-dimensional five-level questionnaire (EQ-5D-5L)

The EQ-5D-5L index comprises 5 dimensions of health (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). For each dimension, respondents select which statement best describes their health on that day from a possible 5 options of increasing levels of severity (no problems, slight problems, moderate problems, severe problems, and extreme problems). A unique EQ-5D health state is referred to by a 5-digit code allowing for a total of 3,125 health states. For example, state 11111 indicates no problems on any of the 5 dimensions. These data will be converted into a weighted health state index by applying scores from EQ-5D value sets elicited from general population samples (the base case will be the United Kingdom valuation set, with other country value sets applied in scenario analyses). Where EQ-5D-5L values sets are not available, the EQ-5D-5L to EQ-5D-3L crosswalk will be applied (Oemar and Oppe 2013).

9.4.7 Definition of compliance and evaluability rates

Compliance rates for the PRO questionnaires should be 85%; this rate will be monitored as the trial goes on. Compliance with the EORTC QLQ-C30 and EORTC QLQ-CX24 will be calculated separately for each questionnaire:

$$\text{Compliance rate} = \frac{\text{number of evaluable forms}}{\text{number of expected forms}} \times 100$$

Evaluability rates for the EORTC QLQ-C30 and EORTC QLQ-CX24 will also be calculated separately for each questionnaire:

$$\text{Evaluability rate} = \frac{\text{number of evaluable forms}}{\text{number of received forms}} \times 100$$

An expected form = a questionnaire that is expected to be completed at a scheduled assessment time, that is, a questionnaire from a patient who has not withdrawn from the study at the scheduled assessment time but excluding patients in countries with no available translation.

An evaluable form = a questionnaire with a completion date and at least 1 subscale that is non-missing.

A received form = a questionnaire that has been received and has a completion date and at least 1 individual item completed.

9.4.8 Calculation or derivation of health care resource use

To investigate the impact of treatment and disease on health care resource use the following variables will be captured:

- Planned and unplanned hospital attendances beyond trial protocol mandated visits (including physician visits, emergency room visits, day cases and admissions)
- Primary sign or symptom the patient presents with
- Length of hospital stay
- Length of any time spent in an intensive care unit (ICU)

Where admitted overnight, the length of hospital stay will be calculated as the difference between the date of hospital discharge (or death date) and the start date of hospitalisation or start of study drug if the start of study drug is after start date of hospitalisation (length of hospital stay = end date of hospitalisation – start date of hospitalisation + 1). Patients with missing discharge dates will be calculated as the difference between the last day with available data and the start date of hospitalisation. The length of ICU stay will be calculated using the same method.

9.4.9 Calculation or derivation of pharmacokinetic variables

9.4.9.1 Population pharmacokinetics and exposure-response/safety analysis

A population PK model may be developed using a non-linear mixed-effects modeling approach. The impact of physiologically-relevant patient characteristics (covariates) and disease on PK may be evaluated. The relationship between the PK exposure and the effect on safety and efficacy endpoints may be evaluated (as data allow). The results of such an analysis will be reported in a separate report. The PK, pharmacodynamics, demographic, safety, and efficacy data collected in this study may also be combined with similar data from other studies and explored using population PK and/or PK-pharmacodynamic methods.

9.4.9.2 Pharmacokinetic analysis

PK concentration data and summary statistics will be tabulated. PK parameters will be determined from the raw data. The following PK parameters will be determined after the first

and steady-state doses: peak and trough concentration (as data allow).

9.4.9.3 Immunogenicity analysis

Immunogenicity results will be analyzed descriptively by summarizing the number and percentage of patients who develop detectable ADAs against durvalumab by treatment group. The immunogenicity titer and presence of neutralizing ADAs will be reported for samples confirmed positive for the presence of ADAs. The effect of immunogenicity on PK, pharmacodynamics, efficacy, and safety will be evaluated, if the data allow.

9.4.10 Calculation or derivation of biomarker variables

Biomarker status, will be assessed for evaluable patients in each cohort according to prespecified criteria that will be detailed in the SAP.

9.4.11 Calculation or derivation of pharmacogenetic variables

In the case of genetic data, only the date that the patient gave consent to participation in the genetic research and the date the blood sample was taken from the patient will be recorded in the eCRF and database. The genetic data generated from the study will be stored in the AstraZeneca Laboratory Information Management System database or other appropriate system. This database is a secure database, which is separate from the database used for the main study. Some or all of the dataset from the main study may be duplicated within the AstraZeneca Laboratory Information Management System database for exploratory genetic analysis. Data will be reported outside the CSR (please see Appendix C).

9.5 Statistical analyses

All personnel involved with the analysis of the study will remain blinded until database lock for the analysis of PFS and Clinical Study Protocol deviations identified.

Analyses will be performed by AstraZeneca or its representatives. A comprehensive SAP will be developed and finalized before database lock and will describe the patient populations to be included in the analyses and the procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints. Any deviations from this plan will be reported in the CSR.

9.5.1 Efficacy analyses

The study has been sized to characterize the PFS benefit of durvalumab + SoC CCRT versus placebo + SoC CCRT. The analysis will be performed when approximately 227 PFS events have occurred across the durvalumab + SoC CCRT and placebo + SoC CCRT treatment arms (32% maturity).

Descriptive statistics will be used for all variables, as appropriate, and will be presented by treatment arm. Continuous variables will be summarized by the number of observations, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized by frequency counts and percentages for each category. Unless otherwise stated, percentages will be calculated out of the population total for the corresponding treatment arm.

Baseline will be the last assessment of the variable under consideration prior to the intake of the first dose of IP, except for efficacy variables. For efficacy variables, baseline is defined as the last visit prior to randomization.

All data collected will be listed. Efficacy and PRO data will be summarized and analyzed based on the FAS. PK data will be summarized and analyzed based on the PK analysis set. Safety data will be summarized on the safety analysis set.

Results of all statistical analysis will be presented using a 95% CI and 2-sided p-value, unless otherwise stated.

Table 14 details which endpoints are to be subjected to formal statistical analysis, together with pre-planned sensitivity analyses, making it clear which analysis is regarded as primary for that endpoint. Note that all endpoints compare durvalumab + SoC CCRT versus placebo + SoC CCRT in all randomized patients (FAS; ITT population), unless otherwise indicated.

Table 14 Pre-planned statistical and sensitivity analyses to be conducted

Endpoints analyzed	Notes
Progression-free survival	Stratified log-rank analysis for: Primary analysis using Investigator RECIST 1.1 assessments or histopathologic confirmation of local tumor progression Sensitivity analyses using BICR assessments (RECIST 1.1) or histopathologic confirmation of local tumor progression
PFS (3 year)	Kaplan Meier estimate of PFS at 3 years

Endpoints analyzed	Notes
PFS in PD-L1 positive patients	Stratified log-rank analysis for: PFS in PD-L1 positive patients
Overall survival	Stratified log-rank analysis for: Overall survival
OS in PD-L1 positive patients	Stratified log-rank analysis for: OS in PD-L1 positive patients
Objective response rate	Secondary analysis for the ITT population Logistic regression for: Secondary analysis for the ITT population using Investigator RECIST 1.1 assessments or histopathologic confirmation of local tumor progression
Complete response rate	Logistic regression for: Secondary analysis for the ITT population using Investigator RECIST 1.1 assessments or histopathologic confirmation of local tumor progression
Duration of Response in Patients with a Complete Response	Summary statistics and KM plot by treatment arm for: Secondary analysis for the ITT population using Investigator RECIST 1.1 assessments or histopathologic confirmation of local tumour progression in patients who have achieved a best objective response of complete response
Incidence of local progression, distant disease progression, and secondary malignancy	Summary statistics and KM plot and cumulative incidence plot by treatment arm for: Secondary analysis for the ITT population
Change from baseline (EORTC QLQ-C30 and EORTC QLQ-CX24)	Average change from baseline using a Mixed Model Repeated Measurements (MMRM) analysis
EQ-5D-5L (health state utility values and Visual Analog Scale)	Summary statistics for health state utilities and visual analogue scale, including change from baseline.
healthcare resource use	Descriptive statistics (as appropriate, including means, median, ranges or frequencies and percentages)

Abbreviations: BICR Blinded independent central review; EORTC European Organisation for Research and Treatment of Cancer; FAS Full analysis set; ITT Intent-to-treat; KM Kaplan-Meier; PK Pharmacokinetic;

QLQ-C30 30 item core quality of life questionnaire; QLQ-CX24 Cervical cancer module; RECIST Response Evaluation Criteria in Solid Tumors.

9.5.1.1 Primary endpoint: Progression-free survival

The primary PFS analysis will be based on the programmatically derived RECIST 1.1 using the Investigator tumor assessments or histopathologic confirmation of local tumor progression. The effect of durvalumab + SoC CCRT versus placebo + SoC CCRT will be analyzed using a log-rank test stratified by disease stage status (FIGO (2009) Stage <III and node positive, FIGO (2009) Stage ≥III and node negative, or FIGO (2009) Stage ≥III and node positive) and region [United States, Canada, European Union, South Korea, and Japan] versus rest of world. In addition, PFS will be analysed using a stratified Cox proportional hazards model using the same strata as for the primary analysis by stratified log rank test and using the Efron approach for ties. The point estimate of the treatment effect, i.e. HR will be obtained by maximing the Cox partial likelihood functions, which is the product of the likelihood of each stratum. (an HR less than 1 will favor durvalumab + SoC CCRT). The 95% CI will be estimated using the profile likelihood approach. The 95% CI and HR from the stratified Cox proportional hazards model will be in support of the p-value from the stratified log rank test, no p-value will be reported from the stratified Cox proportional hazards model.

Stratification variables will be defined according to data from the IWRS. If there are any patients who are mis-stratified, a sensitivity analysis may be carried out using the baseline data collected in the eCRF.

Kaplan-Meier plots of PFS will be presented by treatment arm and by treatment arm and disease stage status (FIGO (2009) Stage <III and node positive, FIGO (2009) Stage ≥III and node negative, or FIGO (2009) Stage ≥III and node positive) and region [United States, Canada, European Union, South Korea, and Japan] versus rest of world subgroups, where appropriate. Summaries of the number and percentage of patients experiencing a PFS event and the type of event (local progression, distant progression, or death) will be provided along with median PFS for each treatment.

Sensitivity analyses will be performed to assess possible evaluation-time bias that may be introduced if scans and physical examinations are not performed at the protocol-scheduled timepoints. The midpoint between the time of progression and the previous evaluable assessment will be analyzed using a log-rank test. For patients whose death was treated as a PFS event, the date of death will be used to derive the PFS time used in the analysis. This approach has been shown to be robust even in highly asymmetric assessment schedules (Sun and Chen 2010).

Attrition bias will be assessed by repeating the PFS analysis, except that the actual PFS event times, rather than the censored times, of patients who progressed or died in the absence of

progression immediately following 2 or more non-evaluable tumor assessments will be included. In addition, patients who take subsequent therapy prior to progression or death will be censored at their last evaluable assessment prior to taking the subsequent therapy. This analysis will be supported by a Kaplan-Meier plot of the time to censoring where the censoring indicator of the PFS analysis is reversed.

A sensitivity analysis will be performed by replacing the investigator assessments with the BICR assessments in the definition of PFS. The stratified log-rank test will be repeated on these data. The HR and CI will be presented. The methodology and acceptance thresholds will be documented in the SAP.

The assumption of proportionality will be assessed first by examining plots of complementary log-log (event times) versus log (time) and, if these raise concerns, by fitting a time-dependent covariate to assess the extent to which this represents random variation. If a lack of proportionality is evident, the variation in treatment effect will be described by presenting piecewise HR calculated over distinct time-periods. In such circumstances, the HR can still be meaningfully interpreted as an average HR over time unless there is extensive crossing of the survival curves. If lack of proportionality is found, this may be a result of treatment-by-covariate interactions, which will be investigated. In addition, the Kaplan-Meier curve along with landmark analyses (eg, 1-year PFS rate) will also help in understanding the treatment benefit.

Subgroup analyses will be conducted comparing PFS (per RECIST 1.1 using Investigator tumor assessments or histopathologic confirmation of local tumor progression) between durvalumab + SoC CCRT and placebo + SoC CCRT in the following (but not limited to) subgroups of the FAS:

- Age at randomization (<65 versus ≥65 years of age)
- PD-L1 status (≥1% vs < 1%)
- Disease stage status (FIGO (2009) Stage <III and node positive, FIGO (2009) Stage ≥III and node negative, or FIGO (2009) Stage ≥III and node positive)
- Intent to administer cisplatin or carboplatin
- Race (Asian versus non-Asian)
- Region [United States, Canada, European Union, South Korea, and Japan] versus rest of the world
- HPV status (HPV 16, HPV 18 versus other)

Other baseline variables may also be assessed if there is clinical justification or an imbalance is observed between the treatment arms. The purpose of the subgroup analyses is to assess the consistency of treatment effect across expected prognostic and/or predictive factors. Forest plot will be performed.

No adjustment to the significance level for testing of the subgroup and sensitivity analyses will be made, since all these analyses will be considered supportive of the analysis of PFS.

Interactions between treatment and stratification factors will also be tested to rule out any qualitative interaction using the approach of Gail and Simon 1985.

Additionally, for each subgroup, the HR (durvalumab + SoC CCRT:placebo + SoC CCRT) and 95% CI will be calculated from a Cox proportional hazards model, with treatment as the only covariate. These will be presented on a Forest plot including the HR and 95% CI from the overall population.

If there are too few events available for a meaningful analysis of a particular subgroup (it is not considered appropriate to present analyses where there are less than 20 events in a subgroup), the relationship between that subgroup and PFS will not be formally analyzed. In this case, only descriptive summaries will be provided.

9.5.1.2 **Progression Free Survival (3 year)**

PFS (3 year) will be summarized (using the Kaplan-Meier curve) and presented by treatment arm.

9.5.1.3 **Progression-free survival in PD-L1 positive patients**

PFS in PD-L1 positive patients will be analyzed using a stratified log-rank test, using the same methodology as for the primary PFS endpoint. The effect of durvalumab + SoC CCRT versus placebo + SoC CCRT will be estimated by the HR together with its corresponding CI and p-value using the same methodology as described for PFS in the subset of patients with PD-L1 status of ≥1%. Kaplan-Meier plots will be presented by treatment arm. Summaries of the number and percentage of patients experiencing a PFS event and type of event (local progression, distant progression, or death) will be provided along with median PFS for each treatment.

9.5.1.4 **Overall survival**

OS in the ITT population will be analyzed using a stratified log-rank tests, using the same methodology as described for the primary PFS endpoint. The effect of durvalumab + SoC CCRT versus placebo + SoC CCRT will be estimated by the HR together with its corresponding CI and p-value using the same methodology as described for PFS. Kaplan-Meier plots will be presented by treatment arm. Summaries of the number and percentage of

patients who have died, those still in survival follow-up, those lost to follow-up, and those who have withdrawn consent will be provided along with the median OS for each treatment.

9.5.1.5 Overall survival in PD-L1 positive patients

OS in PD-L1 positive patients will be analyzed using a stratified log-rank tests, using the same methodology as described for the primary PFS endpoint. The effect of durvalumab + SoC CCRT versus placebo + SoC CCRT will be estimated by the HR together with its corresponding CI and p-value using the same methodology as described for PFS. Kaplan-Meier plots will be presented by treatment arm. Summaries of the number and percentage of patients who have died, those still in survival follow-up, those lost to follow-up, and those who have withdrawn consent will be provided along with the median OS for each treatment.

9.5.1.6 Objective response rate

The ORR will be based on the programmatically derived RECIST 1.1 using the investigator tumor assessments and histopathologic confirmation of local tumor progression. The ORR will be compared between durvalumab + SoC CCRT and placebo + SoC CCRT using logistic regression models, adjusting for the same factors as the primary endpoint. The results of the analysis will be presented in terms of an odds ratio together with its associated profile likelihood CI and p-value (based on twice the change in log-likelihood resulting from the addition of a treatment factor to the model). This analysis will be performed in the ITT population.

Summaries will be produced that present the number and percentage of patients with a tumor response (CR/PR). Overall visit response data will be listed for all patients (ie, the FAS). For each treatment arm, best overall response (BoR) will be summarized by n (%) for each category (CR, PR, SD, PD, and NE). No formal statistical analyses are planned for BoR.

9.5.1.7 Complete response rate

The CR rate as obtained from complete responses will be compared between durvalumab + SoC CCRT and placebo + SoC CCRT using logistic regression models, by using the same methodology as described for the ORR endpoint. This analysis will be performed in the ITT population. Summaries will be produced that present the number and percentage of patients with a tumor response of CR.

9.5.1.8 Incidence of Local Progression, Distant Disease Progression, and Secondary Malignancy

The actual number and percentage of patients with a progression free survival event will be presented by treatment arm according to whether the progression free survival event was a

local progression, distant progression, secondary malignancy, or death.

Time to first local progression, time to first distant disease progression or first secondary malignancy, and time to death will be analyzed separately using KM plots. As discussed in Section 9.4.1.9, distant disease progression, secondary malignancy, and death are considered to be competing risks for local progression. Patients with distant disease progression, secondary malignancy, or death will be censored in the KM plot for local progression. Local progression and death are considered to be competing risks for distant disease recurrence and secondary malignancy, patients with local progression or death will be censored in the KM plot for distant disease progression or secondary malignancy.

The cumulative incidence of local progression, distant disease progression or secondary malignancy, and deaths will be compared between the two treatment groups using competing risk analysis (Gray test, Fine and Gray 1999). Death will be considered a competing risk for local progression and distant disease progression or secondary malignancy. In addition, distant disease progression and secondary malignancy will be considered to be competing risks for local progression and local progression will be considered to be a competing risk for distant disease progression and secondary malignancy. Hazard ratios and 95% confidence intervals from competing risks regression analysis (Fine and Gray 1999) adjusted for treatment and stratification factors will also be presented -- more details of the analysis will be given in the SAP.

9.5.1.9 **Duration of complete response**

Duration of response in patients who have a best objective response of CR will be derived for each treatment arm based on the RECIST 1.1 Investigator assessments or physical exam and on histopathological confirmation of local tumour progression. Descriptive data will be provided by treatment arm for DoR in patients with CR, including the associated Kaplan-Meier curves (without any formal comparison of treatment arms or p-value attached).

9.5.1.10 **Patient-reported outcomes**

All PRO analyses will be based on the FAS. For change from baseline summaries, evaluable patients will have both a baseline and at least 1 post-dose value recorded.

EORTC QLQ-C30

The mean change in symptom and functional scale and the global measure of health status/QoL scale scores from baseline will be analyzed for each measure using a mixed model for repeated measures. Full details of this and appropriate sensitivity analyses will be described in full in the SAP.

Summaries of the original and the change from baseline values of each symptom scale/item, the global health status/QoL score, and each functional domain will be reported by visit for each treatment arm. Graphical presentations may also be produced as appropriate. Summaries of the number and percentage of patients in each response category at each visit for each ordinal item will also be produced for each treatment arm.

EORTC-QLQ-CX24
The mean change from baseline will be analyzed for each EORTC-QLQ-CX24 score using a mixed model for repeated measures. Full details of this and appropriate sensitivity analyses will be described in full in the SAP.

Summaries of the original and the change from baseline values of each symptom and functional domain will be reported by visit for each treatment arm. Graphical presentations may also be produced as appropriate. Summaries of the number and percentage of patients in each response category at each visit for each ordinal item will also be produced for each treatment arm.

PRO-CTCAE
PRO-CTCAE data will be presented using summaries and descriptive statistics. Further details will be provided in the SAP.

PGIC and PGIS
PGIC and PGIS data will be presented using summaries and descriptive statistics. Further details will be provided in the SAP.

EQ-5D-5L
Descriptive statistics and graphs will be reported for health state utility index values (United Kingdom base case).

To support future economic evaluations of the study treatment, additional appropriate analyses may be undertaken, for example, mean health state utility pre- and post-treatment, and pre- and post-progression. These will be outlined in a separate Payer Analysis Plan.

9.5.1.11 Health care resource use

The potential impact the disease and treatment has on health care resource use will be analysed for the purposes of submissions to payers. Descriptive statistics (as appropriate, including means, median, ranges or frequencies and percentages) will be provided for each arm on the different types of hospital admissions, the length of stay of people admitted in to hospital for at least one overnight stay and length of stay of people admitted to intensive care / high dependency units, as well as the primary sign or symptom the patient presents with. To

support submissions to payers, additional analyses may be undertaken and these will be outlined in a separate Payer Analysis Plan.

9.5.2 Safety analyses

Safety is a secondary endpoint in this study. All safety analyses will be performed on the safety population. Safety and tolerability data will be presented by treatment arm using the safety population. Safety data will be summarized descriptively and will not be formally analyzed.

Data from all cycles of treatment will be combined in the presentation of safety data. AEs (both in terms of Medical Dictionary for Regulatory Activities [MedDRA] preferred terms and CTCAE grade) will be listed individually by patient. The number of patients experiencing each AE will be summarized by treatment arm and CTCAE grade. Additionally, data presentations of the rate of AEs per person-year at risk may be produced.

Other safety data will be assessed in terms of AEs (including SAEs), physical examinations, laboratory findings, vital signs, and exposure. Exposure to durvalumab + SoC CCRT and placebo + SoC CCRT will be summarized. Time on study, dose delays and dose reductions will also be summarized. At the end of the study, appropriate summaries of all safety data will be produced, as defined in the SAP.

9.5.3 Pharmacokinetic data

PK concentration data will be listed for each patient in the durvalumab arm and each dosing day, and a summary will be provided for all evaluable durvalumab-treated patients patients.

9.5.4 Immunogenicity data

Immunogenicity results will be listed by patient, and a summary will be provided by the number and percentage of patients who develop detectable anti-drug antibodies by treatment group. The immunogenicity titer and neutralizing ADA data will be listed for samples confirmed positive for the presence of anti-drug antibodies by treatment group.

The effect of immunogenicity as well as the effect of its neutralizing properties on PK, pharmacodynamics, efficacy, and safety may be evaluated, if the data allow. A detailed plan will be written by the AstraZeneca Clinical Pharmacology group or designee.

9.5.5 Pharmacokinetic/pharmacodynamic relationships

If the data are suitable, the relationship between PK exposure and efficacy/safety parameters may be investigated graphically or using an appropriate data modeling approach.

9.5.6 Biomarker data

The relationship of PD-L1 expression and, if applicable, of exploratory biomarkers to clinical outcomes (including but not restricted to) of PFS, and OS will be presented.

PD-L1 expression determined by IHC will be reported in the CSR. Summaries and analyses for exploratory biomarkers will be documented in a separate analysis plan and will be reported outside the CSR in a separate report.

9.5.7 Methods for multiplicity control

The multiple testing procedure (MTP) will define which significance levels should be applied to the interpretation of the raw p-values for the primary endpoint of PFS and the key secondary endpoint of OS.

The overall 5% type I error rate will first be allocated to test the primary endpoint of PFS for durvalumab + SoC CCRT versus placebo + SoC CCRT. If the primary endpoint of PFS is significant, 5% alpha will be recycled to the lower level I the hierarchy, where the 5% alpha will be used for the test of OS for durvalumab + SoC CCRT versus placebo + SoC CCRT.

The primary endpoint of PFS will be tested once. The key secondary endpoint of OS will be tested at 2 timepoints: 1 interim analysis and 1 final analysis. The tests including the interim and the final analysis that are for the comparison of durvalumab + SoC CCRT versus placebo + SoC CCRT for the analyses of OS will be considered as one test family. As long as 1 test in the family can be rejected, the family is rejected. Thus, the assigned total alpha to the family will be recycled to the next MTP level. Details of the interim analyses are provided in Section 9.6.

The details of the multiple testing procedure will be provided in the SAP.

9.6 Interim analyses

No PFS interim analysis is planed in this study.

There will be an interim analysis performed for OS. The OS interim will occur at the time of the PFS analysis, if it is positive. It is anticipated that approximately 86% of the OS events will be available for this OS IA (approximately 195 of 227 OS events). If exactly 86% of the target events are available at the time of the interim analysis, with overall 2-sided alpha level of 5.0%, the 2-sided alpha to be applied at the interim analysis and final analysis would be 3.1% and 4.1%, respectively.

If the criteria for statistical significance is met for PFS but not OS at the time of the analysis for PFS, follow-up will continue until the earlier of 227 OS events or 71 months following randomization of the first patient, at which point OS will be retested.

The SAP will describe the planned interim analysis in greater detail.

9.6.1 Data monitoring committee

The safety of all AstraZeneca clinical studies is closely monitored on an ongoing basis by AstraZeneca representatives in consultation with Patient Safety. Issues identified will be addressed; for instance, this could involve amendments to the study protocol and letters to Investigators.

An IDMC composed of independent experts will be convened to confirm the safety and tolerability of the proposed dose and schedule of durvalumab + SoC CCRT. The first safety review will take place when the first 25 total patients across both treatment arms have completed SoC CCRT and have had at least 28 days of follow-up. The second safety review will take place when the first 60 total patients across both treatment arms have completed SoC CCRT and have had at least 28 days of follow-up. Safety reviews will be carried out by the IDMC in an unblinded manner. After review of the unblinded data, the IDMC will make a recommendation on whether the study should continue recruitment as planned or hold recruitment.

An additional safety review for Japanese patients will take place when the first 9 patients in Japan have completed SoC CCRT and had 28 days of follow-up. This review will be carried out by the IDMC in an unblinded manner. After review of the unblinded data, the IDMC will make a recommendation on whether the study should continue recruitment as planned or hold recruitment in Japan.

In addition, the IDMC will meet approximately every 6 months thereafter to continue safety monitoring.

Full details of the IDMC procedures and processes can be found in the IDMC Charter.

9.7 China Cohort

In China, recruitment will continue until approximately 105 Chinese patients have been randomised, irrespective of whether or not the overall study enrolment has been reached. It is anticipated that this target may not be met before the global recruitment of approximately 714 is achieved.

A patient randomized in the China cohort will be included in both the global FAS and the China FAS. Per China National Medical Products Administration (NMPA) guidance, in addition to the evaluation of the overall data for primary, secondary and safety objectives, evaluation of consistency in efficacy and safety in China and Asia population is required to facilitate the benefit-risk assessment for Chinese patients. Hence, the safety and efficacy data in China cohort will be analyzed separately where the same endpoint definitions and analysis methods (as detailed in Section 9.5) are applied.

Details of this analysis will be in a China supplementary SAP.

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