19 September 2024
EMA/480904/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Keytruda

International non-proprietary name: Pembrolizumab

Procedure No. EMEA/H/C/003820/II/0145

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

Abbreviation	Definition
AE	Adverse event(s)
AEOSI	Adverse events of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
APaT	All Participants as Treated
AST	Aspartate aminotransferase
BICR	Blinded Independent Central Review
CCRT	Concurrent chemoradiotherapy
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CPS	Combined Positive Score
CR	Complete response
CRT	Chemoradiotherapy
CTCAE	Common Terminology Criteria for Adverse Events
DCO	Data cutoff
DILI	Drug-induced liver injury
EBRT	External beam radiotherapy
ECOG PS	Eastern Cooperative Oncology Group Performance Status
E-R	Exposure-response
ESMO	European Society for Medical Oncology
EU	European Union
FIGO	International Federation of Gynecology and Obstetrics (Fédération Internationale de Gynécologie et d'Obstétrique)
HPV	Human papilloma virus
HR	Hazard ratio
IA1	Interim analysis 1
IA2	Interim analysis 2
IFN	Interferon
IGBT	Image guided brachytherapy regimen
IgG	Immunoglobulin G
IL-2	Interleukin-2
IMRT	Intensity modulated radiotherapy
IO	Immunotherapy
ITT	Intention-to-treat
IV	Intravenous
KM	Kaplan–Meier
LACC	Locally advanced cervical cancer
LN	Lymph node
LSmean	Least square mean
mAb	Monoclonal antibody
MAH	Marketing authorisation holder
MedDRA	Medical Dictionary for Regulatory Activities
MSI-H	Microsatellite instability-high
NCI	National Cancer Institute
NSCLC	Non-small cell lung cancer

Abbreviation	Definition
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PD-1	Programmed cell death protein 1
PD-L1	Programmed cell death ligand 1
PD-L2	Programmed cell death ligand 2
PFS	Progression-free survival
PFS2	Progression-free survival 2
PIP	Paediatric investigation plan
PK	Pharmacokinetic
POS	Probability of success
PR	Partial response
PRO	Patient reported outcomes
Q3W	Once every 3 weeks
Q6W	Once every 6 weeks
RECIST	Response Evaluation Criteria In Solid Tumors
RMP	Risk Management Plan
RSD	Reference safety data
RT	Radiotherapy
SAE	Serious adverse event
SmPC	Summary of Product Characteristics
SOC	System organ class
TNFα	Tumor necrosis factor-α
UICC	Union for International Cancer Control
ULN	Upper limit of normal
VMAT	Volumetric arc techniques
WBC	White blood cell

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Merck Sharp & Dohme B.V. submitted to the European Medicines Agency on 11 October 2023 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include in combination with chemoradiotherapy (external beam radiation therapy followed by brachytherapy) the treatment of high-risk locally advanced cervical cancer in adults who have not received prior definitive therapy [Stage IB2-IIB (with node-positive disease) or Stage III-IVA based on FIGO 2014] for Keytruda, based on KEYNOTE-A18: A Randomized, Phase 3, Double-Blind Study of Chemoradiotherapy With or Without Pembrolizumab for the Treatment of High-risk, Locally Advanced Cervical Cancer. As a consequence, sections 4.1 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 44.1 of the Risk Management Plan (RMP) has also been submitted.

The variation requested amendments to the Summary of Product Characteristics and Package Leaflet and to the RMP.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0043/2018 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0043/2018 was completed.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The MAH received Scientific Advice from the CHMP on 17 October 2019 (EMEA/H/SA/2437/23/FU/1/2019/II). The Scientific Advice pertained to clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Paolo Gasparini

Timetable	Actual dates
Submission date	11 October 2023
Start of procedure:	28 October 2023
CHMP Rapporteur Assessment Report	21 December 2023
PRAC Rapporteur Assessment Report	3 January 2024
PRAC Outcome	11 January 2024
CHMP members comments	15 January 2024
Updated CHMP Rapporteur(s) (Joint) Assessment Report	19 January 2024
Request for supplementary information (RSI)	25 January 2024
MAH's responses submitted to the CHMP on	25 April 2024
Re-start of procedure	29 April 2024
CHMP Rapporteur Assessment Report	3 June 2024
CHMP members comments	17 June 2024
Updated CHMP Rapporteur Assessment Report	21 June 2024
2nd Request for supplementary information (RSI)	27 June 2024
MAH's responses submitted to the CHMP on	18 July 2024
Re-start of procedure	22 July 2024
CHMP Rapporteur Assessment Report	28 August 2024
CHMP members comments	9 September 2024
Updated CHMP Rapporteur Assessment Report	N/A
An Oral explanation took place on:	17 September 2024
CHMP opinion:	19 September 2024

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

The initially proposed indication was:

KEYTRUDA, in combination with chemoradiotherapy (external beam radiation therapy followed by brachytherapy), is indicated for the treatment of high-risk locally advanced cervical cancer in adults who have not received prior definitive therapy [Stage IB2-IIB (with node-positive disease) or Stage III-IVA based on FIGO 2014].

Epidemiology and risk factors, screening tools/prevention

Cervical cancer remains a major global health problem for women. Approximately 90% of new cases and deaths worldwide occur in low- and middle-income countries[1]. In the EU, in 2020, there were 30447 new cases and 13437 deaths from cervical cancer, accounting for 2.5% of all new cancer cases diagnosed in women (excluding non-melanoma skin cancers) and for 2.4% of all deaths in women due to cancer[2], although with wide variation within the EU, reflecting differences in HPV prevalence, and HPV vaccination and cervical cancer screening policies among the EU countries. Between 2000 and 2007, the 5-year survival of cervical cancer patients were reported to be the highest in Western Europe and lowest in Eastern Europe.

The most significant cause of cervical cancer is persistent papillomavirus infection. HPV is detected in 99% of cervical tumours, particularly the oncogenic subtypes such as HPV 16 and 18[3].

Biologic features

The 3 main categories of epithelial tumours of the cervix are squamous, glandular (adenocarcinoma) and other epithelial tumours including adenosquamous carcinoma, neuroendocrine tumours and undifferentiated carcinoma. Squamous cell carcinomas account for approximately 70–80% of cervical cancers and adenocarcinomas for 20–25%. Most studies showed that adenocarcinoma carries a worse prognosis with 10–20% differences in 5-year OS rates as compared to squamous disease[5].

Clinical presentation, diagnosis and stage/prognosis

The extent of the disease at the time of diagnosis is a significant prognostic factor in cervical cancer, also recurrence rates worsen by stage. The disease can be cured if diagnosed at an early stage and treated promptly. Due to current screening procedures in Western countries, almost half of newly diagnosed adult cervical cancer patients have localized (Stage I) cancer. Minimally invasive surgery has been shown to be

[1] Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021 May;71(3):209-249.
[2] European Cancer Information System. Cervical cancer burden in EU-27. Brussels (Belgium): European Commission; 2021. 2 p.
[3] Marth C, Landoni F, Mahner S, McCormack M, Gonzalez-Martin A, Colombo N; ESMO Guidelines Committee. Cervical cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2017 Jul 1;28(suppl_4):iv72-iv83.

disadvantageous in women with cervical cancer (Stages IA1, IA2 or IB1 by FIGO 2014)[4] [5]. There is a variation between geographic regions regarding the incidence of LACC[6]. Invasive cervical cancer spreads by direct extension into the parametrium, vagina, uterus, and adjacent organs i.e. bladder and rectum. It also spreads along the lymphatic channels to the regional lymph nodes, namely, obturator, external iliac, internal iliac, and thence to the common iliac and para-aortic nodes. Distant metastasis to lungs, liver, and skeleton by the hematogenous route is a late phenomenon.

Cervical tumours are currently staged using the Fédération Internationale de Gynécologie et d'Obstétrique (FIGO) and the Union for International Cancer Control (UICC) TNM staging classifications. The FIGO classification is based on tumour size, vaginal or parametrial involvement, bladder/rectum extension, and distant metastases. The current staging according to FIGO criteria is 2018 FIGO. Of note, in KEYNOTE-A18 study, the FIGO 2014 staging was used.

Table 1 Changes in FIGO 2014 versus FIGO 2018 staging criteria for cervical cancer[7]

Stage	FIGO 2014	FIGO 2018
IB	Clinical lesions confined to the cervix, or preclinical lesions greater than stage IA.	Invasive carcinoma with measured deepest invasion ≥5 mm (greater than Stage IA), lesion limited to the cervix uteri
IB1	Clinical lesions no greater than 4 cm in size.	Invasive carcinoma ≥5 mm depth of stromal invasion, and <2 cm in greatest dimension
IB2	Clinical lesions > 4 cm in size.	Invasive carcinoma ≥2 cm and <4 cm in greatest dimension
IB3	N/A	Invasive carcinoma ≥4 cm in greatest dimension
IIIC	N/A	Involvement of pelvic and/or para-aortic lymph nodes, irrespective of tumor size and extent (with r and p notations)
IIIC1	N/A	Pelvic lymph node metastasis only
IIIC2	N/A	Para-aortic lymph node metastasis

The FIGO modification in 2018 introduced the new Stage IB subdivisions and new lymph node status considerations in Stage IIIC. The current 2018 FIGO staging for Stage IIIC, only considers lymph node status and omits the extent of the tumour and invasion status. As per literature, this classification of all patients with positive lymph nodes into a single stage (Stage IIIC in FIGO 2018, corresponding to Stages IA1–IIIB in FIGO 2014) results in a group of cervical cancer patients with heterogeneous tumours and with variable survival[8] [9].

[4] Ramirez PT, Frumovitz M, Pareja R et al. Minimally invasive versus abdominal radical hysterectomy for cervical cancer. N Engl J Med 2018; 379:1895–1904.
[5] eUpdate - Cervical Cancer Treatment Recommendations. 01 April 2020. ESMO Guidelines Committee Clinical Practice Guidelines - Cervical cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up.
[6] Monk BJ, Tan DSP, Hernandez Chagui JD, Takyar J, Paskow MJ, Nunes AT, et al. Proportions and incidence of locally advanced cervical cancer: a global systematic literature review. Int J Gynecol Cancer. 2022;32:1531-9.
[7] From Applicant's pre-submission meeting minutes.
[8] Shin W, Ham TY, Park YR, Lim MC, Won YJ. Comparing survival outcomes for cervical cancer based on the 2014 and 2018 International Federation of Gynecology and Obstetrics staging systems. Sci Rep. 2021;11:6988.
[9] Bhatla N, Aoki D, Sharma DN, Sankaranarayanan R. Cancer of the cervix uteri: 2021 update. Int J Gynaecol Obstet. 2021;155(Suppl 1):28-44.

Management

Chemoradiotherapy (CRT) has been the standard of care for patients with bulky IB2–IVA disease (FIGO 2014) for almost two decades[5]. CRT for LACC consists in external beam radiotherapy (EBRT) with concurrent chemotherapy followed by brachytherapy[10]. The most commonly used regimen is weekly cisplatin 40 mg/m2, although the meta-analysis[11] also reported significant benefits with non-platinum agents. Chemoradiation was shown to be superior versus RT alone in a meta-analysis from randomized controlled studies in terms of overall survival, event-free survival and pelvic control, although survival benefit decreased with increasing stage[12,13,14].

Brachytherapy is an absolute requisite component for the curative management of LACC, mainly administered to maximize local control. The retrospective observational study involving 12 institutions worldwide, RetroEMBRACE, demonstrated that image guided brachytherapy regimen (IGBT) combined with radio-chemotherapy leads to better disease control with limited severe morbidity[15].

The intensification of CRT regimen with additional chemotherapy has been attempted. The addition of gemcitabine to concurrent cisplatin CRT and as adjuvant chemotherapy with cisplatin improved PFS at 3 years (from 65% to 74%), although with significant toxicity and no OS data are available[16]. In the OUTBACK study, 4 cycles of adjuvant carboplatin/paclitaxel were added after CRT, but this regimen increased short term toxicity and no improvement in the primary endpoint 5-years OS was observed (from 71% to 72%, HR 0.90 [95% CI: 0.70, 1.17] p=0.81)[17].

Induction chemotherapy before CRT was also evaluated, more recently in the phase 3 GCIG INTERLACE trial, showing that induction chemotherapy with carboplatin/paclitaxel prior to CRT significantly improved PFS and OS rates (PFS rate 73% and an OS rate 80% at 5 years) as compared to CRT (PFS rate at 5 years 64% [HR 0.65; 95% CI: 0.46–0.91; p=0.013] and OS rate at 5 years 72% [HR 0.61; 95% CI: 0.40–0.91; p=0.04]), in locally advanced cervical cancer (FIGO 2008 Stage IB1 node positive, IB2, II, IIIB, IVA)[18]. It was noted that more than half of the patients (58%) enrolled in INTERLACE had node-negative disease, and positive lymph nodes are indicative of a high-risk of relapse[19].

Some data are available on the use of anti-PD-1 or anti-PD-L1 with chemoradiotherapy in LACC. A small randomized phase 2 study evaluating pembrolizumab given either concomitantly or sequentially with pelvic CRT in LACC showed consistent ORRs with both concurrent (98%) and sequential (87%) use of

[10] Thomas GM. Improved treatment for cervical cancer- concurrent chemotherapy and radiotherapy. 1999 Apr 15;340(15):1198-200.
[11] Chemoradiotherapy for Cervical Cancer Meta-Analysis Collaboration. Reducing uncertainties about the effects of chemoradiotherapy for cervical cancer: a systematic review and meta-analysis of individual patient data from 18 randomized trials. J Clin Oncol. 2008 Dec 10;26(35):5802-12
[12] Chemoradiotherapy for Cervical Cancer Meta-Analysis Collaboration. Reducing uncertainties about the effects of chemoradiotherapy for cervical cancer: a systematic review and meta-analysis of individual patient data from 18 randomized trials. J Clin Oncol. 2008 Dec 10;26(35):5802-12.
[13] Green JA, Kirwan JJ, Tierney J, Vale CL, Symonds PR, Fresco LL, et al. Concomitant chemotherapy and radiation therapy for cancer of the uterine cervix [abstract]. Cochrane Database Syst Rev. 2005;(3):CD002225.
[14] Chemoradiotherapy for Cervical Cancer Meta-analysis Collaboration (CCCMAC). Reducing uncertainties about the effects of chemoradiotherapy for cervical cancer: individual patient data meta-analysis. Cochrane Database Syst Rev. 2010;(1):CD008285.
[15] Sturdza A, Potter R, Fokdal LU, Haie-Meder C, Tan LT, Mazeron R, et al. Image guided brachytherapy in locally advanced cervical cancer: improved pelvic control and survival in RetroEMBRACE, a multicenter cohort study. Radiother Oncol. 2016;120:428-33.
[16] Dueñas-González A, Zarbá JJ, Patel F, et al. Phase III, open-label, randomized study comparing concurrent gemcitabine plus cisplatin and radiation followed by adjuvant gemcitabine and cisplatin versus concurrent cisplatin and radiation in patients with stage IIB to IVA carcinoma of the cervix. J Clin Oncol. 2011 May 1;29(13):1678-85.
[17] Mileshkin LR, Moore KN, Barnes EH, et al. Adjuvant chemotherapy following chemoradiotherapy as primary treatment for locally advanced cervical cancer versus chemoradiotherapy alone (OUTBACK): an international, open-label, randomised, phase 3 trial. Lancet Oncol. 2023 May;24(5):468-482.
[18] McCormack M, et al. A randomised phase III trial of induction chemotherapy followed by chemoradiation compared with chemoradiation alone in locally advanced cervical cancer. The GCIG INTERLACE trial. ESMO Congress 2023, LBA8.
[19] Macdonald OK, Chen J, Dodson M, Lee CM, Gaffney DK. Prognostic significance of histology and positive lymph node involvement following radical hysterectomy in carcinoma of the cervix. Am J Clin Oncol. 2009 Aug;32(4):411-6.

pembrolizumab along with CRT[20,21]. Results from the Phase 3 CALLA study in women with high-risk LACC treated with durvalumab plus chemoradiotherapy (cisplatin or carboplatin plus RT) vs placebo plus chemotherapy did not show a statistically significant improvement in the primary endpoint PFS (HR: 0.84; 95% CI: 0.65, 1.08; p=0.174), with 2-year PFS rates of 65.9% and 62.1%, respectively. Eligible patients in CALLA study had untreated histologically confirmed cervical adenocarcinoma, squamous carcinoma, or adenosquamous carcinoma, FIGO 2009 Stage IB2–IIB lymph node positive or FIGO 2009 Stages IIIA–IVA (any lymph node status), with no evidence of metastatic disease[22].

Effective new treatment modalities to reduce the risk of recurrence and increase the cure rate are needed to improve the prognosis of women diagnosed with high-risk LACC.

2.1.2. About the product

Pembrolizumab is a potent and highly selective humanized mAb of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. This blockade enhances functional activity of the target lymphocytes by activation of antitumor T cells and modulation of the level of IL-2, TNFα, IFNγ, and other cytokines to facilitate tumor regression and, ultimately, immune rejection. The antibody potentiates existing immune responses in the presence of antigen only; it does not nonspecifically activate T-cells.

Keytruda is registered and approved worldwide for the treatment of patients with numerous tumour types. Specifically in cervical cancer, Keytruda is approved in the EU in combination with chemotherapy with or without bevacizumab for the treatment of persistent, recurrent, or metastatic cervical cancer in adults whose tumours express PD-L1 with a CPS≥1 (procedure EMEA/H/C/003820/II/0117).

The initially claimed indication was:

Keytruda in combination with chemoradiotherapy (external beam radiation therapy followed by brachytherapy), is indicated for the treatment of high-risk locally advanced cervical cancer in adults who have not received prior definitive therapy [Stage IB2-IIB (with node-positive disease) or Stage III-IVA based on FIGO 2014].

The finally agreed indication was:

Keytruda in combination with chemoradiotherapy (external beam radiation therapy followed by brachytherapy), is indicated for the treatment of FIGO 2014 Stage III - IVA locally advanced cervical cancer in adults who have not received prior definitive therapy.

[20] Duska L, Romano K, Holman L, Crane E, Wethington S, Fields E, et al. A randomized phase II study of chemoradiation and pembrolizumab for locally advanced cervical cancer. Slides presented at: Society of Gynecologic Oncology (SGO) 2023 Annual Meeting on Women's Cancer; 2023 Mar 25-28; Tampa, FL.
[21] Duska LR, Scalici JM, Temkin SM, Schwarz JK, Crane EK, Moxley KM, et al. Results of an early safety analysis of a study of the combination of pembrolizumab and pelvic chemoradiation in locally advanced cervical cancer. Cancer. 2020 Nov 15;126:4948-56.
[22] Monk BJ, Toita T, Wu X, et al. Durvalumab versus placebo with chemoradiotherapy for locally advanced cervical cancer (CALLA): a randomised, double-blind, phase 3 trial. Lancet Oncol. 2023 Dec;24(12):1334-1348.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

Table 2 Phase 3 Studies of Pembrolizumab Plus Standard of Care in Cervical Cancer

Study	Design	Participant Population	Primary Endpoint(s)	Status
KEYNOTE-826	Phase 3, Randomized, Double-Blind, Placebo-Controlled Trial of Pembrolizumab (MK-3475) Plus Chemotherapy Versus Chemotherapy Plus Placebo for the First-Line Treatment of Persistent, Recurrent, or Metastatic Cervical Cancer	617 participants were randomized (69 CPS <1, 548 CPS ≥1). Participants must have persistent, recurrent, or metastatic squamous cell carcinoma, adenosquamous carcinoma, or adenocarcinoma of the cervix which has not been treated with systemic chemotherapy and is not amenable to curative treatment.	PFS per RECIST 1.1 as assessed by investigator OS	Fully enrolled, final OS data available
KEYNOTE-A18	Phase 3, Randomized, Double-Blind Study of Chemoradiotherapy With or Without Pembrolizumab for the Treatment of High-risk, Locally Advanced Cervical Cancer	1060 participants enrolled. Participants must have locally advanced histologically confirmed squamous cell carcinoma, adenocarcinoma, or adenosquamous carcinoma of the cervix which has not previously received any definitive surgical, radiation, or systemic therapy for cervical cancer and is immunotherapy-naïve.	PFS per RECIST 1.1 as assessed by investigator or histopathology confirmation of suspected disease progression OS	Fully enrolled, ongoing
CPS = combined positive score; OS = overall survival; PFS = progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumors				

The MAH received **Scientific Advice** from CHMP on the design of study KEYNOTE-A18 in October 2019, procedure EMEA/H/SA/2437/23/FU/1/2019/II). The CHMP generally agreed with the proposed study design and patient population. In the SA, the CHMP underlined that "*The hypothesized hazard ratio of 0.66, which corresponds to an improvement of 12% on PFS rate at 2 years (57% for the control arm vs. 69% for the treatment arm), can be assessed as clinically significant, taking into account the totality of the data at the end. Nevertheless, some survival curves (Rose et al, 1999[23]) suggest a slow progression and plateau above 60% at 3 years for PFS and a bit later for OS in cervical cancer in concurrent cisplatin-based radiotherapy for locally advanced cervical cancer, indicating potential for cure. Thus, the increasing cure rate at least in some groups would allow stronger proof for the benefit of the treatment and should be kept as a primary outcome after sufficient observation-time for non-progression by the disease natural history (i.e. about 3 years from baseline). Although the proposed dual primary endpoints are considered admissible in this setting, PFS (by BICR) results should be supported by the statistical significance in the OS improvement. Also, the magnitude of benefit and supportive evidence from other secondary endpoints should be taken into account when assessing the benefit-risk ratio. If the superiority in PFS only is shown, the delay in progression would need to be weighed against the fact that most patients treated are at risk of side effects, including irreversible autoimmune disease manifestations. Without benefit in the OS, there would be a considerable uncertainty on the sufficiency of the data on positive benefit-risk balance.*"

The CHMP questioned the plan for interim analyses: "*the range of follow-up durations will be 0-28 months at IA1 and 6-34 months at IA2, i.e. too short to allow assessment of cure rate at 36 months. In fact, three quarters (IA1), and half (IA2) of patients may not yet have finished pembrolizumab at the time of*

[23] Rose PG, Bundy BN, Watkins EB, Thigpen JT, Deppe G, Maiman MA, Clarke-Pearson DL, Insalaco S. Concurrent cisplatin-based radiotherapy and chemotherapy for locally advanced cervical cancer. N Engl J Med. 1999 Apr 15;340(15):1144-53. Erratum in: N Engl J Med 1999 Aug 26;341(9):708.

proposed analyses. Without evidence of an improved cure rate, as indicated by differential PFS plateaus beyond 3+ years, the benefit of the observed delay in recurrences would have to be weighed against the burden of 2+ years of pembrolizumab treatment. OS data would likely be too immature to support a conclusion of clinical benefit (about 20% and 25% event rate at IA1 and IA2, respectively). Accordingly, it is recommended that the analysis plan is revised to allow assessment of more mature PFS data; cure rate could be addressed by a landmark analysis beyond 3 years. The Applicant states that the aim is not to discontinue the trial in the interim stage if superiority in OS has not been demonstrated; however, the design allows that already in the first interim and that is not acceptable. Furthermore, early interim could lead to fairly immature survival data, even though significant difference on survival curves have been demonstrated."

2.1.4. General comments on compliance with GCP

The MAH stated that study KEYNOTE-A18 was conducted in accordance with local and/or national regulations (including all applicable data protection laws and regulations), ICH-GCP, and the ethical principles that have their origin in the Declaration of Helsinki regarding IEC review, informed consent and the protection of human participants in biomedical research. Based on the assessment of the dossier, no issues that may lead to request a GCP inspection have been noted.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity/environmental risk assessment

Pembrolizumab is a protein, which is expected to biodegrade in the environment and not be a significant risk to the environment. Thus, according to the "Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use" (EMEA/CHMP/SWP/4447/00), pembrolizumab is exempt from preparation of an Environmental Risk Assessment as the product and excipients do not pose a significant risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Table 3 Tabular overview of clinical studies

Study	Design	Participant Population	Primary Endpoint(s)	Status
KEYNOTE-A18	Phase 3, Randomized, Double-Blind Study of Chemoradiotherapy With or Without Pembrolizumab for the Treatment of High-risk,	1060 participants enrolled. Participants must have locally advanced histologically confirmed squamous cell carcinoma, adenocarcinoma, or adenosquamous carcinoma of the cervix which has not	PFS per RECIST 1.1 as assessed by investigator or histopathology confirmation of suspected	Fully enrolled, ongoing

Study	Design	Participant Population	Primary Endpoint(s)	Status
	Locally Advanced Cervical Cancer	previously received any definitive surgical, radiation, or systemic therapy for cervical cancer and is immunotherapy-naïve.	disease progression OS	
OS = overall survival; PFS = progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumours				

2.3.2. Clinical pharmacology

A substantial characterization of the PK and immunogenicity of pembrolizumab has been provided in previous applications. No new clinical pharmacology analyses beyond those conducted previously have been generated.

In study KEYNOTE-A18, participants with high-risk LACC received pembrolizumab at 200 mg Q3W for 5 infusions plus chemoradiotherapy, followed by 400 mg Q6W pembrolizumab monotherapy for 15 infusions. An additional dosing regimen of 400 mg IV Q6W has been approved in certain regions including in the EU for all adult monotherapy indications (procedure EMEA/H/C/003820/II/0062) and for all adult indications in combination with other anticancer agents (procedure EMEA/H/C/003820/II/0102). These approvals were mainly supported by PK and E-R bridging using modelling and simulation analysis. Overall, on the basis of the robust understanding of pembrolizumab clinical pharmacology and its well-established flat E-R profiles over a 5-fold dose range, the safety and efficacy of the 400 mg Q6W dosing regimen is expected to be similar to the approved 200 mg Q3W (or 2 mg/kg Q3W) dosing regimen in all treatment settings.

Overall, while no clinical data are currently available in high-risk LACC participants administered with pembrolizumab 400 mg Q6W in combination with chemoradiotherapy, given the integrated body of evidence, 400 mg Q6W in the combination with chemoradiotherapy is expected to have a similar benefit-risk profile as 200 mg Q3W in the same combination setting and is therefore an appropriate additional dosing regimen for high-risk LACC in adults. Similarly, pembrolizumab 200 mg Q3W as monotherapy post combination with chemoradiotherapy would have a similar benefit-risk profile as that of monotherapy 400 mg Q6W as part of the treatment regimen for high-risk LACC in adults.

For locally advanced cervical cancer, patients should be treated with KEYTRUDA concurrent with chemoradiotherapy, followed by KEYTRUDA as monotherapy. KEYTRUDA can be administered as either 200 mg every 3 weeks or 400 mg every 6 weeks until disease progression, unacceptable toxicity or up to 24 months.

2.3.3. Conclusions on clinical pharmacology

No new PK data have been submitted, which is considered acceptable.

The 400 mg Q6W dosing regimen is considered a suitable dosing regimen option for the current extension of indication, based on the justification provided by the MAH.

2.4. Clinical efficacy

2.4.1. Dose response study

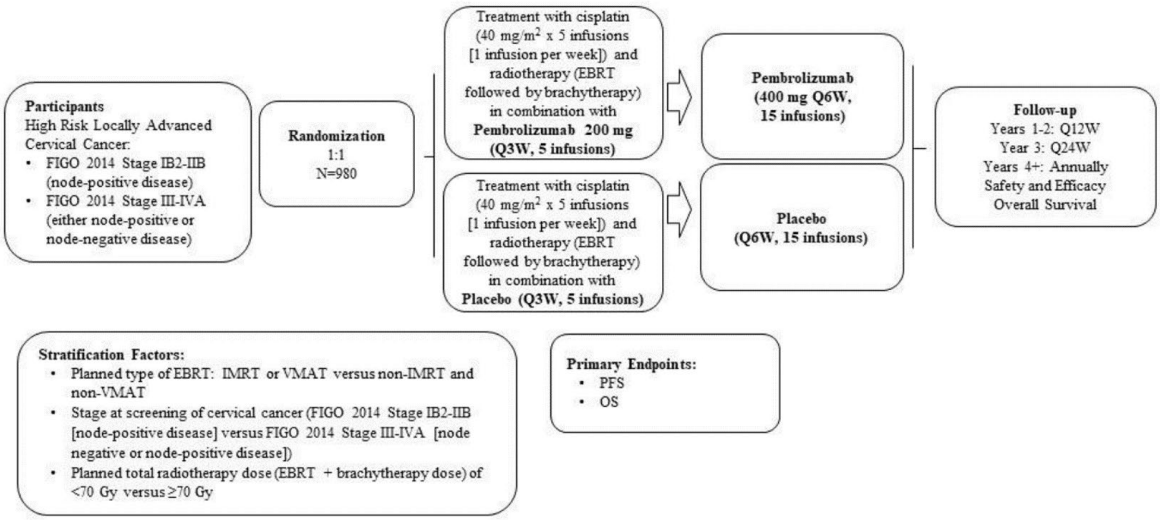
No dose-response studies were submitted as part of this application (see Clinical pharmacology).

2.4.2. Main study

<u>Study KEYNOTE-A18 (ENGOT-cx11/GOG-3047)</u>: A Randomized, Phase 3, Double-Blind Study of Chemoradiotherapy With or Without Pembrolizumab for the Treatment of High-risk, Locally Advanced Cervical Cancer

Methods

Figure 1 Study design for KEYNOTE-A18



EBRT=external beam radiotherapy; FIGO=International Federation of Gynecologists and Obstetricians; IMRT=intensity modulated radiotherapy; OS=overall survival; PFS =progression-free survival; QW3=dosing every 3 weeks; QW6=dosing every 6 weeks; Q12W=every 12 weeks; Q24W=every 24 weeks; VMAT=volumetric modulated arc therapy

Note: For cisplatin, an optional, sixth infusion may be administered according to local practice.

Participants must receive 5 infusions of pembrolizumab 200 mg or placebo at Q3W before proceeding to pembrolizumab 400 mg or placebo Q6W dosing.

Study participants

<u>Key inclusion criteria</u>:

- Had high-risk LACC FIGO 2014 Stage IB2-IIB (with node-positive disease) or Stage III-IVA (either node-positive or node-negative disease).
    - FIGO 2014 Stage IB2-IIB (with node-positive disease) – must meet criteria for positive pelvic lymph node OR para-aortic lymph node involvement up to the L1 cephalad body level.
- Had histologically-confirmed squamous cell carcinoma, adenocarcinoma, or adenosquamous carcinoma of the cervix.
- Had not previously received any definitive surgical, radiation, or systemic therapy for cervical cancer, including investigational agents, and was immunotherapy-naïve.
- Previous surgical procedure for localized cervical tumour was allowed.
- Had an ECOG PS of 0 or 1 within 7 days prior to the first dose of study intervention.

- Female of at least 18 years old.
- Has radiographically evaluable disease, either measurable or non-measurable per RECIST 1.1, as assessed by the local site investigator/radiology.

Key exclusion criteria:

- Had a positive highly sensitive pregnancy test (urine or serum as required by local regulations) within 72 hours (serum) or 24 hours (urine) before the first dose of study intervention.
- Had FIGO 2014 Stage IVB disease.
- Had a known additional malignancy that was progressing or had required active treatment within the past 3 years.
- Had a diagnosis of immunodeficiency, received chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior the first dose of study medication.
- Has an active autoimmune disease that has required systemic treatment in past 2 years (ie, with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment and is allowed.
- Had received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent or with an agent directed to another stimulatory or co-inhibitory T-cell receptor (e.g. CTLA-4, OX40, CD137).
- Had received prior systemic anticancer therapy including investigational agents within 4 weeks prior to randomization.

Treatments

Treatment consisted in concurrent chemoradiotherapy in combination with pembrolizumab/placebo (200 mg Q3W for 5 infusions) followed by pembrolizumab/placebo alone (400 mg Q6W for 15 infusions), for a total duration of the treatment of approximately 2 years.

Standard of care chemoradiotherapy was given during the Q3W dosing period of pembrolizumab or placebo and included the following:

- Cisplatin, 5 infusions given IV QW at 40 mg/m2 (an optional, sixth infusion could be administered according to local practice), plus
- External Beam Radiotherapy (EBRT) over 40 days, followed by
- Brachytherapy.

Brachytherapy should have followed the completion of EBRT and started immediately after completion of EBRT, and the overall treatment time of EBRT and brachytherapy together should not have exceeded 50 days (with an extension to a maximum of 56 days for unforeseen delays). To achieve adequate target coverage and to reduce the dose to the organs at risk, brachytherapy should be intracavitary or a combination of intracavitary and interstitial. The minimum acceptable radiation was 80 Gy for volume-directed and 75 Gy for point-directed. Pelvic external beam radiation therapy (EBRT) is an integral part of the overall treatment strategy with the primary aim of obtaining regional and nodal control. It can be delivered with different techniques: 3D conformal EBRT, intensity-modulated radiation therapy (IMRT) or volumetric modulated arc therapy (VMAT), over 40 days.

Treatment continued up to disease progression is documented per RECIST 1.1 by the investigator, withdrawal of consent, pregnancy, loss to follow-up, or death, whichever occurs first. Treatment beyond documented disease progression may be permitted at the discretion of the investigator after consultation with the Sponsor and informed consent.

Tumour assessment: Baseline imaging was performed within 28 days prior to randomization. The first scheduled post-randomization imaging assessment required were a contrast-enhanced PET/CT scan as well as a chest CT and MRI of abdomen/pelvis that should be performed at 12 weeks after the completion of CCRT. Subsequent tumour imaging should be performed every 12 weeks thereafter from the completion of CCRT during Years 1 and 2, every 24 weeks in Year 3, and once per year in Year 4 onwards. For participants who are lymph node positive at baseline by PET only, a PET scan to confirm disappearance of the FDG uptake in the node(s) is required to determine that a complete response has occurred. For participants who discontinue study intervention, tumour imaging should be performed at the time of treatment discontinuation (if not obtained within 4 weeks). For participants who discontinue study intervention without documented radiographic disease progression, every effort should be made to continue monitoring disease status.

Objectives and outcomes/endpoints

Table 4 Study objectives/endpoints

Objectives	Endpoints
Primary	
To compare concurrent chemoradiotherapy plus pembrolizumab with concurrent chemoradiotherapy plus placebo with respect to PFS per RECIST 1.1 as assessed by investigator or by histopathologic confirmation of suspected disease progression (in the absence of radiographic disease progression per RECIST 1.1) as assessed by investigator Hypothesis (H1): concurrent chemoradiotherapy plus pembrolizumab is superior to concurrent chemoradiotherapy plus placebo with respect to PFS per RECIST 1.1 by investigator or by histopathologic confirmation as indicated	PFS: The time from randomization to the first documented disease progression or death due to any cause, whichever occurs first
To compare concurrent chemoradiotherapy plus pembrolizumab with concurrent chemoradiotherapy plus placebo with respect to OS Hypothesis (H2): concurrent chemoradiotherapy plus pembrolizumab is superior to concurrent chemoradiotherapy plus placebo with respect to OS	OS: The time from randomization to death due to any cause
Secondary	
To compare concurrent chemoradiotherapy plus pembrolizumab with concurrent chemoradiotherapy plus placebo with respect to PFS per RECIST 1.1 as assessed by BICR	PFS: The time from randomization to the first documented disease progression or death due to any cause, whichever occurs first
To compare concurrent chemoradiotherapy plus pembrolizumab with concurrent chemoradiotherapy plus placebo with respect to PFS at 2 years per RECIST 1.1 as assessed by investigator or by histopathologic confirmation of suspected disease progression (in the absence of radiographic disease progression per RECIST 1.1)	PFS at 2 years: The proportion of participants that are PFS event-free at 2 years

Objectives	Endpoints
To compare concurrent chemoradiotherapy plus pembrolizumab with concurrent chemoradiotherapy plus placebo with respect to PFS at 2 years per RECIST 1.1 as assessed by BICR	PFS at 2 years: The proportion of participants that are PFS event-free at 2 years
To compare concurrent chemoradiotherapy plus pembrolizumab with concurrent chemoradiotherapy plus placebo with respect to OS at 3 years	OS at 3 years: The proportion of participants that are OS event-free at 3 years
To compare concurrent chemoradiotherapy plus pembrolizumab with concurrent chemoradiotherapy plus placebo with respect to CR rate at 12 weeks after completion of concurrent chemoradiotherapy per RECIST 1.1 as assessed by investigator in all randomly assigned participants with measurable disease at study entry	CR rate at 12 weeks after completion of concurrent chemoradiotherapy
To compare concurrent chemoradiotherapy plus pembrolizumab with concurrent chemoradiotherapy plus placebo with respect to ORR per RECIST 1.1 as assessed by investigator in all randomly assigned participants with measurable disease at study entry	OR: CR or PR
To compare concurrent chemoradiotherapy plus pembrolizumab with concurrent chemoradiotherapy plus placebo with respect to CR rate at 12 weeks after completion of concurrent chemoradiotherapy per RECIST 1.1 as assessed by BICR in all randomly assigned participants with measurable disease at study entry	CR rate at 12 weeks after completion of concurrent chemoradiotherapy
To compare concurrent chemoradiotherapy plus pembrolizumab with concurrent chemoradiotherapy plus placebo with respect to ORR per RECIST 1.1 as assessed by BICR in all randomly assigned participants with measurable disease at study entry	OR: CR or PR
To compare concurrent chemoradiotherapy plus pembrolizumab with concurrent chemoradiotherapy plus placebo with respect to OS and PFS per RECIST 1.1 as assessed by investigator or by histopathologic confirmation of suspected disease progression (in the absence of radiographic disease progression per RECIST 1.1), by PD-L1 status (by CPS)	OS PFS

Objectives	Endpoints
To compare concurrent chemoradiotherapy plus pembrolizumab with concurrent chemoradiotherapy plus placebo with respect to OS and PFS per RECIST 1.1 as assessed by BICR, by PD-L1 status (by CPS)	OS PFS
To compare concurrent chemoradiotherapy plus pembrolizumab with concurrent chemoradiotherapy plus placebo with respect to PFS after next-line treatment (PFS2) following discontinuation of study treatment administration as determined by the investigator according to the local standard of clinical practice	PFS2: The time from the date of randomization until disease progression on next-line treatment or death due to any cause, whichever occurs first
To compare concurrent chemoradiotherapy plus pembrolizumab with concurrent chemoradiotherapy plus placebo with respect to change from baseline score in global quality of life and physical function using the EORTC QLQ-C30 global health status/Quality of Life scale and Physical Function subscale	EORTC QoL Questionnaire EORTC QLQ-C30 Global Score and Physical Function subscale
To compare concurrent chemoradiotherapy plus pembrolizumab with concurrent chemoradiotherapy plus placebo with respect to change from baseline score in symptom experience using the EORTC QLQ-CX24 (Symptom Score for Cervical Cancer) symptom specific scale (11 items)	The EORTC QoL Questionnaire (Symptom Score for Cervical Cancer) EORTC QLQ-CX24 symptom specific scale
To evaluate the safety and tolerability of pembrolizumab in combination with concurrent chemoradiotherapy	AEs Study treatment discontinuation due to AEs
Tertiary/Exploratory	
To describe concurrent chemoradiotherapy plus pembrolizumab versus concurrent chemoradiotherapy plus placebo with respect to DOR per RECIST 1.1 as assessed by BICR in all randomly assigned participants with measurable disease	DOR: The time from first response (CR or PR) to the first documented disease progression, or death from any cause, whichever occurs first
To describe concurrent chemoradiotherapy plus pembrolizumab versus concurrent chemoradiotherapy plus placebo with respect to DOR per RECIST 1.1 as assessed by investigator in all randomly assigned participants with measurable disease	DOR

Objectives	Endpoints
To describe concurrent chemoradiotherapy plus pembrolizumab versus concurrent chemoradiotherapy plus placebo with respect to DOR in participants with CR at 12 weeks after concurrent chemoradiotherapy per RECIST 1.1 as assessed by investigator in all randomly assigned participants with measurable disease at study entry	DOR
To describe concurrent chemoradiotherapy plus pembrolizumab versus concurrent chemoradiotherapy plus placebo with respect to DOR in participants with CR at 12 weeks after concurrent chemoradiotherapy per RECIST 1.1 as assessed by BICR in all randomly assigned participants with measurable disease at study entry	DOR
To evaluate changes in the Visual Analog Scale and characterize utilities using the European QoL (EQ-5D-5L) instrument	Visual Analog Scale and utilities will be assessed using the EQ-5D-5L

Sample size

KEYNOTE-A18 was powered for both primary endpoints and was planned to randomize 980 patients in a 1:1 ratio between 2 treatment arms, based on the following assumptions:

1) PFS follows a Poisson mixture model with approximately 20% participants achieving long-term results (i.e. cure rate of 20% for both arms) and PFS rate at 2 years of 57% for the control arm versus 69% for the treatment arm (HR = 0.660);

2) OS follows a Poisson mixture model with approximately 20% participants achieving long-term results (i.e., cure rate of 20% for both arms) and OS rate at 3 years of 64.5% for the control arm versus 74.5% for the treatment arm (HR = 0.671);

3) enrolment duration of 28 months with an average accrual rate of 35 participants per month;

4) yearly drop-out rate of 2% for both arms.

The PFS hypothesis testing is designed for one-sided α = 0.025 and power of 95% to detect an HR of 0.660 with approximately 237 and 304 events between the 2 arms at the planned PFS interim and final analyses.

The OS hypothesis testing is designed for one-sided α = 0.025 (only if the null hypothesis for PFS is rejected) and power of 86% to detect an HR of 0.671 with approximately 132, 182 and 240 events between the 2 arms at the planned OS interim and final analyses.

Randomisation

After a screening phase of up to 42 days, eligible participants were randomly assigned in a 1:1 ratio to one of the two treatment arms, stratified by:

- planned type of EBRT: IMRT or VMAT versus non-IMRT and non-VMAT;
- cervical cancer stage at screening: FIGO 2014 Stage IB2-IIB (node-positive) versus FIGO 2014 Stage III-IVA (either node-positive or node-negative);

- planned total radiotherapy dose, defined as EBRT + brachytherapy dose (<70 Gy EQ-2D versus ≥70 Gy EQ-2D).

The combination of these categories resulted in 2x2x2=8 strata. Within each stratum, the fixed block size of 4 was used.

Blinding (masking)

A double-blinding technique with in-house blinding was used. The participant, the investigator, and Sponsor personnel or delegate(s) who were involved in the study intervention administration or clinical evaluation of the participants were unaware of the intervention assignments.

Statistical methods

Protocol Amendments involving statistical methods

The protocol was subject to four general amendments, of which Amendment No. 01 (06 January 2021), Amendment No. 03 (18 March 2022) and Amendment No. 04 (08 November 2022) modified the SAP language.

Interim Analyses

There were two planned interim efficacy analyses (IA) in addition to the final analysis (FA). Results of the interim analyses were reviewed by the eDMC.

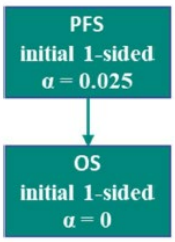
Table 5 Analyses plan

Analyses	Key Endpoints	Timing	Estimated Time after First Participant Randomized	Primary Purpose of Analysis
IA1	PFS OS	Will be triggered on completion of enrollment and when approximately 237 PFS events have been observed. Approximately 132 OS events are expected to be accumulated at this IA	~28 months	• Interim PFS analysis • Interim OS analysis
IA2	PFS OS	Will be triggered when approximately 304 PFS events have been observed. Approximately 182 OS events are expected to be accumulated at this IA	~34 months	• Demonstrate PFS superiority • Interim OS analysis
Final Analysis	OS	Will be triggered when approximately 240 OS events have been observed	~42 months	• Demonstrate OS superiority
Abbreviations: IA=interim analysis; FA=final analysis; OS=overall survival; PFS=progression-free survival. Note for IA1, if the events accrue slower than expected, the Sponsor may conduct the analysis with up to an additional 3 months of follow-up, or when the specified number of events is observed, whichever occurs first. For IA2 and FA, if the events accrue slower than expected, the Sponsor may conduct the analysis with up to an additional 6 months of follow-up, or when the specified number of events is observed, whichever occurs first. IA2 and FA may be kept at least 8 months apart as planned.				

Error probabilities, adjustment for multiplicity

The overall Type I error rate was controlled at a 0.025 (one-sided) alpha level. The trial used the graphical method of Maurer and Bretz to control multiplicity for multiple hypotheses, as well as interim analyses. The figure below shows 1-sided alpha allocation for each hypothesis according to Protocol Amendment 4.

Figure 2 Multiplicity Graph for Type I Error Control of Study Hypothesis



OS=overall survival; PFS=progression-free survival

Progression-free survival: The study initially allocated one-sided alpha = 0.025 to test PFS between 2 treatment arms. If the null hypothesis for PFS was rejected, then its alpha = 0.025 was fully reallocated to the OS test. The actual boundaries were to be calculated based on the observed number of PFS events at the interim and final PFS analyses using the Lan-DeMets O'Brien-Fleming spending function accordingly. The final analysis would use the remaining Type I error that has not been spent at the earlier analyses. The table below demonstrates the bounds and boundary properties for PFS hypothesis testing.

Table 6 Boundary Properties for Planned Analyses of PFS Based on Potential Alpha Levels to be Used for Testing

Analysis[a]	Value	α = 0.025
IA1: 78%	Z	2.3212
N: 980	p (1-sided)	0.0101
Events: 237	HR at bound	0.7387
Month: 28	P(Cross) if HR=1	0.0101
	P(Cross) if HR=0.660	0.8016
IA2: 100%	Z	2.0143
N: 980	p (1-sided)	0.0220
Events: 304	HR at bound	0.7952
Month: 34	P(Cross) if HR=1	0.0250
	P(Cross) if HR=0.660	0.9500

Abbreviations: HR=hazard ratio; IA=interim analysis; PFS=progression-free survival.

[a] This column displays the number (Events) and percentage (%) of needed PFS events, the expected sample size (N) and the estimated months (Month) after the first participant is randomized for each analysis.

p (1-sided): the nominal α for testing.

HR at bound: the approximate hazard ratio required to reach an efficacy bound.

P(Cross if HR=1): the probability of crossing a bound at or before each analysis under the null hypothesis

P(Cross if HR=0.660): the probability of crossing a bound at or before each analysis under the alternative hypothesis.

Overall Survival: The OS hypothesis was tested at alpha = 0.025 (only if the null hypotheses for PFS was rejected). The table below demonstrates the bounds and boundary properties for OS hypothesis testing. The actual boundaries were calculated based on the observed number of OS events at the interim and final OS analyses using the Lan-DeMets O'Brien-Fleming spending function accordingly. The final analysis would use the remaining Type I error that has not been spent at the earlier analyses.

Table 7 Boundary Properties for Planned Analyses of OS Based on Potential Alpha Levels to be Used for Testing

Analysis[a]	Value	α = 0.025
IA1: 55%	Z	2.8059
N: 980	p (1-sided)	0.0025
Events: 132	HR at bound	0.6131
Month: 28	P(Cross) if HR=1	0.0025
	P(Cross) if HR=0.671	0.2985
IA2: 76%	Z	2.3511
N: 980	p (1-sided)	0.0094
Events: 182	HR at bound	0.7056
Month: 34	P(Cross) if HR=1	0.0101
	P(Cross) if HR=0.671	0.6334
Final: 100%	Z	2.0178
N: 980	p (1-sided)	0.0218
Events: 240	HR at bound	0.7703
Month: 42	P(Cross) if HR=1	0.0250
	P(Cross) if HR=0.671	0.8600

Abbreviations: HR=hazard ratio; IA=interim analysis; OS=overall survival.

[a] This column displays the number (Events) and percentage (%) of needed OS events, the expected sample size (N) and the estimated months (Month) after first participant is randomized for each analysis.

p (1-sided): the nominal α for testing.

HR at bound: the approximate hazard ratio required to reach an efficacy bound.

P(Cross if HR=1): the probability of crossing a bound at or before each analysis under the null hypothesis

P(Cross if HR=0.671): the probability of crossing a bound at or before each analysis under the alternative hypothesis.

Statistical Methods for Efficacy Analyses

The Intention-to-Treat (ITT) population served as the population for primary efficacy analyses. All randomized participants were included in this population. Participants were included in the treatment group to which they are randomized. Primary analysis approach for key efficacy endpoints is summarized in the table below.

Table 8 Analysis Strategy for Key Efficacy Endpoints in KEYNOTE-A18

Endpoint	Statistical Method	Analysis Population	Missing Data / Censoring Approach
Primary Objectives			
PFS by investigator per RECIST 1.1 or histopathologic confirmation	Testing: Stratified log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT	Censored according to rules in Table 9
OS	Testing: Stratified log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT	Censored at last known alive date
Secondary Objectives			
PFS by BICR per RECIST 1.1	Testing: Stratified log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT	Censored according to rules in Table 9

Abbreviations: BICR=blinded independent central review; ITT=Intent-to-Treat; OS=overall survival; PFS=progression-free survival; RECIST=Response Evaluation Criteria in Solid Tumors

To evaluate the robustness of the PFS endpoint per RECIST 1.1 based on investigator assessment, 1 primary and 2 sensitivity analyses with a different set of censoring rules were performed as shown in the table below.

Table 9 Censoring Rules for Primary and Secondary Analyses of Progression-free Survival

Situation	Primary Analysis	Sensitivity Analysis 1	Sensitivity Analysis 2
PD or death documented after ≤1 missed disease assessment, and before new anticancer therapy, if any	Progressed at date of documented PD or death	Progressed at date of documented PD or death	Progressed at date of documented PD or death
PD or death documented immediately after ≥2 consecutive missed disease assessments or after new anticancer therapy, if any	Progressed at date of documented PD or death	Censored at last disease assessment prior to the earlier date of ≥2 consecutive missed disease assessment and new anticancer therapy, if any	Progressed at date of documented PD or death
No PD and no death; and new anticancer treatment is not initiated	Censored at last disease assessment	Censored at last disease assessment	Progressed at treatment discontinuation due to reasons other than complete response; otherwise censored at last disease assessment if still on study or completed study treatment
No PD and no death; new anticancer treatment is initiated	Censored at last disease assessment	Censored at last disease assessment before new anticancer treatment	Progressed at date of new anticancer treatment
Abbreviation: PD=progressive disease			

The stratified Miettinen and Nurminen method was used for the comparison of objective response rate (ORR) between the two treatment groups. The difference in ORR and its 95% confidence interval from the stratified Miettinen and Nurminen method with strata weighting by sample size was reported. The stratification factors used for randomization were applied to the analysis.

For participants with measurable disease at baseline who demonstrate CR or PR, DOR was defined as the time from first documented evidence of CR or PR until disease progression or death due to any cause, whichever occurs first.

Subgroup analyses

Subgroup Analyses and Effect of Baseline Factors were planned by stratification factors, age, race and ECOG PS. To determine whether the treatment effect was consistent across various subgroups, the between-group treatment effect for PFS and OS (with a nominal 95% CI) was estimated and plotted by treatment group within each category of the above variables. The consistency of the treatment effect was to be assessed descriptively via summary statistics by category.

PRO analyses

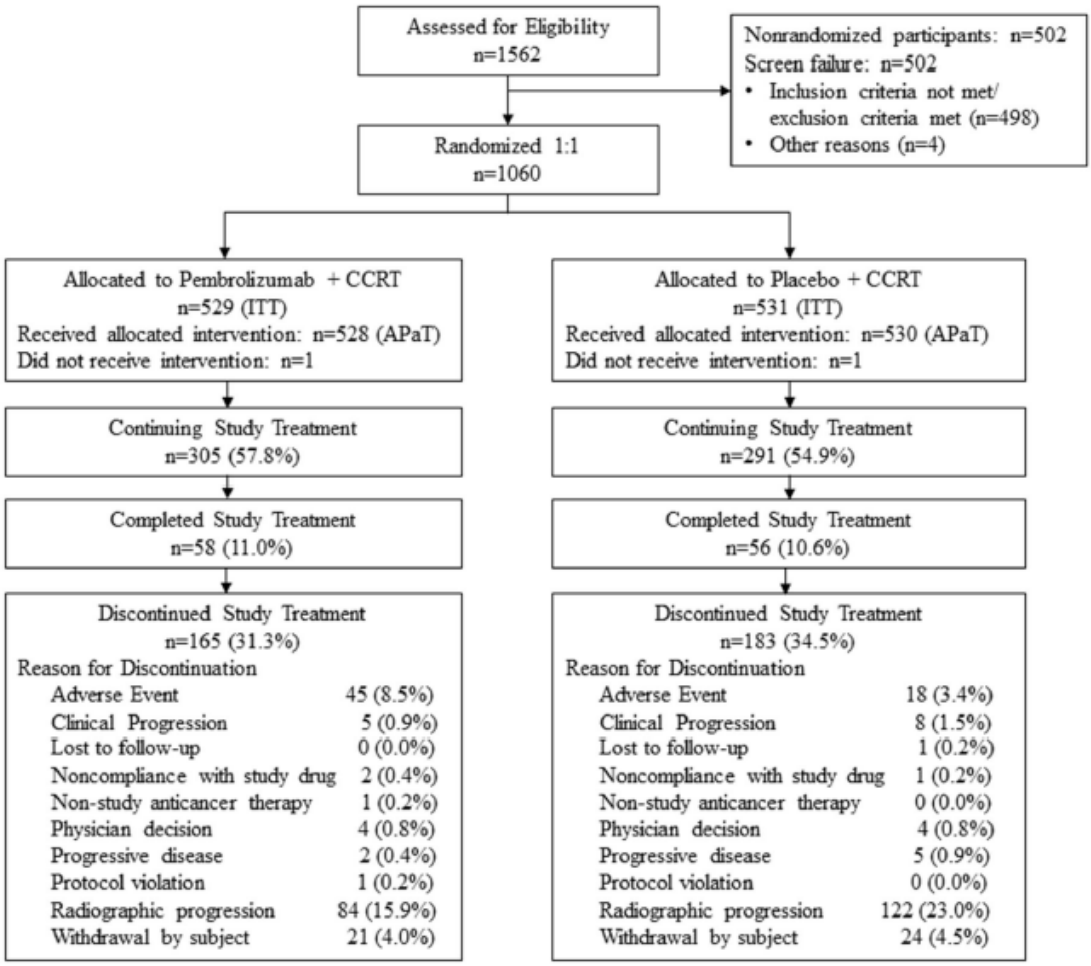
Analyses of PRO endpoints were conducted using the PRO FAS population, defined as all randomized participants who had at least 1 PRO assessment available and received at least 1 dose of study intervention. Participants were analysed in the treatment arm to which they were randomized. To evaluate the treatment effect on the HRQoL outcomes at prespecified time points, a constrained longitudinal data analysis model was applied, with the PRO score as the response variable, and the treatment by time interaction and stratification factors as covariates. Least square mean (LSmean)

change from baseline were summarized. Group-wise comparisons were performed and the model-based LSmean score was provided by treatment group and study visit.

Results

Participant flow

Figure 3 Participant flow diagram KEYNOTE-A18



APaT=All Participants as Treated; CCRT=concurrent chemoradiotherapy; ITT=intention-to-treat

Database Cutoff Date: 09-JAN-2023

A total of 502 participants were screened and not randomized; all were screen failures. The majority of nonrandomized participants did not meet the inclusion criteria or met exclusion criteria (main reason not meeting diagnosis with prescribed FIGO stage and nodal status).

As of the DCO (09 January 2023), a total of 1060 participants were randomized in a 1:1 ratio to pembrolizumab plus chemoradiotherapy (529 participants) or placebo plus chemoradiotherapy (531 participants). All but 2 participants randomly assigned received at least 1 dose of study intervention.

Table 10 Disposition of Participants (ITT Population)

	Pembrolizumab + CCRT		Placebo + CCRT		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	529		531		1060	
Status for Study Medication in Trial						
Started	528		530		1058	
Completed	58	(11.0)	56	(10.6)	114	(10.8)
Discontinued	165	(31.3)	183	(34.5)	348	(32.9)
Adverse Event	45	(8.5)	18	(3.4)	63	(6.0)
Clinical Progression	5	(0.9)	8	(1.5)	13	(1.2)
Lost To Follow-Up	0	(0.0)	1	(0.2)	1	(0.1)
Non-Compliance With Study Drug	2	(0.4)	1	(0.2)	3	(0.3)
Non-Study Anti-Cancer Therapy	1	(0.2)	0	(0.0)	1	(0.1)
Physician Decision	4	(0.8)	4	(0.8)	8	(0.8)
Progressive Disease	2	(0.4)	5	(0.9)	7	(0.7)
Protocol Violation	1	(0.2)	0	(0.0)	1	(0.1)
Radiographic Progression	84	(15.9)	122	(23.0)	206	(19.5)
Withdrawal By Subject	21	(4.0)	24	(4.5)	45	(4.3)
Participants Ongoing	305	(57.8)	291	(54.9)	596	(56.3)
Status for Trial						
Discontinued	54	(10.2)	65	(12.2)	119	(11.2)
Death	42	(7.9)	59	(11.1)	101	(9.5)
Lost To Follow-Up	0	(0.0)	1	(0.2)	1	(0.1)
Withdrawal By Subject	12	(2.3)	5	(0.9)	17	(1.6)
Participants Ongoing	475	(89.8)	466	(87.8)	941	(88.8)

If the overall count of participants is calculated and displayed within a section in the first row, then it is used as the denominator for the percentage calculation. Otherwise, participants in population is used as the denominator for the percentage calculation.

For the status for study medication of treatment phase, participants treated with study medication is used as the denominator for percentage calculation.

For the status for trial, participants in population is used as the denominator for percentage calculation.

CCRT: Concurrent chemoradiotherapy

Database Cutoff Date: 09JAN2023

Recruitment

KEYNOTE-A18 was conducted at 176 centres in 30 countries (Australia, Europe including EU, North and South America, Asia). The first participant first visit was on 12 May 2020, and the last patient was randomized into the study on 15 December 2022.

The study is ongoing. The initial submission was based on the first planned interim analysis (IA1) with data cut-off on 9 January 2023 and database lock on 17 February 2023. Results from IA2 (DCO 8 January 2024) have been further submitted during the procedure.

Conduct of the study

Protocol amendments

The original protocol is dated 14 November 2019. There were 4 protocol amendments up to the first planned interim analysis, which are described below:

Table 11 Protocol Amendments for MK-3475-A18

Document	Date of Issue	Overall Rationale
Amendment 04	08-NOV-2022	To amend the SAP to take into account emerging external data in LACC from the CALLA study. In addition, changes were made throughout to align with the EU CTR.
Amendment 03	18-MAR-2022	To incorporate PET scans into RECIST 1.1 evaluations to evaluate the burden of disease more accurately, and to add flexibility for the timing of efficacy analyses.
Amendment 02	04-JUN-2021	To update the dose modification and toxicity management guidelines for irAEs and provide country-specific treatment administration details for Japan.
Amendment 01	06-JAN-2021	Changes were made to the objectives/endpoints and statistical analysis plan that include changing the PFS by BICR to PFS by investigator and adding PFS by BICR as a secondary endpoint. Numerous administrative changes were also made.

BICR=blinded independent central review; CTR= Clinical Trials Regulation; EU=European Union; irAE=immune-related adverse event; LACC=locally advanced cervical cancer; PET=positron emission tomography; PFS=progression-free survival; RECIST 1.1=Response Evaluation Criteria in Solid Tumors, version 1.1; SAP=statistical analysis plan

Applicant's rationale for Amendment 1: Locally advanced cervical cancer is a setting where disease progression is highly informed by clinical findings correlating with histopathologic confirmation of progression with biopsy. PFS by investigator is therefore considered a more adequate endpoint in this disease setting.

The PFS assessed by investigator was moved to primary endpoint and the PFS by BICR was moved to secondary endpoints. Censoring rules and other details in the statistical analysis plan were modified to account for these changes. The primary analysis followed the complete follow-up intention-to-treat principle.

Applicant's rationale for Amendment 3: Per the original protocol, a contrast-enhanced PET/CT, CT chest and MRI of abdomen/pelvis was to be performed at baseline and at the first efficacy follow-up 12 weeks after the last dose of chemoradiotherapy (±14 days). With the inclusion of the interpretation of FDG-PET for response evaluation by RECIST 1.1, its use has been increasing worldwide. The rationale to incorporate additional PET scans into the protocol amendment 03 was to confirm disappearance of the FDG uptake in the node(s) in order to determine that a complete response following chemoradiotherapy has occurred, specifically for participants who were lymph node-positive at baseline, that were identified by PET only, and not visualized by MRI or CT. This amendment also enabled sites to evaluate complete response at later time points if FDG uptake in the nodes had not yet resolved whenever MRI and/or CT scan suggested complete response.

Amendment to the SAP: More flexibility was implemented for the timing of the interim and final efficacy analyses so that in case of slower than anticipated accrual of PFS and/or OS events the timing of the analysis might be re-evaluated. Censoring rules, changed in amendment 01, were correctly updated. It was clarified that the final analysis of PFS and OS would have used the remaining type I error that had not been spent at earlier analyses. In addition, it was clarified that even if the stratification factors used for randomization were applied to all strafied analysis, in case of small strata, a pooling strategy of smallest strata were used to ensure sufficient number of participants, responses, and events in each stratum.

Applicant's rationale for Amendment 4: The emerging external data from the locally advanced cervical study, CALLA, suggested a longer OS in the control arm compared with the original assumption in KEYNOTE-A18. The original assumptions were based on the RETROEMBRACE study, which observed an OS rate at 3 years of 54% for the control arm versus 66% for the treatment arm (HR = 0.674). The updated OS 3-year assumptions were based on RETROEMBRACE and CALLA of 64.5% for the control arm versus 74.5% for the treatment arm (HR = 0.671, which kept the same treatment effect assumption as the original).

Based on the revised assumption, the targeted number of OS events could not be achieved within a reasonable timeframe and the OS endpoint would have been underpowerd based on the original multiplicity strategy. The multiplicity strategy was amended as follows: the initial one-sided alpha = 0.025 was no more splitted to test PFS and OS hypotheses but was initially fully allocated to PFS hypothesis and then fully re-allocated to OS hypothesis if PFS hypothesis was rejected in a conditional step-down manner. The expected number of OS events was updated accordingly: the approximate number of OS events was updated from 193 to 132 at IA1, from 251 to 182 at IA2 and from 322 to 240 at FA.

The release of Amendment 4 (November 2022) was compatible in terms of timeline with the public disclosure of the results of CALLA study[24] [25].

Protocol deviations

In the pembrolizumab plus chemoradiotherapy and placebo plus chemoradiotherapy groups, 25 (4.7%) participants and 20 (3.8%) participants, respectively, had important protocol deviations considered to be clinically important (i.e. deviations that may compromise critical data analyses pertaining to primary efficacy and/or safety endpoints or the participant's safety). The most frequent clinically important protocol deviations were inclusion/exclusion criteria deviations in both treatment groups, with 9 (1.7%) participants in each treatment group who did not have high-risk LACC defined by FIGO 2014 stages specified by the study protocol. Two participants were enrolled with Stage IVB disease at screening (1 participant in each treatment group); the remaining participants had Stage IB2-IIB (without node positive disease).

Overall, 24 (4.5%) pembrolizumab plus chemoradiotherapy participants and 24 (4.5%) placebo plus chemoradiotherapy participants, respectively, had important protocol deviations considered not clinically important.

[24] AstraZeneca press release - Update on CALLA Phase III trial of concurrent use of Imfinzi and chemoradiotherapy in locally advanced cervical cancer – published 22 March 2022 - https://www.astrazeneca.com/media-centre/press-releases/2022/update-on-calla-phase-iii-trial-for-imfinzi.html

[25] Monk, B, Toita T, Wu X, et al. Durvalumab, in combination with and following chemotherapy, in locally advanced cervical cancer: results from the phase 3 international, randomized, double-blind, placebo-controlled CALLA trial. Presented at: 2022 International Gynecologic Cancer Society Annual Meeting; September 29-October 1, 2022; New York, NY. Abstract O001.

Baseline data

Table 12 Participant Characteristics (ITT Population)

	Pembrolizumab + CCRT		Placebo + CCRT		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	529		531		1,060	
Sex						
Female	529	(100.0)	531	(100.0)	1,060	(100.0)
Age (Years)						
< 65	473	(89.4)	454	(85.5)	927	(87.5)
>= 65	56	(10.6)	77	(14.5)	133	(12.5)
Mean	49.4		50.1		49.8	
SD	11.9		12.3		12.1	
Median	49.0		50.0		50.0	
Range	22 to 87		22 to 78		22 to 87	
Race						
American Indian Or Alaska Native	24	(4.5)	22	(4.1)	46	(4.3)
Asian	155	(29.3)	148	(27.9)	303	(28.6)
Black Or African American	14	(2.6)	8	(1.5)	22	(2.1)
Multiple	78	(14.7)	86	(16.2)	164	(15.5)
Native Hawaiian Or Other Pacific Islander	2	(0.4)	1	(0.2)	3	(0.3)
White	254	(48.0)	264	(49.7)	518	(48.9)
Missing	2	(0.4)	2	(0.4)	4	(0.4)
Ethnicity						
Hispanic Or Latino	161	(30.4)	174	(32.8)	335	(31.6)
Not Hispanic Or Latino	362	(68.4)	355	(66.9)	717	(67.6)
Not Reported	4	(0.8)	0	(0.0)	4	(0.4)
Unknown	1	(0.2)	2	(0.4)	3	(0.3)
Missing	1	(0.2)	0	(0.0)	1	(0.1)
Geographic Region						
Asia Pacific	155	(29.3)	150	(28.2)	305	(28.8)
EMEA	186	(35.2)	183	(34.5)	369	(34.8)
North America	34	(6.4)	45	(8.5)	79	(7.5)

	Pembrolizumab + CCRT		Placebo + CCRT		Total	
	n	(%)	n	(%)	n	(%)
Latin America	154	(29.1)	153	(28.8)	307	(29.0)
Geographic Region 2						
North America	34	(6.4)	45	(8.5)	79	(7.5)
Western Europe	137	(25.9)	127	(23.9)	264	(24.9)
Rest of the World	358	(67.7)	359	(67.6)	717	(67.6)
Age Group (Years)						
< 65	473	(89.4)	454	(85.5)	927	(87.5)
65 - 74	50	(9.5)	70	(13.2)	120	(11.3)
75 - 84	5	(0.9)	7	(1.3)	12	(1.1)
85+	1	(0.2)	0	(0.0)	1	(0.1)
Baseline ECOG						
0	380	(71.8)	397	(74.8)	777	(73.3)
1	149	(28.2)	134	(25.2)	283	(26.7)
FIGO 2014 Stage at Screening						
IB2 to IIB	235	(44.4)	227	(42.7)	462	(43.6)
III to IVA	294	(55.6)	304	(57.3)	598	(56.4)
Presence of Lymph Node						
Positive Pelvic and/or Para-Aortic	445	(84.1)	438	(82.5)	883	(83.3)
No Positive Pelvic nor Para-Aortic	84	(15.9)	93	(17.5)	177	(16.7)
Histology Subtype						
Non-squamous	96	(18.1)	80	(15.1)	176	(16.6)
Squamous	433	(81.9)	451	(84.9)	884	(83.4)
Planned Type of EBRT						
IMRT or VMAT	469	(88.7)	470	(88.5)	939	(88.6)
non-IMRT and non-VMAT	60	(11.3)	61	(11.5)	121	(11.4)
Planned Total Radiationtherapy Dose per (EQ2D)						
< 70 Gy	47	(8.9)	46	(8.7)	93	(8.8)
>= 70 Gy	482	(91.1)	485	(91.3)	967	(91.2)
PD-L1 Status						
CPS<1	22	(4.2)	28	(5.3)	50	(4.7)
CPS>=1	502	(94.9)	498	(93.8)	1,000	(94.3)
Missing	5	(0.9)	5	(0.9)	10	(0.9)

EMEA = Europe, the Middle East and Africa, EBRT = External beam radiotherapy, IMRT = Intensity modulated radiotherapy, VMAT = Volumetric modulated arc therapy.
Database Cutoff Date: 09JAN2023

	Pembrolizumab + CCRT		**Placebo + CCRT**		**Total**	
	n	(%)	n	(%)	n	(%)
Participants in population	529		531		1,060	
PD-L1 Status						
CPS<10	119	(22.5)	117	(22.0)	236	(22.3)
CPS>=10	405	(76.6)	409	(77.0)	814	(76.8)
Missing	5	(0.9)	5	(0.9)	10	(0.9)

CCRT=concurrent chemoradiotherapy; PD-L1= programmed cell death ligand-1; CPS=combined positive score;
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Table 13 Summary of Lymph Node Presence by FIGO 2014 Stage at Screening (ITT Population)

	Pembrolizumab + CCRT n (%)	Placebo + CCRT n (%)	Total n (%)
Participants in population	529	531	1060
Only Positive Pelvic	**326**	**324**	**650**
IB2	22 (6.7)	21 (6.5)	43 (6.6)
IIA1	5 (1.5)	6 (1.9)	11 (1.7)
IIA2	5 (1.5)	7 (2.2)	12 (1.8)
IIB	134 (41.1)	136 (42.0)	270 (41.5)
IIIA	20 (6.1)	31 (9.6)	51 (7.8)
IIIB	112 (34.4)	94 (29.0)	206 (31.7)
IVA	28 (8.6)	29 (9.0)	57 (8.8)
Only Positive Para-Aortic	**14**	**10**	**24**
IB2	3 (21.4)	1 (10.0)	4 (16.7)
IIB	5 (35.7)	3 (30.0)	8 (33.3)
IIIA	0 (0.0)	1 (10.0)	1 (4.2)
IIIB	4 (28.6)	4 (40.0)	8 (33.3)
IVA	1 (7.1)	1 (10.0)	2 (8.3)
IVB	1 (7.1)	0 (0.0)	1 (4.2)
Both Positive Pelvic and Positive Para-Aortic	**105**	**104**	**209**
IB2	2 (1.9)	6 (5.8)	8 (3.8)
IIA1	3 (2.9)	1 (1.0)	4 (1.9)
IIA2	5 (4.8)	2 (1.9)	7 (3.3)
IIB	50 (47.6)	44 (42.3)	94 (45.0)
IIIA	5 (4.8)	3 (2.9)	8 (3.8)
IIIB	33 (31.4)	37 (35.6)	70 (33.5)
IVA	7 (6.7)	10 (9.6)	17 (8.1)
IVB	0 (0.0)	1 (1.0)	1 (0.5)
No Positive Pelvic nor Para-Aortic	**84**	**93**	**177**
IIB	1 (1.2)	0 (0.0)	1 (0.6)
IIIA	21 (25.0)	13 (14.0)	34 (19.2)
IIIB	49 (58.3)	63 (67.7)	112 (63.3)
IVA	13 (15.5)	17 (18.3)	30 (16.9)
Database Cutoff Date: 09JAN2023			

Among patients with lower stage (FIGO 2014 Stage IB2-IIB LN+), most of them were Stage IIB (about 80%). Among patients with higher stage (FIGO 2014 Stage III-IVA), Stage IIIB was the most represented (approximately 66%). All patients with FIGO 2014 Stage IB2-IIB were node positive per protocol, while for patients with higher stage about 70% had positive lymph nodes.

Drug exposure

Participants who completed total radiation treatment were 518/529 (98%) in the experimental arm, and 522/531 (98.3%) in the control arm.

Table 14 Summary of Drug Exposure (All Participants as Treated (APaT) Population) (Participants with Total Radiation Treatment Completed)

Cycles of Cisplatin	**Pembrolizumab + CCRT** (N=518) n (%)	**Placebo + CCRT** (N=522) n (%)
1	4 (0.77)	5 (0.96)
2	7 (1.35)	7 (1.34)
3	13 (2.51)	15 (2.87)
4	41 (7.92)	35 (6.7)
5	368 (71.04)	355 (68.01)
6	84 (16.22)	104 (19.92)
7	1 (0.19)	1 (0.19)
Database Cutoff Date: 09JAN2023		

CCRT= concurrent chemoradiotherapy; N= number of participants who have completed CCRT and whose data reviews have been completed by the vendor.

Table 15 Summary of Drug Exposure by CCRT (APaT Population) (Participants with Total Radiation Treatment Completed)

	Pembrolizumab + CCRT (N=518)	Placebo + CCRT (N=522)
Number of Administrations Cisplatin		
n	518	522
Mean (SD)	4.97 (0.77)	5.00 (0.81)
Median	5.00	5.00
Range	1.00 to 7.00	1.00 to 7.00
Duration on EBRT (days)		
n	518	522
Mean (SD)	39.38 (8.31)	39.11 (9.99)
Median	37.00	37.00
Range	12.00 to 139.00	2.00 to 143.00
Duration on Brachytherapy (days)		
n	505	496
Mean (SD)	12.98 (6.06)	13.04 (5.76)
Median	12.00	12.00
Range	1.00 to 74.00	1.00 to 59.00
N is the number of participants who have final review completed by QARC. n is the number of participants who have the information available. Database Cutoff Date: 09JAN2023		

Table 16 Summary of Radiation Therapy Doses (APaT Population) (Participants with Total Radiation Treatment Completed)

	Pembrolizumab + CCRT (N=518)	Placebo + CCRT (N=522)
Total Cervix Physical Dose		
n	518	522
Mean (SD)	74.30 (8.89)	73.16 (11.31)
Median [Q1, Q3]	76.02 [73.32, 78.72]	75.86 [73.00, 78.32]
Range	14.00 to 93.80	2.70 to 124.60
Total Cervix EQD2 Dose		
n	518	522
Mean (SD)	85.66 (11.66)	84.55 (15.67)
Median [Q1, Q3]	87.24 [82.78, 91.68]	87.11 [83.25, 91.61]
Range	14.00 to 118.18	2.66 to 207.01
EBRT Total Physical Dose to Cervix		
n	518	522
Mean (SD)	46.28 (4.43)	45.73 (5.59)
Median [Q1, Q3]	45.00 [45.00, 50.00]	45.00 [45.00, 50.00]
Range	14.00 to 52.00	2.70 to 54.00
EBRT EQD2 Dose to Cervix		
n	518	522
Mean (SD)	45.80 (4.56)	45.26 (5.69)
Median [Q1, Q3]	44.25 [44.25, 50.00]	44.25 [44.25, 50.00]
Range	14.00 to 52.00	2.66 to 53.10
EBRT Total Physical Dose to Lymph Nodes		
n	438	432
Mean (SD)	56.02 (3.99)	55.71 (5.97)
Median [Q1, Q3]	56.00 [55.00, 57.50]	56.00 [55.00, 57.50]
Range	16.80 to 70.00	3.45 to 70.00
EBRT EQD2 Dose to Positive Nodes		
n	438	432
Mean (SD)	56.86 (4.43)	56.56 (6.32)
Median [Q1, Q3]	55.92 [55.92, 58.94]	56.00 [55.92, 58.94]
Range	17.36 to 71.94	3.54 to 71.94
Number of EBRT fractions (Cervix and Lymph Nodes)		
n	518	522

	Pembrolizumab + CCRT (N=518)	Placebo + CCRT (N=522)
Mean (SD)	25.85 (2.15)	25.63 (2.89)
Median [Q1, Q3]	25.00 [25.00, 27.00]	25.00 [25.00, 25.00]
Range	7.00 to 35.00	2.00 to 35.00
Brachytherapy HDR Physical Dose/Fraction		
n	489	490
Mean (SD)	6.94 (1.10)	7.04 (1.11)
Median [Q1, Q3]	7.00 [6.19, 7.58]	7.04 [6.36, 7.63]
Range	0.08 to 9.93	3.06 to 14.92
Total Brachytherapy HDR Physical Dose		
n	489	490
Mean (SD)	28.61 (4.89)	28.92 (4.89)
Median [Q1, Q3]	29.05 [26.84, 31.00]	28.96 [27.12, 31.16]
Range	0.32 to 45.85	6.78 to 74.60
Brachytherapy HDR EQD2 Dose		
n	490	490
Mean (SD)	41.08 (7.73)	41.56 (9.38)
Median [Q1, Q3]	40.92 [37.00, 45.14]	40.88 [37.77, 45.04]
Range	5.90 to 73.93	9.48 to 157.01
Number Brachytherapy of Fractions		
n	504	496
Mean (SD)	4.08 (0.89)	4.13 (0.72)
Median [Q1, Q3]	4.00 [4.00, 4.00]	4.00 [4.00, 4.00]
Range	1.00 to 7.00	1.00 to 6.00
Brachytherapy PDR/LDR Physical Dose/Fraction		
n	15	4
Mean (SD)	33.79 (8.57)	36.45 (3.96)
Median [Q1, Q3]	35.20 [29.80, 39.60]	36.60 [33.30, 39.60]
Range	7.48 to 41.85	31.80 to 40.80
Total Brachytherapy PDR/LDR Physical Dose		
n	15	4
Mean (SD)	34.78 (5.67)	36.45 (3.96)
Median [Q1, Q3]	35.20 [29.80, 39.60]	36.60 [33.30, 39.60]
Range	22.44 to 41.85	31.80 to 40.80
Overall Treatment Time in Days		
n	518	522
Mean (SD)	54.08 (9.34)	53.53 (11.32)
Median [Q1, Q3]	52.00 [50.00, 57.00]	52.00 [49.00, 57.00]
Range	12.00 to 139.00	2.00 to 166.00

N is the number of participants who have final review completed by QARC.
n is the number of participants who have the information available.
Total Brachytherapy PDR/LDR physical Dose is used as it a close equivalent to Total Brachytherapy PDR/LDR EQD2 Dose.
Database Cutoff Date: 09JAN2023

Subsequent oncological therapies

Table 17 Participants With Concomitant Medications (Incidence > 0% in One or More Treatment Groups) (Subsequent Oncological Therapies) (APaT Population)

	Pembrolizumab + CCRT		Placebo + CCRT	
	n	(%)	n	(%)
Participants in population	528		530	
with one or more concomitant medications	68	(12.9)	107	(20.2)
with no concomitant medication	460	(87.1)	423	(79.8)
OTHER				
Bevacizumab	33	(6.3)	48	(9.1)
Bevacizumab Bvzr	1	(0.2)	0	(0.0)
Cemiplimab	0	(0.0)	2	(0.4)
Durvalumab	1	(0.2)	0	(0.0)
Pembrolizumab	4	(0.8)	19	(3.6)
Sintilimab	1	(0.2)	0	(0.0)
Tisotumab Vedotin	2	(0.4)	1	(0.2)
Zimberelimab	0	(0.0)	1	(0.2)
Antiinfectives For Systemic Use				
Vaccines	**1**	**(0.2)**	**0**	**(0.0)**
Cancer Vaccines	1	(0.2)	0	(0.0)
Antineoplastic And Immunomodulating Agents				
Antineoplastic Agents	**65**	**(12.3)**	**105**	**(19.8)**
Capecitabine	1	(0.2)	1	(0.2)
Carboplatin	45	(8.5)	78	(14.7)
Catequentinib	1	(0.2)	0	(0.0)
Catequentinib Hydrochloride	0	(0.0)	1	(0.2)
Cisplatin	19	(3.6)	24	(4.5)
Cyclophosphamide	0	(0.0)	1	(0.2)
Docetaxel	1	(0.2)	1	(0.2)
Doxorubicin	2	(0.4)	1	(0.2)
Etoposide	1	(0.2)	0	(0.0)
Gemcitabine	3	(0.6)	3	(0.6)
Gemcitabine Hydrochloride	0	(0.0)	1	(0.2)
Ifosfamide	1	(0.2)	0	(0.0)
Irinotecan	0	(0.0)	1	(0.2)
Paclitaxel	59	(11.2)	92	(17.4)
Paclitaxel Nanoparticle Albumin-Bound	1	(0.2)	8	(1.5)
Pembrolizumab;vibostolimab	0	(0.0)	1	(0.2)
Pemetrexed Disodium	2	(0.4)	0	(0.0)
Pemetrexed Disodium Hemipentahydrate	0	(0.0)	1	(0.2)
Topotecan	3	(0.6)	1	(0.2)
Topotecan Hydrochloride	0	(0.0)	3	(0.6)
Vincristine	0	(0.0)	1	(0.2)
Endocrine Therapy	**1**	**(0.2)**	**0**	**(0.0)**
Anastrozole	1	(0.2)	0	(0.0)
Immunostimulants	**1**	**(0.2)**	**0**	**(0.0)**
Cancer Vaccines	1	(0.2)	0	(0.0)
Cardiovascular System				
Cardiac Therapy	**59**	**(11.2)**	**92**	**(17.4)**
Paclitaxel	59	(11.2)	92	(17.4)

	Pembrolizumab + CCRT		Placebo + CCRT	
	n	(%)	n	(%)
Musculo-Skeletal System				
Antiinflammatory And Antirheumatic Products	**0**	**(0.0)**	**1**	**(0.2)**
Boswellia Sacra;commiphora Myrrha Resin;cow Bezoar;musk	0	(0.0)	1	(0.2)
Drugs For Treatment Of Bone Diseases	**1**	**(0.2)**	**1**	**(0.2)**
Denosumab	1	(0.2)	0	(0.0)
Zoledronic Acid	0	(0.0)	1	(0.2)
Sensory Organs				
Ophthalmologicals	**33**	**(6.3)**	**48**	**(9.1)**
Bevacizumab	33	(6.3)	48	(9.1)
Various				
Investigational Drug	**0**	**(0.0)**	**2**	**(0.4)**
Pembrolizumab;vibostolimab	0	(0.0)	1	(0.2)
Zimberelimab	0	(0.0)	1	(0.2)
Unspecified Herbal And Traditional Medicine	**0**	**(0.0)**	**1**	**(0.2)**
Boswellia Sacra;commiphora Myrrha Resin;cow Bezoar;musk	0	(0.0)	1	(0.2)

Every participant is counted a single time for each applicable specific concomitant medication. A participant with multiple concomitant medications within a medication category is counted a single time for that category. Each specific concomitant medication is listed under all relevant medication classes based on the medication's generic name, regardless of route of administration or reason for use. A medication that is not mapped to a second level therapeutic subgroup is classified under Other.

Database Cutoff Date: 09JAN2023

Numbers analysed

Efficacy analyses were performed using the ITT population, which included all 1060 randomized participants (529 vs 531 in the experimental vs the control arm, respectively).

The analysis population for ORR based on investigator assessment consisted of all randomly assigned participants with measurable disease (521 vs 522 in the experimental vs the control arm, respectively).

PRO analyses were based on the PRO FAS population, defined as participants who had at least 1 PRO assessment available and had received at least 1 dose of study intervention.

Outcomes and estimation

The efficacy analyses were based on IA1 (DCO: 09 January 2023), which was the IA to evaluate PFS and OS in the ITT population in the primary analysis. The analysis was performed with a median duration of follow-up of 17 months (range: 0.9 to 31 months) in the overall population. PFS results were based on 269 events (88.5% information fraction). Statistical significance was reached for PFS at IA1.

Updated results from the pre-planned IA2 (DCO: 08 January 2024) have been provided during the procedure, with an additional 10.5 months of follow-up since IA1 (IA2 median follow-up 27.5 months, range 0.9 to 43 months). IA2 corresponded to final analysis for PFS and interim analysis 2 for OS. Since PFS was statistically significant at IA1, this was not statistically tested at IA2, and nominal p-value was provided. At IA2, OS reached statistical significance. Results from IA2 are presented below after IA1.

RESULTS FROM INTERIM ANALYSIS 1

Table 18 Summary of Primary Efficacy Results for KEYNOTE-A18 (ITT Population)

	Pembrolizumab + Chemoradiotherapy (N=529)	Placebo + Chemoradiotherapy (N=531)
PFS by Investigator Assessment per RECIST 1.1 or by Histopathologic Confirmation		
N events (%)	115 (21.7)	154 (29)
Median PFS[a], months (95% CI)	NR (NR, NR)	NR (NR, NR)
HR (95% CI)[b] *p*-value[c]	0.70 (0.55, 0.89) 0.0020	
PFS Rate by Investigator Assessment per RECIST 1.1 or by Histopathologic Confirmation		
12 months (%) (95% CI)	78.2 (73.9, 81.9)	72.2 (67.7, 76.3)
24 months (%) (95% CI)	67.8 (61.8, 73.0)	57.3 (51.2, 62.9)
OS[a]		
N events (%)	44 (8.3)	59 (11.1)
Median OS, months (95% CI)	NR (NR, NR)	NR (NR, NR)
HR (95% CI)[b] *p*-value[c]	0.73 (0.49, 1.07) 0.0541	
Rate at month 12 (%) (95% CI)	94.4 (91.8, 96.2)	93.7 (91.0, 95.6)
Rate at month 24 (%) (95% CI)	87.2 (82.4, 90.8)	80.8 (74.8, 85.5)

CI=confidence interval; HR=hazard ratio; NR=not reached; OS=overall survival PFS=progression-free survival; RECIST 1.1=Response Evaluation Criteria in Solid Tumors version 1.1; sSAP=supplemental statistical analysis plan.

[a] From product-limit (Kaplan-Meier) method for censored data.

[b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by planned type of EBRT (IMRT or VMAT vs non-IMRT and non-VMAT), stage at screening (FIGO [2014] IB2-IIB vs III-IVA) and planned total radiotherapy dose (<70 Gy vs >=70 Gy) with small strata collapsed as prespecified in the sSAP.

[c] One-sided *p*-value based on log-rank test stratified by planned type of EBRT (IMRT or VMAT vs non-IMRT and non-VMAT), Stage at screening (FIGO [2014] IB2-IIB vs III-IVA) and planned total radiotherapy dose (<70 Gy vs >=70 Gy) with small strata collapsed as prespecified in the sSAP.

Database Cutoff Date: 09-JAN-2023

Primary endpoint: PFS by investigator

Table 19 Analysis of Progression-Free Survival (Primary Censoring Rule) Based on Investigator Assessment (ITT Population)

	Pembrolizumab + CCRT (N=529)	Placebo + CCRT (N=531)
Number of Events (%)	115 (21.7)	154 (29.0)
DEATH	13 (2.5)	12 (2.3)
DOCUMENTED PROGRESSION	102 (19.3)	142 (26.7)
Kaplan-Meier Estimates (months)[a]		
Median (95% CI)	NR (NR, NR)	NR (NR, NR)
[Q1, Q3]	[15.2, NR]	[10.1, NR]
Person-months	6576.7	6241.1
Event Rate / 100 Person-months	1.7	2.5
vs Placebo + CCRT		
Hazard Ratio (95% CI)[b]	0.70 (0.55, 0.89)	
p-value[c]	0.0020	
PFS Rate at month 6 (%) (95% CI)	92.0 (89.1, 94.2)	87.3 (83.9, 90.1)
PFS Rate at month 12 (%) (95% CI)	78.2 (73.9, 81.9)	72.2 (67.7, 76.3)
PFS Rate at month 18 (%) (95% CI)	73.6 (68.9, 77.7)	64.3 (59.1, 69.0)
PFS Rate at month 24 (%) (95% CI)	67.8 (61.8, 73.0)	57.3 (51.2, 62.9)

[a] From product-limit (Kaplan-Meier) method for censored data.

[b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by planned type of EBRT (IMRT or VMAT vs non-IMRT and non-VMAT), Stage at screening (FIGO [2014] IB2-IIB vs III-IVA), and Planned total radiotherapy dose (<70 Gy vs >=70 Gy) with small strata collapsed as pre-specified in the sSAP.

[c] One-sided p-value based on log-rank test stratified by planned type of EBRT (IMRT or VMAT vs non-IMRT and non-VMAT), Stage at screening (FIGO [2014] IB2-IIB vs III-IVA), and Planned total radiotherapy dose (<70 Gy vs >=70 Gy) with small strata collapsed as pre-specified in the sSAP.

NR = Not reached.

Progression-free survival based on investigator assessment per RECIST 1.1 or by histopathologic confirmation of suspected disease progression (in the absence of radiographic disease progression per RECIST 1.1)

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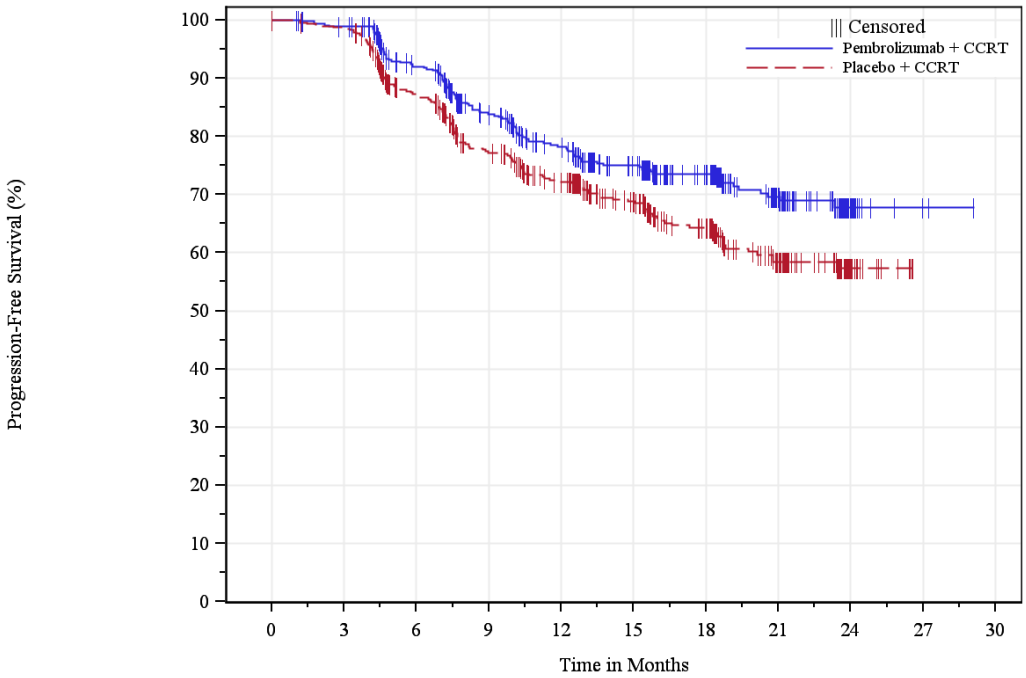
Figure 4 Kaplan-Meier Estimates of Progression-Free Survival (Primary Censoring Rule) Based on Investigator Assessment (ITT Population)



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Sensitivity analyses of PFS per RECIST 1.1 by investigator assessment or per histopathologic confirmation of suspected disease progression, or death, were conducted. For Sensitivity Analysis 1, participants who did not experience progressive disease or death before an interruption event (e.g. starting new anticancer therapy, consecutive missed disease assessment) were censored at the last disease assessment before that, while they were considered as progressed at the interruption event in Sensitivity Analysis 2.

- The PFS HR for Sensitivity Analysis 1 was 0.69 (95% CI: 0.54, 0.89)
- The PFS HR for Sensitivity Analysis 2 was 0.89 (95% CI: 0.73, 1.10).

Primary endpoint: Overall Survival

Table 20 Analysis of Overall Survival (ITT Population)

	Pembrolizumab + CCRT (N=529)	Placebo + CCRT (N=531)
Number of Events (%)	44 (8.3)	59 (11.1)
Kaplan-Meier Estimates (months)[a]		
Median (95% CI)	NR (NR, NR)	NR (NR, NR)
[Q1, Q3]	[NR, NR]	[NR, NR]
Person-months	8127.7	7968.6
Event Rate / 100 Person-months	0.5	0.7
vs Placebo + CCRT		
Hazard Ratio (95% CI)[b]	0.73 (0.49, 1.07)	
p-value[c]	0.0541	
OS Rate at month 6 (%) (95% CI)	99.4 (98.0, 99.8)	97.5 (95.7, 98.6)
OS Rate at month 12 (%) (95% CI)	94.4 (91.8, 96.2)	93.7 (91.0, 95.6)
OS Rate at month 18 (%) (95% CI)	89.6 (85.9, 92.4)	88.0 (84.1, 91.0)
OS Rate at month 24 (%) (95% CI)	87.2 (82.4, 90.8)	80.8 (74.8, 85.5)
OS Rate at month 36 (%) (95% CI)	NR (NR, NR)	NR (NR, NR)

[a] From product-limit (Kaplan-Meier) method for censored data.

[b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by planned type of EBRT (IMRT or VMAT vs non-IMRT and non-VMAT), Stage at screening (FIGO [2014] IB2-IIB vs III-IVA), and Planned total radiotherapy dose (<70 Gy vs >=70 Gy) with small strata collapsed as pre-specified in the sSAP.

[c] One-sided p-value based on log-rank test stratified by planned type of EBRT (IMRT or VMAT vs non-IMRT and non-VMAT), Stage at screening (FIGO [2014] IB2-IIB vs III-IVA), and Planned total radiotherapy dose (<70 Gy vs >=70 Gy) with small strata collapsed as pre-specified in the sSAP.

NR = Not reached.

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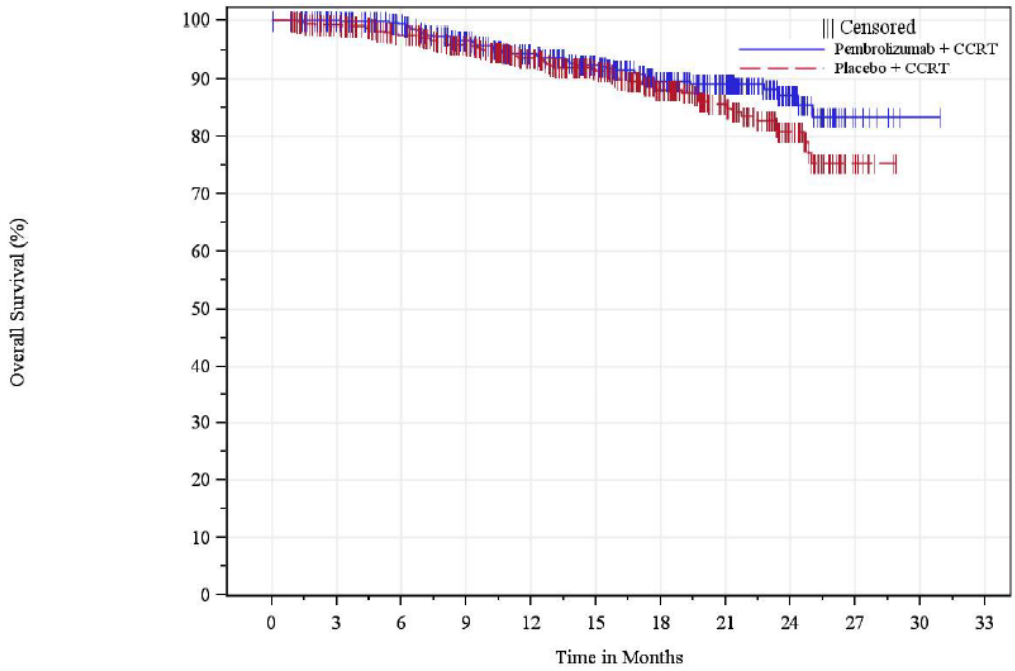
Figure 5 Kaplan-Meier Estimates of Overall Survival (ITT Population)



At Risk

Pembrolizumab + CCRT	529	496	456	405	351	294	223	151	67	10	1	0
Placebo + CCRT	531	498	449	402	339	278	214	139	62	12	0	0

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Secondary endpoint: PFS per RECIST by BICR

Table 21 Analysis of Progression-Free Survival (Primary Censoring Rule) Based on BICR per RECIST 1.1 (ITT Population)

	Pembrolizumab + CCRT (N=529)	Placebo + CCRT (N=531)
Number of Events (%)	91 (17.2)	114 (21.5)
DEATH	21 (4.0)	28 (5.3)
DOCUMENTED PROGRESSION	70 (13.2)	86 (16.2)
Kaplan-Meier Estimates (months)[a]		
Median (95% CI)	NR (25.0, NR)	NR (24.8, NR)
[Q1, Q3]	[22.8, NR]	[15.6, NR]
Person-months	6668.5	6267.7
Event Rate / 100 Person-months	1.4	1.8
vs Placebo + CCRT		
Hazard Ratio (95% CI)[b]	0.76 (0.58, 1.00)	
p-value[c]	0.0259	
PFS Rate at month 6 (%) (95% CI)	93.6 (90.9, 95.5)	90.7 (87.6, 93.1)
PFS Rate at month 12 (%) (95% CI)	83.4 (79.4, 86.7)	79.8 (75.6, 83.4)
PFS Rate at month 18 (%) (95% CI)	79.3 (74.7, 83.1)	73.0 (68.0, 77.3)
PFS Rate at month 24 (%) (95% CI)	71.1 (63.3, 77.5)	65.6 (58.9, 71.4)

[a] From product-limit (Kaplan-Meier) method for censored data.

[b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by planned type of EBRT (IMRT or VMAT vs non-IMRT and non-VMAT), Stage at screening (FIGO [2014] IB2-IIB vs III-IVA), and Planned total radiotherapy dose (<70 Gy vs >=70 Gy) with small strata collapsed as pre-specified in the sSAP.

[c] One-sided p-value based on log-rank test stratified by planned type of EBRT (IMRT or VMAT vs non-IMRT and non-VMAT), Stage at screening (FIGO [2014] IB2-IIB vs III-IVA), and Planned total radiotherapy dose (<70 Gy vs >=70 Gy) with small strata collapsed as pre-specified in the sSAP.

NR = Not reached.

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Table 22 Concordance of Progression-Free Survival (Investigator vs. BICR) (Primary Censoring Rule) (ITT Population)

	Pembrolizumab + CCRT	Placebo + CCRT	Total
Number of Subjects in Population	529	531	1060
Investigator Assessment - PFS events	115	154	269
BICR Agreed	84 (73.0%)	107 (69.5%)	191 (71.0%)
BICR and Investigator agreed on time	48 (41.7%)	67 (43.5%)	115 (42.8%)
BICR has earlier time	18 (15.7%)	21 (13.6%)	39 (14.5%)
BICR has later time	18 (15.7%)	19 (12.3%)	37 (13.8%)
BICR Disagreed	31 (27.0%)	47 (30.5%)	78 (29.0%)
Investigator Assessment - PFS censored	414	377	791
BICR Agreed	407 (98.3%)	370 (98.1%)	777 (98.2%)
BICR Disagreed	7 (1.7 %)	7 (1.9 %)	14 (1.8 %)

CCRT= concurrent chemoradiotherapy; BICR= Blinded Independent Central Review assessment per RECIST 1.; PFS= progression free survival;
Investigator assessment per RECIST 1.1 or by histopathologic confirmation of suspected disease progression (in the absence of radiographic disease progression per RECIST 1.1)
Database Cutoff Date: 09JAN2023

Secondary endpoint: Complete Response Rate at 12 Weeks and Objective Response

Table 23 Summary of Objective Response at 12 Weeks after Completion of CCRT Based on Investigator Assessment per RECIST 1.1 (Participants with Measurable Disease at Baseline)

	Pembrolizumab + CCRT			Placebo + CCRT		
	n	(%)	(95% CI)[a]	n	(%)	(95% CI)[a]
Number of Participants in Population	521			522		
Complete Response (CR)	169	(32.4)	(28.4, 36.6)	158	(30.3)	(26.4, 34.4)
Partial Response (PR)	195	(37.4)	(33.3, 41.7)	177	(33.9)	(29.9, 38.1)
Objective Response (CR+PR)	**364**	**(69.9)**	**(65.7, 73.8)**	**335**	**(64.2)**	**(59.9, 68.3)**
Stable Disease (SD)	12	(2.3)	(1.2, 4.0)	18	(3.4)	(2.1, 5.4)
Disease Control (CR+PR+SD)	**376**	**(72.2)**	**(68.1, 76.0)**	**353**	**(67.6)**	**(63.4, 71.6)**
Progressive Disease (PD)	26	(5.0)	(3.3, 7.2)	38	(7.3)	(5.2, 9.9)
Not Evaluable (NE)	3	(0.6)	(0.1, 1.7)	6	(1.1)	(0.4, 2.5)
No Assessment (NA)	116	(22.3)	(18.8, 26.1)	125	(23.9)	(20.3, 27.8)

[a] Based on binomial exact confidence interval method.
Investigator assessed responses per RECIST 1.1 are included in this table.
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Table 24 Summary of Best Objective Response Based on Investigator Assessment per RECIST 1.1 (Participants with Measurable Disease at Baseline)

	Pembrolizumab + CCRT			Placebo + CCRT		
	n	(%)	(95% CI)[a]	n	(%)	(95% CI)[a]
Number of Participants in Population	521			522		
Complete Response (CR)	264	(50.7)	(46.3, 55.0)	254	(48.7)	(44.3, 53.0)
Partial Response (PR)	149	(28.6)	(24.8, 32.7)	142	(27.2)	(23.4, 31.2)
Objective Response (CR+PR)	**413**	**(79.3)**	**(75.5, 82.7)**	**396**	**(75.9)**	**(72.0, 79.5)**
Stable Disease (SD)	10	(1.9)	(0.9, 3.5)	11	(2.1)	(1.1, 3.7)
Disease Control (CR+PR+SD)	**423**	**(81.2)**	**(77.6, 84.5)**	**407**	**(78.0)**	**(74.2, 81.5)**
Progressive Disease (PD)	33	(6.3)	(4.4, 8.8)	48	(9.2)	(6.9, 12.0)
Not Evaluable (NE)	1	(0.2)	(0.0, 1.1)	1	(0.2)	(0.0, 1.1)
No Assessment (NA)	64	(12.3)	(9.6, 15.4)	66	(12.6)	(9.9, 15.8)

[a] Based on binomial exact confidence interval method.
Investigator assessed responses per RECIST 1.1 are included in this table.
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Tumour responses results by BICR per RECIST 1.1 in patients with measurable disease were the following:

- CR rate at 12 weeks after completion of CCRT: 39% vs 37.6%
- ORR at 12 weeks after completion of CCRT: 71.7% vs 68.4%
- Best CR: 69% vs 67.1%
- Best ORR: 81.6% vs 79.2%.

Secondary endpoint: Progression free survival 2 (PFS2)

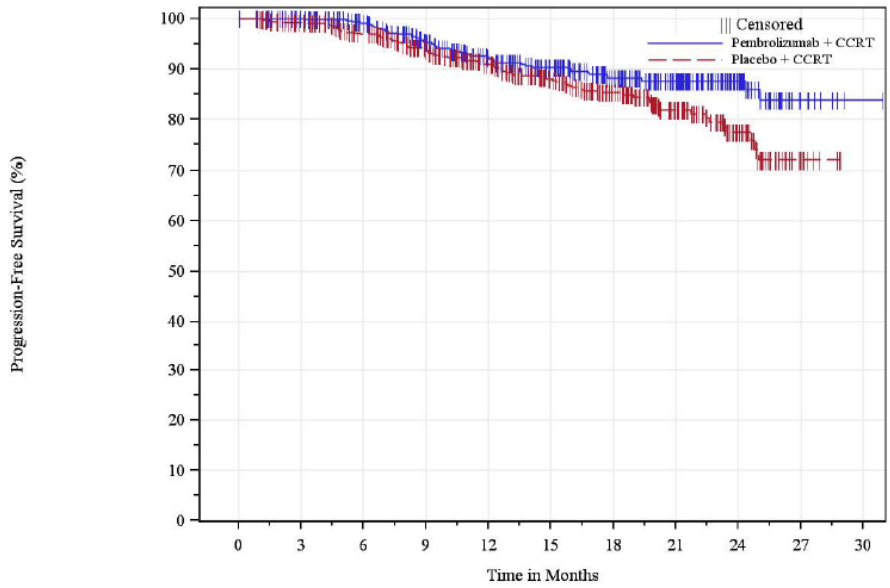
PFS2 was defined as the time from the date of randomization until disease progression on next-line treatment or death.

Table 25 Analysis of Progression-Free Survival After Next-line Treatment (Progression-Free Survival 2) Based on Investigator Assessment (ITT Population)

	Pembrolizumab + CCRT (N=529)	Placebo + CCRT (N=531)
Number of Events (%)	49 (9.3)	73 (13.7)
DEATH	32 (6.0)	45 (8.5)
PROGRESSION AFTER NEXT-LINE THERAPY	17 (3.2)	28 (5.3)
Kaplan-Meier Estimates (months)[a]		
Median (95% CI)	NR (NR, NR)	NR (NR, NR)
[Q1, Q3]	[NR, NR]	[24.8, NR]
Person-months	8052.7	7853.1
Event Rate / 100 Person-months	0.6	0.9
vs Placebo + CCRT		
Hazard Ratio (95% CI)[b]	0.65 (0.45, 0.94)	
p-value[c]	0.0097	

[a] From product-limit (Kaplan-Meier) method for censored data.
[b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by planned type of EBRT (IMRT or VMAT vs non-IMRT and non-VMAT), Stage at screening (FIGO [2014] IB2-IIB vs III-IVA), and Planned total radiotherapy dose (<70 Gy vs >=70 Gy) with small strata collapsed as pre-specified in the sSAP.
[c] One-sided p-value based on log-rank test stratified by planned type of EBRT (IMRT or VMAT vs non-IMRT and non-VMAT), Stage at screening (FIGO [2014] IB2-IIB vs III-IVA), and Planned total radiotherapy dose (<70 Gy vs >=70 Gy) with small strata collapsed as pre-specified in the sSAP.
NR = Not reached.
Database Cutoff Date: 09JAN2023

Figure 6 Kaplan-Meier Estimates of Progression-Free Survival After Next-line Treatment (Progression-Free Survival 2) Based on Investigator Assessment (ITT Population)



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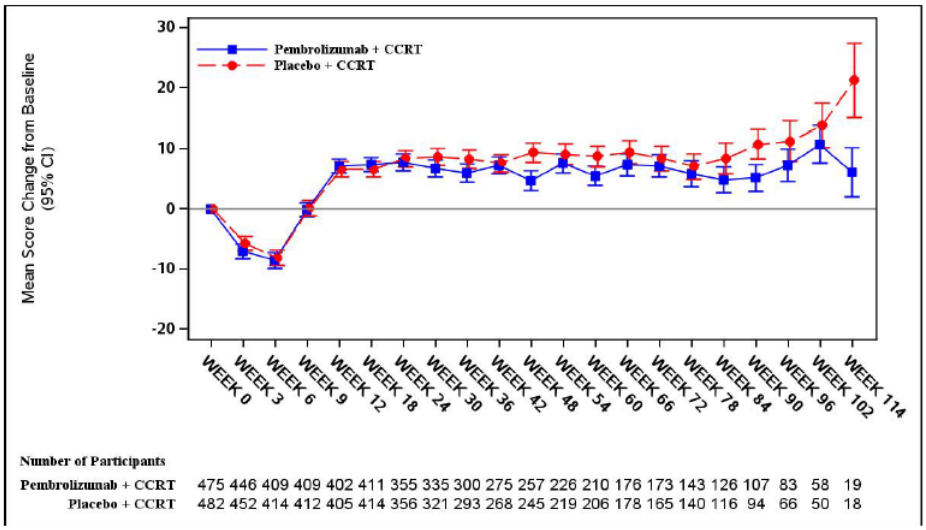
Secondary endpoint: Patient-reported outcomes

EQ-5D-5L, EORTC QLQ-C30 and EORTC QLQ-CX24 were the used instruments to assess PRO.

Completion rates of all questionnaires were similar at baseline for both treatment groups (around 95%) and remained >60% at Week 36. Compliance rates were similar at baseline in both treatment groups and remained high at Week 36 (>95%).

The analyses of EORTC QLQ-C30, global health status/QoL and physical functioning, showed no clinically meaningful differences between participants in the two treatment groups. Both treatment arms initially had decrease in global health status/QoL scores at Weeks 3 and 6, then improved relative to baseline by Week 12 and all subsequent weeks.

Figure 7 Line Plot of Empirical Mean Change from Baseline and 95% CI for the EORTC QLQ-C30 Global Health Status/QoL Over Time by Treatment Group (PRO FAS Population)



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EQ-5D-5L analyses showed no clinically meaningful differences between participants treated in the two arms.

Analyses of the domains of the EORTC QLQ-CX24 cervical symptom score (symptom experience, lymphoedema, menopausal symptoms, peripheral neuropathy, and sexual worry) generally showed no meaningful differences between participants in the two arms, except for sexual worry, where LS mean change from baseline was higher at Week 36 (indicating worsening) in the pembrolizumab plus chemoradiotherapy group.

Exploratory endpoint: duration of response

DOR per RECIST 1.1 by Investigator Assessment:

- In participants with an objective response, median TTR was similar in the two arms (4.6 months).
- Median DOR was not reached in either treatment group. By the KM method, 87.7% vs 85.2% and 81.4% and 77.3% of responders had a response duration of at least 6 and 12 months, respectively, in the experimental vs control arm.

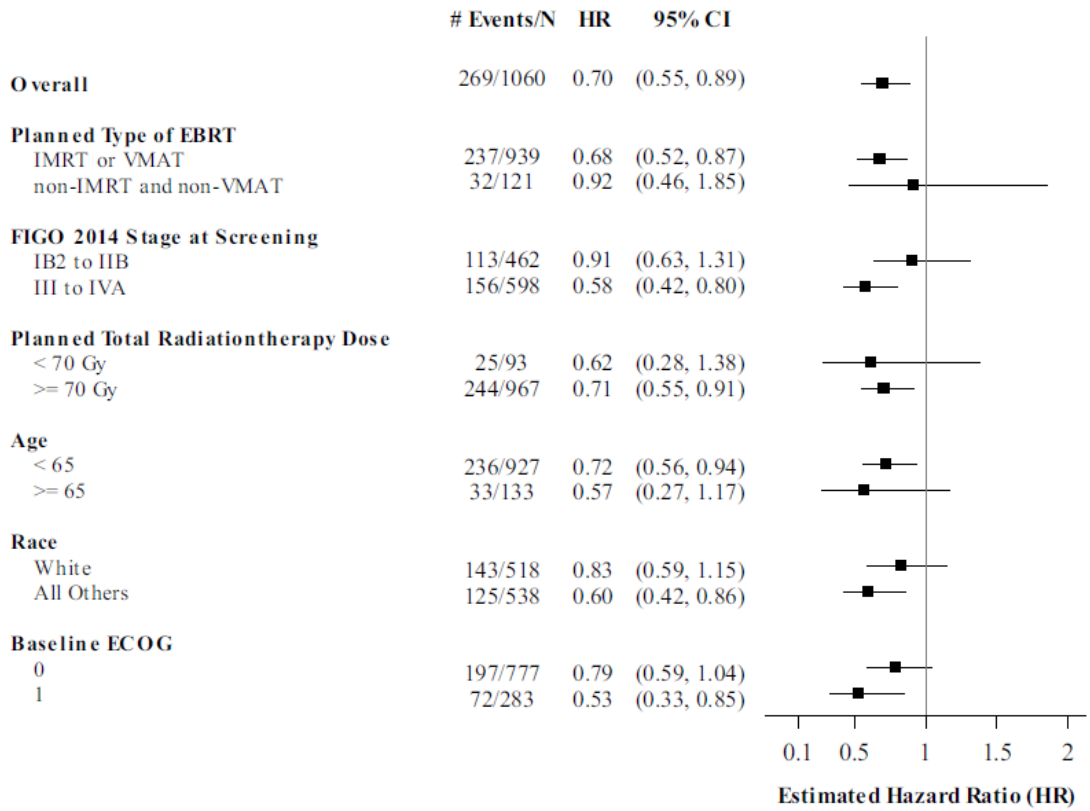
DOR in Participants with CR at 12 Weeks per RECIST 1.1 by Investigator Assessment:

- TTR in participants with a CR at 12 weeks after completion of chemoradiotherapy was similar in the two groups (4.6 months).
- Median DOR was not reached in either treatment group. By the KM method, the extended response duration was higher in the placebo plus chemoradiotherapy for ≥6 months and ≥9 months; however, the KM curve crossed at approximately 12 months in favour of pembrolizumab plus chemoradiotherapy.

Ancillary analyses

Subgroup analyses

Figure 8 Forest Plot of Progression-Free Survival Hazard Ratio by Subgroup Factors Based on Investigator Assessment (Primary Censoring Rule) (ITT Population)



For overall population, analysis is based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by planned type of EBRT (IMRT or VMAT vs non-IMRT and non-VMAT), Stage at screening (FIGO [2014] IB2-IIB vs III-IVA), and Planned total radiotherapy dose (<70 Gy vs >=70 Gy) with small strata collapsed as prespecified in the sSAP. For subgroups, analysis is based on unstratified Cox regression model with treatment as a covariate. If total number of participants in one level of a subgroup is <5%, that particular level will not be displayed.
Progression-free survival based on investigator assessment per RECIST 1.1 or by histopathologic confirmation of suspected disease progression (in the absence of radiographic disease progression per RECIST 1.1).
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Table 26 Progression-Free Survival Based on Investigator Assessment Point - Estimate and Nominal 95% Confidence Interval (Primary Censoring Rule) (ITT Population)

	Pembrolizumab + CCRT (N=529)			Placebo + CCRT (N=531)			Pembrolizumab + CCRT vs. Placebo + CCRT
	N	Number of Events	(%)	N	Number of Events	(%)	Hazard Ratio (95% CI)[a]
Overall	529	115	(21.7)	531	154	(29.0)	0.70 (0.55, 0.89)
Planned Type of EBRT							
IMRT or VMAT	469	99	(21.1)	470	138	(29.4)	0.68 (0.52, 0.87)
non-IMRT and non-VMAT	60	16	(26.7)	61	16	(26.2)	0.92 (0.46, 1.85)
FIGO 2014 Stage at Screening							
IB2 to IIB	235	54	(23.0)	227	59	(26.0)	0.91 (0.63, 1.31)
III to IVA	294	61	(20.7)	304	95	(31.3)	0.58 (0.42, 0.80)
Planned Total Radiationtherapy Dose							
< 70 Gy	47	10	(21.3)	46	15	(32.6)	0.62 (0.28, 1.38)
>= 70 Gy	482	105	(21.8)	485	139	(28.7)	0.71 (0.55, 0.91)
Age							
< 65	473	104	(22.0)	454	132	(29.1)	0.72 (0.56, 0.94)
>= 65	56	11	(19.6)	77	22	(28.6)	0.57 (0.27, 1.17)
Race							
White	254	65	(25.6)	264	78	(29.5)	0.83 (0.59, 1.15)
All Others	273	50	(18.3)	265	75	(28.3)	0.60 (0.42, 0.86)
Baseline ECOG							
0	380	86	(22.6)	397	111	(28.0)	0.79 (0.59, 1.04)
1	149	29	(19.5)	134	43	(32.1)	0.53 (0.33, 0.85)

[a] For overall population, analysis is based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by planned type of EBRT (IMRT or VMAT vs non-IMRT and non-VMAT), Stage at screening (FIGO [2014] IB2-IIB vs III-IVA), and Planned total radiotherapy dose (<70 Gy vs >=70 Gy) with small strata collapsed as pre-specified in the sSAP. For subgroups, analysis is based on unstratified Cox regression model with treatment as a covariate. If total number of participants in one level of a subgroup is <5%, that particular level will not be displayed.

Progression-free survival based on investigator assessment per RECIST 1.1 or by histopathologic confirmation of suspected disease progression (in the absence of radiographic disease progression per RECIST 1.1)

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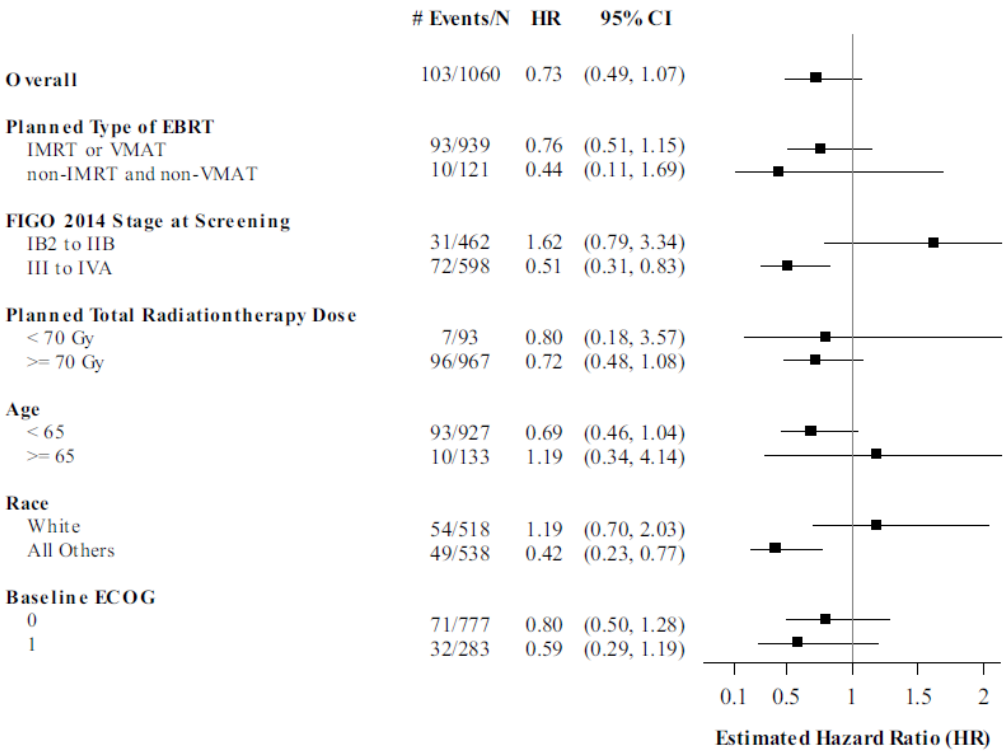
Figure 9 Forest Plot of Overall Survival Hazard Ratio by Subgroup Factors (ITT Population)



For overall population, analysis is based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by planned type of EBRT (IMRT or VMAT vs non-IMRT and non-VMAT), Stage at screening (FIGO [2014] IB2-IIB vs III-IVA), and Planned total radiotherapy dose (<70 Gy vs >=70 Gy) with small strata collapsed as pre-specified in the sSAP. For subgroups, analysis is based on unstratified Cox regression model with treatment as a covariate. If total number of participants in one level of a subgroup is <5%, that particular level will not be displayed.
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Table 27 Overall Survival by Subgroup Factors - Point Estimate and Nominal 95% Confidence Interval (ITT Population)

	Pembrolizumab + CCRT (N=529)			Placebo + CCRT (N=531)			Pembrolizumab + CCRT vs. Placebo + CCRT
	N	Number of Events	(%)	N	Number of Events	(%)	Hazard Ratio (95% CI)[a]
Overall	529	44	(8.3)	531	59	(11.1)	0.73 (0.49, 1.07)
Planned Type of EBRT							
IMRT or VMAT	469	41	(8.7)	470	52	(11.1)	0.76 (0.51, 1.15)
non-IMRT and non-VMAT	60	3	(5.0)	61	7	(11.5)	0.44 (0.11, 1.69)
FIGO 2014 Stage at Screening							
IB2 to IIB	235	19	(8.1)	227	12	(5.3)	1.62 (0.79, 3.34)
III to IVA	294	25	(8.5)	304	47	(15.5)	0.51 (0.31, 0.83)
Planned Total Radiationtherapy Dose							
< 70 Gy	47	3	(6.4)	46	4	(8.7)	0.80 (0.18, 3.57)
>= 70 Gy	482	41	(8.5)	485	55	(11.3)	0.72 (0.48, 1.08)
Age							
< 65	473	39	(8.2)	454	54	(11.9)	0.69 (0.46, 1.04)
>= 65	56	5	(8.9)	77	5	(6.5)	1.19 (0.34, 4.14)
Race							
White	254	29	(11.4)	264	25	(9.5)	1.19 (0.70, 2.03)
All Others	273	15	(5.5)	265	34	(12.8)	0.42 (0.23, 0.77)
Baseline ECOG							
0	380	31	(8.2)	397	40	(10.1)	0.80 (0.50, 1.28)
1	149	13	(8.7)	134	19	(14.2)	0.59 (0.29, 1.19)

[a] For overall population, analysis is based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by planned type of EBRT (IMRT or VMAT vs non-IMRT and non-VMAT), Stage at screening (FIGO [2014] IB2-IIB vs III-IVA), and Planned total radiotherapy dose (<70 Gy vs >=70 Gy) with small strata collapsed as pre-specified in the sSAP. For subgroups, analysis is based on unstratified Cox regression model with treatment as a covariate. If total number of participants in one level of a subgroup is <5%, that particular level will not be displayed.

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Subgroup analyses by PD-L1

CPS≥1 and CPS<1 cutoffs were used in prespecified analyses for secondary endpoints in KEYNOTE-A18. PD-L1 status was not used as a stratification factor in the study. The number of patients with CPS<1 is low, so any correlation of PD-L1 status and efficacy should be interpreted with caution.

Table 28 Progression-Free Survival Based on Investigator Assessment Point Estimate and Nominal 95% Confidence Interval (Primary Censoring Rule) (ITT Population) (By PD-L1 Status)

	Pembrolizumab + CCRT (N=529)			Placebo + CCRT (N=531)			Pembrolizumab + CCRT vs. Placebo + CCRT
	N	Number of Events	(%)	N	Number of Events	(%)	Hazard Ratio (95% CI)[a]
Overall	529	115	(21.7)	531	154	(29.0)	0.70 (0.55, 0.89)
PD-L1 Status							
CPS<1	22	4	(18.2)	28	7	(25.0)	0.61 (0.18, 2.07)
CPS>=1	502	111	(22.1)	498	145	(29.1)	0.72 (0.56, 0.92)

[a] For overall population, analysis is based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by planned type of EBRT (IMRT or VMAT vs non-IMRT and non-VMAT), Stage at screening (FIGO [2014] IB2-IIB vs III-IVA), and Planned total radiotherapy dose (<70 Gy vs >=70 Gy) with small strata collapsed as pre-specified in the sSAP. For subgroups, analysis is based on unstratified Cox regression model with treatment as a covariate.

Progression-free survival based on investigator assessment per RECIST 1.1 or by histopathologic confirmation of suspected disease progression (in the absence of radiographic disease progression per RECIST 1.1)

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Table 29 Overall Survival by Subgroup Factors Point Estimate and Nominal 95% Confidence Interval (ITT Population) (By PD-L1 Status)

	Pembrolizumab + CCRT (N=529)			Placebo + CCRT (N=531)			Pembrolizumab + CCRT vs. Placebo + CCRT
	N	Number of Events	(%)	N	Number of Events	(%)	Hazard Ratio (95% CI)[a]
Overall	529	44	(8.3)	531	59	(11.1)	0.73 (0.49, 1.07)
PD-L1 Status							
CPS<1	22	1	(4.5)	28	2	(7.1)	0.51 (0.05, 5.72)
CPS>=1	502	43	(8.6)	498	57	(11.4)	0.73 (0.49, 1.09)

[a] For overall population, analysis is based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by planned type of EBRT (IMRT or VMAT vs non-IMRT and non-VMAT), Stage at screening (FIGO [2014] IB2-IIB vs III-IVA), and Planned total radiotherapy dose (<70 Gy vs >=70 Gy) with small strata collapsed as pre-specified in the sSAP. For subgroups, analysis is based on unstratified Cox regression model with treatment as a covariate.

Database Cutoff Date: 09JAN2023

Table 30 Progression-Free Survival Based on Investigator Assessment Point Estimate and Nominal 95% Confidence Interval (Primary Censoring Rule) (ITT Population)

	Pembrolizumab + CCRT			Placebo + CCRT			Pembrolizumab + CCRT
	(N=529)			(N=531)			vs. Placebo + CCRT
	N	Number of Events	(%)	N	Number of Events	(%)	Hazard Ratio (95% CI)[a]
Overall	529	115	(21.7)	531	154	(29.0)	0.70 (0.55, 0.89)
PD-L1 Status							
CPS<10	119	26	(21.8)	117	31	(26.5)	0.68 (0.40, 1.14)
CPS>=10	405	89	(22.0)	409	121	(29.6)	0.72 (0.55, 0.94)

CCRT=concurrent chemoradiotherapy; PD-L1= programmed cell death ligand-1; CPS=combined positive score;

[a] For overall population, analysis is based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by planned type of EBRT (IMRT or VMAT vs non-IMRT and non-VMAT), Stage at screening (FIGO [2014] IB2-IIB vs III-IVA), and Planned total radiotherapy dose (<70 Gy vs >=70 Gy) with small strata collapsed as pre-specified in the sSAP. For subgroups, analysis is based on unstratified Cox regression model with treatment as a covariate.

Progression-free survival based on investigator assessment per RECIST 1.1 or by histopathologic confirmation of suspected disease progression (in the absence of radiographic disease progression per RECIST 1.1)

Database Cutoff Date: 09JAN2023

Table 31 Overall Survival by Subgroup Factors Point Estimate and Nominal 95% Confidence Interval (ITT Population)

	Pembrolizumab + CCRT			Placebo + CCRT			Pembrolizumab + CCRT
	(N=529)			(N=531)			vs. Placebo + CCRT
	N	Number of Events	(%)	N	Number of Events	(%)	Hazard Ratio (95% CI)[a]
Overall	529	44	(8.3)	531	59	(11.1)	0.73 (0.49, 1.07)
PD-L1 Status							
CPS<10	119	10	(8.4)	117	12	(10.3)	0.73 (0.32, 1.69)
CPS>=10	405	34	(8.4)	409	47	(11.5)	0.72 (0.46, 1.12)

CCRT=concurrent chemoradiotherapy; PD-L1= programmed cell death ligand-1; CPS=combined positive score;

[a] For overall population, analysis is based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by planned type of EBRT (IMRT or VMAT vs non-IMRT and non-VMAT), Stage at screening (FIGO [2014] IB2-IIB vs III-IVA), and Planned total radiotherapy dose (<70 Gy vs >=70 Gy) with small strata collapsed as pre-specified in the sSAP. For subgroups, analysis is based on unstratified Cox regression model with treatment as a covariate

Database Cutoff Date: 09JAN2023

RESULTS FROM INTERIM ANALYSIS 2

Results from IA2 are summarized below.

Table 32 Disposition of participant (ITT population) at IA2

	Pembrolizumab + CCRT		Placebo + CCRT		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	529		531		1060	
Status for Study Medication in Trial						
Started	528		530		1058	
Completed	219	(41.5)	209	(39.4)	428	(40.5)
Discontinued	223	(42.2)	236	(44.5)	459	(43.4)
Adverse Event	64	(12.1)	24	(4.5)	88	(8.3)
Clinical Progression	4	(0.8)	9	(1.7)	13	(1.2)
Excluded Medication	1	(0.2)	0	(0.0)	1	(0.1)
Lost To Follow-Up	1	(0.2)	1	(0.2)	2	(0.2)
Non-Compliance With Study Drug	3	(0.6)	1	(0.2)	4	(0.4)
Non-Study Anti-Cancer Therapy	1	(0.2)	0	(0.0)	1	(0.1)
Physician Decision	8	(1.5)	7	(1.3)	15	(1.4)
Progressive Disease	2	(0.4)	8	(1.5)	10	(0.9)
Protocol Violation	1	(0.2)	0	(0.0)	1	(0.1)
Radiographic Progression	108	(20.5)	158	(29.8)	266	(25.1)
Withdrawal By Subject	30	(5.7)	28	(5.3)	58	(5.5)
Participants Ongoing	86	(16.3)	85	(16.0)	171	(16.2)
Status for Trial						
Discontinued	91	(17.2)	119	(22.4)	210	(19.8)
Death	71	(13.4)	109	(20.5)	180	(17.0)
Lost To Follow-Up	2	(0.4)	3	(0.6)	5	(0.5)
Withdrawal By Subject	18	(3.4)	7	(1.3)	25	(2.4)
Participants Ongoing	438	(82.8)	412	(77.6)	850	(80.2)

If the overall count of participants is calculated and displayed within a section in the first row, then it is used as the denominator for the percentage calculation. Otherwise, participants in population is used as the denominator for the percentage calculation.
For the status for study medication of treatment phase, participants treated with study medication is used as the denominator for percentage calculation.
For the status for trial, participants in population is used as the denominator for percentage calculation.
CCRT: Concurrent chemoradiotherapy
Database Cutoff Date: 08JAN2024

Primary endpoint: PFS by Investigator

Only nominal p-value at IA2 was provided, as PFS was statistically significant at IA1.

Table 33 Analysis of Progression-Free Survival (Primary Censoring Rule) Based on Investigator Assessment (ITT Population)

	Pembrolizumab + CCRT (N=529)	Placebo + CCRT (N=531)
Number of Events (%)	155 (29.3)	210 (39.5)
DEATH	17 (3.2)	17 (3.2)
DOCUMENTED PROGRESSION	138 (26.1)	193 (36.3)
Kaplan-Meier Estimates (months)[a]		
Median (95% CI)	NR (NR, NR)	NR (32.0, NR)
[Q1, Q3]	[18.1, NR]	[10.4, NR]
Person-months	10786.1	9955.5
Event Rate / 100 Person-months	1.4	2.1
vs Placebo + CCRT		
Hazard Ratio (95% CI)[b]	0.68 (0.56, 0.84)	

p-value[c]	0.0002	
PFS Rate at month 6 (%) (95% CI)	91.9 (89.2, 93.9)	87.8 (84.7, 90.4)
PFS Rate at month 12 (%) (95% CI)	79.9 (76.2, 83.1)	72.9 (68.8, 76.5)
PFS Rate at month 18 (%) (95% CI)	75.0 (71.0, 78.6)	65.4 (61.1, 69.4)
PFS Rate at month 24 (%) (95% CI)	70.6 (66.3, 74.5)	58.6 (54.0, 62.9)
PFS Rate at month 30 (%) (95% CI)	67.6 (62.9, 71.9)	55.2 (50.3, 59.9)
PFS Rate at month 36 (%) (95% CI)	62.7 (56.4, 68.4)	54.5 (49.3, 59.3)

[a] From product-limit (Kaplan-Meier) method for censored data.

[b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by planned type of EBRT (IMRT or VMAT vs non-IMRT and non-VMAT), Stage at screening (FIGO [2014] IB2-IIB vs III-IVA), and Planned total radiotherapy dose (<70 Gy vs >=70 Gy) with small strata collapsed as pre-specified in the sSAP.

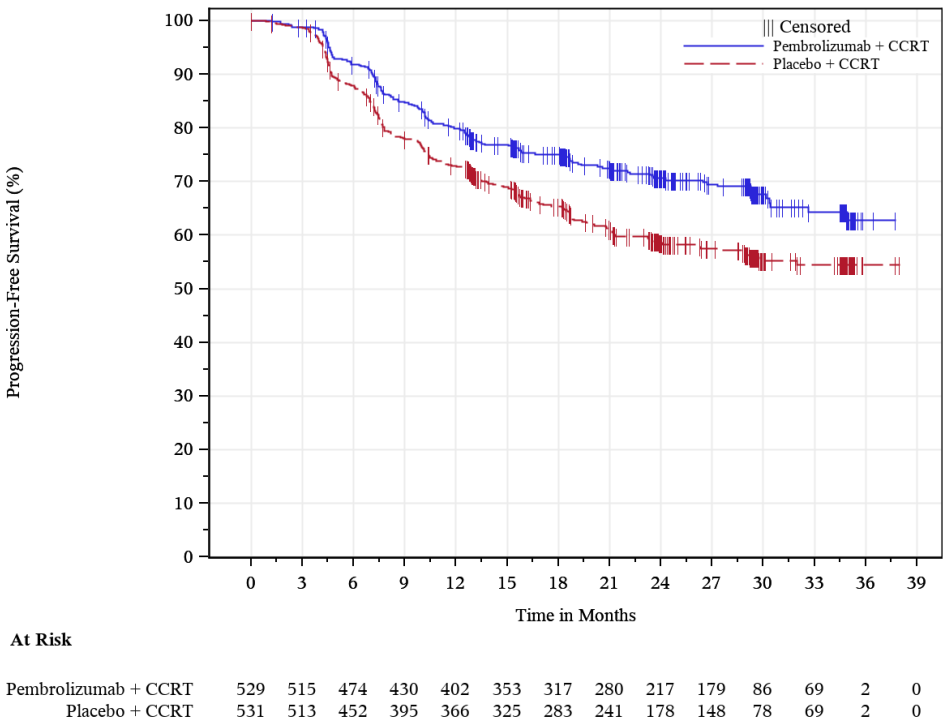
[c] One-sided p-value based on log-rank test stratified by planned type of EBRT (IMRT or VMAT vs non-IMRT and non-VMAT), Stage at screening (FIGO [2014] IB2-IIB vs III-IVA), and Planned total radiotherapy dose (<70 Gy vs >=70 Gy) with small strata collapsed as pre-specified in the sSAP.

NR = Not reached.

Progression-free survival based on investigator assessment per RECIST 1.1 or by histopathologic confirmation of suspected disease progression (in the absence of radiographic disease progression per RECIST 1.1)

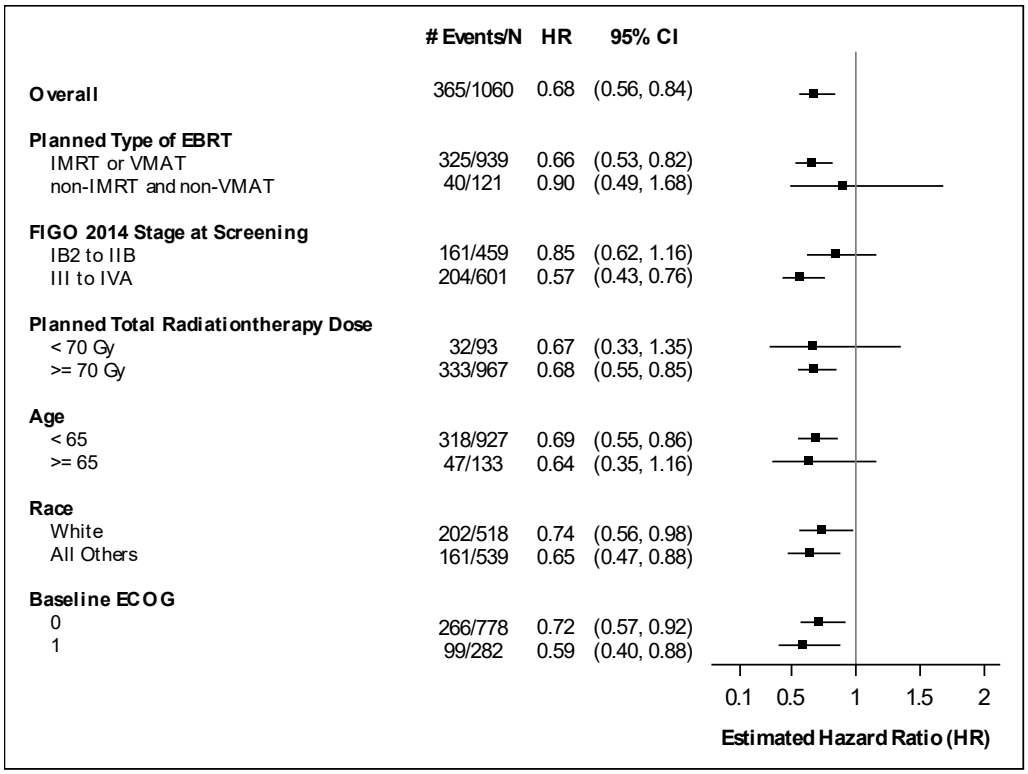
Database Cutoff Date: 08JAN2024

Figure 10 Kaplan-Meier Estimates of Progression-Free Survival (Primary Censoring Rule) Based on Investigator Assessment (ITT Population)



Database Cutoff Date: 08JAN2024

Figure 11 Forest Plot of Progression-Free Survival Hazard Ratio by Subgroup Factors Based on Investigator Assessment (Primary Censoring Rule) (ITT Population)



For overall population, analysis is based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by planned type of EBRT (IMRT or VMAT vs non-IMRT and non-VMAT), Stage at screening (FIGO [2014] IB2-IIB vs III-IVA), and Planned total radiotherapy dose (<70 Gy vs >=70 Gy) with small strata collapsed as pre -specified in the sSAP. For subgroups, analysis is based on unstratified Cox regression model with treatment as a covariate. If total number of participants in one level of a subgroup is <5%, that particular level will not be displayed.

Progression-free survival based on investigator assessment per RECIST 1.1 or by histopathologic confirmation of suspected disease progression (in the absence of radiographic disease progression per RECIST 1.1).

Database Cutoff Date: 08JAN2024

Primary endpoint: OS

OS was not statistically significant at IA1 thus was statistically tested at IA2, reaching statistical significance at this analysis (p=0.0040, p-value boundary 0.01026).

Table 34 Analysis of Overall Survival (ITT Population)

	Pembrolizumab + CCRT (N=529)	Placebo + CCRT (N=531)
Number of Events (%)	75 (14.2)	109 (20.5)
Kaplan-Meier Estimates (months)[a]		
Median (95% CI)	NR (NR, NR)	NR (NR, NR)
[Q1, Q3]	[NR, NR]	[32.0, NR]
Person-months	13763.6	13483.8
Event Rate / 100 Person-months	0.5	0.8
vs Placebo + CCRT		
Hazard Ratio (95% CI)[b]	0.67 (0.50, 0.90)	
p-value[c]	0.0040	
OS Rate at month 6 (%) (95% CI)	99.2 (98.0, 99.7)	97.7 (96.1, 98.7)

OS Rate at month 12 (%) (95% CI)	95.1 (92.8, 96.6)	93.4 (90.9, 95.2)
OS Rate at month 18 (%) (95% CI)	90.4 (87.4, 92.6)	87.9 (84.7, 90.4)
OS Rate at month 24 (%) (95% CI)	87.2 (83.9, 89.9)	82.2 (78.4, 85.4)
OS Rate at month 30 (%) (95% CI)	83.8 (79.9, 87.0)	76.6 (72.2, 80.4)
OS Rate at month 36 (%) (95% CI)	82.6 (78.4, 86.1)	74.8 (70.1, 78.8)

[a] From product-limit (Kaplan-Meier) method for censored data.

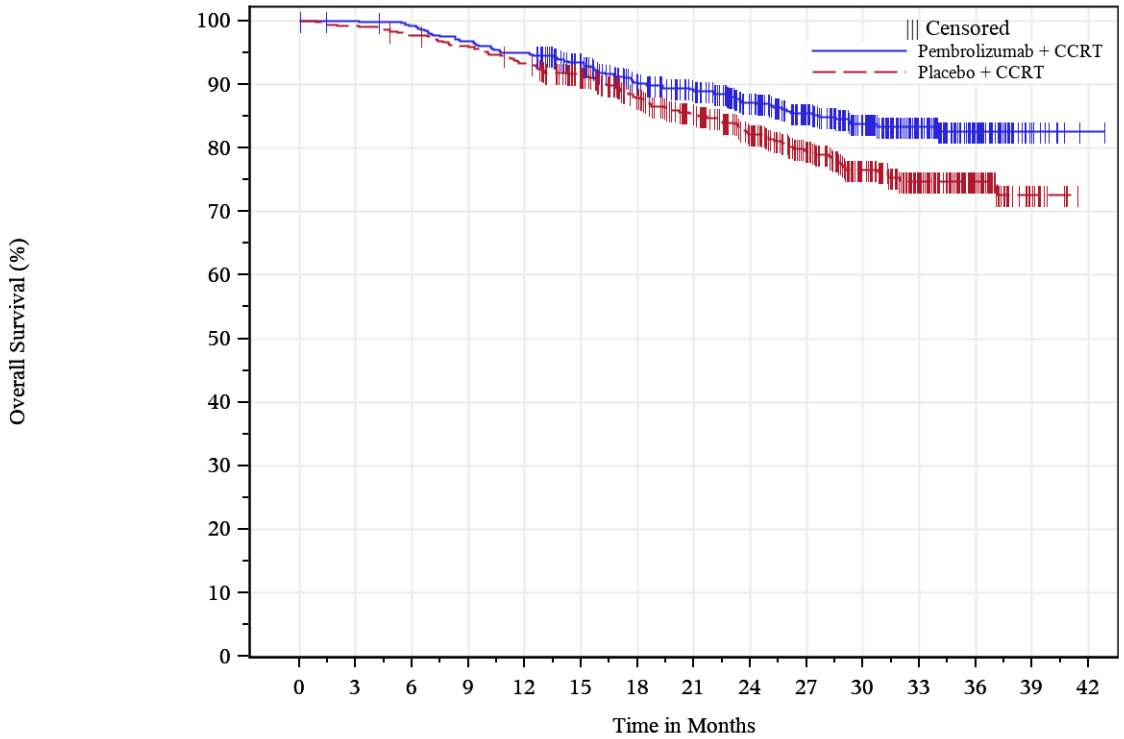
[b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by planned type of EBRT (IMRT or VMAT vs non-IMRT and non-VMAT), Stage at screening (FIGO [2014] IB2-IIB vs III-IVA), and Planned total radiotherapy dose (<70 Gy vs >=70 Gy) with small strata collapsed as pre-specified in the sSAP.

[c] One-sided p-value based on log-rank test stratified by planned type of EBRT (IMRT or VMAT vs non-IMRT and non-VMAT), Stage at screening (FIGO [2014] IB2-IIB vs III-IVA), and Planned total radiotherapy dose (<70 Gy vs >=70 Gy) with small strata collapsed as pre-specified in the sSAP.

NR = Not reached.

Database Cutoff Date: 08JAN2024

Figure 12 Kaplan-Meier Estimates of Overall Survival (ITT Population)



At Risk

Pembrolizumab + CCRT	529	527	522	509	500	463	412	374	326	273	210	136	63	11	1
Placebo + CCRT	531	527	518	508	493	455	405	366	316	259	194	125	58	12	0

Database Cutoff Date: 08JAN2024

On 22 March 2024, six weeks after the database lock date of 12 February 2024, the Sponsor was notified by one Russian site that two patients were incorrectly marked as alive in the previously locked dataset. Those two deaths had occurred before the data cut-off date for IA2 analysis (08 January 2024). One patient was in the pembrolizumab + CRT arm and one patient in the placebo + CRT arm. Both were FIGO 2014 Stage IIB at baseline. A re-analysis of the primary endpoints with the dates of death updated for these two participants was performed by the MAH for the IA2:

- OS HR had changed from 0.67 (95% CI: 0.50, 0.90), *p*=0.0040 to **0.68 (95% CI: 0.50, 0.91), *p*=0.0041**. Updated p-value boundary based on 186 OS events is 0.01069.
- For the FIGO 2014 Stage IB2 to IIB subgroup, the OS HR changed from 0.89 (95% CI: 0.55, 1.44) to **0.90 (95% CI: 0.56, 1.44)**.
- There was no impact on PFS (assessed by investigator).

Updated data at IA2 on **post-progression therapies** were provided:

Table 35 Participants With Subsequent Oncological Therapies (Incidence > 0% in One or More Treatment Groups) (Participants with Disease Progression [a])

	Pembrolizumab + CCRT		Placebo + CCRT	
	n	(%)	n	(%)
Participants in population	138		193	
with one or more subsequent therapies	91	(65.9)	139	(72.0)
with no subsequent therapy	47	(34.1)	54	(28.0)
Antineoplastic And Immunomodulating Agents				
Antineoplastic Agents	**91**	**(65.9)**	**139**	**(72.0)**
Antineoplastic Agents	0	(0.0)	1	(0.5)
Bevacizumab	43	(31.2)	64	(33.2)
Bevacizumab Bvzr	1	(0.7)	1	(0.5)
Cadonilimab	2	(1.4)	1	(0.5)
Capecitabine	2	(1.4)	1	(0.5)
Carboplatin	65	(47.1)	98	(50.8)
Catequentinib	2	(1.4)	0	(0.0)
Catequentinib Hydrochloride	0	(0.0)	1	(0.5)
Cemiplimab	1	(0.7)	8	(4.1)
Cisplatin	25	(18.1)	33	(17.1)
Cyclophosphamide	0	(0.0)	1	(0.5)
Docetaxel	1	(0.7)	0	(0.0)
Doxorubicin	2	(1.4)	1	(0.5)
Doxorubicin Hydrochloride	1	(0.7)	0	(0.0)
Durvalumab	1	(0.7)	0	(0.0)
Etoposide	1	(0.7)	0	(0.0)
Fluorouracil	1	(0.7)	0	(0.0)
Gemcitabine	6	(4.3)	10	(5.2)
Gemcitabine Hydrochloride	1	(0.7)	1	(0.5)
Ifosfamide	1	(0.7)	0	(0.0)
Irinotecan	1	(0.7)	3	(1.6)
Marsdenia Tenacissima Stem	0	(0.0)	1	(0.5)
Paclitaxel	81	(58.7)	122	(63.2)
Paclitaxel Nanoparticle Albumin-Bound	2	(1.4)	9	(4.7)
Pembrolizumab	10	(7.2)	40	(20.7)
Pembrolizumab;vibostolimab	0	(0.0)	1	(0.5)
Pemetrexed Disodium	2	(1.4)	0	(0.0)
Pemetrexed Disodium Hemipentahydrate	0	(0.0)	1	(0.5)
Pemetrexed Disodium Heptahydrate	1	(0.7)	0	(0.0)
Sintilimab	1	(0.7)	0	(0.0)
Tisotumab Vedotin	3	(2.2)	1	(0.5)
Topotecan	6	(4.3)	4	(2.1)
Topotecan Hydrochloride	0	(0.0)	3	(1.6)
Vincristine	0	(0.0)	1	(0.5)

Vinorelbine Tartrate	0	(0.0)	1	(0.5)
Zimberelimab	0	(0.0)	1	(0.5)
Immunostimulants	**1**	**(0.7)**	**1**	**(0.5)**
Cancer Vaccines	1	(0.7)	0	(0.0)
Poria Cocos	0	(0.0)	1	(0.5)

Every participant is counted a single time for each applicable specific subsequent therapy. A participant with multiple subsequent therapies within a therapy category is counted a single time for that category. Each specific subsequent therapy is listed under all relevant therapy classes based on the therapy's generic name, regardless of route of administration or reason for use.

a Participants with documented disease progression per RECIST 1.1 assessed by investigator or by histopathologic confirmation.

Database Cutoff Date: 08JAN2024

Sensitivity analyses were conducted to further characterize the impact of subsequent anti-PD-1/PD-L1 therapy on OS.

Post-progression treatment with pembrolizumab was allowed in the study per investigator's discretion and according to local standard of care. Most global approvals for pembrolizumab in combination with chemotherapy based on KEYNOTE-826 occurred in 2022, which was 2 years after the start of KEYNOTE-A18, and therefore access to pembrolizumab in first line varied across countries. Details on patients who received post-progression immunotherapy are presented below including by disease stage:

Table 36 Summary of Participants who Received Post-Progression Subsequent Immunotherapy (Participants with Disease Progression [a])

	Pembrolizumab + CCRT n (%)	Placebo + CCRT n (%)	Total n (%)
Participants in population	138	193	331
with one or more subsequent therapies	91	139	230
Who received pembrolizumab as post-progression subsequent therapy	10 (7.2)	41 (21.2)	51 (15.4)
Who received anti-PD1/PDL1 post progression subsequent therapy	15 (10.9)	51 (26.4)	66 (19.9)

[a] Participants with documented disease progression per RECIST 1.1 assessed by investigator or by histopathologic confirmation.

Database Cutoff Date: 08JAN2024

Table 37 Summary of Participants who Received Post-Progression Subsequent Immunotherapy (Participants with Disease Progression [a]) (FIGO 2014 Stage IB2 to IIB LN+ Participants)

	Pembrolizumab + CCRT n (%)	Placebo + CCRT n (%)	Total n (%)
Participants in population	68	82	150
Who received pembrolizumab as post-progression subsequent therapy	6 (8.8)	23 (28.0)	29 (19.3)
Who received anti-PD1/PDL1 post progression subsequent therapy	7 (10.3)	29 (35.4)	36 (24.0)

[a] Participants with documented disease progression per RECIST 1.1 assessed by investigator or by histopathologic confirmation.

Database Cutoff Date: 08JAN2024

Table 38 Summary of Participants who Received Post-Progression Subsequent Immunotherapy (Participants with Disease Progression [a]) (FIGO 2014 Stage III to IVA Participants)

	Pembrolizumab + CCRT n (%)	Placebo + CCRT n (%)	Total n (%)
Participants in population	70	111	181
Who received pembrolizumab as post-progression subsequent therapy	4 (5.7)	18 (16.2)	22 (12.2)
Who received anti-PD1/PDL1 post progression subsequent therapy	8 (11.4)	22 (19.8)	30 (16.6)

[a] Participants with documented disease progression per RECIST 1.1 assessed by investigator or by histopathologic confirmation.

Database Cutoff Date: 08JAN2024

Results of OS sensitivity analyses were the following:

- Rank-preserving structural failure time model: OS HR 0.66 (95% CI: 0.49, 0.90).
- 2-stage model: OS HR 0.66 (95% CI: 0.49, 0.90).
- Inverse probability of censoring weighting model: OS HR 0.72 (95% CI: 0.53, 0.99).

Table 39 Analysis of Progression-Free Survival After Next-line Treatment (Progression-Free Survival 2) Based on Investigator Assessment (ITT Population)

	Pembrolizumab + CCRT (N=529)	Placebo + CCRT (N=531)
Number of Events (%)	81 (15.3)	129 (24.3)
DEATH	52 (9.8)	74 (13.9)
PROGRESSION AFTER NEXT-LINE THERAPY	29 (5.5)	55 (10.4)
Kaplan-Meier Estimates (months)[a]		
Median (95% CI)	NR (NR, NR)	NR (NR, NR)
[Q1, Q3]	[NR, NR]	[28.2, NR]
Person-months	13585.2	13049.7
Event Rate / 100 Person-months	0.6	1.0
vs Placebo + CCRT		
Hazard Ratio (95% CI)[b]	0.60 (0.46, 0.80)	
p-value[c]	0.0002	

[a] From product-limit (Kaplan-Meier) method for censored data.

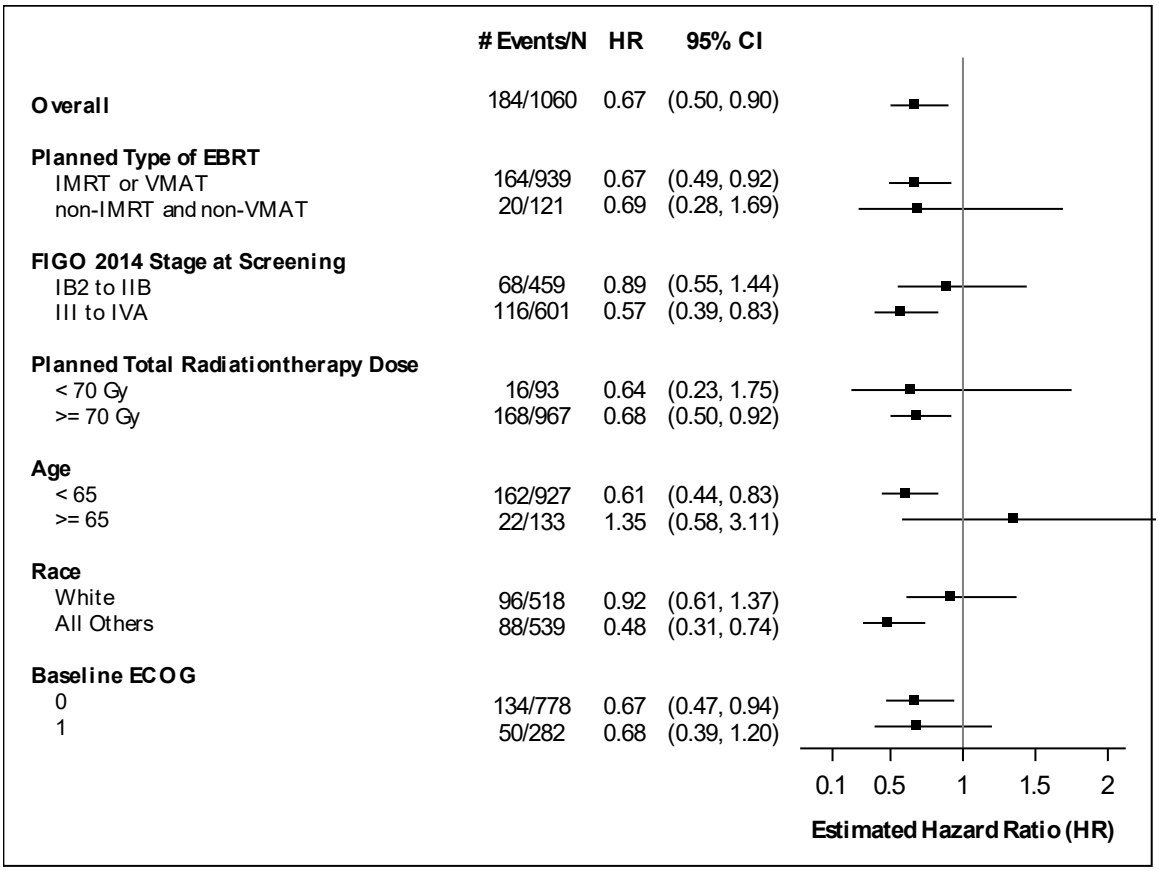
[b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by planned type of EBRT (IMRT or VMAT vs non-IMRT and non-VMAT), Stage at screening (FIGO [2014] IB2-IIB vs III-IVA), and Planned total radiotherapy dose (<70 Gy vs >=70 Gy) with small strata collapsed as pre-specified in the sSAP.

[c] One-sided p-value based on log-rank test stratified by planned type of EBRT (IMRT or VMAT vs non-IMRT and non-VMAT), Stage at screening (FIGO [2014] IB2-IIB vs III-IVA), and Planned total radiotherapy dose (<70 Gy vs >=70 Gy) with small strata collapsed as pre-specified in the sSAP.

NR = Not reached.

Database Cutoff Date: 08JAN2024

Figure 13 Forest Plot of Overall Survival Hazard Ratio by Subgroup Factors (ITT Population)



For overall population, analysis is based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by planned type of EBRT (IMRT or VMAT vs non-IMRT and non-VMAT), Stage at screening (FIGO [2014] IB2-IIB vs III-IVA), and Planned total radiotherapy dose (<70 Gy vs >=70 Gy) with small strata collapsed as pre -specified in the sSAP. For subgroups, analysis is based on unstratified Cox regression model with treatment as a covariate. If total number of participants in one level of a subgroup is <5%, that particular level will not be displayed.

Database Cutoff Date: 08JAN2024

Subgroup analyses by PD-L1

Results according to PD-L1 expression (cut-off: CPS 1) at IA2 are presented below:

Table 40 Progression-Free Survival Based on Investigator Assessment Point Estimate and Nominal 95% Confidence Interval (Primary Censoring Rule) (ITT Population) (By PD-L1 Status)

	Pembrolizumab + CCRT (N=529)			Placebo + CCRT (N=531)			Pembrolizumab + CCRT vs. Placebo + CCRT
	N	Number of Events	(%)	N	Number of Events	(%)	Hazard Ratio (95% CI)[a]
Overall	529	155	(29.3)	531	210	(39.5)	0.68 (0.56, 0.84)
PD-L1 Status							
CPS<1	22	5	(22.7)	28	9	(32.1)	0.57 (0.19, 1.71)
CPS>=1	502	150	(29.9)	498	199	(40.0)	0.69 (0.56, 0.85)

[a] For overall population, analysis is based on Cox regression model with Efron's method of tie handling

with treatment as a covariate stratified by planned type of EBRT (IMRT or VMAT vs non-IMRT and non-VMAT), Stage at screening (FIGO [2014] IB2-IIB vs III-IVA), and Planned total radiotherapy dose (<70 Gy vs >=70 Gy) with small strata collapsed as pre-specified in the sSAP. For subgroups, analysis is based on unstratified Cox regression model with treatment as a covariate.

Progression-free survival based on investigator assessment per RECIST 1.1 or by histopathologic confirmation of suspected disease progression (in the absence of radiographic disease progression per RECIST 1.1)

Database Cutoff Date: 08JAN2024

Table 41 Overall Survival by Subgroup Factors Point Estimate and Nominal 95% Confidence Interval (ITT Population) (By PD-L1 Status)

	Pembrolizumab + CCRT (N=529)			Placebo + CCRT (N=531)			Pembrolizumab + CCRT vs. Placebo + CCRT
	N	Number of Events	(%)	N	Number of Events	(%)	Hazard Ratio (95% CI)[a]
Overall	529	75	(14.2)	531	109	(20.5)	0.67 (0.50, 0.90)
PD-L1 Status							
CPS<1	22	4	(18.2)	28	4	(14.3)	1.06 (0.26, 4.29)
CPS>=1	502	71	(14.1)	498	104	(20.9)	0.66 (0.49, 0.89)

[a] For overall population, analysis is based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by planned type of EBRT (IMRT or VMAT vs non-IMRT and non-VMAT), Stage at screening (FIGO [2014] IB2-IIB vs III-IVA), and Planned total radiotherapy dose (<70 Gy vs >=70 Gy) with small strata collapsed as pre-specified in the sSAP. For subgroups, analysis is based on unstratified Cox regression model with treatment as a covariate.

Database Cutoff Date: 08JAN2024

Subgroup analyses by FIGO stage

Table 42 Analysis of Progression-Free Survival (Primary Censoring Rule) Based on Investigator Assessment (FIGO 2014 Stage IB2 to IIB LN+ Participants) (ITT Population)

	Pembrolizumab + CCRT (N=233)	Placebo + CCRT (N=226)
Number of Events (%)	76 (32.6)	85 (37.6)
DEATH	8 (3.4)	3 (1.3)
DOCUMENTED PROGRESSION	68 (29.2)	82 (36.3)
Kaplan-Meier Estimates (months)[a]		
Median (95% CI)	NR (NR, NR)	NR (28.9, NR)
[Q1, Q3]	[12.8, NR]	[13.0, NR]
Person-months	4663.9	4489.5
Event Rate / 100 Person-months	1.6	1.9
vs Placebo + CCRT		
Hazard Ratio (95% CI)[b]	0.85 (0.62, 1.16)	
p-value[c]	0.1529	
PFS Rate at month 6 (%) (95% CI)	91.8 (87.4, 94.7)	90.0 (85.2, 93.3)
PFS Rate at month 12 (%) (95% CI)	77.1 (71.1, 82.1)	76.2 (70.0, 81.3)
PFS Rate at month 18 (%) (95% CI)	71.8 (65.4, 77.3)	68.9 (62.2, 74.6)

PFS Rate at month 24 (%) (95% CI)	67.7 (60.9, 73.6)	61.0 (53.9, 67.4)
PFS Rate at month 30 (%) (95% CI)	62.7 (55.1, 69.5)	57.5 (49.9, 64.3)
PFS Rate at month 36 (%) (95% CI)	60.8 (52.4, 68.2)	57.5 (49.9, 64.3)

[a] From product-limit (Kaplan-Meier) method for censored data.

[b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate.

[c] One-sided p-value based on log-rank test.

NR = Not reached.

Progression-free survival based on investigator assessment per RECIST 1.1 or by histopathologic confirmation of suspected disease progression (in the absence of radiographic disease progression per RECIST 1.1)

Database Cutoff Date: 08JAN2024

Table 43 Analysis of Progression-Free Survival (Primary Censoring Rule) Based on Investigator Assessment (FIGO 2014 Stage III to IVA Participants) (ITT Population)

	Pembrolizumab + CCRT (N=296)	Placebo + CCRT (N=305)
Number of Events (%)	79 (26.7)	125 (41.0)
DEATH	9 (3.0)	14 (4.6)
DOCUMENTED PROGRESSION	70 (23.6)	111 (36.4)
Kaplan-Meier Estimates (months)[a]		
Median (95% CI)	NR (NR, NR)	NR (26.3, NR)
[Q1, Q3]	[20.6, NR]	[9.0, NR]
Person-months	6122.2	5466.0
Event Rate / 100 Person-months	1.3	2.3
vs Placebo + CCRT		
Hazard Ratio (95% CI)[b]	0.57 (0.43, 0.76)	
p-value[c]	<0.0001	
PFS Rate at month 6 (%) (95% CI)	92.0 (88.2, 94.6)	86.2 (81.7, 89.7)
PFS Rate at month 12 (%) (95% CI)	82.1 (77.2, 86.1)	70.4 (64.8, 75.3)
PFS Rate at month 18 (%) (95% CI)	77.6 (72.2, 82.0)	62.8 (56.9, 68.2)
PFS Rate at month 24 (%) (95% CI)	72.9 (67.1, 77.9)	56.9 (50.7, 62.6)
PFS Rate at month 30 (%) (95% CI)	71.6 (65.6, 76.8)	53.7 (47.0, 59.9)
PFS Rate at month 36 (%) (95% CI)	64.2 (54.6, 72.3)	NR (NR, NR)

[a] From product-limit (Kaplan-Meier) method for censored data.

[b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate.

[c] One-sided p-value based on log-rank test.

NR = Not reached.

Progression-free survival based on investigator assessment per RECIST 1.1 or by histopathologic confirmation of suspected disease progression (in the absence of radiographic disease progression per RECIST 1.1)

Database Cutoff Date: 08JAN2024

Table 44 Analysis of Overall Survival (FIGO 2014 Stage IB2 to IIB LN+ Participants) (ITT Population)

	Pembrolizumab + CCRT (N=233)	Placebo + CCRT (N=226)
Number of Events (%)	32 (13.7)	36 (15.9)
Kaplan-Meier Estimates (months)[a]		
Median (95% CI)	NR (NR, NR)	NR (NR, NR)
[Q1, Q3]	[NR, NR]	[NR, NR]
Person-months	6134.2	6104.4
Event Rate / 100 Person-months	0.5	0.6
vs Placebo + CCRT		
Hazard Ratio (95% CI)[b]	0.89 (0.55, 1.44)	
p-value[c]	0.3213	
OS Rate at month 6 (%) (95% CI)	99.1 (96.6, 99.8)	99.6 (96.9, 99.9)
OS Rate at month 12 (%) (95% CI)	96.1 (92.7, 98.0)	97.3 (94.2, 98.8)
OS Rate at month 18 (%) (95% CI)	91.0 (86.4, 94.1)	93.1 (88.9, 95.8)
OS Rate at month 24 (%) (95% CI)	87.7 (82.3, 91.5)	87.8 (82.4, 91.6)
OS Rate at month 30 (%) (95% CI)	83.1 (76.7, 87.9)	82.1 (75.6, 87.1)
OS Rate at month 36 (%) (95% CI)	83.1 (76.7, 87.9)	80.0 (72.9, 85.5)

[a] From product-limit (Kaplan-Meier) method for censored data.

[b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate.

[c] One-sided p-value based on log-rank test.

NR = Not reached.

Database Cutoff Date: 08JAN2024

Table 45 Analysis of Overall Survival (FIGO 2014 Stage III to IVA Participants) (ITT Population)

	Pembrolizumab + CCRT (N=296)	Placebo + CCRT (N=305)
Number of Events (%)	43 (14.5)	73 (23.9)
Kaplan-Meier Estimates (months)[a]		
Median (95% CI)	NR (NR, NR)	NR (NR, NR)
[Q1, Q3]	[NR, NR]	[26.9, NR]
Person-months	7629.5	7379.3
Event Rate / 100 Person-months	0.6	1.0
vs Placebo + CCRT		
Hazard Ratio (95% CI)[b]	0.57 (0.39, 0.83)	
p-value[c]	0.0016	
OS Rate at month 6 (%) (95% CI)	99.3 (97.3, 99.8)	96.4 (93.6, 98.0)
OS Rate at month 12 (%) (95% CI)	94.2 (90.8, 96.4)	90.4 (86.5, 93.3)
OS Rate at month 18 (%) (95% CI)	89.8 (85.7, 92.8)	83.9 (79.2, 87.7)
OS Rate at month 24 (%) (95% CI)	86.8 (82.2, 90.4)	78.0 (72.5, 82.5)
OS Rate at month 30 (%) (95% CI)	84.3 (79.2, 88.2)	72.4 (66.2, 77.6)
OS Rate at month 36 (%) (95% CI)	82.2 (76.2, 86.8)	70.7 (64.3, 76.3)

[a] From product-limit (Kaplan-Meier) method for censored data.
[b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate.
[c] One-sided p-value based on log-rank test.
NR = Not reached.
Database Cutoff Date: 08JAN2024

Figure 14 Kaplan-Meier Estimates of Progression-Free Survival (Primary Censoring Rule) Based on Investigator Assessment, and of Overall Survival (FIGO 2014 Stage IB2 to IIB LN+ and FIGO 2014 Stage III to IVA Participants) (ITT Population)

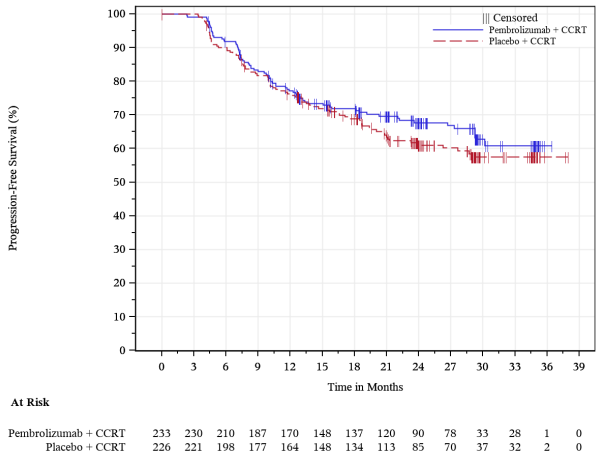
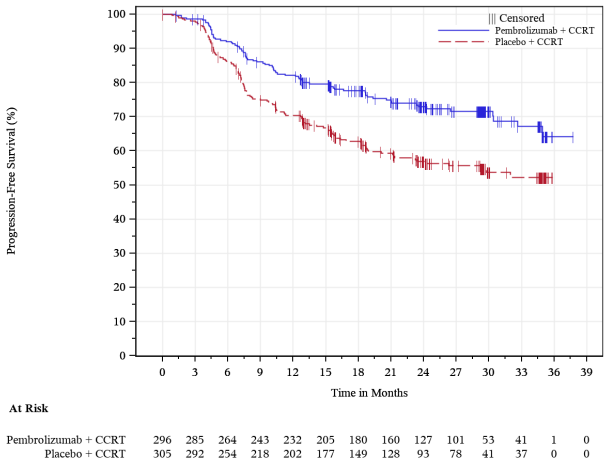
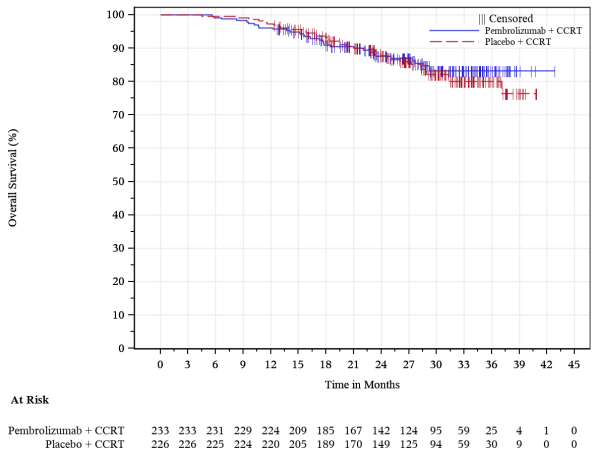
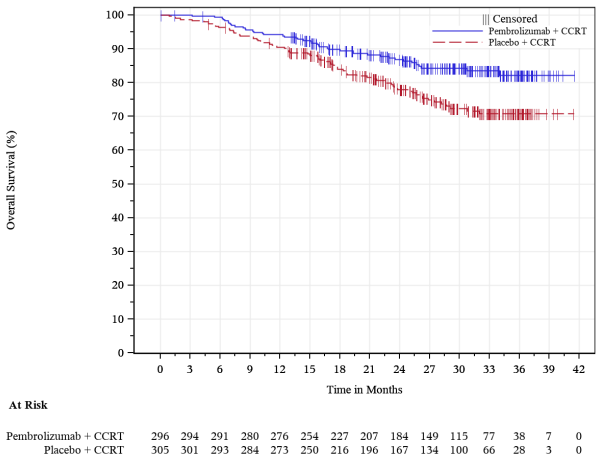
FIGO 2014 Stage IB2 to IIB LN+	**FIGO 2014 Stage III to IVA**
PFS - HR 0.85 (95% CI: 0.62, 1.16) Events 32.6% vs 37.6%	**PFS** – HR 0.57 (95% CI: 0.43, 0.76) Events 26.7% vs 41%
	
OS – HR 0.89 (95% CI: 0.55, 1.44) Events 13.7% vs 15.9%	**OS** – HR 0.57 (95% CI: 0.39, 0.83) Events 14.5% vs 23.9%
	

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Table 46 Summary of Best Objective Response Based on Investigator Assessment per RECIST 1.1 (FIGO 2014 Stage IB2 to IIB LN+ Participants) (Participants with Measurable Disease at Baseline)

	Pembrolizumab + CCRT			Placebo + CCRT		
	n	(%)	(95% CI)[a]	n	(%)	(95% CI)[a]
Number of Participants in Population	229			222		
Complete Response (CR)	141	(61.6)	(54.9, 67.9)	131	(59.0)	(52.2, 65.5)
Partial Response (PR)	64	(27.9)	(22.2, 34.2)	63	(28.4)	(22.5, 34.8)
Objective Response (CR+PR)	**205**	**(89.5)**	**(84.8, 93.2)**	**194**	**(87.4)**	**(82.3, 91.5)**
Stable Disease (SD)	2	(0.9)	(0.1, 3.1)	4	(1.8)	(0.5, 4.5)
Disease Control (CR+PR+SD)	**207**	**(90.4)**	**(85.8, 93.9)**	**198**	**(89.2)**	**(84.3, 92.9)**
Progressive Disease (PD)	16	(7.0)	(4.0, 11.1)	19	(8.6)	(5.2, 13.0)
Not Evaluable (NE)	0	(0.0)	(0.0, 1.6)	0	(0.0)	(0.0, 1.6)
No Assessment (NA)	6	(2.6)	(1.0, 5.6)	5	(2.3)	(0.7, 5.2)

[a] Based on binomial exact confidence interval method.

Investigator assessed responses per RECIST 1.1 are included in this table.

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Table 47 Summary of Best Objective Response Based on Investigator Assessment per RECIST 1.1 (FIGO 2014 Stage III to IVA Participants) (Participants with Measurable Disease at Baseline)

	Pembrolizumab + CCRT			Placebo + CCRT		
	n	(%)	(95% CI)[a]	n	(%)	(95% CI)[a]
Number of Participants in Population	292			300		
Complete Response (CR)	187	(64.0)	(58.2, 69.5)	164	(54.7)	(48.8, 60.4)
Partial Response (PR)	64	(21.9)	(17.3, 27.1)	79	(26.3)	(21.4, 31.7)
Objective Response (CR+PR)	**251**	**(86.0)**	**(81.4, 89.7)**	**243**	**(81.0)**	**(76.1, 85.3)**
Stable Disease (SD)	8	(2.7)	(1.2, 5.3)	10	(3.3)	(1.6, 6.0)
Disease Control (CR+PR+SD)	**259**	**(88.7)**	**(84.5, 92.1)**	**253**	**(84.3)**	**(79.7, 88.3)**
Progressive Disease (PD)	22	(7.5)	(4.8, 11.2)	33	(11.0)	(7.7, 15.1)
Not Evaluable (NE)	1	(0.3)	(0.0, 1.9)	1	(0.3)	(0.0, 1.8)
No Assessment (NA)	10	(3.4)	(1.7, 6.2)	13	(4.3)	(2.3, 7.3)

[a] Based on binomial exact confidence interval method.

Investigator assessed responses per RECIST 1.1 are included in this table.

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Subgroup analyses by lymph nodes status (FIGO 2014 Stage III-IVA)

All patients with FIGO 2014 Stage IB2-IIB had lymph node-positive disease, as per inclusion criterion.

Patients with FIGO 2014 Stage III-IVA had either node-positive (approximately 70%) or node-negative disease. Thus, subgroup analysis by lymph node status is applicable to FIGO 2014 Stage III to IVA participants only.

Table 48 Progression-Free Survival Based on Investigator Assessment (Primary Censoring Rule) and Overall Survival by Subgroup Factors (ITT Population) (FIGO 2014 Stage III to IVA Participants)

	Pembrolizumab + CCRT (N=296)			Placebo + CCRT (N=305)			Pembrolizumab + CCRT vs. Placebo + CCRT
PFS							
	N	Number of Events	(%)	N	Number of Events	(%)	Hazard Ratio (95% CI)[a]
Overall	296	79	(26.7)	305	125	(41.0)	0.57 (0.43, 0.76)
Presence of Lymph Node							
Positive Pelvic and/or Para-Aortic	213	63	(29.6)	212	94	(44.3)	0.57 (0.41, 0.79)
No Positive Pelvic nor Para-Aortic	83	16	(19.3)	93	31	(33.3)	0.53 (0.29, 0.97)
OS							
	N	Number of Events	(%)	N	Number of Events	(%)	Hazard Ratio (95% CI)[a]
Overall	296	43	(14.5)	305	73	(23.9)	0.57 (0.39, 0.83)
Presence of Lymph Node							
Positive Pelvic and/or Para-Aortic	213	35	(16.4)	212	59	(27.8)	0.54 (0.35, 0.82)
No Positive Pelvic nor Para-Aortic	83	8	(9.6)	93	14	(15.1)	0.65 (0.27, 1.54)

[a] For both overall and subgroups, analyses are based on unstratified Cox regression model with Efron's method of tie handling with treatment as a covariate.

Progression-free survival based on investigator assessment per RECIST 1.1 or by histopathologic confirmation of suspected disease progression (in the absence of radiographic disease progression per RECIST 1.1)

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Subgroup analyses by histology

Table 49 Progression-Free Survival Based on Investigator Assessment (Primary Censoring Rule) and Overall Survival by Subgroup Factors (ITT Population)

	Pembrolizumab + CCRT (N=529)			Placebo + CCRT (N=531)			Pembrolizumab + CCRT vs. Placebo + CCRT
PFS							
	N	Number of Events	(%)	N	Number of Events	(%)	Hazard Ratio (95% CI)[a]
Overall	529	155	(29.3)	531	210	(39.5)	0.68 (0.56, 0.84)
Histology Subtype							
Non-squamous	95	34	(35.8)	80	35	(43.8)	0.79 (0.49, 1.27)
Squamous	434	121	(27.9)	451	175	(38.8)	0.66 (0.52, 0.83)
OS							
	N	Number of Events	(%)	N	Number of Events	(%)	Hazard Ratio (95% CI)[a]

Overall	529	75	(14.2)	531	109	(20.5)	0.67 (0.50, 0.90)
Histology Subtype							
Non-squamous	95	16	(16.8)	80	15	(18.8)	0.83 (0.41, 1.69)
Squamous	434	59	(13.6)	451	94	(20.8)	0.64 (0.46, 0.89)

[a] For overall population, analysis is based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by planned type of EBRT (IMRT or VMAT vs non-IMRT and non-VMAT), Stage at screening (FIGO [2014] IB2-IIB vs III-IVA), and Planned total radiotherapy dose (<70 Gy vs >=70 Gy) with small strata collapsed as pre-specified in the sSAP. For subgroups, analysis is based on unstratified Cox regression model with treatment as a covariate.

Progression-free survival based on investigator assessment per RECIST 1.1 or by histopathologic confirmation of suspected disease progression (in the absence of radiographic disease progression per RECIST 1.1)

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Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 50 Summary of Efficacy for trial KEYNOTE A18

Title: A Randomized, Phase 3, Double-Blind Study of Chemoradiotherapy With or Without Pembrolizumab for the Treatment of High-risk, Locally Advanced Cervical Cancer (KEYNOTE-A18/ENGOT-cx11/GOG-3047)			
Study identifier	IND: 126191; EudraCT: 2019-003152-37; EU CT: 2022-501972-25-00; NCT: NCT04221945		
Design	Phase 3, randomized, multicenter, double-blind, placebo-controlled, interventional study		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		Approximately 2.6 years Not applicable Not applicable
Hypothesis	Superiority		
Treatments groups	Pembrolizumab plus chemoradiotherapy		Concurrent chemoradiotherapy (cisplatin+EBRT followed by brachytherapy) in combination with pembrolizumab (200 mg Q3W for 5 infusions) followed by pembrolizumab monotherapy (400 mg Q6W for 15 infusions) 529 participants randomized (ITT population)
	Placebo plus chemoradiotherapy		Concurrent chemoradiotherapy (cisplatin+EBRT followed by brachytherapy) in combination with placebo (Q3W for 5 infusions) followed by placebo alone (Q6W for 15 infusions) 531 participants randomized (ITT population)
Endpoints and definitions	Primary endpoints	PFS (Investigator assessed or per histopathologic confirmation of suspected disease progression or death)	Time from randomization to the first documented disease progression or death due to any cause, whichever occurs first, assessed by investigator
		OS	Time from randomization to death due to any cause
Database	DCO IA1: 09-Jan-2023; DCO IA2: 08-Jan-2024		

lock			
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent-to-treat population **(IA2)**		
Descriptive statistics and estimate variability	**Treatment group**	**Pembrolizumab plus chemoradiotherapy**	**Placebo plus chemoradiotherapy**
	Number of subjects	529	531
	PFS (Investigator Assessed)		
	Median, months (95% CI)	NR (NR, NR)	NR (32, NR)
	OS		
	Median, months (95% CI)	NR (NR, NR)	NR (NR, NR)
Effect estimate per comparison		**Comparison groups**	**Pembrolizumab plus chemoRT vs Placebo plus chemoRT**
	Primary endpoint: PFS (Investigator Assessed)	Hazard ratio	0.68
		95% CI	(0.56, 0.84)
		p-value	0.0002
	Primary endpoint: OS	Hazard ratio	0.67
		95% CI	(0.50, 0.90)
		p-value	0.0040
Note	PFS was statistically significant at IA1 (HR 0.70, 95% CI: 0.55, 0.89, p=0.0020). At IA2, PFS was not tested only nominal p-value was provided. OS was not statistically significant at IA1, reached statistical significance at IA2		
Analysis population and time point description	FIGO 2014 Stage III to IVA Subgroup (IA2)		
Descriptive statistics and estimate variability	Treatment group	**Pembrolizumab plus chemoradiotherapy**	**Placebo plus chemoradiotherapy**
	Number of subjects	296	305
	PFS (Investigator Assessed)		
	Median, months (95% CI)	NR (NR, NR)	NR (26.3, NR)
	OS		
	Median, months (95% CI)	NR (NR, NR)	NR (NR, NR)
Effect estimate per comparison		**Comparison groups**	**Pembrolizumab plus chemoradiotherapy vs Placebo plus chemoradiotherapy**
	Primary endpoint: PFS (Investigator Assessed)	Hazard ratio	0.57
		95% CI	(0.43, 0.76)
		Nominal p-value	<0.0001
	Primary endpoint: OS	Hazard ratio	0.57
		95% CI	(0.39, 0.83)

		Nominal p-value	0.0016

Clinical studies in special populations

Table 51 Clinical studies in special populations

	Controlled Trials	Non-controlled trials
Renal impairment* patients (Subjects number /total number)	0/1060	0
Hepatic impairment** patients (Subjects number /total number)	0/1060	0
Paediatric patients <18 years (Subjects number /total number)	0/1060	0
Age 65-74 (Subjects number /total number)	120/1060	0
Age 75-84 (Subjects number /total number)	12/1060	0
Age 85+ (Subjects number /total number)	1/1060	0

* Renal impairment is defined as having CKD Stage 3b, 4 or 5 (KDIGO definition)
** Hepatic impairment is defined as having Child-Pugh score B or C

2.4.3. Discussion on clinical efficacy

In the context of this application, the MAH is seeking authorisation for the use of pembrolizumab in combination with chemoradiotherapy (external beam radiation therapy followed by brachytherapy) for the treatment of locally advanced cervical cancer in adults who have not received prior definitive therapy [Stage IB2-IIB (with node-positive disease) or Stage III-IVA based on FIGO 2014], based on the results from the KEYNOTE-A18 study.

Design and conduct of clinical studies

KEYNOTE-A18 is a phase III, randomized, double-blind, placebo controlled, multicentre clinical trial. Eligible patients had LACC who have not previously received any treatment, either local (surgery/RT) or systemic. The two main histologies of epithelial tumours of the cervix, squamous cell and adenocarcinoma (and mixed adenosquamous), were included. Staging was defined as FIGO 2014 Stage IB2-IIB (with node-positive disease, pelvic or para-aortic lymph-nodes) or Stage III-IVA (either node-positive or node-negative disease), and patients were stratified accordingly. Although FIGO 2018 staging classification was already in place at the time of study start, the use of an earlier version was justified by the fact that comparison of results by disease extension and tumour size for patients with nodal positivity would not have been possible with FIGO 2018 staging, as all participants categorized as node-positive Stage IB-IIIB based on FIGO 2014 would have been classified as Stage IIIC in FIGO 2018, resulting in an

heterogeneous group of patients with highly variable survival rates[26,27]. The staging system, FIGO 2014, used in KEYNOTE-A18 is specified in the wording of the indication and in section 5.1 of the SmPC.

Patients in both treatment arms received concurrent chemoradiotherapy (CCRT) with curative intent. RT included external beam radiotherapy (EBRT) followed by brachytherapy, to be delivered in maximum 50 days overall, together with 5 (or 6 according to local practice) cycles of weekly cisplatin. Approximately 90% of patients received IMRT or VMAT as EBRT and had planned RT dose >70Gy. Both planned type of EBRT and planned total RT dose were stratification factors. CCRT received (in terms of median duration, RT dose, and cycles of cisplatin) was balanced between treatment arms, thus the addition of pembrolizumab does not appear to negatively impact on the delivery of scheduled CCRT. Pembrolizumab/placebo was started concurrently with CCRT, administered for the first 5 cycles at 200 mg dose Q3W, then for 15 cycles at 400 mg dose Q6W, for a total of approximately 2 years of treatment. Both dose regimens are currently approved in the EU. The 2-years therapy of pembrolizumab was justified as being standard for the pembrolizumab development program for majority of indications. More interestingly, data from the EMBRACE[28] showed a rate of relapse of at least 30% after surgery alone, and a plateau at about month 24-30 in FIGO stage IB-IVA or FIGO stage IVB disease restricted to paraaortic LN. It is acknowledged that a decreased rate of events and an observed plateau at about 24 months may justify the 2-year treatment duration with pembrolizumab, although the study was not designed to assess different treatment durations of pembrolizumab.

Tumour was assessed at baseline and 12 weeks after the completion of CCRT and then every 12 weeks thereafter during years 1 and 2, every 24 weeks in year 3, and once per year from year 4.

PFS by investigator per RECIST 1.1 and OS were defined as primary endpoints. Of note, the primary endpoint PFS was changed with Amendment 1 from BICR to investigator assessment, justified as in LACC disease progression is highly informed by clinical findings correlating with histopathologic confirmation of progression with biopsy, thus considered more adequate in this setting.

Overall, statistical methods were well reported and considered appropriate. The sample size calculation is comprehensible and reproducible, and the protocol amendments did not affect the sample size and power calculation. The blinding/unblinding procedure was well explained in the study protocol, with no changes in the planned analyses following study unblinding. Stratification factors are acceptable. The changes introduced in KEYNOTE-A18 from a statistical perspective should not have affected the consistency of study results, with exception of Amendment No. 04, approved just two months before the data cut-off of IA1, that substantially modified both protocol and SAP, since the study could have been underpowered for OS, based on emerging external data from the CALLA study. To power the OS analysis based on the revised expected number of events, the initial one-sided alpha=0.025 was initially fully allocated to PFS hypothesis and then fully re-allocated to OS hypothesis if PFS hypothesis was rejected in a conditional step-down manner. As this strategy would have given a higher probability of success (POS) on PFS that would also have been transferred to a higher POS on OS, the term "dual-primary endpoints" for PFS and OS was changed in "primary endpoints" and statement regarding claiming study success based on either PFS or OS was removed. Since the OS hypothesis was tested only after the hypothesis for PFS was rejected, OS was formally considered as key secondary endpoint. However, taking into account the clinical importance of OS, this strategy can be considered acceptable.

The MAH received Scientific Advice at the time of study planning. While the CHMP generally agreed with the study design and the patient population, the plan for interim analyses was highly questioned as those

[26] Jason DW, Koji M, Yongmei H et al. Prognostic Performance of the 2018 International Federation of Gynecology and Obstetrics Cervical Cancer Staging Guidelines. Obstet Gynecol. 2019; 134(1): 49.
[27] Shin W, Ham TY, Park YR, Lim MC, Won YJ. Comparing survival outcomes for cervical cancer based on the 2014 and 2018 International Federation of Gynecology and Obstetrics staging systems. Sci Rep. 2021;11:6988.
[28] Potter R, Tanderup K, Schmid MP, Jurgenliemk-Schulz I, Haie-Meder C, Fokdal LU, et al. MRI-guided adaptive brachytherapy in locally advanced cervical cancer (EMBRACE-I): a multicentre prospective cohort study. Lancet Oncol. 2021 Apr;22:538-47.

were considered immature to conclude on B/R. The CHMP further noted that "Without evidence of an improved cure rate, as indicated by differential PFS plateaus beyond 3+ years, the benefit of the observed delay in recurrences would have to be weighed against the burden of 2+ years of pembrolizumab treatment. OS data would likely be too immature [at interim analyses] to support a conclusion of clinical benefit."

Efficacy data and additional analyses

KEYNOTE-A18 study recruited worldwide a total of 1060 patients (24.9% from Western Europe), randomised 1:1 to two treatment arms (529 to pembrolizumab arm and 531 to placebo arm). The MAH informed that recruitment was slower than originally planned (32 months instead of 28) because of COVID-19 and the conflict between Russia vs Ukraine. Additional patients (rather than the 980 planned) were thus enrolled to mitigate the risk of potentially losing patients due to these unforeseen circumstances.

The reported reasons for screening failure (502 patients) do not raise concern.

There were four global protocol amendments. Important protocol deviations occurred in low and similar rate in both arms, thus not raising concern.

The demographic and baseline disease characteristics were generally balanced between the pembrolizumab plus chemoradiotherapy and placebo plus chemoradiotherapy groups. At IA1, patients were all female with median age of 50 years (87.5% were <65y), mainly with good PS (ECOG 0 73.3%). At screening, stages were well represented: 43.6% FIGO 2014 Stage IB2 to IIB LN+ and 56.4% FIGO 2014 Stage III to IVA. Most participants (83.4%) had positive pelvic and/or positive para-aortic LN presence at screening. Overall, stage distribution and lymph node positivity were balanced between treatment arms. Most participants (83.4%) had squamous histology, which is consistent with the known epidemiology of the disease. Almost all patients had known PD-L1 status, most of them (94.3%) having CPS≥1 score. The number of low PD-L1 tumours (CPS<1: <5%) was balanced between the two arms but limited, consistent with prior Keytruda studies showing that cervical tumours are usually expressing PD-L1 (patients with CPS<1 were 11% in KEYNOTE-826, and 15% in KEYNOTE-158[29]). PD-L1 expression was not a stratification factor. It was clarified that MSI-H was not tested because MSI-H is only present in <5% of patients with locally advanced cervical cancer.

The efficacy analyses initially submitted were based on the pre-planned IA1, which was the IA for both PFS and OS in the ITT population. At IA1, median duration of follow-up was 17 months (range: 0.9 to 31 months). The last patient was randomized only one month before the data cut-off for IA1; at that time, 56% of the patients were still under active treatment, although only 2% (18/1058) of the APaT participants did not yet complete CCRT. As the data from IA1 were considered too immature by the CHMP to make conclusion on the B/R of the proposed experimental treatment in the sought potential curative setting, the results from IA2 were provided during the procedure, corresponding to final PFS analysis and the second interim analysis for OS. At IA2, median follow-up was 27.5 months. There were 16% of patients in both arms still under treatment with pembrolizumab/placebo, with approximately 40% of subjects able to complete the entire 2-years treatment.

At IA1, KEYNOTE-A18 met its primary endpoint **PFS by investigator** per RECIST 1.1: PFS HR was 0.70 (95% CI: 0.55, 0.89) in favour of pembrolizumab plus chemoradiotherapy, and the observed p-value of 0.0020 (1-sided) crossed the prespecified nominal boundary of 0.0172 (1-sided). The KM curves for PFS separated early at approximately 3 months and remained separated over time in favour of

[29] EMA/224169/2022 - EPAR Keytruda EMEA/H/C/003820/II/0117 https://www.ema.europa.eu/en/documents/variation-report/keytruda-h-c-003820-ii-0117-epar-assessment-report-variation_en.pdf

pembrolizumab plus CCRT (improvement in PFS rate is approximately of 5% at month 6 and 12, and approximately of 10% at month 18 and 24), with medians not yet reached. The 3-year PFS in the control arm is in line with the assumptions initially made. Participants experiencing a PFS event were less in the experimental arm (21.7% vs 29%), although the number of events is still low overall and quite high rate of censoring is observed. Result of **PFS by BICR** assessment (which was the primary endpoint before protocol Amendment 1) did not show a significant difference between arms (HR 0.76, 95% CI: 0.58, 1.00, p=0.0259), however this endpoint was not adjusted for multiplicity. Although the rationale for switching the primary endpoint from PFS by BICR to PFS by investigator was found acceptable (see above) and KEYNOTE-A18 was double blinded, unmasking due to toxicity may still occur. However, concordance analysis between PFS by Investigator and by BICR seems reassuring, as the rates and the type of concordance/discordance were generally similar and comparable between the two arms, and occurred similarly within each arm in both directions (i.e. BICR has earlier time or later time than Inv). The PFS sensitivity analysis 2 confirms that additional toxicity of pembrolizumab had some impact on treatment discontinuation, although it is of reassurance that pembrolizumab addition did not appear to affect the ability of patients to complete standard CCRT.

As PFS reached statistical significance in the ITT population at IA1, this endpoint was not re-tested and only descriptive analysis was provided at IA2. With about 29% and 39% of PFS events in the pembrolizumab vs control arm (approximately 10% more than at IA1), HR was 0.68 (95% CI: 0.56, 0.84), with nominal p-value 0.0002. Median PFS in both arms were still not reached. KM curves remain separated. Updated PFS data is thus consistent and confirmed with longer follow-up the results of IA1.

OS did not reach statistical significance at IA1 although showing a trend in favour of the pembrolizumab plus chemoradiotherapy arm: OS HR was 0.73 (95% CI: 0.49, 1.07), 1-sided p-value of 0.0541 (boundary for statistical significance of 0.00006). OS KM curves are mostly overlapping but highly censored. While HR point estimate was below 1, the data were considered immature in terms of number of events and follow-up time.

OS was tested again at IA2 and statistical significance was reached at this analysis. A total of 184 OS events occurred (182 planned), in 14.2% of the experimental group vs 20.5% of the control group. HR was 0.67 (95% CI: 0.50, 0.90), with p=0.004 (boundary p=0.01026). Median OS were still not reached in either arm. No crossing of OS curves was observed, however, experimental and control are almost overlapping. Curves separate after month 12, and a 5% increase in OS rate at 24 months is seen (from 82.2% to 87.2%), although with high censoring from month 12-15. The clinical relevance of the OS result is still difficult to assess at this not yet mature OS analysis. Of those who were treated at relapse, approximately 30% of patients in the control arm received an anti-PD(L)1 agent (mostly pembrolizumab). A higher use of pembrolizumab in 1L advanced/metastatic setting might be expected in the current European context, given the authorisation of this indication in April 2022 (Variation EMEA/H/C/003820/II/0117) and the recommendation by international guidelines. The use of post-progression IO does not appear to have influenced OS result in the ITT population, based on sensitivity analyses.

In the ITT population, a positive PFS2 trend in favour of the pembrolizumab arm overall was supportive of the OS results. The HR of PFS2 at IA2 was 0.60 (95% CI: 0.46, 0.80), while at IA1 PFS2 was 0.65 (95% CI: 0.45, 0.94), representing a longer-term clinical benefit of pembrolizumab plus chemoradiotherapy and delayed progression on the next anti-cancer therapy.

Objective response rates, evaluated in patients with measurable disease at baseline (521/529 in the pembrolizumab arm and 522/531 in the control arm) was similar in both treatment arms at IA1, thus providing limited support to the addition of pembrolizumab to standard of care. Indeed, ORR (69.9% vs 64.2%) and CR rate (32.4% vs 30.3%) assessed at 12 weeks after CCRT by investigator are similar between treatment arms, as well as best ORR (79.3% vs 75.9%) and best CR rate (50.7% vs 48.7%).

Also response rates by BICR were similar between treatment arms. About 23% of patients did not have radiological tumour assessment at 12 weeks after CCRT, and about 12% overall, but this rate is similar in both arms.

The difference between treatment arms in **DOR** did not appear relevant at IA1 but the follow up time was limited for meaningful interpretation.

No clear differences between treatment arms were observed in secondary **PRO** endpoints. Regarding EORTC QLQ-C30 global health score/QoL, the initial decrease at Weeks 3 and 6, followed by an improvement, was expected due to the initial CCRT treatment.

With regard to **subgroup analysis** of PFS, at IA2 forest plot were overall consistent with prior IA1 data, with CIs crossing 1 for non-IMR and non-VMAT, FIGO 2014 Stage IB2-IIB LN+ and planned RT dose <70Gy subgroups. Regarding OS subgroup analysis, CIs cross 1 for non-IMRT and non-VMAT, FIGO 2014 Stage IB2-IIB LN+, planned RT dose <70Gy, age ≥65, white and baseline ECOG1. However, as compared to IA1, the point estimate of HR is now <1 in FIGO 2014 Stage IB2-IIB LN+ and white, while it remains above 1 in patients over 65 years old.

With regard to subgroup analyses by **disease stage**, it was observed that the use of pembrolizumab in earlier disease stages provided a lower additional benefit as compared to higher stages. Indeed, at IA1, PFS HR was 0.91 in FIGO 2014 Stage IB2-IIB LN+ vs 0.58 in FIGO 2014 Stage III-IVA. Concerning OS, an HR estimate of 1.62 (95% CI: 0.79, 3.34) was reported in FIGO 2014 Stages IB2-IIB LN+, while HR was 0.51 (95% CI: 0.31, 0.83) in FIGO 2014 Stage III-IVA.

Similar trend was observed at IA2. Indeed, in patients with FIGO 2014 Stage III-IVA, PFS HR was 0.57 (95% CI: 0.43, 0.76) and OS HR was 0.57 (95% CI: 0.39, 0.83). PFS KM curves divided from month 3 and separation increased over time (difference in PFS rate: +6% at 6 months, +12% at 12m, +16% at 24m, +18% at 30m). OS KM curves also diverged from the beginning, although highly censored after month 12. ORR was similar between the two treatment arms (86% vs 81%), but slightly higher rate of CR was observed (64% vs 54.7%). Therefore, updated results from IA2 overall confirmed the clinically relevant benefit of adding pembrolizumab to standard of care in patients with FIGO 2014 Stage III-IVA LACC.

At IA2, in FIGO 2014 Stage IB2-IIB, improvement in PFS and OS HR point estimates was reassuringly observed with respect to IA1. In detail, with approximately 33% vs 38% PFS events in pembrolizumab vs placebo arm, PFS HR was 0.85 (95% CI: 0.62, 1.16), with median PFS not reached in either arm. KM curves were however overlapping up to month 15, then separated (PFS difference rate at 24 months +6.7%) although such separation was apparently not maintained (PFS difference rate at 30 months +5.2%, at 36 months 3.3%), noting that the numbers at risk are quite small at 30 months and 36 months, and rate difference change should be interpreted by caution. Therefore, although the HR point estimate was in the positive direction, the clinical relevance of the benefit in terms of PFS from addition of pembrolizumab is questionable. Further, should there be few patients benefitting from the treatment, the study did not allow to identify predictive markers for response.

In any case, benefit in PFS does not seems to translate in OS advantage. In patients with FIGO 2014 Stage IB2-IIB LN+ disease, although OS HR point estimate improved as compared to IA1 [0.89 (95% CI: 0.55, 1.44) at IA2], OS curves are overlapping and not interpretable after month 12 due to censoring. OS result is considered still immature, with only 14% vs 16% of patients experiencing an OS event, and available follow-up (median 27 months) is not yet allowing sufficient observation-time for non-progression based on the disease natural history and risk of recurrence (i.e. about 3 years from baseline), and treatment duration (24 months). An apparent low use of anti-PD(L)1 at relapse in the control arm add further uncertainty (relapsing subjects may still receive anti-PD(L)1 at recurrence with no impact on survival).

In addition, no difference in ORR and CR between treatment arms is observed in patients with FIGO 2014 Stage IB2-IIB LN+ disease.

It was concluded that the overall data suggest that the results seen in the ITT population are driven by patients with disease FIGO 2014 Stage III-IVA.

Acknowledging that those results are from subgroup analysis for which the study was not powered, disease stage was one of the stratification factors. Further, patients with FIGO 2014 Stage IB2-IIB LN+ were almost half of the ITT population, as such, the subgroup can be considered represented well enough for the results to be interpretable.

The observed absolute magnitude of the effect over a lower background risk of recurrence/death in FIGO 2014 Stage IB2-IIB LN+ disease appears marginal, and of questionable clinical relevance: this is consequently impacting on the B/R, that might change depending on the baseline risk of relapse. Indeed, such marginal (if any) benefit does not counterbalance the risks and the burden related to the addition of pembrolizumab to CCRT followed by 2 years of maintenance treatment (vs observation) in this subgroup with better prognosis, where a fraction of patients is already cured by CCRT alone. Although the adverse effects of anti-PD(L)1 agents are well known and generally manageable, an increased toxicity over the comparator arm was seen in this add-on setting, including the risk of fatal and long-term toxicities in potentially cured patients.

In conclusion, in patients with FIGO 2014 Stage IB2-IIB LN+ cervical cancer patients, the B/R of pembrolizumab added to CCRT and then continued as maintenance therapy was considered negative, and the indication was restricted to higher disease stage (FIGO 2014 Stage III-IVA).

Results by **race** were also discussed, as White patients showed overall worse results as compared to All-Others. However, this might be due to different stage distributions across race (60% of White patients had FIGO 2014 Stage IB2-IIB LN+ disease, while 70% of All-Other patients had FIGO 2014 Stage III-IVA disease). In addition, the majority (78%) of patients who progressed in the placebo plus CCRT arm and received pembrolizumab as subsequent therapy were White. Thus, no concern was raised.

Analyses by **PD-L1 status** were not prespecified and performed post-hoc. Consistent results by PD-L1 CPS <10 and ≥10 were observed. When analysed according to PD-L1 CPS<1 and ≥1 (the cut-off used in the indication for pembrolizumab in combination with chemotherapy in 1L advanced cervical cancer), the number of patients with CPS<1 was too limited (<5% overall). Some biological plausibility on the predictive value of PD-L1 expression in the sought setting should be still considered, based on the results of advanced cervical cancer studies e.g. KEYNOTE-826[30] and EMPOWER-Cervical 1[31], as well as in the locally advanced cervical cancer setting in CALLA[32] study. It was concluded that, although biological plausibility of a possible predictive effect of PD-L1 expression in the sought setting cannot be excluded, in KEYNOTE-A18 PD-L1 status was not a stratification factor, furthermore the number of participants and OS events in the CPS<1 subgroup are too limited to draw any meaningful conclusions. Thus, restricting the indication based on PD-L1 status was not considered sufficiently justified by available data from the study. Taking into account the low number of PD-L1 negative tumours in this disease, the clinical utility of selecting patients by PD-L1 expression is expected to be low.

2.4.4. Conclusions on the clinical efficacy

The results from IA1 of KEYNOTE-A18 showed statistically significant improvement in PFS as assessed by

[30] EPAR Keytruda II/117
[31] EPAR Libtayo II/26
[32] Monk BJ, Toita T, Wu X, et al. Durvalumab versus placebo with chemoradiotherapy for locally advanced cervical cancer (CALLA): a randomised, double-blind, phase 3 trial. Lancet Oncol. 2023 Dec;24(12):1334-1348.

investigator or per histopathologic confirmation of local disease progression for pembrolizumab plus CCRT compared to placebo plus CCRT in the ITT population of patients with LACC (FIGO 2014 Stage IB2-IIB LN+ and Stage III-IVA), confirmed at IA2 with longer follow-up. OS reached statistical significance at IA2 in the ITT population, although the data was considered not sufficiently mature in the context of a curative setting.

Despite the limit of subgroup analyses, the results in the subset of patients with FIGO 2014 Stage IB2-IIB LN+ disease raised concern. The currently shown absolute benefit in this subgroup, with better prognosis, is not considered as clinically relevant as compared to FIGO 2014 Stage III-IVA disease, considering the burden of the addition of pembrolizumab for 2 years in a setting where some patients are cured with standard CCRT alone (with treatment-free maintenance). In conclusion, the indication was restricted to the higher disease stage (FIGO 2014 Stage III-IVA) (see B/R discussion in section 3.7).

2.5. Clinical safety

Introduction

Safety results for pembrolizumab in combination with chemoradiotherapy in the context of its intended use for high-risk, locally advanced cervical cancer are based on IA1 of the pivotal Phase 3 KEYNOTE-A18 study, with the data cut-off of 09 January 2023.

Safety analyses were conducted using the APaT population, defined as all randomized participants who received at least 1 dose of study treatment and whose safety data were analysed according to the study treatment they actually received. There were 1058 participants included in the APaT population (pembrolizumab arm: 528; placebo arm: 530). Safety results are reported for IA1 unless otherwise noted.

In addition, safety data have been presented side by side with pembrolizumab monotherapy database for comparison (see table below):

Table 52 Summary of Clinical Safety Datasets and Nomenclature

Dataset	Population	Treatment	Dataset Nomenclature in Tables	Nomenclature in Text
KEYNOTE-A18 pembrolizumab plus chemoradiotherapy[d]	N=528: Safety data from participants with high-risk LACC who received pembrolizumab in combination with chemoradiotherapy in KEYNOTE-A18	Pembrolizumab plus chemotherapy (cisplatin) with radiation (EBRT followed by brachytherapy)	KN-A18 Pembrolizumab + CCRT[a]	Pembrolizumab plus chemoradiotherapy
KEYNOTE-A18 placebo plus chemoradiotherapy[d]	N=530: Safety data from participants with high-risk LACC who received placebo in combination with chemoradiotherapy in KEYNOTE-A18	Placebo plus chemotherapy (cisplatin) with radiation (EBRT followed by brachytherapy)	KN-A18 Placebo + CCRT[b]	Placebo plus chemoradiotherapy
Pembrolizumab monotherapy global reference safety	N=7631: Pooled safety data from participants treated with pembrolizumab monotherapy, including participants with advanced	Pembrolizumab monotherapy	Pembrolizumab Monotherapy Reference Safety Dataset	RSD

Dataset	Population	Treatment	Dataset Nomenclature in Tables	Nomenclature in Text
	melanoma in KN-001 Part B1, B2, B3, D, C, F1, F2, and F3, KN-002, KN-006, KN-054, and KN-716; NSCLC in KN-001 Part B1, B2, B3, D, C, F1, F2, and F3, KN-010, KN-024, and KN-042; HNSCC in KN-012 Cohort B, and B2, KN-040, KN-048, KN-055; cHL in KN-013 Cohort 3, KN-087, and KN-204; bladder in KN-045, and KN-052; MSI-H in KN-158 Cohort K; colorectal in KN-164 Cohort A, B, and KN-177; and RCC in KN-564			

CCRT = concurrent chemoradiotherapy; cHL = classic Hodgkin lymphoma; EBRT = external beam radiation therapy; HNSCC = head and neck squamous cell carcinoma; KN = KEYNOTE; LACC = locally advanced cervical cancer; MSI-H = microsatellite instability-high; N = number; NSCLC = non-small cell lung cancer; RCC = renal cell carcinoma; RSD = reference safety dataset.

[a] Includes all participants who received at least 1 dose of pembrolizumab or chemoradiotherapy in KEYNOTE-A18.

[b] Includes all participants who received at least 1 dose of placebo or chemoradiotherapy in KEYNOTE-A18.

Database Cutoff Date: 09JAN2023.

The analysis strategy for safety parameters followed a tiered approach as shown in the table below.

Table 53 Analysis Strategy for Safety Parameters

Safety Tier	Safety Endpoint	p-Value	95% CI for Treatment Comparison	Descriptive Statistics
Tier 2	Grade 3 to 5 AE (incidence ≥5% of participants in one of the treatment groups)		X	X
	Serious AE (incidence ≥5% of participants in one of the treatment groups)		X	X
	AEs (incidence ≥5% of participants in one of the treatment groups)		X	X
Tier 3	Any AE			X
	Any Grade 3 to 5 AE			X
	Any Serious AE			X
	Any Drug-related AE			X
	Any Serious and Drug-related AE			X
	Any Grade 3 to 5 and Drug-related AE			X
	Discontinuation due to AE			X
	Death			X
	Specific AEs, SOCs (incidence <5% of participants in all of the treatment groups)			X
	Change from Baseline Results (laboratory toxicity shift, vital signs)			X

Abbreviations: AE = adverse event; CI = confidence interval; SOC = system organ class.

Patient exposure

Table 54 Summary of Drug Exposure (APaT Population)

	KN-A18 Pembrolizumab+CCRT (N=528)	KN-A18 Placebo+CCRT (N=530)	Pembrolizumab Monotherapy Reference Safety Dataset[g] (N=7631)
Duration of Exposure (month)			
Mean	12.08	11.80	7.85
Median	11.76	10.92	5.78
SD	7.51	7.48	6.91
Range	0.03 to 27.01	0.07 to 26.58	0.03 to 38.01
Number of Cycles			
Mean	11.59	11.42	12.31
Median	11.00	11.00	9.00
SD	5.68	5.63	10.10
Range	1.00 to 20.00	1.00 to 20.00	1.00 to 59.00

Each participant is counted once on each applicable duration category row.

Duration of Exposure is calculated as last dose date - first dose date + 1.

In KN-A18, number of cycles of Pembro/Placebo refer to Q3W cycles from C1 to C5 and Q6W from C6 onward.

[g] Includes all participants who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN024, KN013 cohort 3, KN087, KN204, KN045, KN052, KN164 - cohort A + B, KN177, KN012 cohort B and B2, KN055, KN040, KN048, KN054, KN716, KN042, KN564, KN158 (Cohort K).

Database cutoff date for Cervical Cancer (KN-A18: 09JAN2023).

Adverse events

AEs were coded using MedDRA (version 25.1) and reported according to NCI CTCAE version 5.0.

Table 55 Adverse Event Summary (APaT Population)

	KN-A18 Pembrolizumab+ CCRT		KN-A18 Placebo+CCRT		Pembrolizumab Monotherapy Reference Safety Dataset[g]	
	n	(%)	n	(%)	n	(%)
Subjects in population	528		530		7,631	
with one or more adverse events	525	(99.4)	526	(99.2)	7,375	(96.6)
with no adverse event	3	(0.6)	4	(0.8)	256	(3.4)
with drug-related[a] adverse events	507	(96.0)	509	(96.0)	5,462	(71.6)
with toxicity grade 3-5 adverse events	394	(74.6)	364	(68.7)	3,514	(46.0)
with toxicity grade 3-5 drug-related adverse events	354	(67.0)	321	(60.6)	1,208	(15.8)
with serious adverse events	150	(28.4)	131	(24.7)	2,742	(35.9)
with serious drug-related adverse events	91	(17.2)	65	(12.3)	840	(11.0)
who died	5	(0.9)	6	(1.1)	346	(4.5)
who died due to a drug-related adverse event	2	(0.4)	2	(0.4)	42	(0.6)
discontinued drug due to an adverse event	92	(17.4)	75	(14.2)	1,066	(14.0)
discontinued drug due to a drug-related adverse event	81	(15.3)	67	(12.6)	639	(8.4)

discontinued drug due to a serious adverse event	26	(4.9)	20	(3.8)	714	(9.4)
discontinued drug due to a serious drug-related adverse event	20	(3.8)	13	(2.5)	347	(4.5)

[a] Determined by the investigator to be related to the drug.

Grades for KN-A18 are based on NCI CTCAE version 5.0

Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.

MedDRA 25.1 preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.

[g] Includes all participants who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN024, KN013 cohort 3, KN087, KN204, KN045, KN052, KN164 - cohort A + B, KN177, KN012 cohort B and B2, KN055, KN040, KN048, KN054, KN716, KN042, KN564, KN158 (Cohort K).

Database cutoff date for Cervical Cancer (KN-A18: 09JAN2023).

Table 56 Adverse Event Summary (APaT Population) <u>at IA2</u>

	Pembrolizumab + CCRT		Placebo + CCRT	
	n	(%)	n	(%)
Participants in population	528		530	
with one or more adverse events	528	(100.0)	526	(99.2)
with no adverse event	0	(0.0)	4	(0.8)
with drug-related[a] adverse events	512	(97.0)	513	(96.8)
with toxicity grade 3-5 adverse events	413	(78.2)	371	(70.0)
with toxicity grade 3-5 drug-related adverse events	365	(69.1)	325	(61.3)
with serious adverse events	172	(32.6)	151	(28.5)
with serious drug-related adverse events	102	(19.3)	71	(13.4)
who died	5	(0.9)	7	(1.3)
who died due to a drug-related adverse event	2	(0.4)	2	(0.4)
discontinued any drug due to an adverse event	109	(20.6)	79	(14.9)
discontinued MK-3475/PLACEBO	50	(9.5)	22	(4.2)
discontinued CISPLATIN	67	(12.7)	62	(11.7)
discontinued EBRT	3	(0.6)	2	(0.4)
discontinued BRACHYTHERAPY	2	(0.4)	2	(0.4)
discontinued All Drugs	1	(0.2)	2	(0.4)
discontinued any drug due to a drug-related adverse event	99	(18.8)	69	(13.0)
discontinued MK-3475/PLACEBO	44	(8.3)	14	(2.6)
discontinued CISPLATIN	61	(11.6)	57	(10.8)
discontinued EBRT	0	(0.0)	1	(0.2)
discontinued BRACHYTHERAPY	2	(0.4)	2	(0.4)
discontinued All Drugs	0	(0.0)	1	(0.2)
discontinued any drug due to a serious adverse event	35	(6.6)	23	(4.3)
discontinued MK-3475/PLACEBO	28	(5.3)	14	(2.6)
discontinued CISPLATIN	10	(1.9)	12	(2.3)
discontinued EBRT	2	(0.4)	2	(0.4)
discontinued BRACHYTHERAPY	1	(0.2)	1	(0.2)
discontinued All Drugs	1	(0.2)	2	(0.4)
discontinued any drug due to a serious drug-related adverse event	29	(5.5)	14	(2.6)
discontinued MK-3475/PLACEBO	24	(4.5)	6	(1.1)
discontinued CISPLATIN	6	(1.1)	9	(1.7)
discontinued EBRT	0	(0.0)	1	(0.2)
discontinued BRACHYTHERAPY	1	(0.2)	1	(0.2)
discontinued All Drugs	0	(0.0)	1	(0.2)

[a] Determined by the investigator to be related to the drug.

Grades are based on NCI CTCAE version 5.0.

Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.

MedDRA V26.1 preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.

Database Cutoff Date: 08JAN2024

Table 57 Exposure-Adjusted Adverse Event Summary (Including Multiple Occurrences of Events) (APaT Population)

	Event Count and Rate (Events/100 person-months)[†]			
	Pembrolizumab + CCRT		Placebo + CCRT	
Number of Participants exposed	528		530	
Total exposure[‡] in person-months	6800.64		6661.20	
Total events (rate)				
adverse events	8,194	(120.49)	7,918	(118.87)
drug-related[§] adverse events	5,619	(82.62)	5,139	(77.15)
toxicity grade 3-5 adverse events	1,137	(16.72)	1,049	(15.75)
toxicity grade 3-5 drug-related adverse events	894	(13.15)	784	(11.77)
serious adverse events	275	(4.04)	219	(3.29)
serious drug-related adverse events	145	(2.13)	89	(1.34)
adverse events resulting in dose modification[‖]	856	(12.59)	699	(10.49)
adverse events leading to death	5	(0.07)	6	(0.09)
drug-related adverse events leading to death	2	(0.03)	2	(0.03)
adverse events resulting in drug discontinuation	111	(1.63)	93	(1.40)
drug-related adverse events resulting in drug discontinuation	97	(1.43)	82	(1.23)
serious adverse events resulting in drug discontinuation	28	(0.41)	22	(0.33)
serious drug-related adverse events resulting in drug discontinuation	21	(0.31)	14	(0.21)

[†] Event rate per 100 person-months of exposure = event count *100/person-months of exposure.

[‡] Drug exposure is defined as the between the first dose date + 1 day and the earlier of the last dose date + 30 or the database cutoff date.

[§] Determined by the investigator to be related to the drug.

[‖] Defined as an action taken of dose reduced, drug interrupted or drug withdrawn.

MedDRA V25.1 preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.

Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.

Database Cutoff Date: 09JAN2023

Common Adverse events

Table 58 Participants With Adverse Events (Incidence ≥10% in One or More Treatment Groups) By Decreasing Frequency of Preferred Term (APaT Population)

	KN-A18 Pembrolizumab+ CCRT		KN-A18 Placebo+CCRT		Pembrolizumab Monotherapy Reference Safety Dataset[g]	
	n	(%)	n	(%)	n	(%)
Participants in population	528		530		7,631	
with one or more adverse events	525	(99.4)	526	(99.2)	7,375	(96.6)
with no adverse events	3	(0.6)	4	(0.8)	256	(3.4)
Anaemia	353	(66.9)	343	(64.7)	982	(12.9)
Nausea	317	(60.0)	334	(63.0)	1,534	(20.1)
Diarrhoea	296	(56.1)	297	(56.0)	1,678	(22.0)
White blood cell count decreased	175	(33.1)	184	(34.7)	70	(0.9)
Neutrophil count decreased	160	(30.3)	151	(28.5)	53	(0.7)
Vomiting	154	(29.2)	173	(32.6)	945	(12.4)

Hypomagnesaemia	130	(24.6)	122	(23.0)	184	(2.4)
Leukopenia	129	(24.4)	97	(18.3)	52	(0.7)
Neutropenia	120	(22.7)	107	(20.2)	82	(1.1)
Platelet count decreased	118	(22.3)	112	(21.1)	95	(1.2)
Hypokalaemia	114	(21.6)	86	(16.2)	324	(4.2)
Constipation	109	(20.6)	118	(22.3)	1,179	(15.5)
Urinary tract infection	108	(20.5)	130	(24.5)	511	(6.7)
Hypothyroidism	101	(19.1)	24	(4.5)	937	(12.3)
Alanine aminotransferase increased	98	(18.6)	82	(15.5)	572	(7.5)
Fatigue	94	(17.8)	108	(20.4)	2,368	(31.0)
Aspartate aminotransferase increased	93	(17.6)	66	(12.5)	538	(7.1)
Decreased appetite	92	(17.4)	103	(19.4)	1,312	(17.2)
Asthenia	90	(17.0)	72	(13.6)	880	(11.5)
Thrombocytopenia	80	(15.2)	66	(12.5)	117	(1.5)
Pyrexia	79	(15.0)	73	(13.8)	934	(12.2)
Dysuria	78	(14.8)	73	(13.8)	126	(1.7)
Lymphocyte count decreased	78	(14.8)	92	(17.4)	130	(1.7)
Weight decreased	75	(14.2)	78	(14.7)	628	(8.2)
Abdominal pain	70	(13.3)	70	(13.2)	674	(8.8)
Headache	66	(12.5)	66	(12.5)	946	(12.4)
Hyperthyroidism	60	(11.4)	11	(2.1)	398	(5.2)
Hyponatraemia	57	(10.8)	58	(10.9)	387	(5.1)
COVID-19	53	(10.0)	46	(8.7)	4	(0.1)
Blood creatinine increased	51	(9.7)	58	(10.9)	358	(4.7)
Lymphopenia	51	(9.7)	55	(10.4)	93	(1.2)
Arthralgia	50	(9.5)	57	(10.8)	1,436	(18.8)
Pelvic pain	47	(8.9)	62	(11.7)	59	(0.8)
Rash	40	(7.6)	23	(4.3)	1,175	(15.4)
Back pain	39	(7.4)	41	(7.7)	847	(11.1)
Pruritus	30	(5.7)	26	(4.9)	1,435	(18.8)
Cough	25	(4.7)	23	(4.3)	1,392	(18.2)
Dyspnoea	9	(1.7)	22	(4.2)	1,130	(14.8)

Every participant is counted a single time for each applicable row and column.

A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

Grades for KN-A18 are based on NCI CTCAE version 5.0

Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.

MedDRA 25.1 preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.

[g] Includes all participants who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN024, KN013 cohort 3, KN087, KN204, KN045, KN052, KN164 - cohort A + B, KN177, KN012 cohort B and B2, KN055, KN040, KN048, KN054, KN716, KN042, KN564, KN158 (Cohort K).

Database cutoff date for Cervical Cancer (KN-A18: 09JAN2023).

Drug-related Adverse Events

Table 59 Participants With Drug-Related Adverse Events (Incidence ≥5% in One or More Treatment Groups) By Decreasing Frequency of Preferred Term (APaT Population)

	KN-A18 Pembrolizumab+ CCRT		KN-A18 Placebo+CCRT		Pembrolizumab Monotherapy Reference Safety Dataset[g]	
	n	(%)	n	(%)	n	(%)
Participants in population	528		530		7,631	
with one or more adverse events	507	(96.0)	509	(96.0)	5,462	(71.6)
with no adverse events	21	(4.0)	21	(4.0)	2,169	(28.4)
Anaemia	313	(59.3)	292	(55.1)	234	(3.1)
Nausea	302	(57.2)	315	(59.4)	675	(8.8)
Diarrhoea	266	(50.4)	271	(51.1)	904	(11.8)
White blood cell count decreased	172	(32.6)	181	(34.2)	34	(0.4)
Neutrophil count decreased	153	(29.0)	148	(27.9)	34	(0.4)
Vomiting	132	(25.0)	150	(28.3)	248	(3.2)
Leukopenia	125	(23.7)	92	(17.4)	32	(0.4)
Platelet count decreased	116	(22.0)	108	(20.4)	43	(0.6)
Neutropenia	113	(21.4)	92	(17.4)	49	(0.6)
Hypothyroidism	93	(17.6)	19	(3.6)	810	(10.6)
Hypomagnesaemia	89	(16.9)	86	(16.2)	37	(0.5)
Decreased appetite	82	(15.5)	85	(16.0)	525	(6.9)
Alanine aminotransferase increased	80	(15.2)	57	(10.8)	336	(4.4)
Fatigue	80	(15.2)	93	(17.5)	1,476	(19.3)
Asthenia	75	(14.2)	63	(11.9)	491	(6.4)
Aspartate aminotransferase increased	74	(14.0)	48	(9.1)	312	(4.1)
Hypokalaemia	72	(13.6)	57	(10.8)	43	(0.6)
Thrombocytopenia	72	(13.6)	58	(10.9)	56	(0.7)
Constipation	69	(13.1)	64	(12.1)	184	(2.4)
Lymphocyte count decreased	67	(12.7)	82	(15.5)	64	(0.8)
Dysuria	60	(11.4)	49	(9.2)	7	(0.1)
Hyperthyroidism	54	(10.2)	11	(2.1)	352	(4.6)
Weight decreased	52	(9.8)	53	(10.0)	148	(1.9)
Lymphopenia	48	(9.1)	47	(8.9)	45	(0.6)
Hyponatraemia	43	(8.1)	44	(8.3)	63	(0.8)
Blood creatinine increased	39	(7.4)	42	(7.9)	105	(1.4)
Urinary tract infection	35	(6.6)	33	(6.2)	15	(0.2)
Pyrexia	33	(6.3)	22	(4.2)	314	(4.1)
Arthralgia	32	(6.1)	30	(5.7)	661	(8.7)
Radiation skin injury	32	(6.1)	30	(5.7)	1	(0.0)
Abdominal pain	30	(5.7)	33	(6.2)	148	(1.9)
Pelvic pain	27	(5.1)	27	(5.1)	4	(0.1)
Hypocalcaemia	26	(4.9)	28	(5.3)	34	(0.4)
Rash	26	(4.9)	18	(3.4)	884	(11.6)
Tinnitus	26	(4.9)	33	(6.2)	7	(0.1)
Pruritus	22	(4.2)	15	(2.8)	1,143	(15.0)
Dysgeusia	21	(4.0)	28	(5.3)	79	(1.0)

Every participant is counted a single time for each applicable row and column.

A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

Grades for KN-A18 are based on NCI CTCAE version 5.0

Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.

[g] Includes all participants who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2,

F3, KN002 (original phase), KN006, KN010, KN024, KN013 cohort 3, KN087, KN204, KN045, KN052, KN164 - cohort A + B, KN177, KN012 cohort B and B2, KN055, KN040, KN048, KN054, KN716, KN042, KN564, KN158 (Cohort K).

Database cutoff date for Cervical Cancer (KN-A18: 09JAN2023).

Grade 3 to 5 adverse events

Table 60 Participants With Grade 3-5 Adverse Events (Incidence ≥5% in One or More Treatment Groups) By Decreasing Frequency of Preferred Term (APaT Population)

	KN-A18 Pembrolizumab+CCRT		KN-A18 Placebo+CCRT		Pembrolizumab Monotherapy Reference Safety Dataset[g]	
	n	(%)	n	(%)	n	(%)
Participants in population	528		530		7,631	
with one or more adverse events	394	(74.6)	364	(68.7)	3,514	(46.0)
with no adverse events	134	(25.4)	166	(31.3)	4,117	(54.0)
Anaemia	119	(22.5)	115	(21.7)	275	(3.6)
White blood cell count decreased	104	(19.7)	113	(21.3)	5	(0.1)
Neutrophil count decreased	81	(15.3)	80	(15.1)	10	(0.1)
Lymphocyte count decreased	73	(13.8)	85	(16.0)	33	(0.4)
Leukopenia	69	(13.1)	58	(10.9)	7	(0.1)
Neutropenia	61	(11.6)	56	(10.6)	21	(0.3)
Lymphopenia	46	(8.7)	44	(8.3)	20	(0.3)
Hypokalaemia	29	(5.5)	20	(3.8)	70	(0.9)

Every participant is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
Grades for KN-A18 are based on NCI CTCAE version 5.0
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
MedDRA 25.1 preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.
[g] Includes all participants who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN024, KN013 cohort 3, KN087, KN204, KN045, KN052, KN164 - cohort A + B, KN177, KN012 cohort B and B2, KN055, KN040, KN048, KN054, KN716, KN042, KN564, KN158 (Cohort K).
Database cutoff date for Cervical Cancer (KN-A18: 09JAN2023).

Grade 3 to 5 adverse events related to the study intervention

Table 61 Participants With Drug-Related Grade 3-5 Adverse Events (Incidence ≥1% in One or More Treatment Groups) By Decreasing Frequency of Preferred Term (APaT Population)

	KN-A18 Pembrolizumab+ CCRT		KN-A18 Placebo+CCRT		Pembrolizumab Monotherapy Reference Safety Dataset[g]	
	n	(%)	n	(%)	n	(%)
Participants in population	528		530		7,631	
with one or more adverse events	354	(67.0)	321	(60.6)	1,208	(15.8)
with no adverse events	174	(33.0)	209	(39.4)	6,423	(84.2)
White blood cell count decreased	102	(19.3)	111	(20.9)	2	(0.0)
Anaemia	99	(18.8)	84	(15.8)	33	(0.4)
Neutrophil count decreased	77	(14.6)	78	(14.7)	6	(0.1)
Leukopenia	67	(12.7)	57	(10.8)	3	(0.0)
Lymphocyte count decreased	63	(11.9)	75	(14.2)	9	(0.1)
Neutropenia	56	(10.6)	51	(9.6)	13	(0.2)
Lymphopenia	44	(8.3)	39	(7.4)	6	(0.1)
Platelet count decreased	25	(4.7)	13	(2.5)	2	(0.0)

Diarrhoea	22	(4.2)	23	(4.3)	75	(1.0)
Hypokalaemia	22	(4.2)	15	(2.8)	12	(0.2)
Hypomagnesaemia	12	(2.3)	11	(2.1)	1	(0.0)
Alanine aminotransferase increased	9	(1.7)	5	(0.9)	56	(0.7)
Febrile neutropenia	8	(1.5)	5	(0.9)	0	(0.0)
Gamma-glutamyltransferase increased	8	(1.5)	2	(0.4)	25	(0.3)
Nausea	7	(1.3)	9	(1.7)	13	(0.2)
Thrombocytopenia	7	(1.3)	6	(1.1)	11	(0.1)
Hypocalcaemia	6	(1.1)	4	(0.8)	2	(0.0)
Urinary tract infection	6	(1.1)	2	(0.4)	0	(0.0)
Hyponatraemia	5	(0.9)	7	(1.3)	32	(0.4)
Fatigue	4	(0.8)	4	(0.8)	75	(1.0)
Vomiting	3	(0.6)	7	(1.3)	12	(0.2)
Pneumonitis	2	(0.4)	0	(0.0)	91	(1.2)

Every participant is counted a single time for each applicable row and column.

A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

Grades for KN-A18 are based on NCI CTCAE version 5.0

Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.

g Includes all participants who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN024, KN013 cohort 3, KN087, KN204, KN045, KN052, KN164 - cohort A + B, KN177, KN012 cohort B and B2, KN055, KN040, KN048, KN054, KN716, KN042, KN564, KN158 (Cohort K).

Database cutoff date for Cervical Cancer (KN-A18: 09JAN2023).

Adverse Drug Reactions (ADRs)

The MAH has updated section 4.8 of the SmPC to include the population of locally advanced cervical cancer patients, receiving pembrolizumab in combination with chemoradiotherapy (study KEYNOTE-A18) based on IA1 safety data (DCO of 09 January 2023), into the "Pembrolizumab in combination with chemotherapy or chemoradiotherapy" pooled dataset (RSD) which includes all chemotherapy or chemoradiotherapy combination indications approved in the EU or expected to be approved concurrently with the KEYNOTE-A18 procedure, i.e. the population of primary advanced or recurrent endometrial cancer patients from KEYNOTE-868 (EMEA/H/C/003820/II/0153). Therefore, the changes included in section 4.8 of the current procedure EMEA/H/C/003820/II/0145 represent the most updated safety pool and a consolidated version that includes also the changes from EMEA/H/C/003820/II/0153.

In addition, the MAH proposed revisions to align the adverse reactions by decreased frequency within each System Organ Class in Table 2 of section 4.8 of the SmPC, for pembrolizumab in combination with chemotherapy or radiotherapy, including KEYNOTE-A18 and KEYNOTE-868 safety data.

As a result of the updated safety pool, several ADRs frequencies were updated as follows:

- Haemolytic anaemia: from rare to uncommon
- Dizziness: from common to very common
- Uveitis: from rare to uncommon
- Lichenoid keratosis: from rare to uncommon
- Oedema: from common to very common
- Blood creatinine increased: from common to very common

Meningitis (aseptic), which was already reflected in the monotherapy column, was added to the combination with chemotherapy column with frequency rare.

The paragraph for laboratory abnormalities for the combination with chemotherapy was updated to include the data from KEYNOTE A-18 and KEYNOTE-868.

Tables supporting the updates made in section 4.8 of the SmPC are presented below.

Table 62 Adverse Reactions in Patients Treated With Pembrolizumab in Combination With Chemotherapy (APaT Population)

		Combination Therapy (N=6093)	
		All AEs % (n)	Gr 3-5 AEs n
Infections and infestations			
Common	Pneumonia	6.6% (405)	223
Blood and lymphatic system disorders			
Very common	Anaemia	53.3% (3248)	1129
Very common	Neutropenia	24.0% (1462)	885
Very common	Thrombocytopenia	13.2% (804)	241
Common	Febrile Neutropenia	5.1% (310)	299
Common	Leukopenia	9.6% (584)	234
Common	Lymphopenia	3.3% (200)	91
Uncommon	Haemolytic Anaemia[a]	0.1% (8)	7
Uncommon	Eosinophilia	0.7% (45)	4
Rare	Immune Thrombocytopenia	0.05% (3)	2
Immune system disorders			
Common	Infusion Reactions[b]	7.1% (435)	77
Rare	Sarcoidosis	0.03% (2)	0
Endocrine disorders			
Very common	Hypothyroidism[c]	13.7% (834)	18
Common	Adrenal Insufficiency[d]	1.1% (66)	26
Common	Hyperthyroidism[e]	5.8% (355)	8
Common	Thyroiditis[f]	1.2% (72)	7
Uncommon	Hypophysitis[g]	0.7% (42)	23
Rare	Hypoparathyroidism	0.03% (2)	0
Metabolism and nutrition disorders			
Very common	Hypokalaemia	12.3% (747)	222
Very common	Decreased Appetite	26.7% (1629)	119
Common	Hyponatraemia	8.5% (520)	188
Common	Hypocalcaemia	4.7% (289)	43
Uncommon	Type 1 Diabetes Mellitus[h]	0.3% (20)	19
Psychiatric disorders			
Very common	Insomnia	10.7% (654)	9

Nervous system disorders			
Very common	Neuropathy Peripheral	14.1% (861)	57
Very common	Headache	14.0% (852)	19
Very common	Dizziness	10.0% (612)	15
Common	Dysgeusia	8.5% (516)	3
Common	Lethargy	1.0% (61)	2
Uncommon	Encephalitis[i]	0.1% (9)	9
Uncommon	Epilepsy	0.1% (7)	3
Rare	Myasthenic Syndrome[j]	0.08% (5)	5
Rare	Guillain-Barre Syndrome[k]	0.07% (4)	4
Rare	Optic Neuritis	0.02% (1)	1
Rare	Meningitis (Aseptic)	0.02% (1)	1
Eye disorders			
Common	Dry Eye	3.0% (180)	1
Uncommon	Uveitis[l]	0.2% (10)	0
Cardiac disorders			
Common	Cardiac Arrhythmia (Including Atrial Fibrillation)[m]	3.9% (236)	56
Uncommon	Myocarditis[n]	0.2% (11)	9
Uncommon	Pericardial Effusion	0.4% (24)	8
Uncommon	Pericarditis	0.1% (7)	2
Vascular disorders			
Common	Hypertension	6.9% (419)	175
Uncommon	Vasculitis[o]	0.5% (33)	5
Respiratory, thoracic and mediastinal disorders			
Very common	Dyspnoea	11.7% (710)	77
Very common	Cough	15.0% (916)	5
Common	Pneumonitis[p]	3.8% (232)	86
Gastrointestinal disorders			
Very common	Diarrhoea	35.6% (2168)	240
Very common	Nausea	52.4% (3190)	184
Very common	Vomiting	27.9% (1699)	184
Very common	Abdominal Pain[q]	19.1% (1161)	76
Very common	Constipation	32.2% (1964)	22
Common	Colitis[r]	2.7% (162)	76
Common	Gastritis[s]	2.1% (126)	9
Common	Dry Mouth	4.4% (267)	1
Uncommon	Pancreatitis[t]	0.4% (25)	19
Uncommon	Gastrointestinal Ulceration[u]	0.4% (24)	4
Rare	Pancreatic Exocrine Insufficiency	(0)	0
Rare	Small Intestinal Perforation	0.03% (2)	2
Rare	Coeliac Disease	(0)	0
Hepatobiliary disorders			
Common	Hepatitis[v]	1.1% (65)	47
Rare	Cholangitis Sclerosing[w]	0.03% (2)	2
Skin and subcutaneous tissue disorders			
Very common	Alopecia	23.6% (1438)	6
Very common	Pruritus[x]	14.0% (851)	6
Very common	Rash[y]	20.4% (1245)	4
Common	Severe Skin Reactions[z]	2.5% (153)	129
Common	Dermatitis	1.5% (93)	4
Common	Erythema	3.3% (199)	3
Common	Dry Skin	5.2% (314)	2
Common	Dermatitis Acneiform	2.0% (119)	2
Common	Eczema	1.2% (74)	1
Uncommon	Psoriasis	0.6% (37)	5
Uncommon	Lichenoid Keratosis[aa]	0.1% (8)	1
Uncommon	Vitiligo[bb]	0.5% (33)	0
Uncommon	Papule	0.2% (10)	0
Rare	Stevens-Johnson Syndrome	0.03% (2)	2
Rare	Erythema Nodosum	0.07% (4)	0

Rare	Hair Colour Changes	0.02% (1)	0
Musculoskeletal and connective tissue disorders			
Very common	Musculoskeletal Pain[cc]	13.2% (807)	41
Very common	Arthralgia	16.0% (973)	38
Common	Myositis[dd]	9.1% (556)	23
Common	Pain In Extremity	7.2% (441)	12
Common	Arthritis[ee]	1.6% (95)	9
Uncommon	Tenosynovitis[ff]	0.3% (20)	1
Rare	Sjogren's Syndrome	0.02% (1)	0
Renal and urinary disorders			
Common	Acute Kidney Injury	3.2% (194)	100
Uncommon	Nephritis[gg]	0.7% (40)	22
Uncommon	Cystitis Noninfective	0.2% (14)	0
General disorders and administration site conditions			
Very common	Fatigue	35.1% (2141)	256
Very common	Asthenia	17.7% (1077)	164
Very common	Pyrexia	17.6% (1074)	48
Very common	Oedema[hh]	13.2% (804)	24
Common	Influenza Like Illness	2.5% (155)	2
Common	Chills	3.0% (181)	0
Investigations			
Very common	Alanine Aminotransferase Increased	17.4% (1063)	177
Very common	Aspartate Aminotransferase Increased	17.0% (1038)	149
Very common	Blood Creatinine Increased	10.2% (623)	32
Common	Blood Bilirubin Increased	4.9% (296)	50
Common	Blood Alkaline Phosphatase Increased	6.8% (417)	44
Common	Hypercalcaemia	1.7% (106)	21
Uncommon	Amylase Increased	0.7% (40)	10

Serious adverse event/deaths/other significant events

Deaths due to adverse events

Table 63 Participants With Adverse Events Resulting in Death Up to 90 Days of Last Dose (Incidence > 0% in One or More Treatment Groups of KEYNOTE-A18) By Decreasing Frequency of Preferred Term (APaT Population)

	KN-A18 Pembrolizumab+ CCRT		KN-A18 Placebo+CCRT		Pembrolizumab Monotherapy Reference Safety Dataset[g]	
	n	(%)	n	(%)	n	(%)
Participants in population	528		530		7,631	
with one or more adverse events	5	(0.9)	6	(1.1)	346	(4.5)
with no adverse events	523	(99.1)	524	(98.9)	7,285	(95.5)
Immune-mediated gastritis	1	(0.2)	0	(0.0)	0	(0.0)
Large intestine perforation	1	(0.2)	0	(0.0)	2	(0.0)
Sepsis	1	(0.2)	0	(0.0)	11	(0.1)
Urosepsis	1	(0.2)	0	(0.0)	5	(0.1)
Vaginal haemorrhage	1	(0.2)	1	(0.2)	0	(0.0)
Acute myocardial infarction	0	(0.0)	1	(0.2)	1	(0.0)
Bone marrow failure	0	(0.0)	1	(0.2)	0	(0.0)
Completed suicide	0	(0.0)	1	(0.2)	3	(0.0)
Death	0	(0.0)	1	(0.2)	49	(0.6)
Neutropenic colitis	0	(0.0)	1	(0.2)	0	(0.0)

Every participant is counted a single time for each applicable row and column.

A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

Grades for KN-A18 are based on NCI CTCAE version 5.0

Serious adverse events up to 90 days of last dose are included.

MedDRA 25.1 preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.

[g] Includes all participants who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN024, KN013 cohort 3, KN087, KN204, KN045, KN052, KN164 - cohort A + B, KN177, KN012 cohort B and B2, KN055, KN040, KN048, KN054, KN716, KN042, KN564, KN158 (Cohort K).

Database cutoff date for Cervical Cancer (KN-A18: 09JAN2023).

Of the AEs leading to death, the AEs that were considered to be drug-related by the investigator were for 2 (0.4%) participants in the pembrolizumab plus chemoradiotherapy group (immune-mediated gastritis and large intestine perforation) and for 2 (0.4%) participants in the placebo plus chemoradiotherapy group (bone marrow failure and neutropenic colitis).

Serious adverse events (SAE)

Table 64 Participants With Serious Adverse Events Up to 90 Days of Last Dose (Incidence ≥1% in One or More Treatment Groups) By Decreasing Frequency of Preferred Term (APaT Population)

	KN-A18 Pembrolizumab+ CCRT		KN-A18 Placebo+CCRT		Pembrolizumab Monotherapy Reference Safety Dataset[g]	
	n	(%)	n	(%)	n	(%)
Participants in population	528		530		7,631	
with one or more adverse events	150	(28.4)	131	(24.7)	2,742	(35.9)
with no adverse events	378	(71.6)	399	(75.3)	4,889	(64.1)
Anaemia	15	(2.8)	13	(2.5)	65	(0.9)
Urinary tract infection	15	(2.8)	11	(2.1)	67	(0.9)
Pyrexia	13	(2.5)	10	(1.9)	79	(1.0)
Diarrhoea	9	(1.7)	6	(1.1)	70	(0.9)
Sepsis	6	(1.1)	3	(0.6)	56	(0.7)
Vaginal haemorrhage	6	(1.1)	5	(0.9)	1	(0.0)
Acute kidney injury	4	(0.8)	6	(1.1)	65	(0.9)
Pleural effusion	3	(0.6)	0	(0.0)	88	(1.2)
Pyelonephritis	3	(0.6)	6	(1.1)	10	(0.1)
Pneumonitis	2	(0.4)	0	(0.0)	136	(1.8)
Pulmonary embolism	2	(0.4)	1	(0.2)	78	(1.0)
Dyspnoea	1	(0.2)	0	(0.0)	91	(1.2)
Pneumonia	0	(0.0)	0	(0.0)	272	(3.6)

Every participant is counted a single time for each applicable row and column.

A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

Grades for KN-A18 are based on NCI CTCAE version 5.0

Serious adverse events up to 90 days of last dose are included.

MedDRA 25.1 preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.

[g] Includes all participants who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN024, KN013 cohort 3, KN087, KN204, KN045, KN052, KN164 - cohort A + B, KN177, KN012 cohort B and B2, KN055, KN040, KN048, KN054, KN716, KN042, KN564, KN158 (Cohort K).

Database cutoff date for Cervical Cancer (KN-A18: 09JAN2023).

Serious adverse events related to the study intervention

Table 65 Participants With Drug-Related Serious Adverse Events Up to 90 Days of Last Dose (Incidence ≥1% in One or More Treatment Groups) By Decreasing Frequency of Preferred Term (APaT Population)

	KN-A18 Pembrolizumab+ CCRT		KN-A18 Placebo+CCRT		Pembrolizumab Monotherapy Reference Safety Dataset[g]	
	n	(%)	n	(%)	n	(%)
Participants in population	528		530		7,631	
with one or more adverse events	91	(17.2)	65	(12.3)	840	(11.0)
with no adverse events	437	(82.8)	465	(87.7)	6,791	(89.0)
Anaemia	14	(2.7)	7	(1.3)	6	(0.1)
Pyrexia	9	(1.7)	5	(0.9)	22	(0.3)
Diarrhoea	8	(1.5)	4	(0.8)	44	(0.6)
Pneumonitis	2	(0.4)	0	(0.0)	129	(1.7)

Every participant is counted a single time for each applicable row and column.

A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

Grades for KN-A18 are based on NCI CTCAE version 5.0

Serious adverse events up to 90 days of last dose are included.

[g] Includes all participants who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN024, KN013 cohort 3, KN087, KN204, KN045, KN052, KN164 - cohort A + B, KN177, KN012 cohort B and B2, KN055, KN040, KN048, KN054, KN716, KN042, KN564, KN158 (Cohort K).

Database cutoff date for Cervical Cancer (KN-A18: 09JAN2023).

Adverse Events of Special Interest for Pembrolizumab

Adverse Events of Special Interest (AEOSI) are immune-mediated events and infusion-related reactions causally associated with pembrolizumab.

No new indication-specific, immune-mediated AEs causally associated with pembrolizumab were identified with the addition of chemoradiotherapy. No AEOSI-related fatal events were reported in the pembrolizumab plus chemoradiotherapy group. The types and severity of AEOSI observed in the pembrolizumab plus chemoradiotherapy group were generally consistent with the safety profile of pembrolizumab monotherapy.

The overall incidence of AEOSI was higher (≥5 percentage point difference) in the pembrolizumab plus chemoradiotherapy group compared with the RSD (32.6% vs 26.8%). This was primarily driven by hypothyroidism and hyperthyroidism. When adjusted for exposure, these rates were similar between the pembrolizumab plus chemoradiotherapy group and the RSD.

The most frequently reported AEOSI (incidence ≥1%) for participants in the pembrolizumab plus chemoradiotherapy group were hypothyroidism, hyperthyroidism, colitis, and pneumonitis; of these, hyperthyroidism (11.4% vs 5.2%) and hypothyroidism (19.1% vs 12.3%) occurred in a higher proportion of participants compared with the RSD. Most AEOSI reported in the pembrolizumab plus chemoradiotherapy group were mild to moderate in severity (Grade 1 or 2 [11.2% and 17.2%, respectively]).

The time to onset of the first AEOSI in the pembrolizumab plus chemoradiotherapy group after the first administration of pembrolizumab and median duration were generally consistent with the RSD. The use of systemic corticosteroids to treat AEOSI in the pembrolizumab plus chemoradiotherapy group was consistent with the RSD. At data cut-off, the incidences of participants with AEOSI that were resolved (39.5% vs 42.7%), resolved with sequelae (1.2% vs 3.3%), resolving (22.1% vs 8.7%), and not resolved (37.2% vs 43.2%) were generally consistent between the pembrolizumab plus chemoradiotherapy group and the RSD, respectively.

Table 66 Adverse Event Summary For AEOSI (APaT Population)

	KN-A18 Pembrolizumab+ CCRT		KN-A18 Placebo+CCRT		Pembrolizumab Monotherapy Reference Safety Dataset[g]	
	n	(%)	n	(%)	n	(%)
Subjects in population	528		530		7,631	
with one or more adverse events	172	(32.6)	62	(11.7)	2,047	(26.8)
with no adverse event	356	(67.4)	468	(88.3)	5,584	(73.2)
with drug-related[a] adverse events	156	(29.5)	52	(9.8)	1,795	(23.5)
with toxicity grade 3-5 adverse events	22	(4.2)	6	(1.1)	527	(6.9)
with toxicity grade 3-5 drug-related adverse events	21	(4.0)	6	(1.1)	465	(6.1)
with serious adverse events	15	(2.8)	6	(1.1)	506	(6.6)
with serious drug-related adverse events	15	(2.8)	6	(1.1)	453	(5.9)
who died	0	(0.0)	0	(0.0)	13	(0.2)
who died due to a drug-related adverse event	0	(0.0)	0	(0.0)	13	(0.2)
discontinued drug due to an adverse event	12	(2.3)	2	(0.4)	358	(4.7)
discontinued drug due to a drug-related adverse event	12	(2.3)	2	(0.4)	352	(4.6)
discontinued drug due to a serious adverse event	7	(1.3)	1	(0.2)	227	(3.0)
discontinued drug due to a serious drug-related adverse event	7	(1.3)	1	(0.2)	225	(2.9)

[a] Determined by the investigator to be related to the drug.

Grades for KN-A18 are based on NCI CTCAE version 5.0

Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.

[g] Includes all participants who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN024, KN013 cohort 3, KN087, KN204, KN045, KN052, KN164 - cohort A + B, KN177, KN012 cohort B and B2, KN055, KN040, KN048, KN054, KN716, KN042, KN564, KN158 (Cohort K).

Database cutoff date for Cervical Cancer (KN-A18: 09JAN2023).

Table 67 Adverse Event Summary - Adverse Events of Special Interest (AEOSI) (APaT Population) <u>at IA2</u>

	Pembrolizumab + CCRT		Placebo + CCRT	
	n	(%)	n	(%)
Participants in population	528		530	
with one or more adverse events	212	(40.2)	97	(18.3)
with no adverse event	316	(59.8)	433	(81.7)
with drug-related[a] adverse events	188	(35.6)	76	(14.3)
with toxicity grade 3-5 adverse events	26	(4.9)	8	(1.5)
with toxicity grade 3-5 drug-related adverse events	25	(4.7)	8	(1.5)
with serious adverse events	20	(3.8)	7	(1.3)
with serious drug-related adverse events	19	(3.6)	7	(1.3)
who died	1	(0.2)	0	(0.0)
who died due to a drug-related adverse event	1	(0.2)	0	(0.0)
discontinued any drug due to an adverse event	17	(3.2)	4	(0.8)

discontinued MK-3475/PLACEBO	15	(2.8)	2	(0.4)
discontinued CISPLATIN	3	(0.6)	2	(0.4)
discontinued EBRT	0	(0.0)	0	(0.0)
discontinued BRACHYTHERAPY	0	(0.0)	0	(0.0)
discontinued All Drugs	0	(0.0)	0	(0.0)
discontinued any drug due to a drug-related adverse event	17	(3.2)	4	(0.8)
discontinued MK-3475/PLACEBO	15	(2.8)	2	(0.4)
discontinued CISPLATIN	3	(0.6)	2	(0.4)
discontinued EBRT	0	(0.0)	0	(0.0)
discontinued BRACHYTHERAPY	0	(0.0)	0	(0.0)
discontinued All Drugs	0	(0.0)	0	(0.0)
discontinued any drug due to a serious adverse event	10	(1.9)	2	(0.4)
discontinued MK-3475/PLACEBO	10	(1.9)	1	(0.2)
discontinued CISPLATIN	1	(0.2)	1	(0.2)
discontinued EBRT	0	(0.0)	0	(0.0)
discontinued BRACHYTHERAPY	0	(0.0)	0	(0.0)
discontinued All Drugs	0	(0.0)	0	(0.0)
discontinued any drug due to a serious drug-related adverse event	10	(1.9)	2	(0.4)
discontinued MK-3475/PLACEBO	10	(1.9)	1	(0.2)
discontinued CISPLATIN	1	(0.2)	1	(0.2)
discontinued EBRT	0	(0.0)	0	(0.0)
discontinued BRACHYTHERAPY	0	(0.0)	0	(0.0)
discontinued All Drugs	0	(0.0)	0	(0.0)

[a] Determined by the investigator to be related to the drug.

Grades are based on NCI CTCAE version 5.0.

Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.

MedDRA V26.1 preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.

Database Cutoff Date: 08JAN2024

Laboratory findings

The incidences of the most frequently reported laboratory abnormalities (including Grade 3 or 4 events) in the pembrolizumab plus chemoradiotherapy group were similar compared with the placebo plus chemoradiotherapy group.

The most frequently observed (≥20%) Grade 3 or 4 laboratory abnormalities in both treatment groups were similar and consistent with chemoradiotherapy-associated myelosuppression (lymphocytes decreased, leukocytes decreased, neutrophils decreased, and haemoglobin decreased).

The proportion of participants with laboratory abnormalities in both treatment groups were generally higher than the RSD.

The following laboratory abnormalities were reported with an incidence ≥20% and were higher (≥20 percentage point difference) in the pembrolizumab plus chemoradiotherapy group versus the RSD: WBC count decreased (96% vs 12.9%), neutrophil count decreased (72.5% vs 9.2%), lymphocyte count decreased (99.1% vs 35.0%), platelet count decreased (65.1% vs 12.3%), hypomagnesemia (59.2% vs 15.5%), haemoglobin decreased (anaemia) (85.6% vs 41.3%), potassium decreased (hypokalaemia) (39.5% vs 13.5%), and ALT increased (48.0% vs 26.5%).

The following Grade 3-4 laboratory AEs were reported with an incidence ≥5% in the pembrolizumab plus chemoradiotherapy group and were higher (≥5 percentage point difference) compared with the RSD: lymphocyte count decreased (96.4% vs 9.4%), WBC count decreased (50.3% vs 0.8%), neutrophil count

decreased (32.6% vs 1.9%), haemoglobin decreased (24.1% vs 5.7%), magnesium decreased (10.5% vs 0.2%), platelet count decreased (7.6% vs 1.7%). These higher incidences are generally consistent with the safety profile of the chemoradiotherapy administered.

There were no participants in either treatment group that met predetermined criteria for significance for potential DILI events, predefined as ALT or AST ≥3 x ULN, bilirubin ≥2 x ULN, and ALP <2 x ULN.

Safety in special populations

The safety findings in the pembrolizumab plus chemoradiotherapy group based on age, race, ECOG performance status, and geographic region were generally consistent with the established safety profile of pembrolizumab monotherapy, known safety profile of the chemoradiotherapy regimen, and the disease under study.

Age

The overall incidence of AEs in participants in each age category (<65, 65 to 74, 75 to 84, and ≥85 years of age) were generally similar in both treatment groups, except for the following differences:

- The incidences of drug-related SAEs in the pembrolizumab plus chemoradiotherapy group were higher in the 65 to 74 years of age category compared with <65 years of age.
- The incidences of discontinuations due to an AE (all and drug-related) in the placebo plus chemoradiotherapy group were higher in the 65 to 74 years of age category compared with <65 years of age.

In the RSD, no other differences were noted, except that the frequencies of Grade 3 to 5 AEs and SAEs tended to increase with age and were higher for participants ≥85 years compared with participants <65 years of age in the placebo plus chemoradiotherapy group.

Table 68 Adverse Event Summary by Age Category (<65, 65-74, 75-84, ≥85 Years) (APaT Population)

	KN-A18 Pembrolizumab+CCRT								KN-A18 Placebo+CCRT							
	<65		65-74		75-84		>=85		<65		65-74		75-84		>=85	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	472		50		5		1		453		70		7		0	
with one or more adverse events	469	(99.4)	50	(100.0)	5	(100.0)	1	(100.0)	449	(99.1)	70	(100.0)	7	(100.0)	0	(0.0)
with no adverse event	3	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)	4	(0.9)	0	(0.0)	0	(0.0)	0	(0.0)
with drug-related[a] adverse events	452	(95.8)	49	(98.0)	5	(100.0)	1	(100.0)	434	(95.8)	68	(97.1)	7	(100.0)	0	(0.0)
with toxicity grade 3-5 adverse events	353	(74.8)	36	(72.0)	4	(80.0)	1	(100.0)	309	(68.2)	49	(70.0)	6	(85.7)	0	(0.0)
with toxicity grade 3-5 drug-related adverse events	316	(66.9)	33	(66.0)	4	(80.0)	1	(100.0)	273	(60.3)	42	(60.0)	6	(85.7)	0	(0.0)
with serious adverse events	132	(28.0)	17	(34.0)	1	(20.0)	0	(0.0)	106	(23.4)	21	(30.0)	4	(57.1)	0	(0.0)
with serious drug-related adverse events	77	(16.3)	13	(26.0)	1	(20.0)	0	(0.0)	54	(11.9)	8	(11.4)	3	(42.9)	0	(0.0)
who died	4	(0.8)	1	(2.0)	0	(0.0)	0	(0.0)	4	(0.9)	2	(2.9)	0	(0.0)	0	(0.0)
who died due to a drug-related adverse event	2	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued drug due to an adverse event	80	(16.9)	11	(22.0)	0	(0.0)	1	(100.0)	56	(12.4)	16	(22.9)	3	(42.9)	0	(0.0)
discontinued drug due to a drug-related adverse event	69	(14.6)	11	(22.0)	0	(0.0)	1	(100.0)	52	(11.5)	13	(18.6)	2	(28.6)	0	(0.0)
discontinued drug due to a serious	22	(4.7)	4	(8.0)	0	(0.0)	0	(0.0)	12	(2.6)	6	(8.6)	2	(28.6)	0	(0.0)

adverse event								
discontinued drug due to a serious drug-related adverse event	16 (3.4)	4 (8.0)	0 (0.0)	0 (0.0)	9 (2.0)	3 (4.3)	1 (14.3)	0 (0.0)

	Pembrolizumab Monotherapy Reference Safety Dataset[g]							
	<65		65-74		75-84		>=85	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	4,524		2,173		824		110	
with one or more adverse events	4,364	(96.5)	2,097	(96.5)	805	(97.7)	109	(99.1)
with no adverse event	160	(3.5)	76	(3.5)	19	(2.3)	1	(0.9)
with drug-related[a] adverse events	3,231	(71.4)	1,552	(71.4)	594	(72.1)	85	(77.3)
with toxicity grade 3-5 adverse events	1,917	(42.4)	1,071	(49.3)	457	(55.5)	69	(62.7)
with toxicity grade 3-5 drug-related adverse events	629	(13.9)	391	(18.0)	163	(19.8)	25	(22.7)
with serious adverse events	1,457	(32.2)	839	(38.6)	387	(47.0)	59	(53.6)
with serious drug-related adverse events	451	(10.0)	265	(12.2)	105	(12.7)	19	(17.3)
who died	158	(3.5)	113	(5.2)	63	(7.6)	12	(10.9)
who died due to a drug-related adverse event	21	(0.5)	13	(0.6)	7	(0.8)	1	(0.9)
discontinued drug due to an adverse event	554	(12.2)	327	(15.0)	168	(20.4)	17	(15.5)
discontinued drug due to a drug-related adverse event	333	(7.4)	206	(9.5)	92	(11.2)	8	(7.3)
discontinued drug due to a serious adverse event	366	(8.1)	214	(9.8)	120	(14.6)	14	(12.7)
discontinued drug due to a serious drug-related adverse event	177	(3.9)	113	(5.2)	52	(6.3)	5	(4.5)

[a] Determined by the investigator to be related to the drug.

Grades for KN-A18 are based on NCI CTCAE version 5.0

Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.

MedDRA 25.1 preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.

[g] Includes all participants who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN024, KN013 cohort 3, KN087, KN204, KN045, KN052, KN164 - cohort A + B, KN177, KN012 cohort B and B2, KN055, KN040, KN048, KN054, KN716, KN042, KN564, KN158 (Cohort K).

Database cutoff date for Cervical Cancer (KN-A18: 09JAN2023).

Eastern Cooperative Oncology Group (ECOG) Performance Status

The overall incidence of AEs in participants with an ECOG status of 0 and 1 were similar. The AE profile in the pembrolizumab plus chemoradiotherapy group was generally similar between participants who had ECOG PS of 0 or 1 except for the following differences:

- The incidences of SAEs and discontinuations due to a drug-related AE in the pembrolizumab plus chemoradiotherapy group were higher in participants with an ECOG PS of 1.

A similar pattern was generally observed in both the placebo plus chemoradiotherapy group and the RSD, except for the following differences:

- In the placebo plus chemoradiotherapy group, the incidences of Grade 3-5 AEs (all and drug-related), SAEs, discontinuations due to an AE (all and drug-related), were higher in participants with an ECOG PS of 1.
- In the RSD, the incidences of discontinuations due to drug-related AEs were similar for participants with an ECOG PS of 0 or 1.

Geographic Region

The AE profile in the pembrolizumab plus chemoradiotherapy group was generally similar between participants enrolled in the EU and participants enrolled outside of EU except for the following differences:

- Within the pembrolizumab plus CRT group, the incidences of drug-related Grade 3 to 5 and drug-related SAEs were higher in participants from the ex-EU regions, and there were higher incidences of discontinuations of any drug due to an AE (all and drug-related) in participants from the EU.
- Within the placebo plus CRT group, the incidences of Grade 3 to 5 AEs (all and drug-related) were higher in participants from the ex-EU region, while SAEs (all and drug-related) were higher in participants from the EU.

These results were not noted in the RSD.

Table 69 Adverse Event Summary by Region (EU, Ex-EU) (APaT Population)

	KN-A18 Pembrolizumab+CCRT				KN-A18 Placebo+CCRT				Pembrolizumab Monotherapy Reference Safety Dataset[g]			
	EU		Ex-EU		EU		Ex-EU		EU		Ex-EU	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	137		391		127		403		2,856		4,775	
with one or more adverse events	135	(98.5)	390	(99.7)	125	(98.4)	401	(99.5)	2,745	(96.1)	4,630	(97.0)
with no adverse event	2	(1.5)	1	(0.3)	2	(1.6)	2	(0.5)	111	(3.9)	145	(3.0)
with drug-related[a] adverse events	127	(92.7)	380	(97.2)	118	(92.9)	391	(97.0)	2,018	(70.7)	3,444	(72.1)
with toxicity grade 3-5 adverse events	98	(71.5)	296	(75.7)	77	(60.6)	287	(71.2)	1,251	(43.8)	2,263	(47.4)
with toxicity grade 3-5 drug-related adverse events	79	(57.7)	275	(70.3)	63	(49.6)	258	(64.0)	447	(15.7)	761	(15.9)
with serious adverse events	43	(31.4)	107	(27.4)	40	(31.5)	91	(22.6)	1,019	(35.7)	1,723	(36.1)
with serious drug-related adverse events	18	(13.1)	73	(18.7)	21	(16.5)	44	(10.9)	332	(11.6)	508	(10.6)
who died	1	(0.7)	4	(1.0)	0	(0.0)	6	(1.5)	126	(4.4)	220	(4.6)
who died due to a drug-related adverse event	1	(0.7)	1	(0.3)	0	(0.0)	2	(0.5)	13	(0.5)	29	(0.6)
discontinued drug due to an adverse event	30	(21.9)	62	(15.9)	16	(12.6)	59	(14.6)	400	(14.0)	666	(13.9)
discontinued drug due to a drug-related adverse event	27	(19.7)	54	(13.8)	13	(10.2)	54	(13.4)	260	(9.1)	379	(7.9)
discontinued drug due to a serious adverse event	6	(4.4)	20	(5.1)	6	(4.7)	14	(3.5)	264	(9.2)	450	(9.4)
discontinued drug due to a serious drug-related adverse event	4	(2.9)	16	(4.1)	3	(2.4)	10	(2.5)	140	(4.9)	207	(4.3)

[a] Determined by the investigator to be related to the drug.
Grades for KN-A18 are based on NCI CTCAE version 5.0
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
MedDRA 25.1 preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.
[g] Includes all participants who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN024, KN013 cohort 3, KN087, KN204, KN045, KN052, KN164 - cohort A + B, KN177, KN012 cohort B and B2, KN055, KN040, KN048, KN054, KN716, KN042, KN564, KN158 (Cohort K).

The safety profile separately for the RT-concomitant and then pembrolizumab or placebo-single agent treatment (concurrent and monotherapy phases) is presented in the tables below:

Table 70 Adverse Event Summary (APaT Population) (Concurrent Phase)

	Pembrolizumab + CCRT		Placebo + CCRT	
	n	(%)	n	(%)
Participants in population	528		530	
with one or more adverse events	520	(98.5)	522	(98.5)
with no adverse event	8	(1.5)	8	(1.5)
with drug-related[a] adverse events	499	(94.5)	507	(95.7)
with toxicity grade 3-5 adverse events	361	(68.4)	338	(63.8)
with toxicity grade 3-5 drug-related adverse events	331	(62.7)	307	(57.9)
with serious adverse events	94	(17.8)	79	(14.9)

with serious drug-related adverse events	61	(11.6)	51	(9.6)
who died	0	(0.0)	0	(0.0)
who died due to a drug-related adverse event	0	(0.0)	0	(0.0)
discontinued any drug due to an adverse event	68	(12.9)	65	(12.3)
discontinued MK-3475/PLACEBO	9	(1.7)	6	(1.1)
discontinued CISPLATIN	63	(11.9)	60	(11.3)
discontinued EBRT	3	(0.6)	0	(0.0)
discontinued BRACHYTHERAPY	0	(0.0)	1	(0.2)
discontinued All Drugs	1	(0.2)	0	(0.0)
discontinued any drug due to a drug-related adverse event	60	(11.4)	62	(11.7)
discontinued MK-3475/PLACEBO	8	(1.5)	5	(0.9)
discontinued CISPLATIN	55	(10.4)	57	(10.8)
discontinued EBRT	0	(0.0)	0	(0.0)
discontinued BRACHYTHERAPY	0	(0.0)	1	(0.2)
discontinued All Drugs	0	(0.0)	0	(0.0)
discontinued any drug due to a serious adverse event	13	(2.5)	12	(2.3)
discontinued MK-3475/PLACEBO	7	(1.3)	4	(0.8)
discontinued CISPLATIN	10	(1.9)	10	(1.9)
discontinued EBRT	2	(0.4)	0	(0.0)
discontinued BRACHYTHERAPY	0	(0.0)	0	(0.0)
discontinued All Drugs	1	(0.2)	0	(0.0)
discontinued any drug due to a serious drug-related adverse event	9	(1.7)	10	(1.9)
discontinued MK-3475/PLACEBO	6	(1.1)	3	(0.6)
discontinued CISPLATIN	5	(0.9)	8	(1.5)
discontinued EBRT	0	(0.0)	0	(0.0)
discontinued BRACHYTHERAPY	0	(0.0)	0	(0.0)
discontinued All Drugs	0	(0.0)	0	(0.0)

a Determined by the investigator to be related to the drug.

Grades are based on NCI CTCAE version 5.0.

Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.

MedDRA V25.1 preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.

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Table 71 Adverse Event Summary (APaT Population) (Monotherapy Phase)

	Pembrolizumab + CCRT		Placebo + CCRT	
	n	(%)	n	(%)
Participants in population	528		530	
with one or more adverse events	455	(86.2)	435	(82.1)
with no adverse event	73	(13.8)	95	(17.9)
with drug-related[a] adverse events	384	(72.7)	318	(60.0)
with toxicity grade 3-5 adverse events	130	(24.6)	115	(21.7)
with toxicity grade 3-5 drug-related adverse events	88	(16.7)	51	(9.6)
with serious adverse events	82	(15.5)	72	(13.6)
with serious drug-related adverse events	44	(8.3)	17	(3.2)
who died	5	(0.9)	6	(1.1)
who died due to a drug-related adverse event	2	(0.4)	2	(0.4)
discontinued any drug due to an adverse event	28	(5.3)	11	(2.1)
discontinued MK-3475/PLACEBO	28	(5.3)	10	(1.9)
discontinued CISPLATIN	0	(0.0)	2	(0.4)
discontinued EBRT	0	(0.0)	2	(0.4)
discontinued BRACHYTHERAPY	1	(0.2)	1	(0.2)
discontinued All Drugs	0	(0.0)	2	(0.4)

discontinued any drug due to a drug-related adverse event	25	(4.7)	6	(1.1)
discontinued MK-3475/PLACEBO	24	(4.5)	5	(0.9)
discontinued CISPLATIN	0	(0.0)	1	(0.2)
discontinued EBRT	0	(0.0)	1	(0.2)
discontinued BRACHYTHERAPY	1	(0.2)	1	(0.2)
discontinued All Drugs	0	(0.0)	1	(0.2)
discontinued any drug due to a serious adverse event	13	(2.5)	8	(1.5)
discontinued MK-3475/PLACEBO	12	(2.3)	7	(1.3)
discontinued CISPLATIN	0	(0.0)	2	(0.4)
discontinued EBRT	0	(0.0)	2	(0.4)
discontinued BRACHYTHERAPY	1	(0.2)	1	(0.2)
discontinued All Drugs	0	(0.0)	2	(0.4)
discontinued any drug due to a serious drug-related adverse event	11	(2.1)	3	(0.6)
discontinued MK-3475/PLACEBO	10	(1.9)	2	(0.4)
discontinued CISPLATIN	0	(0.0)	1	(0.2)
discontinued EBRT	0	(0.0)	1	(0.2)
discontinued BRACHYTHERAPY	1	(0.2)	1	(0.2)
discontinued All Drugs	0	(0.0)	1	(0.2)

[a] Determined by the investigator to be related to the drug.

Grades are based on NCI CTCAE version 5.0.

Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.

MedDRA V25.1 preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.

Database Cutoff Date: 09JAN2023

Table 72 Participants With Adverse Events by Decreasing Incidence (Incidence ≥10% in One or More Treatment Groups) (APaT Population) (Concurrent Phase)

	Pembrolizumab + CCRT		Placebo + CCRT	
	n	(%)	n	(%)
Participants in population	528		530	
with one or more adverse events	520	(98.5)	522	(98.5)
with no adverse events	8	(1.5)	8	(1.5)
Anaemia	324	(61.4)	310	(58.5)
Nausea	310	(58.7)	325	(61.3)
Diarrhoea	272	(51.5)	290	(54.7)
White blood cell count decreased	173	(32.8)	180	(34.0)
Neutrophil count decreased	148	(28.0)	144	(27.2)
Vomiting	137	(25.9)	162	(30.6)
Leukopenia	124	(23.5)	89	(16.8)
Hypomagnesaemia	116	(22.0)	119	(22.5)
Neutropenia	114	(21.6)	97	(18.3)
Platelet count decreased	113	(21.4)	107	(20.2)
Hypokalaemia	102	(19.3)	79	(14.9)
Constipation	95	(18.0)	100	(18.9)
Decreased appetite	87	(16.5)	95	(17.9)
Fatigue	82	(15.5)	91	(17.2)
Asthenia	80	(15.2)	66	(12.5)
Thrombocytopenia	80	(15.2)	66	(12.5)
Lymphocyte count decreased	78	(14.8)	88	(16.6)
Urinary tract infection	64	(12.1)	68	(12.8)
Pyrexia	61	(11.6)	49	(9.2)
Dysuria	58	(11.0)	60	(11.3)

Weight decreased	57	(10.8)	67	(12.6)
Hyponatraemia	53	(10.0)	57	(10.8)

Every participant is counted a single time for each applicable row and column.

A specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.

MedDRA V25.1 preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.

Database Cutoff Date: 09JAN2023

Table 73 Participants With Adverse Events by Decreasing Incidence (Incidence ≥10% in One or More Treatment Groups) (APaT Population) (Monotherapy Phase)

	Pembrolizumab + CCRT		Placebo + CCRT	
	n	(%)	n	(%)
Participants in population	528		530	
with one or more adverse events	455	(86.2)	435	(82.1)
with no adverse events	73	(13.8)	95	(17.9)
Anaemia	107	(20.3)	91	(17.2)
Hypothyroidism	92	(17.4)	19	(3.6)
Diarrhoea	77	(14.6)	42	(7.9)
Alanine aminotransferase increased	67	(12.7)	52	(9.8)
White blood cell count decreased	65	(12.3)	75	(14.2)
Aspartate aminotransferase increased	62	(11.7)	44	(8.3)
Urinary tract infection	56	(10.6)	81	(15.3)

Every participant is counted a single time for each applicable row and column.

A specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.

MedDRA V25.1 preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.

Database Cutoff Date: 09JAN2023

Table 74 Participants With Grade 3-5 Adverse Events by Decreasing Incidence (Incidence ≥1% in One or More Treatment Groups) (APaT Population) (Concurrent Phase)

	Pembrolizumab + CCRT		Placebo + CCRT	
	n	(%)	n	(%)
Participants in population	528		530	
with one or more adverse events	361	(68.4)	338	(63.8)
with no adverse events	167	(31.6)	192	(36.2)
White blood cell count decreased	103	(19.5)	111	(20.9)
Anaemia	101	(19.1)	97	(18.3)
Neutrophil count decreased	76	(14.4)	75	(14.2)
Lymphocyte count decreased	73	(13.8)	82	(15.5)
Leukopenia	69	(13.1)	57	(10.8)
Neutropenia	58	(11.0)	55	(10.4)
Lymphopenia	45	(8.5)	43	(8.1)
Hypokalaemia	27	(5.1)	20	(3.8)
Platelet count decreased	23	(4.4)	13	(2.5)
Diarrhoea	19	(3.6)	26	(4.9)

Hypomagnesaemia	14	(2.7)	13	(2.5)
Thrombocytopenia	10	(1.9)	6	(1.1)
Urinary tract infection	10	(1.9)	5	(0.9)
Febrile neutropenia	8	(1.5)	5	(0.9)
Hyponatraemia	8	(1.5)	9	(1.7)
Alanine aminotransferase increased	6	(1.1)	6	(1.1)
Hypertension	6	(1.1)	5	(0.9)
Nausea	6	(1.1)	9	(1.7)
Hypocalcaemia	4	(0.8)	6	(1.1)

Every participant is counted a single time for each applicable row and column.

A specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.

MedDRA V25.1 preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.

Database Cutoff Date: 09JAN2023

Table 75 Participants With Grade 3-5 Adverse Events by Decreasing Incidence (Incidence ≥1% in One or More Treatment Groups) (APaT Population) (Monotherapy Phase)

	Pembrolizumab + CCRT		Placebo + CCRT	
	n	(%)	n	(%)
Participants in population	528		530	
with one or more adverse events	130	(24.6)	115	(21.7)
with no adverse events	398	(75.4)	415	(78.3)
Anaemia	25	(4.7)	23	(4.3)
Neutrophil count decreased	10	(1.9)	11	(2.1)
Diarrhoea	8	(1.5)	0	(0.0)
Hypertension	7	(1.3)	2	(0.4)
Urinary tract infection	7	(1.3)	12	(2.3)
Neutropenia	6	(1.1)	2	(0.4)
White blood cell count decreased	6	(1.1)	6	(1.1)
Lymphocyte count decreased	2	(0.4)	9	(1.7)

Every participant is counted a single time for each applicable row and column.

A specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.

MedDRA V25.1 preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.

Database Cutoff Date: 09JAN2023

Use in pregnancy and lactation

There were no reports of pregnancy in the pembrolizumab plus chemoradiotherapy group.

Safety related to drug-drug interactions and other interactions

No dedicated DDI studies have been performed for this application.

Discontinuation due to adverse events

Adverse Events Leading to Discontinuation of Study Intervention.

The overall incidence of participants with an AE leading to discontinuation of any study treatment in the pembrolizumab plus chemoradiotherapy group was similar to the placebo plus chemoradiotherapy group (17.4% vs 14.2%).

The most frequently reported AEs (≥1% incidence) leading to discontinuation of any study treatment for participants in the pembrolizumab plus chemoradiotherapy group were neutropenia, leukopenia, anaemia, diarrhoea, neutrophil count decreased, and WBC count decreased with generally similar incidences reported in the placebo plus chemoradiotherapy group. These AEs are known adverse reactions to chemoradiotherapy. No AEs in the pembrolizumab plus chemoradiotherapy group resulted in discontinuation of any study treatment in ≥2% of participants.

The incidence of participants with an AE leading to discontinuation of any study treatment in the pembrolizumab plus chemoradiotherapy group was similar to the RSD (17.4% vs 14.0%).

All AEs leading to discontinuation of pembrolizumab/placebo occurred in <1% of participants.

A similar proportion (7.0% vs 3.0%) of participants discontinued pembrolizumab/placebo due to AEs in both treatment groups. The most frequently reported AEs (≥2 participants [0.4% incidence]) leading to discontinuation of pembrolizumab in the pembrolizumab plus chemoradiotherapy group were colitis, diarrhoea, pneumonitis, ALT increased, AST increased, and pruritus. These rates were lower than the RSD (14.0%), with no clinically meaningful differences in AEs between the groups.

Only 4 (0.8%) participants in each treatment group discontinued radiation therapy due to an AE.

Drug-related Adverse Events Leading to Discontinuation of Study Intervention

The overall incidence of participants with a drug-related AE leading to discontinuation of any study treatment was similar in both treatment groups (15.3% vs 12.6%).

The most frequently reported (incidence ≥1%) drug-related AEs leading to discontinuation of any study treatment for participants in the pembrolizumab plus chemoradiotherapy group were neutropenia, leukopenia, neutrophil count decreased, WBC count decreased and diarrhoea, with similar incidences of these AEs reported in the placebo plus chemoradiotherapy group.

The overall incidence of participants with a drug-related AE leading to discontinuation of any study treatment in the pembrolizumab plus chemoradiotherapy group was higher (≥5 percentage point difference) than the RSD (15.3% vs 8.4%).

All drug-related AEs leading to discontinuation of pembrolizumab/placebo occurred in <1% of participants.

Drug-related AEs which led to discontinuation of pembrolizumab/placebo were consistent between pembrolizumab plus chemoradiotherapy group (6.1%) and the RSD (8.4%). The most frequently reported drug-related AEs (≥2 participants [0.4% incidence]) leading to discontinuation of pembrolizumab in the pembrolizumab plus chemoradiotherapy group were colitis, diarrhoea, pneumonitis, ALT increased, and AST increased. These events are either immune-mediated adverse events, or associated symptoms or laboratory abnormalities, known to be associated with pembrolizumab.

Only 1 (0.2%) participant in the pembrolizumab plus chemoradiotherapy and 3 (0.6%) in the placebo plus chemoradiotherapy group discontinued radiation therapy due to a drug-related AE.

Adverse Events Leading to Interruption of Study Intervention

The overall incidence of participants with an AE leading to interruption of any study treatment in the pembrolizumab plus chemoradiotherapy group was higher (≥5 percentage point difference) than the placebo plus chemoradiotherapy group (58.7% vs 50.0%). This difference was primarily driven by events in the blood and lymphatic system disorders SOC, general disorders and administration site conditions SOC, infections and infestations SOC and investigations SOC.

The overall incidence of participants with an AE leading to interruption of any study treatment in the pembrolizumab plus chemoradiotherapy group was higher (≥5 percentage point difference) than the RSD (58.7% vs 26.1%). This was primarily driven by events in the blood and lymphatic system disorders SOC, infections and infestations SOC, and investigations SOC.

The proportion of participants with AEs resulting in interruptions of pembrolizumab/placebo was higher (≥5 percentage point difference) in the pembrolizumab plus chemoradiotherapy group compared with placebo plus chemoradiotherapy group (42.6% vs 35.5%). The most frequently reported AEs (≥5% incidence) leading to pembrolizumab/placebo interruptions included anaemia and COVID-19 and were similar in the pembrolizumab plus chemoradiotherapy and placebo plus chemoradiotherapy groups.

The overall incidence of AEs leading to interruption of pembrolizumab was higher in the pembrolizumab plus chemoradiotherapy group (42.6%) compared with the RSD (26.1%).

Drug-related Adverse Events Leading to Interruption of Study Intervention

The overall incidence of participants with a drug-related AE leading to interruption of any study treatment in the pembrolizumab plus chemoradiotherapy group was higher than the placebo plus chemoradiotherapy group (45.3% vs 37.7%). The most frequently reported (incidence ≥5%) drug-related AEs leading to interruption of any study treatment for participants in the pembrolizumab plus chemoradiotherapy group were anaemia, diarrhoea, neutrophil count decreased, platelet count decreased, WBC count decreased with generally similar incidences in the placebo plus chemoradiotherapy group.

The overall incidence of participants with a drug-related AE leading to interruption of any study treatment in the pembrolizumab plus chemoradiotherapy group was higher than the RSD (45.3% vs 14.7%). The proportions of participants with the following drug-related AEs leading to interruption of study treatment were higher (≥5 percentage point difference) in the pembrolizumab plus chemoradiotherapy group compared with the RSD: anaemia, platelet count decreased, neutrophil count decreased, and WBC cell count decreased. The higher incidences of these AEs in the pembrolizumab plus chemoradiotherapy group are consistent with the known safety profile of the chemoradiotherapy regimen and are therefore expected with the addition of chemoradiotherapy to pembrolizumab.

The overall incidence of drug-related AEs leading to interruption of pembrolizumab was higher in the pembrolizumab plus chemoradiotherapy group (18.6%) compared with the RSD (14.7%). The most frequently reported drug-related AEs leading to pembrolizumab interruptions in the pembrolizumab plus chemoradiotherapy group were anaemia, diarrhoea, AST and ALT increased, and rash. There was a higher (≥1% difference) proportion of participants with neutrophil count decreased in the pembrolizumab plus chemoradiotherapy group compared with the RSD, consistent with chemoradiotherapy-related toxicity in this treatment group and expected with the addition of chemoradiotherapy to pembrolizumab.

Post marketing experience

No revocation or withdrawal of pembrolizumab registration for safety reasons has occurred in any country.

2.5.1. Discussion on clinical safety

KEYNOTE-A18 is a randomized, phase 3, placebo-controlled clinical trial testing the addition of pembrolizumab to chemo-radiotherapy for patients with high-risk LACC. The safety profile in this report is based on the IA1 analysis, at the the data cutoff of 09 January 2023.

The median duration of exposure to study treatment was similar between patients in the 2 treatment groups (11.76 and 10.92 months).

The overall incidence of participants with 1 or more AEs was similar in the 2 treatment groups of KEYNOTE-A18.

When compared with the RSD for pembrolizumab monotherapy, the proportions of participants with drug-related AEs, Grade 3-5 AEs, Grade 3-5 drug-related AEs, drug-related SAEs, and discontinuations due to drug-related AEs were higher (≥5 percentage point difference) in the pembrolizumab plus chemoradiotherapy group. The higher rates for these AEs were anticipated, as participants in KEYNOTE-A18 received cisplatin and radiation in addition to pembrolizumab.

It can be assumed that the large majority of participants in KEYNOTE-A18 completed the combined phase of treatment with pembrolizumab or placebo and chemoradiotherapy within the 0-3 months observation period, as Q3 for the duration of radiotherapy was 57 days (**Table 16**). The analysis of exposure-adjusted events by observation period suggests that the safety profile of the pembrolizumab plus concurrent chemoradiotherapy phase (0-3 months observation period) appears to be as expected and generally consistent with the well-established safety profiles of pembrolizumab, platinum-based chemotherapy and radiotherapy. The safety profile of the pembrolizumab monotherapy phase (>3 months observation periods) is consistent with the well-established safety profile of pembrolizumab monotherapy, with the exception of some residual chemoradiation AEs.

The overall incidences of AEs, and the most frequently reported AEs (incidence ≥10%) were generally similar between the 2 treatment groups. Higher proportions of patients experienced leukopenia (24.4% vs 18.3%), hypokalaemia (21.6% vs 16.2%), AST increased (17.6% vs 12.5%), hypothyroidism (19.1% vs 4.5%), and hyperthyroidism (11.4%vs 2.1%) in the pembrolizumab plus chemoradiotherapy group. Of these events hypothyroidism and hyperthyroidism are immune-mediated AEs associated with pembrolizumab, while leukopenia and hypokalaemia are typically associated with cisplatin-based chemoradiotherapy. When adjusted for exposure, rates (in events per 100 person-months) of these AEs were generally similar between the 2 treatment groups. The AEs generally associated with chemoradiotherapy such as anaemia, nausea, diarrhoea, neutropenia, neutrophil count decreased, platelet count decreased, WBC count decreased, hypomagnesemia, and alopecia were similar in both treatment groups. The overall incidence of participants with 1 or more AEs in the pembrolizumab plus chemoradiotherapy group was similar to the RSD (99.4% vs 96.6%). The proportions of participants with the following AEs were higher (≥20% point difference) in the pembrolizumab plus chemoradiotherapy group compared with the RSD: anaemia, nausea, diarrhoea, WBC count decreased, neutrophil count decreased, hypomagnesemia, leukopenia, neutropenia, platelet count decreased. These AEs are consistent with the safety profile of cisplatin-based chemoradiotherapy.

The overall incidence of patients with a Grade 3 to 5 AE in the pembrolizumab plus chemoradiotherapy group was higher compared with the placebo plus chemoradiotherapy group (74.6% vs 68.7%), as it was for drug-related Grade 3 to 5 AE (67.0% vs 60.6%). The most frequently reported (incidence ≥10%) AEs in 2 treatment groups were WBC count decreased, anemia, neutrophil count decreased, leukopenia, lymphocyte count decreased, and neutropenia, events typically associated with cisplatin-based chemoradiotherapy. The overall incidence of participants with a Grade 3 to 5 AE in the pembrolizumab plus chemoradiotherapy group was higher (74.6% vs 46%) compared with the RSD, as well as for the

drug-related Grade 3 to 5 AE (67% vs 15.8%). The drug-related Grade 3 to 5 AEs reported in higher proportions in the pembrolizumab plus chemoradiotherapy group compared with the RSD (≥10% difference) were WBC count decreased, anemia, neutrophil count decreased, leukopenia, lymphocyte count decreased, and neutropenia. These AEs known to be associated with chemoradiotherapy, are expected with the addition of chemoradiotherapy to pembrolizumab.

The overall incidence of patients with 1 or more drug-related AEs in the pembrolizumab plus chemoradiotherapy group was the same as in the placebo plus chemoradiotherapy group (96.0% in each group). The observed incidences of the most frequently reported drug-related AEs (incidence ≥30%) were generally similar between the 2 treatment groups. The observed incidences of hypothyroidism (17.6% vs 3.6%) and hyperthyroidism (10.2% vs 2.1%) were higher in the pembrolizumab plus chemoradiotherapy group, compared with the placebo plus chemoradiotherapy group, consistently with an immune-mediated AEs associated with pembrolizumab.

The rate of drug-related AEs was generally similar across all toxicity grades in both treatment groups. The overall incidence of participants with drug-related AEs was higher in the pembrolizumab plus chemoradiotherapy group compared with the RSD (96.0% vs 71.6%).

The incidences of the following drug-related AEs were higher (≥20 percentage point difference) in the pembrolizumab plus chemoradiotherapy group compared with the RSD: anaemia, nausea, diarrhoea, WBC count decreased, neutrophil count decreased, vomiting, leukopenia, platelet count decreased, neutropenia. The differences are consistent with the safety profile of the chemoradiotherapy regimen administered.

The overall incidence of patients with an AE resulting in death in the pembrolizumab plus chemoradiotherapy group was similar (0.9% vs 1.1%) to the placebo plus chemoradiotherapy group and generally consistent with the RSD (4.5%). Overall, 5 patients in the pembrolizumab plus chemoradiotherapy and 6 patients in the placebo plus chemoradiotherapy groups, respectively, died due to an AE. Of these, AEs were considered to be drug-related, as assessed by the investigator, for 2 (0.4%) patients in the pembrolizumab plus chemoradiotherapy group (immune-mediated gastritis and large intestine perforation) and for 2 (0.4%) patients in the placebo plus chemoradiotherapy group (bone marrow failure and neutropenic colitis).

The overall incidence of patients with an SAE in the pembrolizumab plus chemoradiotherapy group was higher with pembrolizumab (28.4% vs 24.7%) compared with the placebo plus chemoradiotherapy group. Anemia, urinary tract infection, pyrexia, and diarrhea were reported most frequently (incidence ≥1%) for patients in both treatment groups. In addition, frequently reported SAEs (incidence ≥1%) included sepsis and vaginal hemorrhage in the pembrolizumab plus chemoradiotherapy group and acute kidney injury and pyelonephritis in the placebo plus chemoradiotherapy group. The overall incidence of patients with a drug-related SAE in the pembrolizumab plus chemoradiotherapy group was higher (17.2% vs 12.3%) compared with the placebo plus chemoradiotherapy group. Drug-related SAEs reported most frequently (incidence ≥1%) for patients included known chemoradiotherapy-related toxicities, anemia, pyrexia, and diarrhea in the pembrolizumab plus chemoradiotherapy group, and anemia in the placebo plus chemoradiotherapy group.

Incidence of AEOSI was higher with pembrolizumab compared to placebo (32.6% vs 11.7%). The most frequently reported AEOSI (incidence ≥1%) for patients in the pembrolizumab plus chemoradiotherapy group were hypothyroidism, hyperthyroidism, colitis, and pneumonitis.

The overall incidence of AEOSI was higher in the pembrolizumab plus chemoradiotherapy group compared with the well-established safety profile of pembrolizumab monotherapy in the RSD, primarily driven by events of hypothyroidism and hyperthyroidism.

Laboratory abnormalities were as expected, and mirrored the common AEs, and the addition of chemotherapy to pembrolizumab.

The overall incidence of patients with an AE leading to discontinuation of any study treatment in the pembrolizumab plus chemoradiotherapy group was slightly higher in the placebo plus chemoradiotherapy group (17.4% vs 14.2%) and was higher for AE leading to interruption of any study treatment (58.7% vs 50.0%). The most frequently reported AEs (≥1% incidence) leading to discontinuation of any study treatment for patients in the pembrolizumab plus chemoradiotherapy group were neutropenia, leukopenia, anemia, diarrhea, neutrophil count decreased, and WBC count decreased with generally similar incidences reported in the placebo plus chemoradiotherapy group.

With regard to the toxicity in special populations, the safety findings for pembrolizumab plus chemoradiotherapy based on age, race (data not shown), ECOG performance status, and geographic region were generally consistent with the established safety profile of pembrolizumab monotherapy, known safety profile of the chemoradiotherapy regimen, and the disease under study. Some regional differences were seen but appropriately discussed.

In more details, the safety profile of the combination appeared consistent across age ranges. However, in the 65 to 74 years old patients, incidences of drug-related SAEs and of discontinuations due to an AE (all causality and drug-related) were higher in the pembrolizumab plus chemoradiotherapy group compared with <65 years of age patients. Also, within the pembrolizumab plus chemoradiotherapy group, the incidences of drug-related Grade 3 to 5 and drug-related SAEs were higher in patients from the ex-EU regions, and there were higher incidences of discontinuations of any drug due to an AE (all and drug-related) in patients from the EU. Within the placebo plus chemoradiotherapy group, the incidences of Grade 3 to 5 AEs (all and drug-related) were higher in patients from the ex-EU region, while SAEs (all and drug-related) were higher in patients from the EU. The MAH provided additional data showing that some of the differences likely reflect differing styles of reporting toxicity AEs across regions (i.e. different terms used to express the same AE), especially haematological ones. Furthermore, Asia Pacific, EMEA and Latin America regions each accounted for approximately 30% of study patients, while the North America region accounted for only 7.5% of total patients enrolled in the study, therefore safety data from the latter subset should be interpreted with caution. The above is acknowledged, and no concern is raised.

The MAH was requested to discuss the safety according to the number of platinum cycles received. The standard in the study was 5 cycles, with an optional 6th cycle as per local practice. Most patients received 5 cycles of cisplatin (approximately 70% in both arms), while 6 cycles of cisplatin were received by 16-20% of the patents. Overall, 12% received 4 cycles or less. This was pretty similar between treatment arms, suggesting that the addition of pembrolizumab did not impair the possibility to receive the standard of care of cisplatin in terms of number of cycles. Overall safety was similar between patients who received 5 or 6 cycles of cisplatin, with the exception of some higher haematological toxicity in patients who received 5 rather than 6 cycles of cisplatin. However, this was observed both in the experimental and in the placebo arm. It is generally assumed that the majority of those patients went on to receive the 6th dose of cisplatin if they were able to tolerate the drug's side effects reasonably well. Furthermore, it is acknowledged the smaller sample size for patients who received 6 cycles.

The safety profile of pembrolizumab plus RT may not be the same as pembrolizumab alone. When safety was analysed by treatment phase, in the concurrent treatment phase, the majority of the most frequently observed AEs were those known to be associated with chemotherapy (e.g. haematological and GI AEs) and those known to be associated with pelvic radiation (e.g. diarrhoea, fatigue, urinary tract infection) in both treatment arms, with overall similar frequencies. In the monotherapy phase, the most frequently observed AEs included immune-mediated AEs known to be associated with pembrolizumab. It is agreed that no relevant increase in the frequencies of the individual AEs is seen when pembrolizumab is added to CCRT, and that the increase in immune-mediated AEs vs placebo is as expected.

The MAH's proposal to pool safety data from studies KEYNOTE-A18 and KEYNOTE-868 (primary advanced or recurrent endometrial cancer patients from procedure EMEA/H/C/003820/II/0153 running in parallel) with the pembrolizumab combo dataset in section 4.8 of the SmPC is considered acceptable. As a result of the updated safety pool, several ADRs frequencies as well as the paragraph for laboratory abnormalities for the combination with chemotherapy to include the data from KEYNOTE A-18 and KEYNOTE-868 have been updated in section 4.8 of the SmPC.

In addition, during procedure II-145 the MAH implemented corrections to the 'Laboratory abnormalities' paragraphs of SmPC Section 4.8 for pembrolizumab monotherapy and pembrolizumab in combination with axitinib or lenvatinib. Errors were identified in laboratory toxicity grade derivation for magnesium and incorrect classification and selection of other laboratory records for analysis for pembrolizumab clinical trials. It was concluded that these errors are not clinically significant and therefore, do not change the benefit-risk conclusion for the identified pembrolizumab clinical studies.

The corrections made to the laboratory toxicity grade values for pembrolizumab in combination with chemotherapy or chemoradiotherapy were included together with KEYNOTE-A18 safety updates in SmPC section 4.8.

2.5.2. Conclusions on clinical safety

Overall, the safety profile of pembrolizumab plus chemoradiotherapy is consistent with the established safety profiles of each component of the treatment (pembrolizumab, platinum-based chemotherapy, pelvic RT) and the site of the disease, and it was overall consistent with the safety profile of the pembrolizumab plus chemotherapy pooled dataset. In study KEYNOTE-A18, the addition of pembrolizumab appears to worsen to some extent the toxicity of CCRT which management is reflected in the SmPC. No new major safety concerns emerged. No changes to the Safety concerns, PhV plan and RMM were needed.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The MAH submitted an updated RMP version 44.1 with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 44 is acceptable.

The CHMP endorsed the Risk Management Plan version 44 with the following content:

Safety concerns

Table SVIII.1:Summary of Safety Concerns

Summary of safety concerns	
Important identified risks	Immune-mediated adverse reactions

Table SVIII.1:Summary of Safety Concerns

Summary of safety concerns	
Important potential risks	For hematologic malignancies: increased risk of severe complications of allogeneic stem cell transplantation (SCT) in patients who have previously received pembrolizumab Graft versus host disease (GVHD) after pembrolizumab administration in patients with a history of allogeneic stem cell transplant (SCT)
Missing information	None

Pharmacovigilance plan

There are no ongoing or planned additional pharmacovigilance studies that are required for pembrolizumab.

Risk minimisation measures

Table V.3.1: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	**Risk minimisation Measures**	**Pharmacovigilance Activities**
Important Identified Risks: Immune-Mediated Adverse Reactions		
Immune-mediated adverse reactions	Routine risk minimisation measures: • The risk of the immune-mediated adverse reactions associated with the use of pembrolizumab is described in the SmPC, Section 4.2, 4.4, 4.8 and appropriate advice is provided to the prescriber to minimize the risk.	Routine pharmacovigilance activities
	Additional risk minimisation measures: • Patient card	Additional pharmacovigilance including: • Safety monitoring in all ongoing MAH-sponsored clinical trials for pembrolizumab in various tumor types
Important Potential Risks		

Table V.3.1: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk minimisation Measures	Pharmacovigilance Activities
For hematologic malignancies: increased risk of severe complications of allogeneic SCT in patients who have previously received pembrolizumab	Routine risk minimisation measures: • For Hematologic malignancies: the increased risk of severe complications of allogeneic SCT in patients who have previously received pembrolizumab is described in the SmPC, Section 4.4, 4.8 and appropriate advice is provided to the prescriber to minimize the risk.	Routine pharmacovigilance activities
	No additional risk minimisation measures warranted	Additional pharmacovigilance including: • Safety monitoring in the ongoing HL trial (KN204).
GVHD after pembrolizumab administration in patients with a history of allogeneic SCT	Routine risk minimisation measures: • GVHD after pembrolizumab administration in patients with a history of allogeneic SCT is described in the SmPC, Section 4.4 and appropriate advice is provided to the prescriber to minimize the risk. No additional risk minimisation measures warranted	Routine pharmacovigilance activities Additional pharmacovigilance including: • Safety monitoring in all ongoing MAH-sponsored clinical trials for pembrolizumab in various tumor types

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons: the changes to the patient leaflet are minimal; in particular the key messages for the safe use of the medicinal product are not impacted. Furthermore, the design, layout and format of the package leaflet will not be affected by the proposed revisions.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

KEYTRUDA, in combination with chemoradiotherapy (external beam radiation therapy followed by brachytherapy), is indicated for the treatment of FIGO 2014 Stage III - IVA locally advanced cervical cancer in adults who have not received prior definitive therapy.

The initially sought indication by the MAH also encompassed patients with Stage IB2-IIB (with node-positive) disease.

3.1.2. Available therapies and unmet medical need

Concurrent chemoradiotherapy (CRT) is the standard of care for LACC (FIGO 2014 Stage IB2–IVA disease) and has a curative intent. Weekly cisplatin is the most commonly used regimen as radiosensitizer, given concomitantly with RT. Brachytherapy should be added to chemoRT to maximize disease control[33]. The addition of durvalumab to CCRT and continued thereafter did not show statistically significant PFS improvement in the recent CALLA study[34]. Effective new treatment modalities to reduce the risk of recurrence and increase the cure rate are needed to improve the prognosis of women diagnosed with high-risk LACC.

3.1.3. Main clinical studies

The pivotal study is KEYNOTE-A18, an ongoing phase III randomized double-blind placebo-controlled multicenter clinical trial of chemoradiotherapy (CCRT) with or without pembrolizumab in 1060 patients with LACC (FIGO 2014 Stage IB2-IIB [with node-positive disease] or Stage III-IVA [either node-positive or node-negative disease]). Pembrolizumab (200 mg Q3W for 5 infusions) was administered in combination with CCRT (max 56 days), then continued as monotherapy (400 mg Q6W for 15 infusions) for a total treatment duration of 2 years. The efficacy data initially submitted was the IA1 analysis (DCO 09-JAN-2023) with median follow-up of 17 months (range: 0.9 to 31 months). During the procedure, updated results from IA2 (DCO 08-JAN-2024) with median follow-up of 27.5 months (range: 0.9 to 43 months). At the DCO, approximately 16% of patients were still under pembrolizumab/placebo treatment in both arms.

3.2. Favourable effects

- KEYNOTE-A18 met its primary endpoint PFS by investigator per RECIST1.1 in ITT population at IA1 [PFS HR 0.70 (95% CI: 0.55, 0.89), p 0.0020 1-sided]. At IA2, descriptive updated PFS analysis confirmed prior results.
- At the IA2, also OS reached statistical significance in the ITT population [OS HR 0.67 (95% CI 0.50, 0.90), p=0.0040].

[33] Marth C, Landoni F, Mahner S, McCormack M, Gonzalez-Martin A, Colombo N; ESMO Guidelines Committee. Cervical cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2017 Jul 1;28(suppl_4):iv72-iv83.
[34] Monk BJ, Toita T, Wu X, et al. Durvalumab versus placebo with chemoradiotherapy for locally advanced cervical cancer (CALLA): a randomised, double-blind, phase 3 trial. Lancet Oncol. 2023 Dec;24(12):1334-1348.

- The results in the ITT appeared driven by patients with higher disease stage III-IVA according to FIGO 2014. In patients with Stage III-IVA disease, subgroup analysis results at IA2 showed PFS and OS improvement with the addition of pembrolizumab: PFS HR 0.57 (95% CI: 0.43, 0.76), OS HR 0.57 (95% CI: 0.39, 0.83). PFS KM curves diverge from month 3 and remain well separated, OS KM curves also diverge since the beginning, although highly censored after month 12. Although this is a subgroup analysis for which the study was not powered for, disease stage was a stratification factor and both subgroups were well represented (approximately 43% of the ITT population were FIGO 2014 Stage IB2-IIB LN+, vs 57% FIGO 2014 Stage III-IVA).

3.3. Uncertainties and limitations about favourable effects

- Although biological plausibility of a possible predictive effect of PD-L1 expression in the LACC setting cannot be excluded, the subgroup of patients with CPS<1 is too small (<5% of the ITT population, 22 vs 28 patients) and number of events low to make any meaningful conclusion over the results in PD-L1 negative subjects. Thus, restricting the indication based on PD-L1 status does not seem sufficiently justified by available data from KEYNOTE-A18. Taking into account the low number of PD-L1 negative tumours in this disease setting, the clinical utility of selecting patients by PD-L1 expression is limited.

3.4. Unfavourable effects

- The addition of pembrolizumab to RT in LACC is associated with an increase in selected AEs, particularly leukopenia, hypokalaemia, AST increased, hypothyroidism, and hyperthyroidism.
- KEYNOTE-A18 showed that the addition of pembrolizumab appear to worsen to some extent toxicity of CCRT, however the overall safety profile of the pembrolizumab + CCRT combination is consistent with the well-established safety profiles of pembrolizumab monotherapy and the chemoradiotherapy regimen in this LACC participant population, and the management of them is articulated in the SmPC.
- No new major safety concerns emerged.

3.5. Uncertainties and limitations about unfavourable effects

None.

3.6. Effects Table

Table 76: Effects Table for Keytruda in combination with chemoradiotherapy (external beam radiation therapy followed by brachytherapy) in adults with FIGO 2014 Stage III - IVA locally advanced cervical cancer who have not received prior definitive therapy

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects (IA2)						
PFS by Inv per RECIST 1.1 in patients with stage III - IVA disease	Progression free survival	HR (95 %CI)	0.57 (0.43, 0.76)		Subgroup analysis not adjusted for multiplicity Primary analysis in ITT was statistically significant at IA1 and, at IA2 confirmed prior result with longer FU (34% of events in the	CSR

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
					selected subpopulation) Median PFS time were not reached in any of the arms	
OS in patients with stage III - IVA disease	Overall survival	HR (95 %CI)	0.57 (0.39, 0.83)		Subgroup analysis not adjusted for multiplicity Primary OS analysis in ITT reached statistical significance at IA2; Maturity remains low, 19% of events in the selected sub population	
Unfavourable Effects (IA1)						
Drug-related AE		%	96	96	The safety profile of pembrolizumab added to RT and chemotherapy appears to worsen, but the reported AEs are well known and management of them articulated in the SmPC. No new major safety concerns emerged.	CSR
G3-5 drug-related AE		%	67	61		
Drug-related SAE		%	17.2	12.3		
Drug-related deaths		%	0.4	0.4		
Discontinuation due to drug-related AE		%	15.3	12.6		
Leukopenia		%	24.4	18.3		
Hypokalaemia		%	21.6 (5.5 G3-4)	16.2 (3.8 G3-4)		
AST increased			17.6	12.5		
Hypothyroidism		%	19.1	4.5		
Hyperthyroidism		%	11.4	2.1		

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

KEYNOTE-A18 showed a statistically significant improvement in PFS by Investigator (at IA1) and also in OS (at IA2) for the addition of pembrolizumab to concurrent chemoradiotherapy then continued as monotherapy for the treatment of locally advanced cervical cancer patients in the ITT population (FIGO 2014 Stage IB2-IIB LN+ and Stage III-IVA). PFS2 data represent a longer-term clinical benefit of pembrolizumab plus chemoradiotherapy and delayed progression on the next anti-cancer therapy. In general, the activity in terms of ORR was similar between treatment arms thus mostly due to chemo-RT rather than by the activity of the added pembrolizumab. PFS advantage was confirmed at IA2 with longer follow-up, which is reassuring. OS analysis at IA2 is not yet the final one, and it is still considered not sufficiently mature and interpretable especially in patients with earlier disease stage (Stage IB2-IIB LN+) having with better prognosis and lower risk of recurrence. Based on subgroup analysis, the result in the ITT population was driven by patients with higher disease FIGO 2014 Stage III-IVA, in whom the advantage in PFS and OS is not questioned. On the contrary, in FIGO 2014 Stage IB2-IIB LN+, the benefit was considered marginal in PFS, with no OS benefit seen. Even though the study was not powered to measure treatment effect within these subgroups, disease stage was a stratification factor and each subset (601 patients in higher stages, and 459 in the lower stages) represented a significant fraction of

the ITT population. Although the apparent difference in clinical benefit between disease stage subgroups could be due to the lower maturity of OS data in patients with stage IB2-IIB LN+ disease, this remains hypothetical.

The overall safety of the pembrolizumab + CCRT combination is consistent with the well-established safety profiles of pembrolizumab monotherapy and the chemoradiotherapy regimen in this LACC population, with no new safety concern. While some additional toxicity is inevitable due to the addition of pembrolizumab with its well-known immune side effect, it is of reassurance that no relevant difference in the frequencies is seen in the concomitant phase when pembrolizumab is added to CCRT, and that the additional toxicity does not seem to impair the possibility to receive full standard radiotherapy treatment. On the other hand, some increased toxicity especially in some selected AEs is noted, and immune-related side effects (including long-term or irreversible ones) may occur with pembrolizumab, which is of particular relevance when patients are potentially cured.

3.7.2. Balance of benefits and risks

Efficacy in the ITT population was driven by patients with higher disease FIGO 2014 Stage III-IVA, in whom, based on updated data, a positive benefit/risk balance is concluded.

Subgroup analyses results from a reasonably sized subset used as stratification factor suggest marginal PFS absolute benefit with no OS difference in FIGO 2014 Stage IB2-IIB LN+ cervical cancer patients. A plateau in PFS curve is not yet reached and OS is still immature, and available follow-up (median 27 months) does not yet allow sufficient observation-time for non-progression based on the disease natural history, risk of recurrence (i.e. about 3 years from baseline) and treatment duration (24 months). The observed benefit does not counterbalance the risks and burden for the addition of pembrolizumab to CCRT followed by 2 years of maintenance in this subgroup with better prognosis where a fraction of patients is already cured by CCRT alone. In conclusion, in patients with Stage IB2-IIB LN+ cervical cancer patients, the B/R of pembrolizumab added to CCRT and then continued as maintenance therapy is considered negative, and the indication was restricted to only for higher disease Stages FIGO 2014 Stage III-IVA.

3.7.3. Additional considerations on the benefit-risk balance

None.

3.8. Conclusions

The overall B/R of Keytruda is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends, by a majority of 31 out of 32 votes, the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include in combination with chemoradiotherapy (external beam radiation therapy followed by brachytherapy), the treatment of FIGO 2014 Stage III - IVA locally advanced cervical cancer in adults who have not received prior definitive therapy for Keytruda, based on the results from pivotal Phase III study KEYNOTE-A18. As a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet and the Risk Management Plan version 44 are updated in accordance.

The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annexes I and IIIB and to the Risk Management Plan are recommended.

Divergent position to the majority recommendation is appended to this report.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'Keytruda-3820-II-0145'.

Attachments

1. Product information (changes highlighted) as adopted by the CHMP on 19 September 2024.

Appendix

5.1. Divergent position to the majority recommendation

DIVERGENT POSITION DATED 19 September 2024

EMEA/H/C/003820/II/0145

The undersigned member of the CHMP did not agree with the CHMP's opinion recommending the variation to the terms of the marketing authorisation for Keytruda, concerning the extension of indication to include, in combination with chemoradiotherapy (external beam radiation therapy followed by brachytherapy), the treatment of high-risk locally advanced cervical cancer in adults who have not received prior definitive therapy [Stage III-IVA based on FIGO 2014], while the initially sought indication also encompassed patients with *Stage IB2-IIB (with node-positive disease)* high-risk locally advanced cervical cancer*.*

The reason for divergent opinion was the following:

The pivotal Keynote-018 study met its primary PFS endpoint in the ITT population, with a HR of 0.70 in the inferential analysis. At the second prespecified analysis, an OS gain was established (HR=0.67).
Subgroup results in node positive Stage IB2-IIB and Stage III – IVA differ. In the former, the PFS HR point estimate and 95% CI is 0.85 (0.62, 1.16). In the latter, the PFS HR is 0.57 (0.43, 0.76).
These subgroup results are not type 1 error controlled; moreover, the precision of estimates is obviously lower than for the ITT population.
There is no clear biological rationale why the relative efficacy of pembrolizumab would differ depending on disease stage and the consequent absolute risk of a progression event. Therefore, the ITT estimate rather than subgroup results may be the most reliable estimation of relative efficacy in both the abovementioned subgroups.
Whereas relative efficacy may not be anticipated to differ depending on disease stage, absolute benefit for an adjuvant therapy will differ depending on the absolute risk of relapse.
As stated above, an overall OS benefit was shown in the ITT population. HR estimates for the lower and higher risk subgroups are 0.90 (0.56, 1.44) and 0.57 (0.39, 0.83). As anticipated, the event rate is lower in lower risk patients, and the estimate therefore less precise. The side effect profile of PD-1 targeting drugs is well described and no new findings have emerged. There is no indication of a detrimental OS in either of the mentioned subgroups.
Drawing a line with respect to what anticipated absolute benefit merits the use of an adjuvant therapy, including its adverse effect burden, in an individual patient, is a matter of personal preference rather than scientific determination. This is decided by patient and doctor.
In summary, a 30% reduction in the risk of progression and an overall survival gain has been shown for the treatment of locally advanced cervical cancer in adults who have not received prior definitive therapy [Stage IB2-IIB (with node-positive disease) or Stage III-IVA based on FIGO 2014]. The adverse effects profile is acceptable given the proposed use. The rationale for restricting use to patients with stage III-IVA disease based on subgroup analysis is not agreed.

Kristina Dunder

Reminders to the MAH

1. In accordance with Article 13(3) of Regulation (EC) No 726/2004 the Agency makes available a European Public Assessment Report (EPAR) on the medicinal product assessed by the Committee for Medicinal Products for Human Use. The EPAR is first published after the granting of the initial marketing authorisation (MA) and is continuously updated during the lifecycle of the medicinal product. In particular, following a major change to the MA, the Agency further publishes the assessment report of the CHMP and the reasons for its opinion in favour of granting the change to the authorisation, after deletion of any information of a commercially confidential nature.

   Should you consider that the CHMP assessment report contains commercially confidential information, **please provide the EMA Procedure Assistant your proposal for deletion of commercially confidential information** (CCI) in "track changes" and with detailed justification by **11 October 2024**. The principles to be applied for the deletion of CCI are published on the EMA website at https://www.ema.europa.eu/en/documents/other/heads-medicines-agencies/european-medicines-agency-guidance-document-identification-commercially-confidential-information_en.pdf

   In addition, should you consider that the CHMP assessment report contains personal data, please provide the EMA Procedure Assistant your proposal for deletion of these data in "track changes" and with detailed justification by **11 October 2024**. We would like to remind you that, according to Article 4(1) of Regulation (EU) 2016/679 (General Data Protection Regulation, "GDPR") 'personal data' means any information, relating to an identified or identifiable natural person (the 'data subject'). An identifiable natural person is one who can be identified, directly or indirectly, in particular by reference to an identifier such as a name, an identification number, location data, an online identifier or to one or more factors specific to the physical, physiological, genetic, mental, economic, cultural or social identity of that natural person.

   It is important to clarify that pseudonymised data are also considered personal data. According to Article 4(5) of GDPR pseudonymisation means that personal data is processed in a manner that the personal data can no longer be attributed to a specific data subject without the use of additional information (e.g. key-coded data).

   Accordingly, the name and the patient identification number are two examples of personal data which may relate to an identified or identifiable natural person. The definitions also encompass for instance: office e-mail address or phone number of a company, data concerning health, e.g. information in medical records, clinical reports or case narratives which relates to an identifiable individual."

2. The MAH is reminded to submit an eCTD closing sequence with the final documents provided by Eudralink during the procedure (including final PI translations, if applicable) within 15 days after the Commission Decision, if there will be one within 2 months from adoption of the CHMP Opinion, or prior to the next regulatory activity, whichever is first. If the Commission Decision will be adopted within 12 months from CHMP Opinion, the closing sequence should be submitted within 30 days after the Opinion. For additional guidance see chapter 4.1 of the Harmonised Technical Guidance for eCTD Submissions in the EU.

3. If a revised RMP is being approved as part of this procedure, **please send to the EMA Procedure Assistant** one redacted PDF document containing the RMP body, Annex 4 and Annex 6, as applicable, together with a redacted RMP file that can show the content that is proposed for redaction, and the signed RMP Publication Declaration, **by 11 October 2024**.