Clinical Study Report	
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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)

Study dates: First subject enrolled: 15 February 2019

Last subject enrolled: 10 December 2020

The analyses presented in this report are based on a clinical data lock date of 11 March 2022

Phase of development: Therapeutic confirmatory (III)

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This study was performed in compliance with International Council for Harmonisation (ICH) Good Clinical Practice, including the archiving of essential documents.

This document contains trade secrets and confidential commercial information, disclosure of which is prohibited without providing advance notice to AstraZeneca and opportunity to object.

2.   SYNOPSIS

Study Centre(s)

The study was conducted by 126 Principal Investigators at 111 sites in 15 countries: Brazil (13 centres), Chile (7 centres), China (14 centres), Hungary (5 centres), India (6 centres), Japan (11 centres), Mexico (7 centres), Peru (7 centres), Philippines (6 centres), Poland (5 centres), Russia (7 centres), South Africa (2 centres), South Korea (4 centres), Taiwan (7 centres), and United States of America (10 centres).

Publications

None at the time of writing this report.

Objectives and Criteria for Evaluation

The study objectives and endpoints described in Table S1 are per protocol.

Table S1   Objectives and Endpoints

Objectives	Endpoints
Primary	
• 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 tumour progression: ° PFS: Time from date of randomisation until tumour progression or death due to any cause
Secondary	
• 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, OS (key), OS in PD-L1 positive patients, ORR, CR rate, and DoR in patients with a CR	° OS: Time from date of randomisation until the date of death by any cause ° OS in PD-L1 positive patients: Time from date of randomisation until date of death by any cause in patients who are PD-L1 positive ($\geq 1\%$) based on either tumour or immune cell staining • 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 randomisation until tumour progression or death due to any cause in patients who are PD-L1 positive ($\geq 1\%$) based on either tumour or immune cell staining ° ORR: The percentage of evaluable patients with an Investigator-assessed visit response of CR or PR

Table S1   Objectives and Endpoints

Objectives	Endpoints
	° 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 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	
• 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	
• 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)** [a]	• Analysis of blood/tissue samples to assess exploratory biomarkers, which may include, but is not limited to ctDNA, mRNA signatures, CD8 by IHC, and TMB
• To assess treatment-related symptoms using the 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 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 hospitalisation, outpatient visits, or emergency department visits

[a]   These data will be reported separately from the CSR.

The CSP used the terms PD-L1 positive and PD-L1 negative. PD-L1 positive has the same meaning as PD-L1 high and PD-L1 negative has the same meaning as PD-L1 low. The SAP and the CSR use the terms PD-L1 high/low.

ADA = Anti-drug antibody; AE = Adverse event; CCRT = Concurrent chemoradiotherapy; CD = Cluster of differentiation; CR = Complete response; CSP = Clinical Study Protocol; CSR = Clinical Study Report; ctDNA = Circulating tumour DNA; CX24 = Cervical cancer module; DNA = Deoxyribonucleic acid; DoR = Duration of response; EORTC = European Organisation for Research and Treatment of Cancer; EQ-5D-5L = EuroQol five-dimensional five-level questionnaire; HRQoL = Health-related quality of life; IHC = Immunohistochemistry; mRNA = Messenger ribonucleic acid; ORR = Objective response rate; OS = Overall survival; PD-L1 = Programmed cell death ligand 1; 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; RECIST = Response Evaluation Criteria in Solid Tumours; SAP = Statistical Analysis Plan; SoC = Standard of care; TMB = Tumour mutational burden.

Study Design

The CALLA study is an ongoing Phase III, randomised, multi-centre, double-blind, global study to determine the efficacy and safety of durvalumab in combination with and following standard of care (SoC) concurrent chemoradiotherapy (CCRT) (Durva + SoC CCRT) compared to placebo with SoC CCRT (Placebo + SoC CCRT) for treatment of women with locally advanced cervical cancer (International Federation of Gynaecology and Obstetrics [FIGO] [2009] Stage IB2 to IVA).

Following confirmation of eligibility, all patients were centrally assigned to randomised study treatment using an interactive web response system. Randomisation was 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 were randomised in a 1:1 ratio to receive either durvalumab 1500 mg or placebo every 4 weeks (q4w) for 24 doses. Patients in both groups were to receive SoC CCRT consisting of external beam radiotherapy (EBRT) + brachytherapy, and concurrent cisplatin 40 mg/m^2 every week (q1w) × 5 weeks (prior to Protocol Version 3.0, use of carboplatin area under the serum drug concentration time curve 2 [AUC 2] q1w × 5 weeks was also allowed). A sixth week of platinum agent could have been given per Investigator discretion.

Target Population and Sample Size

Eligible patients were adult females with histologically confirmed FIGO (2009) Stages IB2 to IIB node positive (N ≥ 1) or Stages IIIA to IVA with any node stage (N ≥ 0) locally advanced cervical cancer. Patients could not have previously received chemotherapy or radiation therapy for the management of cervical cancer or have been exposed to immune-mediated therapy for any indication. Patients were required to have a baseline Eastern Cooperative Oncology Group performance status of 0 or 1. Patients with brain metastases or spinal cord

compression, active or prior documented autoimmune of inflammatory disease, or who received immunosuppressive medications within 14 days of the study treatment were excluded.

Approximately 714 patients (357 per treatment group) were planned to be randomised in a 1:1 ratio to receive either Durva + SoC CCRT or Placebo + SoC CCRT. In China, recruitment was to continue until approximately 105 Chinese patients had been randomised, irrespective of whether the overall study enrolment had been reached. The patients from China were initially planned to be analysed outside of the global cohort based on the expected recruitment rate. However, due to rapid recruitment in China, with the last patient in China enrolled within 2 months of the last patient in the global cohort, these patients for China have now been included into the global cohort and were analysed as part of this global cohort (at the time of the final progression-free survival [PFS] data cut-off [DCO]: N = 770).

The PFS analysis was to occur when approximately 32% maturity had been reached across the Durva + SoC CCRT and Placebo + SoC CCRT treatment groups. If the true hazard ratio (HR) was 0.65 (likely to correspond to a 11% increase in the proportion of patients progression-free at 3 years from 65% to 76%), this analysis would have 90% power to demonstrate a statistically significant difference for PFS, assuming a 2-sided 5% significance level.

Investigational Product and Comparator(s): Dosage, Mode of Administration and Batch Numbers

Details of the investigational products are presented in Table S2.

Table S2   Study Treatments

| | | | Chemoradiotherapy (SoC) | | |
| | | | EBRT + brachytherapy | Chemotherapy | |
	Durvalumab	**Placebo**			
Study treatment name:	Durvalumab (MEDI4736) [a]	Saline solution	External beam radiotherapy and brachytherapy	Cisplatin	Carboplatin
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	As sourced locally
Route of administration:	IV	IV	Whole pelvic or pelvic and para-aortic radiation and brachytherapy [b]	IV	IV
Provider:	AstraZeneca	Sourced locally by site	Sourced locally by site [c]	Sourced locally by site [c]	Sourced locally by site [c]

Table S2   **Study Treatments**

			Chemoradiotherapy (SoC)		
	Durvalumab	**Placebo**	**EBRT + brachytherapy**	**Chemotherapy**	
Batch numbers:	The list of individual batch numbers and further information are included in the CSR.	The list of individual batch numbers and further information are included in the CSR.	NA	NA	NA

a   Label text prepared for durvalumab (MEDI4736) showed 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 were correct during this transitional period.

b   Pelvic and para-aortic radiotherapy was added based on extent of disease at baseline.

c   Under certain circumstances when local sourcing was not feasible, an SoC treatment may have been supplied centrally through AstraZeneca.

CSR = Clinical Study Report; EBRT = External beam radiotherapy; IV = Intravenous; NA = Not applicable; SoC = Standard of care; w/v = Weight per volume.

Duration of Treatment

Patients were to receive either durvalumab 1500 mg or placebo q4w for 24 doses. Patients were to receive their assigned treatment until completion of planned therapy, clinical progression, or Response Evaluation Criteria in Solid Tumours 1.1 (RECIST 1.1)-defined radiological progression or histopathologic progression on biopsy unless there was unacceptable toxicity, withdrawal of consent, or another discontinuation criteria was met.

Statistical Methods

Demographics, baseline characteristics, medical/surgical history, concomitant medications/procedures, and efficacy data (including patient-reported outcomes [PROs]) were analysed and summarised based on the Full Analysis Set. Further efficacy analyses of PFS and overall survival (OS) based on programmed cell death ligand 1 (PD-L1) expression were analysed and summarised based on the PD-L1 Analysis Set. Pharmacokinetic (PK) data were analysed and summarised based on the PK Analysis Set. Safety and anti-drug antibody (ADA) data were summarised based on the Safety Analysis Set.

In order to strongly control the Type I error at 5% (2-sided), a multiple testing procedure (MTP) was applied to the primary endpoint of PFS and the key secondary endpoint of OS. The overall 5% Type I error rate was first allocated to test the primary endpoint of PFS for Durva + SoC CCRT versus Placebo + SoC CCRT. If the primary endpoint of PFS was significant, then the 5% alpha was to be recycled to the lower level of the hierarchy, where the 5% alpha would be used for the test of OS for Durva + SoC CCRT versus Placebo + SoC CCRT. Hypotheses were to be tested using a MTP with an alpha-exhaustive recycling

strategy. With this approach, hypotheses were to be tested in a pre-defined order with the hypothesis for PFS tested before the hypothesis for OS. According to alpha (test mass) splitting and alpha recycling, the test mass that became available after each rejected hypothesis was recycled to secondary hypotheses not yet rejected.

The primary endpoint of PFS was to be tested once; no PFS interim analysis (IA) was conducted for this study. The key secondary endpoint of OS was to be tested up to 2 timepoints: one IA and one final analysis. The IA for OS was planned to occur at the time of the PFS analysis, if PFS was statistically significant. It was anticipated that approximately 86% of the OS events would be available for this OS IA.

As statistical significance for PFS was not met at this DCO, no alpha could be recycled to test OS at this DCO or at a later timepoint.

Study Population

Data are presented for the analysis of PFS (DCO: 20 January 2022) when 240 PFS events out of 770 patients (31.2% of the events) had occurred.

Of the 1040 patients enrolled, 770 patients were randomised in a 1:1 ratio to receive either Durva + SoC CCRT (385 patients) or Placebo + SoC CCRT (385 patients). At the time of the DCO date of 20 January 2022, treatment with durvalumab/placebo was ongoing in 141 (36.6%) patients in the Durva + SoC CCRT group and 130 (33.9%) patients in the Placebo + SoC CCRT group.

The patients randomised to treatment in this study were representative of the intended target population of patients with locally advanced cervical cancer. The demographics and disease characteristics were representative of the intended patient population and were balanced between the 2 treatment groups. Overall, patients had a median age of 49.0 years, 44.0% of patients were within the 'Hispanic or Latino' ethnic group, and, in terms of race, 39.0% were Asian and 13.4% were American Indian or Alaska Native. Within this high-risk population, the proportion of patients who were lymph node positive at initial diagnosis was balanced across the 2 treatment groups; in total, 85 patients had para-aortic lymph nodes and 514 patients had pelvic lymph nodes; of these, 31 patients had both pelvic lymph nodes and para-aortic lymph nodes.

Summary of Efficacy Results

At the time of the PFS analysis (DCO: 20 January 2022), 240 PFS events (31.2% maturity) had occurred across the 2 treatment groups. CALLA did not meet its primary objective, demonstrating no statistically significant improvement in PFS, by Investigator assessment or histopathological confirmation of local tumour progression, for patients treated with Durva + SoC CCRT compared with Placebo + SoC CCRT (HR: 0.84; 95% confidence

interval [CI]: 0.65, 1.08; 2-sided p-value = 0.174). The Kaplan-Meier estimate of the median PFS could not be calculated at the time of DCO.

Radiotherapy in CALLA consisted of SoC EBRT and brachytherapy, for which there are regional variations in delivery. To account for these regional differences within the global CALLA study, and in an effort to standardise the SoC for radiotherapy across treatment groups, a comprehensive radiotherapy plan and quality control process was built into the study design and region was included as a stratification factor. These measures were considered sufficient to address any potential variations in radiotherapy delivery. Overall, SoC CCRT was rigorously controlled and delivered to a high quality within both treatment groups.

The results of the pre-specified sensitivity analyses for PFS were consistent with those of the primary analysis. The results of the sensitivity analyses of concordance in PFS between the Blinded Independent Central Review and Investigator assessments of RECIST 1.1 progression were consistent with those of the primary analyses. A potential benefit with Durva + SoC CCRT was observed in pre-specified subgroups of patients with poor prognostic factors with a HR < 1 for most subgroups; however, none of these met nominal statistical significance. Of interest, HRs favouring Durva + SoC CCRT compared with Placebo + SoC CCRT were observed for the subgroups of FIGO (2009) Stage ≥ III and node positive, para-aortic lymph nodes, and Stage III, IV pelvic or para-aortic lymph node positive. Treatment with EBRT plus brachytherapy administered > 59 days also resulted in a HR favouring Durva + SoC CCRT compared with Placebo + SoC CCRT; however, due to low patient numbers and potential 'survival bias', these data should be interpreted with caution. CCI

In addition, PFS for PD-L1 high patients (PD-L1 expression of ≥ 1% and ≥ 5% based on either tumour or immune cell staining) was also consistent with the primary analysis of PFS.

The secondary endpoint of PFS at 3 years could not be calculated; however, the Kaplan-Meier estimates of PFS at one and 2 years were not significant for Durva + SoC CCRT compared with Placebo + SoC CCRT. The secondary endpoint of analyses of PFS in PD-L1 high patients, showed PFS was similar for patients treated with Durva + SoC CCRT and Placebo + SoC CCRT (HR: 0.84; 95% CI: 0.64, 1.10). Due to low patient numbers in the PD-L1 low group, the PFS data should be interpreted with caution.

As of the DCO for the study, 59 patients in the Durva + SoC CCRT and 74 patients in the Placebo + SoC CCRT groups had died (17.3% maturity). CALLA did not demonstrate a statistically significant benefit in OS (not formally tested per MTP) for patients treated with Durva + SoC CCRT compared with Placebo + SoC CCRT (HR: 0.78; 95% CI: 0.55, 1.10). A sensitivity analysis of OS was performed and there was no attrition bias.

The secondary endpoint of complete response rate demonstrated a similar rate of 42.9% for Durva + SoC CCRT and 40.3% for Placebo + SoC CCRT. The additional secondary endpoint of objective response rate showed a similar rate between the 2 treatment groups. Of the patients who reported a first disease progression event, local progression was reported for 42/116 (36.2%) and 40/131 (30.5%) patients in the Durva + SoC CCRT and Placebo + SoC CCRT groups, respectively, and distant disease progression in 52/116 (44.8%) and 69/131 (52.7%) patients, respectively.

The key PRO scores were similar in the Durva + SoC CCRT group compared with the Placebo + SoC CCRT group. Patterns of hospital admissions during treatment were similar between both treatment groups.

Summary of Pharmacokinetic Results

No formal non-compartmental analysis was conducted due to the sparse PK sampling scheme of durvalumab in this study.

As of the DCO date, PK data (serum concentration of durvalumab) were available for a total of 380 patients in the Durva + SoC CCRT group. Following Durva (1500 mg q4w) + SoC CCRT, geometric mean (n, percentage coefficient of variation [%CV]) of peak concentrations on Cycle 1 Day 1 was 454.1 μg/mL (n = 350, 88.80%). The geometric mean (n, %CV) of trough concentrations on Cycle 2 and Cycle 4 were 72.11 μg/mL (n = 330, 102.1%) and 128.2 μg/mL (n = 332, 91.94%), respectively.

Durvalumab PK concentrations were within the expected exposure range following 1500 mg q4w in combination with SoC CCRT.

Summary of Immunogenicity Results

Anti-drug antibody prevalence and incidence to durvalumab in the Durva + SoC CCRT group were 9.0% (33 of 366 patients) and 4.1% (15 of 366 patients), respectively. Both ADA prevalence and incidence were low and comparable between the treatment groups, suggesting that the formation of ADA was unrelated to durvalumab treatment. The majority of ADA-positive patients in the Durva + SoC CCRT group were classified as non-treatment-emergent ADA and transiently positive. The median of maximum ADA titre observed in treatment-emergent ADA-positive patients was close to the limit of detection of 1. Overall, 0.5% of patients who were evaluable for ADA in the Durva + SoC CCRT group tested positive for neutralising antibodies against durvalumab. Anti-drug antibodies had no apparent effect on PK or safety of durvalumab. The overall immunogenicity results of durvalumab are consistent with the known immunogenicity profile of durvalumab.

Summary of Safety Results

Overall, Durva + SoC CCRT demonstrated a tolerable and manageable safety profile for the treatment of women with locally advanced cervical cancer. The type, frequency, and severity of AEs in the Durva + SoC CCRT group were consistent with the established safety profiles of durvalumab and SoC CCRT given separately, with more immune-mediated AEs (imAEs) reported in the Durva + SoC CCRT group as expected. The addition of durvalumab to SoC CCRT did not exacerbate known durvalumab-related (ie, imAEs) or SoC CCRT-related toxicities. The imAEs were generally manageable and/or reversible with appropriate medical management, which included the use of steroids or endocrine therapy, withholding durvalumab until the event resolved, or permanent discontinuation of durvalumab.

The median relative dose intensity for both durvalumab and placebo was ≥ 95%, which indicated similar tolerability to Durva + SoC CCRT compared with Placebo + SoC CCRT. In addition, treatment with chemotherapy (cisplatin or carboplatin) and radiotherapy (EBRT and brachytherapy) was consistent between the 2 treatment groups, showing that addition of durvalumab did not reduce exposure to SoC CCRT.

While numerical increases in AE categories were noted in patients receiving Durva + SoC CCRT compared with those receiving Placebo + SoC CCRT, most events were Common Terminology Criteria for Adverse Events (CTCAE) Grade 1 or 2. Events of CTCAE Grade 3 or 4 were infrequent and occurred in a similar proportion of patients in the Durva + SoC CCRT group compared with the Placebo + SoC CCRT group. The majority of AEs were manageable and treated according to standard treatment guidelines.

The most frequently reported AEs (> 20%) were: anaemia (56.6%), nausea (55.3%), diarrhoea (45.7%), vomiting (27.3%), urinary tract infection (25.7%), constipation (24.9%), and decreased appetite (23.4%) for the Durva + SoC CCRT group and anaemia (54.4%), nausea (52.3%), diarrhoea (49.5%), vomiting (27.6%), urinary tract infection (24.5%), constipation (22.7%), neutrophil count decreased (22.4%), and white blood cell count decreased (22.1%) for the Placebo + SoC CCRT group. Of the most common AEs (> 10%), those with a > 5% higher frequency in the Durva + SoC CCRT group compared with the Placebo + SoC CCRT group were: decreased appetite and hypothyroidism; the AE with a > 5% higher frequency in the Placebo + SoC CCRT group compared with the Durva + SoC CCRT group was: fatigue. The most common AEs were consistent with the known toxicity of SoC CCRT.

Consistent with the durvalumab mechanism of action, imAEs were reported at a higher incidence in the Durva + SoC CCRT group (22.3% of patients) compared with the Placebo + SoC CCRT group (8.1% of patients). The nature and incidence of imAEs reported with Durva + SoC CCRT were consistent with the established safety profile of durvalumab, which could be managed per standard treatment guidelines.

The incidence of AEs leading to treatment discontinuation (durvalumab/placebo) was low and similar across the 2 treatment groups, indicating that Durva + SoC CCRT was well tolerated in this early line setting. In addition, discontinuation of SoC CCRT due to AEs was consistent between the 2 treatment groups for both EBRT and brachytherapy. A similar proportion of patients discontinued durvalumab/placebo compared with SoC CCRT.

Serious AEs regardless of causality were reported for a similar proportion of patients in the Durva + SoC CCRT and Placebo + SoC CCRT groups. Adverse events with an outcome of death were comparable between treatment groups (3.4% versus 1.3% of patients receiving Durva + SoC CCRT and Placebo + SoC CCRT, respectively).

Increases in transaminases and creatinine, and changes in thyroid function observed in this study were consistent with previous studies of durvalumab. No new safety signals were observed for laboratory parameters and vital signs.

A review of the adverse event (AE), serious AE, and other data line listings, and relevant safety narratives for ADA-positive and ADA-negative patients who were treated with Durva + SoC CCRT was performed. Anti-drug antibodies had no apparent effect on PK or safety of durvalumab.

In conclusion, no new safety concerns were identified for the combination of Durva + SoC CCRT.

Conclusion(s)

- CALLA did not meet its primary objective, demonstrating no statistically significant improvement in PFS, by Investigator assessment or histopathologic confirmation of local tumour progression, for patients treated with Durva + SoC CCRT compared with Placebo + SoC CCRT with locally advanced cervical cancer (HR: 0.84; 95% CI: 0.65, 1.08; 2-sided p-value = 0.174).
  - A potential benefit with Durva + SoC CCRT was observed in pre-specified subgroups of patients with poor prognostic factors; however, none of these met nominal statistical significance. Of interest, HRs favouring Durva + SoC CCRT compared with Placebo + SoC CCRT were observed for the subgroups of FIGO (2009) Stage ≥ III and node positive, para-aortic lymph nodes, and Stage III, IV pelvic or para-aortic lymph node positive. Treatment with EBRT plus brachytherapy administered > 59 days also resulted in a HR favouring Durva + SoC CCRT compared with Placebo + SoC CCRT; however, due to low patient numbers and potential 'survival bias', these data should be interpreted with caution. CCI

- – Regardless of PD-L1 high expression (PD-L1 expression of ≥ 1% and ≥ 5% based on either tumour or immune cell staining), PFS by Investigator assessment or histopathologic confirmation of local tumour progression was consistent with the primary analysis.

- CALLA did not demonstrate a statistically significant benefit in OS (not formally tested per MTP) for patients treated with Durva + SoC CCRT compared with Placebo + SoC CCRT (HR: 0.78; 95% CI: 0.55, 1.10).

  - – The Kaplan-Meier estimate of median OS could not be calculated at the time of DCO.

- Overall, durvalumab given concurrently with and following platinum-based chemo-radiotherapy and pelvic brachytherapy demonstrated a tolerable and manageable safety profile for the treatment of patients with locally advanced cervical cancer. Generally, the type, incidence, and severity of AEs were comparable between the treatment groups. Where not comparable, these were consistent with the established durvalumab and CCRT safety profiles to date.

- The imAEs reported in the study were typical of the PD-1/PD-L1 class of immunotherapies and were generally manageable and/or reversible with appropriate treatment guidelines, which included the use of steroids or endocrine therapy, withholding durvalumab until the event resolved, or permanent discontinuation of durvalumab.

- Durvalumab PK exposures were within the expected exposure range following 1500 mg q4w in combination with CCRT. Anti-drug antibodies had no apparent effect on PK or safety of durvalumab.