24 March 2022
EMA/224169/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Keytruda

International non-proprietary name: pembrolizumab

Procedure No. EMEA/H/C/003820/II/0117

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
1L	First-line
AE	Adverse event(s)
AEOSI	Adverse events of special interest
APaT	All Participants as Treated
BICR	Blinded Independent Central Review
cHL	Classical Hodgkin lymphoma
CI	Confidence interval
CIN	Cervical intraepithelial neoplasia
CPS	Combined Positive Score
CR	Complete response
CRC	Colorectal cancer
dMMR	Mismatch repair deficient
DOR	Duration of response
ECOG PS	Eastern Cooperative Oncology Group Performance Status
ESMO	European Society for Medical Oncology
EU	European Union
US FDA	United States Food and Drug Administration
HNSCC	Head and neck squamous cell carcinoma
HR	Hazard ratio
IA1	Interim analysis 1
ITT	Intention-to-treat
mAb	Monoclonal antibody
MSI-H	Microsatellite instability-high
NCCN	National Comprehensive Cancer Network
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PD-L1	Programmed cell death ligand 1

Abbreviation	Definition
PD-L2	Programmed cell death ligand 2
PFS	Progression-free survival
PK	Pharmacokinetic
PR	Partial response
PRO	Patient-reported outcomes
Q6W	Every 6 weeks
RCC	Renal cell carcinoma
RECIST	Response Evaluation Criteria In Solid Tumors
RSD	Reference safety data
SAE	Serious adverse event
TNBC	Triple-negative breast cancer
US	United States
USPI	United States Package Insert
WBC	White blood cell
WOCBP	Women of childbearing potential

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 12 October 2021 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 a new indication for Keytruda, in combination with chemotherapy, with or without bevacizumab, for the treatment of persistent, recurrent, or metastatic cervical cancer in adults; as a consequence, sections 4.1 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 38.1 of the RMP has also been submitted.

The variation requested amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (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 not yet completed as some measures were deferred.

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 28 June 2018 (EMEA/H/SA/2437/23/2018/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: Armando Genazzani Co-Rapporteur: Jan Mueller-Berghaus

Timetable	Actual dates
Submission date	12 October 2021
Start of procedure	30 October 2021
CHMP Rapporteur's preliminary assessment report circulated on	22 December 2021
PRAC Rapporteur's preliminary assessment report circulated on	30 December 2021
CHMP Co-Rapporteur Critique circulated on	5 January 2022
PRAC RMP advice and assessment overview adopted by PRAC on	13 January 2022
Request for supplementary information adopted by the CHMP on	27 January 2022
MAH's responses submitted to the CHMP on	1 February 2022
CHMP Rapporteur's preliminary assessment report on the MAH's responses circulated on	11 March 2022
CHMP Opinion	24 March 2022

2. Scientific discussion

2.1. Introduction

The scope of this type II variation is to include a new indication for KEYTRUDA in combination with chemotherapy, with or without bevacizumab, for the treatment of persistent, recurrent, or metastatic cervical cancer in adults, based on the results from KEYNOTE-826 study.

2.1.1. Problem statement

Disease or condition

The initial claimed indication is "KEYTRUDA, in combination with chemotherapy with or without bevacizumab, is indicated for the treatment of persistent, recurrent, or metastatic cervical cancer in adults".

The indication was updated during the procedure to "KEYTRUDA, in combination with chemotherapy with or without bevacizumab, is indicated for the treatment of persistent, recurrent, or metastatic cervical cancer in adults whose tumours express PD-L1 with a CPS ≥ 1".

Epidemiology and risk factors, screening tools/prevention

Globally, cervical cancer is the fourth most common cancer in women, with approximately estimated 600,000 new cases in 2020, representing 6.5% of all female cancers (Sung H, 2021). Approximately 350,000 deaths from cervical cancer occurred in 2020, 90% of them in low- and middle-income

countries. Rates in EU and US are much lower, ranking 20th (1%) among all new cancer cases. In Europe, incidence (age standardized rate per 100,000) ranges from 7 in Western Europe to 14.5 in Eastern Europe (Sung H, 2021), yielding roughly 61,000 new cases in 2018. Mortality (per 100,000) ranges from 2.1 (Northern) to 6.6 (Central/Eastern) with nearly 26,000 deaths in 2018 (Ferlay J, 2018).

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 (ESMO GL Marth C, 2017). Immunization against HPV prevents infection with the types of HPV against which the vaccine is designed and thus is expected to prevent specific HPV cancer in women (NCCN GL). Cervical cancer screening programmes have reduced incidence and death rates. For many years, the Papanicolaou (Pap) test has been the standard method for cervical cancer screening. More recently, an HPV test has been introduced as a screening tool as HPV DNA is present in almost all cervical cancers and it has demonstrated higher sensitivity for high grade cervical intraepithelial neoplasia (CIN2+) than that achieved by cytology in several studies (ESMO GL). The WHO recommends the screening of the general population of women aged 30 to 49 years using HPV DNA detection as the primary screening test at a regular screening interval of every 5 to 10 years. Where HPV DNA testing is not yet operational, WHO suggests a regular screening interval of every 3 years when using visual inspection with acetic acid or cytology as the primary screening test. Screening should be coupled with timely and efficacious treatment of precancerous lesions (WHO, 2021).

Therefore, primary prevention of cervical cancer is possible via immunisation with HPV vaccines and secondary prevention has gained impetus with the advent of sensitive HPV DNA testing to improve traditional Pap cytology screening programmes (Marth C, 2017).

Other important cofactors include smoking, some sexually transmittable infections, a higher number of childbirths, early age of onset of coitus, large number of sexual partners, long-term use of oral contraceptives, and chronic immunosuppression (NCCN GL; Herrero R, 2018).

Biologic features

Squamous cell carcinomas account for 70%–80% of cervical cancers and adenocarcinomas for 20%–25% (ESMO GL). Patients with adenocarcinoma and squamous cell carcinoma undergo the same standard treatment, even though these histologic subtypes differ substantially in terms of HPV and mutation status (HPV16 for SCC, HPV18 for adenocarcinoma), immune infiltrate, response to therapy, and patient outcome. Several retrospective studies showed that patients with adenocarcinoma have a higher risk of developing metastases, resulting in a poorer prognosis (Rotman J, 2020).

Approximately 5–11% of all cervical cancers are reported to be HPV-negative, which can be attributed to truly negative and false-negative results. The truly HPV-negative cervical cancers are almost all cervical adenocarcinomas with unclear aetiology (Xing B, 2021).

Clinical presentation, diagnosis and stage/prognosis

Due to current screening procedures used in Western countries for the early detection of CIN and cervical cancer, almost half of the newly diagnosed adult cervical cancer patients have Stage I localized cancer, with a 5-year survival rate of over 90%. Five-year survival rates decrease with stage at diagnosis, becoming as low as 15-17% for metastatic disease (Lorin, 2015; Munich cancer registry 2016; SEER Cervical Cancer).

The median age at the diagnosis of cervical cancer is 50 years (CDC statistics).

Management

Treatment options for cervical cancer in adults include surgery (conization and hysterectomy), radiation, and chemotherapy alone or in combination, depending on the stage of the disease (NCCN).

Chemotherapy is often recommended for patients with extrapelvic metastases or recurrent disease who are not candidates for RT or exenterative surgery. Patients who develop distant metastases, either at initial presentation or at relapse, are rarely curable, and systemic treatment is provided for palliation, aiming of relieving symptoms and improving quality of life, is indicated if the patient has a performance status (PS) <=2 and no formal contraindications (NCCN, ESMO). Cisplatin-based doublets with topotecan or paclitaxel have demonstrated superiority to cisplatin monotherapy in terms of response rate and PFS, especially in patients previously exposed to CRT where cisplatin was used as radiosensitizer (Moore, 2004; Long, 2005). A large randomised phase III trial (GOG-204) comparing four different cisplatin-based doublets with paclitaxel, topotecan, gemcitabine or vinorelbine was unable to demonstrate the superiority of any regimen. Nevertheless, paclitaxel–cisplatin showed the highest response rate (29%), median PFS (5.8 months) and median OS (12.8 months) and was considered the preferred regimen based on the balance between efficacy and toxicity profile (ESMO GL; Monk BJ, 2009). The GOG-240 study explored the addition of bevacizumab to chemotherapy in a randomised phase III trial with a 2x2 factorial design in which OS was the primary endpoint. Patients with primary stage IVB or recurrent/persistent, PS 0 or 1 and measurable disease were randomised to paclitaxel–cisplatin or paclitaxel–topotecan, both with or without bevacizumab. The median OS was significantly prolonged by the addition of bevacizumab (16.8 vs 13.3 months; HR 0.765; 95% CI: 0.62–0.95; p=0.0068) and non-platinum doublet resulted not superior to cisplatin–paclitaxel, even in the population previously treated with cisplatin. Patients treated with bevacizumab had a higher risk of grade 2 hypertension (25% vs 1.8%), grade 3 venous thromboembolic events (8.2% vs 1.8%) and grade 2 fistula (8.6% vs 1%) (Tewari KS, 2014). A 2017 systemic review and meta-analysis found a trend towards improved OS with the addition of bevacizumab to chemotherapy. Paclitaxel and cisplatin combined with bevacizumab is considered the preferred first-line regimen in metastatic or recurrent cervical cancer, based on the balance between efficacy and toxicity profile (ESMO, NCCN). Based on the results of GOG-240 study, bevacizumab was approved in EU in 2015 with the following indication: "Bevacizumab, in combination with paclitaxel and cisplatin or, alternatively, paclitaxel and topotecan in patients who cannot receive platinum therapy, is indicated for the treatment of adult patients with persistent, recurrent, or metastatic carcinoma of the cervix (see Section 5.1)." (EPAR Avastin II/72).

The combination of paclitaxel and carboplatin could be considered an alternative for patients that are not candidates for cisplatin, especially in patients who have already received cisplatin based on the results of a Japanese randomised clinical trial (JCOG0505) (ESMO GL, NCCN, Kitagawa 2015). Based on the collective findings of GOG-240 and JCOG0505, the NCCN guidelines added the combination carboplatin/paclitaxel/bevacizumab as an alternative treatment option. Approximately 59% of patients in the US in clinical setting receive a 1L bevacizumab-containing regimen (Kantar Health, cervical cancer U.S., 2021). The single-arm CECILIA study evaluated bevacizumab in combination with carboplatin–paclitaxel for advanced cervical cancer. The study concluded that bevacizumab can be combined with carboplatin–paclitaxel in this population, and the fistula/gastrointestinal perforation incidence was in line with GOG-0240; efficacy results were encouraging, within the limits of the single arm study (Redondo A, 2020).

According to ESMO guidelines, in patients progressing following first-line therapy, different cytostatic agents, including vinorelbine, topotecan, gemcitabine or nanoparticle albumin-bound paclitaxel have been evaluated. However, response rates are low and duration of responses is short. Therefore, no recommendation can be given about the most effective second-line treatment (ESMO GL).

KEYTRUDA received FDA accelerated approval for second and later lines of treatment for recurrent or metastatic cervical cancer which has progressed on or after chemotherapy in participants who are PD-L1 positive (CPS ≥1) based on ORR of 14.3% with 91% of responses lasting for at least 6 months based on the results of KEYNOTE-158 (Chung HC, 2019).

To date, a recently completed RCT (EMPOWER-Cervical 1) with another anti-PD1 agent cemiplimab (not yet approved in any country) showed significantly improved OS compared with chemotherapy in recurrent or metastatic cervical cancer following progression after 1L platinum-based chemotherapy. Median OS for cemiplimab was 12.0 months versus 8.5 months for chemotherapy alone (HR 0.69). In this study, patients treated with cemiplimab who had positive PD-L1 expression on tumor cells benefited the most (median OS, 13.9 months) in comparison with those with negative PD-L1 expression (7.7 months) and those treated with chemotherapy (0.70 in PD-L1 positive, 0.98 in PD-L1 negative; PFS HR 0.75 vs 1, and ORR 18.3% vs 11.4% in PD-L1 positive vs negative tumors, respectively) (Tewari KS, 2021).

2.1.2. About the product

Pembrolizumab is a highly selective humanized monoclonal antibody that binds to human programmed cell death 1 (PD-1) and blocks the interaction between the PD-1 pathway receptor and its ligands, programmed cell death 1 ligand 1 (PD-L1) and 2 (PD-L2) on antigen presenting tumor cells.

In the EU, pembrolizumab is currently approved, as monotherapy and in combination with other agents, for the treatment of melanoma, NSCLC, RCC, HNSCC, MSI-H or dMMR tumours (CRC, endometrial carcinoma, gastric, small intestine, or biliary cancer), urothelial cancer, oesophageal cancer, breast cancer, endometrial carcinoma and cHL. This is the first extension of indication requested for cervical cancer.

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

An overview of the Phase 3 clinical development program for cervical cancer is provided in the table below:

Table 1. 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, ongoing

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, Locally Advanced Cervical Cancer	Enrollment ongoing (~980 participants expected to be 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 OS	Enrolling, Ongoing
Abbreviations: BICR = blinded independent central review; CPS = combined positive score; OS = overall survival; PD-L1 = programmed cell death ligand 1; PFS = progression-free survival				

CHMP scientific advice was obtained on the study design of the pivotal study KEYNOTE-826 in EU on 28-JUN-2018 (EMEA/H/SA/2437/23/2018/II). CHMP concluded that the trial may be acceptable as such but would present a difficult case to assess due to the heterogeneity in the study population and the potential that efficacy gains may be offset by toxicity. In the proposed setting, the CHMP considered OS as the preferred primary endpoint, and commented to be in the position to assess mature OS data in order to properly assess the B/R in all subgroups.

The change of primary endpoint PFS from BICR to investigator assessment was discussed with FDA (Meeting type B, 23 Feb 2021, minutes included in the dossier). FDA noted that the proposed change is at the Sponsor's discretion and the acceptability of the approach will be a review issue.

Additionally, a pre-submission meeting was held with the EU Rapporteurs and EMA on 26-JUL-2021, where results from the KEYNOTE-826 study were presented and discussed in view of the planned Type II variation application.

2.1.4. General comments on compliance with GCP

The MAH claimed that KEYNOTE-826 study was conducted in conformance with applicable country or local requirements regarding ethical committee review, informed consent, and other statutes or regulations regarding the protection of the rights and welfare of human participants in biomedical research.

The assessment of KEYNOTE-826 data did not raise concern over GCP compliance leading to request for GCP inspection.

2.2. Non-clinical aspects

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

2.2.1. Ecotoxicity/environmental risk assessment

According to the Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00) proteins are exempted from the submission of ERA studies because they are unlikely to result in significant risk to the environment. Pembrolizumab is a protein, therefore an ERA has not been submitted by the MAH. This is acceptable.

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 2. Tabular overview of clinical studies

Study ID	Phase	Country/ Region	Study Title	Study design	Dosing regimen	Study population	Participant exposure
KEYNOTE-826 [Ref. 5.3.5.1: P826V01MK3475]	3	Australia Asia (Israel, Japan, South Korea, Taiwan) Central America (Mexico) Europe (France, Germany, Italy, Spain, Ukraine) North America (Canada, USA) Russia South America (Argentina, Chile, Colombia, Peru) Turkey	A 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 (KEYNOTE-826)	Randomized, double-blind, placebo-controlled, multicenter, global study	Pembrolizumab: 200 mg by intravenous infusion every 3 weeks (Q3W) Placebo (saline solution): 0 mg by intravenous infusion Q3W	Females Age: 22 to 82 years with persistent, recurrent, or metastatic squamous cell carcinoma, adenosquamous carcinoma, or adenocarcinoma of the cervix which had not been treated with systemic chemotherapy and was not amenable to curative treatment (such as with surgery and/or radiation)	Pembrolizumab: 307 Placebo: 309

2.3.2. Pharmacokinetics

Pembrolizumab PK disposition has been characterized via pooled population PK analyses using serum concentration-time data contributed from subjects across various clinical studies using a time-dependent PK (TDPK) model. The PK reference dataset for monotherapy includes all available PK data from subjects enrolled on KEYNOTE-001, KEYNOTE-002, KEYNOTE-006, KEYNOTE-010, and KEYNOTE-024, with an overall sample size of 2993. This serves as the PK reference analysis to support descriptions of pembrolizumab pharmacokinetics in the USPI and EU SmPC.

Absorption

Pembrolizumab is dosed via the intravenous route and therefore is immediately and completely bioavailable.

Distribution

Consistent with a limited extravascular distribution, the volume of distribution of pembrolizumab at steady state is small (6.0 L; coefficient of variation [CV]: 20%). As expected for an antibody, pembrolizumab does not bind to plasma proteins in a specific manner.

Elimination

Pembrolizumab CL is approximately 23% lower (geometric mean, 195 mL/day [CV%: 40%]) after achieving maximal change at steady state compared with the first dose (252 mL/day [CV%: 37%]); this decrease in CL with time is not considered clinically meaningful. The geometric mean value (CV%) for the terminal half-life is 22 days (32%) at steady-state.

Pharmacokinetic in subjects with cervical cancer

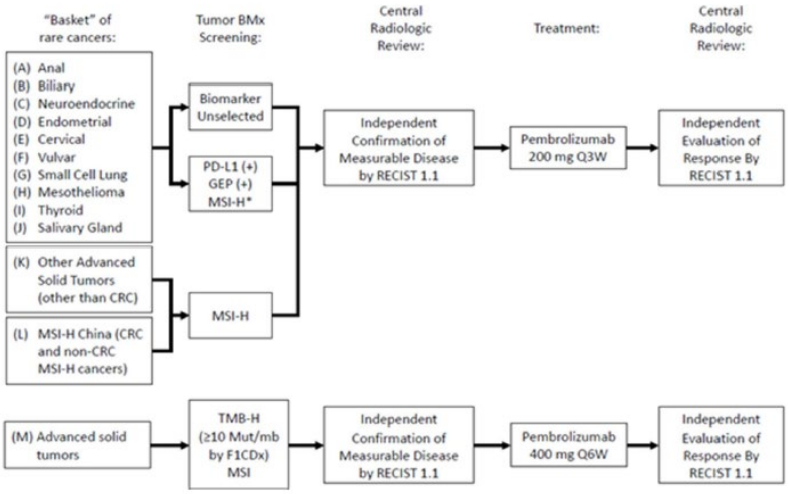
Efficacy and safety data in support of the current submission were obtained from study KEYNOTE-826 where patients were treated with the combination of pembrolizumab plus chemotherapy with or without bevacizumab.
As part of the agreement established in 2017 with the EMA to streamline the clinical pharmacology content in the clinical development program of KEYTRUDA, pharmacokinetic and immunogenicity data were not collected in KEYNOTE-826.
The focus of the clinical pharmacology report is on the clinical PK data from participants with cervical cancer in Group E of study KEYNOTE-158 (a Phase 2, multicohort, open-label, nonrandomized study designed to evaluate the efficacy and safety of pembrolizumab monotherapy in participants with unresectable or metastatic solid tumors).

Data from KEYNOTE-158, Group E are supportive of the proposed pembrolizumab dose of 200 mg Q3W for adults with cervical cancer.
Moreover, the MAH is also applying for the 400 mg Q6W dosing regimen. This dosing regimen was approved in the EU for all adult monotherapy indications (EMEA/H/C/003820/II/0062 [March 2019]) and for all adult indications in combination with other anticancer agents (EMEA/H/C/003820/II/0102 [May 2021]). The dosing regimen of 400 mg Q6W is then applicable across all adult indications, including this proposed indication for cervical cancer, regardless of the combination treatment type.

PK Data Keynote-158

KEYNOTE-158 is *an ongoing*, non-randomized, single arm, multi-site, open-label study of pembrolizumab in previously treated participants who have locally advanced unresectable or metastatic rare cancers for whom prior standard first-line treatment had failed. Eligible participants received pembrolizumab 200 mg IV Q3W.

Figure 1. Study design



*Selection of BMx(s) for biomarker enrichment may occur after interim analyses.

Abbreviations: BMx=Biomarker; CRC=Colorectal carcinoma; GEP=Gene expression profile; MSI-H=Microsatellite instability-high; PD L1=Programmed Cell Death-Ligand 1; Q3W=Every 3 weeks; RECIST=Response Evaluation Criteria in Solid Tumors.

For Cohort M, MSI= MSI-H excluded.

PK schedule in KEYNOTE-158 200 mg Q3W: Predose pembrolizumab serum concentrations (Ctrough) were obtained within 24 hours prior to dosing at Cycles 1 and 4. Postdose serum concentrations (Cmax) were drawn within approximately 30 minutes after the end of the infusion in Cycle 1.

Summary descriptive statistics of the predose concentrations by cycle are presented in the following table:

Table 3. Summary Statistics of Pembrolizumab Cycle 1 Postdose and Cycle 4 Predose, Serum Concentration Values Following Administration of Multiple 200 mg I.V. Doses with a 3 Week Dosing Interval in KEYNOTE-158 Cervical Carcinoma Subjects

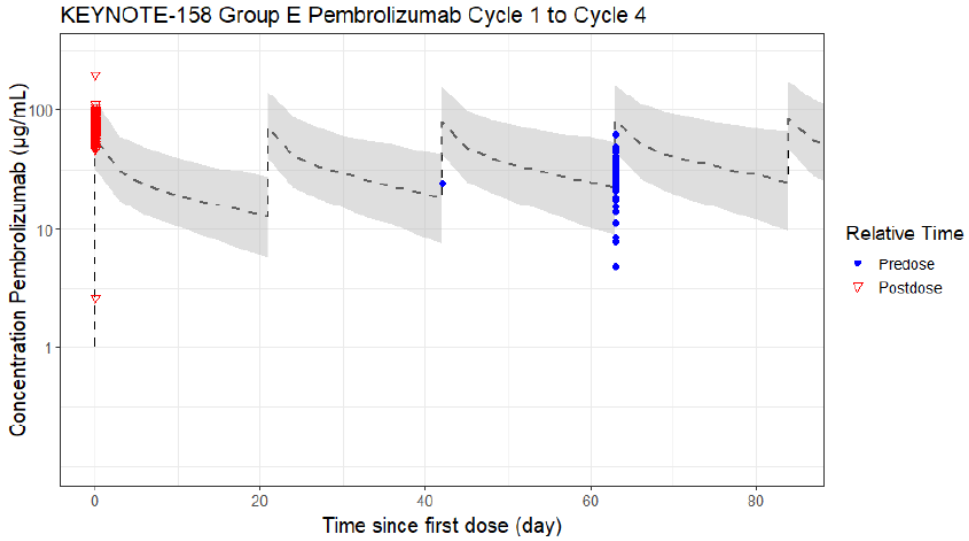
Cycle	NOMTAFD (Day)	N	GM (%CV)	GM (SD)	AM (SD) (µg/mL)	Min	Median	Max
Cycle 1 (Week 0)	0.021	95	71.4 (42.2)	71.4 (20.2)	75.0 (20.2)	2.61	75.0	199
Cycle 4 (Week 9)	63	59	26.1 (47.0)	26.1 (10.4)	28.3 (10.4)	4.75	28.4	62.5

NOMTAFD = Nominal time after first pembrolizumab administration;
GM = Geometric Mean; %CV = Geometric Coefficient of Variation;
SD = Standard Deviation; AM = Arithmetic Mean;
Results for time points with N ≥ 3.

Data Source: [06DF8S: analysis-p158pkdm24cerv]

Observed pembrolizumab concentration data in KEYNOTE-158 group E for pembrolizumab are overlaid on the simulated profile using the reference PK model as shown in the following figure:

Figure 2. Observed Concentration Data in KEYNOTE-158 Group E subjects with Cervical Carcinoma Receiving 200 mg Q3W Pembrolizumab with Reference Model-Predicted Pharmacokinetic Profile for 200 mg/kg Q3W Dose Regimen



Note: Pembrolizumab model predictions and observed concentration data for KEYNOTE-158 group E subjects After 1st dose; and at cycle 4, with a 28 day time since last dose sample cut off. Symbols are individual observed data (nominal time); black dashed line is median predicted concentrations from the model for a regimen of 200 mg Q3W and the grey shaded area represents the 90% prediction interval; plots are displayed on log scale. Data Source: [06DF8S: analysis-p158pkdm24cerv]

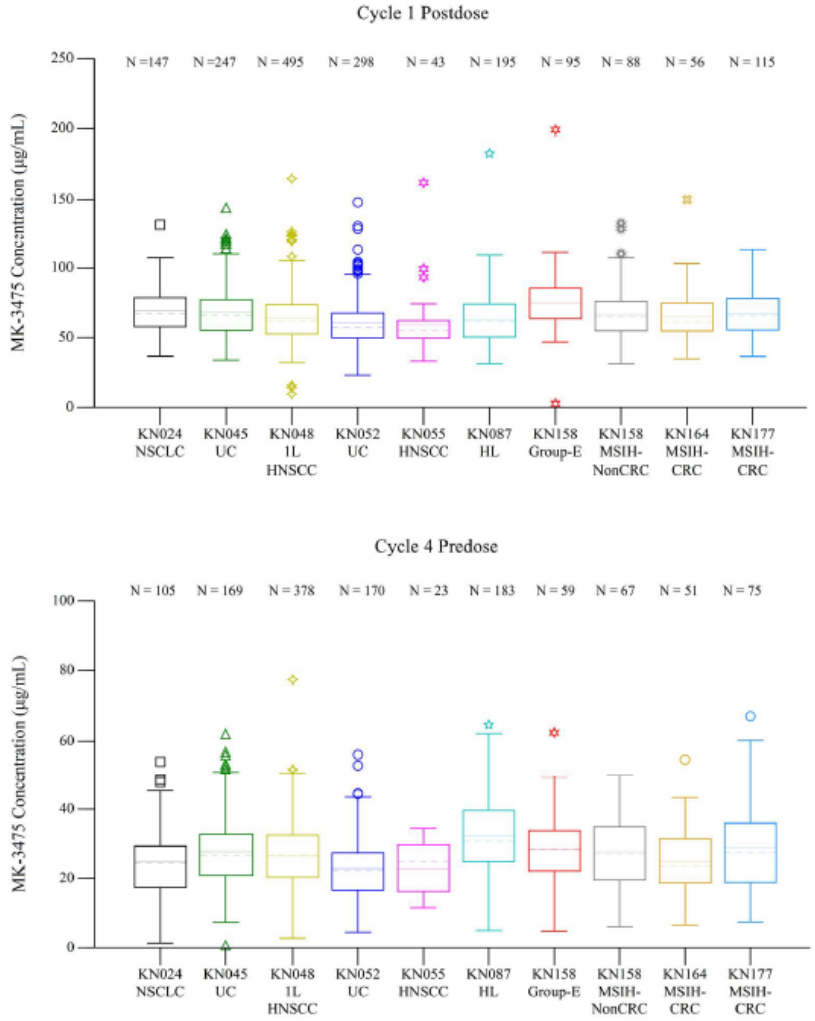
Tabular summaries of descriptive statistics and boxplots from early drug treatment at Cycle 1 end of infusion (postdose) and at predose Cycle 4, comparing observed pembrolizumab concentrations of 200 mg every 3 weeks (Q3W) from participants with cervical carcinoma in KEYNOTE-158 group E and monotherapy trials in non-small cell lung cancer (NSCLC, KEYNOTE-024), urothelial cancer (UC, KEYNOTE-045 and KEYNOTE-052), head and neck squamous cell cancer (HNSCC, KEYNOTE-048 and KEYNOTE-055), classical Hodgkin Lymphoma (HL, KEYNOTE-087), microsatellite instability-high cancer (MSI-H, KEYNOTE-158) and MSI-H colorectal cancer (MSI-H-CRC, KEYNOTE-164 and KEYNOTE-177), are presented in the following table and figure.

Table 4. Summary Statistics of Observed Pembrolizumab Trough Concentrations at Cycle 1 Postdose and Cycle 4 Predose in Various Monotherapy Trials (KEYNOTE-024, -045, -048, -052, -055, -087, 158 MSIH non CRC, -164, -177) and KEYNOTE-158 Group E Cervical Cancer

Time point	dose	Study/ Indication	N	GM(CV%) (µg/mL)	AM(SD) (µg/mL)	Min (µg/mL)	Median (µg/mL)	Max (µg/mL)
Cycle 1 Postdose	200mg	KN024 NSCLC	147	67.5 (23.1)	69.3 (16.2)	36.6	66.8	132
	200mg	KN045 UC	247	65.7 (26.2)	67.9 (18.2)	33.9	65.9	144
	200mg	KN048 1L HNSCC	495	61.8 (28.7)	64.2 (17.6)	9.48	61.7	165
	200mg	KN052 UC	298	58.0 (27.9)	60.2 (17.3)	22.8	57.4	148
	200mg	KN055 HNSCC	43	56.5 (27.8)	58.9 (20.7)	33.1	54.9	162
	200mg	KN087 HL	195	60.7 (28.0)	63.1 (18.3)	31.2	61.3	183
	200mg	KN158 Group-E	95	71.4 (42.2)	75.0 (20.2)	2.61	75.0	199
	200mg	KN158 MSIH-NonCRC	88	64.2 (27.3)	66.5 (18.4)	31.2	65.2	133
	200mg	KN164 MSIH-CRC	56	62.2 (27.8)	64.6 (19.1)	34.9	61.2	150
	200mg	KN177 MSIH-CRC	115	65.0 (25.7)	67.1 (17.1)	36.4	65.7	113
Cycle 4 Predose	200mg	KN024 NSCLC	105	22.5 (51.6)	24.7 (9.6)	1.35	24.5	54.0
	200mg	KN045 UC	169	25.3 (51.5)	27.7 (10.6)	0.677	26.6	62.1
	200mg	KN048 1L HNSCC	378	24.8 (44.1)	26.8 (9.8)	2.67	26.4	77.3
	200mg	KN052 UC	170	20.6 (51.0)	22.8 (9.4)	4.41	22.4	56.1
	200mg	KN055 HNSCC	23	21.5 (35.6)	22.7 (7.3)	11.5	24.9	34.4
	200mg	KN087 HL	183	30.3 (40.0)	32.3 (11.1)	4.93	30.7	64.7
	200mg	KN158 Group-E	59	26.1 (47.0)	28.3 (10.4)	4.75	28.4	62.5
	200mg	KN158 MSIH-NonCRC	67	25.2 (50.2)	27.7 (11.2)	6.01	26.9	49.7
	200mg	KN164 MSIH-CRC	51	23.1 (42.2)	24.9 (9.4)	6.52	23.4	54.7
	200mg	KN177 MSIH-CRC	75	26.0 (51.5)	28.9 (12.9)	7.41	27.5	67.2

GM = Geometric Mean; %CV = Geometric Coefficient of Variation; AM = Arithmetic Mean; SD = Standard Deviation; NSCLC = non-small cell lung cancer; UC = urothelial cancer; HNSCC = head and neck squamous cell carcinoma; HL = Hodgkin lymphoma; MSIH CRC= micro satellite instability high cancer colorectal cancer.

Figure 3. Pembrolizumab Observed Trough Pembrolizumab Concentrations at Cycle 1 Postdose and Cycle 4 Predose in Various Monotherapy Trials (KEYNOTE-024, -045, -048, -052, -055, -087, 158 MSIH non CRC, -164, -177) and KEYNOTE-158 Group E



Data Source: [06DF8S: analysis-p158pkdm24cerv]

2.3.3. Pharmacodynamics

Mechanism of action

KEYTRUDA is an antibody that binds to the programmed cell death-1 (PD-1) receptor and blocks its interaction with ligands PD-L1 and PD-L2. The PD-1 receptor is a negative regulator of T-cell activity that has been shown to be involved in the control of T-cell immune responses. KEYTRUDA potentiates T-cell responses, including anti-tumour responses, through blockade of PD-1 binding to PD-L1 and PD-L2, which are expressed in antigen presenting cells and may be expressed by tumours or other cells in the tumour microenvironment.

2.3.4. PK/PD modelling

No new information regarding PK/PD modelling for pembrolizumab is available within this extension of indication.

2.3.5. Discussion on clinical pharmacology

While the efficacy and safety data of the current submission are based on the combination of pembrolizumab plus chemotherapy with or without bevacizumab from KEYNOTE-826, the focus on the clinical Pharmacology is on data from participants with cervical cancer in Group E of KEYNOTE-158 a Phase 2 study of pembrolizumab monotherapy in participants with unresectable or metastatic solid tumours, including cervical carcinoma.

The observed serum concentration values in subjects with cervical cancer from KEYNOTE-158 study are contained within the 90% CI of the reference PK model, which indicate that pembrolizumab data from KEYNOTE-158 group E is consistent with the historical data in both cycle 1 postdose and cycle 4 predose. PK concentrations reached ~ 88% of the steady-state concentrations at the end of cycle 3 (timepoint for cycle 4 pre-dose).

Observed pembrolizumab concentration data in KEYNOTE-158 group E for subjects with cervical carcinoma were compared with simulated profiles for female subjects only using the reference PK model and resulted to fall within predicted concentrations.

Tabular summaries of descriptive statistics and boxplots comparing observed pembrolizumab concentrations of 200 mg Q3W from participants with cervical carcinoma in KEYNOTE-158 group E and female subjects in other monotherapy trials, showed consistent concentration values between female subjects with cervical cancer and other approved monotherapy trials in NSCLC, UC, HNSCC, HL and MSI-H.

Although a substantial characterization of the clinical pharmacology and immunogenicity profile of pembrolizumab has been provided in previous applications as monotherapy and in combination with small molecules or chemotherapy, the immunogenicity profile when another biologic drug is administered in combination with pembrolizumab is unknown.

No new ADA data are provided in this submission based on the following consideration argued by the MAH:

- the existing immunogenicity assessment for pembrolizumab for the monotherapy setting is based on a sufficiently large dataset of patients across several indications, with very low observed rates of total treatment ADA across different pembrolizumab regimens (1.4 – 3.8%) as well as of neutralizing antibodies (0.4 – 1.6%). This analysis has not demonstrated impact on efficacy or safety, as currently summarized in the EU SmPC and USPI.
- the low rate of immunogenicity has been shown to be consistent across tumor type and no clinically meaningful consequences have been observed in the subjects with a positive immunogenicity reading.
- the incidence of ADA has not been impacted by the presence of another small molecule or chemotherapy in combination with pembrolizumab.

In 2017, the MAH was recommended "to assess immunogenicity for co-administered biologics and also to collect ADA samples for pembrolizumab at least until results form a sufficient number of cases will provide characterization of the pembrolizumab immunogenicity profile in such combinations, making unnecessary further analysis".

During this procedure, the Applicant provided data from study KEYNOTE-021 cohort B where 24 patients were treated with pembrolizumab in combination with paclitaxel, carboplatin and bevacizumab.

Among these patients, only 16 subjects were evaluable for immunogenicity and although data showed that only 1 subject/16 was found to be treatment-emergent positive and had no antibodies with neutralizing capacity, the number of analysed subjects is very low and the Applicant is encouraged to further collect PK and ADA samples in study MK-3475-B96/KEYNOTE-B96/ENGOT-ov65 that is still recruiting and to provide data in the context of future procedure.

2.3.6. Conclusions on clinical pharmacology

The PK of pembrolizumab when used in combination with chemotherapy has been extensively evaluated in a number of cancer indications and demonstrates that the PK of pembrolizumab is consistent across tumour types and it is not impacted by concomitant chemotherapy. However, a comprehensive characterization of the immunogenicity profile of pembrolizumab in combination with other biologic drugs and in particular with bevacizumab is lacking and should be better defined in future procedures.

2.4. Clinical efficacy

2.4.1. Dose response study(ies)

No dose-response studies have been conducted specifically for this indication, nor for the combination of pembrolizumab with bevacizumab.

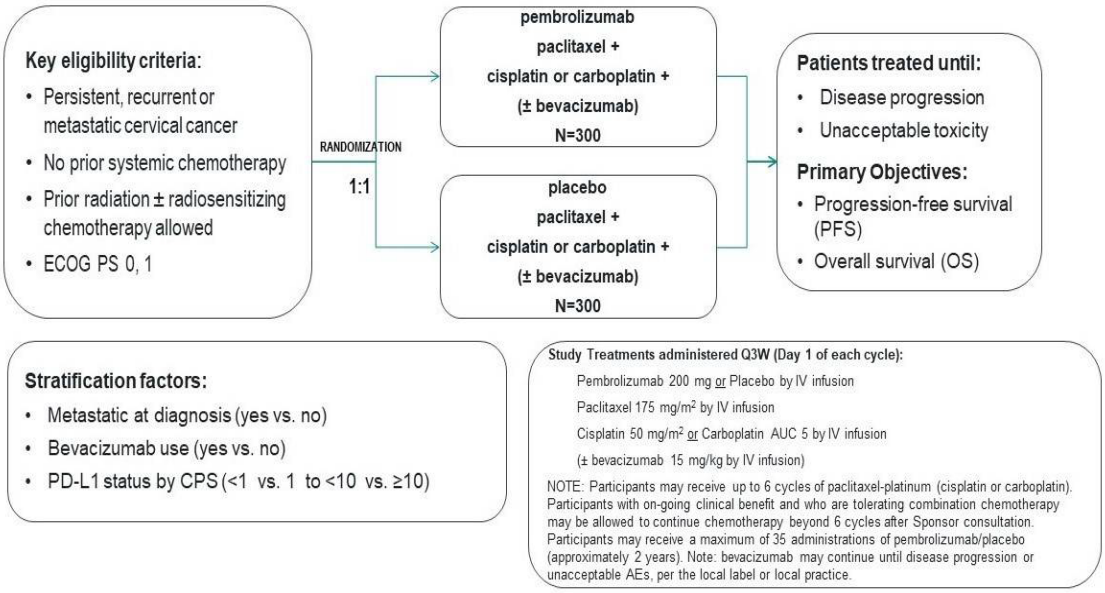
2.4.2. Main study(ies)

Title of Study

A 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 (KEYNOTE-826)

Methods

Figure 4. Study Design for KEYNOTE-826



Abbreviations: AEs=adverse events; AUC= area under the concentration-time curve; CPS=combined positive score; ECOG PS=Eastern Cooperative Oncology Group Performance Score; IV=intravenous; OS=overall survival; PD-L1=Programmed cell death 1 ligand 1; PFS=progression-free survival; Q3W=every 3 weeks.

Study participants

Key inclusion criteria:

- Had 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 (such as with surgery and/or radiation). *NOTE: Prior chemotherapy utilized as a radiosensitizing agent and completed at least 2 weeks prior to randomization with resolution of all treatment-related toxicities is allowed. AEs due to previous treatments should be resolved to ≤Grade 1 or baseline. Participants with ≤Grade 2 neuropathy or ≤Grade 2 alopecia are eligible.*
- Had measurable disease per RECIST 1.1 as assessed by the local site investigator/radiology. Lesions situated in a previously irradiated area are considered measurable only if progression has been demonstrated in such lesions.
- Had provided archival tumour tissue sample or newly obtained core or excisional biopsy of a tumour lesion not previously irradiated for prospective determination of PD-L1 status prior to randomization.
- Had an ECOG PS of 0 to 1 within 14 days prior to randomization.
- Have adequate organ function as indicated by the laboratory values within 14 days prior to randomization as defined in the protocol.

Key exclusion criteria:

- Had a positive urine pregnancy test within 72 hours prior to randomization (WOCBP only).
- Had known active CNS metastases and/or carcinomatous meningitis. Participants with known brain metastases may participate provided that the brain metastases have been previously treated (except with chemotherapy) and are radiographically stable.
- Had a known additional malignancy that was progressing or had required active treatment within the past 3 years.
- Had a diagnosis of immunodeficiency or was receiving chronic systemic steroid therapy (in doses exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior to randomization.
- 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 (eg, CTLA-4, OX-40, CD137).
- 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.
- Has a history of (non-infectious) pneumonitis that required steroids or has current pneumonitis.
- Has an active infection requiring systemic therapy, known history of HIV, Hepatitis B or known active Hepatitis C, known history of active tuberculosis.
- Had received prior systemic chemotherapy for treatment of cervical cancer (chemotherapy used as a radiosensitizing agent and completed at least 2 weeks prior to randomization was permitted).
- Has received prior radiotherapy within 2 weeks prior to randomization.

Treatments

Table 5. Study interventions

Intervention	Unit Dose and Frequency	Route of Administration
Pembrolizumab	200 mg Q3W	IV
Placebo	0 mg Q3W	IV
Paclitaxel	175 mg/m^2	IV
Carboplatin	AUC 5	IV
Cisplatin	50 mg/m^2	IV
Bevacizumab	15 mg/kg	IV

IV=intravenous; Q3W=every 3 weeks; AUC=area under the curve

All drugs were administered on day 1 of each 3-week treatment cycle.

As of protocol amendment 2, the maximum duration of chemotherapy was 6 cycles; patients with ongoing clinical benefit who were tolerating chemotherapy could continue chemotherapy beyond 6 administrations after consultation with the study sponsor.

There was no maximum number of bevacizumab administrations.

The maximum number of pembrolizumab or placebo administrations was 35 (i.e. approximately 2 years).

Objectives and endpoints

Table 6. Objectives and endpoints

Objective/ Hypothesis	***Endpoint***
Primary	
Objective: To compare PFS per RECIST 1.1 as assessed by investigator Hypothesis (H1): The combination of pembrolizumab + chemotherapy is superior to placebo plus chemotherapy with respect to PFS per RECIST 1.1 as assessed by investigator for the CPS ≥1 group. Hypothesis (H2): The combination of pembrolizumab + chemotherapy is superior to placebo plus chemotherapy with respect to PFS per RECIST 1.1 as assessed by investigator for all-comers. Hypothesis (H3): The combination of pembrolizumab + chemotherapy is superior to placebo plus chemotherapy with respect to PFS per RECIST 1.1 as assessed by investigator for the CPS ≥10 group.	PFS: The time from randomization to the first documented disease progression or death due to any cause, whichever occurs first.
Objective: To compare OS Hypothesis (H4): The combination of pembrolizumab + chemotherapy is superior to placebo plus chemotherapy with respect to OS for the CPS ≥1 group. Hypothesis (H5): The combination of pembrolizumab + chemotherapy is superior to placebo plus chemotherapy with respect to OS for all-comers. Hypothesis (H6): The combination of pembrolizumab + chemotherapy is superior to placebo plus chemotherapy with respect to OS for the CPS ≥10 group.	OS: The time from randomization to death due to any cause.
Secondary	
Objective: To evaluate the ORR, DOR, and 12-month PFS rate per RECIST 1.1 as assessed by investigator.	OR: Participants who have a best overall response of either confirmed CR or PR. DOR: The time from the first documented evidence of CR or PR until the first documented disease progression or death due to any cause, whichever occurs first.

	PFS-12: The proportion of participants that are PFS event-free at 12 months.
Objective: To evaluate 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.
Objective: To compare the safety and tolerability by the proportion of AEs.	Participants experiencing AEs, serious AEs, and immune-related AEs. Participants discontinuing study treatment due to AEs.
Objective: To evaluate changes in HRQoL assessments using the global score of the EORTC QLQ-C30.	The EORTC QLQ-C30 global score.
Exploratory	
Objective: To evaluate the ORR, DOR, and 12-month PFS rate per RECIST 1.1 as assessed by BICR.	OR: Participants who have a best overall response of either confirmed CR or PR. DOR: The time from the first documented evidence of CR or PR until the first documented disease progression or death due to any cause, whichever occurs first. PFS-12: The proportion of participants that are PFS event-free at 12 months.
Objective: To evaluate PFS using iRECIST, as assessed by investigator.	PFS per iRECIST is defined as time from the date of randomization to the date of the first documentation of confirmed immune-related progressive disease (iPD) or death (whichever occurs first).
Objective: To identify molecular (genomic, metabolic, and/or proteomic) biomarkers that may be indicative of clinical response/resistance, safety, pharmacodynamic activity, and/or the mechanism of action of pembrolizumab and other treatments.	Germline genetic variation, genetic (DNA) mutations from tumor, tumor and blood RNA variation, proteomics and IHC, and other biomarkers.
To evaluate changes in HRQoL assessments using the EORTC QLQ-C30, EORTC QLQCX24, and European Quality of Life (EuroQoL) EQ-5D-5L instruments.	HRQoL will be assessed using the EORTC QLQ-C30 (scores other than global score), EORTC QLQ CX24, and EuroQoL EQ-5D-5L.
To characterize utilities using the EuroQoL EQ-5D-5L.	Utilities will be assessed using the EuroQoL EQ-5D-5L.

Sample size

The study was planned to randomize approximately 600 participants (all-comers) in a 1:1 ratio between the two arms, over a period of 16 months. Approximately 510 participants were expected to be CPS≥1

and 300 participants were expected to be CPS≥10. The study is event-driven and completes after accumulation of sufficient events to determine efficacy for PFS and for OS.

Sample Size and Power Calculations for PFS and OS

The study includes dual-primary efficacy endpoints: 1) PFS per RECIST 1.1 as assessed by investigator and 2) OS. The study includes multiple hypotheses testing the superiority of pembrolizumab compared to placebo, and it was to be considered positive if it is positive for either the PFS or OS hypothesis test for any of the 3 groups: CPS≥1 group, all-comers, and CPS≥10 group.

PFS

The duration of PFS in the control arm is assumed to follow an exponential distribution with a median of 7.1 months based on historical data. The PFS hypothesis testing was designed as follows:

H1: CPS≥1 group (expected N=510): It was expected that with approximately 370 and 435 PFS events at the planned IA1 and IA2 (final analysis for PFS), the trial has a power of 91% to detect a hazard ratio of 0.68 at one-sided α = 0.004.

H2: All-comers (N=600): It was expected that with approximately 432 and 508 events at the planned IA1 and IA2 (final analysis for PFS), the trial has a power of 91% to detect a hazard ratio of 0.70 at one-sided α = 0.004 (when H1 is rejected).

H3: CPS ≥ 10 group (N=300): It was expected that with approximately 210 and 247 PFS events at the planned IA1 and IA2 (final analysis for PFS), the trial has a power of 92% to detect a hazard ratio of 0.60 at one-sided α = 0.005 (when H1 and H2 are rejected).

OS

The duration of OS in the control arm is assumed to follow an exponential distribution with a median of 15.1 months based on historical data. The OS hypothesis testing was designed as follows:

H4: CPS ≥1 group (N=510): It was expected that with approximately 246, 321, and 378 events at the planned IA1, IA2 and final OS analyses, the trial has a power of 90% to detect a hazard ratio of 0.70 at one-sided α = 0.016.

H5: All-comers (N=600): It was expected that with approximately 289, 378, and 445 events at the planned IA1, IA2 and final OS analyses, the trial has a and power of 90% to detect a hazard ratio of 0.72 at one-sided α = 0.016 (when H4 is rejected).

H6: CPS ≥10 group (N=300): It was expected that with approximately 127, 167, and 196 events at the planned IA1, IA2 and final OS analyses, the trial has a power of 93% to detect a hazard ratio of 0.60 at one-sided α = 0.020 (when H4 and H5 are rejected).

Software used for sample size calculation

The sample size and power calculations were performed using EAST 6.4 software.

Randomisation

Randomization occurred centrally using an interactive voice response system / integrated web response system (IVRS/IWRS). There were 2 treatment arms. Participants were assigned randomly in a 1:1 ratio to pembrolizumab plus chemotherapy or placebo plus chemotherapy, respectively. The choice of chemotherapy (cisplatin or carboplatin) and +/- bevacizumab was determined prior to randomization and documented in the IVRS/IWRS.

Treatment randomization was stratified based on the following criteria:

1) Metastatic (FIGO [2009] Stage IVB) at initial diagnosis (yes vs. no)

2) Investigator decision to use bevacizumab (yes vs. no), and

3) PD-L1 status (CPS <1, CPS 1 to <10, CPS ≥10).

A total of 12 strata have been utilized in this study.

Blinding (masking)

A double-blinding technique with in-house blinding has been used. The participant, the investigator, and Sponsor personnel or delegates who were involved in the study were unaware of treatment group assignments. Therefore, pembrolizumab and placebo were prepared and/or dispensed in a blinded fashion by an unblinded pharmacist or other qualified site personnel, who provided the investigative staff with ready-to-use blinded pembrolizumab or saline infusion solutions, packaged identically to maintain the blinding, for administration at scheduled infusion visits.

Results of the interim analyses were reviewed by an external DMC, which made recommendations for discontinuation of the study or protocol modification to an EOC of the Sponsor, who might have been unblinded to study results at the treatment level together with limited additional Sponsor personnel in order to act on these recommendations or facilitate regulatory filing.

A total of 84 participants discontinued treatment before the IVRS unblinding and the main reason for the unblinding was the progression of the disease.

Statistical methods

Protocol Amendments involving statistical methods

In global amendment 03 (31-JAN-2020) and global amendment 04 (02-APR-2020) the objectives and hypotheses were modified with an updated multiplicity strategy based on updated results from the KEYTRUDA program. Statistical analysis (timing and required events, alpha passing strategy, efficacy boundaries) approach was modified to address changes in primary objectives and hypotheses. Finally, in global amendment 05 (30-OCT-2020), the objectives including primary efficacy endpoints were modified. The primary PFS endpoint per RECIST 1.1 has been assessed by the investigator instead of by BICR (blinded independent central review), the purpose of this amendment was to address discordance between BICR-confirmed progressive disease (PD) and investigator assessed PD that could affect the power of the trial. The table below shows the history of changes.

Table 7. Summary of Key Revisions to the Protocol Amendments

Document	Date of Issue	Overall Rationale
Amendment 5/ Global amendment	30-OCT-2020	The objectives including primary efficacy endpoints were modified. The primary PFS endpoint per RECIST 1.1 will be assessed by the investigator.
Amendment 4/ Global amendment	02-APR-2020	Amendment 4 supersedes Amendment 3. The objectives and hypotheses were modified with an updated multiplicity strategy based on updated results from the KEYTRUDA program.
Amendment 3/ Global amendment	31-JAN-2020	The objectives and hypotheses were modified with an updated multiplicity strategy based on updated results from the KEYTRUDA program.
Amendment 2/ Global amendment	25-JUN-2019	Clarification of stratification factors and treatment duration
Amendment 1/ Germany-specific amendment	13-NOV-2018	Insertion of the requirements to perform HIV, hepatitis B and C testing at Screening, monthly pregnancy testing, and urinalysis at every cycle during which bevacizumab is administered
Original Protocol	13-JUN-2018	Not applicable

Amendments 3 and 4 were mainly driven by the new external data from other studies, such as KEYNOTE-158 and by additional changes in study procedures, respectively. In Amendment 5, the modification of the primary endpoint to PFS by investigator was intended to protect the study from a loss of power, the BICR assessment was retained as a secondary endpoint.

Interim Analyses

There are two planned interim analyses (IA) in addition to the final analysis (FA) for this study. The efficacy analyses in this submission are based on IA1. The analyses planned, endpoints evaluated, and drivers of timing are summarized in the table below.

Table 8. Summary of Interim and Final Analyses Strategy

Analysis	Criteria	Endpoint	Time after last Subject Randomized	Primary Purpose of Analysis
IA1 (interim analysis for PFS and OS)	**PFS IA1 was to be conducted when ~ 370 PFS events for CPS ⩾1 group has been observed. It is estimated that ~210 PFS events for CPS ⩾10 group and ~432 PFS events for all-comers will be observed at the same time.**	**PFS**	**~ 22 months**	**Demonstrate PFS superiority at interim analysis for CPS ⩾1 group, CPS ⩾10 group, and all-comers**
	OS IA1 was to be conducted at the same time. It is estimated ~246 OS events for CPS ⩾1 group, ~127 OS events for CPS ⩾10 group and ~289 OS events for all-comers will be observed.	**OS**		**Demonstrate OS superiority at interim analysis for CPS ⩾1 group, CPS ⩾10 group, and all-comers**

IA2 (final analysis for PFS/interim analysis for OS)	PFS IA2 will be triggered when at least 435 PFS events for CPS ⩾1 group have been observed. It is estimated that ~247 PFS events for CPS ⩾ 10 group and ~508 PFS events for all-comers will be observed by then. OS IA2 will be performed at the same time. It is estimated ~321 OS events for CPS ⩾1 group, ~167 OS events for CPS ⩾10 group and ~378 OS events for all-comers will be observed.	PFS OS	~ 30 months	Demonstrate PFS superiority for CPS ⩾1 group, CPS ⩾10 group, and all-comers Demonstrate OS superiority at interim analysis for CPS ⩾1 group, CPS ⩾10 group, and all-comers
FA	FA will be triggered when at least 378 OS events for CPS ⩾1 group has been observed. It is estimated that ~196 OS events for CPS ⩾10 group and 445 OS events for all-comers will be observed by then.	OS	~ 40 months	Demonstrate OS superiority for CPS ⩾1 group, CPS ⩾10 group, and all-comers

IA1 was performed after approximately 355 PFS events had been observed among participants with CPS ≥1, of which 157 occurred in pembrolizumab arm and 198 in the placebo arm.

PFS events had been accruing significantly slower than expected at the time the analysis plan was constructed, but the number of 355 at IA1 was considered sufficiently close to the target number (n=370).

Error probabilities, adjustment for multiplicity

Based on emerging data external to this study, the multiplicity strategy including the testing order among the 6 primary hypotheses was revised in Protocol Amendments 03 and 04. The update of the multiplicity strategy occurred prior to the conduct of efficacy IA1. The overall Type-I error rate among the multiple hypotheses was strongly controlled at 2.5% (one-sided). The study used the graphical method of Maurer and Bretz to provide strong multiplicity control among the hypotheses of PFS and OS for CPS ≥1 group, all-comers, and CPS ≥10 group. Lan-DeMets O'Brien-Fleming group sequential methods has been used to allocate alpha among the interim and final analyses for the PFS and OS endpoints. The Figures below display the revised multiplicity strategy diagram of the study according to Protocol Amendment 05 on the right side and the former multiplicity strategy diagram of the study according to amendment 02 on the left side.

Figure 5A. Amendment 2: Multiplicity Graph for Graph Study Type I Error Control of Study Hypotheses

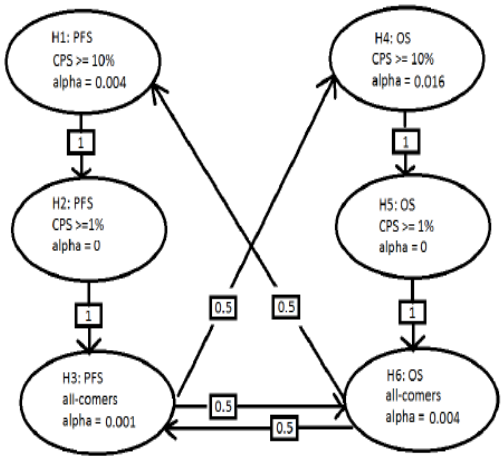
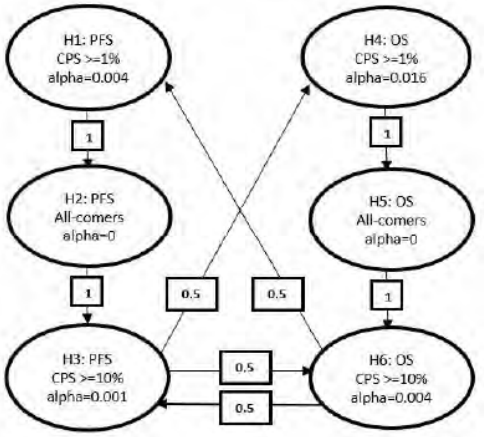


Figure 5B. Amendment 5: Multiplicity



The initial one-sided alpha allocation for each hypothesis is shown in the ellipse representing the hypothesis. The weights for re-allocation from each hypothesis to the others are in the boxes on the lines connecting hypotheses. According to this approach, study hypotheses may be tested more than once, and when a particular null hypothesis is rejected, the alpha allocated to that hypothesis can be reallocated to other hypothesis tests.

PFS

The study initially allocates one-sided α=0.005 to test PFS between two treatment groups for CPS ≥1 group, all-comers, and CPS ≥10 group. If the null hypothesis of PFS for CPS ≥1 group was rejected, its α=0.004 was reallocated to the PFS analysis for all-comers, and if the null hypothesis of PFS for all-comers was rejected, its α=0.004 was reallocated to the PFS analysis for CPS ≥10 group. The boundary properties for each of these alpha-levels for the interim analyses were derived using a Lan-DeMets O'Brien-Fleming spending function. The bounds and boundary properties for PFS testing are shown in the table below.

Table 8A. Efficacy Boundaries and Properties for PFS Analyses

Population	Analysis[a]	Value	α=0.004	
CPS ≥1	IA1: 85%	Z	2.911	
	N: 510	p (1-sided)	0.002	
	Events:370	~HR at bound	0.739	
	Month: 22	P(Cross) if HR=1	0.002	
		P(Cross) if HR=0.68	0.788	
	IA2: 100%	Z	2.700	
	N: 510	p (1-sided)	0.003	
	Events: 435	~HR at bound	0.772	
	Month: 30	P(Cross) if HR=1	0.004	
		P(Cross) if HR=0.68	0.911	
Population	Analysis[a]	Value	α=0.004	
All-comers	IA1: 85%	Z	2.911	
	N: 600	p (1-sided)	0.002	
	Events: 432	~HR at bound	0.756	
	Month: 22	P(Cross) if HR=1	0.002	
		P(Cross) if HR=0.70	0.787	
	IA2: 100%	Z	2.700	
	N: 600	p (1-sided)	0.003	
	Events: 508	~HR at bound	0.787	
	Month: 30	P(Cross) if HR=1	0.004	
		P(Cross) if HR=0.70	0.910	
Population	Analysis[a]	Value	α=0.005	α=0.001
CPS ≥10	IA1: 85%	Z	2.829	3.383
	N: 300	p (1-sided)	0.002	0.0004
	Events: 210	~HR at bound	0.677	0.627
	Month: 22	P(Cross) if HR=1	0.002	0.0004
		P(Cross) if HR=0.60	0.808	0.625
	IA2: 100%	Z	2.627	3.125
	N: 300	p (1-sided)	0.004	0.001
	Events: 247	~HR at bound	0.716	0.672
	Month: 30	P(Cross) if HR=1	0.005	0.001
		P(Cross) if HR=0.60	0.921	0.817

CPS = combined positive score; HR = hazard ratio; IAX = interim analysis X; 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 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=0.68 or 0.70 or 0.60): the probability of crossing a bound at or before each analysis under the alternative hypothesis.

OS

The study initially allocates one-sided α=0.020 to test OS between two treatment groups for CPS ≥1 group, all-comers, and CPS ≥10 group. The OS hypothesis for CPS ≥1 group may be tested at one-sided α=0.016 (initially allocated) or higher if one or more null hypotheses for PFS test are rejected. If the null hypothesis of OS for CPS ≥1 group was rejected, its α was allocated to the OS analysis for all-comers, and if the null hypothesis of OS for all-comers was rejected, its α was reallocated to the OS analysis for CPS ≥10 group. The table below shows the bounds and boundary properties for OS testing which were derived using a Lan-DeMets O'Brien-Fleming α-spending function. Further details of statistical analyses were described in the SAP.

Table 8B. Efficacy Boundaries and Properties for OS Analysis.

Population	Analysis[a]	Parameter	α=0.016	
CPS ≥ 1	IA1: 65%	Z	2.767	
	N: 510	p (1-sided)	0.003	
	Events: 246	~HR at bound	0.703	
	Month: 22	P(Cross) if HR=1	0.003	
		P(Cross) if HR=0.70	0.512	
	IA2: 85%	Z	2.405	
	N: 510	p (1-sided)	0.008	
	Events: 321	~HR at bound	0.765	
	Month: 30	P(Cross) if HR=1	0.009	
		P(Cross) if HR=0.70	0.791	
	Final: 100%	Z	2.221	
	N: 510	p (1-sided)	0.013	
	Events: 378	~HR at bound	0.796	
	Month: 40	P(Cross) if HR=1	0.016	
		P(Cross) if HR=0.70	0.901	
Population	Analysis[a]	Parameter	α=0.016	
All-comers	IA1: 65%	Z	2.771	
	N: 600	p (1-sided)	0.003	
	Events: 289	~HR at bound	0.722	
	Month: 22	P(Cross) if HR=1	0.003	
		P(Cross) if HR=0.72	0.509	
	IA2: 85%	Z	2.404	
	N: 600	p (1-sided)	0.008	
	Events: 378	~HR at bound	0.781	
	Month: 30	P(Cross) if HR=1	0.009	
		P(Cross) if HR=0.72	0.790	
	Final: 100%	Z	2.221	
	N: 600	p (1-sided)	0.013	
	Events: 445	~HR at bound	0.810	
	Month: 40	P(Cross) if HR=1	0.016	
		P(Cross) if HR=0.72	0.901	
Population	Analysis[a]	Parameter	α=0.020	α=0.004
CPS ≥ 10	IA1: 65%	Z	2.665	3.339
	N: 300	p (1-sided)	0.004	0.0004

Population	Analysis[a]	Parameter	α=0.016	
	Events: 127	~HR at bound	0.623	0.548
	Month: 22	P(Cross) if HR=1	0.004	0.0004
		P(Cross) if HR=0.60	0.585	0.304
	IA2: 85%	Z	2.306	2.928
	N: 300	p (1-sided)	0.011	0.002
	Events: 167	~HR at bound	0.700	0.636
	Month: 30	P(Cross) if HR=1	0.012	0.002
		P(Cross) if HR=0.60	0.845	0.648
	Final : 100%	Z	2.137	2.704
	N: 300	p (1-sided)	0.016	0.003
	Events: 196	~HR at bound	0.737	0.680
	Month: 40	P(Cross) if HR=1	0.020	0.004
		P(Cross) if HR=0.60	0.931	0.815

CPS = combined positive score; HR = hazard ratio; IAX = interim analysis X; OS = overall 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 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=0.70 or 0.72 or 0.60): the probability of crossing a bound at or before each analysis under the alternative hypothesis.

Efficacy analyses

The Intention-to-Treat (ITT) population served as the population for the primary efficacy analyses. All randomized participants were included in this population. Participants were analysed in the treatment arm to which they are randomized, regardless of whether they received study treatment. A summary of the analysis strategy for key efficacy endpoints is presented in the following table:

Table 8C. Efficacy Analysis Methods for Key Efficacy Endpoints

Endpoint/Variable	Statistical Method	Analysis Population	Missing Data Approach
Primary Analyses:			
PFS (RECIST 1.1) by investigator	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 Analyses:			
ORR (RECIST 1.1) by investigator	Estimation: Stratified Miettinen and Nurminen method	ITT	Participants with missing data are considered non-responders
DOR (RECIST 1.1) by investigator	Summary statistics using Kaplan-Meier method	All responders in ITT	Non-responders are excluded from the analysis
PFS rate at 12 months (RECIST 1.1) by investigator	Kaplan-Meier estimation with CI	ITT	Censored according to rules in Table 9
PFS (RECIST 1.1) by BICR	Estimation: Stratified Cox model with Efron's tie handling method	ITT	Censored according to rules in Table 9

BICR = blinded independent central review; CI = confidence interval; DOR = duration of response; ITT = Intention-to-Treat; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors 1.1.

Table 9. Censoring rules for Primary and Sensitivity Analysis 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 anti-cancer 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
Death or progression after ≥ 2 consecutive missed disease assessments without further valid non-PD disease assessments, or after new anti-cancer therapy	Censored at last disease assessment prior to the earlier date of ≥2 consecutive missed disease assessment and new anti-cancer therapy, if any	Progressed at date of documented PD or death	Progressed at date of documented PD or death
No PD and no death and new anti-cancer 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 anti-cancer treatment is initiated	Censored at last disease assessment before new anti-cancer treatment	Censored at last disease assessment	Progressed at date of new anti-cancer treatment

Table 10. Censoring Rules for DOR

Situation	Date of Progression or Censoring	Outcome
No progression nor death, no new anti-cancer therapy initiated	Last adequate disease assessment	Censor (non-event)
No progression nor death, new anti-cancer therapy initiated	Last adequate disease assessment before new anti-cancer therapy initiated	Censor (non-event)
Death or progression after ≥2 consecutive missed disease assessments	Last adequate disease assessment prior to the ≥2 missed adequate disease assessments	Censor (non-event)
Death or progression after ≤1 missed adequate disease assessments	PD or death	End of response (Event)
A missed disease assessment includes any assessment that is not obtained or is considered inadequate for evaluation of response.		

The non-parametric Kaplan-Meier method was used to estimate the PFS and OS curve in each treatment group. The treatment difference in PFS and OS was assessed by the stratified log-rank test. For PFS and OS a stratified Cox proportional hazard model with Efron's method of tie handling was used to assess the magnitude of the treatment difference between the treatment arms. The hazard ratio and its 95% confidence interval from the stratified Cox model with Efron's method of tie handling and with a single treatment covariate was reported. The same stratification factors used for randomization were applied to both the stratified log-rank test and the stratified Cox model. Death is always considered as a confirmed PD event. Participants who do not experience PFS event were censored at the last disease assessment, while participants without documented death at the time of analysis were censored at the date of last known contact. Restricted Mean Survival Time (RMST) method may be conducted for OS to account for the possible non-proportional hazards effect.

In order to evaluate the robustness of the PFS endpoint, one primary and two sensitivity analyses with a different set of censoring rules were performed. The censoring rules for primary and sensitivity analyses are summarized in Table 9.

The stratified Miettinen and Nurminen method was used for the comparison of the 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.

DOR was summarised descriptively using Kaplan-Meier medians and quartiles and was assessed using RECIST 1.1 by investigator and BICR, respectively. Only the subset of patients who show a complete response or partial response were included in this analysis. For each DOR analysis, a corresponding summary of the censoring reasons for responding participant were also provided. Censoring rules for DOR are summarized in Table 10.

Sensitivity analyses are adequate.

Subgroup analyses

Subgroup Analyses and Effect of Baseline Factors are planned. To determine whether the treatment effect is 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 following classification variables: Stratification factors, Metastatic at diagnosis (Yes vs. No), Bevacizumab use (Yes vs. No), PD-L1 status (CPS<1 vs. CPS 1 to < 10 vs. CPS ≥ 10), Age group (<65 years vs. ≥65 years),

Race (white, non-white), ECOG performance status (0, 1). A Forest plot was produced, which provides the estimated point estimates and confidence intervals for the treatment effect across the categories of subgroups listed above. The consistency of the treatment effect was assessed descriptively via summary statistics by category for the classification variables listed above.

Safety analyses

The safety analyses were based on the APaT populations, which included all randomized participants who received at least 1 dose of study treatment. The analysis of safety results followed a tiered approach. There were no Tier 1 endpoints in this study, and Tier 2 parameters were assessed via point estimates with 95% confidence intervals (CIs) provided for differences in the proportion of participants with events; only point estimates by intervention arm were provided for Tier 3 safety parameters. The 95% CIs for the between-treatment differences in percentages were provided using the Miettinen and Nurminen method.

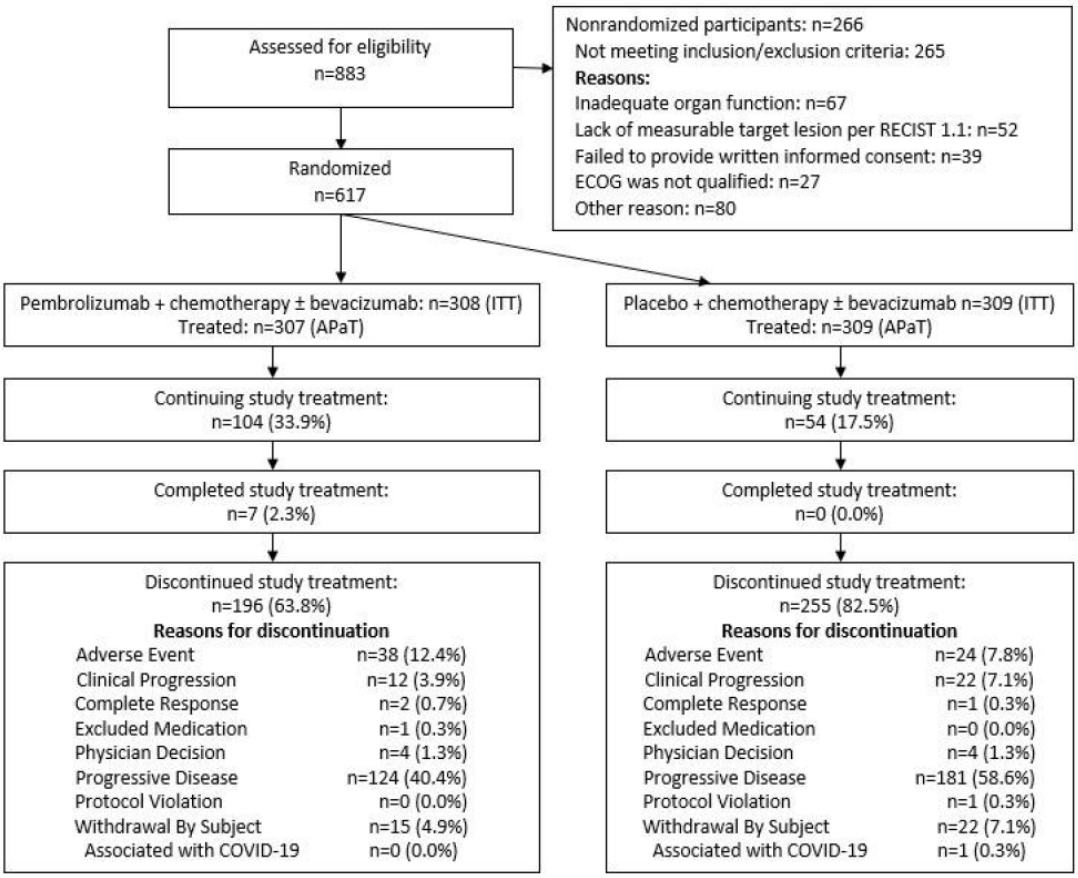
PRO analyses

PRO analyses were based on the PRO FAS population, defined as all randomized participants who received at least 1 dose of study intervention and had completed at least 1 PRO assessment. Participants were included in the treatment arm to which they were randomly assigned in the PRO analyses.

Results

Participant flow

Figure 6. Participant flow in all comer participants



Abbreviations: APaT=all participants as treated; COVID-19=Coronavirus disease caused by severe acute respiratory syndrome coronavirus 2ECOG=Eastern Cooperative Oncology Group; ITT=intent to treat; RECIST=Response Evaluation Criteria in Solid Tumor.

A total of 266 patients screened were not randomized due to screen failure. The main reason for screen failure were inadequate organ functions per laboratory value (18.9%), lack of measurable disease per RECIST 1.1 (16.6%), not providing informed consent (12.5%), ECOG not 0 or 1 (8.3%), other condition that may confound result or interfere with participation (7.9%).

Table 11. Disposition of Participants Including Association with COVID-19 (ITT Population)

	Pembro Combo		Control		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	308		309		617	
Status for Trial						
Discontinued	140	(45.5)	180	(58.3)	320	(51.9)
Death	134	(43.5)	171	(55.3)	305	(49.4)
Associated with COVID-19	0	(0.0)	1	(0.3)	1	(0.2)
Lost To Follow-Up	0	(0.0)	1	(0.3)	1	(0.2)
Withdrawal By Subject	6	(1.9)	8	(2.6)	14	(2.3)
COVID-19 association unspecified, Subsequently died	4	(1.3)	3	(1.0)	7	(1.1)
Participants Ongoing	168	(54.5)	129	(41.7)	297	(48.1)
Status for Study Medication in Trial						
Started	307		309		616	
Completed	7	(2.3)	0	(0.0)	7	(1.1)
Discontinued	196	(63.8)	255	(82.5)	451	(73.2)
Adverse Event	38	(12.4)	24	(7.8)	62	(10.1)
Clinical Progression	12	(3.9)	22	(7.1)	34	(5.5)
Complete Response	2	(0.7)	1	(0.3)	3	(0.5)
Excluded Medication	1	(0.3)	0	(0.0)	1	(0.2)
Physician Decision	4	(1.3)	4	(1.3)	8	(1.3)
Progressive Disease	124	(40.4)	181	(58.6)	305	(49.5)
Protocol Violation	0	(0.0)	1	(0.3)	1	(0.2)
Withdrawal By Subject	15	(4.9)	22	(7.1)	37	(6.0)
Associated with COVID-19	0	(0.0)	1	(0.3)	1	(0.2)
Participants Ongoing	104	(33.9)	54	(17.5)	158	(25.6)

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.
Database Cutoff Date: 03MAY2021

Recruitment

This study was conducted at 151 centers in 19 countries. First patient first visit was on 25-OCT-2018. Randomization occurred between 20 November 2018 and 31 January 2020 (Colombo, 2021).

Data Cut-off for IA1 was on 03-MAY-2021.

The last patient randomized was observed for approximately 15 months. The median follow-up was approximately 17 months (see tables below):

Table 12. Summary of Follow-up Duration (CPS>=1 Participants) (ITT Population)

Follow-up duration (months)[a]	Pembro Combo (N=273)	Control (N=275)	Total (N=548)
Median (Range)	18.3 (0.5, 29.4)	16.3 (0.3, 29.2)	17.2 (0.3, 29.4)
Mean (SD)	17.2 (6.9)	15.0 (7.3)	16.1 (7.1)

[a] Follow-up duration is defined as the time from randomization to the date of death or the database cutoff date if the participant is still alive.
Database Cutoff Date: 03MAY2021

Table 13. Summary of Follow-up Duration (All-comer Participants) (ITT Population)

Follow-up duration (months)[a]	Pembro Combo (N=308)	Control (N=309)	Total (N=617)
Median (Range)	18.2 (0.5, 29.4)	16.3 (0.3, 29.2)	17.2 (0.3, 29.4)
Mean (SD)	17.0 (7.0)	15.1 (7.1)	16.1 (7.1)

[a] Follow-up duration is defined as the time from randomization to the date of death or the database cutoff date if the participant is still alive.
Database Cutoff Date: 03MAY2021

Table 14. Summary of Follow-up Duration (CPS>=10 Participants) (ITT Population)

Follow-up duration (months)[a]	Pembro Combo (N=158)	Control (N=159)	Total (N=317)
Median (Range)	18.3 (0.5, 28.4)	16.3 (0.9, 29.2)	17.2 (0.5, 29.2)
Mean (SD)	17.2 (6.9)	14.9 (7.4)	16.0 (7.3)

[a] Follow-up duration is defined as the time from randomization to the date of death or the database cutoff date if the participant is still alive.
Database Cutoff Date: 03MAY2021

Conduct of the study

Protocol amendments: original protocol was dated 13 June 2018. A total of 5 global protocol amendments were released by data cut-off date for IA1 (see statistical methods).

Protocol deviations: overall, 6.3% of patients were with one or more not clinically important protocol deviation, 22 (7.1%) vs 17 (5.5%) in the pembro combo vs control arm, respectively. Clinically important protocol deviations were recorded in 14 patients, 5 (1.6%) in the pembro combo arm and 9 (2.9%) in the control arm.

Table 15. Summary of Important Protocol Deviations Considered to be Clinically Important (ITT Population)

	Pembro Combo		Control		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	308		309		617	
with one or more clinically important protocol deviations	5	(1.6)	9	(2.9)	14	(2.3)
with no clinically important protocol deviations	303	(98.4)	300	(97.1)	603	(97.7)
Inclusion/ Exclusion Criteria	**4**	**(1.3)**	**2**	**(0.6)**	**6**	**(1.0)**
Participant did not have persistent, recurrent, or metastatic squamous cell carcinoma, adenosquamous carcinoma, or adenocarcinoma of the cervix.	0	(0.0)	1	(0.3)	1	(0.2)
Participant was previously treated with systemic chemotherapy for the treatment of cervical cancer.	3	(1.0)	0	(0.0)	3	(0.5)
Participants entered into the trial who did not have the correct tumor histology per the I/E criteria.	1	(0.3)	1	(0.3)	2	(0.3)
Informed Consent	**0**	**(0.0)**	**1**	**(0.3)**	**1**	**(0.2)**
Participant had no documented initial consent to enter the trial.	0	(0.0)	1	(0.3)	1	(0.2)
Safety Reporting	**1**	**(0.3)**	**1**	**(0.3)**	**2**	**(0.3)**
Participant had a reportable Safety Event and/or follow up Safety Event information that was not reported per the timelines outlined in the protocol.	1	(0.3)	1	(0.3)	2	(0.3)
Study Intervention	**0**	**(0.0)**	**6**	**(1.9)**	**6**	**(1.0)**
Participant was administered improperly stored study intervention that was deemed unacceptable for use.	0	(0.0)	6	(1.9)	6	(1.0)

Every participant is counted a single time for each applicable row and column.
Database Cutoff Date: 03MAY2021

Table 16. Accounting of Selected Protocol Deviations Associated With COVID-19 (ITT Population)

	Pembro Combo		Control		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	308		309		617	
Subjects with >=1 Disease Assessment deviation	**2**	**(0.6)**	**2**	**(0.6)**	**4**	**(0.6)**
>=1 Disease Assessment Alternate Method-Alternative Location	0	(0.0)	2	(0.6)	2	(0.3)
>=1 Disease Assessment Missed	1	(0.3)	0	(0.0)	1	(0.2)
>=1 Disease Assessment Partially Missed	1	(0.3)	0	(0.0)	1	(0.2)
Subjects with >=1 Dose deviation	**6**	**(1.9)**	**3**	**(1.0)**	**9**	**(1.5)**
>=1 Dose Delayed	6	(1.9)	3	(1.0)	9	(1.5)
Subjects with >=1 Imaging Scan deviation	**27**	**(8.8)**	**13**	**(4.2)**	**40**	**(6.5)**
>=1 Imaging Scan Delayed	23	(7.5)	11	(3.6)	34	(5.5)
>=1 Imaging Scan Missed	4	(1.3)	2	(0.6)	6	(1.0)
Subjects with >=1 Patient -Reported Outcome deviation	**14**	**(4.5)**	**20**	**(6.5)**	**34**	**(5.5)**
>=1 Patient -Reported Outcome Alternate Method-Alternative Location	11	(3.6)	10	(3.2)	21	(3.4)
>=1 Patient -Reported Outcome Missed	5	(1.6)	13	(4.2)	18	(2.9)
>=1 Patient -Reported Outcome Partially Missed	0	(0.0)	2	(0.6)	2	(0.3)
Subjects with >=1 Procedure deviation	**17**	**(5.5)**	**13**	**(4.2)**	**30**	**(4.9)**
>=1 Procedure Alternate Method	3	(1.0)	2	(0.6)	5	(0.8)
>=1 Procedure Alternate Process	3	(1.0)	0	(0.0)	3	(0.5)
>=1 Procedure Delayed	5	(1.6)	4	(1.3)	9	(1.5)
>=1 Procedure Missed	6	(1.9)	6	(1.9)	12	(1.9)
>=1 Procedure Telemedicine	2	(0.6)	2	(0.6)	4	(0.6)
Subjects with >=1 Safety Assessment deviation	**12**	**(3.9)**	**6**	**(1.9)**	**18**	**(2.9)**
>=1 Safety Assessment Alternate Method-Alternative Location	4	(1.3)	2	(0.6)	6	(1.0)
>=1 Safety Assessment Delayed	1	(0.3)	0	(0.0)	1	(0.2)
>=1 Safety Assessment Missed	6	(1.9)	3	(1.0)	9	(1.5)
>=1 Safety Assessment Other	1	(0.3)	1	(0.3)	2	(0.3)
Subjects with >=1 Scan deviation	**4**	**(1.3)**	**3**	**(1.0)**	**7**	**(1.1)**
>=1 Scan Delayed	3	(1.0)	2	(0.6)	5	(0.8)
>=1 Scan Missed	1	(0.3)	1	(0.3)	2	(0.3)
Subjects with >=1 Visit deviation	**47**	**(15.3)**	**42**	**(13.6)**	**89**	**(14.4)**
>=1 Visit Alternate Method-Alternative Location	13	(4.2)	5	(1.6)	18	(2.9)
>=1 Visit Delayed	33	(10.7)	34	(11.0)	67	(10.9)
>=1 Visit Missed	5	(1.6)	6	(1.9)	11	(1.8)
>=1 Visit Telemedicine	8	(2.6)	4	(1.3)	12	(1.9)

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This table reflects all protocol deviations reported as associated with COVID-19 that are deemed to have the potential to impact interpretation of study results.

Each block of rows (i.e., within horizontal grid lines) reflects deviations recorded according to the bolded text (e.g., visit, dose). Impacts of COVID-19 counted in the blocks of rows subsequent to visit deviations may or may not also be counted within the block of rows for visit deviations, and vice versa, depending on whether the impacts were reported both as visit deviations and as other deviations.

Baseline data

Table 17. Participant Characteristics (CPS≥1 Participants) (ITT Population)

	Pembro Combo		Control		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	273		275		548	
Sex						
Female	273	(100.0)	275	(100.0)	548	(100.0)
Age (Years)						
<50	123	(45.1)	124	(45.1)	247	(45.1)
50 to 64	109	(39.9)	105	(38.2)	214	(39.1)
65 to 74	32	(11.7)	37	(13.5)	69	(12.6)
>=75	9	(3.3)	9	(3.3)	18	(3.3)
Mean	51.2		50.7		51.0	
SD	12.0		12.6		12.3	
Median	51.0		51.0		51.0	
Range	25 to 82		22 to 78		22 to 82	
Race						
American Indian Or Alaska Native	13	(4.8)	17	(6.2)	30	(5.5)
Asian	57	(20.9)	41	(14.9)	98	(17.9)
Black Or African American	4	(1.5)	2	(0.7)	6	(1.1)
Multiple	28	(10.3)	27	(9.8)	55	(10.0)
American Indian Or Alaska Native And Black Or African American	7	(2.6)	7	(2.5)	14	(2.6)
American Indian Or Alaska Native And White	15	(5.5)	13	(4.7)	28	(5.1)
American Indian Or Alaska Native And White And Asian	0	(0.0)	1	(0.4)	1	(0.2)
Black Or African American And White	6	(2.2)	6	(2.2)	12	(2.2)
Not Applicable[a]	17	(6.2)	16	(5.8)	33	(6.0)
White	153	(56.0)	172	(62.5)	325	(59.3)
Missing	1	(0.4)	0	(0.0)	1	(0.2)
Ethnicity						
Hispanic Or Latino	97	(35.5)	106	(38.5)	203	(37.0)

Not Hispanic Or Latino	170	(62.3)	165	(60.0)	335	(61.1)
Not Reported	5	(1.8)	4	(1.5)	9	(1.6)
Unknown	1	(0.4)	0	(0.0)	1	(0.2)
Geographic Region						
Asia Pacific	54	(19.8)	38	(13.8)	92	(16.8)
EU/EMEA	91	(33.3)	98	(35.6)	189	(34.5)
North America	35	(12.8)	38	(13.8)	73	(13.3)
Latin America	93	(34.1)	101	(36.7)	194	(35.4)
ECOG Performance Scale						
0	160	(58.6)	148	(53.8)	308	(56.2)
1	111	(40.7)	127	(46.2)	238	(43.4)
2	1	(0.4)	0	(0.0)	1	(0.2)
Missing	1	(0.4)	0	(0.0)	1	(0.2)
Stage at Initial Diagnosis[b]						
I	55	(20.1)	48	(17.5)	103	(18.8)
II	76	(27.8)	85	(30.9)	161	(29.4)
III	5	(1.8)	7	(2.5)	12	(2.2)
IIIA	4	(1.5)	7	(2.5)	11	(2.0)
IIIB	41	(15.0)	37	(13.5)	78	(14.2)
IVA	6	(2.2)	3	(1.1)	9	(1.6)
IVB	86	(31.5)	88	(32.0)	174	(31.8)
Disease Status at Study Entry						
Metastatic[c]	56	(20.5)	59	(21.5)	115	(21.0)
Persistent or Recurrent with distant metastases at study entry	170	(62.3)	156	(56.7)	326	(59.5)
Persistent or Recurrent without distant metastases at study entry	47	(17.2)	60	(21.8)	107	(19.5)
Histology of Subtype of Cervical Cancer						
Adenocarcinoma	47	(17.2)	66	(24.0)	113	(20.6)
Adenosquamous/Both - Squamous And Adenocarcinoma	13	(4.8)	12	(4.4)	25	(4.6)
Epidermoide Carcinom	1	(0.4)	0	(0.0)	1	(0.2)
Indiferenciated Carcinoma	1	(0.4)	0	(0.0)	1	(0.2)
Squamous Cell/Squamous Cell Carcinoma	211	(77.3)	197	(71.6)	408	(74.5)
PD-L1 Status						
1=<CPS<10	115	(42.1)	116	(42.2)	231	(42.2)
CPS>=10	158	(57.9)	159	(57.8)	317	(57.8)
Bevacizumab Use						
Yes	175	(64.1)	171	(62.2)	346	(63.1)
No	98	(35.9)	104	(37.8)	202	(36.9)
Prior Therapy						
Chemoradiation (CRT) and Surgery	43	(15.8)	48	(17.5)	91	(16.6)
Radiation and Surgery	18	(6.6)	21	(7.6)	39	(7.1)
CRT Only	112	(41.0)	103	(37.5)	215	(39.2)
Radiation Only	28	(10.3)	21	(7.6)	49	(8.9)
Surgery Only	16	(5.9)	23	(8.4)	39	(7.1)
None	56	(20.5)	59	(21.5)	115	(21.0)

Database Cutoff Date: 03MAY2021

[a] Participants in France cannot report race by law.

[b] Stage at Initial Diagnosis determined using FIGO 2009/ NCCN 2017 criteria.

[c] Metastatic includes participants with para-aortic lymph node involvement.

Table 18. Participant Characteristics (All-comer Participants) (ITT Population)

	Pembro Combo		Control		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	308		309		617	
Sex						
Female	308	(100.0)	309	(100.0)	617	(100.0)
Age (Years)						
<50	134	(43.5)	143	(46.3)	277	(44.9)
50 to 64	126	(40.9)	114	(36.9)	240	(38.9)
65 to 74	38	(12.3)	42	(13.6)	80	(13.0)
>=75	10	(3.2)	10	(3.2)	20	(3.2)
Mean	51.7		50.7		51.2	
SD	11.9		12.7		12.3	
Median	51.0		50.0		51.0	
Range	25 to 82		22 to 79		22 to 82	
Race						
American Indian Or Alaska Native	18	(5.8)	21	(6.8)	39	(6.3)
Asian	65	(21.1)	45	(14.6)	110	(17.8)
Black Or African American	4	(1.3)	2	(0.6)	6	(1.0)
Multiple	32	(10.4)	34	(11.0)	66	(10.7)
American Indian Or Alaska Native And Black Or African American	7	(2.3)	7	(2.3)	14	(2.3)
American Indian Or Alaska Native And White	17	(5.5)	19	(6.1)	36	(5.8)
American Indian Or Alaska Native And White And Asian	0	(0.0)	1	(0.3)	1	(0.2)
Black Or African American And White	8	(2.6)	7	(2.3)	15	(2.4)
Not Applicablea	18	(5.8)	17	(5.5)	35	(5.7)
White	170	(55.2)	190	(61.5)	360	(58.3)
Missing	1	(0.3)	0	(0.0)	1	(0.2)
Ethnicity						
Hispanic Or Latino	110	(35.7)	121	(39.2)	231	(37.4)
Not Hispanic Or Latino	192	(62.3)	184	(59.5)	376	(60.9)
Not Reported	5	(1.6)	4	(1.3)	9	(1.5)
Unknown	1	(0.3)	0	(0.0)	1	(0.2)
Geographic Region						
Asia Pacific	63	(20.5)	42	(13.6)	105	(17.0)
EU/EMEA	103	(33.4)	108	(35.0)	211	(34.2)
North America	39	(12.7)	43	(13.9)	82	(13.3)
Latin America	103	(33.4)	116	(37.5)	219	(35.5)
ECOG Performance Scale						
0	178	(57.8)	170	(55.0)	348	(56.4)
1	128	(41.6)	139	(45.0)	267	(43.3)
2	1	(0.3)	0	(0.0)	1	(0.2)
Missing	1	(0.3)	0	(0.0)	1	(0.2)
Stage at Initial Diagnosisb						
I	67	(21.8)	58	(18.8)	125	(20.3)
II	85	(27.6)	93	(30.1)	178	(28.8)
III	5	(1.6)	8	(2.6)	13	(2.1)
IIIA	4	(1.3)	8	(2.6)	12	(1.9)
IIIB	46	(14.9)	42	(13.6)	88	(14.3)
IVA	7	(2.3)	4	(1.3)	11	(1.8)
IVB	94	(30.5)	96	(31.1)	190	(30.8)
Disease Status at Study Entry						
Metastaticc	58	(18.8)	64	(20.7)	122	(19.8)
Persistent or Recurrent with distant metastases at study entry	199	(64.6)	179	(57.9)	378	(61.3)
Persistent or Recurrent without distant metastases at study entry	51	(16.6)	66	(21.4)	117	(19.0)
Histology of Subtype of Cervical Cancer						
Adenocarcinoma	56	(18.2)	84	(27.2)	140	(22.7)

Adenosquamous/Both - Squamous And Adenocarcinoma	15	(4.9)	14	(4.5)	29	(4.7)
Epidermoide Carcinom	1	(0.3)	0	(0.0)	1	(0.2)
Indiferenciated Carcinoma	1	(0.3)	0	(0.0)	1	(0.2)
Squamous Cell/Squamous Cell Carcinoma	235	(76.3)	211	(68.3)	446	(72.3)
PD-L1 Status						
CPS<1	35	(11.4)	34	(11.0)	69	(11.2)
1=<CPS<10	115	(37.3)	116	(37.5)	231	(37.4)
CPS>=10	158	(51.3)	159	(51.5)	317	(51.4)
Bevacizumab Use						
Yes	196	(63.6)	193	(62.5)	389	(63.0)
No	112	(36.4)	116	(37.5)	228	(37.0)
Prior Therapy						
Chemoradiation (CRT) and Surgery	49	(15.9)	56	(18.1)	105	(17.0)
Radiation and Surgery	22	(7.1)	23	(7.4)	45	(7.3)
CRT Only	125	(40.6)	118	(38.2)	243	(39.4)
Radiation Only	31	(10.1)	24	(7.8)	55	(8.9)
Surgery Only	23	(7.5)	24	(7.8)	47	(7.6)
None	58	(18.8)	64	(20.7)	122	(19.8)

Database Cutoff Date: 03MAY2021

[a] Participants in France cannot report race by law.

[b] Stage at Initial Diagnosis determined using FIGO 2009/ NCCN 2017 criteria.

[c] Metastatic includes participants with para-aortic lymph node involvement. These patients are the participants diagnosed with stage IVB disease and enter the study without any prior treatment for their cervical cancer.

In the CPS≥10 participants, demographics and other baseline characteristics were generally consistent with those of the all-comer participants.

Numbers analysed

A total of 617 participants were randomized (308 to pembrolizumab + chemotherapy ± bevacizumab, 309 to placebo + chemotherapy ± bevacizumab). All randomized participants were included in the Intention-to-Treat (ITT) population, which served as the population for the primary efficacy analyses.

Table 18A. Populations analysed per ITT, CPS≥1 and CPS≥10

	Pembro combo	**Placebo control**	**Total**
ITT	308	309	617
PD-L1 CPS ≥1	273 (88.6%)	275 (89%)	548 (88.8%)
PD-L1 CPS ≥10	158 (51.3%)	159 (51.5%)	317 (51.4%)

Outcomes and estimation

The efficacy analyses were based on IA1 (database cutoff: 03-MAY-2021), which was the first interim analysis of PFS and OS in all-comer participants and participants whose tumours express PD-L1 (CPS ≥1 and CPS ≥10).

PD-L1 CPS ≥1 Participants

Table 19. Summary of Key Efficacy Results in Participants With CPS≥1 Persistent, Recurrent, or Metastatic Cervical Cancer (ITT Population)

Endpoint	Pembrolizumab + Chemotherapy ± Bevacizumab (N=273)	Placebo + Chemotherapy ± Bevacizumab (N=275)
PFS as Assessed by Investigator per RECIST 1.1		
Number of Events (%)	157 (57.5)	198 (72.0)
Median PFS[a], months (95% CI)	10.4 (9.7, 12.3)	8.2 (6.3, 8.5)
HR (95% CI)[b] p-value[c,d]	0.62 (0.50, 0.77) <0.0001	
OS		
Number of Events (%)	118 (43.2)	154 (56.0)
Median OS[a], months (95% CI)	NR (19.8, NR)	16.3 (14.5, 19.4)
HR (95% CI)[b] p-value[c,e]	0.64 (0.50, 0.81) 0.0001	
ORR, % (95% CI)	68.1 (62.2, 73.6)	50.2 (44.1, 56.2)
ORR Difference % (95% CI)[f]	18.0 (10.1, 25.7)	
DOR, (months), median (range)[a]	18.0 (1.3+, 24.2+)	10.4 (1.5+, 22.0+)
PFS as Assessed by BICR per RECIST 1.1		
Median PFS[a], months (95% CI)	12.8 (10.4, 20.6)	8.3 (7.7, 9.2)
HR (95% CI)[b]	0.60 (0.48, 0.75)	

Abbreviations: BICR = blinded independent central review; CI = confidence interval; CPS = Combined Positive Score; HR = hazard ratio; ITT = intent-to-treat; NR = not reached; OS = overall survival; PFS = progression-free survival; PD-L1 = programmed cell death ligand 1; RECIST = Response Evaluation Criteria In Solid Tumors

[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 metastatic at initial diagnosis (FIGO [2009] stage IVB) (yes or no), bevacizumab use (yes or no) and PD-L1 status (CPS <1, CPS 1 to <10, CPS ≥10).

[c] One-sided p-value based on log-rank test stratified by metastatic at initial diagnosis (FIGO [2009] stage IVB) (yes or no), bevacizumab use (yes or no) and PD-L1 status (CPS <1, CPS 1 to <10, CPS ≥10).

[d] Based on stratified log-rank test (compared to an alpha boundary of 0.0014426).

[e] Based on stratified log-rank test (compared to an alpha boundary of 0.0054906).

[f] Based on Miettinen & Nurminen method stratified by metastatic at initial diagnosis (FIGO [2009] stage IVB) (yes or no), bevacizumab use (yes or no) and PD-L1 status (CPS <1, CPS 1 to <10, CPS ≥10).

Database Cutoff Date: 03-MAY-2021

All-comer Participants

Table 20. Summary of Key Efficacy Results in All-comer Participants With Persistent, Recurrent, or Metastatic Cervical Cancer (ITT Population)

Endpoint	Pembrolizumab + Chemotherapy ± Bevacizumab (N=308)	Placebo + Chemotherapy ± Bevacizumab (N=309)
PFS as Assessed by Investigator per RECIST 1.1		
Number of Events (%)	180 (58.4)	226 (73.1)
Median PFS[a], months (95% CI)	10.4 (9.1, 12.1)	8.2 (6.4, 8.4)
HR (95% CI)[b] p-value[c,d]	0.65 (0.53, 0.79) <0.0001	

Endpoint	Pembrolizumab + Chemotherapy ± Bevacizumab (N=308)	Placebo + Chemotherapy ± Bevacizumab (N=309)
OS		
Number of Events (%)	138 (44.8)	174 (56.3)
Median OS[a], months (95% CI)	24.4 (19.2, NR)	16.5 (14.5, 19.4)
HR (95% CI)[b] p-value[c,e]	0.67 (0.54, 0.84) 0.0003	
ORR, % (95% CI)	65.9 (60.3, 71.2)	50.8 (45.1, 56.5)
ORR Difference % (95% CI)[f]	15.3 (7.8, 22.6)	
DOR, (months), median (range)[a]	18.0 (1.3+, 24.2+)	10.4 (1.5+, 22.0+)
PFS as Assessed by BICR per RECIST 1.1		
Median PFS[a], months (95% CI)	12.3 (10.3, 17.9)	8.3 (8.1, 9.0)
HR (95% CI)[b]	0.63 (0.51, 0.77)	

Abbreviations: BICR = blinded independent central review; CI = confidence interval; CPS = Combined Positive Score; HR = hazard ratio; ITT = intent-to-treat; NR = not reached; OS = overall survival; PFS = progression-free survival; PD-L1 = programmed cell death ligand 1; RECIST = Response Evaluation Criteria In Solid Tumors

[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 metastatic at initial diagnosis (FIGO [2009] stage IVB) (yes or no), bevacizumab use (yes or no) and PD-L1 status (CPS <1, CPS 1 to <10, CPS ≥10).

[c] One-sided p-value based on log-rank test stratified by metastatic at initial diagnosis (FIGO [2009] stage IVB) (yes or no), bevacizumab use (yes or no) and PD-L1 status (CPS <1, CPS 1 to <10, CPS ≥10).

[d] Based on stratified log-rank test (compared to an alpha boundary of 0.0012843).

[e] Based on stratified log-rank test (compared to an alpha boundary of 0.0049074).

[f] Based on Miettinen & Nurminen method stratified by metastatic at initial diagnosis (FIGO [2009] stage IVB) (yes or no), bevacizumab use (yes or no) and PD-L1 status (CPS <1, CPS 1 to <10, CPS ≥10).

Database Cutoff Date: 03-MAY-2021

PD-L1 CPS ≥10 Participants

Table 21. Summary of Key Efficacy Results in Participants With CPS≥10 Persistent, Recurrent, or Metastatic Cervical Cancer (ITT Population)*

Endpoint	Pembrolizumab + Chemotherapy ± Bevacizumab (N=158)	Placebo + Chemotherapy ± Bevacizumab (N=159)
PFS as Assessed by Investigator per RECIST 1.1		
Number of Events (%)	87 (55.1)	116 (73.0)
Median PFS, months (95% CI)	10.4 (8.9, 15.1)	8.1 (6.2, 8.8)
HR (95% CI) p-value	0.58 (0.44, 0.77) <0.0001	
OS		
Number of Events (%)	66 (41.8)	88 (55.3)
Median OS, months (95% CI)	NR (19.1, NR)	16.4 (14.0, 25.0)
HR (95% CI) p-value	0.61 (0.44, 0.84) 0.0013	
ORR by inv, % (95% CI)	69.6 (61.8, 76.7)	49.1 (41.1, 57.1)
ORR Difference % (95% CI)	20.5 (10.1, 30.5)	
DOR by inv, (months), median (range)	21.1 (1.3+, 24.2+)	9.4 (2.1+, 21.5+)

Endpoint	Pembrolizumab + Chemotherapy ± Bevacizumab (N=158)	Placebo + Chemotherapy ± Bevacizumab (N=159)
PFS as Assessed by BICR per RECIST 1.1		
Median PFS, months (95% CI)	15.1 (8.9, NR)	8.3 (7.1, 10.2)
HR (95% CI)	0.55 (0.41, 0.74)	
Abbreviations: BICR = blinded independent central review; CI = confidence interval; CPS = Combined Positive Score; HR = hazard ratio; ITT = intent-to-treat; NR = not reached; OS = overall survival; PFS = progression-free survival; PD-L1 = programmed cell death ligand 1; RECIST = Response Evaluation Criteria In Solid Tumors Database Cutoff Date: 03-MAY-2021		

* Summary presented by the assessment team

Results in the CPS 1-<10 subgroup: OS HR 0.67 (0.46, 0.97); PFS by inv HR 0.68 (0.49, 0.94); ORR difference 14.58 (2.24, 26.5).

Dual primary endpoint – Overall survival

Pembrolizumab + chemotherapy ± bevacizumab provided a statistically significant improvement in OS compared with placebo + chemotherapy ± bevacizumab in participants with PD-L1 CPS ≥1, all-comer participants and in patients whose tumors express PD-L1 CPS ≥10.

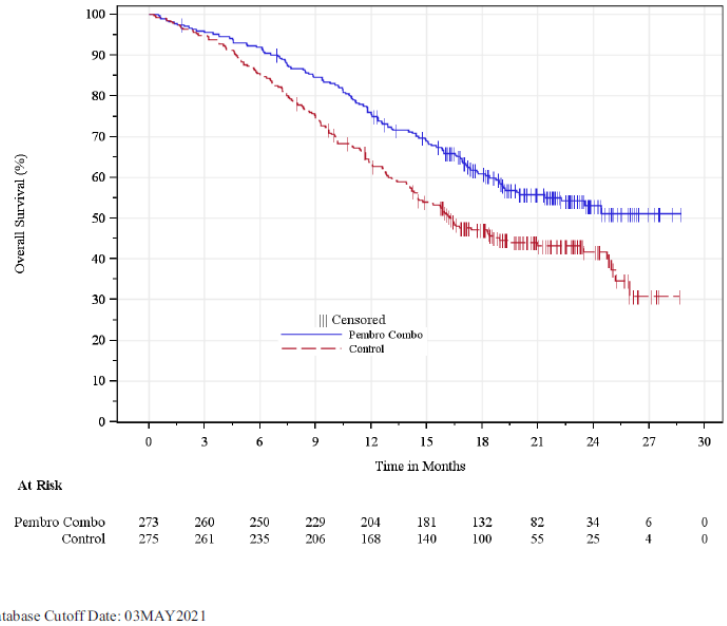
CPS≥1

Table 22. Analysis of Overall Survival (CPS>=1 Participants) (ITT Population)

	Pembro Combo (N=273)	Control (N=275)
Number of Events (%)	118 (43.2)	154 (56.0)
DEATH	118 (43.2)	154 (56.0)
Kaplan-Meier Estimates (months)[a]		
Median (95% CI)	NR (19.8, NR)	16.3 (14.5, 19.4)
[Q1, Q3]	[12.0,]	[9.0,]
Person-months	4559.1	3988.5
Event Rate / 100 Person-months	2.6	3.9
vs Control		
Hazard Ratio (95% CI)[b]	0.64 (0.50, 0.81)	
p-value[c]	0.0001	
OS Rate at month 6 (%) (95% CI)	91.9 (88.0, 94.6)	85.5 (80.7, 89.1)
OS Rate at month 12 (%) (95% CI)	75.3 (69.7, 80.0)	63.1 (57.0, 68.5)
OS Rate at month 18 (%) (95% CI)	60.8 (54.6, 66.4)	47.1 (41.0, 53.0)
OS Rate at month 24 (%) (95% CI)	53.0 (46.0, 59.4)	41.7 (34.9, 48.2)

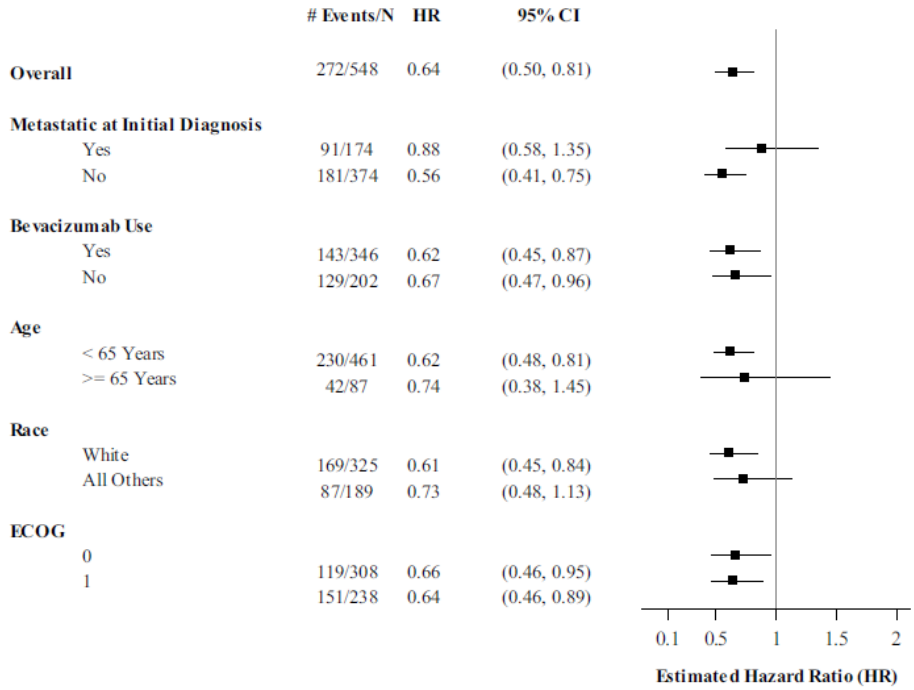
[a] From product-limit (Kaplan-Meier) method for censored data.
[b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by metastatic at initial diagnosis (FIGO [2009] stage IVB) (yes or no), bevacizumab use (yes or no) and PD-L1 status (CPS <1, CPS 1 to <10, CPS >=10).
[c] One-sided p-value based on log-rank test stratified by metastatic at initial diagnosis (FIGO [2009] stage IVB) (yes or no), bevacizumab use (yes or no) and PD-L1 status (CPS <1, CPS 1 to <10, CPS >=10).
NR = Not reached.
Database Cutoff Date: 03MAY2021

Figure 7. Kaplan-Meier Estimates of Overall Survival (CPS>=1 Participants) (ITT Population)



Database Cutoff Date: 03MAY2021

Figure 8. Forest Plot of Overall Survival Hazard Ratio by Subgroup Factors (CPS>=1 Participants) (ITT Population)



NR = Not Reached. Based on Cox regression model with Efrons method of tie handling with treatment as a covariate stratified by metastatic at initial diagnosis (FIGO [2009] stage IVB) (yes or no), bevacizumab use (yes or no) and PD-L1 status (CPS <1, CPS 1 to <10, CPS >=10). If total number of participants in one level of a subgroup is <20, that particular level will not be displayed. Database Cutoff Date: 03MAY2021

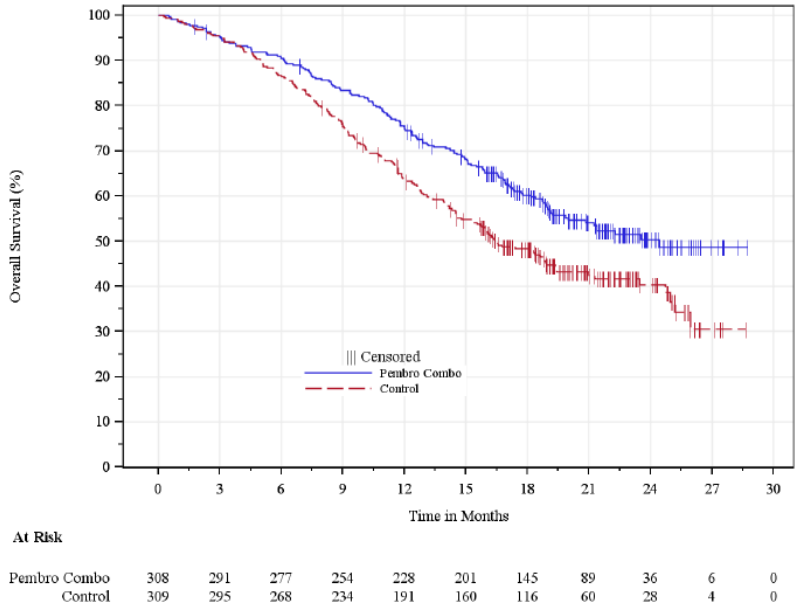
All-comers

Table 23. Analysis of Overall Survival (All-comer Participants) (ITT Population)

	Pembro Combo (N=308)	Control (N=309)
Number of Events (%)	138 (44.8)	174 (56.3)
DEATH	138 (44.8)	174 (56.3)
Kaplan-Meier Estimates (months)[a]		
Median (95% CI)	24.4 (19.2, NR)	16.5 (14.5, 19.4)
[Q1, Q3]	[12.0,]	[9.1,]
Person-months	5055.9	4516.2
Event Rate / 100 Person-months	2.7	3.9
vs Control		
Hazard Ratio (95% CI)[b]	0.67 (0.54, 0.84)	
p-value[c]	0.0003	
OS Rate at month 6 (%) (95% CI)	90.5 (86.7, 93.3)	86.7 (82.4, 90.1)
OS Rate at month 12 (%) (95% CI)	74.8 (69.5, 79.3)	63.6 (57.9, 68.7)
OS Rate at month 18 (%) (95% CI)	60.2 (54.3, 65.5)	48.3 (42.6, 53.9)
OS Rate at month 24 (%) (95% CI)	50.4 (43.8, 56.6)	40.4 (34.0, 46.6)

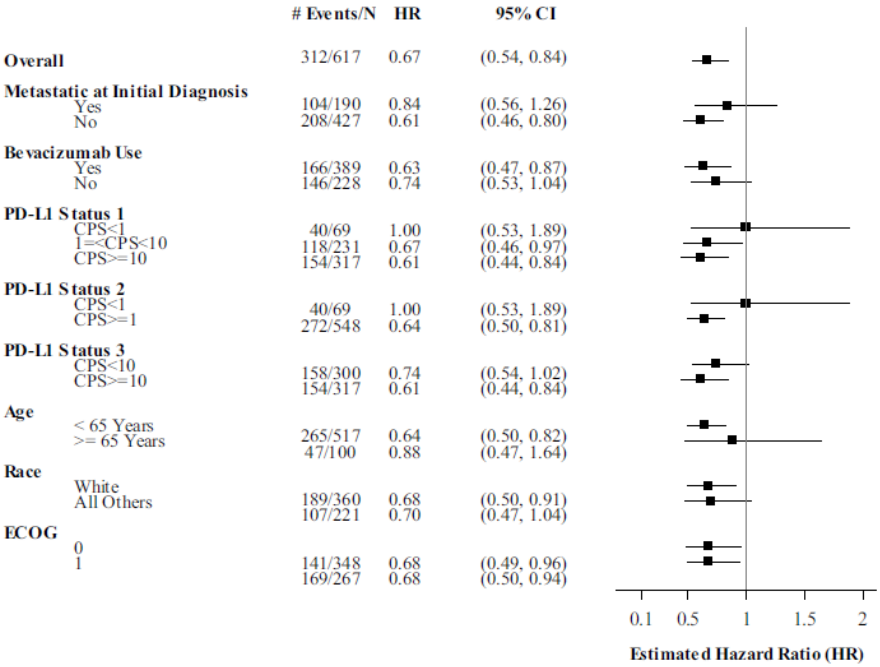
[a] From product-limit (Kaplan-Meier) method for censored data.
[b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by metastatic at initial diagnosis (FIGO [2009] stage IVB) (yes or no), bevacizumab use (yes or no) and PD-L1 status (CPS <1, CPS 1 to <10, CPS >=10).
[c] One-sided p-value based on log-rank test stratified by metastatic at initial diagnosis (FIGO [2009] stage IVB) (yes or no), bevacizumab use (yes or no) and PD-L1 status (CPS <1, CPS 1 to <10, CPS >=10).
NR = Not reached.
Database Cutoff Date: 03MAY2021

Figure 9. Kaplan-Meier Estimates of Overall Survival (All-comer Participants) (ITT Population)



Database Cutoff Date: 03MAY2021

Figure 10. Forest Plot of Overall Survival Hazard Ratio by Subgroup Factors (All-comer Participants) (ITT Population)



CPS≥10

Table 24. Analysis of Overall Survival (CPS>=10 Participants) (ITT Population)

	Pembro Combo (N=158)	Control (N=159)
Number of Events (%)	66 (41.8)	88 (55.3)
DEATH	66 (41.8)	88 (55.3)
Kaplan-Meier Estimates (months)[a]		
Median (95% CI)	NR (19.1, NR)	16.4 (14.0, 25.0)
[Q1, Q3]	[12.6,]	[8.3,]
Person-months	2627.9	2271.4
Event Rate / 100 Person-months	2.5	3.9
vs Control		
Hazard Ratio (95% CI)[b]	0.61 (0.44, 0.84)	
p-value[c]	0.0013	
OS Rate at month 6 (%) (95% CI)	91.7 (86.2, 95.1)	84.9 (78.3, 89.6)
OS Rate at month 12 (%) (95% CI)	75.7 (68.2, 81.7)	61.5 (53.4, 68.6)
OS Rate at month 18 (%) (95% CI)	61.2 (52.9, 68.5)	48.4 (40.2, 56.1)
OS Rate at month 24 (%) (95% CI)	54.4 (45.5, 62.4)	44.6 (36.3, 52.5)

[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 stratified by metastatic at initial diagnosis (FIGO [2009] stage IVB) (yes or no), bevacizumab use (yes or no) and PD-L1 status (CPS <1, CPS 1 to <10, CPS >=10).
[c] One-sided p-value based on log-rank test stratified by metastatic at initial diagnosis (FIGO [2009] stage IVB) (yes or no), bevacizumab use (yes or no) and PD-L1 status (CPS <1, CPS 1 to <10, CPS >=10).
NR = Not reached.
Database Cutoff Date: 03MAY2021

Figure 11. Kaplan-Meier Estimates of Overall Survival (CPS>=10 Participants) (ITT Population)

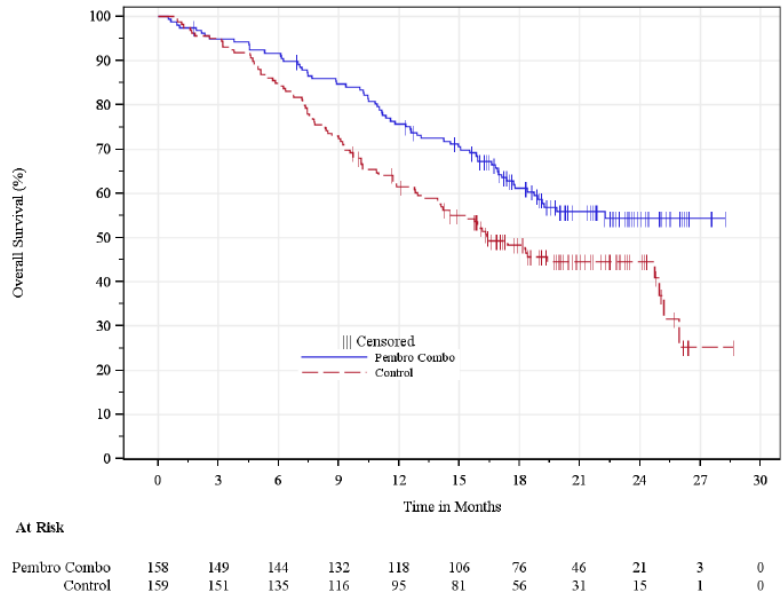
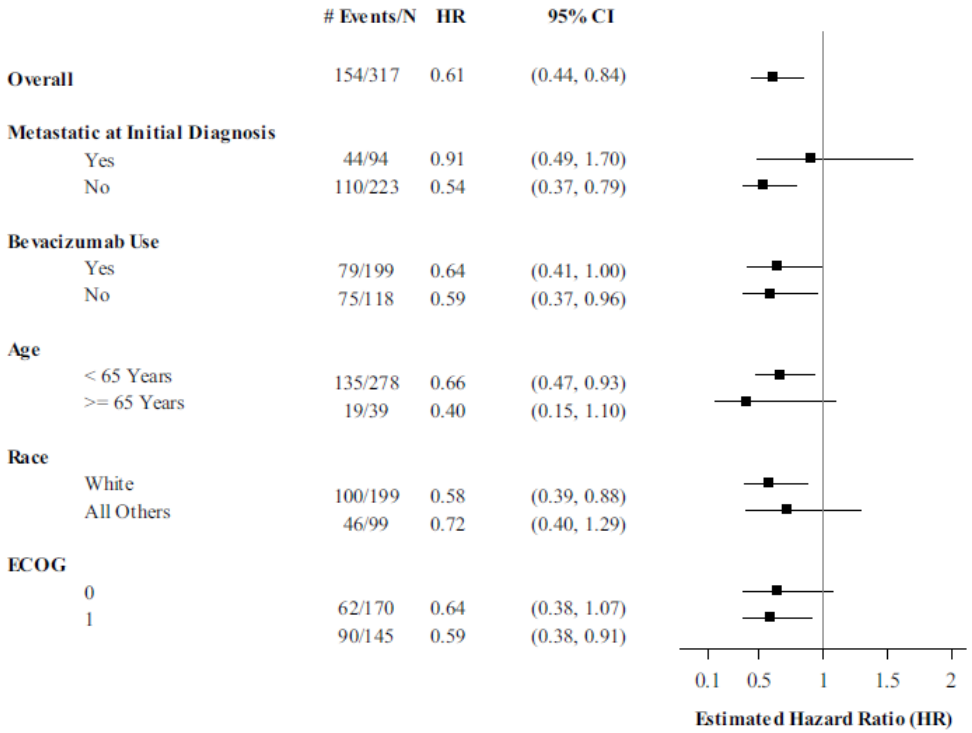


Figure 12. Forest Plot of Overall Survival Hazard Ratio by Subgroup Factors (CPS>=10 Participants) (ITT Population)



Dual primary endpoint – Progression free survival (by investigator)

Pembrolizumab + chemotherapy ± bevacizumab was superior to placebo + chemotherapy ± bevacizumab with a statistically significant improvement in PFS per RECIST 1.1 as assessed by

investigator in participants with persistent, recurrent, or metastatic cervical cancer whose tumors express PD-L1 CPS ≥1, in all-comer participants as well as in PD-L1 CPS ≥10 population.

CPS≥1

Table 25. Analysis of Progression-Free Survival Based on Investigator Assessment per RECIST 1.1 (Primary Analysis) (CPS>=1 Participants) (ITT Population)

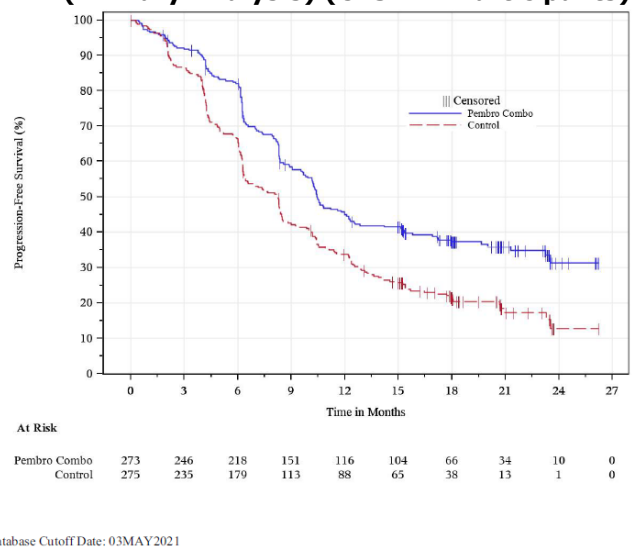
	Pembro Combo (N=273)	Control (N=275)
Number of Events (%)	157 (57.5)	198 (72.0)
DEATH	25 (9.2)	26 (9.5)
DOCUMENTED PROGRESSION	132 (48.4)	172 (62.5)
Kaplan-Meier Estimates (months)[a]		
Median (95% CI)	10.4 (9.7, 12.3)	8.2 (6.3, 8.5)
[Q1, Q3]	[6.2,]	[4.2, 17.1]
Person-months	3110.2	2460.4
Event Rate / 100 Person-months	5.0	8.0
vs Control		
Hazard Ratio (95% CI)[b]	0.62 (0.50, 0.77)	
p-value[c]	<0.0001	
PFS Rate at month 6 (%) (95% CI)	81.5 (76.2, 85.7)	67.1 (61.0, 72.4)
PFS Rate at month 12 (%) (95% CI)	45.5 (39.2, 51.5)	34.1 (28.3, 40.0)
PFS Rate at month 18 (%) (95% CI)	39.3 (33.2, 45.4)	23.8 (18.6, 29.4)
PFS Rate at month 24 (%) (95% CI)	33.1 (25.7, 40.7)	14.0 (7.7, 22.3)

[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 metastatic at initial diagnosis (FIGO [2009] stage IVB) (yes or no), bevacizumab use (yes or no) and PD-L1 status (CPS <1, CPS 1 to <10, CPS >=10).
[c] One-sided p-value based on log-rank test stratified by metastatic at initial diagnosis (FIGO [2009] stage IVB) (yes or no), bevacizumab use (yes or no) and PD-L1 status (CPS <1, CPS 1 to <10, CPS >=10).
NR = Not reached.
Database Cutoff Date: 03MAY2021

PFS by BICR (secondary endpoint) in the CPS ≥1 population was median PFS 12.8 (10.4, 20.6) vs 8.3 (7.7, 9.2), Hazard Ratio 0.60 (95%CI 0.48, 0.75).

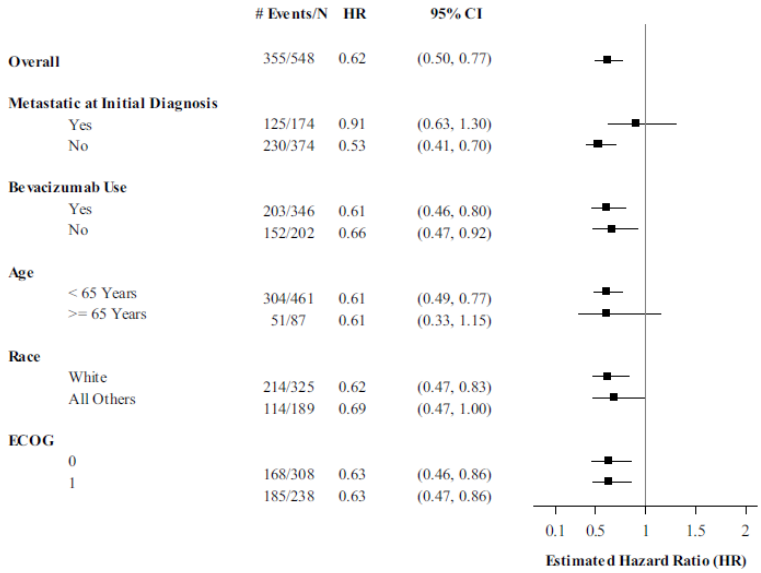
PFS sensitivity analyses in the CPS ≥1 population were consistent with primary analysis (sensitivity 1 HR 0.62, sensitivity 2 HR 0.66).

Figure 13. Kaplan-Meier Estimates of Progression-Free Survival Based on Investigator Assessment per RECIST 1.1 (Primary Analysis) (CPS>=1 Participants) (ITT Population)



Database Cutoff Date: 03MAY2021

Figure 14. Forest Plot of Progression-Free Survival Hazard Ratio by Subgroup Factors Based on Investigator Assessment per RECIST 1.1 (Primary Analysis) (CPS>=1 Participants) (ITT Population)



NR = Not Reached. Based on Cox regression model with Efrons method of tie handling with treatment as a covariate stratified by metastatic at initial diagnosis (FIGO [2009] stage IVB) (yes or no), bevacizumab use (yes or no) and PD-L1 status (CPS <1, CPS 1 to <10, CPS >=10). If total number of participants in one level of a subgroup is <20, that particular level will not be displayed. Database Cutoff Date: 03MAY2021

All-comers

Table 26. Analysis of Progression-Free Survival Based on Investigator Assessment per RECIST 1.1 (Primary Analysis) (All-comer Participants) (ITT Population)

	Pembro Combo (N=308)	Control (N=309)
Number of Events (%)	180 (58.4)	226 (73.1)
DEATH	27 (8.8)	27 (8.7)
DOCUMENTED PROGRESSION	153 (49.7)	199 (64.4)
Kaplan-Meier Estimates (months)[a]		
Median (95% CI)	10.4 (9.1, 12.1)	8.2 (6.4, 8.4)
[Q1, Q3]	[6.2,]	[4.3, 15.5]
Person-months	3412.5	2753.4
Event Rate / 100 Person-months	5.3	8.2
vs Control		
Hazard Ratio (95% CI)[b]	0.65 (0.53, 0.79)	
p-value[c]	<0.0001	
PFS Rate at month 6 (%) (95% CI)	80.5 (75.4, 84.6)	68.5 (62.8, 73.4)
PFS Rate at month 12 (%) (95% CI)	44.7 (38.8, 50.4)	33.5 (28.0, 39.1)
PFS Rate at month 18 (%) (95% CI)	38.0 (32.3, 43.7)	21.7 (16.9, 26.9)
PFS Rate at month 24 (%) (95% CI)	31.6 (24.7, 38.8)	12.8 (7.0, 20.4)

[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 metastatic at initial diagnosis (FIGO [2009] stage IVB) (yes or no), bevacizumab use (yes or no) and PD-L1 status (CPS <1, CPS 1 to <10, CPS >=10).
[c] One-sided p-value based on log-rank test stratified by metastatic at initial diagnosis (FIGO [2009] stage IVB) (yes or no), bevacizumab use (yes or no) and PD-L1 status (CPS <1, CPS 1 to <10, CPS >=10).
NR = Not reached.
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PFS by BICR in the all-comer population was median PFS 12.3 (10.3, 17.9) vs 8.3 (8.1, 9.0), Hazard Ratio 0.63 (95% CI 0.51, 0.77).

PFS sensitivity analyses were consistent with primary analysis (sensitivity 1 HR 0.65, sensitivity 2 HR 0.69).

Figure 15. Kaplan-Meier Estimates of Progression-Free Survival Based on Investigator Assessment per RECIST 1.1 (Primary Analysis) (All-comer Participants) (ITT Population)

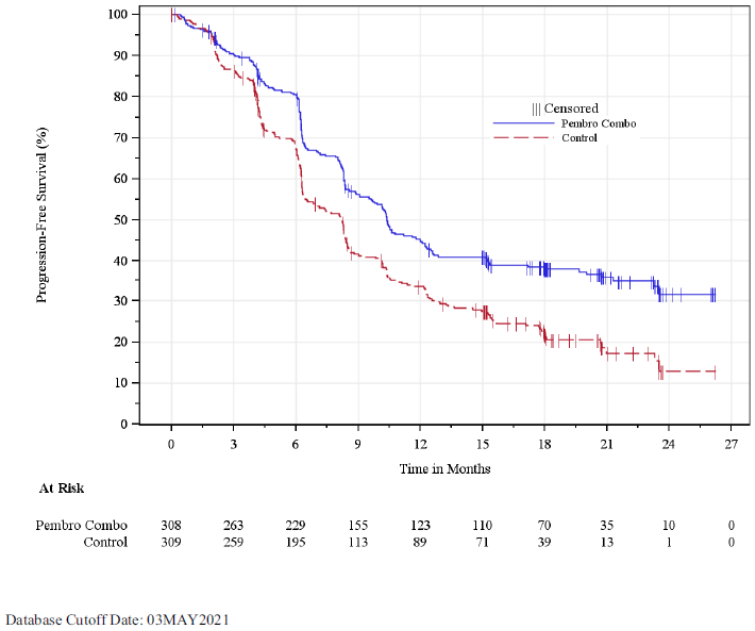
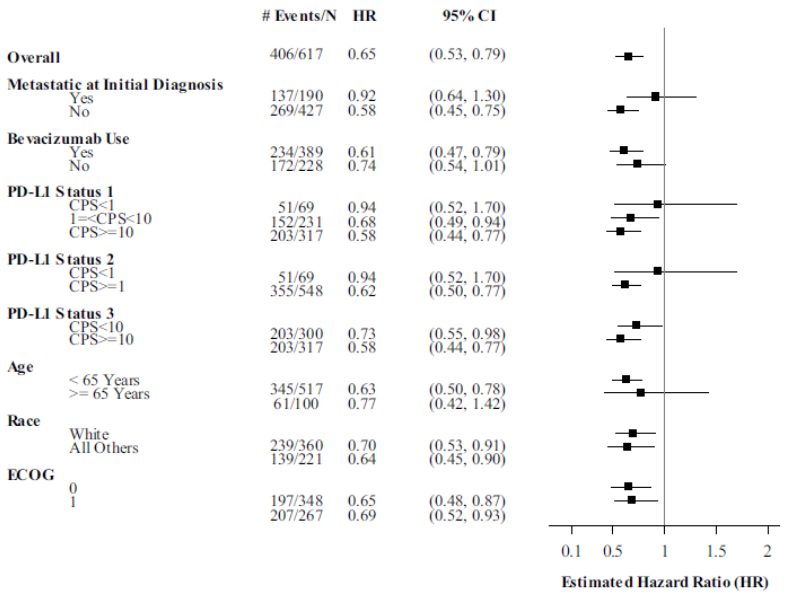


Figure 16. Forest Plot of Progression-Free Survival Hazard Ratio by Subgroup Factors Based on Investigator Assessment per RECIST 1.1 (Primary Analysis) (All-comer Participants) (ITT Population)



CPS≥10

Table 27. Analysis of Progression-Free Survival Based on Investigator Assessment per RECIST 1.1 (Primary Analysis) (CPS>=10 Participants) (ITT Population)

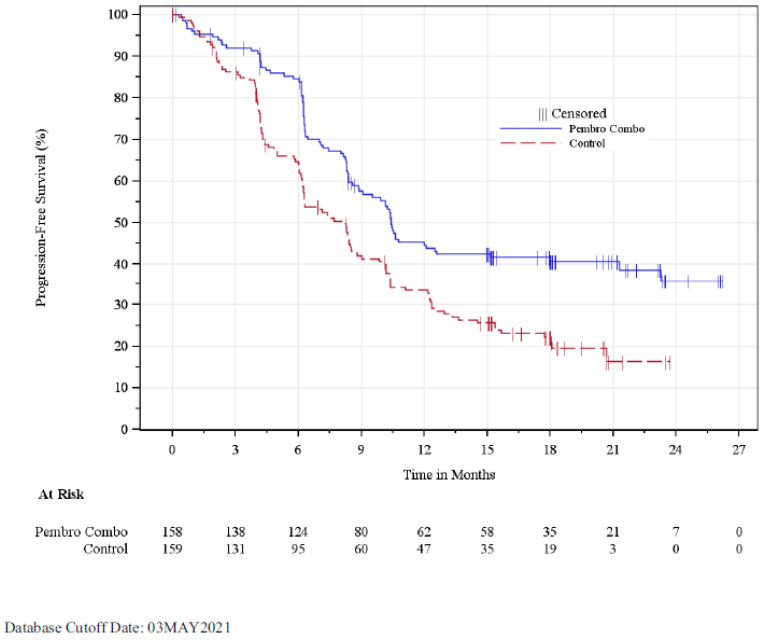
	Pembro Combo (N=158)	Control (N=159)
Number of Events (%)	87 (55.1)	116 (73.0)
DEATH	16 (10.1)	16 (10.1)
DOCUMENTED PROGRESSION	71 (44.9)	100 (62.9)
Kaplan-Meier Estimates (months)[a]		
Median (95% CI)	10.4 (8.9, 15.1)	8.1 (6.2, 8.8)
[Q1, Q3]	[6.3,]	[4.2, 15.4]
Person-months	1777.4	1364.8
Event Rate / 100 Person-months	4.9	8.5
vs Control		
Hazard Ratio (95% CI)[b]	0.58 (0.44, 0.77)	
p-value[c]	<0.0001	
PFS Rate at month 6 (%) (95% CI)	84.6 (77.7, 89.5)	64.7 (56.5, 71.8)
PFS Rate at month 12 (%) (95% CI)	44.6 (36.3, 52.5)	33.5 (25.9, 41.2)
PFS Rate at month 18 (%) (95% CI)	40.6 (32.4, 48.6)	22.2 (15.6, 29.4)
PFS Rate at month 24 (%) (95% CI)	35.8 (26.4, 45.3)	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 stratified by metastatic at initial diagnosis (FIGO [2009] stage IVB) (yes or no), bevacizumab use (yes or no) and PD-L1 status (CPS <1, CPS 1 to <10, CPS >=10).
[c] One-sided p-value based on log-rank test stratified by metastatic at initial diagnosis (FIGO [2009] stage IVB) (yes or no), bevacizumab use (yes or no) and PD-L1 status (CPS <1, CPS 1 to <10, CPS >=10).
NR = Not reached.
Database Cutoff Date: 03MAY2021

PFS by BICR in the CPS≥10 population was median PFS 15.1 (8.9, NR) vs 8.3 (7.1, 10.2), Hazard Ratio 0.55 (95%CI 0.41, 0.74).

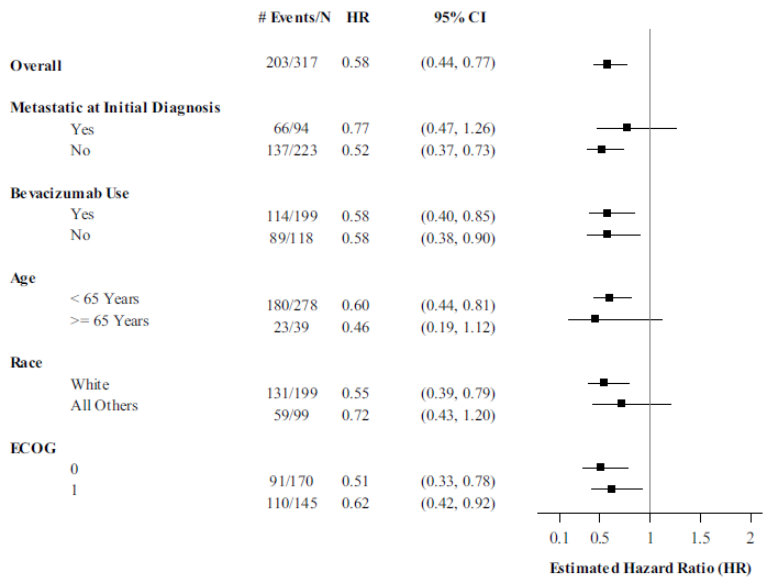
PFS sensitivity analyses in the CPS≥10 population were consistent with primary analysis (sensitivity 1 HR 0.59, sensitivity 2 HR 0.61).

Figure 17. Kaplan-Meier Estimates of Progression-Free Survival Based on Investigator Assessment per RECIST 1.1 (Primary Analysis) (CPS>=10 Participants) (ITT Population)



Database Cutoff Date: 03MAY2021

Figure 18. Forest Plot of Progression-Free Survival Hazard Ratio by Subgroup Factors Based on Investigator Assessment per RECIST 1.1 (Primary Analysis) (CPS>=10 Participants) (ITT Population)



Secondary endpoint – Overall response rate (by investigator)

Pembrolizumab + chemotherapy ± bevacizumab provided improvement in ORR (per RECIST 1.1 by the investigator, confirmed response) compared with placebo + chemotherapy ± bevacizumab in participants whose tumors express PD-L1 CPS ≥1 (68.1% vs 50.2%), all-comers (65.9% vs 50.8%) and CPS ≥10 (69.6% vs 49.1%).

CPS≥1

Table 28. Summary of Best Objective Response (Confirmed) Based on Investigator Assessment per RECIST 1.1 (CPS>=1 Participants) (ITT Population)

	Pembro Combo			Control		
	n	(%)	(95% CI)[a]	n	(%)	(95% CI)[a]
Number of Participants in Population	273			275		
Complete Response (CR)	62	(22.7)	(17.9, 28.1)	36	(13.1)	(9.3, 17.7)
Partial Response (PR)	124	(45.4)	(39.4, 51.5)	102	(37.1)	(31.4, 43.1)
Objective Response (CR+PR)	**186**	**(68.1)**	**(62.2, 73.6)**	**138**	**(50.2)**	**(44.1, 56.2)**
Stable Disease (SD)	58	(21.2)	(16.5, 26.6)	88	(32.0)	(26.5, 37.9)
Progressive Disease (PD)	9	(3.3)	(1.5, 6.2)	29	(10.5)	(7.2, 14.8)
Not Evaluable (NE)	1	(0.4)	(0.0, 2.0)	2	(0.7)	(0.1, 2.6)
No Assessment (NA)	19	(7.0)	(4.2, 10.7)	18	(6.5)	(3.9, 10.1)

[a] Based on binomial exact confidence interval method.
Investigator assessed responses per RECIST 1.1 (confirmed) are included in this table.
Database Cutoff Date: 03MAY2021

Confirmed ORR per BICR in the CPS ≥1 participants was 64.8% (58.9,70.5) vs 53.1% (47.0,59.1) in the pembro combo vs control arm, respectively.

All comers

Table 29. Summary of Best Objective Response (Confirmed) Based on Investigator Assessment per RECIST 1.1 (All-comer Participants) (ITT Population)

	Pembro Combo			Control		
	n	(%)	(95% CI)[a]	n	(%)	(95% CI)[a]
Number of Participants in Population	308			309		
Complete Response (CR)	66	(21.4)	(17.0, 26.4)	40	(12.9)	(9.4, 17.2)
Partial Response (PR)	137	(44.5)	(38.8, 50.2)	117	(37.9)	(32.4, 43.5)
Objective Response (CR+PR)	**203**	**(65.9)**	**(60.3, 71.2)**	**157**	**(50.8)**	**(45.1, 56.5)**
Stable Disease (SD)	69	(22.4)	(17.9, 27.5)	99	(32.0)	(26.9, 37.6)
Progressive Disease (PD)	15	(4.9)	(2.8, 7.9)	33	(10.7)	(7.5, 14.7)
Not Evaluable (NE)	1	(0.3)	(0.0, 1.8)	2	(0.6)	(0.1, 2.3)
No Assessment (NA)	20	(6.5)	(4.0, 9.9)	18	(5.8)	(3.5, 9.1)

[a] Based on binomial exact confidence interval method.
Investigator assessed responses per RECIST 1.1 (confirmed) are included in this table.
Database Cutoff Date: 03MAY2021

Confirmed ORR per BICR in the all-comer population was 61.7% (56.0, 67.1) vs 53.7% (48.0, 59.4) in the pembro combo vs control arm, respectively.

Table 30. Summary of Best Objective Response (Confirmed) Based on BICR Assessment per RECIST 1.1 (All-comer Participants) (ITT Population)

	Pembro Combo			Control		
	n	(%)	(95% CI)[a]	n	(%)	(95% CI)[a]
Number of Participants in Population	308			309		
Complete Response (CR)	105	(34.1)	(28.8, 39.7)	64	(20.7)	(16.3, 25.7)
Partial Response (PR)	85	(27.6)	(22.7, 33.0)	102	(33.0)	(27.8, 38.6)
Objective Response (CR+PR)	**190**	**(61.7)**	**(56.0, 67.1)**	**166**	**(53.7)**	**(48.0, 59.4)**
Stable Disease (SD)	77	(25.0)	(20.3, 30.2)	89	(28.8)	(23.8, 34.2)
Progressive Disease (PD)	13	(4.2)	(2.3, 7.1)	30	(9.7)	(6.6, 13.6)
Not Evaluable (NE)	10	(3.2)	(1.6, 5.9)	8	(2.6)	(1.1, 5.0)
No Assessment (NA)	18	(5.8)	(3.5, 9.1)	16	(5.2)	(3.0, 8.3)

[a] Based on binomial exact confidence interval method.
BICR assessed responses per RECIST 1.1 (confirmed) are included in this table.
Database Cutoff Date: 03MAY2021

Table 31. Concordance of Progression Events (Investigator vs. BICR) (All-comer Participants) (ITT Population)

	Pembro Combo	Control	Total
Number of Subjects in Population	308	309	617
Investigator Assessment - PD	155	204	359
BICR Agreed	119 (76.8%)	161 (78.9%)	280 (78.0%)
BICR and Investigator agreed on time	60 (38.7%)	90 (44.1%)	150 (41.8%)
BICR has earlier time	31 (20.0%)	41 (20.1%)	72 (20.1%)
BICR has later time	28 (18.1%)	30 (14.7%)	58 (16.2%)
BICR Disagreed	35 (22.6%)	42 (20.6%)	77 (21.4%)
No BICR Assessment	1 (0.6%)	1 (0.5%)	2 (0.6%)
Investigator Assessment - Non PD	133	85	218
BICR Agreed	122 (91.7%)	70 (82.4%)	192 (88.1%)
BICR Disagreed	6 (4.5%)	10 (11.8%)	16 (7.3%)
No BICR Assessment	5 (3.8%)	5 (5.9%)	10 (4.6%)

PD: Progressive Disease.
BICR: Blinded Independent Central Review.
Database Cutoff Date: 03MAY2021

CPS≥10

Table 32. Summary of Best Objective Response (Confirmed) Based on Investigator Assessment per RECIST 1.1 (CPS>=10 Participants) (ITT Population)

	Pembro Combo			Control		
	n	(%)	(95% CI)[a]	n	(%)	(95% CI)[a]
Number of Participants in Population	158			159		
Complete Response (CR)	35	(22.2)	(15.9, 29.4)	18	(11.3)	(6.8, 17.3)
Partial Response (PR)	75	(47.5)	(39.5, 55.6)	60	(37.7)	(30.2, 45.8)
Objective Response (CR+PR)	**110**	**(69.6)**	**(61.8, 76.7)**	**78**	**(49.1)**	**(41.1, 57.1)**
Stable Disease (SD)	29	(18.4)	(12.7, 25.3)	53	(33.3)	(26.1, 41.2)
Progressive Disease (PD)	4	(2.5)	(0.7, 6.4)	16	(10.1)	(5.9, 15.8)
Not Evaluable (NE)	1	(0.6)	(0.0, 3.5)	2	(1.3)	(0.2, 4.5)
No Assessment (NA)	14	(8.9)	(4.9, 14.4)	10	(6.3)	(3.1, 11.3)

[a] Based on binomial exact confidence interval method.
Investigator assessed responses per RECIST 1.1 (confirmed) are included in this table.
Database Cutoff Date: 03MAY2021

Confirmed ORR per BICR in the CPS ≥10 participants was 70.3% (62.5,77.3) vs 52.8% (44.8,60.8) in the pembro combo vs control arm, respectively.

Secondary endpoint – Duration of response (by investigator)

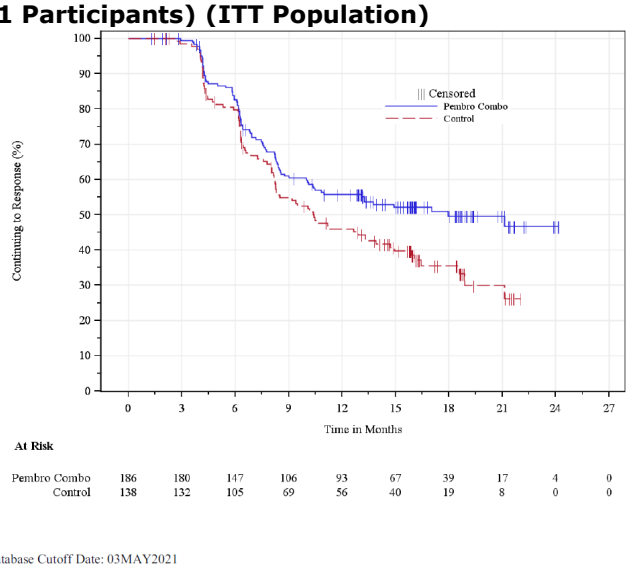
CPS≥1

Table 33. Summary of Time to Response and Duration of Response Based on Investigator Assessment per RECIST 1.1 in Participants with Confirmed Response (CPS>=1 Participants) (ITT Population)

	Pembro Combo (N=273)	Control (N=275)	Total (N=548)
Number of participants with response[a]	186	138	324
Time to Response (months)			
Mean (SD)	2.8 (2.1)	2.4 (0.9)	2.6 (1.7)
Median (Range)	2.1 (1.7-20.6)	2.1 (1.3-7.1)	2.1 (1.3-20.6)
Response Duration[b] (months)			
Median (Range)	18.0 (1.3+ - 24.2+)	10.4 (1.5+ - 22.0+)	13.2 (1.3+ - 24.2+)
Number (%[b]) of Participants with Extended Response Duration:			
≥6 months	147 (82.7)	105 (79.8)	252 (81.4)
≥12 months	93 (55.7)	56 (46.0)	149 (51.6)
≥18 months	39 (49.6)	19 (35.4)	58 (43.5)
≥24 months	4 (46.7)	0 (NR)	4 (38.2)

[a] Includes participants with best objective response with confirmation as complete response or partial response
[b] From product-limit (Kaplan-Meier) method for censored data.
"+" indicates there is no progressive disease by the time of last disease assessment.
NR = Not Reached.
Database Cutoff Date: 03MAY2021

Figure 19. Kaplan-Meier Estimates of Duration of Response Based on Investigator Assessment per RECIST 1.1 (CPS>=1 Participants) (ITT Population)



Database Cutoff Date: 03MAY2021

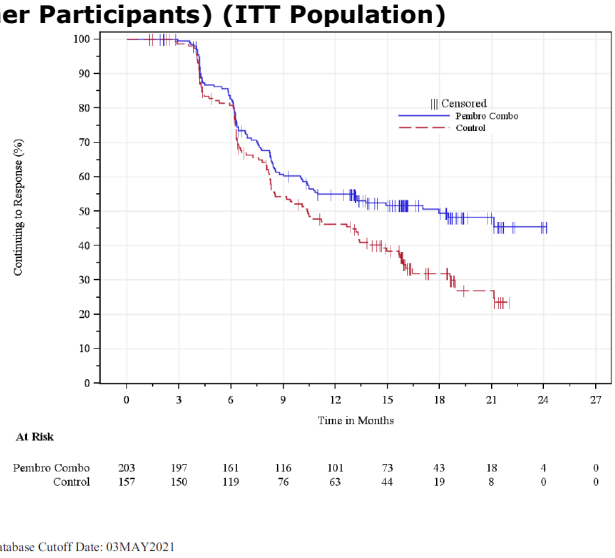
All comers

Table 34. Summary of Time to Response and Duration of Response Based on Investigator Assessment per RECIST 1.1 in Participants with Confirmed Response (All-comer Participants) (ITT Population)

	Pembro Combo (N=308)	Control (N=309)	Total (N=617)
Number of participants with response[a]	203	157	360
Time to Response (months)			
Mean (SD)	2.8 (2.0)	2.4 (1.0)	2.6 (1.6)
Median (Range)	2.1 (1.7-20.6)	2.1 (1.3-8.8)	2.1 (1.3-20.6)
Response Duration[b] (months)			
Median (Range)	18.0 (1.3+ - 24.2+)	10.4 (1.5+ - 22.0+)	13.2 (1.3+ - 24.2+)
Number (%[b]) of Participants with Extended Response Duration:			
≥6 months	161 (82.6)	119 (80.7)	280 (81.8)
≥12 months	101 (55.0)	63 (46.3)	164 (51.3)
≥18 months	43 (49.4)	19 (31.9)	62 (41.7)
≥24 months	4 (45.5)	0 (NR)	4 (36.1)

[a] Includes participants with best objective response with confirmation as complete response or partial response
[b] From product-limit (Kaplan-Meier) method for censored data.
"+" indicates there is no progressive disease by the time of last disease assessment.
NR = Not Reached.
Database Cutoff Date: 03MAY2021

Figure 20. Kaplan-Meier Estimates of Duration of Response Based on Investigator Assessment per RECIST 1.1 (All-comer Participants) (ITT Population)



Database Cutoff Date: 03MAY2021

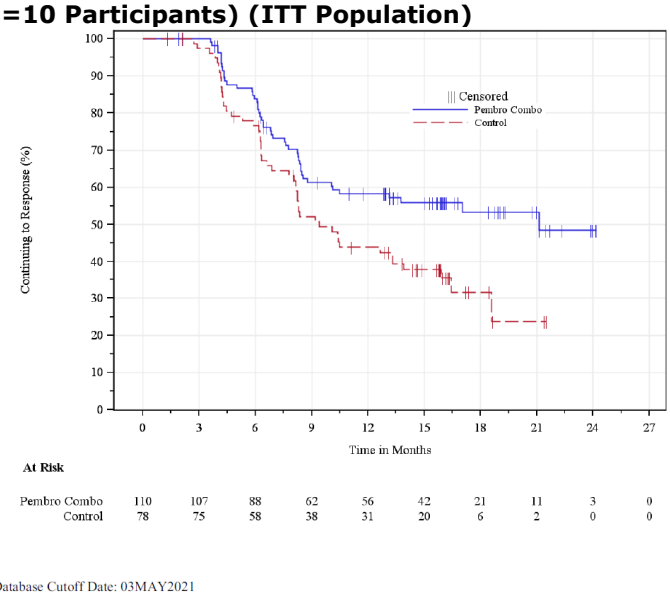
CPS≥10

Table 35. Summary of Time to Response and Duration of Response Based on Investigator Assessment per RECIST 1.1 in Participants with Confirmed Response (CPS>=10 Participants) (ITT Population)

	Pembro Combo (N=158)	Control (N=159)	Total (N=317)
Number of participants with response[a]	110	78	188
Time to Response (months)			
Mean (SD)	2.6 (1.2)	2.4 (1.0)	2.5 (1.1)
Median (Range)	2.2 (1.7-8.4)	2.1 (1.3-7.1)	2.1 (1.3-8.4)
Response Duration[b] (months)			
Median (Range)	21.1 (1.3+ - 24.2+)	9.4 (2.1+ - 21.5+)	13.3 (1.3+ - 24.2+)
Number (%[b]) of Participants with Extended Response Duration:			
≥6 months	88 (83.8)	58 (76.6)	146 (80.8)
≥12 months	56 (58.3)	31 (43.9)	87 (52.3)
≥18 months	21 (53.3)	6 (31.6)	27 (44.3)
≥24 months	3 (48.5)	0 (NR)	3 (39.2)

[a] Includes participants with best objective response with confirmation as complete response or partial response
[b] From product-limit (Kaplan-Meier) method for censored data.
"+" indicates there is no progressive disease by the time of last disease assessment.
NR = Not Reached.
Database Cutoff Date: 03MAY2021

Figure 21. Kaplan-Meier Estimates of Duration of Response Based on Investigator Assessment per RECIST 1.1 (CPS>=10 Participants) (ITT Population)



Database Cutoff Date: 03MAY2021

Ancillary analyses

PD-L1 CPS <1 Participants (post-hoc analysis)

In KEYNOTE-826, of the total of 617 participants, 69 (approximately 11%) were in the CPS <1 subgroup (35 in pembrolizumab + chemotherapy ± bevacizumab group and 34 in placebo + chemotherapy ± bevacizumab group). Efficacy in this group was explored via post hoc efficacy analyses at the Agency's request. KEYNOTE-826 was not designed or powered to make the comparison of pembrolizumab + chemotherapy ± bevacizumab versus placebo + chemotherapy ± bevacizumab in participants whose tumors express CPS <1.

Table 36. Summary of Key Efficacy Results in Participants With CPS<1 Persistent, Recurrent, or Metastatic Cervical Cancer (ITT Population)*

Endpoint	Pembrolizumab + Chemotherapy ± Bevacizumab (N=35)	Placebo + Chemotherapy ± Bevacizumab (N=34)
PFS as Assessed by Investigator per RECIST 1.1		
Number of Events (%)	23 (65.7)	28 (82.4)
Median PFS, months (95% CI)	8.1 (6.1, 12.6)	8.2 (6.2, 10.4)
HR (95% CI)	0.94 (0.52, 1.70)	
OS		
Number of Events (%)	20 (57.1)	20 (58.8)
Median OS, months (95% CI)	19.0 (12.6, 21.4)	18.9 (11.7, 21.3)
HR (95% CI)	1.00 (0.53, 1.89)	
ORR by inv, % (95% CI)	48.6 (31.4,66.0)	55.9 (37.9,72.8)
ORR Difference % (95% CI)	-6.4 (-29.0,16.7)	
DOR by inv, (months), median (range)	10.7 (4.2 - 21.6+)	8.5 (2.4+ - 17.3+)

Abbreviations: BICR = blinded independent central review; CI = confidence interval; CPS = Combined Positive Score; HR = hazard ratio; ITT = intent-to-treat; NR = not reached; OS = overall survival; PFS = progression-free survival; PD-L1 = programmed cell death ligand 1; RECIST = Response Evaluation Criteria In Solid Tumors
Database Cutoff Date: 03-MAY-2021

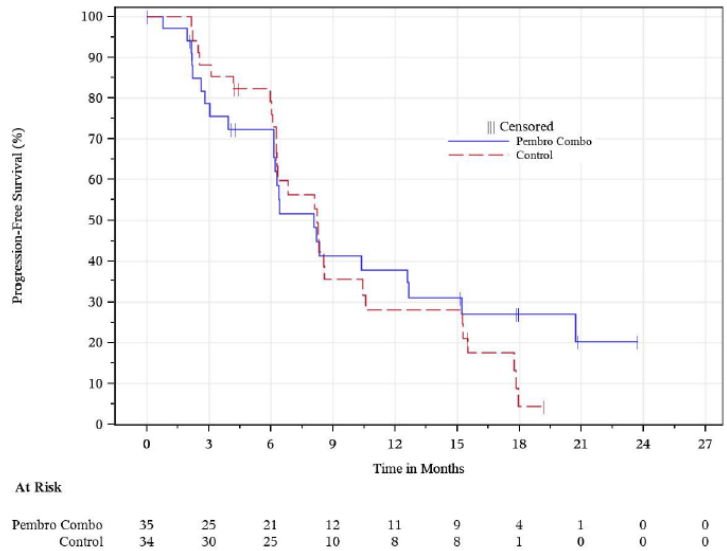
* Summary presented by the assessment team

Table 37. Analysis of Progression-Free Survival Based on Investigator Assessment per RECIST 1.1 (CPS<1 Participants) (ITT Population)

	Pembro Combo (N=35)	Control (N=34)
Number of Events (%)	23 (65.7)	28 (82.4)
DEATH	2 (5.7)	1 (2.9)
DOCUMENTED PROGRESSION	21 (60.0)	27 (79.4)
Kaplan-Meier Estimates (months)[a]		
Median (95% CI)	8.1 (6.1, 12.6)	8.2 (6.2, 10.4)
[Q1, Q3]	[3.9, 20.7]	[6.1, 15.2]
Person-months	302.3	293.0
Event Rate / 100 Person-months	7.6	9.6
vs Control		
Hazard Ratio (95% CI)[b]	0.94 (0.52, 1.70)	
p-value[c]	0.4185	
PFS Rate at month 6 (%) (95% CI)	72.3 (53.5, 84.5)	79.2 (61.2, 89.5)
PFS Rate at month 12 (%) (95% CI)	37.9 (21.0, 54.7)	28.2 (13.5, 44.8)
PFS Rate at month 18 (%) (95% CI)	27.1 (12.7, 43.8)	4.4 (0.3, 18.0)
PFS Rate at month 24 (%) (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 metastatic at initial diagnosis (FIGO [2009] stage IVB) (yes or no), bevacizumab use (yes or no) and PD-L1 status (CPS <1, CPS 1 to <10, CPS >=10).
[c] One-sided p-value based on log-rank test stratified by metastatic at initial diagnosis (FIGO [2009] stage IVB) (yes or no), bevacizumab use (yes or no) and PD-L1 status (CPS <1, CPS 1 to <10, CPS >=10).
NR = Not reached.
Database Cutoff Date: 03MAY2021

Figure 22. Kaplan-Meier Estimates of Progression-Free Survival Based on Investigator Assessment per RECIST 1.1 (CPS<1 Participants) (ITT Population)



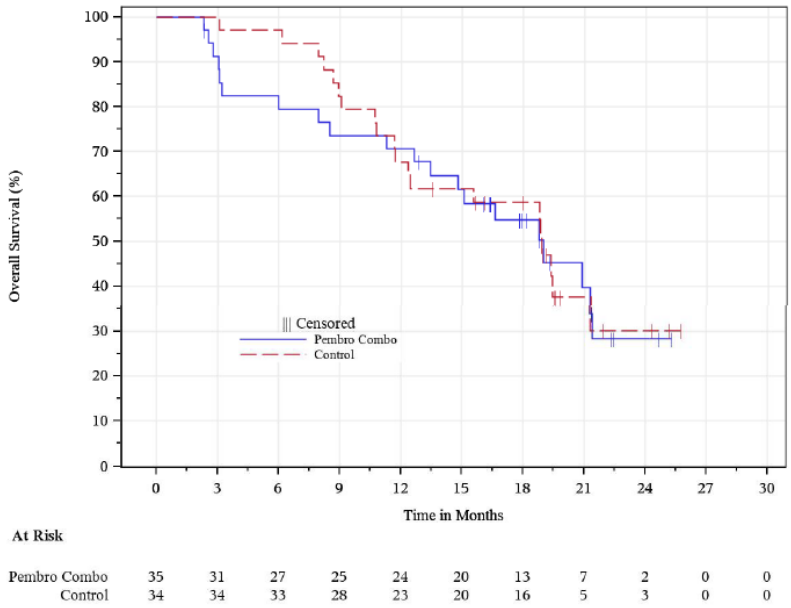
Database Cutoff Date: 03MAY2021

Table 38. Analysis of Overall Survival (CPS<1 Participants) (ITT Population)

	Pembro Combo (N=35)	Control (N=34)
Number of Events (%)	20 (57.1)	20 (58.8)
DEATH	20 (57.1)	20 (58.8)
Kaplan-Meier Estimates (months)[a]		
Median (95% CI)	19.0 (12.6, 21.4)	18.9 (11.7, 21.3)
[Q1, Q3]	[8.5, NR]	[10.8, NR]
Person-months	496.8	527.7
Event Rate / 100 Person-months	4.0	3.8
vs Control		
Hazard Ratio (95% CI)[b]	1.00 (0.53, 1.89)	
p-value[c]	0.5026	
OS Rate at month 6 (%) (95% CI)	79.5 (61.7, 89.6)	97.1 (80.9, 99.6)
OS Rate at month 12 (%) (95% CI)	70.6 (52.3, 83.0)	67.6 (49.2, 80.6)
OS Rate at month 18 (%) (95% CI)	54.8 (36.4, 69.9)	58.7 (40.4, 73.1)
OS Rate at month 24 (%) (95% CI)	28.3 (11.6, 47.7)	30.0 (12.5, 49.9)

[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 metastatic at initial diagnosis (FIGO [2009] stage IVB) (yes or no), bevacizumab use (yes or no) and PD-L1 status (CPS <1, CPS 1 to <10, CPS >=10).
[c] One-sided p-value based on log-rank test stratified by metastatic at initial diagnosis (FIGO [2009] stage IVB) (yes or no), bevacizumab use (yes or no) and PD-L1 status (CPS <1, CPS 1 to <10, CPS >=10).
NR = Not reached.
Database Cutoff Date: 03MAY2021

Figure 23. Kaplan-Meier Estimates of Overall Survival (CPS<1 Participants) (ITT Population)



Database Cutoff Date: 03MAY2021

Table 39. Analysis of Confirmed Objective Response Based on Investigator Assessment per RECIST 1.1 (CPS<1 Participants) (ITT Population)

Treatment	N	Number of Confirmed Objective Response	Objective Response Rate (%) (95% CI)	Difference in Percentage Pembro Combo vs. Control	
				Estimate (95% CI)[a]	p-Value[b]
Pembro Combo	35	17	48.6 (31.4,66.0)	-6.4 (-29.0,16.7)	0.7037
Control	34	19	55.9 (37.9,72.8)		

[a] Based on Miettinen & Nurminen method stratified by metastatic at initial diagnosis (FIGO [2009] stage IVB) (yes or no), bevacizumab use (yes or no) and PD-L1 status (CPS <1, CPS 1 to <10, CPS >=10).
[b] One-sided p-value for testing. H0: difference in % = 0 versus H1: difference in % > 0.
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Table 40. Summary of Best Objective Response (Confirmed) Based on Investigator Assessment per RECIST 1.1 (CPS<1 Participants) (ITT Population)

	Pembro Combo			Control		
	n	(%)	(95% CI)[a]	n	(%)	(95% CI)[a]
Number of Participants in Population	35			34		
Complete Response (CR)	4	(11.4)	(3.2, 26.7)	4	(11.8)	(3.3, 27.5)
Partial Response (PR)	13	(37.1)	(21.5, 55.1)	15	(44.1)	(27.2, 62.1)
Objective Response (CR+PR)	**17**	**(48.6)**	**(31.4, 66.0)**	**19**	**(55.9)**	**(37.9, 72.8)**
Stable Disease (SD)	11	(31.4)	(16.9, 49.3)	11	(32.4)	(17.4, 50.5)
Progressive Disease (PD)	6	(17.1)	(6.6, 33.6)	4	(11.8)	(3.3, 27.5)
Not Evaluable (NE)	0	(0.0)	(0.0, 10.0)	0	(0.0)	(0.0, 10.3)
No Assessment (NA)	1	(2.9)	(0.1, 14.9)	0	(0.0)	(0.0, 10.3)

[a] Based on binomial exact confidence interval method.
Investigator assessed responses per RECIST 1.1 (confirmed) are included in this table.
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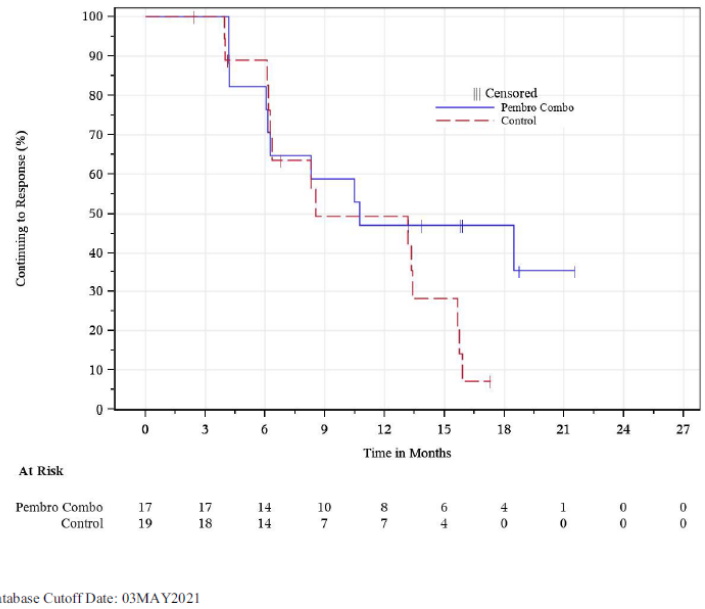
Table 41. Summary of Time to Response and Duration of Response Based on Investigator Assessment per RECIST 1.1 in Participants with Confirmed Response (CPS<1 Participants) (ITT Population)

	Pembro Combo (N=35)	Control (N=34)	Total (N=69)
Number of participants with response[a]	17	19	36
Time to Response (months)			
Mean (SD)	2.2 (0.5)	2.5 (1.5)	2.3 (1.2)
Median (Range)	2.1 (1.9-4.0)	2.1 (1.9-8.8)	2.1 (1.9-8.8)
Response Duration[b] (months)			
Median (Range)	10.7 (4.2 - 21.6+)	8.5 (2.4+ - 17.3+)	10.7 (2.4+ - 21.6+)
Number (%[b]) of Participants with Extended Response Duration:			
≥6 months	14 (82.4)	14 (88.9)	28 (85.4)
≥12 months	8 (47.1)	7 (49.4)	15 (48.1)
≥18 months	4 (47.1)	0 (NR)	4 (26.0)

[a] Includes participants with best objective response with confirmation as complete response or partial response
[b] From product-limit (Kaplan-Meier) method for censored data.
"+" indicates there is no progressive disease by the time of last disease assessment.
NR = Not Reached.
Database Cutoff Date: 03MAY2021

Figure 24. Kaplan-Meier Estimates of Duration of Response Based on Investigator Assessment per RECIST 1.1 (CPS<1 Participants) (ITT Population)



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Results according to bevacizumab use

The use of bevacizumab (yes/no) was a stratification factor. Subgroup analyses according to bevacizumab use were pre-specified. Approximately 60% of patients received bevacizumab.

Table 42. Summary of Efficacy Results in All-comer Participants by Bevacizumab Use (ITT Population)

Endpoint	With Bevacizumab		Without Bevacizumab	
	Pembrolizumab + Chemotherapy (N=196)	Placebo + Chemotherapy (N=193)	Pembrolizumab + Chemotherapy (N=112)	Placebo + Chemotherapy (N=116)
PFS as Assessed by Investigator per RECIST 1.1				
Median PFS[a], months (95% CI)	15.2 (10.5, 21.3)	10.2 (8.3, 12.3)	6.3 (6.1, 8.3)	6.2 (4.4, 6.3)
HR (95% CI)[b]	0.61 (0.47, 0.79)		0.74 (0.54, 1.01)	
OS				
Median OS[a], months (95% CI)	NR (24.4, NR)	24.7 (16.4, 26.0)	16.8 (14.2, 19.8)	12.6 (10.0, 14.8)
HR (95% CI)[b]	0.63 (0.47, 0.87)		0.74 (0.53, 1.04)	
Objective Response Rate				
ORR (%) (95% CI)	75.5 (68.9, 81.4)	60.6 (53.3, 67.6)	49.1 (39.5, 58.7)	34.5 (25.9, 43.9)
ORR Difference % (95% CI)[c]	15.1 (5.8, 24.3)		14.6 (1.8, 27.0)	
DOR				
DOR[a], (months), median (range)	21.1 (1.3+ - 24.2+)	12.9 (2.1+ - 22.0+)	8.2 (1.9+ - 24.1+)	6.3 (1.5+ - 18.6+)

CI=confidence interval; CPS=combined positive score; HR=hazard ratio; ITT=intent-to-treat; NR=not reached; OS=overall survival; PD-L1=programmed cell death ligand 1; PFS=progression-free survival; RECIST 1.1=response evaluation criteria in solid tumors version 1.1.

[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 metastatic at initial diagnosis (FIGO [2009] stage IVB) (yes or no), bevacizumab use (yes or no) and PD-L1 status (CPS <1, CPS 1 to <10, CPS >=10).

[c] Based on Miettinen & Nurminen method stratified by metastatic at initial diagnosis (FIGO [2009] stage IVB) (yes or no), bevacizumab use (yes or no) and PD-L1 status (CPS <1, CPS 1 to <10, CPS >=10).

"+" indicates there is no progressive disease by the time of last disease assessment.

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Figure 25. Kaplan-Meier Estimates of Progression-Free Survival Based on Investigator Assessment per RECIST 1.1 (Primary Analysis) (All-comer Participants by Bevacizumab Use) (ITT Population)

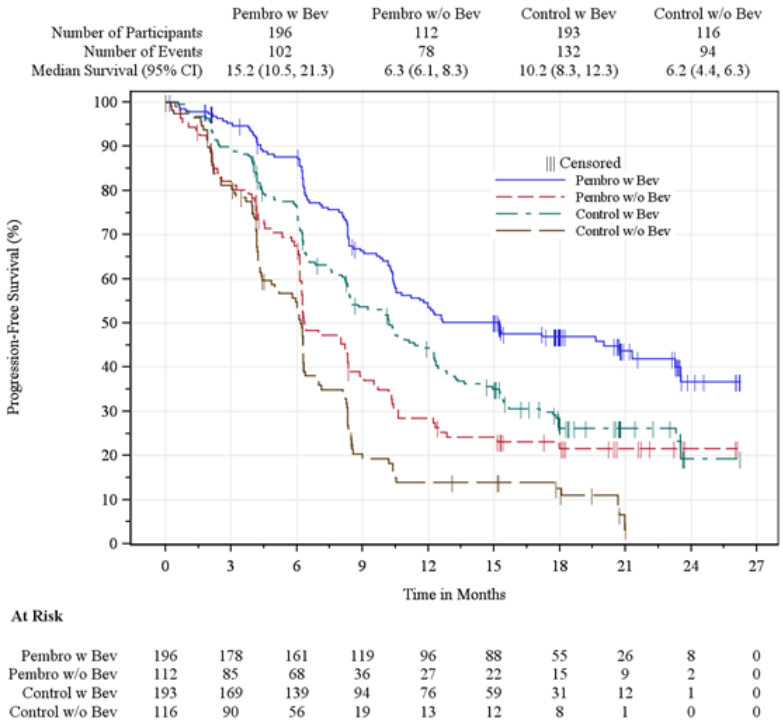

Figure 26. Kaplan-Meier Estimates of Overall Survival (All-comer Participants by Bevacizumab Use) (ITT Population)

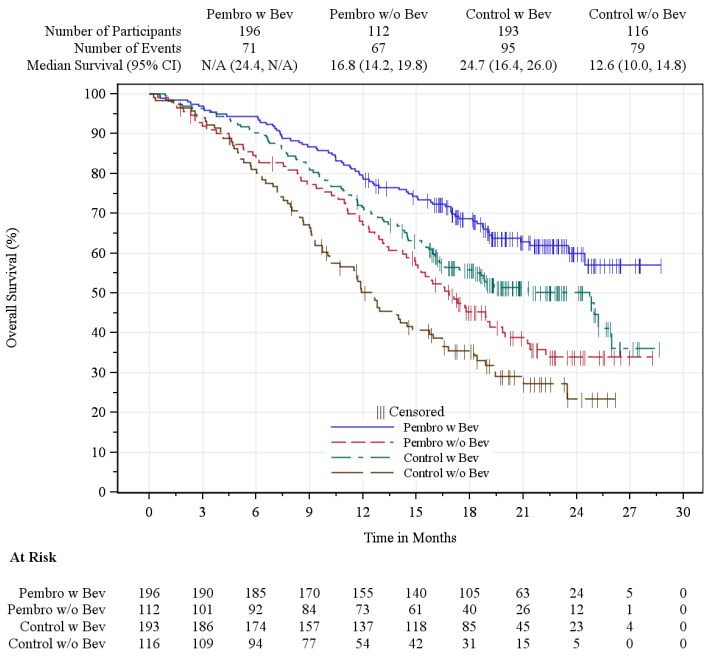

Table 43. Summary of Efficacy Results in CPS ≥1 Participants by Bevacizumab Use (ITT Population)

Endpoint	With Bevacizumab		Without Bevacizumab	
	Pembrolizumab + Chemotherapy (N=175)	Placebo + Chemotherapy (N=171)	Pembrolizumab + Chemotherapy (N=98)	Placebo + Chemotherapy (N=104)
PFS as Assessed by Investigator per RECIST 1.1				
Median PFS[a], months (95% CI)	15.3 (10.5, 23.5)	10.3 (8.4, 12.3)	7.0 (6.2, 9.1)	6.0 (4.3, 6.3)
HR (95% CI)[b]	0.61 (0.46, 0.80)		0.66 (0.47, 0.92)	
OS				
Median OS[a], months (95% CI)	NR (24.4, NR)	25.0 (16.3, NR)	17.1 (14.9, 20.0)	11.9 (9.7, 14.5)
HR (95% CI)[b]	0.62 (0.45, 0.87)		0.67 (0.47, 0.96)	
Objective Response Rate				
ORR (%) (95% CI)	77.1 (70.2, 83.1)	60.2 (52.5, 67.6)	52.0 (41.7, 62.2)	33.7 (24.7, 43.6)
ORR Difference % (95% CI)[c]	17.3 (7.5, 26.9)		18.3 (4.7, 31.3)	
DOR				
DOR[a], (months), median (range)	21.1 (1.3+ - 24.2+)	12.6 (2.1+ - 22.0+)	8.5 (1.9+ - 24.1+)	6.3 (1.5+ - 18.6+)

CI=confidence interval; CPS=combined positive score; DOR= duration of response; HR=hazard ratio; ITT=intent-to-treat; NR=not reached; OS=overall survival; PD-L1=programmed cell death ligand 1; PFS=progression-free survival; RECIST 1.1=response evaluation criteria in solid tumors version 1.1.

[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 metastatic at initial diagnosis (FIGO [2009] stage IVB) (yes or no), bevacizumab use (yes or no) and PD-L1 status (CPS <1, CPS 1 to <10, CPS >=10).

[c] Based on Miettinen & Nurminen method stratified by metastatic at initial diagnosis (FIGO [2009] stage IVB) (yes or no), bevacizumab use (yes or no) and PD-L1 status (CPS <1, CPS 1 to <10, CPS >=10).

"+" indicates there is no progressive disease by the time of last disease assessment.

NR = Not reached.

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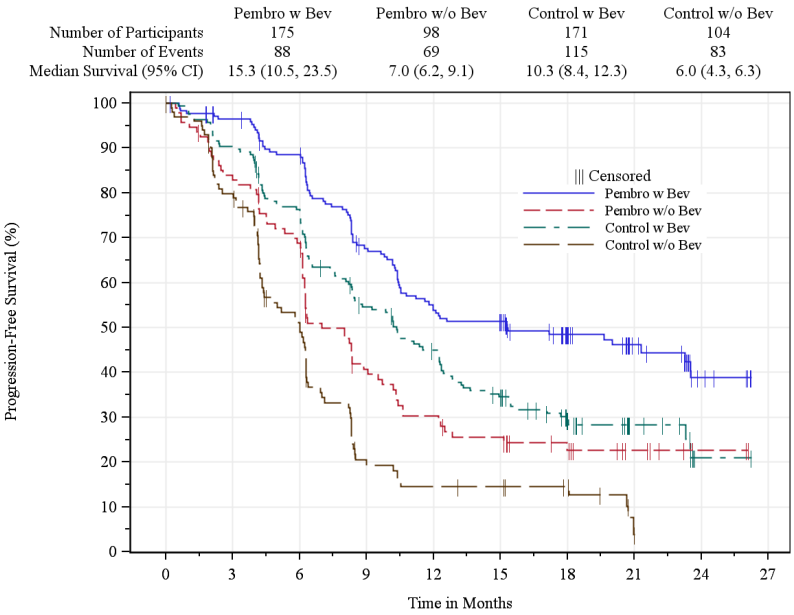
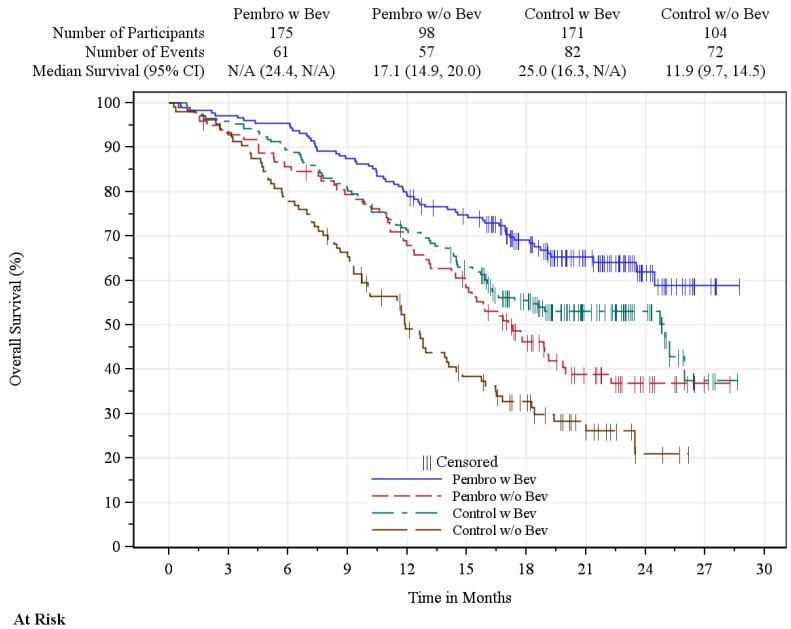
Figure 27. Kaplan-Meier Estimates of Progression-Free Survival Based on Investigator Assessment per RECIST 1.1 (Primary Analysis) (CPS ≥1 Participants by Bevacizumab Use) (ITT Population)



At Risk

Pembro w Bev	175	161	145	108	86	80	52	26	8	0
Pembro w/o Bev	98	77	63	35	26	21	14	8	2	0
Control w Bev	171	150	124	86	69	52	30	12	1	0
Control w/o Bev	104	79	46	17	12	11	8	1	0	0

Figure 28. Kaplan-Meier Estimates of Overall Survival (CPS ≥1 Participants by Bevacizumab Use) (ITT Population)



At Risk

Pembro w Bev	175	170	167	153	139	126	95	59	23	5	0
Pembro w/o Bev	98	90	83	76	65	55	37	23	11	1	0
Control w Bev	171	164	153	138	121	105	75	43	22	4	0
Control w/o Bev	104	97	82	68	47	35	25	12	3	0	0

Results by histology

Table 44. PD-L1 Expression in All-comer Participants by Histology (ITT Population)

	Participants with Squamous Cell Carcinoma				Participants with Non-squamous Cell Carcinoma			
	Pembrolizumab + Chemotherapy		Placebo + Chemotherapy		Pembrolizumab + Chemotherapy		Placebo + Chemotherapy	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	236		211		71		98	
PD-L1 Status								
CPS <1	24	(10.2)	14	(6.6)	11	(15.5)	20	(20.4)
1⩽ CPS <10	78	(33.1)	77	(36.5)	36	(50.7)	39	(39.8)
CPS ⩾10	134	(56.8)	120	(56.9)	24	(33.8)	39	(39.8)

CPS=combined positive score; ITT=intent-to-treat; PD-L1=programmed cell death ligand 1.
Non-squamous subgroup included participants with Adenocarcinoma and Adenosquamous. One participant with Epidermoide Carcinoma was included in Squamous subgroup.

PFS and OS results by histology in the all comers and PD-L1 CPS≥1 population are presented in the tables below:

Table 45. Progression-Free Survival Based on Investigator Assessment per RECIST 1.1 by Subgroup Factors (All-comers)

	Pembro Combo (N=308)			Control (N=309)			Pembro Combo vs. Control
	N	Number of Events	(%)	N	Number of Events	(%)	Hazard Ratio (95% CI)[a]
Overall	308	180	(58.4)	309	226	(73.1)	0.65 (0.53, 0.79)
Histology of Subtype of Cervical Cancer[b]							
Non-squamous	71	41	(57.7)	98	67	(68.4)	0.66 (0.43, 1.00)
Squamous	236	138	(58.5)	211	159	(75.4)	0.63 (0.50, 0.80)

NR = Not Reached

[a] Based on Cox regression model with Efrons method of tie handling with treatment as a covariate stratified by metastatic at initial diagnosis (FIGO [2009] stage IVB) (yes or no), bevacizumab use (yes or no) and PD-L1 status (CPS <1, CPS 1 to <10, CPS >=10).

[b] Non-squamous subgroup included participants with Adenocarcinoma and Adenosquamous. One participant with Epidermoide Carcinoma was included in Squamous subgroup.

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Table 46. Overall Survival by Subgroup Factors

	Pembro Combo (N=308)			Control (N=309)			Pembro Combo vs. Control
	N	Number of Events	(%)	N	Number of Events	(%)	Hazard Ratio (95% CI)[a]
Overall	308	138	(44.8)	309	174	(56.3)	0.67 (0.54, 0.84)
Histology of Subtype of Cervical Cancer[b]							
Non-squamous	71	29	(40.8)	98	46	(46.9)	0.76 (0.47, 1.23)
Squamous	236	109	(46.2)	211	128	(60.7)	0.61 (0.47, 0.80)

NR = Not Reached

[a] Based on Cox regression model with Efrons method of tie handling with treatment as a covariate stratified by metastatic at initial diagnosis (FIGO [2009] stage IVB) (yes or no), bevacizumab use (yes or no) and PD-L1 status (CPS <1, CPS 1 to <10, CPS >=10).

[b] Non-squamous subgroup included participants with Adenocarcinoma and Adenosquamous. One participant with Epidermoide Carcinoma was included in Squamous subgroup.

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Table 47. Summary of Efficacy Results in CPS ≥1 Participants by Histology (ITT Population)

	Participants with Squamous Cell Carcinoma		Participants with Non-squamous Cell Carcinoma	
Endpoint	Pembrolizumab + Chemotherapy (N=212)	Placebo + Chemotherapy (N=197)	Pembrolizumab + Chemotherapy (N=60)	Placebo + Chemotherapy (N=78)
PFS as Assessed by Investigator per RECIST 1.1				
Median PFS[a], months (95% CI)	10.4 (8.6, 12.3)	6.6 (6.2, 8.3)	11.8 (9.6, NR)	8.5 (7.0, 11.5)
HR (95% CI)[b]	0.61 (0.48, 0.78)		0.59 (0.37, 0.93)	
OS				
Median OS[a], months (95% CI)	24.4 (19.1, NR)	14.2 (12.1, 18.4)	NR (17.3, NR)	23.5 (16.3, NR)
HR (95% CI)[b]	0.60 (0.46, 0.79)		0.70 (0.41, 1.20)	
Objective Response Rate				
ORR (%) (95% CI)	67.0 (60.2, 73.3)	46.2 (39.1, 53.4)	71.7 (58.6, 82.5)	60.3 (48.5, 71.2)
ORR Difference % (95% CI)[c]	20.4 (11.1, 29.4)		13.8 (-2.2, 28.1)	

CI=confidence interval; CPS=combined positive score; HR=hazard ratio; ITT=intent-to-treat; NR=not reached; ORR=objective response rate; OS=overall survival; PD-L1=programmed cell death ligand 1; PFS=progression-free survival; RECIST 1.1=response evaluation criteria in solid tumors version 1.1.

[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 metastatic at initial diagnosis (FIGO [2009] stage IVB) (yes or no), bevacizumab use (yes or no) and PD-L1 status (CPS <1, CPS 1 to <10, CPS >=10).

[c] Based on Miettinen & Nurminen method stratified by metastatic at initial diagnosis (FIGO [2009] stage IVB) (yes or no), bevacizumab use (yes or no) and PD-L1 status (CPS <1, CPS 1 to <10, CPS >=10).

"+" indicates there is no progressive disease by the time of last disease assessment.

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Results by platinum compound

Approximately 20% of patients received cisplatin. Summary of efficacy results in all-comer participants by platinum compound used are provided in Table 48.

Table 48. Summary of Efficacy Results in All-comer Participants by Platinum Compound Used (ITT Population)

Endpoint	Pembrolizumab + Chemotherapy ± Bevacizumab	Placebo + Chemotherapy ± Bevacizumab
Participants Treated with Carboplatin		
	(N=246)	(N=249)
PFS as Assessed by Investigator per RECIST 1.1		
Median PFS[a], months (95% CI)	10.2 (8.3, 10.6)	7.4 (6.3, 8.4)
HR (95% CI)[b]	0.69 (0.55, 0.86)	
OS		
Median OS[a], months (95% CI)	21.4 (18.7, NR)	15.9 (13.4, 18.8)
HR (95% CI)[b]	0.69 (0.54, 0.89)	
ORR		
Objective Response Rate (%) (95% CI)	62.2 (55.8, 68.3)	48.6 (42.2, 55.0)
ORR Difference % (95% CI)[c]	14.0 (5.4, 22.3)	
Participants Treated with Cisplatin		
	(N=61)	(N=59)
PFS as Assessed by Investigator per RECIST 1.1		
Median PFS[a], months (95% CI)	15.2 (10.5, NR)	8.4 (6.4, 12.3)
HR (95% CI)[b]	0.47 (0.28, 0.77)	
OS		
Median OS[a], months (95% CI)	NR (20.9, NR)	21.3 (16.0, NR)
HR (95% CI)[b]	0.59 (0.32, 1.09)	
ORR		
Objective Response Rate (%) (95% CI)	82.0 (70.0, 90.6)	61.0 (47.4, 73.5)
ORR Difference % (95% CI)[c]	19.6 (3.5, 35.2)	

CI=confidence interval; CPS=combined positive score; HR=hazard ratio; NR = not reached; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; RECIST 1.1=response evaluation criteria in solid tumors version 1.1.

[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 metastatic at initial diagnosis (FIGO [2009] stage IVB) (yes or no), bevacizumab use (yes or no) and PD-L1 status (CPS <1, CPS 1 to <10, CPS ≥10).

[c] Based on Miettinen & Nurminen method stratified by metastatic at initial diagnosis (FIGO [2009] stage IVB) (yes or no), bevacizumab use (yes or no) and PD-L1 status (CPS <1, CPS 1 to <10, CPS >=10).

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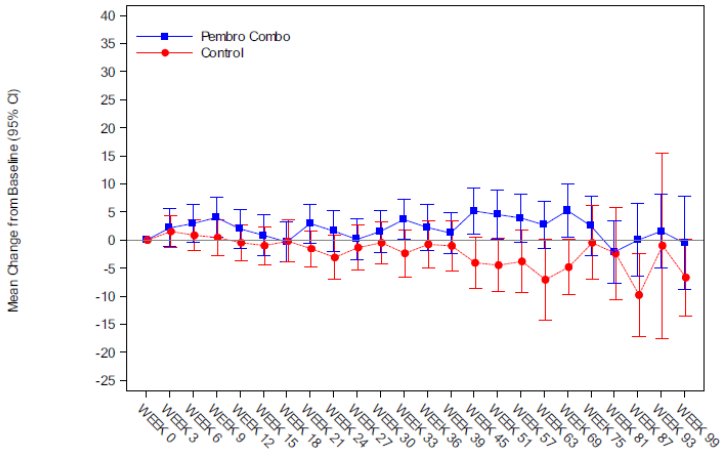
Patient-reported Outcomes

More participants treated with pembrolizumab + chemotherapy ± bevacizumab had improved or stable health status/QoL using the EQ-5D-5L compared with participants receiving placebo + chemotherapy ± bevacizumab (78.3% vs 71.7%, nominal p=0.033, not adjusted for multiplicity). A prolonged time to deterioration in EQ-5D-5L was observed for patients treated with pembrolizumab + chemotherapy ± bevacizumab compared to those treated with placebo + chemotherapy ± bevacizumab (HR 0.75; 95% CI: 0.58, 0.97; nominal p=0.027, not adjusted for multiplicity). Differences in the EORTC QLQ-C30 global health status score were not statistically different between the 2 groups.

Figure 29. Empirical Mean Change from Baseline and 95% CI for the EORTC QLQ-C30 Global Health Status/QoL Over Time by Treatment Group (CPS >=1 Full Analysis Set)



Number of Participants

Pembro Combo	246	226	216	204	191	184	185	181	180	177	173	159	151	145	127	112	108	101	100	82	74	61	42	30
Control	253	231	223	216	200	187	169	169	159	138	141	117	112	114	99	86	77	65	59	53	42	29	17	10

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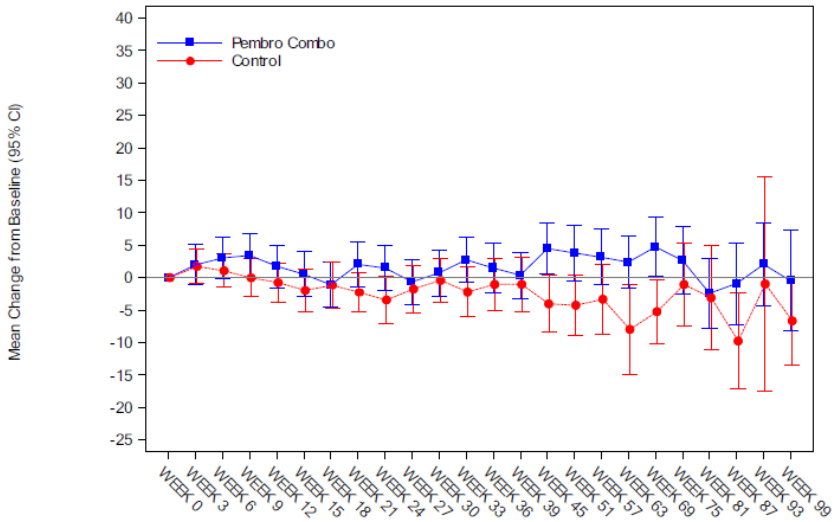
Figure 30. Empirical Mean Change from Baseline and 95% CI for the EORTC QLQ-C30 Global Health Status/QoL Over Time by Treatment Group (All-comer Full Analysis Set)



Number of Participants

Pembro Combo	279	256	245	231	215	205	206	203	197	196	192	174	165	160	141	125	119	112	109	88	79	64	45	32
Control	283	261	252	246	227	211	191	194	182	161	162	135	127	129	109	96	80	70	62	55	43	29	17	10

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Subsequent systemic anticancer treatment

After discontinuation of study treatment, a similar proportion of all-comer participants in the pembrolizumab + chemotherapy ± bevacizumab and the placebo + chemotherapy ± bevacizumab groups received subsequent systemic anti-cancer treatment.

Table 49. Summary of Subsequent Systemic Anti-Cancer Treatment (All-comer Participants) (ITT Population)

	Pembro Combo (N=308)	Control (N=309)	Total (N=617)
Started Study Treatment	307 (99.7)	309 (100.0)	616 (99.8)
Discontinued Study Treatment	196 (63.6)	255 (82.5)	451 (73.1)
Received Any Subsequent Systemic Anti-cancer Therapy	80 (26.0)	96 (31.1)	176 (28.5)
Subsequent systemic therapy by type			
Any PD1/PD-L1 checkpoint	3 (1.0)	15 (4.9)	18 (2.9)
Atezolizumab	0 (0.0)	1 (0.3)	1 (0.2)
Cemiplimab	0 (0.0)	1 (0.3)	1 (0.2)
Dostarlimab	0 (0.0)	1 (0.3)	1 (0.2)
Durvalumab	1 (0.3)	1 (0.3)	2 (0.3)
Nivolumab	0 (0.0)	1 (0.3)	1 (0.2)
Pembrolizumab	2 (0.6)	11 (3.6)	13 (2.1)
Any VEGF/VEGFR inhibitor	9 (2.9)	17 (5.5)	26 (4.2)
Bevacizumab	9 (2.9)	17 (5.5)	26 (4.2)
Chemotherapy	77 (25.0)	81 (26.2)	158 (25.6)
Capecitabine	2 (0.6)	2 (0.6)	4 (0.6)
Carboplatin	28 (9.1)	30 (9.7)	58 (9.4)
Cisplatin	14 (4.5)	17 (5.5)	31 (5.0)
Cyclophosphamide	1 (0.3)	0 (0.0)	1 (0.2)
Docetaxel	2 (0.6)	2 (0.6)	4 (0.6)
Doxorubicin	2 (0.6)	0 (0.0)	2 (0.3)
Fluorouracil	4 (1.3)	2 (0.6)	6 (1.0)
Gemcitabine	19 (6.2)	29 (9.4)	48 (7.8)
Gemcitabine Hydrochloride	4 (1.3)	1 (0.3)	5 (0.8)
Ifosfamide	0 (0.0)	1 (0.3)	1 (0.2)
Irinotecan	10 (3.2)	8 (2.6)	18 (2.9)
Oxaliplatin	0 (0.0)	1 (0.3)	1 (0.2)
Paclitaxel	32 (10.4)	19 (6.1)	51 (8.3)
Pemetrexed Disodium	1 (0.3)	2 (0.6)	3 (0.5)
Platinum	1 (0.3)	0 (0.0)	1 (0.2)
Topotecan	13 (4.2)	12 (3.9)	25 (4.1)
Vinorelbine Tartrate	6 (1.9)	6 (1.9)	12 (1.9)
Targeted therapy	2 (0.6)	4 (1.3)	6 (1.0)
Cabozantinib	0 (0.0)	1 (0.3)	1 (0.2)
Everolimus	1 (0.3)	0 (0.0)	1 (0.2)
Obinutuzumab	1 (0.3)	0 (0.0)	1 (0.2)
Selumetinib	0 (0.0)	1 (0.3)	1 (0.2)
Temsirolimus	0 (0.0)	1 (0.3)	1 (0.2)
Tremelimumab	0 (0.0)	1 (0.3)	1 (0.2)
Hormonal therapy	0 (0.0)	1 (0.3)	1 (0.2)
Letrozole	0 (0.0)	1 (0.3)	1 (0.2)
Megestrol Acetate	0 (0.0)	1 (0.3)	1 (0.2)
ADC	0 (0.0)	3 (1.0)	3 (0.5)
Tisotumab Vedotin	0 (0.0)	3 (1.0)	3 (0.5)
PARP inhibitor	0 (0.0)	2 (0.6)	2 (0.3)
Niraparib	0 (0.0)	1 (0.3)	1 (0.2)
Olaparib	0 (0.0)	1 (0.3)	1 (0.2)
Other	5 (1.6)	14 (4.5)	19 (3.1)

Dimesna	0 (0.0)	1 (0.3)	1 (0.2)
Naptumomab Estafenatox	1 (0.3)	0 (0.0)	1 (0.2)
Unspecified	4 (1.3)	8 (2.6)	12 (1.9)
Unspecified Monoclonal Antibody	0 (0.0)	5 (1.6)	5 (0.8)
Database Cutoff Date: 03MAY2021			

Summary of main study(ies)

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-826

Title: A 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 (KEYNOTE-826)			
Study identifier	IND: 126191; EudraCT: 2018-001440-53		
Design	Phase 3, multicenter, double-blind, placebo-controlled, interventional study		
	Duration of Main phase:		Approximately 2 years
	Duration of Run-in phase:		Not applicable
	Duration of Extension phase:		Not applicable
Hypothesis	Superiority		
Treatment groups	Pembrolizumab + chemotherapy ± bevacizumab		Pembrolizumab 200 mg by IV infusion plus chemotherapy (with or without bevacizumab) Q3W for up to 35 cycles (approximately 2 years) 308 participants randomized (ITT population)
	Placebo + chemotherapy ± bevacizumab		Placebo by IV infusion plus chemotherapy (with or without bevacizumab) Q3W for up to 35 cycles (approximately 2 years) 309 participants randomized (ITT population)
Endpoints and definitions	Dual primary endpoint	PFS (Investigator assessed)	Defined as time from randomization to the first documented disease progression per RECIST 1.1 as assessed by investigator or death due to any cause, whichever occurs first
	Dual primary endpoint	OS	Defined as the time from randomization to death due to any cause
	Secondary Endpoint	ORR	Defined as the proportion of participants who have a best overall response of either confirmed CR or PR per RECIST 1.1 as assessed by investigator
	Secondary Endpoint	DOR	Defined as the time from the first documented evidence of CR or PR until the first documented disease progression assessed per RECIST 1.1 by investigator or death due to any cause, whichever occurs first.
	Secondary Endpoint	PFS (Assessed by BICR)	Defined as the time from randomization to the first documented disease progression per RECIST 1.1 as assessed by BICR or death due to any cause, whichever occurs first.

Database lock	28-MAY-2021		
Results and Analysis			
Analysis Description	**Primary Analysis (CPS ≥1, all-comer, CPS ≥10 participants) – interim analysis 1**		
Analysis population and time point description	Intent-to-treat population (IA1; data cutoff 03-MAY-2021)		
Descriptive statistics and estimate variability	Treatment group	Pembrolizumab + chemotherapy ± bevacizumab	Placebo + chemotherapy ± bevacizumab
	CPS ≥1 Participants		
	Number of subjects	273	275
	PFS (Investigator Assessed) Median, months (95% CI)	10.4 (9.7, 12.3)	8.2 (6.3, 8.5)
	OS Median, months (95% CI)	NR (19.8, NR)	16.3 (14.5, 19.4)
	ORR % (95% CI)	68.1 (62.2, 73.6)	50.2 (44.1, 56.2)
	DOR Median months (range)	18.0 (1.3+ - 24.2+)	10.4 (1.5+ - 22.0+)
	PFS by BICR Median, months (95% CI)	12.8 (10.4, 20.6)	8.3 (7.7, 9.2)
	All-comer Participants		
	Number of subjects	308	309
	PFS (Investigator Assessed) Median, months (95% CI)	10.4 (9.1, 12.1)	8.2 (6.4, 8.4)
	OS Median, months (95% CI)	24.4 (19.2, NR)	16.5 (14.5, 19.4)
	ORR % (95% CI)	65.9 (60.3, 71.2)	50.8 (45.1, 56.5)
	DOR Median, months (range)	18.0 (1.3+ - 24.2+)	10.4 (1.5+ - 22.0+)
	PFS by BICR Median, months (95% CI)	12.3 (10.3, 17.9)	8.3 (8.1, 9.0)
	CPS ≥10 Participants		
	Number of subjects	158	159
	PFS (Investigator Assessed) Median, months (95% CI)	10.4 (8.9, 15.1)	8.1 (6.2, 8.8)
	OS Median, months (95% CI)	NR (19.1, NR)	16. 4 (14.0, 25.0)
	ORR		

	% (95% CI)	69.6 (61.8, 76.7)	49.1 (41.1, 57.1)
	DOR		
	Median, months (range)	21.1 (1.3+ - 24.2+)	9.4 (2.1+ - 21.5+)
	PFS by BICR		
	Median, months (95% CI)	15.1 (8.9, NR)	8.3 (7.1, 10.2)
Effect estimate per comparison	**CPS ≥1 Participants**		
		Comparison groups	Pembrolizumab + Chemotherapy ± Bevacizumab vs. Placebo + Chemotherapy ± Bevacizumab
	Dual primary endpoint: PFS (Investigator Assessed)	Hazard ratio	0.62
		95% CI	(0.50, 0.77)
		P-value	<0.0001
	Dual primary endpoint: OS	Hazard ratio	0.64
		95% CI	(0.50, 0.81)
		P-value	0.0001
	Secondary Endpoint: ORR	Difference %	18.0
		95% CI	(10.1, 25.7)
	Secondary Endpoint: PFS by BICR	Hazard ratio	0.60
		95% CI	(0.48, 0.75)
	All-comer Participants		
		Comparison groups	Pembrolizumab + Chemotherapy ± Bevacizumab vs. Placebo + Chemotherapy ± Bevacizumab
	Dual primary endpoint: PFS (Investigator Assessed)	Hazard ratio	0.65
		95% CI	(0.53, 0.79)
		P-value	<0.0001
	Dual primary endpoint: OS	Hazard ratio	0.67
		95% CI	(0.54, 0.84)
		P-value	0.0003
	Secondary Endpoint: ORR	Difference %	15.3
		95% CI	(7.8, 22.6)
	Secondary Endpoint: PFS by BICR	Hazard ratio	0.63
		95% CI	(0.51, 0.77)
	CPS ≥10 Participants		

		Comparison groups	Pembrolizumab + Chemotherapy ± Bevacizumab vs. Placebo + Chemotherapy ± Bevacizumab
	Dual primary endpoint: PFS (Investigator Assessed)	Hazard ratio	0.58
		95% CI	(0.44, 0.77)
		P-value	<0.0001
	Dual primary endpoint: OS	Hazard ratio	0.61
		95% CI	(0.44, 0.84)
		P-value	0.0013
	Secondary Endpoint: ORR	Difference %	20.5
		95% CI	(10.1, 30.5)
	Secondary Endpoint: PFS by BICR	Hazard ratio	0.55
		95% CI	(0.41, 0.74)

Analysis performed across trials (pooled analyses and meta-analysis)

Not applicable.

Clinical studies in special populations

None performed.

Supportive study(ies)

A brief summary of efficacy data, based on clinical study reports for KEYNOTE-028 and KEYNOTE-158 which have been included in the dossier by the MAH to support safety assessment, is presented below.

KEYNOTE-028 is an ongoing, Phase 1b, multicenter, nonrandomized, multicohort study of pembrolizumab (10 mg/kg every 2 weeks) in participants with PD-L1 positive metastatic/refractory solid tumours. Cohort B4 enrolled participants with cervical squamous cell cancer (N=24). Efficacy data are related only to PD-L1 positive population. ORR by investigator assessment of all subjects in Cohort B4 (n=24) was 16.7% (95% CI: 4.7, 37.4) and included 4 subjects with a confirmed PR. ORR by central radiology assessment (n=20) was 10.0% (95% CI: 1.2, 31.7), with 2 subjects with confirmed PR.

KEYNOTE-158 is an ongoing, Phase 2, multicenter, nonrandomized, multicohort study of pembrolizumab (200 mg every 3 weeks) as monotherapy in previously treated participants with advanced solid tumours, independent of PD-L1 status. The study included 13 cohorts in various advanced solid tumour indications; Cohort E enrolled participants with cervical cancer (N=98). Of the 98 participants in the ASaT population, PD-L1 IHC test results were available for 97 participants. Cervical carcinoma specimens from 82 (84.5%) participants expressed PD-L1 at a CPS ≥1, while specimens from 15 (15.5%) participants were negative for PD-L1 expression. All participants with confirmed response (CR or PR) had tumours that were positive for PD-L1 expression (ORR 17.1%, 14/82).

Table 51. Summary of Best Objective Response Based on RECIST 1.1 per Central Radiology Assessment (Baseline PD-L1 Positive vs. PD-L1 Negative) (Cohort E: Cervical Carcinoma) (MK3475 200mg Q3W) (ASaT Population)

Response Evaluation	Baseline PD-L1 Positive (N=82)			Baseline PD-L1 Negative (N=15)		
	n	%	95% CI[†]	n	%	95% CI[†]
Complete Response (CR)	5	6.1	(2.0, 13.7)	0	0.0	(0.0, 21.8)
Partial Response (PR)	9	11.0	(5.1, 19.8)	0	0.0	(0.0, 21.8)
Objective Response (CR+PR)	**14**	**17.1**	**(9.7, 27.0)**	**0**	**0.0**	**(0.0, 21.8)**
Stable Disease (SD)	13	15.9	(8.7, 25.6)	3	20.0	(4.3, 48.1)
Progressive Disease (PD)	44	53.7	(42.3, 64.7)	10	66.7	(38.4, 88.2)
Non-evaluable (NE)	3	3.7	(0.8, 10.3)	1	6.7	(0.2, 31.9)
No Assessment	8	9.8	(4.3, 18.3)	1	6.7	(0.2, 31.9)

Central radiology assessed responses per RECIST 1.1 (confirmed) are included in this table.

[†] Based on binomial exact confidence interval method.

'No Assessment' (NA) counts subjects who had a baseline assessment evaluated by the central radiology assessment but no post-baseline assessment on the data cutoff date including missing, discontinuing or death before the first post-baseline scan.

(Database Cutoff Date: 27JUN2019).

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

KEYNOTE-826 is a phase 3 randomized, double-blind, placebo-controlled trial of pembrolizumab plus chemotherapy (cisplatin or carboplatin plus paclitaxel) with or without bevacizumab vs placebo plus chemotherapy with or without bevacizumab for the 1L treatment of persistent, recurrent, or metastatic cervical cancer.

In study KEYNOTE-826, patients not amenable to radical treatment and who have not received prior systemic chemotherapy (with the exception of radiosensitizing cisplatin) were allowed. All histologies were included and disease should be measurable. Patients were fit (ECOG 0-1) and have the usual exclusion criteria for immunotherapy. Overall, the enrolment criteria were acceptable. Stratification was made according to stage at initial diagnosis, use of bevacizumab and PD-L1 status, which is acceptable.

Maximum 6 cycles of platinum-based chemotherapy were allowed. Participants with on-going clinical benefit and who were tolerating combination chemotherapy were allowed to continue chemotherapy beyond 6 cycles after Sponsor consultation. Bevacizumab and pembrolizumab/placebo (max 2 years) were to be continued until disease progression. Bevacizumab demonstrated overall survival advantage when added to chemotherapy compared to chemotherapy alone in GOG-240 study, so it is considered the preferred first line regimen by international guidelines (ESMO, NCCN). It is however acknowledged that its use might not always be feasible related to the safety profile of this drug. In this study, approximately 63% of patients received bevacizumab. Baseline characteristics by bevacizumab use showed less older patients (over 75) treated with bevacizumab, as well as more patients with ECOG 0. This is comprehensible. It is noted that bevacizumab was less used in EU, as compared to North America and Asia.

In the EU, bevacizumab is approved for 1L cervical cancer with cisplatin plus paclitaxel, and not with carboplatin; it is acknowledged though that carboplatin is considered an alternative to cisplatin in subjects who are not candidate to cisplatin by ESMO guidelines, and the triplet combination with

carboplatin is included as an alternative in the NCCN guidelines. As discussed in the Scientific Advice, population in KEYNOTE-826 was randomised to receive a number of treatment options that are expected to impact differently in terms of efficacy/safety.

Dual primary endpoints were PFS and OS, and the study was considered positive if it was positive for either the PFS or OS hypothesis test for any of the 3 groups: CPS⩾1, all-comers, and CPS⩾10. Regarding PFS, the primary endpoint was modified from assessment by independent review (BICR) to by investigator (inv) with Amendment 5, released after enrolment was completed but before any formal study analysis. The rate of discordance was 21.4% when investigator assessed PD was not confirmed by independent assessment based on IA1, which was attributed by the MAH to the investigators' ability to determine radiographic progression with greater sensitivity than assessment by BICR. Since PD event determination in metastatic cervical cancer takes into consideration symptoms and other clinical findings in addition to imaging, investigators with all evidence at their disposal, are anticipated to corroborate radiographic changes as progressive disease. Additional clinical input beyond imaging is used to assess progression, suggesting that BICR-determined PFS alone may not have adequate sensitivity to identify PD (disease progression) events. Clinical progression without radiographic evidence did not have any significant impact on the discordance. Overall, this explanation can be followed. The MAH declared that the modification of the primary endpoint to PFS by investigator was intended to protect the study from a loss of power while the important and objective assessment by BICR was retained as a secondary endpoint. Considering the consistent PFS benefit between the assessments by investigators and BICR, this issue can be considered solved. The MAH clarified that external pembrolizumab data from KEYNOTE-158 in 2L cervical cancer and from KEYNOTE-048 in 1L head and neck cancer motivated the change of hierarchical testing order. Overall, the MAH got greater confidence that the PD-L1 positive patient population as defined by the CPS ⩾1 cutoff would derive sufficient benefit. By that, the hypothesis testing in this population was prioritized above the testing in the CPS ⩾10 population. This can be followed.

The used methods for the statistical analysis were appropriate and the type one-error was overall controlled at the one-sided 0.025 level.

Efficacy data and additional analyses

Results have been provided for the interim analysis 1 (data cut-off date 3 May 2021), after a median follow up of approximately 17 months (last patient randomized was observed for 15 months at least). Although an interim analysis, the overall number of PFS and OS events were about 65% and 50%, respectively. Data are considered of sufficient maturity for B/R assessment.

A total of 617 patients were enrolled (308 in the pembro combo and 309 in the control arm). At the data cut-off date, 63.8% and 82.5% in the experimental and control arm have discontinued treatment, with higher rate of progression in the control arm, while discontinuation due to adverse events were more frequent in the pembro combo arm (12.4% vs 7.8%). Important protocol deviations occurred at a limited and similar rate in both arms and are not considered impacting relevantly on study results.

The majority of women were white with a median age of 51 years (16% were over 65). About 80% had distant metastases; of those, 31% had primary metastatic disease. Most patients (~70%) had squamous cell carcinoma and 20% adenocarcinoma, consistent with epidemiology of this cancer. Prior chemoradiation was received by more than half of the patient. Baseline characteristics were similar in both treatment arms, although adenocarcinomas were slightly less represented in the pembrolizumab arm (18.2% vs 27.2%).

At the interim analysis 1, PFS by investigator and OS results were statistically significant in all the 3 populations analysed (CPS≥1, all comers, CPS≥10).

The results in the **all-comers** showed statistically significant and clinically relevant improvement in **OS** with the addition of pembrolizumab to chemotherapy +/- bevacizumab, with HR of 0.67 (95%CI 0.54, 0.84) and a gain in median OS was approximately 8 months (from 16.5 to 24.4 months); 12 months OS rate increased of 10% (from 64 to 75%). The OS KM curves separated at 4.5 months and remained separated throughout the evaluation period in favour of pembrolizumab combination. **PFS** by investigator was also improved in the pembro combo arm (HR 0.65, 95%CI 0.53, 0.79), with median PFS 10.4 vs 8.2 months. Improvement was also observed in **ORR** [65.9% (95%CI 60.3, 71.2) vs 50.8% (95%CI 45.1, 56.5)] and median **DOR** (18 vs 10.4 months).

Overall 89% of all comers expressed PD-L1 as CPS≥1 (273 and 275 patients in pembro and control arm), and 51.4% of the population has high PD-L1 expression, defined as CPS≥10 (158 and 159 patients). Baseline characteristics of these two subpopulations were overall consistent with all comers.

In the **CPS≥1 population**, results were consistent with the overall population, showing statistically significant and clinically relevant benefit for the pembrolizumab combination arm vs placebo combination arm. **OS** HR was 0.64 (0.5, 0.81), with median OS NR in the experimental arm (19.8, NR) vs 16.3 months (14.5, 19.4) in the control arm. The OS KM curves separated in favour of the pembro combo arm at month 3. HR for **PFS** by inv was 0.62 (95%CI 0.50, 0.77), median PFS was 10.4 vs 8.2 months. Higher **ORR** by inv was shown in the pembro combo arm (68.1% vs 50.2%) as well as longer median **DOR** (18 vs 10.4 months).

The advantage for pembrolizumab + standard treatment over standard treatment was more pronounced in the **CPS≥10 population** with respect to all-comers: **OS** HR 0.61, **PFS** by inv HR 0.58, **ORR** by inv 69.6% vs 49.1% (95%CI 41.1, 57.1), median **DOR** 21.1 vs 9.4.

A post hoc efficacy analysis in the PD-L1 negative population (**CPS<1 subgroup**) was also performed, which included approximately 11% of all comers (35 in the pembrolizumab arm and 34 in the placebo arm). The results in this subgroup showed hazard ratio for **PFS** by investigator of 0.94 (95%CI 0.52, 1.70), with KM curves roughly superimposed; number of PFS events were more in the control arm though (65.7% vs 82.4%). **OS** HR was 1.00 (95%CI 0.53, 1.89), with almost same event rate in both treatment arms (57.1% vs 58.8%). OS KM curves initially are in favour of the control arm, then overlap. **ORR** difference was slightly in favour of the control arm (ORR 48.6% vs 55.9%). Slight advantage in median **DOR** is instead seen in the pembrolizumab arm (10.7 vs 8.5 months).

It is acknowledged that the study was not designed or powered to make comparison in the CPS<1 population, which has not been prespecified in the hierarchical testing, and results in this small subgroup should be interpreted with caution. This cannot however be raised as a sufficient argument against the validity of the results considering that the complementary population of CPS>1 has been pre-specified. The available data did not suggest a benefit in this subgroup of patients (and detriment cannot be excluded). This is further supported by the apparent lack of activity of pembrolizumab monotherapy in CPS<1 patients in KEYNOTE-158 in cervical cancer: no objective responses among the 15 PD-L1 negative patients were seen, as compared to ORR 17.1% (14/82) in PD-L1 positive tumours. Another recent RCT in more advanced cervical cancer with an anti PD1 inhibitor showed differential benefit based on PD-L1 expression (Tewari KS, 2021). The low prevalence of PD-L1 negative patient population is acknowledged in this indication; however, the biological rationale of PD-L1 expression status and the lack of benefit for the PD-L1 negative subgroup are supported by the external data in 2L cervical cancer above. PD-L1 expression was determined centrally (Neogenomics Laboratories) using a validated assay (the investigational PD-L1 IHC 22C3 pharmDx kit). There were no missing data. PD-L1 expression status was a stratification factor resulting in a balanced distribution of PD-L1 expression status between treatment arms. In conclusion, the CHMP considers the evidence of the subgroup results sufficiently reliable to draw conclusions.

In addition, as this is an add-on treatment, patients would be inevitably exposed to supplementary pembrolizumab toxicity.

Taking everything into account, the use of pembrolizumab in combination of chemotherapy+/- bevacizumab does not appear justified in the CPS<1 population, in whom the B/R is not considered favourable. Following CHMP request, the MAH restricted the indication to the PD-L1 CPS⩾1 population.

With regard to subgroup analyses, the treatment benefit observed in the primary analysis populations was generally consistent across all subgroups analysed, with the exception of CPS<1 as discussed above, and patients who have metastatic disease at study entry, showing lower efficacy in primary metastatic disease (PFS HR 0.92, OS HR 0.84). The MAH noted that Stage IVB newly diagnosed is an independent poor prognostic factor. Based on additional analyses provided, it does not appear justified to exclude difficult to treat patients with newly diagnosed metastatic disease from the proposed indication.

With regard to subgroup according to bevacizumab use (received by 63% of patients), as already discussed during the EMA SA, it is considered unfortunate that the study design does not allow to fully evaluate the benefit/risk of the additional and rather toxic treatment compound bevacizumab. It is observed that in the control arm the outcome of patients not using bevacizumab is inferior in all endpoints (OS, PFS, ORR, DOR) as compared to subjects treated with bevacizumab. This is consistent with the survival advantage showed with the addition of bevacizumab to chemotherapy in GOG-240 study, supporting the approval of bevacizumab in 1L cervical cancer. Patients receiving bevacizumab with chemotherapy in the control arm appear to have even better outcome than patients receiving pembrolizumab with chemotherapy. However, there is a subset of patients who do not receive bevacizumab due to risk posed by side effect of bevacizumab. The benefit of adding pembrolizumab to backbone chemotherapy is consistent in subgroups with and without bevacizumab.

The MAH provided subgroup analysis by platinum compound (about 20% of patients received cisplatin). Considering that the investigator's choice of carboplatin vs cisplatin might possibly select a heterogeneous patient population regarding prognostic patient and disease characteristics, it is reassuring that results by platinum agent are consistent. These data would be also considered relevant to support the general indication "in combination with chemotherapy".

Approximately 70% of patients had squamous cell carcinoma, and about 25% were adenocarcinoma, which reflects the real distribution of histology. Histology was not used as stratification factor. In baseline characteristics there was indeed no complete balance among treatment arms by histology in the all comers and in the CPS>=1 population. PD-L1 expression by histology data showed lower PD-L1 positivity in adenocarcinoma. In the updated sought indication in CPS>=1 population, benefit of pembrolizumab addition was consistent in both histologies, which is reassuring.

2.4.4. Conclusions on the clinical efficacy

KEYNOTE-826 study showed statistically significant improvement in PFS at the interim analysis in all the primary populations analysed (all-comers, CPS≥1 and CPS≥10), together with statistically significant and clinically relevant improvement in OS with the addition of pembrolizumab to platinum/paclitaxel chemotherapy +/- bevacizumab as first line treatment of persistent, recurrent or metastatic cervical cancer patients not amenable to curative treatment. This was supported by improvement in ORR and DOR. However, no benefit is seen in the small PD-L1 negative subgroup, in whom the addition of pembrolizumab to standard treatment does not appear justified. As a result, per CHMP request, the indication was restricted to CPS≥1 population.

2.5. Clinical safety

Introduction

Safety results were presented from the following datasets:

Table 52. Safety Datasets and Treatment Group Nomenclature

Dataset	Population	Treatment	Nomenclature in Tables	Nomenclature in Text
KEYNOTE-826 pembrolizumab + chemotherapy ± bevacizumab	N=307: Safety data from participants with persistent, recurrent, or metastatic cervical cancer, who received pembrolizumab in combination with chemotherapy with or without bevacizumab in KEYNOTE-826	Pembrolizumab + chemotherapy (paclitaxel plus cisplatin or carboplatin) with or without bevacizumab	KN826 Pembrolizumab + Chemotherapy[a]	Pembrolizumab + chemotherapy ± bevacizumab group
KEYNOTE-826 placebo + chemotherapy ± bevacizumab	N=309: Safety data from participants with persistent, recurrent, or metastatic cervical cancer, who received placebo in combination with chemotherapy with or without bevacizumab in KEYNOTE-826	Placebo + chemotherapy (paclitaxel plus cisplatin or carboplatin) with or without bevacizumab	KN826 Placebo + Chemotherapy[b]	Placebo + chemotherapy ± bevacizumab group
Pooled pembrolizumab + chemotherapy	N=2033: Pooled safety data from participants treated with pembrolizumab + chemotherapy, including participants with NSCLC in KEYNOTE-021 Cohorts A, C, and G, KEYNOTE-189 and KEYNOTE-407, HNSCC in KEYNOTE-048, TNBC in KEYNOTE-355, and esophageal carcinoma in KEYNOTE-590	Pembrolizumab + chemotherapy	Pooled Safety Dataset for Pembrolizumab + Chemotherapy[c]	Pooled pembrolizumab + chemotherapy group
Advanced cervical cancer pembrolizumab monotherapy	N=122: Pooled safety data from participants with advanced cervical cancer treated with pembrolizumab monotherapy in Cohort B4 of KEYNOTE-028 and Cohort E of KEYNOTE-158	Pembrolizumab monotherapy	Cervical Safety Dataset for Pembrolizumab Monotherapy[d]	Advanced cervical cancer monotherapy group

Dataset	Population	Treatment	Nomenclature in Tables	Nomenclature in Text
Pembrolizumab monotherapy reference safety	N=6185: Pooled safety data from participants treated with pembrolizumab monotherapy in the following populations and studies: melanoma (n=2076) in KEYNOTE-001, KEYNOTE-002, KEYNOTE-006 and KEYNOTE-054; NSCLC (n=2022) in KEYNOTE- 001, KEYNOTE-010, KEYNOTE-024 and KEYNOTE-042; HNSCC (n=909) in KEYNOTE-012 (Cohorts B and B2), KEYNOTE-040, KEYNOTE-048 and KEYNOTE 055; HL (n=389) in KEYNOTE-013 Cohort 3), KEYNOTE-087 and KEYNOTE-204; bladder (n=636) in KEYNOTE-045 and KEYNOTE-052; CRC (n=153) in KEYNOTE-177	Pembrolizumab monotherapy	Pembrolizumab Monotherapy Reference Safety Dataset[e]	Pembrolizumab monotherapy RSD

Abbreviations: CRC=colorectal cancer; HL=Hodgkin lymphoma; HNSCC=head and neck squamous cell carcinoma; ISS = Integrated Summary of Safety; N = number; NSCLC = Non-small cell lung cancer; RSD = reference safety dataset, TNBC=triple-negative breast cancer.

[a] Includes all participants who received at least 1 dose of pembrolizumab or chemotherapy in KEYNOTE-826.

[b] Includes all participants who received at least 1 dose of placebo or chemotherapy in KEYNOTE-826.

[c] Includes all participants who received at least 1 dose of pembrolizumab combination therapy in KEYNOTE-021 Cohorts A, C and G, KEYNOTE-048, KEYNOTE-189, KEYNOTE-355, KEYNOTE-407, and KEYNOTE-590.

[d] Includes all participants who received at least 1 dose of pembrolizumab in Cohort B4 of KEYNOTE-028 and Cohort E of KEYNOTE-158.

[e] The studies that comprise the Pembrolizumab Monotherapy RSD are listed in the footnotes of the data tables in this document and in the ISS.

Additional subsets of the KEYNOTE-826 datasets were provided by bevacizumab use:

Table 53. Additional Safety Datasets for KEYNOTE-826 by Bevacizumab Use

Dataset	Population	Treatment	Nomenclature in Tables	Nomenclature in Text
KEYNOTE-826 pembrolizumab + chemotherapy with bevacizumab	N=196: Safety data from participants with persistent, recurrent, or metastatic cervical cancer, who received pembrolizumab in combination with chemotherapy plus bevacizumab in KEYNOTE-826	Pembrolizumab + chemotherapy (paclitaxel plus cisplatin or carboplatin) with bevacizumab	KN826 Pembrolizumab + Chemotherapy w/ Bevacizumab[a]	Pembrolizumab + chemotherapy with bevacizumab group
KEYNOTE-826 pembrolizumab + chemotherapy without bevacizumab	N=111: Safety data from participants with persistent, recurrent, or metastatic cervical cancer, who received pembrolizumab in combination with chemotherapy without bevacizumab in KEYNOTE-826	Pembrolizumab + chemotherapy (paclitaxel plus cisplatin or carboplatin) without bevacizumab	KN826 Pembrolizumab + Chemotherapy w/o Bevacizumab[b]	Pembrolizumab + chemotherapy without bevacizumab group
KEYNOTE-826 placebo + chemotherapy with bevacizumab	N=193: Safety data from participants with persistent, recurrent, or metastatic cervical cancer, who received placebo in combination with chemotherapy with bevacizumab in KEYNOTE-826	Placebo + chemotherapy (paclitaxel plus cisplatin or carboplatin) with bevacizumab	KN826 Placebo + Chemotherapy w/ Bevacizumab[c]	Placebo + chemotherapy with bevacizumab group
KEYNOTE-826 placebo + chemotherapy without bevacizumab	N=116: Safety data from participants with persistent, recurrent, or metastatic cervical cancer, who received placebo in combination with chemotherapy without bevacizumab in KEYNOTE-826	Placebo + chemotherapy (paclitaxel plus cisplatin or carboplatin) without bevacizumab	KN826 Placebo + Chemotherapy w/o Bevacizumab[d]	Placebo + chemotherapy without bevacizumab group

Abbreviations: N=number; w/=with; w/o=without.
Note: Pembrolizumab Monotherapy Reference Safety Dataset is also included in additional safety dataset tables.
a Includes all participants who received at least 1 dose of pembrolizumab or chemotherapy and bevacizumab in KEYNOTE-826.
b Includes all participants who received at least 1 dose of pembrolizumab or chemotherapy in KEYNOTE-826.
[c] Includes all participants who received at least 1 dose of placebo or chemotherapy and bevacizumab in KEYNOTE-826.
[d] Includes all participants who received at least 1 dose of placebo or chemotherapy in KEYNOTE-826.

Patient exposure

Table 54. Drug Exposure Summary (APaT Population)

	KN826 Pembrolizumab + Chemotherapy (N=307)	KN826 Placebo + Chemotherapy (N=309)	Pooled Safety Dataset for Pembrolizumab + Chemotherapy[f] (N=2033)	Cervical Safety Dataset for Pembrolizumab Monotherapy[d] (N=122)	Pembrolizumab Monotherapy Reference Safety Dataset[e] (N=6185)
Duration of Exposure (month)					
n	307	309	2033	122	6185
Mean	11.79	9.42	9.02	5.53	7.52
Median	9.99	7.66	6.28	2.84	4.90
SD	8.047	6.788	7.802	7.042	7.029
Range	0.03 to 26.88	0.03 to 27.37	0.03 to 48.00	0.03 to 40.05	0.03 to 30.62
Number of Cycles					
n	307	309	2033	122	6185
Mean	16.53	13.37	12.77	8.91	11.96
Median	14.00	11.00	9.00	5.00	8.00
SD	11.014	9.167	10.587	9.489	10.403

Duration of exposure is the time from the first dose date to the last dose date.

[d] Includes all participants who received at least one dose of pembrolizumab in KN028 cohort B4 and KN158 cohort E.

[e] 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, KN012 cohort B and B2, KN013 cohort 3, KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN087, KN177, and KN204.

[f] Includes all subjects who received at least one dose of pembrolizumab combo therapy in KN021 cohort A/C/G, KN048, KN189, KN355, KN407, and KN590.

Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 03APR2020)

Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEP2018, KN021: 19AUG2019, KN189: 20MAY2019, KN407: 09MAY2019)

Database cutoff date for HNSCC (KN012 cohort B and B2: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)

Database cutoff date for cHL (KN013 cohort 3: 28SEP2018, KN087: 21MAR2019, KN204: 16JAN2020)

Database cutoff date for Bladder (KN045: 26OCT2017, KN052: 26SEP2018)

Database cutoff date for Esophageal (KN590: 02JUL2020)

Database cutoff date for CRC (KN177: 19FEB2020)

Database cutoff date for TNBC (KN355: 11DEC2019)

Database cutoff date for Cervical (KN826: 03MAY2021, KN028 cohort B4: 20FEB2017, KN158 cohort E: 27JUN2019)

Table 55. Drug Exposure by Duration (APaT Population)

	KN826 Pembrolizumab + Chemotherapy (N=307)			KN826 Placebo + Chemotherapy (N=309)			Pooled Safety Dataset for Pembrolizumab + Chemotherapy[f] (N=2033)			Cervical Safety Dataset for Pembrolizumab Monotherapy[d] (N=122)			Pembrolizumab Monotherapy Reference Safety Dataset[e] (N=6185)		
	n	(%)	Person-years	n	(%)	Person-years	n	(%)	Person-years	n	(%)	Person-years	n	(%)	Person-years
Duration of exposure															
>0 m	307	(100.0)	(301.7)	309	(100.0)	(242.4)	2,033	(100.0)	(1,528.7)	122	(100.0)	(56.2)	6,185	(100.0)	(3,875.4)
>=1 m	280	(91.2)	(301.2)	288	(93.2)	(241.9)	1,846	(90.8)	(1,522.4)	103	(84.4)	(55.7)	5,314	(85.9)	(3,846.7)
>=3 m	256	(83.4)	(297.1)	257	(83.2)	(236.8)	1,562	(76.8)	(1,473.2)	57	(46.7)	(48.2)	3,860	(62.4)	(3,604.5)
>=6 m	209	(68.1)	(278.4)	186	(60.2)	(209.2)	1,068	(52.5)	(1,288.4)	29	(23.8)	(38.3)	2,808	(45.4)	(3,222.1)
>=12 m	139	(45.3)	(228.6)	96	(31.1)	(145.5)	550	(27.1)	(923.8)	18	(14.8)	(30.2)	1,431	(23.1)	(2,179.8)

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

Duration of exposure is the time from the first dose date to the last dose date.

[d] Includes all participants who received at least one dose of pembrolizumab in KN028 cohort B4 and KN158 cohort E.

[e] 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, KN012 cohort B and B2, KN013 cohort 3, KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN087, KN177, and KN204.

[f] Includes all subjects who received at least one dose of pembrolizumab combo therapy in KN021 cohort A/C/G, KN048, KN189, KN355, KN407, and KN590.

Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 03APR2020)

Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEP2018, KN021: 19AUG2019, KN189: 20MAY2019, KN407: 09MAY2019)

Database cutoff date for HNSCC (KN012 cohort B and B2: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)

Database cutoff date for cHL (KN013 cohort 3: 28SEP2018, KN087: 21MAR2019, KN204: 16JAN2020)

Database cutoff date for Bladder (KN045: 26OCT2017, KN052: 26SEP2018)

Database cutoff date for Esophageal (KN590: 02JUL2020)

Database cutoff date for CRC (KN177: 19FEB2020)

Database cutoff date for TNBC (KN355: 11DEC2019)

Database cutoff date for Cervical (KN826: 03MAY2021, KN028 cohort B4: 20FEB2017, KN158 cohort E: 27JUN2019)

Table 56. Drug Exposure Summary (APaT Population)

	KN826 Pembrolizumab + Chemotherapy w/ Bevacizumab (N=196)	KN826 Pembrolizumab + Chemotherapy w/o Bevacizumab (N=111)	KN826 Placebo + Chemotherapy w/ Bevacizumab (N=193)	KN826 Placebo + Chemotherapy w/o Bevacizumab (N=116)	Pembrolizumab Monotherapy Reference Safety Dataset[e] (N=6185)
Duration of Exposure (month)					
n	196	111	193	116	6185
Mean	13.36	9.02	11.05	6.69	7.52
Median	13.91	6.31	9.69	5.39	4.90
SD	7.841	7.681	6.918	5.612	7.029
Range	0.03 to 26.88	0.03 to 25.43	0.03 to 27.37	0.03 to 22.05	0.03 to 30.62
Number of Cycles					
n	196	111	193	116	6185
Mean	18.66	12.78	15.61	9.66	11.96
Median	18.00	9.00	14.00	8.00	8.00
SD	10.884	10.257	9.373	7.488	10.403
Range	1.00 to 39.00	1.00 to 35.00	1.00 to 38.00	1.00 to 31.00	1.00 to 59.00

Duration of exposure is the time from the first dose date to the last dose date.

[e] 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, KN012 cohort B and B2, KN013 cohort 3, KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN087, KN177, and KN204.

Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 03APR2020)

Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEP2018)

Database cutoff date for HNSCC (KN012 cohort B and B2: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)

Database cutoff date for cHL (KN013 cohort 3: 28SEP2018, KN087: 21MAR2019, KN204: 16JAN2020)

Database cutoff date for Bladder (KN045: 26OCT2017, KN052: 26SEP2018)

Database cutoff date for CRC (KN177: 19FEB2020)

Database cutoff date for Cervical (KN826: 03MAY2021)

Source: [ISS: adam-adsl; adexsum]

Table 57. Drug Exposure by Duration by Bevacizumab use (APaT Population)

	KN826 Pembrolizumab + Chemotherapy w/ Bevacizumab (N=196)			KN826 Pembrolizumab + Chemotherapy w/o Bevacizumab (N=111)			KN826 Placebo + Chemotherapy w/ Bevacizumab (N=193)			KN826 Placebo + Chemotherapy w/o Bevacizumab (N=116)			Pembrolizumab Monotherapy Reference Safety Dataset[e] (N=6185)		
	n	(%)	Person-years	n	(%)	Person-years	n	(%)	Person-years	n	(%)	Person-years	n	(%)	Person-years
Duration of exposure															
>0 m	196	(100.0)	(218.3)	111	(100.0)	(83.4)	193	(100.0)	(177.8)	116	(100.0)	(64.6)	6,185	(100.0)	(3,875.4)
>=1 m	183	(93.4)	(218.1)	97	(87.4)	(83.0)	183	(94.8)	(177.5)	105	(90.5)	(64.5)	5,314	(85.9)	(3,846.7)
>=3 m	173	(88.3)	(216.4)	83	(74.8)	(80.7)	172	(89.1)	(175.5)	85	(73.3)	(61.3)	3,860	(62.4)	(3,604.5)
>=6 m	151	(77.0)	(207.7)	58	(52.3)	(70.7)	137	(71.0)	(161.7)	49	(42.2)	(47.5)	2,808	(45.4)	(3,222.1)
>=12 m	107	(54.6)	(175.5)	32	(28.8)	(53.1)	79	(40.9)	(120.0)	17	(14.7)	(25.5)	1,431	(23.1)	(2,179.8)

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

Duration of exposure is the time from the first dose date to the last dose date.

[e] 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, KN012 cohort B and B2, KN013 cohort 3, KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN087, KN177, and KN204.

Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 03APR2020)

Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEP2018)

Database cutoff date for HNSCC (KN012 cohort B and B2: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)

Database cutoff date for cHL (KN013 cohort 3: 28SEP2018, KN087: 21MAR2019, KN204: 16JAN2020)

Database cutoff date for Bladder (KN045: 26OCT2017, KN052: 26SEP2018)

Database cutoff date for CRC (KN177: 19FEB2020)

Database cutoff date for Cervical (KN826: 03MAY2021)

Source: [ISS: adam-adsl; adexsum]

Adverse events

Table 58. Participant Characteristics (APaT Population)

	KN826 Pembrolizumab + Chemotherapy		KN826 Placebo + Chemotherapy		Pooled Safety Dataset for Pembrolizumab + Chemotherapy[f]		Cervical Safety Dataset for Pembrolizumab Monotherapy[d]		Pembrolizumab Monotherapy Reference Safety Dataset[e]	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	307		309		2,033		122		6,185	
Sex										
Male	0	(0.0)	0	(0.0)	1,041	(51.2)	0	(0.0)	4,039	(65.3)
Female	307	(100.0)	309	(100.0)	992	(48.8)	122	(100.0)	2,146	(34.7)
Age (Years)										
<65	259	(84.4)	257	(83.2)	1,218	(59.9)	114	(93.4)	3,587	(58.0)
>=65	48	(15.6)	52	(16.8)	815	(40.1)	8	(6.6)	2,598	(42.0)
Mean	51.7		50.7		60.2		46.7		60.2	
SD	11.9		12.7		11.4		11.0		13.6	
Median	51.0		50.0		62.0		45.0		62.0	
Range	25 to 82		22 to 79		20 to 94		24 to 75		15 to 94	
Race										
American Indian Or Alaska Native	18	(5.9)	21	(6.8)	23	(1.1)	1	(0.8)	30	(0.5)
Asian	65	(21.2)	45	(14.6)	472	(23.2)	16	(13.1)	695	(11.2)
Black Or African American	4	(1.3)	2	(0.6)	66	(3.2)	2	(1.6)	121	(2.0)
Multiracial	32	(10.4)	34	(11.0)	19	(0.9)	1	(0.8)	70	(1.1)
Native Hawaiian Or Other Pacific Islander	0	(0.0)	0	(0.0)	1	(0.0)	1	(0.8)	5	(0.1)
White	169	(55.0)	190	(61.5)	1,416	(69.7)	93	(76.2)	4,673	(75.6)
Missing	19	(6.2)	17	(5.5)	36	(1.8)	8	(6.6)	591	(9.6)
Ethnicity										
Hispanic Or Latino	109	(35.5)	121	(39.2)	235	(11.6)	3	(2.5)	424	(6.9)
Not Hispanic Or Latino	192	(62.5)	184	(59.5)	1,695	(83.4)	103	(84.4)	4,927	(79.7)
Not Reported	5	(1.6)	4	(1.3)	54	(2.7)	10	(8.2)	708	(11.4)
Unknown	1	(0.3)	0	(0.0)	46	(2.3)	2	(1.6)	117	(1.9)
Missing	0	(0.0)	0	(0.0)	3	(0.1)	4	(3.3)	9	(0.1)
Age Category (year)										
<65	259	(84.4)	257	(83.2)	1,218	(59.9)	114	(93.4)	3,587	(58.0)
65-74	38	(12.4)	42	(13.6)	653	(32.1)	7	(5.7)	1,797	(29.1)
75-84	10	(3.3)	10	(3.2)	157	(7.7)	1	(0.8)	694	(11.2)
>=85	0	(0.0)	0	(0.0)	5	(0.2)	0	(0.0)	107	(1.7)
ECOG Performance Status										
[0] Normal Activity	178	(58.0)	170	(55.0)	913	(44.9)	40	(32.8)	2,942	(47.6)
[1] Symptoms, but ambulatory	127	(41.4)	139	(45.0)	1,116	(54.9)	82	(67.2)	3,069	(49.6)
Other/Missing	2	(0.7)	0	(0.0)	4	(0.2)	0	(0.0)	174	(2.8)
Geographic Region										
EU	103	(33.6)	108	(35.0)	690	(33.9)	61	(50.0)	2,217	(35.8)
Ex-EU	204	(66.4)	201	(65.0)	1,343	(66.1)	61	(50.0)	3,968	(64.2)

[d] Includes all participants who received at least one dose of pembrolizumab in KN028 cohort B4 and KN158 cohort E.

[e] 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, KN012 cohort B and B2, KN013 cohort 3, KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN087, KN177, and KN204.

[f] Includes all subjects who received at least one dose of pembrolizumab combo therapy in KN021 cohort A/C/G, KN048, KN189, KN355, KN407, and KN590.

Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 03APR2020)

Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEP2018, KN021: 19AUG2019, KN189: 20MAY2019, KN407: 09MAY2019)

Database cutoff date for HNSCC (KN012 cohort B and B2: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)

Database cutoff date for cHL (KN013 cohort 3: 28SEP2018, KN087: 21MAR2019, KN204: 16JAN2020)

Database cutoff date for Bladder (KN045: 26OCT2017, KN052: 26SEP2018)

Database cutoff date for Esophageal (KN590: 02JUL2020)

Database cutoff date for CRC (KN177: 19FEB2020)

Database cutoff date for TNBC (KN355: 11DEC2019)

Database cutoff date for Cervical (KN826: 03MAY2021, KN028 cohort B4: 20FEB2017, KN158 cohort E: 27JUN2019)

Table 59. Participant Characteristics by Bevacizumab use (APaT Population)

	KN826 Pembrolizumab + Chemotherapy w/ Bevacizumab		KN826 Pembrolizumab + Chemotherapy w/o Bevacizumab		KN826 Placebo + Chemotherapy w/ Bevacizumab		KN826 Placebo + Chemotherapy w/o Bevacizumab		Pembrolizumab Monotherapy Reference Safety Dataset[e]	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	196		111		193		116		6,185	
Sex										
Male	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	4,039	(65.3)
Female	196	(100.0)	111	(100.0)	193	(100.0)	116	(100.0)	2,146	(34.7)
Age (Years)										
<65	170	(86.7)	89	(80.2)	165	(85.5)	92	(79.3)	3,587	(58.0)
>=65	26	(13.3)	22	(19.8)	28	(14.5)	24	(20.7)	2,598	(42.0)
Mean	50.9		53.1		49.9		52.1		60.2	
SD	11.5		12.5		12.7		12.6		13.6	
Median	51.0		53.0		50.0		50.0		62.0	
Range	25 to 82		30 to 82		22 to 77		31 to 79		15 to 94	
Race										
American Indian Or Alaska Native	9	(4.6)	9	(8.1)	10	(5.2)	11	(9.5)	30	(0.5)
Asian	49	(25.0)	16	(14.4)	37	(19.2)	8	(6.9)	695	(11.2)
Black Or African American	4	(2.0)	0	(0.0)	2	(1.0)	0	(0.0)	121	(2.0)
Multiracial	22	(11.2)	10	(9.0)	22	(11.4)	12	(10.3)	70	(1.1)
Native Hawaiian Or Other Pacific Islander	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	5	(0.1)
White	103	(52.6)	66	(59.5)	115	(59.6)	75	(64.7)	4,673	(75.6)
Missing	9	(4.6)	10	(9.0)	7	(3.6)	10	(8.6)	591	(9.6)
Ethnicity										
Hispanic Or Latino	72	(36.7)	37	(33.3)	81	(42.0)	40	(34.5)	424	(6.9)
Not Hispanic Or Latino	121	(61.7)	71	(64.0)	111	(57.5)	73	(62.9)	4,927	(79.7)
Not Reported	2	(1.0)	3	(2.7)	1	(0.5)	3	(2.6)	708	(11.4)
Unknown	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)	117	(1.9)
Missing	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	9	(0.1)
Age Category (year)										
<65	170	(86.7)	89	(80.2)	165	(85.5)	92	(79.3)	3,587	(58.0)
65-74	22	(11.2)	16	(14.4)	24	(12.4)	18	(15.5)	1,797	(29.1)
75-84	4	(2.0)	6	(5.4)	4	(2.1)	6	(5.2)	694	(11.2)
>=85	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	107	(1.7)
ECOG Performance Status										
[0] Normal Activity	127	(64.8)	51	(45.9)	107	(55.4)	63	(54.3)	2,942	(47.6)
[1] Symptoms, but ambulatory	68	(34.7)	59	(53.2)	86	(44.6)	53	(45.7)	3,069	(49.6)
Other/Missing	1	(0.5)	1	(0.9)	0	(0.0)	0	(0.0)	174	(2.8)
Geographic Region										
EU	55	(28.1)	48	(43.2)	50	(25.9)	58	(50.0)	2,217	(35.8)

	KN826 Pembrolizumab + Chemotherapy w/ Bevacizumab		KN826 Pembrolizumab + Chemotherapy w/o Bevacizumab		KN826 Placebo + Chemotherapy w/ Bevacizumab		KN826 Placebo + Chemotherapy w/o Bevacizumab		Pembrolizumab Monotherapy Reference Safety Dataset[e]	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Ex-EU	141	(71.9)	63	(56.8)	143	(74.1)	58	(50.0)	3,968	(64.2)

[e] 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, KN012 cohort B and B2, KN013 cohort 3, KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN087, KN177, and KN204.

Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 03APR2020)

Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEP2018)

Database cutoff date for HNSCC (KN012 cohort B and B2: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)

Database cutoff date for cHL (KN013 cohort 3: 28SEP2018, KN087: 21MAR2019, KN204: 16JAN2020)

Database cutoff date for Bladder (KN045: 26OCT2017, KN052: 26SEP2018)

Database cutoff date for CRC (KN177: 19FEB2020)

Database cutoff date for Cervical (KN826: 03MAY2021)

Source: [ISS: adam-adsl]

Table 60. Adverse Event Summary (APaT Population)

	KN826 Pembrolizumab + Chemotherapy		KN826 Placebo + Chemotherapy		Pooled Safety Dataset for Pembrolizumab + Chemotherapy[f]		Cervical Safety Dataset for Pembrolizumab Monotherapy[d]		Pembrolizumab Monotherapy Reference Safety Dataset[e]	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	307		309		2,033		122		6,185	
with one or more adverse events	305	(99.3)	307	(99.4)	2,015	(99.1)	119	(97.5)	5,989	(96.8)
with no adverse event	2	(0.7)	2	(0.6)	18	(0.9)	3	(2.5)	196	(3.2)
with drug-related[a] adverse events	298	(97.1)	300	(97.1)	1,948	(95.8)	82	(67.2)	4,366	(70.6)
with toxicity grade 3-5 adverse events	251	(81.8)	232	(75.1)	1,583	(77.9)	65	(53.3)	2,984	(48.2)
with toxicity grade 3-5 drug-related adverse events	210	(68.4)	198	(64.1)	1,285	(63.2)	17	(13.9)	975	(15.8)
with serious adverse events	153	(49.8)	131	(42.4)	962	(47.3)	52	(42.6)	2,371	(38.3)
with serious drug-related adverse events	93	(30.3)	71	(23.0)	550	(27.1)	12	(9.8)	701	(11.3)
who died	14	(4.6)	14	(4.5)	139	(6.8)	4	(3.3)	321	(5.2)
who died due to a drug-related adverse event	2	(0.7)	4	(1.3)	43	(2.1)	0	(0.0)	39	(0.6)
discontinued any drug due to an adverse event	115	(37.5)	82	(26.5)	551	(27.1)	11	(9.0)	832	(13.5)
discontinued pembrolizumab or placebo	46	(15.0)	25	(8.1)	345	(17.0)	11	(9.0)	832	(13.5)
discontinued all drugs	18	(5.9)	15	(4.9)	125	(6.1)	11	(9.0)	832	(13.5)
discontinued any drug due to a drug-related adverse event	96	(31.3)	69	(22.3)	434	(21.3)	6	(4.9)	444	(7.2)
discontinued pembrolizumab or placebo	31	(10.1)	12	(3.9)	234	(11.5)	6	(4.9)	444	(7.2)
discontinued all drugs	10	(3.3)	6	(1.9)	76	(3.7)	6	(4.9)	444	(7.2)
discontinued any drug due to a serious adverse event	51	(16.6)	32	(10.4)	327	(16.1)	9	(7.4)	598	(9.7)
discontinued pembrolizumab or placebo	33	(10.7)	16	(5.2)	268	(13.2)	9	(7.4)	598	(9.7)
discontinued all drugs	17	(5.5)	11	(3.6)	110	(5.4)	9	(7.4)	598	(9.7)
discontinued any drug due to a serious drug-related adverse event	39	(12.7)	23	(7.4)	220	(10.8)	4	(3.3)	265	(4.3)
discontinued pembrolizumab or placebo	22	(7.2)	8	(2.6)	167	(8.2)	4	(3.3)	265	(4.3)
discontinued all drugs	10	(3.3)	4	(1.3)	63	(3.1)	4	(3.3)	265	(4.3)

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

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

Grades are based on NCI CTCAE version 4.0.

[d] Includes all participants who received at least one dose of pembrolizumab in KN028 cohort B4 and KN158 cohort E.

[e] 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, KN012 cohort B and B2, KN013 cohort 3, KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN087, KN177, and KN204.

[f] Includes all subjects who received at least one dose of pembrolizumab combo therapy in KN021 cohort A/C/G, KN048, KN189, KN355, KN407, and KN590.

Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 03APR2020)

Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEP2018, KN021: 19AUG2019, KN189: 20MAY2019, KN407: 09MAY2019)

Database cutoff date for HNSCC (KN012 cohort B and B2: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)

Database cutoff date for cHL (KN013 cohort 3: 28SEP2018, KN087: 21MAR2019, KN204: 16JAN2020)

Database cutoff date for Bladder (KN045: 26OCT2017, KN052: 26SEP2018)

Database cutoff date for Esophageal (KN590: 02JUL2020)

Database cutoff date for CRC (KN177: 19FEB2020)

Database cutoff date for TNBC (KN355: 11DEC2019)

Database cutoff date for Cervical (KN826: 03MAY2021, KN028 cohort B4: 20FEB2017, KN158 cohort E: 27JUN2019)

Table 61. Adverse Event Summary by Bevacizumab use (APaT Population)

	KN826 Pembrolizumab + Chemotherapy w/ Bevacizumab		KN826 Pembrolizumab + Chemotherapy w/o Bevacizumab		KN826 Placebo + Chemotherapy w/ Bevacizumab		KN826 Placebo + Chemotherapy w/o Bevacizumab		Pembrolizumab Monotherapy Reference Safety Dataset[e]	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	196		111		193		116		6,185	
with one or more adverse events	196	(100.0)	109	(98.2)	193	(100.0)	114	(98.3)	5,989	(96.8)
with no adverse event	0	(0.0)	2	(1.8)	0	(0.0)	2	(1.7)	196	(3.2)
with drug-related[a] adverse events	191	(97.4)	107	(96.4)	190	(98.4)	110	(94.8)	4,366	(70.6)
with toxicity grade 3-5 adverse events	164	(83.7)	87	(78.4)	144	(74.6)	88	(75.9)	2,984	(48.2)
with toxicity grade 3-5 drug-related adverse events	143	(73.0)	67	(60.4)	126	(65.3)	72	(62.1)	975	(15.8)
with serious adverse events	99	(50.5)	54	(48.6)	87	(45.1)	44	(37.9)	2,371	(38.3)
with serious drug-related adverse events	65	(33.2)	28	(25.2)	48	(24.9)	23	(19.8)	701	(11.3)
who died	10	(5.1)	4	(3.6)	11	(5.7)	3	(2.6)	321	(5.2)
who died due to a drug-related adverse event	1	(0.5)	1	(0.9)	3	(1.6)	1	(0.9)	39	(0.6)
discontinued any drug due to an adverse event	88	(44.9)	27	(24.3)	61	(31.6)	21	(18.1)	832	(13.5)
discontinued pembrolizumab or placebo	35	(17.9)	11	(9.9)	12	(6.2)	13	(11.2)	832	(13.5)
discontinued all drugs	14	(7.1)	4	(3.6)	7	(3.6)	8	(6.9)	832	(13.5)
discontinued any drug due to a drug-related adverse event	74	(37.8)	22	(19.8)	55	(28.5)	14	(12.1)	444	(7.2)
discontinued pembrolizumab or placebo	25	(12.8)	6	(5.4)	6	(3.1)	6	(5.2)	444	(7.2)
discontinued all drugs	8	(4.1)	2	(1.8)	2	(1.0)	4	(3.4)	444	(7.2)
discontinued any drug due to a serious adverse event	41	(20.9)	10	(9.0)	26	(13.5)	6	(5.2)	598	(9.7)
discontinued pembrolizumab or placebo	27	(13.8)	6	(5.4)	11	(5.7)	5	(4.3)	598	(9.7)
discontinued all drugs	13	(6.6)	4	(3.6)	6	(3.1)	5	(4.3)	598	(9.7)
discontinued any drug due to a serious drug-related adverse event	31	(15.8)	8	(7.2)	20	(10.4)	3	(2.6)	265	(4.3)
discontinued pembrolizumab or placebo	19	(9.7)	3	(2.7)	6	(3.1)	2	(1.7)	265	(4.3)
discontinued all drugs	8	(4.1)	2	(1.8)	2	(1.0)	2	(1.7)	265	(4.3)

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

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

Grades are based on NCI CTCAE version 4.0.

[e] 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, KN012 cohort B and B2, KN013 cohort 3, KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN087, KN177, and KN204.

Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 03APR2020)

Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEP2018)

Database cutoff date for HNSCC (KN012 cohort B and B2: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)

Database cutoff date for cHL (KN013 cohort 3: 28SEP2018, KN087: 21MAR2019, KN204: 16JAN2020)

Database cutoff date for Bladder (KN045: 26OCT2017, KN052: 26SEP2018)

Database cutoff date for CRC (KN177: 19FEB2020)

Database cutoff date for Cervical (KN826: 03MAY2021)

Source: [ISS: adam-adsl; adae]

Table 62. Exposure-Adjusted Adverse Event Summary (Including Multiple Occurrences of Events) (APaT Population)

	Event Count and Rate (Events/100 person-years)[a]				
	KN826 Pembrolizumab + Chemotherapy	KN826 Placebo + Chemotherapy	Pooled Safety Dataset for Pembrolizumab + Chemotherapy[f]	Cervical Safety Dataset for Pembrolizumab Monotherapy[d]	Pembrolizumab Monotherapy Reference Safety Dataset[e]
Number of subjects exposed	307	309	2033	122	6185
Total exposure[b] in person-years	322.11	265.35	1688.88	66.15	4336.02
Total events (rate)					
adverse events	6260 (1943.41)	5628 (2120.94)	40308 (2386.67)	1110 (1678.05)	64173 (1480.00)
drug-related[c] adverse events	3661 (1136.55)	3152 (1187.85)	23303 (1379.79)	280 (423.29)	20041 (462.20)
toxicity grade 3-5 adverse events	1009 (313.24)	851 (320.70)	6238 (369.36)	152 (229.79)	6478 (149.40)
toxicity grade 3-5 drug-related adverse events	660 (204.90)	505 (190.31)	4288 (253.90)	22 (33.26)	1467 (33.83)
serious adverse events	340 (105.55)	266 (100.24)	1939 (114.81)	86 (130.01)	4264 (98.34)
serious drug-related adverse events	151 (46.88)	106 (39.95)	887 (52.52)	15 (22.68)	971 (22.39)
adverse events leading to death	14 (4.35)	14 (5.28)	143 (8.47)	4 (6.05)	328 (7.56)
drug-related adverse events leading to death	2 (0.62)	4 (1.51)	43 (2.55)	0 (0.00)	39 (0.90)
adverse events resulting in drug discontinuation	151 (46.88)	104 (39.19)	656 (38.84)	11 (16.63)	904 (20.85)
drug-related adverse events resulting in drug discontinuation	122 (37.87)	87 (32.79)	515 (30.49)	6 (9.07)	481 (11.09)
serious adverse events resulting in drug discontinuation	58 (18.01)	38 (14.32)	363 (21.49)	9 (13.61)	635 (14.64)
serious drug-related adverse events resulting in drug discontinuation	42 (13.04)	29 (10.93)	242 (14.33)	4 (6.05)	279 (6.43)

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

[b] Drug exposure is defined as the time from the first dose date to the earlier of the last dose date + 30 or the database cut-off date.

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

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

Grades are based on NCI CTCAE version 4.0.

[d] Includes all participants who received at least one dose of pembrolizumab in KN028 cohort B4 and KN158 cohort E.

[e] 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, KN012 cohort B and B2, KN013 cohort 3, KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN087, KN177, and KN204.

[f] Includes all subjects who received at least one dose of pembrolizumab combo therapy in KN021 cohort A/C/G, KN048, KN189, KN355, KN407, and KN590.

Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 03APR2020)

Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEP2018, KN021: 19AUG2019, KN189: 20MAY2019, KN407: 09MAY2019)

Database cutoff date for HNSCC (KN012 cohort B and B2: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)

Database cutoff date for cHL (KN013 cohort 3: 28SEP2018, KN087: 21MAR2019, KN204: 16JAN2020)

Database cutoff date for Bladder (KN045: 26OCT2017, KN052: 26SEP2018)

Database cutoff date for Esophageal (KN590: 02JUL2020)

Database cutoff date for CRC (KN177: 19FEB2020)

Database cutoff date for TNBC (KN355: 11DEC2019)

Database cutoff date for Cervical (KN826: 03MAY2021, KN028 cohort B4: 20FEB2017, KN158 cohort E: 27JUN2019)

Source: [ISS: adam-adsl; adae]

Table 63. Exposure-Adjusted Adverse Event Summary by Bevacizumab use (Including Multiple Occurrences of Events) (APaT Population)

	Event Count and Rate (Events/100 person-years)[a]				
	KN826 Pembrolizumab + Chemotherapy w/ Bevacizumab	KN826 Pembrolizumab + Chemotherapy w/o Bevacizumab	KN826 Placebo + Chemotherapy w/ Bevacizumab	KN826 Placebo + Chemotherapy w/o Bevacizumab	Pembrolizumab Monotherapy Reference Safety Dataset[e]
Number of subjects exposed	196	111	193	116	6185
Total exposure[b] in person-years	230.72	91.39	191.67	73.69	4336.02
Total events (rate)					
adverse events	4410 (1911.41)	1850 (2024.19)	3862 (2014.97)	1766 (2396.57)	64173 (1480.00)
drug-related[c] adverse events	2576 (1116.51)	1085 (1187.16)	2165 (1129.57)	987 (1339.42)	20041 (462.20)
toxicity grade 3-5 adverse events	670 (290.40)	339 (370.92)	560 (292.18)	291 (394.91)	6478 (149.40)
toxicity grade 3-5 drug-related adverse events	444 (192.44)	216 (236.34)	342 (178.44)	163 (221.20)	1467 (33.83)
serious adverse events	227 (98.39)	113 (123.64)	180 (93.91)	86 (116.71)	4264 (98.34)
serious drug-related adverse events	106 (45.94)	45 (49.24)	76 (39.65)	30 (40.71)	971 (22.39)
adverse events leading to death	10 (4.33)	4 (4.38)	11 (5.74)	3 (4.07)	328 (7.56)
drug-related adverse events leading to death	1 (0.43)	1 (1.09)	3 (1.57)	1 (1.36)	39 (0.90)
adverse events resulting in drug discontinuation	118 (51.14)	33 (36.11)	79 (41.22)	25 (33.93)	904 (20.85)
drug-related adverse events resulting in drug discontinuation	96 (41.61)	26 (28.45)	70 (36.52)	17 (23.07)	481 (11.09)
serious adverse events resulting in drug discontinuation	47 (20.37)	11 (12.04)	32 (16.70)	6 (8.14)	635 (14.64)

	Event Count and Rate (Events/100 person-years)[a]				
	KN826 Pembrolizumab + Chemotherapy w/ Bevacizumab	KN826 Pembrolizumab + Chemotherapy w/o Bevacizumab	KN826 Placebo + Chemotherapy w/ Bevacizumab	KN826 Placebo + Chemotherapy w/o Bevacizumab	Pembrolizumab Monotherapy Reference Safety Dataset[e]
serious drug-related adverse events resulting in drug discontinuation	34 (14.74)	8 (8.75)	26 (13.57)	3 (4.07)	279 (6.43)

[a] Event rate per 100 person-years of exposure=event count *100/person-years of exposure.
[b] Drug exposure is defined as the time from the first dose date to the earlier of the last dose date + 30 or the database cut-off date.
[c] Determined by the investigator to be related to the drug.
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 preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
Grades are based on NCI CTCAE version 4.0.
[e] 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, KN012 cohort B and B2, KN013 cohort 3, KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN087, KN177, and KN204.
Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 03APR2020)
Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEP2018)
Database cutoff date for HNSCC (KN012 cohort B and B2: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)
Database cutoff date for cHL (KN013 cohort 3: 28SEP2018, KN087: 21MAR2019, KN204: 16JAN2020)
Database cutoff date for Bladder (KN045: 26OCT2017, KN052: 26SEP2018)
Database cutoff date for CRC (KN177: 19FEB2020)
Database cutoff date for Cervical (KN826: 03MAY2021)

Source: [ISS: adam-adsl; adae]

Table 64. Participants With Adverse Events by Decreasing Incidence (Incidence ≥ 10% in One or More Treatment Groups) (APaT Population)

	KN826 Pembrolizumab + Chemotherapy		KN826 Placebo + Chemotherapy		Pooled Safety Dataset for Pembrolizumab + Chemotherapy[f]		Cervical Safety Dataset for Pembrolizumab Monotherapy[d]		Pembrolizumab Monotherapy Reference Safety Dataset[e]	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	307		309		2,033		122		6,185	
with one or more adverse events	305	(99.3)	307	(99.4)	2,015	(99.1)	119	(97.5)	5,989	(96.8)
with no adverse events	2	(0.7)	2	(0.6)	18	(0.9)	3	(2.5)	196	(3.2)
Anaemia	188	(61.2)	165	(53.4)	1,053	(51.8)	36	(29.5)	872	(14.1)
Alopecia	173	(56.4)	179	(57.9)	449	(22.1)	1	(0.8)	98	(1.6)
Nausea	122	(39.7)	135	(43.7)	1,051	(51.7)	22	(18.0)	1,282	(20.7)
Diarrhoea	109	(35.5)	92	(29.8)	644	(31.7)	27	(22.1)	1,295	(20.9)
Fatigue	88	(28.7)	84	(27.2)	744	(36.6)	28	(23.0)	1,967	(31.8)
Constipation	87	(28.3)	102	(33.0)	692	(34.0)	21	(17.2)	1,032	(16.7)
Arthralgia	82	(26.7)	80	(25.9)	363	(17.9)	14	(11.5)	1,149	(18.6)
Neuropathy peripheral	81	(26.4)	79	(25.6)	221	(10.9)	0	(0.0)	123	(2.0)
Vomiting	81	(26.4)	84	(27.2)	560	(27.5)	24	(19.7)	784	(12.7)
Hypertension	74	(24.1)	71	(23.0)	120	(5.9)	2	(1.6)	318	(5.1)
Urinary tract infection	73	(23.8)	80	(25.9)	147	(7.2)	18	(14.8)	414	(6.7)
Neutropenia	72	(23.5)	60	(19.4)	663	(32.6)	1	(0.8)	62	(1.0)
Peripheral sensory neuropathy	71	(23.1)	79	(25.6)	166	(8.2)	0	(0.0)	71	(1.1)
Asthenia	63	(20.5)	66	(21.4)	379	(18.6)	21	(17.2)	692	(11.2)
Decreased appetite	61	(19.9)	52	(16.8)	611	(30.1)	25	(20.5)	1,181	(19.1)
Thrombocytopenia	61	(19.9)	62	(20.1)	401	(19.7)	3	(2.5)	100	(1.6)
Myalgia	57	(18.6)	59	(19.1)	151	(7.4)	6	(4.9)	446	(7.2)
Hypothyroidism	56	(18.2)	28	(9.1)	260	(12.8)	12	(9.8)	699	(11.3)
Neutrophil count decreased	56	(18.2)	48	(15.5)	374	(18.4)	0	(0.0)	42	(0.7)
Pyrexia	55	(17.9)	44	(14.2)	354	(17.4)	28	(23.0)	802	(13.0)
Abdominal pain	50	(16.3)	53	(17.2)	161	(7.9)	20	(16.4)	527	(8.5)
Platelet count decreased	49	(16.0)	41	(13.3)	250	(12.3)	1	(0.8)	76	(1.2)
Headache	48	(15.6)	57	(18.4)	290	(14.3)	13	(10.7)	747	(12.1)
Rash	47	(15.3)	35	(11.3)	363	(17.9)	12	(9.8)	936	(15.1)
Alanine aminotransferase increased	43	(14.0)	28	(9.1)	283	(13.9)	5	(4.1)	429	(6.9)
Proteinuria	41	(13.4)	27	(8.7)	32	(1.6)	8	(6.6)	60	(1.0)
Back pain	40	(13.0)	44	(14.2)	230	(11.3)	13	(10.7)	709	(11.5)
Cough	40	(13.0)	31	(10.0)	426	(21.0)	12	(9.8)	1,200	(19.4)
Leukopenia	40	(13.0)	33	(10.7)	229	(11.3)	2	(1.6)	46	(0.7)
Pruritus	38	(12.4)	26	(8.4)	283	(13.9)	10	(8.2)	1,111	(18.0)
White blood cell count decreased	37	(12.1)	22	(7.1)	314	(15.4)	0	(0.0)	58	(0.9)
Pain in extremity	36	(11.7)	25	(8.1)	161	(7.9)	7	(5.7)	421	(6.8)
Aspartate aminotransferase increased	34	(11.1)	22	(7.1)	269	(13.2)	7	(5.7)	422	(6.8)

Insomnia	33	(10.7)	26	(8.4)	206	(10.1)	6	(4.9)	447	(7.2)
Weight decreased	33	(10.7)	35	(11.3)	275	(13.5)	6	(4.9)	574	(9.3)
Epistaxis	31	(10.1)	42	(13.6)	112	(5.5)	2	(1.6)	86	(1.4)
Hypokalaemia	31	(10.1)	30	(9.7)	216	(10.6)	9	(7.4)	288	(4.7)
Vaginal haemorrhage	30	(9.8)	35	(11.3)	8	(0.4)	11	(9.0)	20	(0.3)
Blood creatinine increased	28	(9.1)	30	(9.7)	241	(11.9)	13	(10.7)	268	(4.3)
Oedema peripheral	26	(8.5)	27	(8.7)	251	(12.3)	18	(14.8)	539	(8.7)
Stomatitis	22	(7.2)	21	(6.8)	288	(14.2)	4	(3.3)	159	(2.6)
Dizziness	21	(6.8)	24	(7.8)	224	(11.0)	4	(3.3)	460	(7.4)
Mucosal inflammation	21	(6.8)	10	(3.2)	230	(11.3)	1	(0.8)	99	(1.6)
Dyspnoea	20	(6.5)	30	(9.7)	306	(15.1)	13	(10.7)	1,020	(16.5)
Pelvic pain	18	(5.9)	35	(11.3)	13	(0.6)	6	(4.9)	47	(0.8)
Pneumonia	7	(2.3)	15	(4.9)	218	(10.7)	1	(0.8)	451	(7.3)

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

[d] Includes all participants who received at least one dose of pembrolizumab in KN028 cohort B4 and KN158 cohort E.

[e] 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, KN012 cohort B and B2, KN013 cohort 3, KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN087, KN177, and KN204.

[f] Includes all subjects who received at least one dose of pembrolizumab combo therapy in KN021 cohort A/C/G, KN048, KN189, KN355, KN407, and KN590.

Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 03APR2020)

Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEP2018, KN021: 19AUG2019, KN189: 20MAY2019, KN407: 09MAY2019)

Database cutoff date for HNSCC (KN012 cohort B and B2: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)

Database cutoff date for cHL (KN013 cohort 3: 28SEP2018, KN087: 21MAR2019, KN204: 16JAN2020)

Database cutoff date for Bladder (KN045: 26OCT2017, KN052: 26SEP2018)

Database cutoff date for Esophageal (KN590: 02JUL2020)

Database cutoff date for CRC (KN177: 19FEB2020)

Database cutoff date for TNBC (KN355: 11DEC2019)

Database cutoff date for Cervical (KN826: 03MAY2021, KN028 cohort B4: 20FEB2017, KN158 cohort E: 27JUN2019)

Table 65. Participants with Adverse Events by System Organ Class and Preferred Term (Incidence >0% in One or More Treatment Groups (APaT Population)

	KN826 Pembrolizumab + Chemotherapy		KN826 Placebo + Chemotherapy		Pooled Safety Dataset for Pembrolizumab + Chemotherapy[f]		Cervical Safety Dataset for Pembrolizumab Monotherapy[d]		Pembrolizumab Monotherapy Reference Safety Dataset[e]	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	307		309		2,033		122		6,185	
with one or more adverse events	305	(99.3)	307	(99.4)	2,015	(99.1)	119	(97.5)	5,989	(96.8)
with no adverse events	2	(0.7)	2	(0.6)	18	(0.9)	3	(2.5)	196	(3.2)
Blood and lymphatic system disorders	**222**	**(72.3)**	**207**	**(67.0)**	**1,373**	**(67.5)**	**45**	**(36.9)**	**1,183**	**(19.1)**
Anaemia	188	(61.2)	165	(53.4)	1,053	(51.8)	36	(29.5)	872	(14.1)
Anaemia macrocytic	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)	1	(0.0)
Anaemia of chronic disease	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)	2	(0.0)
Anaemia of malignant disease	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	4	(0.1)
Autoimmune haemolytic anaemia	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)	1	(0.0)
Bicytopenia	1	(0.3)	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Blood loss anaemia	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Bone marrow failure	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)	0	(0.0)
Bone marrow oedema	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	3	(0.0)
Coagulopathy	0	(0.0)	0	(0.0)	3	(0.1)	0	(0.0)	2	(0.0)
Disseminated intravascular coagulation	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	4	(0.1)
Eosinopenia	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Eosinophilia	12	(3.9)	0	(0.0)	4	(0.2)	0	(0.0)	40	(0.6)
Febrile neutropenia	24	(7.8)	14	(4.5)	94	(4.6)	0	(0.0)	10	(0.2)
Haemolytic anaemia	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Haemorrhagic diathesis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Hypercoagulation	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)	4	(0.1)
Hypochromic anaemia	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Hypofibrinogenaemia	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)	0	(0.0)

	KN826 Pembrolizumab + Chemotherapy		KN826 Placebo + Chemotherapy		Pooled Safety Dataset for Pembrolizumab + Chemotherapy[f]		Cervical Safety Dataset for Pembrolizumab Monotherapy[d]		Pembrolizumab Monotherapy Reference Safety Dataset[e]	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Blood and lymphatic system disorders	**222**	**(72.3)**	**207**	**(67.0)**	**1,373**	**(67.5)**	**45**	**(36.9)**	**1,183**	**(19.1)**
Immune thrombocytopenia	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	6	(0.1)
Increased tendency to bruise	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)	3	(0.0)
Iron deficiency anaemia	0	(0.0)	0	(0.0)	4	(0.2)	1	(0.8)	10	(0.2)
Leukaemoid reaction	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Leukocytosis	2	(0.7)	4	(1.3)	18	(0.9)	4	(3.3)	55	(0.9)
Leukopenia	40	(13.0)	33	(10.7)	229	(11.3)	2	(1.6)	46	(0.7)
Lymph node pain	0	(0.0)	1	(0.3)	6	(0.3)	1	(0.8)	23	(0.4)
Lymphadenitis	1	(0.3)	0	(0.0)	3	(0.1)	0	(0.0)	5	(0.1)
Lymphadenopathy	0	(0.0)	1	(0.3)	8	(0.4)	1	(0.8)	22	(0.4)
Lymphadenopathy mediastinal	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Lymphatic obstruction	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)	1	(0.0)
Lymphocytosis	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Lymphoid tissue hyperplasia	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Lymphopenia	13	(4.2)	6	(1.9)	55	(2.7)	1	(0.8)	73	(1.2)
Macrocytosis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Microcytic anaemia	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)	3	(0.0)
Monocytopenia	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)	1	(0.0)
Myelosuppression	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)	0	(0.0)
Neutropenia	72	(23.5)	60	(19.4)	663	(32.6)	1	(0.8)	62	(1.0)
Neutrophilia	1	(0.3)	2	(0.6)	6	(0.3)	0	(0.0)	9	(0.1)
Normocytic anaemia	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)	1	(0.0)
Pancytopenia	3	(1.0)	4	(1.3)	14	(0.7)	0	(0.0)	3	(0.0)
Pernicious anaemia	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)

	KN826 Pembrolizumab + Chemotherapy		KN826 Placebo + Chemotherapy		Pooled Safety Dataset for Pembrolizumab + Chemotherapy[f]		Cervical Safety Dataset for Pembrolizumab Monotherapy[d]		Pembrolizumab Monotherapy Reference Safety Dataset[e]	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Cardiac disorders	**26**	**(8.5)**	**27**	**(8.7)**	**210**	**(10.3)**	**9**	**(7.4)**	**505**	**(8.2)**
Tachycardia	5	(1.6)	10	(3.2)	37	(1.8)	6	(4.9)	92	(1.5)
Ventricular arrhythmia	0	(0.0)	0	(0.0)	2	(0.1)	0	(0.0)	0	(0.0)
Ventricular extrasystoles	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)	4	(0.1)
Ventricular fibrillation	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Ventricular tachycardia	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Wolff-Parkinson-White syndrome	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Congenital, familial and genetic disorders	**0**	**(0.0)**	**0**	**(0.0)**	**6**	**(0.3)**	**0**	**(0.0)**	**11**	**(0.2)**
Accessory spleen	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Hepato-lenticular degeneration	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)	0	(0.0)
Ichthyosis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Naevus flammeus	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Peutz-Jeghers syndrome	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Phimosis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Preauricular cyst	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Pseudohypoparathyroidism	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)	0	(0.0)
Pyloric stenosis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Syndactyly	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Tracheo-oesophageal fistula	0	(0.0)	0	(0.0)	3	(0.1)	0	(0.0)	2	(0.0)
Type V hyperlipidaemia	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)	0	(0.0)
Ear and labyrinth disorders	**17**	**(5.5)**	**12**	**(3.9)**	**206**	**(10.1)**	**2**	**(1.6)**	**299**	**(4.8)**
Auricular swelling	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)

	KN826 Pembrolizumab + Chemotherapy		KN826 Placebo + Chemotherapy		Pooled Safety Dataset for Pembrolizumab + Chemotherapy[f]		Cervical Safety Dataset for Pembrolizumab Monotherapy[d]		Pembrolizumab Monotherapy Reference Safety Dataset[e]	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Ear and labyrinth disorders	**17**	**(5.5)**	**12**	**(3.9)**	**206**	**(10.1)**	**2**	**(1.6)**	**299**	**(4.8)**
Paraesthesia ear	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Presbyacusis	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)	0	(0.0)
Tinnitus	7	(2.3)	5	(1.6)	74	(3.6)	0	(0.0)	57	(0.9)
Tympanic membrane perforation	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Vertigo	6	(2.0)	3	(1.0)	60	(3.0)	1	(0.8)	95	(1.5)
Vertigo positional	0	(0.0)	0	(0.0)	3	(0.1)	0	(0.0)	8	(0.1)
Vestibular disorder	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)	4	(0.1)
Endocrine disorders	**79**	**(25.7)**	**39**	**(12.6)**	**359**	**(17.7)**	**17**	**(13.9)**	**949**	**(15.3)**
Addison's disease	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)	2	(0.0)
Adrenal disorder	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)	0	(0.0)
Adrenal haemorrhage	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Adrenal insufficiency	4	(1.3)	0	(0.0)	15	(0.7)	0	(0.0)	47	(0.8)
Adrenocortical insufficiency acute	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Autoimmune thyroiditis	1	(0.3)	0	(0.0)	3	(0.1)	0	(0.0)	16	(0.3)
Basedow's disease	1	(0.3)	0	(0.0)	1	(0.0)	0	(0.0)	0	(0.0)
Cushing's syndrome	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)	1	(0.0)
Cushingoid	0	(0.0)	0	(0.0)	7	(0.3)	0	(0.0)	5	(0.1)
Diabetes insipidus	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Endocrine disorder	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Euthyroid sick syndrome	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)	3	(0.0)
Glucocorticoid deficiency	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	3	(0.0)
Goitre	1	(0.3)	1	(0.3)	2	(0.1)	0	(0.0)	3	(0.0)

	KN826 Pembrolizumab + Chemotherapy		KN826 Placebo + Chemotherapy		Pooled Safety Dataset for Pembrolizumab + Chemotherapy[f]		Cervical Safety Dataset for Pembrolizumab Monotherapy[d]		Pembrolizumab Monotherapy Reference Safety Dataset[e]	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Eye disorders	**23**	**(7.5)**	**23**	**(7.4)**	**333**	**(16.4)**	**7**	**(5.7)**	**663**	**(10.7)**
Abnormal sensation in eye	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Accommodation disorder	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Age-related macular degeneration	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)	2	(0.0)
Altered visual depth perception	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Amaurosis	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)	1	(0.0)
Angle closure glaucoma	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)	2	(0.0)
Anterior chamber inflammation	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)	0	(0.0)
Asthenopia	1	(0.3)	0	(0.0)	1	(0.0)	0	(0.0)	2	(0.0)
Blepharitis	0	(0.0)	0	(0.0)	7	(0.3)	0	(0.0)	8	(0.1)
Blepharospasm	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)	2	(0.0)
Blindness	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0)	3	(0.0)
Blindness unilateral	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Cataract	1	(0.3)	1	(0.3)	15	(0.7)	0	(0.0)	46	(0.7)
Chalazion	0	(0.0)	1	(0.3)	1	(0.0)	0	(0.0)	5	(0.1)
Choroidal neovascularisation	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Ciliary muscle spasm	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Conjunctival deposit	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)	0	(0.0)
Conjunctival haemorrhage	0	(0.0)	1	(0.3)	9	(0.4)	0	(0.0)	12	(0.2)
Conjunctival hyperaemia	0	(0.0)	0	(0.0)	3	(0.1)	0	(0.0)	8	(0.1)
Conjunctival irritation	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)	0	(0.0)
Conjunctival oedema	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Conjunctivalisation	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)	0	(0.0)
Conjunctivitis allergic	0	(0.0)	0	(0.0)	3	(0.1)	0	(0.0)	9	(0.1)

	KN826 Pembrolizumab + Chemotherapy		KN826 Placebo + Chemotherapy		Pooled Safety Dataset for Pembrolizumab + Chemotherapy[f]		Cervical Safety Dataset for Pembrolizumab Monotherapy[d]		Pembrolizumab Monotherapy Reference Safety Dataset[e]	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Gastrointestinal disorders	**241**	**(78.5)**	**236**	**(76.4)**	**1,641**	**(80.7)**	**76**	**(62.3)**	**3,565**	**(57.6)**
Change of bowel habit	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Chapped lips	0	(0.0)	0	(0.0)	1	(0.0)	1	(0.8)	1	(0.0)
Cheilitis	1	(0.3)	0	(0.0)	7	(0.3)	0	(0.0)	10	(0.2)
Chronic gastritis	0	(0.0)	1	(0.3)	2	(0.1)	0	(0.0)	4	(0.1)
Coating in mouth	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Colitis	12	(3.9)	3	(1.0)	44	(2.2)	3	(2.5)	105	(1.7)
Colitis microscopic	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)	4	(0.1)
Colonic fistula	0	(0.0)	0	(0.0)	0	(0.0)	2	(1.6)	1	(0.0)
Constipation	87	(28.3)	102	(33.0)	692	(34.0)	21	(17.2)	1,032	(16.7)
Defaecation urgency	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)	3	(0.0)
Dental caries	4	(1.3)	0	(0.0)	10	(0.5)	0	(0.0)	25	(0.4)
Dental discomfort	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)	1	(0.0)
Diaphragmatic hernia	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)	0	(0.0)
Diarrhoea	109	(35.5)	92	(29.8)	644	(31.7)	27	(22.1)	1,295	(20.9)
Diarrhoea haemorrhagic	0	(0.0)	0	(0.0)	2	(0.1)	0	(0.0)	2	(0.0)
Diverticular perforation	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)	0	(0.0)
Diverticulum	0	(0.0)	0	(0.0)	2	(0.1)	0	(0.0)	7	(0.1)
Diverticulum gastric	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Diverticulum intestinal	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Diverticulum intestinal haemorrhagic	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)	0	(0.0)
Dry mouth	5	(1.6)	8	(2.6)	91	(4.5)	3	(2.5)	304	(4.9)
Dumping syndrome	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)	0	(0.0)
Duodenal obstruction	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)

	KN826 Pembrolizumab + Chemotherapy		KN826 Placebo + Chemotherapy		Pooled Safety Dataset for Pembrolizumab + Chemotherapy[f]		Cervical Safety Dataset for Pembrolizumab Monotherapy[d]		Pembrolizumab Monotherapy Reference Safety Dataset[e]	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
General disorders and administration site conditions	**192**	**(62.5)**	**189**	**(61.2)**	**1,498**	**(73.7)**	**80**	**(65.6)**	**3,760**	**(60.8)**
Vascular device occlusion	1	(0.3)	0	(0.0)	3	(0.1)	0	(0.0)	0	(0.0)
Vessel puncture site pain	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Withdrawal syndrome	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.8)	0	(0.0)
Xerosis	0	(0.0)	1	(0.3)	7	(0.3)	1	(0.8)	29	(0.5)
Hepatobiliary disorders	**19**	**(6.2)**	**15**	**(4.9)**	**84**	**(4.1)**	**7**	**(5.7)**	**205**	**(3.3)**
Acute hepatic failure	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Alcoholic liver disease	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Autoimmune hepatitis	1	(0.3)	0	(0.0)	12	(0.6)	0	(0.0)	26	(0.4)
Bile duct stenosis	0	(0.0)	1	(0.3)	0	(0.0)	1	(0.8)	1	(0.0)
Bile duct stone	0	(0.0)	0	(0.0)	2	(0.1)	0	(0.0)	3	(0.0)
Biliary colic	1	(0.3)	1	(0.3)	0	(0.0)	0	(0.0)	2	(0.0)
Biliary dilatation	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Biliary obstruction	0	(0.0)	1	(0.3)	1	(0.0)	0	(0.0)	3	(0.0)
Cholangitis	0	(0.0)	0	(0.0)	2	(0.1)	0	(0.0)	5	(0.1)
Cholangitis sclerosing	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)	0	(0.0)
Cholecystitis	0	(0.0)	0	(0.0)	2	(0.1)	0	(0.0)	10	(0.2)
Cholecystitis acute	0	(0.0)	1	(0.3)	1	(0.0)	1	(0.8)	2	(0.0)
Cholecystitis chronic	0	(0.0)	1	(0.3)	1	(0.0)	0	(0.0)	1	(0.0)
Cholelithiasis	1	(0.3)	1	(0.3)	5	(0.2)	0	(0.0)	6	(0.1)
Cholestasis	2	(0.7)	2	(0.6)	3	(0.1)	1	(0.8)	20	(0.3)
Drug-induced liver injury	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0)	7	(0.1)
Gallbladder enlargement	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

	KN826 Pembrolizumab + Chemotherapy		KN826 Placebo + Chemotherapy		Pooled Safety Dataset for Pembrolizumab + Chemotherapy[f]		Cervical Safety Dataset for Pembrolizumab Monotherapy[d]		Pembrolizumab Monotherapy Reference Safety Dataset[e]	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Immune system disorders	**27**	**(8.8)**	**31**	**(10.0)**	**69**	**(3.4)**	**1**	**(0.8)**	**180**	**(2.9)**
Food allergy	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)	2	(0.0)
Hypersensitivity	14	(4.6)	16	(5.2)	22	(1.1)	1	(0.8)	51	(0.8)
Hypogammaglobulinaemia	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Immune system disorder	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Iodine allergy	1	(0.3)	2	(0.6)	0	(0.0)	0	(0.0)	1	(0.0)
Sarcoidosis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	10	(0.2)
Seasonal allergy	1	(0.3)	0	(0.0)	18	(0.9)	0	(0.0)	35	(0.6)
Serum sickness	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Type III immune complex mediated reaction	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)	0	(0.0)
Infections and infestations	**166**	**(54.1)**	**176**	**(57.0)**	**1,092**	**(53.7)**	**41**	**(33.6)**	**2,769**	**(44.8)**
Abdominal abscess	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Abdominal infection	1	(0.3)	0	(0.0)	2	(0.1)	0	(0.0)	0	(0.0)
Abdominal sepsis	0	(0.0)	1	(0.3)	1	(0.0)	0	(0.0)	1	(0.0)
Abdominal wall abscess	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Abscess	1	(0.3)	0	(0.0)	3	(0.1)	0	(0.0)	4	(0.1)
Abscess jaw	1	(0.3)	0	(0.0)	1	(0.0)	0	(0.0)	0	(0.0)
Abscess limb	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Abscess neck	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	4	(0.1)
Abscess oral	1	(0.3)	0	(0.0)	1	(0.0)	0	(0.0)	1	(0.0)
Acarodermatitis	0	(0.0)	1	(0.3)	2	(0.1)	0	(0.0)	4	(0.1)
Acinetobacter infection	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)	1	(0.0)
Acne pustular	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)	0	(0.0)

	KN826 Pembrolizumab + Chemotherapy		KN826 Placebo + Chemotherapy		Pooled Safety Dataset for Pembrolizumab + Chemotherapy[f]		Cervical Safety Dataset for Pembrolizumab Monotherapy[d]		Pembrolizumab Monotherapy Reference Safety Dataset[e]	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Injury, poisoning and procedural complications	**69**	**(22.5)**	**58**	**(18.8)**	**270**	**(13.3)**	**13**	**(10.7)**	**778**	**(12.6)**
Back injury	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)	1	(0.0)
Bone contusion	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Brain herniation	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Burn oesophageal	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)	0	(0.0)
Burn oral cavity	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)	0	(0.0)
Burns second degree	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Cervical vertebral fracture	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Chest injury	0	(0.0)	1	(0.3)	2	(0.1)	0	(0.0)	3	(0.0)
Chillblains	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Clavicle fracture	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)	6	(0.1)
Concussion	0	(0.0)	0	(0.0)	2	(0.1)	0	(0.0)	1	(0.0)
Contrast media toxicity	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Contusion	3	(1.0)	5	(1.6)	31	(1.5)	0	(0.0)	63	(1.0)
Corneal abrasion	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0)	1	(0.0)
Craniocerebral injury	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)	0	(0.0)
Cystitis radiation	3	(1.0)	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Dental restoration failure	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Dislocation of vertebra	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)	0	(0.0)
Ear canal abrasion	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Epicondylitis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Eschar	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	3	(0.0)
Eye contusion	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)	2	(0.0)
Eye injury	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)

	KN826 Pembrolizumab + Chemotherapy		KN826 Placebo + Chemotherapy		Pooled Safety Dataset for Pembrolizumab + Chemotherapy[f]		Cervical Safety Dataset for Pembrolizumab Monotherapy[d]		Pembrolizumab Monotherapy Reference Safety Dataset[e]	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Investigations	**180**	**(58.6)**	**165**	**(53.4)**	**1,170**	**(57.6)**	**36**	**(29.5)**	**2,090**	**(33.8)**
Aortic bruit	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Aspartate aminotransferase	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Aspartate aminotransferase increased	34	(11.1)	22	(7.1)	269	(13.2)	7	(5.7)	422	(6.8)
Autoantibody positive	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Bacterial test positive	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	4	(0.1)
Band neutrophil count decreased	0	(0.0)	0	(0.0)	2	(0.1)	0	(0.0)	0	(0.0)
Band neutrophil count increased	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Base excess increased	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)	0	(0.0)
Basophil count decreased	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)	0	(0.0)
Basophil percentage increased	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)	0	(0.0)
Bilirubin conjugated increased	0	(0.0)	0	(0.0)	6	(0.3)	0	(0.0)	17	(0.3)
Bilirubin urine present	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Biopsy skin	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Blood 25-hydroxycholecalciferol decreased	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Blood acid phosphatase increased	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Blood albumin decreased	1	(0.3)	2	(0.6)	17	(0.8)	0	(0.0)	25	(0.4)
Blood albumin increased	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	3	(0.0)
Blood alkaline phosphatase	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Blood alkaline phosphatase decreased	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Blood alkaline phosphatase increased	27	(8.8)	18	(5.8)	104	(5.1)	12	(9.8)	266	(4.3)
Blood bicarbonate decreased	0	(0.0)	0	(0.0)	3	(0.1)	0	(0.0)	5	(0.1)
Blood bicarbonate increased	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)	11	(0.2)
Blood bilirubin	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)

	KN826 Pembrolizumab + Chemotherapy		KN826 Placebo + Chemotherapy		Pooled Safety Dataset for Pembrolizumab + Chemotherapy[f]		Cervical Safety Dataset for Pembrolizumab Monotherapy[d]		Pembrolizumab Monotherapy Reference Safety Dataset[e]	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Metabolism and nutrition disorders	**135**	**(44.0)**	**124**	**(40.1)**	**1,073**	**(52.8)**	**51**	**(41.8)**	**2,347**	**(37.9)**
Food intolerance	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Glucose tolerance impaired	0	(0.0)	1	(0.3)	1	(0.0)	0	(0.0)	5	(0.1)
Gout	0	(0.0)	0	(0.0)	8	(0.4)	0	(0.0)	25	(0.4)
Hyperalbuminaemia	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	5	(0.1)
Hyperammonaemia	0	(0.0)	0	(0.0)	2	(0.1)	0	(0.0)	0	(0.0)
Hyperamylasaemia	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	4	(0.1)
Hypercalcaemia	8	(2.6)	7	(2.3)	46	(2.3)	10	(8.2)	185	(3.0)
Hyperchloraemia	2	(0.7)	1	(0.3)	4	(0.2)	0	(0.0)	1	(0.0)
Hypercholesterolaemia	3	(1.0)	3	(1.0)	7	(0.3)	0	(0.0)	31	(0.5)
Hypercreatininaemia	1	(0.3)	0	(0.0)	1	(0.0)	0	(0.0)	2	(0.0)
Hyperglycaemia	14	(4.6)	18	(5.8)	122	(6.0)	1	(0.8)	303	(4.9)
Hyperglycaemic hyperosmolar nonketotic syndrome	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)	0	(0.0)
Hyperkalaemia	14	(4.6)	12	(3.9)	82	(4.0)	1	(0.8)	158	(2.6)
Hyperlipasaemia	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0)	1	(0.0)
Hyperlipidaemia	4	(1.3)	1	(0.3)	5	(0.2)	0	(0.0)	10	(0.2)
Hypermagnesaemia	0	(0.0)	0	(0.0)	4	(0.2)	0	(0.0)	23	(0.4)
Hypernatraemia	0	(0.0)	4	(1.3)	13	(0.6)	0	(0.0)	18	(0.3)
Hyperphagia	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	3	(0.0)
Hyperphosphataemia	5	(1.6)	1	(0.3)	9	(0.4)	1	(0.8)	7	(0.1)
Hyperproteinaemia	2	(0.7)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Hypertriglyceridaemia	1	(0.3)	3	(1.0)	8	(0.4)	0	(0.0)	88	(1.4)
Hyperuricaemia	4	(1.3)	3	(1.0)	37	(1.8)	3	(2.5)	104	(1.7)
Hypervolaemia	0	(0.0)	0	(0.0)	2	(0.1)	0	(0.0)	1	(0.0)

	KN826 Pembrolizumab + Chemotherapy		KN826 Placebo + Chemotherapy		Pooled Safety Dataset for Pembrolizumab + Chemotherapy[f]		Cervical Safety Dataset for Pembrolizumab Monotherapy[d]		Pembrolizumab Monotherapy Reference Safety Dataset[e]	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Musculoskeletal and connective tissue disorders	**172**	**(56.0)**	**161**	**(52.1)**	**890**	**(43.8)**	**41**	**(33.6)**	**2,721**	**(44.0)**
Axillary mass	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Back disorder	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Back pain	40	(13.0)	44	(14.2)	230	(11.3)	13	(10.7)	709	(11.5)
Bone fistula	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Bone lesion	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Bone loss	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)	0	(0.0)
Bone pain	21	(6.8)	19	(6.1)	57	(2.8)	1	(0.8)	119	(1.9)
Bone swelling	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	3	(0.0)
Bursa disorder	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Bursitis	0	(0.0)	0	(0.0)	3	(0.1)	0	(0.0)	25	(0.4)
Cervical spinal stenosis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Chest wall haematoma	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)	0	(0.0)
Chest wall mass	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Chondrocalcinosis pyrophosphate	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)	1	(0.0)
Chondropathy	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)	0	(0.0)
Chondrosis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Clubbing	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Coccydynia	0	(0.0)	0	(0.0)	2	(0.1)	0	(0.0)	3	(0.0)
Connective tissue disorder	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)	2	(0.0)
Costochondritis	1	(0.3)	0	(0.0)	3	(0.1)	0	(0.0)	2	(0.0)
Crystal arthropathy	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0)	1	(0.0)
Dupuytren's contracture	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Enthesopathy	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

	KN826 Pembrolizumab + Chemotherapy		KN826 Placebo + Chemotherapy		Pooled Safety Dataset for Pembrolizumab + Chemotherapy[f]		Cervical Safety Dataset for Pembrolizumab Monotherapy[d]		Pembrolizumab Monotherapy Reference Safety Dataset[e]	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**6**	**(2.0)**	**7**	**(2.3)**	**109**	**(5.4)**	**4**	**(3.3)**	**581**	**(9.4)**
Acrochordon	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Adenocarcinoma	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Adenocarcinoma gastric	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Adenocarcinoma of colon	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)	0	(0.0)
Anogenital warts	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Appendix cancer	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Astrocytoma, low grade	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Basal cell carcinoma	0	(0.0)	0	(0.0)	3	(0.1)	0	(0.0)	48	(0.8)
Basosquamous carcinoma	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Benign lung neoplasm	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Benign lymph node neoplasm	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Benign neoplasm	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)	1	(0.0)
Benign neoplasm of skin	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Benign neoplasm of testis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Bladder cancer	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Bladder neoplasm	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Bladder papilloma	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)	0	(0.0)
Bladder transitional cell carcinoma	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Bone cancer metastatic	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Bowen's disease	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)	7	(0.1)
Breast cancer	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Cancer pain	3	(1.0)	3	(1.0)	29	(1.4)	2	(1.6)	71	(1.1)

	KN826 Pembrolizumab + Chemotherapy		KN826 Placebo + Chemotherapy		Pooled Safety Dataset for Pembrolizumab + Chemotherapy[f]		Cervical Safety Dataset for Pembrolizumab Monotherapy[d]		Pembrolizumab Monotherapy Reference Safety Dataset[e]	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Nervous system disorders	**210**	**(68.4)**	**203**	**(65.7)**	**1,075**	**(52.9)**	**35**	**(28.7)**	**1,995**	**(32.3)**
Ataxia	0	(0.0)	0	(0.0)	4	(0.2)	1	(0.8)	15	(0.2)
Auditory nerve disorder	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Autoimmune neuropathy	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Axonal neuropathy	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Balance disorder	2	(0.7)	1	(0.3)	8	(0.4)	1	(0.8)	31	(0.5)
Bell's palsy	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	6	(0.1)
Brachial plexopathy	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Brain oedema	0	(0.0)	0	(0.0)	7	(0.3)	0	(0.0)	12	(0.2)
Brain stem infarction	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)	0	(0.0)
Brown-Sequard syndrome	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Burning sensation	5	(1.6)	0	(0.0)	2	(0.1)	0	(0.0)	9	(0.1)
Carotid arteriosclerosis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	4	(0.1)
Carotid artery occlusion	0	(0.0)	0	(0.0)	2	(0.1)	0	(0.0)	0	(0.0)
Carotid artery perforation	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)	0	(0.0)
Carotid artery stenosis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	4	(0.1)
Carotid artery thrombosis	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)	1	(0.0)
Carpal tunnel syndrome	0	(0.0)	0	(0.0)	4	(0.2)	0	(0.0)	11	(0.2)
Cauda equina syndrome	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Central nervous system haemorrhage	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Central nervous system lesion	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Central nervous system necrosis	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)	0	(0.0)
Central nervous system vasculitis	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)	0	(0.0)
Cerebellar infarction	1	(0.3)	0	(0.0)	1	(0.0)	0	(0.0)	0	(0.0)

	KN826 Pembrolizumab + Chemotherapy		KN826 Placebo + Chemotherapy		Pooled Safety Dataset for Pembrolizumab + Chemotherapy[f]		Cervical Safety Dataset for Pembrolizumab Monotherapy[d]		Pembrolizumab Monotherapy Reference Safety Dataset[e]	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Psychiatric disorders	**52**	**(16.9)**	**46**	**(14.9)**	**397**	**(19.5)**	**14**	**(11.5)**	**1,043**	**(16.9)**
Abnormal dreams	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	3	(0.0)
Abulia	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Adjustment disorder	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0)	1	(0.0)
Adjustment disorder with depressed mood	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	4	(0.1)
Affect lability	1	(0.3)	1	(0.3)	0	(0.0)	0	(0.0)	3	(0.0)
Affective disorder	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.8)	3	(0.0)
Aggression	0	(0.0)	0	(0.0)	2	(0.1)	0	(0.0)	1	(0.0)
Agitation	2	(0.7)	0	(0.0)	11	(0.5)	1	(0.8)	35	(0.6)
Anhedonia	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	3	(0.0)
Anxiety	15	(4.9)	11	(3.6)	89	(4.4)	2	(1.6)	264	(4.3)
Anxiety disorder	0	(0.0)	0	(0.0)	3	(0.1)	0	(0.0)	5	(0.1)
Apathy	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)	2	(0.0)
Autoscopy	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)	0	(0.0)
Behaviour disorder	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)	0	(0.0)
Binge eating	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Bipolar disorder	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Bradyphrenia	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	4	(0.1)
Bruxism	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)	0	(0.0)
Bulimia nervosa	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Claustrophobia	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Completed suicide	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	3	(0.0)
Confusional state	1	(0.3)	2	(0.6)	25	(1.2)	1	(0.8)	104	(1.7)
Delirium	2	(0.7)	1	(0.3)	14	(0.7)	0	(0.0)	36	(0.6)

	KN826 Pembrolizumab + Chemotherapy		KN826 Placebo + Chemotherapy		Pooled Safety Dataset for Pembrolizumab + Chemotherapy[f]		Cervical Safety Dataset for Pembrolizumab Monotherapy[d]		Pembrolizumab Monotherapy Reference Safety Dataset[e]	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Psychiatric disorders	**52**	**(16.9)**	**46**	**(14.9)**	**397**	**(19.5)**	**14**	**(11.5)**	**1,043**	**(16.9)**
Substance-induced psychotic disorder	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Suicidal ideation	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)	7	(0.1)
Suicide attempt	0	(0.0)	0	(0.0)	2	(0.1)	0	(0.0)	1	(0.0)
Tension	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Thermophobia	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Trance	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Renal and urinary disorders	**114**	**(37.1)**	**115**	**(37.2)**	**325**	**(16.0)**	**25**	**(20.5)**	**728**	**(11.8)**
Acute kidney injury	19	(6.2)	14	(4.5)	86	(4.2)	4	(3.3)	122	(2.0)
Autoimmune nephritis	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)	3	(0.0)
Azotaemia	3	(1.0)	1	(0.3)	2	(0.1)	0	(0.0)	5	(0.1)
Bilirubinuria	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Bladder cyst	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Bladder discomfort	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Bladder diverticulum	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Bladder irritation	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)	0	(0.0)
Bladder neck obstruction	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Bladder obstruction	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)	0	(0.0)
Bladder pain	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)	3	(0.0)
Bladder prolapse	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)	1	(0.0)
Bladder spasm	3	(1.0)	6	(1.9)	1	(0.0)	1	(0.8)	6	(0.1)
Calculus bladder	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Calculus urinary	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0)	1	(0.0)

	KN826 Pembrolizumab + Chemotherapy		KN826 Placebo + Chemotherapy		Pooled Safety Dataset for Pembrolizumab + Chemotherapy[f]		Cervical Safety Dataset for Pembrolizumab Monotherapy[d]		Pembrolizumab Monotherapy Reference Safety Dataset[e]	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Reproductive system and breast disorders	**84**	**(27.4)**	**98**	**(31.7)**	**119**	**(5.9)**	**22**	**(18.0)**	**290**	**(4.7)**
Breast inflammation	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)	0	(0.0)
Breast mass	0	(0.0)	0	(0.0)	4	(0.2)	0	(0.0)	2	(0.0)
Breast oedema	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)	1	(0.0)
Breast pain	1	(0.3)	0	(0.0)	30	(1.5)	1	(0.8)	21	(0.3)
Breast swelling	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	6	(0.1)
Breast tenderness	0	(0.0)	1	(0.3)	3	(0.1)	0	(0.0)	1	(0.0)
Breast ulceration	0	(0.0)	0	(0.0)	2	(0.1)	0	(0.0)	0	(0.0)
Cervical discharge	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Cervical polyp	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)	0	(0.0)
Cervix disorder	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Cervix enlargement	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Cervix oedema	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Coital bleeding	0	(0.0)	2	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
Dysmenorrhoea	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)	3	(0.0)
Dyspareunia	0	(0.0)	1	(0.3)	1	(0.0)	0	(0.0)	1	(0.0)
Ejaculation disorder	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Endometrial hyperplasia	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Endometrial hypertrophy	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Endometriosis	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)	1	(0.0)
Erectile dysfunction	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)	24	(0.4)
Female genital tract fistula	11	(3.6)	18	(5.8)	0	(0.0)	1	(0.8)	1	(0.0)
Female reproductive tract disorder	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Galactorrhoea	2	(0.7)	0	(0.0)	0	(0.0)	0	(0.0)	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.

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

[d] Includes all participants who received at least one dose of pembrolizumab in KN028 cohort B4 and KN158 cohort E.

[e] 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, KN012 cohort B and B2, KN013 cohort 3, KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN087, KN177, and KN204.

[f] Includes all subjects who received at least one dose of pembrolizumab combo therapy in KN021 cohort A/C/G, KN048, KN189, KN355, KN407, and KN590.

Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 03APR2020)

Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEP2018, KN021: 19AUG2019, KN189: 20MAY2019, KN407: 09MAY2019)

Database cutoff date for HNSCC (KN012 cohort B and B2: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)

Database cutoff date for cHL (KN013 cohort 3: 28SEP2018, KN087: 21MAR2019, KN204: 16JAN2020)

Database cutoff date for Bladder (KN045: 26OCT2017, KN052: 26SEP2018)

Database cutoff date for Esophageal (KN590: 02JUL2020)

Database cutoff date for CRC (KN177: 19FEB2020)
Database cutoff date for TNBC (KN355: 11DEC2019)
Database cutoff date for Cervical (KN826: 03MAY2021, KN028 cohort B4: 20FEB2017, KN158 cohort E: 27JUN2019)

As requested, exposure adjusted AE tables were reported by period and the incidence of AEs in the first two intervals (0-3 months and 3-6 months) to take into account the time windows for chemotherapy administration. Results showed that the AE profiles of the treatment arms are in alignment with the overall findings and no new safety concerns are raised when the exposure is adjusted for chemotherapy duration. As expected, some AEs related to myelosuppression (such as anemia, leukopenia, neutropenia, and thrombocytopenia) were seen predominantly in the first 6 months as these are associated with the chemotherapy components of the combination treatment.

Table 66. Participants with Adverse Events by Decreasing Incidence by Bevacizumab use (Incidence ≥10% in One or More Treatment Groups) (APaT Population)

	KN826 Pembrolizumab + Chemotherapy w/ Bevacizumab		KN826 Pembrolizumab + Chemotherapy w/o Bevacizumab		KN826 Placebo + Chemotherapy w/ Bevacizumab		KN826 Placebo + Chemotherapy w/o Bevacizumab		Pembrolizumab Monotherapy Reference Safety Dataset[e]	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	196		111		193		116		6,185	
with one or more adverse events	196	(100.0)	109	(98.2)	193	(100.0)	114	(98.3)	5,989	(96.8)
with no adverse events	0	(0.0)	2	(1.8)	0	(0.0)	2	(1.7)	196	(3.2)
Alopecia	113	(57.7)	60	(54.1)	121	(62.7)	58	(50.0)	98	(1.6)
Anaemia	108	(55.1)	80	(72.1)	94	(48.7)	71	(61.2)	872	(14.1)
Nausea	81	(41.3)	41	(36.9)	80	(41.5)	55	(47.4)	1,282	(20.7)
Diarrhoea	76	(38.8)	33	(29.7)	66	(34.2)	26	(22.4)	1,295	(20.9)
Fatigue	69	(35.2)	19	(17.1)	56	(29.0)	28	(24.1)	1,967	(31.8)
Hypertension	68	(34.7)	6	(5.4)	65	(33.7)	6	(5.2)	318	(5.1)
Arthralgia	61	(31.1)	21	(18.9)	54	(28.0)	26	(22.4)	1,149	(18.6)
Constipation	61	(31.1)	26	(23.4)	70	(36.3)	32	(27.6)	1,032	(16.7)
Neuropathy peripheral	59	(30.1)	22	(19.8)	54	(28.0)	25	(21.6)	123	(2.0)
Vomiting	59	(30.1)	22	(19.8)	53	(27.5)	31	(26.7)	784	(12.7)
Urinary tract infection	52	(26.5)	21	(18.9)	51	(26.4)	29	(25.0)	414	(6.7)
Peripheral sensory neuropathy	46	(23.5)	25	(22.5)	51	(26.4)	28	(24.1)	71	(1.1)
Hypothyroidism	43	(21.9)	13	(11.7)	21	(10.9)	7	(6.0)	699	(11.3)
Neutropenia	42	(21.4)	30	(27.0)	38	(19.7)	22	(19.0)	62	(1.0)
Decreased appetite	41	(20.9)	20	(18.0)	33	(17.1)	19	(16.4)	1,181	(19.1)
Asthenia	40	(20.4)	23	(20.7)	39	(20.2)	27	(23.3)	692	(11.2)
Neutrophil count decreased	39	(19.9)	17	(15.3)	34	(17.6)	14	(12.1)	42	(0.7)
Proteinuria	39	(19.9)	2	(1.8)	25	(13.0)	2	(1.7)	60	(1.0)
Abdominal pain	38	(19.4)	12	(10.8)	37	(19.2)	16	(13.8)	527	(8.5)
Headache	37	(18.9)	11	(9.9)	44	(22.8)	13	(11.2)	747	(12.1)
Rash	36	(18.4)	11	(9.9)	29	(15.0)	6	(5.2)	936	(15.1)
Myalgia	35	(17.9)	22	(19.8)	35	(18.1)	24	(20.7)	446	(7.2)
Platelet count decreased	35	(17.9)	14	(12.6)	31	(16.1)	10	(8.6)	76	(1.2)
Pyrexia	35	(17.9)	20	(18.0)	26	(13.5)	18	(15.5)	802	(13.0)
Thrombocytopenia	33	(16.8)	28	(25.2)	33	(17.1)	29	(25.0)	100	(1.6)
Alanine aminotransferase increased	32	(16.3)	11	(9.9)	22	(11.4)	6	(5.2)	429	(6.9)
Cough	30	(15.3)	10	(9.0)	23	(11.9)	8	(6.9)	1,200	(19.4)
Back pain	27	(13.8)	13	(11.7)	28	(14.5)	16	(13.8)	709	(11.5)
Epistaxis	27	(13.8)	4	(3.6)	41	(21.2)	1	(0.9)	86	(1.4)
Pruritus	27	(13.8)	11	(9.9)	17	(8.8)	9	(7.8)	1,111	(18.0)
Aspartate aminotransferase increased	25	(12.8)	9	(8.1)	20	(10.4)	2	(1.7)	422	(6.8)
Insomnia	25	(12.8)	8	(7.2)	21	(10.9)	5	(4.3)	447	(7.2)
Pain in extremity	25	(12.8)	11	(9.9)	17	(8.8)	8	(6.9)	421	(6.8)
Weight decreased	25	(12.8)	8	(7.2)	23	(11.9)	12	(10.3)	574	(9.3)

	KN826 Pembrolizumab + Chemotherapy w/ Bevacizumab		KN826 Pembrolizumab + Chemotherapy w/o Bevacizumab		KN826 Placebo + Chemotherapy w/ Bevacizumab		KN826 Placebo + Chemotherapy w/o Bevacizumab		Pembrolizumab Monotherapy Reference Safety Dataset[e]	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
White blood cell count decreased	24	(12.2)	13	(11.7)	15	(7.8)	7	(6.0)	58	(0.9)
Abdominal pain upper	22	(11.2)	8	(7.2)	20	(10.4)	8	(6.9)	239	(3.9)
Leukopenia	22	(11.2)	18	(16.2)	19	(9.8)	14	(12.1)	46	(0.7)
Blood alkaline phosphatase increased	20	(10.2)	7	(6.3)	9	(4.7)	9	(7.8)	266	(4.3)
Paraesthesia	20	(10.2)	7	(6.3)	14	(7.3)	13	(11.2)	169	(2.7)
Vaginal haemorrhage	19	(9.7)	11	(9.9)	23	(11.9)	12	(10.3)	20	(0.3)
Hypokalaemia	18	(9.2)	13	(11.7)	16	(8.3)	14	(12.1)	288	(4.7)
Blood creatinine increased	17	(8.7)	11	(9.9)	23	(11.9)	7	(6.0)	268	(4.3)
Dyspnoea	14	(7.1)	6	(5.4)	22	(11.4)	8	(6.9)	1,020	(16.5)
Pelvic pain	14	(7.1)	4	(3.6)	25	(13.0)	10	(8.6)	47	(0.8)
Vaginal discharge	12	(6.1)	4	(3.6)	10	(5.2)	14	(12.1)	14	(0.2)

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

[e] 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, KN012 cohort B and B2, KN013 cohort 3, KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN087, KN177, and KN204.

Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 03APR2020)

Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEP2018)

Database cutoff date for HNSCC (KN012 cohort B and B2: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)

Database cutoff date for cHL (KN013 cohort 3: 28SEP2018, KN087: 21MAR2019, KN204: 16JAN2020)

Database cutoff date for Bladder (KN045: 26OCT2017, KN052: 26SEP2018)

Database cutoff date for CRC (KN177: 19FEB2020)

Database cutoff date for Cervical (KN826: 03MAY2021)

Source: [ISS: adam-adsl; adae]

Table 67. Exposure-Adjusted Adverse Event by Decreasing Incidence (including Multiple Occurrences of Events) APaT Population

	Event Count and Rate (Events/100 person-years)[a]				
	KN826 Pembrolizumab + Chemotherapy w/ Bevacizumab	KN826 Pembrolizumab + Chemotherapy w/o Bevacizumab	KN826 Placebo + Chemotherapy w/ Bevacizumab	KN826 Placebo + Chemotherapy w/o Bevacizumab	Pembrolizumab Monotherapy Reference Safety Dataset[c]
Number of subjects exposed	196	111	193	116	6185
Total exposure[b] in person-years	230.72	91.39	191.67	73.69	4336.02
Total events (rate)	4410 (1911.41)	1850 (2024.19)	3862 (2014.97)	1766 (2396.57)	64173 (1480.00)
Anaemia	156 (67.6)	116 (126.9)	140 (73.0)	114 (154.7)	1078 (24.9)
Nausea	156 (67.6)	100 (109.4)	163 (85.0)	121 (164.2)	1602 (36.9)
Diarrhoea	125 (54.2)	59 (64.6)	115 (60.0)	47 (63.8)	1971 (45.5)
Alopecia	113 (49.0)	60 (65.6)	122 (63.7)	58 (78.7)	102 (2.4)
Neutrophil count decreased	105 (45.5)	47 (51.4)	99 (51.7)	41 (55.6)	63 (1.5)
Fatigue	102 (44.2)	45 (49.2)	89 (46.4)	56 (76.0)	2453 (56.6)
Hypertension	101 (43.8)	6 (6.6)	84 (43.8)	7 (9.5)	456 (10.5)
Urinary tract infection	92 (39.9)	38 (41.6)	76 (39.7)	43 (58.4)	545 (12.6)
Arthralgia	91 (39.4)	34 (37.2)	90 (47.0)	36 (48.9)	1590 (36.7)
Constipation	90 (39.0)	44 (48.1)	100 (52.2)	43 (58.4)	1210 (27.9)
Neutropenia	89 (38.6)	57 (62.4)	70 (36.5)	47 (63.8)	98 (2.3)
Vomiting	87 (37.7)	40 (43.8)	94 (49.0)	47 (63.8)	1038 (23.9)
Asthenia	84 (36.4)	34 (37.2)	85 (44.3)	44 (59.7)	930 (21.4)
Neuropathy peripheral	77 (33.4)	29 (31.7)	63 (32.9)	32 (43.4)	142 (3.3)
Platelet count decreased	68 (29.5)	32 (35.0)	55 (28.7)	12 (16.3)	94 (2.2)
White blood cell count decreased	68 (29.5)	41 (44.9)	44 (23.0)	17 (23.1)	82 (1.9)

	Event Count and Rate (Events/100 person-years)[a]				
	KN826 Pembrolizumab + Chemotherapy w/ Bevacizumab	KN826 Pembrolizumab + Chemotherapy w/o Bevacizumab	KN826 Placebo + Chemotherapy w/ Bevacizumab	KN826 Placebo + Chemotherapy w/o Bevacizumab	Pembrolizumab Monotherapy Reference Safety Dataset[e]
Decreased appetite	65 (28.2)	28 (30.6)	49 (25.6)	25 (33.9)	1337 (30.8)
Myalgia	60 (26.0)	39 (42.7)	71 (37.0)	42 (57.0)	530 (12.2)
Peripheral sensory neuropathy	57 (24.7)	25 (27.4)	55 (28.7)	34 (46.1)	80 (1.8)
Proteinuria	55 (23.8)	3 (3.3)	31 (16.2)	3 (4.1)	72 (1.7)
Headache	53 (23.0)	17 (18.6)	77 (40.2)	15 (20.4)	993 (22.9)
Thrombocytopenia	53 (23.0)	43 (47.0)	55 (28.7)	47 (63.8)	126 (2.9)
Rash	52 (22.5)	14 (15.3)	39 (20.3)	6 (8.1)	1304 (30.1)
Pyrexia	49 (21.2)	32 (35.0)	34 (17.7)	23 (31.2)	1056 (24.4)
Alanine aminotransferase increased	47 (20.4)	14 (15.3)	29 (15.1)	7 (9.5)	520 (12.0)
Epistaxis	46 (19.9)	6 (6.6)	59 (30.8)	1 (1.4)	102 (2.4)
Hypothyroidism	46 (19.9)	14 (15.3)	25 (13.0)	7 (9.5)	772 (17.8)
Abdominal pain	45 (19.5)	17 (18.6)	49 (25.6)	24 (32.6)	646 (14.9)
Leukopenia	43 (18.6)	26 (28.4)	32 (16.7)	23 (31.2)	66 (1.5)
Pain in extremity	43 (18.6)	12 (13.1)	28 (14.6)	12 (16.3)	490 (11.3)
Aspartate aminotransferase increased	41 (17.8)	13 (14.2)	27 (14.1)	2 (2.7)	513 (11.8)
Pruritus	41 (17.8)	15 (16.4)	25 (13.0)	13 (17.6)	1489 (34.3)
Cough	36 (15.6)	12 (13.1)	29 (15.1)	8 (10.9)	1492 (34.4)
Back pain	32 (13.9)	17 (18.6)	35 (18.3)	19 (25.8)	805 (18.6)
Vaginal haemorrhage	30 (13.0)	12 (13.1)	29 (15.1)	16 (21.7)	21 (0.5)
Abdominal pain upper	29 (12.6)	15 (16.4)	28 (14.6)	10 (13.6)	263 (6.1)

	Event Count and Rate (Events/100 person-years)[a]				
	KN826 Pembrolizumab + Chemotherapy w/ Bevacizumab	KN826 Pembrolizumab + Chemotherapy w/o Bevacizumab	KN826 Placebo + Chemotherapy w/ Bevacizumab	KN826 Placebo + Chemotherapy w/o Bevacizumab	Pembrolizumab Monotherapy Reference Safety Dataset[e]
Paraesthesia	28 (12.1)	9 (9.8)	14 (7.3)	21 (28.5)	184 (4.2)
Blood creatinine increased	27 (11.7)	15 (16.4)	26 (13.6)	10 (13.6)	343 (7.9)
Hypokalaemia	27 (11.7)	18 (19.7)	18 (9.4)	16 (21.7)	394 (9.1)
Dysphonia	26 (11.3)	0 (0.0)	8 (4.2)	0 (0.0)	136 (3.1)
Insomnia	26 (11.3)	8 (8.8)	22 (11.5)	6 (8.1)	474 (10.9)
Mucosal inflammation	25 (10.8)	2 (2.2)	12 (6.3)	2 (2.7)	114 (2.6)
Weight decreased	25 (10.8)	8 (8.8)	23 (12.0)	13 (17.6)	623 (14.4)
Hypomagnesaemia	23 (10.0)	13 (14.2)	16 (8.3)	14 (19.0)	200 (4.6)
Stomatitis	23 (10.0)	3 (3.3)	21 (11.0)	6 (8.1)	180 (4.2)
Blood alkaline phosphatase increased	22 (9.5)	9 (9.8)	9 (4.7)	11 (14.9)	310 (7.1)
Rectal haemorrhage	21 (9.1)	7 (7.7)	11 (5.7)	8 (10.9)	43 (1.0)
Bone pain	20 (8.7)	3 (3.3)	20 (10.4)	3 (4.1)	131 (3.0)
Febrile neutropenia	20 (8.7)	9 (9.8)	13 (6.8)	2 (2.7)	10 (0.2)
Oedema peripheral	20 (8.7)	11 (12.0)	21 (11.0)	10 (13.6)	604 (13.9)
Dyspnoea	19 (8.2)	8 (8.8)	26 (13.6)	8 (10.9)	1185 (27.3)
Dysuria	19 (8.2)	5 (5.5)	18 (9.4)	10 (13.6)	108 (2.5)
Dyspepsia	17 (7.4)	3 (3.3)	15 (7.8)	1 (1.4)	190 (4.4)
Gingival bleeding	17 (7.4)	1 (1.1)	6 (3.1)	0 (0.0)	10 (0.2)
Haematuria	17 (7.4)	8 (8.8)	12 (6.3)	8 (10.9)	200 (4.6)
Hyperthyroidism	17 (7.4)	5 (5.5)	6 (3.1)	4 (5.4)	282 (6.5)
Infusion related reaction	17 (7.4)	9 (9.8)	14 (7.3)	4 (5.4)	73 (1.7)

	Event Count and Rate (Events/100 person-years)[a]				
	KN826 Pembrolizumab + Chemotherapy w/ Bevacizumab	KN826 Pembrolizumab + Chemotherapy w/o Bevacizumab	KN826 Placebo + Chemotherapy w/ Bevacizumab	KN826 Placebo + Chemotherapy w/o Bevacizumab	Pembrolizumab Monotherapy Reference Safety Dataset[e]
Gastritis	11 (4.8)	2 (2.2)	12 (6.3)	1 (1.4)	44 (1.0)
Sepsis	11 (4.8)	1 (1.1)	6 (3.1)	0 (0.0)	55 (1.3)
Lymphopenia	10 (4.3)	12 (13.1)	3 (1.6)	3 (4.1)	94 (2.2)
Urticaria	10 (4.3)	0 (0.0)	4 (2.1)	1 (1.4)	64 (1.5)
Dysgeusia	9 (3.9)	8 (8.8)	19 (9.9)	5 (6.8)	133 (3.1)
Fall	9 (3.9)	3 (3.3)	0 (0.0)	1 (1.4)	169 (3.9)
Female genital tract fistula	9 (3.9)	3 (3.3)	11 (5.7)	8 (10.9)	1 (0.0)
Hypoalbuminaemia	9 (3.9)	7 (7.7)	7 (3.7)	3 (4.1)	223 (5.1)
Proctalgia	9 (3.9)	2 (2.2)	5 (2.6)	3 (4.1)	16 (0.4)
Pain	8 (3.5)	0 (0.0)	3 (1.6)	2 (2.7)	197 (4.5)
Anal haemorrhage	7 (3.0)	0 (0.0)	9 (4.7)	1 (1.4)	7 (0.2)
Colitis	7 (3.0)	7 (7.7)	1 (0.5)	2 (2.7)	141 (3.3)
Cystitis	7 (3.0)	5 (5.5)	7 (3.7)	11 (14.9)	69 (1.6)
Dermatitis	7 (3.0)	0 (0.0)	4 (2.1)	2 (2.7)	70 (1.6)
Haemorrhoids	7 (3.0)	1 (1.1)	12 (6.3)	2 (2.7)	49 (1.1)
Hypoaesthesia	7 (3.0)	7 (7.7)	0 (0.0)	2 (2.7)	100 (2.3)
Hypocalcaemia	7 (3.0)	2 (2.2)	6 (3.1)	3 (4.1)	141 (3.3)
Malaise	7 (3.0)	5 (5.5)	4 (2.1)	0 (0.0)	142 (3.3)
Palpitations	7 (3.0)	4 (4.4)	7 (3.7)	1 (1.4)	58 (1.3)
Peripheral motor neuropathy	7 (3.0)	5 (5.5)	1 (0.5)	4 (5.4)	9 (0.2)
Pneumonia	7 (3.0)	1 (1.1)	13 (6.8)	3 (4.1)	523 (12.1)
Radiation proctitis	7 (3.0)	3 (3.3)	3 (1.6)	1 (1.4)	1 (0.0)
Thyroiditis	7 (3.0)	3 (3.3)	1 (0.5)	0 (0.0)	45 (1.0)

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

[b] Drug exposure is defined as the time from the first dose date to the earlier of the last dose date + 30 or the database cut-off date. 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 preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.

[e] 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, KN012 cohort B and B2, KN013 cohort 3, KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN087, KN177, and KN204.

Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 03APR2020)

Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEP2018)

Database cutoff date for HNSCC (KN012 cohort B and B2: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)

Database cutoff date for cHL (KN013 cohort 3: 28SEP2018, KN087: 21MAR2019, KN204: 16JAN2020)

Database cutoff date for Bladder (KN045: 26OCT2017, KN052: 26SEP2018)

Database cutoff date for CRC (KN177: 19FEB2020)

Database cutoff date for Cervical (KN826: 03MAY2021)

Drug-related AEs

Table 68. Participants with Drug-Related Adverse Events by Decreasing Incidence (Incidence ≥5% in One or More Treatment Groups) (APaT Population)

	KN826 Pembrolizumab + Chemotherapy		KN826 Placebo + Chemotherapy		Pooled Safety Dataset for Pembrolizumab + Chemotherapy[f]		Cervical Safety Dataset for Pembrolizumab Monotherapy[d]		Pembrolizumab Monotherapy Reference Safety Dataset[e]	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	307		309		2,033		122		6,185	
with one or more adverse events	298	(97.1)	300	(97.1)	1,948	(95.8)	82	(67.2)	4,366	(70.6)
with no adverse events	9	(2.9)	9	(2.9)	85	(4.2)	40	(32.8)	1,819	(29.4)
Alopecia	171	(55.7)	172	(55.7)	430	(21.2)	1	(0.8)	51	(0.8)
Anaemia	149	(48.5)	132	(42.7)	887	(43.6)	3	(2.5)	212	(3.4)
Nausea	104	(33.9)	120	(38.8)	914	(45.0)	7	(5.7)	561	(9.1)
Diarrhoea	76	(24.8)	58	(18.8)	431	(21.2)	10	(8.2)	681	(11.0)
Neuropathy peripheral	75	(24.4)	76	(24.6)	180	(8.9)	0	(0.0)	45	(0.7)
Fatigue	70	(22.8)	77	(24.9)	639	(31.4)	13	(10.7)	1,216	(19.7)
Peripheral sensory neuropathy	69	(22.5)	78	(25.2)	154	(7.6)	0	(0.0)	32	(0.5)
Neutropenia	68	(22.1)	57	(18.4)	641	(31.5)	1	(0.8)	35	(0.6)
Vomiting	63	(20.5)	66	(21.4)	430	(21.2)	7	(5.7)	208	(3.4)
Neutrophil count decreased	56	(18.2)	47	(15.2)	362	(17.8)	0	(0.0)	30	(0.5)
Thrombocytopenia	55	(17.9)	58	(18.8)	376	(18.5)	1	(0.8)	49	(0.8)
Hypertension	54	(17.6)	55	(17.8)	19	(0.9)	1	(0.8)	32	(0.5)
Arthralgia	53	(17.3)	57	(18.4)	141	(6.9)	7	(5.7)	490	(7.9)
Myalgia	53	(17.3)	53	(17.2)	107	(5.3)	4	(3.3)	236	(3.8)
Hypothyroidism	52	(16.9)	25	(8.1)	220	(10.8)	12	(9.8)	605	(9.8)
Asthenia	51	(16.6)	56	(18.1)	273	(13.4)	10	(8.2)	376	(6.1)
Constipation	49	(16.0)	49	(15.9)	272	(13.4)	4	(3.3)	160	(2.6)
Platelet count decreased	49	(16.0)	40	(12.9)	240	(11.8)	1	(0.8)	35	(0.6)
Decreased appetite	45	(14.7)	33	(10.7)	463	(22.8)	9	(7.4)	479	(7.7)
Leukopenia	38	(12.4)	31	(10.0)	220	(10.8)	0	(0.0)	29	(0.5)
Proteinuria	38	(12.4)	22	(7.1)	18	(0.9)	4	(3.3)	16	(0.3)
White blood cell count decreased	37	(12.1)	21	(6.8)	297	(14.6)	0	(0.0)	29	(0.5)
Rash	33	(10.7)	27	(8.7)	267	(13.1)	9	(7.4)	702	(11.4)
Alanine aminotransferase increased	31	(10.1)	23	(7.4)	219	(10.8)	1	(0.8)	254	(4.1)
Pruritus	29	(9.4)	17	(5.5)	202	(9.9)	8	(6.6)	871	(14.1)
Epistaxis	26	(8.5)	36	(11.7)	53	(2.6)	1	(0.8)	6	(0.1)
Paraesthesia	26	(8.5)	24	(7.8)	69	(3.4)	0	(0.0)	43	(0.7)
Aspartate aminotransferase increased	22	(7.2)	16	(5.2)	207	(10.2)	4	(3.3)	244	(3.9)
Febrile neutropenia	21	(6.8)	13	(4.2)	85	(4.2)	0	(0.0)	0	(0.0)
Mucosal inflammation	20	(6.5)	9	(2.9)	207	(10.2)	0	(0.0)	52	(0.8)
Stomatitis	20	(6.5)	15	(4.9)	256	(12.6)	2	(1.6)	80	(1.3)
Hyperthyroidism	19	(6.2)	7	(2.3)	92	(4.5)	9	(7.4)	231	(3.7)
Pain in extremity	17	(5.5)	11	(3.6)	49	(2.4)	2	(1.6)	73	(1.2)
Rash maculo-papular	17	(5.5)	8	(2.6)	73	(3.6)	3	(2.5)	166	(2.7)
Weight decreased	17	(5.5)	15	(4.9)	134	(6.6)	1	(0.8)	143	(2.3)
Blood creatinine increased	16	(5.2)	13	(4.2)	174	(8.6)	3	(2.5)	70	(1.1)
Infusion related reaction	16	(5.2)	13	(4.2)	24	(1.2)	3	(2.5)	61	(1.0)
Pyrexia	16	(5.2)	9	(2.9)	137	(6.7)	11	(9.0)	287	(4.6)
Urinary tract infection	16	(5.2)	12	(3.9)	23	(1.1)	1	(0.8)	14	(0.2)
Abdominal pain	15	(4.9)	19	(6.1)	45	(2.2)	6	(4.9)	123	(2.0)
Headache	15	(4.9)	19	(6.1)	75	(3.7)	4	(3.3)	199	(3.2)
Dysgeusia	12	(3.9)	19	(6.1)	158	(7.8)	1	(0.8)	63	(1.0)

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.
[d] Includes all participants who received at least one dose of pembrolizumab in KN028 cohort B4 and KN158 cohort E.
[e] 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, KN012 cohort B and B2, KN013 cohort 3, KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN087, KN177, and KN204.
[f] Includes all subjects who received at least one dose of pembrolizumab combo therapy in KN021 cohort A/C/G, KN048, KN189, KN355, KN407, and KN590.
Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 03APR2020)
Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEP2018, KN021: 19AUG2019, KN189: 20MAY2019, KN407: 09MAY2019)
Database cutoff date for HNSCC (KN012 cohort B and B2: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)
Database cutoff date for cHL (KN013 cohort 3: 28SEP2018, KN087: 21MAR2019, KN204: 16JAN2020)
Database cutoff date for Bladder (KN045: 26OCT2017, KN052: 26SEP2018)
Database cutoff date for Esophageal (KN590: 02JUL2020)
Database cutoff date for CRC (KN177: 19FEB2020)
Database cutoff date for TNBC (KN355: 11DEC2019)
Database cutoff date for Cervical (KN826: 03MAY2021, KN028 cohort B4: 20FEB2017, KN158 cohort E: 27JUN2019)

Source: [ISS: adam-adsl; adae]

Table 69. Participants With Drug-Related Adverse Events by Decreasing Incidence by Bevacizumab Use (Incidence ≥5% in One or More Treatment Groups) (APaT Population)

	KN826 Pembrolizumab + Chemotherapy w/ Bevacizumab		KN826 Pembrolizumab + Chemotherapy w/o Bevacizumab		KN826 Placebo + Chemotherapy w/ Bevacizumab		KN826 Placebo + Chemotherapy w/o Bevacizumab		Pembrolizumab Monotherapy Reference Safety Dataset[e]	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	196		111		193		116		6,185	
with one or more adverse events	191	(97.4)	107	(96.4)	190	(98.4)	110	(94.8)	4,366	(70.6)
with no adverse events	5	(2.6)	4	(3.6)	3	(1.6)	6	(5.2)	1,819	(29.4)
Alopecia	111	(56.6)	60	(54.1)	118	(61.1)	54	(46.6)	51	(0.8)
Anaemia	81	(41.3)	68	(61.3)	74	(38.3)	58	(50.0)	212	(3.4)
Nausea	66	(33.7)	38	(34.2)	72	(37.3)	48	(41.4)	561	(9.1)
Fatigue	54	(27.6)	16	(14.4)	50	(25.9)	27	(23.3)	1,216	(19.7)
Hypertension	54	(27.6)	0	(0.0)	54	(28.0)	1	(0.9)	32	(0.5)
Diarrhoea	53	(27.0)	23	(20.7)	38	(19.7)	20	(17.2)	681	(11.0)
Neuropathy peripheral	53	(27.0)	22	(19.8)	53	(27.5)	23	(19.8)	45	(0.7)
Peripheral sensory neuropathy	45	(23.0)	24	(21.6)	51	(26.4)	27	(23.3)	32	(0.5)
Vomiting	44	(22.4)	19	(17.1)	43	(22.3)	23	(19.8)	208	(3.4)
Hypothyroidism	41	(20.9)	11	(9.9)	19	(9.8)	6	(5.2)	605	(9.8)
Neutropenia	39	(19.9)	29	(26.1)	36	(18.7)	21	(18.1)	35	(0.6)
Neutrophil count decreased	39	(19.9)	17	(15.3)	33	(17.1)	14	(12.1)	30	(0.5)
Proteinuria	37	(18.9)	1	(0.9)	22	(11.4)	0	(0.0)	16	(0.3)
Arthralgia	36	(18.4)	17	(15.3)	35	(18.1)	22	(19.0)	490	(7.9)
Platelet count decreased	35	(17.9)	14	(12.6)	31	(16.1)	9	(7.8)	35	(0.6)
Asthenia	33	(16.8)	18	(16.2)	34	(17.6)	22	(19.0)	376	(6.1)
Constipation	33	(16.8)	16	(14.4)	34	(17.6)	15	(12.9)	160	(2.6)
Decreased appetite	32	(16.3)	13	(11.7)	20	(10.4)	13	(11.2)	479	(7.7)
Myalgia	32	(16.3)	21	(18.9)	30	(15.5)	23	(19.8)	236	(3.8)
Thrombocytopenia	29	(14.8)	26	(23.4)	31	(16.1)	27	(23.3)	49	(0.8)
Rash	26	(13.3)	7	(6.3)	22	(11.4)	5	(4.3)	702	(11.4)
Epistaxis	24	(12.2)	2	(1.8)	36	(18.7)	0	(0.0)	6	(0.1)
White blood cell count decreased	24	(12.2)	13	(11.7)	14	(7.3)	7	(6.0)	29	(0.5)
Alanine aminotransferase increased	21	(10.7)	10	(9.0)	19	(9.8)	4	(3.4)	254	(4.1)
Leukopenia	21	(10.7)	17	(15.3)	17	(8.8)	14	(12.1)	29	(0.5)
Paraesthesia	20	(10.2)	6	(5.4)	12	(6.2)	12	(10.3)	43	(0.7)
Pruritus	20	(10.2)	9	(8.1)	10	(5.2)	7	(6.0)	871	(14.1)
Mucosal inflammation	18	(9.2)	2	(1.8)	8	(4.1)	1	(0.9)	52	(0.8)
Stomatitis	17	(8.7)	3	(2.7)	10	(5.2)	5	(4.3)	80	(1.3)
Aspartate aminotransferase increased	14	(7.1)	8	(7.2)	15	(7.8)	1	(0.9)	244	(3.9)
Febrile neutropenia	14	(7.1)	7	(6.3)	11	(5.7)	2	(1.7)	0	(0.0)
Hyperthyroidism	14	(7.1)	5	(4.5)	4	(2.1)	3	(2.6)	231	(3.7)
Pain in extremity	14	(7.1)	3	(2.7)	8	(4.1)	3	(2.6)	73	(1.2)
Weight decreased	14	(7.1)	3	(2.7)	8	(4.1)	7	(6.0)	143	(2.3)

	KN826 Pembrolizumab + Chemotherapy w/ Bevacizumab		KN826 Pembrolizumab + Chemotherapy w/o Bevacizumab		KN826 Placebo + Chemotherapy w/ Bevacizumab		KN826 Placebo + Chemotherapy w/o Bevacizumab		Pembrolizumab Monotherapy Reference Safety Dataset[e]	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Dysphonia	13	(6.6)	0	(0.0)	4	(2.1)	0	(0.0)	17	(0.3)
Headache	13	(6.6)	2	(1.8)	17	(8.8)	2	(1.7)	199	(3.2)
Blood creatinine increased	12	(6.1)	4	(3.6)	11	(5.7)	2	(1.7)	70	(1.1)
Pyrexia	12	(6.1)	4	(3.6)	4	(2.1)	5	(4.3)	287	(4.6)
Urinary tract infection	12	(6.1)	4	(3.6)	9	(4.7)	3	(2.6)	14	(0.2)
Rash maculo-papular	11	(5.6)	6	(5.4)	6	(3.1)	2	(1.7)	166	(2.7)
Abdominal pain	10	(5.1)	5	(4.5)	13	(6.7)	6	(5.2)	123	(2.0)
Blood alkaline phosphatase increased	10	(5.1)	4	(3.6)	6	(3.1)	3	(2.6)	100	(1.6)
Bone pain	10	(5.1)	1	(0.9)	8	(4.1)	2	(1.7)	25	(0.4)
Hypomagnesaemia	9	(4.6)	6	(5.4)	3	(1.6)	6	(5.2)	32	(0.5)
Infusion related reaction	8	(4.1)	8	(7.2)	9	(4.7)	4	(3.4)	61	(1.0)
Hypersensitivity	7	(3.6)	4	(3.6)	10	(5.2)	2	(1.7)	16	(0.3)
Hypokalaemia	7	(3.6)	6	(5.4)	4	(2.1)	3	(2.6)	40	(0.6)
Dysgeusia	6	(3.1)	6	(5.4)	16	(8.3)	3	(2.6)	63	(1.0)
Vaginal haemorrhage	4	(2.0)	0	(0.0)	10	(5.2)	0	(0.0)	0	(0.0)
Drug hypersensitivity	3	(1.5)	6	(5.4)	8	(4.1)	3	(2.6)	6	(0.1)
Lymphopenia	3	(1.5)	6	(5.4)	3	(1.6)	3	(2.6)	33	(0.5)

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.

[e] 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, KN012 cohort B and B2, KN013 cohort 3, KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN087, KN177, and KN204.

Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 03APR2020)

Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEP2018)

Database cutoff date for HNSCC (KN012 cohort B and B2: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)

Database cutoff date for cHL (KN013 cohort 3: 28SEP2018, KN087: 21MAR2019, KN204: 16JAN2020)

Database cutoff date for Bladder (KN045: 26OCT2017, KN052: 26SEP2018)

Database cutoff date for CRC (KN177: 19FEB2020)

Database cutoff date for Cervical (KN826: 03MAY2021)

Source: [ISS: adam-adsl; adae]

Grade 3-5 AEs

Table 70. Participants with Grade 3-5 Adverse Events by Decreasing Incidence (Incidence ≥5% in One or More Treatment Groups) (APaT Population)

	KN826 Pembrolizumab + Chemotherapy		KN826 Placebo + Chemotherapy		Pooled Safety Dataset for Pembrolizumab + Chemotherapy[d]		Cervical Safety Dataset for Pembrolizumab Monotherapy[d]		Pembrolizumab Monotherapy Reference Safety Dataset[e]	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	307		309		2,033		122		6,185	
with one or more adverse events	251	(81.8)	232	(75.1)	1,583	(77.9)	65	(53.3)	2,984	(48.2)
with no adverse events	56	(18.2)	77	(24.9)	450	(22.1)	57	(46.7)	3,201	(51.8)
Anaemia	93	(30.3)	83	(26.9)	374	(18.4)	17	(13.9)	247	(4.0)
Neutrophil count decreased	40	(13.0)	26	(8.4)	254	(12.5)	0	(0.0)	9	(0.1)
Neutropenia	38	(12.4)	30	(9.7)	413	(20.3)	1	(0.8)	19	(0.3)
Hypertension	29	(9.4)	33	(10.7)	54	(2.7)	0	(0.0)	113	(1.8)
Urinary tract infection	27	(8.8)	25	(8.1)	19	(0.9)	5	(4.1)	74	(1.2)
Thrombocytopenia	23	(7.5)	14	(4.5)	157	(7.7)	0	(0.0)	21	(0.3)
Febrile neutropenia	22	(7.2)	14	(4.5)	93	(4.6)	0	(0.0)	10	(0.2)
Platelet count decreased	21	(6.8)	14	(4.5)	71	(3.5)	0	(0.0)	8	(0.1)
White blood cell count decreased	21	(6.8)	13	(4.2)	136	(6.7)	0	(0.0)	4	(0.1)
Fatigue	11	(3.6)	14	(4.5)	117	(5.8)	3	(2.5)	150	(2.4)

	KN826 Pembrolizumab + Chemotherapy		KN826 Placebo + Chemotherapy		Pooled Safety Dataset for Pembrolizumab + Chemotherapy[d]		Cervical Safety Dataset for Pembrolizumab Monotherapy[d]		Pembrolizumab Monotherapy Reference Safety Dataset[e]	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Pneumonia	2	(0.7)	9	(2.9)	138	(6.8)	0	(0.0)	255	(4.1)

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 preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.
Grades are based on NCI CTCAE version 4.0.
[d] Includes all participants who received at least one dose of pembrolizumab in KN028 cohort B4 and KN158 cohort E.
[e] 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, KN012 cohort B and B2, KN013 cohort 3, KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN087, KN177, and KN204.
[f] Includes all subjects who received at least one dose of pembrolizumab combo therapy in KN021 cohort A/C/G, KN048, KN189, KN355, KN407, and KN590.
Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 03APR2020)
Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEP2018, KN021: 19AUG2019, KN189: 20MAY2019, KN407: 09MAY2019)
Database cutoff date for HNSCC (KN012 cohort B and B2: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)
Database cutoff date for cHL (KN013 cohort 3: 28SEP2018, KN087: 21MAR2019, KN204: 16JAN2020)
Database cutoff date for Bladder (KN045: 26OCT2017, KN052: 26SEP2018)
Database cutoff date for Esophageal (KN590: 02JUL2020)
Database cutoff date for CRC (KN177: 19FEB2020)
Database cutoff date for TNBC (KN355: 11DEC2019)
Database cutoff date for Cervical (KN826: 03MAY2021, KN028 cohort B4: 20FEB2017, KN158 cohort E: 27JUN2019)

Source: [ISS: adam-adsl; adae]

Table 71. Participants with Grade 3-5 Drug-related Adverse Events by Decreasing Incidence (Incidence ≥5% in One or More Treatment Groups) (APaT Population)

	KN826 Pembrolizumab + Chemotherapy		KN826 Placebo + Chemotherapy		Pooled Safety Dataset for Pembrolizumab + Chemotherapy[f]		Cervical Safety Dataset for Pembrolizumab Monotherapy[d]		Pembrolizumab Monotherapy Reference Safety Dataset[e]	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	307		309		2,033		122		6,185	
with one or more adverse events	210	(68.4)	198	(64.1)	1,285	(63.2)	17	(13.9)	975	(15.8)
with no adverse events	97	(31.6)	111	(35.9)	748	(36.8)	105	(86.1)	5,210	(84.2)
Anaemia	76	(24.8)	65	(21.0)	307	(15.1)	1	(0.8)	32	(0.5)
Neutrophil count decreased	40	(13.0)	26	(8.4)	242	(11.9)	0	(0.0)	5	(0.1)
Neutropenia	37	(12.1)	29	(9.4)	403	(19.8)	1	(0.8)	12	(0.2)
Febrile neutropenia	21	(6.8)	13	(4.2)	85	(4.2)	0	(0.0)	0	(0.0)
Platelet count decreased	21	(6.8)	14	(4.5)	68	(3.3)	0	(0.0)	2	(0.0)
Thrombocytopenia	21	(6.8)	12	(3.9)	143	(7.0)	0	(0.0)	9	(0.1)
White blood cell count decreased	21	(6.8)	12	(3.9)	130	(6.4)	0	(0.0)	1	(0.0)

	KN826 Pembrolizumab + Chemotherapy		KN826 Placebo + Chemotherapy		Pooled Safety Dataset for Pembrolizumab + Chemotherapy[f]		Cervical Safety Dataset for Pembrolizumab Monotherapy[d]		Pembrolizumab Monotherapy Reference Safety Dataset[e]	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Hypertension	20	(6.5)	23	(7.4)	10	(0.5)	0	(0.0)	11	(0.2)

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.
Grades are based on NCI CTCAE version 4.0.
[d] Includes all participants who received at least one dose of pembrolizumab in KN028 cohort B4 and KN158 cohort E.
[e] 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, KN012 cohort B and B2, KN013 cohort 3, KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN087, KN177, and KN204.
[f] Includes all subjects who received at least one dose of pembrolizumab combo therapy in KN021 cohort A/C/G, KN048, KN189, KN355, KN407, and KN590.
Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 03APR2020)
Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEP2018, KN021: 19AUG2019, KN189: 20MAY2019, KN407: 09MAY2019)
Database cutoff date for HNSCC (KN012 cohort B and B2: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)
Database cutoff date for cHL (KN013 cohort 3: 28SEP2018, KN087: 21MAR2019, KN204: 16JAN2020)
Database cutoff date for Bladder (KN045: 26OCT2017, KN052: 26SEP2018)
Database cutoff date for Esophageal (KN590: 02JUL2020)
Database cutoff date for CRC (KN177: 19FEB2020)
Database cutoff date for TNBC (KN355: 11DEC2019)
Database cutoff date for Cervical (KN826: 03MAY2021, KN028 cohort B4: 20FEB2017, KN158 cohort E: 27JUN2019)

Source: [ISS: adam-adsl; adae]

Table 72. Participants with Grade 3-5 Adverse Events by Decreasing Incidence by Bevacizumab Use (Incidence ≥5% in One or More Treatment Groups) (APaT Population)

	KN826 Pembrolizumab + Chemotherapy w/ Bevacizumab		KN826 Pembrolizumab + Chemotherapy w/o Bevacizumab		KN826 Placebo + Chemotherapy w/ Bevacizumab		KN826 Placebo + Chemotherapy w/o Bevacizumab		Pembrolizumab Monotherapy Reference Safety Dataset[e]	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	196		111		193		116		6,185	
with one or more adverse events	164	(83.7)	87	(78.4)	144	(74.6)	88	(75.9)	2,984	(48.2)
with no adverse events	32	(16.3)	24	(21.6)	49	(25.4)	28	(24.1)	3,201	(51.8)
Anaemia	52	(26.5)	41	(36.9)	37	(19.2)	46	(39.7)	247	(4.0)
Neutrophil count decreased	29	(14.8)	11	(9.9)	20	(10.4)	6	(5.2)	9	(0.1)
Hypertension	26	(13.3)	3	(2.7)	29	(15.0)	4	(3.4)	113	(1.8)
Neutropenia	26	(13.3)	12	(10.8)	17	(8.8)	13	(11.2)	19	(0.3)
Urinary tract infection	20	(10.2)	7	(6.3)	16	(8.3)	9	(7.8)	74	(1.2)
Platelet count decreased	16	(8.2)	5	(4.5)	13	(6.7)	1	(0.9)	8	(0.1)
Febrile neutropenia	15	(7.7)	7	(6.3)	12	(6.2)	2	(1.7)	10	(0.2)
Thrombocytopenia	12	(6.1)	11	(9.9)	6	(3.1)	8	(6.9)	21	(0.3)
White blood cell count decreased	12	(6.1)	9	(8.1)	10	(5.2)	3	(2.6)	4	(0.1)
Sepsis	10	(5.1)	1	(0.9)	4	(2.1)	0	(0.0)	47	(0.8)
Acute kidney injury	7	(3.6)	6	(5.4)	4	(2.1)	5	(4.3)	56	(0.9)
Fatigue	5	(2.6)	6	(5.4)	7	(3.6)	7	(6.0)	150	(2.4)

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

Grades are based on NCI CTCAE version 4.0.

[e] 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, KN012 cohort B and B2, KN013 cohort 3, KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN087, KN177, and KN204.

Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 03APR2020)

Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEP2018)

Database cutoff date for HNSCC (KN012 cohort B and B2: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)

Database cutoff date for cHL (KN013 cohort 3: 28SEP2018, KN087: 21MAR2019, KN204: 16JAN2020)

Database cutoff date for Bladder (KN045: 26OCT2017, KN052: 26SEP2018)

Database cutoff date for CRC (KN177: 19FEB2020)

Database cutoff date for Cervical (KN826: 03MAY2021)

Source: [ISS: adam-adsl; adae]

Table 73. Participants with Grade 3-5 Drug-related Adverse Events by Decreasing Incidence by Bevacizumab Use (Incidence ≥5% in One or More Treatment Groups) (APaT Population)

	KN826 Pembrolizumab + Chemotherapy w/ Bevacizumab		KN826 Pembrolizumab + Chemotherapy w/o Bevacizumab		KN826 Placebo + Chemotherapy w/ Bevacizumab		KN826 Placebo + Chemotherapy w/o Bevacizumab		Pembrolizumab Monotherapy Reference Safety Dataset[e]	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	196		111		193		116		6,185	
with one or more adverse events	143	(73.0)	67	(60.4)	126	(65.3)	72	(62.1)	975	(15.8)
with no adverse events	53	(27.0)	44	(39.6)	67	(34.7)	44	(37.9)	5,210	(84.2)
Anaemia	40	(20.4)	36	(32.4)	28	(14.5)	37	(31.9)	32	(0.5)
Neutrophil count decreased	29	(14.8)	11	(9.9)	20	(10.4)	6	(5.2)	5	(0.1)
Neutropenia	25	(12.8)	12	(10.8)	16	(8.3)	13	(11.2)	12	(0.2)
Hypertension	20	(10.2)	0	(0.0)	22	(11.4)	1	(0.9)	11	(0.2)
Platelet count decreased	16	(8.2)	5	(4.5)	13	(6.7)	1	(0.9)	2	(0.0)
Febrile neutropenia	14	(7.1)	7	(6.3)	11	(5.7)	2	(1.7)	0	(0.0)
Thrombocytopenia	12	(6.1)	9	(8.1)	5	(2.6)	7	(6.0)	9	(0.1)
White blood cell count decreased	12	(6.1)	9	(8.1)	9	(4.7)	3	(2.6)	1	(0.0)
Fatigue	3	(1.5)	5	(4.5)	7	(3.6)	6	(5.2)	66	(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.

Grades are based on NCI CTCAE version 4.0.

[e] 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, KN012 cohort B and B2, KN013 cohort 3, KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN087, KN177, and KN204.

Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 03APR2020)

Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEP2018)

Database cutoff date for HNSCC (KN012 cohort B and B2: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)

Database cutoff date for cHL (KN013 cohort 3: 28SEP2018, KN087: 21MAR2019, KN204: 16JAN2020)

Database cutoff date for Bladder (KN045: 26OCT2017, KN052: 26SEP2018)

Database cutoff date for CRC (KN177: 19FEB2020)

Database cutoff date for Cervical (KN826: 03MAY2021)

Source: [ISS: adam-adsl; adae]

Serious adverse event/deaths/other significant events

SAEs

Table 74. Participants with Serious Adverse Events by Decreasing Incidence (Incidence ≥5% in One or More Treatment Groups) (APaT Population)

	KN826 Pembrolizumab + Chemotherapy		KN826 Placebo + Chemotherapy		Pooled Safety Dataset for Pembrolizumab + Chemotherapy[f]		Cervical Safety Dataset for Pembrolizumab Monotherapy[d]		Pembrolizumab Monotherapy Reference Safety Dataset[e]	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	307		309		2,033		122		6,185	
with one or more adverse events	153	(49.8)	131	(42.4)	962	(47.3)	52	(42.6)	2,371	(38.3)
with no adverse events	154	(50.2)	178	(57.6)	1,071	(52.7)	70	(57.4)	3,814	(61.7)
Febrile neutropenia	21	(6.8)	13	(4.2)	78	(3.8)	0	(0.0)	7	(0.1)
Urinary tract infection	16	(5.2)	18	(5.8)	10	(0.5)	4	(3.3)	59	(1.0)
Anaemia	14	(4.6)	12	(3.9)	52	(2.6)	7	(5.7)	61	(1.0)

	KN826 Pembrolizumab + Chemotherapy		KN826 Placebo + Chemotherapy		Pooled Safety Dataset for Pembrolizumab + Chemotherapy[f]		Cervical Safety Dataset for Pembrolizumab Monotherapy[d]		Pembrolizumab Monotherapy Reference Safety Dataset[e]	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Pneumonia	1	(0.3)	7	(2.3)	137	(6.7)	1	(0.8)	257	(4.2)

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 preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.
[d] Includes all participants who received at least one dose of pembrolizumab in KN028 cohort B4 and KN158 cohort E.
[e] 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, KN012 cohort B and B2, KN013 cohort 3, KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN087, KN177, and KN204.
[f] Includes all subjects who received at least one dose of pembrolizumab combo therapy in KN021 cohort A/C/G, KN048, KN189, KN355, KN407, and KN590.
Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 03APR2020)
Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEP2018, KN021: 19AUG2019, KN189: 20MAY2019, KN407: 09MAY2019)
Database cutoff date for HNSCC (KN012 cohort B and B2: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)
Database cutoff date for cHL (KN013 cohort 3: 28SEP2018, KN087: 21MAR2019, KN204: 16JAN2020)
Database cutoff date for Bladder (KN045: 26OCT2017, KN052: 26SEP2018)
Database cutoff date for Esophageal (KN590: 02JUL2020)
Database cutoff date for CRC (KN177: 19FEB2020)
Database cutoff date for TNBC (KN355: 11DEC2019)
Database cutoff date for Cervical (KN826: 03MAY2021, KN028 cohort B4: 20FEB2017, KN158 cohort E: 27JUN2019)

Source: [ISS: adam-adsl; adae]

Table 75. Participants with Serious Adverse Events by Decreasing Incidence by Bevacizumab Use (Incidence ≥5% in One or More Treatment Groups) (APaT Population)

	KN826 Pembrolizumab + Chemotherapy w/ Bevacizumab		KN826 Pembrolizumab + Chemotherapy w/o Bevacizumab		KN826 Placebo + Chemotherapy w/ Bevacizumab		KN826 Placebo + Chemotherapy w/o Bevacizumab		Pembrolizumab Monotherapy Reference Safety Dataset[e]	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	196		111		193		116		6,185	
with one or more adverse events	99	(50.5)	54	(48.6)	87	(45.1)	44	(37.9)	2,371	(38.3)
with no adverse events	97	(49.5)	57	(51.4)	106	(54.9)	72	(62.1)	3,814	(61.7)
Febrile neutropenia	14	(7.1)	7	(6.3)	11	(5.7)	2	(1.7)	7	(0.1)
Urinary tract infection	12	(6.1)	4	(3.6)	12	(6.2)	6	(5.2)	59	(1.0)
Anaemia	11	(5.6)	3	(2.7)	5	(2.6)	7	(6.0)	61	(1.0)
Acute kidney injury	4	(2.0)	6	(5.4)	3	(1.6)	2	(1.7)	55	(0.9)

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 preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.
[e] 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, KN012 cohort B and B2, KN013 cohort 3, KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN087, KN177, and KN204.
Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 03APR2020)
Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEP2018)
Database cutoff date for HNSCC (KN012 cohort B and B2: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)
Database cutoff date for cHL (KN013 cohort 3: 28SEP2018, KN087: 21MAR2019, KN204: 16JAN2020)
Database cutoff date for Bladder (KN045: 26OCT2017, KN052: 26SEP2018)
Database cutoff date for CRC (KN177: 19FEB2020)
Database cutoff date for Cervical (KN826: 03MAY2021)

Source: [ISS: adam-adsl; adae]

Deaths

Table 76. Participants with Adverse Events Resulting in Death by Decreasing Incidence (Incidence ≥0% in One or More Treatment Groups) (APaT Population)

	KN826 Pembrolizumab + Chemotherapy		KN826 Placebo + Chemotherapy		Pooled Safety Dataset for Pembrolizumab + Chemotherapy[f]		Cervical Safety Dataset for Pembrolizumab Monotherapy[d]		Pembrolizumab Monotherapy Reference Safety Dataset[e]	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	307		309		2,033		122		6,185	
with one or more adverse events	14	(4.6)	14	(4.5)	139	(6.8)	4	(3.3)	321	(5.2)
with no adverse events	293	(95.4)	295	(95.5)	1,894	(93.2)	118	(96.7)	5,864	(94.8)
Death	2	(0.7)	3	(1.0)	15	(0.7)	3	(2.5)	44	(0.7)
Sepsis	2	(0.7)	1	(0.3)	6	(0.3)	0	(0.0)	9	(0.1)
Shock haemorrhagic	2	(0.7)	0	(0.0)	1	(0.0)	0	(0.0)	0	(0.0)
Acute myocardial infarction	1	(0.3)	0	(0.0)	2	(0.1)	0	(0.0)	1	(0.0)
Cardiac arrest	1	(0.3)	0	(0.0)	9	(0.4)	0	(0.0)	9	(0.1)
Cerebrovascular accident	1	(0.3)	0	(0.0)	1	(0.0)	0	(0.0)	5	(0.1)
Encephalitis autoimmune	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Femur fracture	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Intestinal perforation	1	(0.3)	0	(0.0)	1	(0.0)	0	(0.0)	1	(0.0)
Pelvic infection	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Uterine haemorrhage	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Abdominal sepsis	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0)	1	(0.0)
Accidental death	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Acute coronary syndrome	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Acute graft versus host disease	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Acute kidney injury	0	(0.0)	0	(0.0)	4	(0.2)	0	(0.0)	3	(0.0)
Acute respiratory failure	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)	5	(0.1)
Adenocarcinoma gastric	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Alcohol poisoning	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Anaemia	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)

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

[d] Includes all participants who received at least one dose of pembrolizumab in KN028 cohort B4 and KN158 cohort E.

[e] 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, KN012 cohort B and B2, KN013 cohort 3, KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN087, KN177, and KN204.

[f] Includes all subjects who received at least one dose of pembrolizumab combo therapy in KN021 cohort A/C/G, KN048, KN189, KN355, KN407, and KN590.

Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 03APR2020)

Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEP2018, KN021: 19AUG2019, KN189: 20MAY2019, KN407: 09MAY2019)

Database cutoff date for HNSCC (KN012 cohort B and B2: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)

Database cutoff date for cHL (KN013 cohort 3: 28SEP2018, KN087: 21MAR2019, KN204: 16JAN2020)

Database cutoff date for Bladder (KN045: 26OCT2017, KN052: 26SEP2018)

Database cutoff date for Esophageal (KN590: 02JUL2020)

Database cutoff date for CRC (KN177: 19FEB2020)

Database cutoff date for TNBC (KN355: 11DEC2019)

Database cutoff date for Cervical (KN826: 03MAY2021, KN028 cohort B4: 20FEB2017, KN158 cohort E: 27JUN2019)

Table 77. Participants with Adverse Events Resulting in Death by Decreasing Incidence by Bevacizumab Use (Incidence ≥0% in One or More Treatment Groups) (APaT Population)

	KN826 Pembrolizumab + Chemotherapy w/ Bevacizumab		KN826 Pembrolizumab + Chemotherapy w/o Bevacizumab		KN826 Placebo + Chemotherapy w/ Bevacizumab		KN826 Placebo + Chemotherapy w/o Bevacizumab		Pembrolizumab Monotherapy Reference Safety Dataset[e]	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	196		111		193		116		6,185	
with one or more adverse events	10	(5.1)	4	(3.6)	11	(5.7)	3	(2.6)	321	(5.2)
with no adverse events	186	(94.9)	107	(96.4)	182	(94.3)	113	(97.4)	5,864	(94.8)
Death	2	(1.0)	0	(0.0)	3	(1.6)	0	(0.0)	44	(0.7)
Sepsis	2	(1.0)	0	(0.0)	1	(0.5)	0	(0.0)	9	(0.1)
Shock haemorrhagic	2	(1.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Acute myocardial infarction	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Cardiac arrest	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)	9	(0.1)
Intestinal perforation	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Pelvic infection	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Abdominal sepsis	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)	1	(0.0)
Accidental death	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Acute coronary syndrome	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Acute graft versus host disease	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Acute kidney injury	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	3	(0.0)
Acute respiratory failure	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	5	(0.1)
Adenocarcinoma gastric	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Alcohol poisoning	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Anaemia	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Anaphylactic shock	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Arterial injury	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Aspiration	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	3	(0.0)
Atypical pneumonia	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Autoinflammatory disease	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Brain oedema	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
COVID-19 pneumonia	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)	0	(0.0)
Cachexia	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	3	(0.0)
Cardiac complication associated with device	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Cardiac failure	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Cardiac failure acute	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Cardiac failure congestive	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Cardiac tamponade	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Cardio-respiratory arrest	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	4	(0.1)
Cardiopulmonary failure	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Cellulitis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Cerebral haemorrhage	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Cerebral ischaemia	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)	0	(0.0)

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

[e] 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, KN012 cohort B and B2, KN013 cohort 3, KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN087, KN177, and KN204.

Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 03APR2020)

Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEP2018)

Database cutoff date for HNSCC (KN012 cohort B and B2: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)

Database cutoff date for cHL (KN013 cohort 3: 28SEP2018, KN087: 21MAR2019, KN204: 16JAN2020)

Database cutoff date for Bladder (KN045: 26OCT2017, KN052: 26SEP2018)

Database cutoff date for CRC (KN177: 19FEB2020)

Database cutoff date for Cervical (KN826: 03MAY2021)

Adverse Events of Special Interest (AEOSIs)

Table 78. Adverse Event Summary for AEOSI (APaT Population)

	KN826 Pembrolizumab + Chemotherapy		KN826 Placebo + Chemotherapy		Pooled Safety Dataset for Pembrolizumab + Chemotherapy[f]		Cervical Safety Dataset for Pembrolizumab Monotherapy[d]		Pembrolizumab Monotherapy Reference Safety Dataset[e]	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	307		309		2,033		122		6,185	
with one or more adverse events	126	(41.0)	82	(26.5)	585	(28.8)	29	(23.8)	1,579	(25.5)
with no adverse event	181	(59.0)	227	(73.5)	1,448	(71.2)	93	(76.2)	4,606	(74.5)
with drug-related[a] adverse events	115	(37.5)	70	(22.7)	514	(25.3)	26	(21.3)	1,368	(22.1)
with toxicity grade 3-5 adverse events	41	(13.4)	16	(5.2)	169	(8.3)	7	(5.7)	406	(6.6)
with toxicity grade 3-5 drug-related adverse events	36	(11.7)	13	(4.2)	151	(7.4)	7	(5.7)	351	(5.7)
with serious adverse events	26	(8.5)	12	(3.9)	143	(7.0)	5	(4.1)	406	(6.6)
with serious drug-related adverse events	22	(7.2)	9	(2.9)	129	(6.3)	5	(4.1)	359	(5.8)
who died	1	(0.3)	0	(0.0)	6	(0.3)	0	(0.0)	11	(0.2)
who died due to a drug-related adverse event	1	(0.3)	0	(0.0)	6	(0.3)	0	(0.0)	11	(0.2)
discontinued any drug due to an adverse event	27	(8.8)	11	(3.6)	116	(5.7)	4	(3.3)	256	(4.1)
discontinued pembrolizumab or placebo	17	(5.5)	2	(0.6)	98	(4.8)	4	(3.3)	256	(4.1)
discontinued all drugs	3	(1.0)	0	(0.0)	17	(0.8)	4	(3.3)	256	(4.1)
discontinued any drug due to a drug-related adverse event	26	(8.5)	11	(3.6)	113	(5.6)	4	(3.3)	252	(4.1)
discontinued pembrolizumab or placebo	16	(5.2)	2	(0.6)	95	(4.7)	4	(3.3)	252	(4.1)
discontinued all drugs	3	(1.0)	0	(0.0)	17	(0.8)	4	(3.3)	252	(4.1)
discontinued any drug due to a serious adverse event	11	(3.6)	3	(1.0)	85	(4.2)	3	(2.5)	172	(2.8)
discontinued pembrolizumab or placebo	11	(3.6)	1	(0.3)	78	(3.8)	3	(2.5)	172	(2.8)
discontinued all drugs	3	(1.0)	0	(0.0)	14	(0.7)	3	(2.5)	172	(2.8)
discontinued any drug due to a serious drug-related adverse event	11	(3.6)	3	(1.0)	82	(4.0)	3	(2.5)	170	(2.7)
discontinued pembrolizumab or placebo	11	(3.6)	1	(0.3)	75	(3.7)	3	(2.5)	170	(2.7)
discontinued all drugs	3	(1.0)	0	(0.0)	14	(0.7)	3	(2.5)	170	(2.7)

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

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

Grades are based on NCI CTCAE version 4.0.

[d] Includes all participants who received at least one dose of pembrolizumab in KN028 cohort B4 and KN158 cohort E.

[e] 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, KN012 cohort B and B2, KN013 cohort 3, KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN087, KN177, and KN204.

[f] Includes all subjects who received at least one dose of pembrolizumab combo therapy in KN021 cohort A/C/G, KN048, KN189, KN355, KN407, and KN590.

Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 03APR2020)

Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEP2018, KN021: 19AUG2019, KN189: 20MAY2019, KN407: 09MAY2019)

Database cutoff date for HNSCC (KN012 cohort B and B2: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)

Database cutoff date for cHL (KN013 cohort 3: 28SEP2018, KN087: 21MAR2019, KN204: 16JAN2020)

Database cutoff date for Bladder (KN045: 26OCT2017, KN052: 26SEP2018)

Database cutoff date for Esophageal (KN590: 02JUL2020)

Database cutoff date for CRC (KN177: 19FEB2020)

Database cutoff date for TNBC (KN355: 11DEC2019)

Database cutoff date for Cervical (KN826: 03MAY2021, KN028 cohort B4: 20FEB2017, KN158 cohort E: 27JUN2019)

Source: [ISS: adam-adsl; adae]

Table 79. Exposure-Adjusted Adverse Event of Special Interest Summary (Including Multiple Occurrences of Events) (APaT Population)

	Event Count and Rate (Events/100 person-years)[a]				
	KN826 Pembrolizumab + Chemotherapy	KN826 Placebo + Chemotherapy	Pooled Safety Dataset for Pembrolizumab + Chemotherapy[f]	Cervical Safety Dataset for Pembrolizumab Monotherapy[d]	Pembrolizumab Monotherapy Reference Safety Dataset[e]
Number of subjects exposed	307	309	2033	122	6185
Total exposure[b] in person-years	322.11	265.35	1688.88	66.15	4336.02
Total events (rate)					
adverse events	223 (69.23)	108 (40.70)	852 (50.45)	41 (61.98)	2271 (52.38)
drug-related[c] adverse events	195 (60.54)	88 (33.16)	727 (43.05)	38 (57.45)	1951 (45.00)
toxicity grade 3-5 adverse events	51 (15.83)	17 (6.41)	198 (11.72)	8 (12.09)	483 (11.14)
toxicity grade 3-5 drug-related adverse events	46 (14.28)	14 (5.28)	179 (10.60)	8 (12.09)	418 (9.64)
serious adverse events	31 (9.62)	12 (4.52)	167 (9.89)	6 (9.07)	479 (11.05)
serious drug-related adverse events	27 (8.38)	9 (3.39)	151 (8.94)	6 (9.07)	426 (9.82)
adverse events leading to death	1 (0.31)	0 (0.00)	6 (0.36)	0 (0.00)	11 (0.25)
drug-related adverse events leading to death	1 (0.31)	0 (0.00)	6 (0.36)	0 (0.00)	11 (0.25)
adverse events resulting in drug discontinuation	29 (9.00)	12 (4.52)	118 (6.99)	4 (6.05)	262 (6.04)
drug-related adverse events resulting in drug discontinuation	27 (8.38)	12 (4.52)	115 (6.81)	4 (6.05)	258 (5.95)
serious adverse events resulting in drug discontinuation	12 (3.73)	3 (1.13)	85 (5.03)	3 (4.54)	177 (4.08)
serious drug-related adverse events resulting in drug discontinuation	12 (3.73)	3 (1.13)	82 (4.86)	3 (4.54)	175 (4.04)

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

[b] Drug exposure is defined as the time from the first dose date to the earlier of the last dose date + 30 or the database cut-off date.

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

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

Grades are based on NCI CTCAE version 4.0.

[d] Includes all participants who received at least one dose of pembrolizumab in KN028 cohort B4 and KN158 cohort E.

[e] 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, KN012 cohort B and B2, KN013 cohort 3, KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN087, KN177, and KN204.

[f] Includes all subjects who received at least one dose of pembrolizumab combo therapy in KN021 cohort A/C/G, KN048, KN189, KN355, KN407, and KN590.

Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 03APR2020)

Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEP2018, KN021: 19AUG2019, KN189: 20MAY2019, KN407: 09MAY2019)

Database cutoff date for HNSCC (KN012 cohort B and B2: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)

Database cutoff date for cHL (KN013 cohort 3: 28SEP2018, KN087: 21MAR2019, KN204: 16JAN2020)

Database cutoff date for Bladder (KN045: 26OCT2017, KN052: 26SEP2018)

Database cutoff date for Esophageal (KN590: 02JUL2020)

Database cutoff date for CRC (KN177: 19FEB2020)

Database cutoff date for TNBC (KN355: 11DEC2019)

Database cutoff date for Cervical (KN826: 03MAY2021, KN028 cohort B4: 20FEB2017, KN158 cohort E: 27JUN2019)

Source: [ISS: adam-adsl; adae]

Table 80. Adverse Event Summary for AEOSI by Bevacizumab Use (APaT Population)

	KN826 Pembrolizumab + Chemotherapy w/ Bevacizumab		KN826 Pembrolizumab + Chemotherapy w/o Bevacizumab		KN826 Placebo + Chemotherapy w/ Bevacizumab		KN826 Placebo + Chemotherapy w/o Bevacizumab		Pembrolizumab Monotherapy Reference Safety Dataset[e]	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	196		111		193		116		6,185	
with one or more adverse events	85	(43.4)	41	(36.9)	59	(30.6)	23	(19.8)	1,579	(25.5)
with no adverse event	111	(56.6)	70	(63.1)	134	(69.4)	93	(80.2)	4,606	(74.5)
with drug-related[a] adverse events	78	(39.8)	37	(33.3)	50	(25.9)	20	(17.2)	1,368	(22.1)
with toxicity grade 3-5 adverse events	30	(15.3)	11	(9.9)	11	(5.7)	5	(4.3)	406	(6.6)
with toxicity grade 3-5 drug-related adverse events	27	(13.8)	9	(8.1)	10	(5.2)	3	(2.6)	351	(5.7)
with serious adverse events	19	(9.7)	7	(6.3)	9	(4.7)	3	(2.6)	406	(6.6)
with serious drug-related adverse events	16	(8.2)	6	(5.4)	7	(3.6)	2	(1.7)	359	(5.8)
who died	0	(0.0)	1	(0.9)	0	(0.0)	0	(0.0)	11	(0.2)
who died due to a drug-related adverse event	0	(0.0)	1	(0.9)	0	(0.0)	0	(0.0)	11	(0.2)
discontinued any drug due to an adverse event	20	(10.2)	7	(6.3)	9	(4.7)	2	(1.7)	256	(4.1)
discontinued pembrolizumab or placebo	12	(6.1)	5	(4.5)	1	(0.5)	1	(0.9)	256	(4.1)
discontinued all drugs	2	(1.0)	1	(0.9)	0	(0.0)	0	(0.0)	256	(4.1)
discontinued any drug due to a drug-related adverse event	20	(10.2)	6	(5.4)	9	(4.7)	2	(1.7)	252	(4.1)
discontinued pembrolizumab or placebo	12	(6.1)	4	(3.6)	1	(0.5)	1	(0.9)	252	(4.1)
discontinued all drugs	2	(1.0)	1	(0.9)	0	(0.0)	0	(0.0)	252	(4.1)
discontinued any drug due to a serious adverse event	9	(4.6)	2	(1.8)	3	(1.6)	0	(0.0)	172	(2.8)
discontinued pembrolizumab or placebo	9	(4.6)	2	(1.8)	1	(0.5)	0	(0.0)	172	(2.8)
discontinued all drugs	2	(1.0)	1	(0.9)	0	(0.0)	0	(0.0)	172	(2.8)
discontinued any drug due to a serious drug-related adverse event	9	(4.6)	2	(1.8)	3	(1.6)	0	(0.0)	170	(2.7)
discontinued pembrolizumab or placebo	9	(4.6)	2	(1.8)	1	(0.5)	0	(0.0)	170	(2.7)

	KN826 Pembrolizumab + Chemotherapy w/ Bevacizumab		KN826 Pembrolizumab + Chemotherapy w/o Bevacizumab		KN826 Placebo + Chemotherapy w/ Bevacizumab		KN826 Placebo + Chemotherapy w/o Bevacizumab		Pembrolizumab Monotherapy Reference Safety Dataset[e]	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
discontinued all drugs	2	(1.0)	1	(0.9)	0	(0.0)	0	(0.0)	170	(2.7)

[a] Determined by the investigator to be related to the drug.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
Grades are based on NCI CTCAE version 4.0.
[c] 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, KN012 cohort B and B2, KN013 cohort 3, KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN087, KN177, and KN204.
Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 03APR2020)
Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEP2018)
Database cutoff date for HNSCC (KN012 cohort B and B2: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)
Database cutoff date for cHL (KN013 cohort 3: 28SEP2018, KN087: 21MAR2019, KN204: 16JAN2020)
Database cutoff date for Bladder (KN045: 26OCT2017, KN052: 26SEP2018)
Database cutoff date for CRC (KN177: 19FEB2020)
Database cutoff date for Cervical (KN826: 03MAY2021)

Source: [ISS: adam-adsl; adae]

Table 81. Exposure-Adjusted Adverse Event of Special Interest by AEOSI Category and Preferred Term (Including Multiple Occurrences of Events) (APaT Population)

	Event Count and Rate (Events/100 person-years)[a]				
	KN826 Pembrolizumab + Chemotherapy	KN826 Placebo + Chemotherapy	Pooled Safety Dataset for Pembrolizumab + Chemotherapy[f]	Cervical Safety Dataset for Pembrolizumab Monotherapy[d]	Pembrolizumab Monotherapy Reference Safety Dataset[e]
Number of subjects exposed	307	309	2033	122	6185
Total exposure[b] in person-years	322.11	265.35	1688.88	66.15	4336.02
Total events (rate)	223 (69.23)	108 (40.70)	852 (50.45)	41 (61.98)	2271 (52.38)
AEOSI Category and Preferred Term					
Adrenal Insufficiency	**4 (1.2)**	**0 (0.0)**	**16 (0.9)**	**1 (1.5)**	**54 (1.2)**
Adrenal insufficiency	4 (1.2)	0 (0.0)	15 (0.9)	0 (0.0)	48 (1.1)
Addison's disease	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	2 (0.0)
Adrenocortical insufficiency acute	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.0)
Primary adrenal insufficiency	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.5)	0 (0.0)
Secondary adrenocortical insufficiency	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.0)
Cholangitis Sclerosing	**1 (0.3)**	**0 (0.0)**	**1 (0.1)**	**0 (0.0)**	**0 (0.0)**
Immune-mediated cholangitis	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cholangitis sclerosing	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
Colitis	**21 (6.5)**	**5 (1.9)**	**60 (3.6)**	**4 (6.0)**	**170 (3.9)**
Colitis	14 (4.3)	3 (1.1)	49 (2.9)	4 (6.0)	140 (3.2)

	Event Count and Rate (Events/100 person-years)[a]				
	KN826 Pembrolizumab + Chemotherapy	KN826 Placebo + Chemotherapy	Pooled Safety Dataset for Pembrolizumab + Chemotherapy[f]	Cervical Safety Dataset for Pembrolizumab Monotherapy[d]	Pembrolizumab Monotherapy Reference Safety Dataset[e]
Colitis	**21 (6.5)**	**5 (1.9)**	**60 (3.6)**	**4 (6.0)**	**170 (3.9)**
Enterocolitis	5 (1.6)	1 (0.4)	7 (0.4)	0 (0.0)	8 (0.2)
Immune-mediated enterocolitis	2 (0.6)	1 (0.4)	0 (0.0)	0 (0.0)	11 (0.3)
Autoimmune colitis	0 (0.0)	0 (0.0)	3 (0.2)	0 (0.0)	5 (0.1)
Colitis microscopic	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	6 (0.1)
Encephalitis	**1 (0.3)**	**0 (0.0)**	**2 (0.1)**	**0 (0.0)**	**4 (0.1)**
Encephalitis autoimmune	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
Encephalitis	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)	3 (0.1)
Guillain-Barre Syndrome	**0 (0.0)**	**0 (0.0)**	**2 (0.1)**	**1 (1.5)**	**4 (0.1)**
Axonal neuropathy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
Demyelinating polyneuropathy	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.0)
Guillain-Barre syndrome	0 (0.0)	0 (0.0)	1 (0.1)	1 (1.5)	2 (0.0)
Hepatitis	**5 (1.6)**	**1 (0.4)**	**28 (1.7)**	**2 (3.0)**	**77 (1.8)**
Immune-mediated hepatitis	3 (0.9)	0 (0.0)	3 (0.2)	0 (0.0)	2 (0.0)
Autoimmune hepatitis	1 (0.3)	0 (0.0)	13 (0.8)	0 (0.0)	31 (0.7)
Hepatitis	1 (0.3)	0 (0.0)	12 (0.7)	2 (3.0)	35 (0.8)
Drug-induced liver injury	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	8 (0.2)
Hepatitis acute	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)

	Event Count and Rate (Events/100 person-years)[a]				
	KN826 Pembrolizumab + Chemotherapy	KN826 Placebo + Chemotherapy	Pooled Safety Dataset for Pembrolizumab + Chemotherapy[f]	Cervical Safety Dataset for Pembrolizumab Monotherapy[d]	Pembrolizumab Monotherapy Reference Safety Dataset[e]
Hyperthyroidism	**23 (7.1)**	**10 (3.8)**	**114 (6.8)**	**10 (15.1)**	**282 (6.5)**
Hyperthyroidism	22 (6.8)	10 (3.8)	113 (6.7)	10 (15.1)	282 (6.5)
Basedow's disease	1 (0.3)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
Hypophysitis	**1 (0.3)**	**1 (0.4)**	**13 (0.8)**	**0 (0.0)**	**45 (1.0)**
Hypophysitis	1 (0.3)	1 (0.4)	7 (0.4)	0 (0.0)	26 (0.6)
Hypopituitarism	0 (0.0)	0 (0.0)	6 (0.4)	0 (0.0)	18 (0.4)
Lymphocytic hypophysitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
Hypothyroidism	**62 (19.2)**	**32 (12.1)**	**292 (17.3)**	**12 (18.1)**	**774 (17.9)**
Hypothyroidism	60 (18.6)	32 (12.1)	292 (17.3)	12 (18.1)	772 (17.8)
Immune-mediated hypothyroidism	2 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Myxoedema	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
Primary hypothyroidism	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
Infusion Reactions	**61 (18.9)**	**55 (20.7)**	**87 (5.2)**	**7 (10.6)**	**182 (4.2)**
Infusion related reaction	26 (8.1)	18 (6.8)	42 (2.5)	6 (9.1)	73 (1.7)
Hypersensitivity	22 (6.8)	18 (6.8)	26 (1.5)	1 (1.5)	58 (1.3)
Drug hypersensitivity	9 (2.8)	18 (6.8)	13 (0.8)	0 (0.0)	21 (0.5)
Anaphylactic reaction	3 (0.9)	1 (0.4)	5 (0.3)	0 (0.0)	10 (0.2)
Cytokine release syndrome	1 (0.3)	0 (0.0)	1 (0.1)	0 (0.0)	19 (0.4)
Anaphylactoid reaction	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
Myasthenic Syndrome	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**5 (0.1)**

	Event Count and Rate (Events/100 person-years)[a]				
	KN826 Pembrolizumab + Chemotherapy	KN826 Placebo + Chemotherapy	Pooled Safety Dataset for Pembrolizumab + Chemotherapy[f]	Cervical Safety Dataset for Pembrolizumab Monotherapy[d]	Pembrolizumab Monotherapy Reference Safety Dataset[e]
Myasthenic Syndrome	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**5 (0.1)**
Myasthenia gravis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.1)
Myasthenic syndrome	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.0)
Myelitis	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**2 (0.0)**
Myelitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
Myelitis transverse	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
Myocarditis	**1 (0.3)**	**0 (0.0)**	**3 (0.2)**	**0 (0.0)**	**8 (0.2)**
Myocarditis	1 (0.3)	0 (0.0)	2 (0.1)	0 (0.0)	8 (0.2)
Autoimmune myocarditis	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
Myositis	**2 (0.6)**	**0 (0.0)**	**7 (0.4)**	**1 (1.5)**	**24 (0.6)**
Autoimmune myositis	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Myositis	1 (0.3)	0 (0.0)	2 (0.1)	1 (1.5)	15 (0.3)
Dermatomyositis	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
Myopathy	0 (0.0)	0 (0.0)	4 (0.2)	0 (0.0)	5 (0.1)
Necrotising myositis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
Rhabdomyolysis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.1)
Nephritis	**1 (0.3)**	**0 (0.0)**	**18 (1.1)**	**0 (0.0)**	**26 (0.6)**
Tubulointerstitial nephritis	1 (0.3)	0 (0.0)	5 (0.3)	0 (0.0)	12 (0.3)
Acute kidney injury	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.0)
Autoimmune nephritis	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	3 (0.1)
Glomerulonephritis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)

	Event Count and Rate (Events/100 person-years)[a]				
	KN826 Pembrolizumab + Chemotherapy	KN826 Placebo + Chemotherapy	Pooled Safety Dataset for Pembrolizumab + Chemotherapy[f]	Cervical Safety Dataset for Pembrolizumab Monotherapy[d]	Pembrolizumab Monotherapy Reference Safety Dataset[e]
Nephritis	**1 (0.3)**	**0 (0.0)**	**18 (1.1)**	**0 (0.0)**	**26 (0.6)**
Glomerulonephritis membranous	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
Nephritis	0 (0.0)	0 (0.0)	12 (0.7)	0 (0.0)	4 (0.1)
Nephrotic syndrome	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
Renal failure	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.0)
Pancreatitis	**3 (0.9)**	**1 (0.4)**	**7 (0.4)**	**0 (0.0)**	**24 (0.6)**
Pancreatitis	2 (0.6)	0 (0.0)	5 (0.3)	0 (0.0)	19 (0.4)
Pancreatitis acute	1 (0.3)	1 (0.4)	2 (0.1)	0 (0.0)	4 (0.1)
Autoimmune pancreatitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
Pneumonitis	**6 (1.9)**	**1 (0.4)**	**116 (6.9)**	**0 (0.0)**	**344 (7.9)**
Pneumonitis	5 (1.6)	1 (0.4)	106 (6.3)	0 (0.0)	310 (7.1)
Immune-mediated lung disease	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Interstitial lung disease	0 (0.0)	0 (0.0)	9 (0.5)	0 (0.0)	30 (0.7)
Organising pneumonia	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	4 (0.1)
Sarcoidosis	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**12 (0.3)**
Sarcoidosis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	12 (0.3)
Severe Skin Reactions	**16 (5.0)**	**1 (0.4)**	**46 (2.7)**	**2 (3.0)**	**112 (2.6)**
Rash maculo-papular	7 (2.2)	0 (0.0)	15 (0.9)	1 (1.5)	17 (0.4)
Rash	3 (0.9)	1 (0.4)	22 (1.3)	1 (1.5)	33 (0.8)
Dermatitis bullous	2 (0.6)	0 (0.0)	2 (0.1)	0 (0.0)	9 (0.2)
Pruritus	2 (0.6)	0 (0.0)	2 (0.1)	0 (0.0)	12 (0.3)

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

[b] Drug exposure is defined as the time from the first dose date to the earlier of the last dose date + 30 or the database cut-off date. Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.

[d] Includes all participants who received at least one dose of pembrolizumab in KN028 cohort B4 and KN158 cohort E.

[e] 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, KN012 cohort B and B2, KN013 cohort 3, KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN087, KN177, and KN204.

[f] Includes all subjects who received at least one dose of pembrolizumab combo therapy in KN021 cohort A/C/G, KN048, KN189, KN355, KN407, and KN590.

Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 03APR2020)

Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEP2018, KN021: 19AUG2019, KN189: 20MAY2019, KN407: 09MAY2019)

Database cutoff date for HNSCC (KN012 cohort B and B2: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)

Database cutoff date for cHL (KN013 cohort 3: 28SEP2018, KN087: 21MAR2019, KN204: 16JAN2020)

Database cutoff date for Bladder (KN045: 26OCT2017, KN052: 26SEP2018)

Database cutoff date for Esophageal (KN590: 02JUL2020)

Database cutoff date for CRC (KN177: 19FEB2020)

Database cutoff date for TNBC (KN355: 11DEC2019)

Database cutoff date for Cervical (KN826: 03MAY2021, KN028 cohort B4: 20FEB2017, KN158 cohort E: 27JUN2019)

Laboratory findings

The most frequently reported (≥50%) laboratory abnormalities were similar in the pembrolizumab + chemotherapy ± bevacizumab group and the placebo + chemotherapy ± bevacizumab group, and the majority were CTCAE Grade 1 to 2 toxicity.

The most frequently reported laboratory abnormalities in the pembrolizumab + chemotherapy ± bevacizumab group were generally similar to the pembrolizumab monotherapy RSD, though the frequency of these abnormalities was higher in the pembrolizumab + chemotherapy ± bevacizumab group. The increased incidence of these abnormalities reflects myelosuppression (decreased white blood cell, red blood cell, and platelet counts) associated with the chemotherapy components of the combination treatment.

No clinically meaningful differences in Grade 3 to 4 laboratory anomalies (incidence ≥0%) were observed between the pembrolizumab + chemotherapy ± bevacizumab and placebo + chemotherapy ± bevacizumab groups.

The most frequently reported Grade 3 to 4 laboratory abnormalities in the pembrolizumab + chemotherapy ± bevacizumab group were consistent with myelosuppression (decreased white blood cell, red blood cell, and platelet counts), a known risk of the administered chemotherapy. As such, the frequencies of these abnormalities in the pembrolizumab + chemotherapy ± bevacizumab group were higher compared with the pembrolizumab monotherapy RSD.

In KEYNOTE-826, there was no trend in laboratory abnormalities suggesting any safety concerns for use of bevacizumab with pembrolizumab + chemotherapy. Although some laboratory abnormalities (notably liver function abnormalities and neutropenia) occurred at a higher incidence in participants who received bevacizumab compared with those who did not receive bevacizumab, these abnormalities were generally consistent with the known safety profile of bevacizumab, and showed a similar trend in the pembrolizumab + chemotherapy ± bevacizumab and the placebo + chemotherapy ± bevacizumab groups.

Safety in special populations

Age

Table 82. Adverse Event Summary by age Category (<65, ≥65 Years) (APaT Population)

	KN826 Pembrolizumab + Chemotherapy				KN826 Placebo + Chemotherapy				Pooled Safety Dataset for Pembrolizumab + Chemotherapy[f]				Cervical Safety Dataset for Pembrolizumab Monotherapy[d]				Pembrolizumab Monotherapy Reference Safety Dataset[e]			
	<65		>=65		<65		>=65		<65		>=65		<65		>=65		<65		>=65	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	259		48		257		52		1,218		815		114		8		3,587		2,598	
with one or more adverse events	257	(99.2)	48	(100.0)	256	(99.6)	51	(98.1)	1,207	(99.1)	808	(99.1)	111	(97.4)	8	(100.0)	3,469	(96.7)	2,520	(97.0)
with no adverse event	2	(0.8)	0	(0.0)	1	(0.4)	1	(1.9)	11	(0.9)	7	(0.9)	3	(2.6)	0	(0.0)	118	(3.3)	78	(3.0)
with drug-related[f] adverse events	250	(96.5)	48	(100.0)	249	(96.9)	51	(98.1)	1,165	(95.6)	783	(96.1)	76	(66.7)	6	(75.0)	2,521	(70.3)	1,845	(71.0)
with toxicity grade 3-5 adverse events	209	(80.7)	42	(87.5)	190	(73.9)	42	(80.8)	940	(77.2)	643	(78.9)	64	(56.1)	1	(12.5)	1,596	(44.5)	1,388	(53.4)
with toxicity grade 3-5 drug-related adverse events	169	(65.3)	41	(85.4)	165	(64.2)	33	(63.5)	760	(62.4)	525	(64.4)	17	(14.9)	0	(0.0)	495	(13.8)	480	(18.5)
with serious adverse events	127	(49.0)	26	(54.2)	112	(43.6)	19	(36.5)	512	(42.0)	450	(55.2)	51	(44.7)	1	(12.5)	1,236	(34.5)	1,135	(43.7)
with serious drug-related adverse events	75	(29.0)	18	(37.5)	57	(22.2)	14	(26.9)	289	(23.7)	261	(32.0)	12	(10.5)	0	(0.0)	371	(10.3)	330	(12.7)
who died	9	(3.5)	5	(10.4)	12	(4.7)	2	(3.8)	58	(4.8)	81	(9.9)	4	(3.5)	0	(0.0)	148	(4.1)	173	(6.7)
who died due to a drug-related adverse event	1	(0.4)	1	(2.1)	4	(1.6)	0	(0.0)	17	(1.4)	26	(3.2)	0	(0.0)	0	(0.0)	21	(0.6)	18	(0.7)
discontinued any drug due to an adverse event	95	(36.7)	20	(41.7)	68	(26.5)	14	(26.9)	275	(22.6)	276	(33.9)	11	(9.6)	0	(0.0)	423	(11.8)	409	(15.7)
discontinued pembrolizumab or placebo	38	(14.7)	8	(16.7)	23	(8.9)	2	(3.8)	162	(13.3)	183	(22.5)	11	(9.6)	0	(0.0)	423	(11.8)	409	(15.7)
discontinued all drugs	13	(5.0)	5	(10.4)	13	(5.1)	2	(3.8)	58	(4.8)	67	(8.2)	11	(9.6)	0	(0.0)	423	(11.8)	409	(15.7)
discontinued any drug due to a drug-related adverse event	82	(31.7)	14	(29.2)	57	(22.2)	12	(23.1)	228	(18.7)	206	(25.3)	6	(5.3)	0	(0.0)	228	(6.4)	216	(8.3)
discontinued pembrolizumab or placebo	27	(10.4)	4	(8.3)	11	(4.3)	1	(1.9)	116	(9.5)	118	(14.5)	6	(5.3)	0	(0.0)	228	(6.4)	216	(8.3)
discontinued all drugs	6	(2.3)	4	(8.3)	5	(1.9)	1	(1.9)	39	(3.2)	37	(4.5)	6	(5.3)	0	(0.0)	228	(6.4)	216	(8.3)
discontinued any drug due to a serious adverse event	43	(16.6)	8	(16.7)	27	(10.5)	5	(9.6)	154	(12.6)	173	(21.2)	9	(7.9)	0	(0.0)	301	(8.4)	297	(11.4)
discontinued pembrolizumab or placebo	27	(10.4)	6	(12.5)	14	(5.4)	2	(3.8)	120	(9.9)	148	(18.2)	9	(7.9)	0	(0.0)	301	(8.4)	297	(11.4)
discontinued all drugs	13	(5.0)	4	(8.3)	9	(3.5)	2	(3.8)	50	(4.1)	60	(7.4)	9	(7.9)	0	(0.0)	301	(8.4)	297	(11.4)
discontinued any drug due to a serious drug-related adverse event	33	(12.7)	6	(12.5)	19	(7.4)	4	(7.7)	112	(9.2)	108	(13.3)	4	(3.5)	0	(0.0)	135	(3.8)	130	(5.0)
discontinued pembrolizumab or placebo	18	(6.9)	4	(8.3)	7	(2.7)	1	(1.9)	79	(6.5)	88	(10.8)	4	(3.5)	0	(0.0)	135	(3.8)	130	(5.0)
discontinued all drugs	6	(2.3)	4	(8.3)	3	(1.2)	1	(1.9)	31	(2.5)	32	(3.9)	4	(3.5)	0	(0.0)	135	(3.8)	130	(5.0)

[a] Determined by the investigator to be related to the drug.
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 preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.
Grades are based on NCI CTCAE version 4.0.
[d] Includes all participants who received at least one dose of pembrolizumab in KN028 cohort B4 and KN158 cohort E.
[e] 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, KN012 cohort B and B2, KN013 cohort 3, KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN087, KN177, and KN204.
[f] Includes all subjects who received at least one dose of pembrolizumab combo therapy in KN021 cohort A/C/G, KN048, KN189, KN355, KN407, and KN590.
Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 03APR2020)
Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEP2018, KN021: 19AUG2019, KN189: 20MAY2019, KN407: 09MAY2019)
Database cutoff date for HNSCC (KN012 cohort B and B2: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)
Database cutoff date for cHL (KN013 cohort 3: 28SEP2018, KN087: 21MAR2019, KN204: 16JAN2020)
Database cutoff date for Bladder (KN045: 26OCT2017, KN052: 26SEP2018)
Database cutoff date for Esophageal (KN590: 02JUL2020)
Database cutoff date for CRC (KN177: 19FEB2020)
Database cutoff date for TNBC (KN355: 11DEC2019)
Database cutoff date for Cervical (KN826: 03MAY2021, KN028 cohort B4: 20FEB2017, KN158 cohort E: 27JUN2019)

Source: [ISS: adam-adsl; adae]

Table 83. Adverse Event summary by age Category (>65, 65-74, 75-84, ≥85 Years) (APaT Population)

	KN826 Pembrolizumab + Chemotherapy								KN826 Placebo + Chemotherapy							
	<65		65-74		75-84		>=85		<65		65-74		75-84		>=85	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	259		38		10		0		257		42		10		0	
with one or more adverse events	257	(99.2)	38	(100.0)	10	(100.0)	0	(0.0)	256	(99.6)	41	(97.6)	10	(100.0)	0	(0.0)
with no adverse event	2	(0.8)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.4)	1	(2.4)	0	(0.0)	0	(0.0)
with drug-related[†] adverse events	250	(96.5)	38	(100.0)	10	(100.0)	0	(0.0)	249	(96.9)	41	(97.6)	10	(100.0)	0	(0.0)
with toxicity grade 3-5 adverse events	209	(80.7)	34	(89.5)	8	(80.0)	0	(0.0)	190	(73.9)	34	(81.0)	8	(80.0)	0	(0.0)
with toxicity grade 3-5 drug-related adverse events	169	(65.3)	33	(86.8)	8	(80.0)	0	(0.0)	165	(64.2)	25	(59.5)	8	(80.0)	0	(0.0)
with serious adverse events	127	(49.0)	21	(55.3)	5	(50.0)	0	(0.0)	112	(43.6)	17	(40.5)	2	(20.0)	0	(0.0)
with serious drug-related adverse events	75	(29.0)	13	(34.2)	5	(50.0)	0	(0.0)	57	(22.2)	12	(28.6)	2	(20.0)	0	(0.0)
who died	9	(3.5)	3	(7.9)	2	(20.0)	0	(0.0)	12	(4.7)	2	(4.8)	0	(0.0)	0	(0.0)
who died due to a drug-related adverse event	1	(0.4)	1	(2.6)	0	(0.0)	0	(0.0)	4	(1.6)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued any drug due to an adverse event	95	(36.7)	16	(42.1)	4	(40.0)	0	(0.0)	68	(26.5)	12	(28.6)	2	(20.0)	0	(0.0)
discontinued pembrolizumab or placebo	38	(14.7)	6	(15.8)	2	(20.0)	0	(0.0)	23	(8.9)	2	(4.8)	0	(0.0)	0	(0.0)
discontinued all drugs	13	(5.0)	4	(10.5)	1	(10.0)	0	(0.0)	13	(5.1)	2	(4.8)	0	(0.0)	0	(0.0)
discontinued any drug due to a drug-related adverse event	82	(31.7)	12	(31.6)	2	(20.0)	0	(0.0)	57	(22.2)	10	(23.8)	2	(20.0)	0	(0.0)
discontinued pembrolizumab or placebo	27	(10.4)	4	(10.5)	0	(0.0)	0	(0.0)	11	(4.3)	1	(2.4)	0	(0.0)	0	(0.0)
discontinued all drugs	6	(2.3)	4	(10.5)	0	(0.0)	0	(0.0)	5	(1.9)	1	(2.4)	0	(0.0)	0	(0.0)
discontinued any drug due to a serious adverse event	43	(16.6)	6	(15.8)	2	(20.0)	0	(0.0)	27	(10.5)	5	(11.9)	0	(0.0)	0	(0.0)
discontinued pembrolizumab or placebo	27	(10.4)	5	(13.2)	1	(10.0)	0	(0.0)	14	(5.4)	2	(4.8)	0	(0.0)	0	(0.0)
discontinued all drugs	13	(5.0)	4	(10.5)	0	(0.0)	0	(0.0)	9	(3.5)	2	(4.8)	0	(0.0)	0	(0.0)
discontinued any drug due to a serious drug-related adverse event	33	(12.7)	5	(13.2)	1	(10.0)	0	(0.0)	19	(7.4)	4	(9.5)	0	(0.0)	0	(0.0)
discontinued pembrolizumab or placebo	18	(6.9)	4	(10.5)	0	(0.0)	0	(0.0)	7	(2.7)	1	(2.4)	0	(0.0)	0	(0.0)

	Pooled Safety Dataset for Pembrolizumab + Chemotherapy[f]								Cervical Safety Dataset for Pembrolizumab Monotherapy[d]							
	<65		65-74		75-84		>=85		<65		65-74		75-84		>=85	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	1,218		653		157		5		114		7		1		0	
with one or more adverse events	1,207	(99.1)	647	(99.1)	156	(99.4)	5	(100.0)	111	(97.4)	7	(100.0)	1	(100.0)	0	(0.0)
with no adverse event	11	(0.9)	6	(0.9)	1	(0.6)	0	(0.0)	3	(2.6)	0	(0.0)	0	(0.0)	0	(0.0)
with drug-related[†] adverse events	1,165	(95.6)	629	(96.3)	150	(95.5)	4	(80.0)	76	(66.7)	5	(71.4)	1	(100.0)	0	(0.0)
with toxicity grade 3-5 adverse events	940	(77.2)	506	(77.5)	132	(84.1)	5	(100.0)	64	(56.1)	1	(14.3)	0	(0.0)	0	(0.0)
with toxicity grade 3-5 drug-related adverse events	760	(62.4)	422	(64.6)	99	(63.1)	4	(80.0)	17	(14.9)	0	(0.0)	0	(0.0)	0	(0.0)
with serious adverse events	512	(42.0)	353	(54.1)	93	(59.2)	4	(80.0)	51	(44.7)	1	(14.3)	0	(0.0)	0	(0.0)
with serious drug-related adverse events	289	(23.7)	205	(31.4)	53	(33.8)	3	(60.0)	12	(10.5)	0	(0.0)	0	(0.0)	0	(0.0)
who died	58	(4.8)	49	(7.5)	28	(17.8)	4	(80.0)	4	(3.5)	0	(0.0)	0	(0.0)	0	(0.0)
who died due to a drug-related adverse event	17	(1.4)	15	(2.3)	8	(5.1)	3	(60.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued any drug due to an adverse event	275	(22.6)	209	(32.0)	63	(40.1)	4	(80.0)	11	(9.6)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued pembrolizumab or placebo	162	(13.3)	131	(20.1)	48	(30.6)	4	(80.0)	11	(9.6)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued all drugs	58	(4.8)	42	(6.4)	21	(13.4)	4	(80.0)	11	(9.6)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued any drug due to a drug-related adverse event	228	(18.7)	161	(24.7)	42	(26.8)	3	(60.0)	6	(5.3)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued pembrolizumab or placebo	116	(9.5)	88	(13.5)	27	(17.2)	3	(60.0)	6	(5.3)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued all drugs	39	(3.2)	24	(3.7)	10	(6.4)	3	(60.0)	6	(5.3)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued any drug due to a serious adverse event	154	(12.6)	122	(18.7)	47	(29.9)	4	(80.0)	9	(7.9)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued pembrolizumab or placebo	120	(9.9)	101	(15.5)	43	(27.4)	4	(80.0)	9	(7.9)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued all drugs	50	(4.1)	37	(5.7)	19	(12.1)	4	(80.0)	9	(7.9)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued any drug due to a serious drug-related adverse event	112	(9.2)	78	(11.9)	27	(17.2)	3	(60.0)	4	(3.5)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued pembrolizumab or placebo	79	(6.5)	62	(9.5)	23	(14.6)	3	(60.0)	4	(3.5)	0	(0.0)	0	(0.0)	0	(0.0)

	Pembrolizumab Monotherapy Reference Safety Dataset[e]							
	<65		65-74		75-84		>=85	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	3,587		1,797		694		107	
with one or more adverse events	3,469	(96.7)	1,737	(96.7)	677	(97.6)	106	(99.1)
with no adverse event	118	(3.3)	60	(3.3)	17	(2.4)	1	(0.9)
with drug-related[†] adverse events	2,521	(70.3)	1,272	(70.8)	491	(70.7)	82	(76.6)
with toxicity grade 3-5 adverse events	1,596	(44.5)	928	(51.6)	392	(56.5)	68	(63.6)
with toxicity grade 3-5 drug-related adverse events	495	(13.8)	321	(17.9)	135	(19.5)	24	(22.4)
with serious adverse events	1,236	(34.5)	749	(41.7)	329	(47.4)	57	(53.3)
with serious drug-related adverse events	371	(10.3)	223	(12.4)	90	(13.0)	17	(15.9)
who died	148	(4.1)	106	(5.9)	55	(7.9)	12	(11.2)
who died due to a drug-related adverse event	21	(0.6)	12	(0.7)	5	(0.7)	1	(0.9)
discontinued any drug due to an adverse event	423	(11.8)	255	(14.2)	138	(19.9)	16	(15.0)
discontinued pembrolizumab or placebo	423	(11.8)	255	(14.2)	138	(19.9)	16	(15.0)
discontinued all drugs	423	(11.8)	255	(14.2)	138	(19.9)	16	(15.0)
discontinued any drug due to a drug-related adverse event	228	(6.4)	142	(7.9)	67	(9.7)	7	(6.5)
discontinued pembrolizumab or placebo	228	(6.4)	142	(7.9)	67	(9.7)	7	(6.5)
discontinued all drugs	228	(6.4)	142	(7.9)	67	(9.7)	7	(6.5)
discontinued any drug due to a serious adverse event	301	(8.4)	181	(10.1)	103	(14.8)	13	(12.1)
discontinued pembrolizumab or placebo	301	(8.4)	181	(10.1)	103	(14.8)	13	(12.1)
discontinued all drugs	301	(8.4)	181	(10.1)	103	(14.8)	13	(12.1)
discontinued any drug due to a serious drug-related adverse event	135	(3.8)	86	(4.8)	40	(5.8)	4	(3.7)
discontinued pembrolizumab or placebo	135	(3.8)	86	(4.8)	40	(5.8)	4	(3.7)

	KN826 Pembrolizumab + Chemotherapy								KN826 Placebo + Chemotherapy							
	<65		65-74		75-84		>=85		<65		65-74		75-84		>=85	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
discontinued all drugs	6	(2.3)	4	(10.5)	0	(0.0)	0	(0.0)	3	(1.2)	1	(2.4)	0	(0.0)	0	(0.0)

	Pooled Safety Dataset for Pembrolizumab + Chemotherapy[f]								Cervical Safety Dataset for Pembrolizumab Monotherapy[d]							
	<65		65-74		75-84		>=85		<65		65-74		75-84		>=85	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
discontinued all drugs	31	(2.5)	20	(3.1)	9	(5.7)	3	(60.0)	4	(3.5)	0	(0.0)	0	(0.0)	0	(0.0)

	Pembrolizumab Monotherapy Reference Safety Dataset[e]							
	<65		65-74		75-84		>=85	
	n	(%)	n	(%)	n	(%)	n	(%)
discontinued all drugs	135	(3.8)	86	(4.8)	40	(5.8)	4	(3.7)

[a] Determined by the investigator to be related to the drug.
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 preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.
Grades are based on NCI CTCAE version 4.0.
[d] Includes all participants who received at least one dose of pembrolizumab in KN028 cohort B4 and KN158 cohort E.
[e] 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, KN012 cohort B and B2, KN013 cohort 3, KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN087, KN177, and KN204.
[f] Includes all subjects who received at least one dose of pembrolizumab combo therapy in KN021 cohort A/C/G, KN048, KN189, KN355, KN407, and KN590.
Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 03APR2020)
Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEP2018, KN021: 19AUG2019, KN189: 20MAY2019, KN407: 09MAY2019)
Database cutoff date for HNSCC (KN012 cohort B and B2: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)
Database cutoff date for cHL (KN013 cohort 3: 28SEP2018, KN087: 21MAR2019, KN204: 16JAN2020)
Database cutoff date for Bladder (KN045: 26OCT2017, KN052: 26SEP2018)
Database cutoff date for Esophageal (KN590: 02JUL2020)
Database cutoff date for CRC (KN177: 19FEB2020)
Database cutoff date for TNBC (KN355: 11DEC2019)
Database cutoff date for Cervical (KN826: 03MAY2021, KN028 cohort B4: 20FEB2017, KN158 cohort E: 27JUN2019)

Source: [ISS: adam-adsl; adae]

Table 84. Adverse Event Summary by age Category by Bevacizumab Use (<65, ≥65 Years) (APaT Population)

	KN826 Pembrolizumab + Chemotherapy w/ Bevacizumab				KN826 Pembrolizumab + Chemotherapy w/o Bevacizumab				KN826 Placebo + Chemotherapy w/ Bevacizumab				KN826 Placebo + Chemotherapy w/o Bevacizumab				Pembrolizumab Monotherapy Reference Safety Dataset[e]			
	<65		>=65		<65		>=65		<65		>=65		<65		>=65		<65		>=65	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	170		26		89		22		165		28		92		24		3,587		2,598	
with one or more adverse events	170	(100.0)	26	(100.0)	87	(97.8)	22	(100.0)	165	(100.0)	28	(100.0)	91	(98.9)	23	(95.8)	3,469	(96.7)	2,520	(97.0)
with no adverse event	0	(0.0)	0	(0.0)	2	(2.2)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.1)	1	(4.2)	118	(3.3)	78	(3.0)
with drug-related[a] adverse events	165	(97.1)	26	(100.0)	85	(95.5)	22	(100.0)	162	(98.2)	28	(100.0)	87	(94.6)	23	(95.8)	2,521	(70.3)	1,845	(71.0)
with toxicity grade 3-5 adverse events	140	(82.4)	24	(92.3)	69	(77.5)	18	(81.8)	120	(72.7)	24	(85.7)	70	(76.1)	18	(75.0)	1,596	(44.5)	1,388	(53.4)
with toxicity grade 3-5 drug-related adverse events	119	(70.0)	24	(92.3)	50	(56.2)	17	(77.3)	106	(64.2)	20	(71.4)	59	(64.1)	13	(54.2)	495	(13.8)	480	(18.5)
with serious adverse events	85	(50.0)	14	(53.8)	42	(47.2)	12	(54.5)	74	(44.8)	13	(46.4)	38	(41.3)	6	(25.0)	1,236	(34.5)	1,135	(43.7)
with serious drug-related adverse events	56	(32.9)	9	(34.6)	19	(21.3)	9	(40.9)	38	(23.0)	10	(35.7)	19	(20.7)	4	(16.7)	371	(10.3)	330	(12.7)
who died	7	(4.1)	3	(11.5)	2	(2.2)	2	(9.1)	10	(6.1)	1	(3.6)	2	(2.2)	1	(4.2)	148	(4.1)	173	(6.7)
who died due to a drug-related adverse event	1	(0.6)	0	(0.0)	0	(0.0)	1	(4.5)	3	(1.8)	0	(0.0)	1	(1.1)	0	(0.0)	21	(0.6)	18	(0.7)
discontinued any drug due to an adverse event	75	(44.1)	13	(50.0)	20	(22.5)	7	(31.8)	50	(30.3)	11	(39.3)	18	(19.6)	3	(12.5)	423	(11.8)	409	(15.7)
discontinued pembrolizumab or placebo	30	(17.6)	5	(19.2)	8	(9.0)	3	(13.6)	12	(7.3)	0	(0.0)	11	(12.0)	2	(8.3)	423	(11.8)	409	(15.7)
discontinued all drugs	10	(5.9)	4	(15.4)	3	(3.4)	1	(4.5)	7	(4.2)	0	(0.0)	6	(6.5)	2	(8.3)	423	(11.8)	409	(15.7)
discontinued any drug due to a drug-related adverse event	65	(38.2)	9	(34.6)	17	(19.1)	5	(22.7)	45	(27.3)	10	(35.7)	12	(13.0)	2	(8.3)	228	(6.4)	216	(8.3)
discontinued pembrolizumab or placebo	22	(12.9)	3	(11.5)	5	(5.6)	1	(4.5)	6	(3.6)	0	(0.0)	5	(5.4)	1	(4.2)	228	(6.4)	216	(8.3)
discontinued all drugs	5	(2.9)	3	(11.5)	1	(1.1)	1	(4.5)	2	(1.2)	0	(0.0)	3	(3.3)	1	(4.2)	228	(6.4)	216	(8.3)
discontinued any drug due to a serious adverse event	35	(20.6)	6	(23.1)	8	(9.0)	2	(9.1)	23	(13.9)	3	(10.7)	4	(4.3)	2	(8.3)	301	(8.4)	297	(11.4)
discontinued pembrolizumab or placebo	23	(13.5)	4	(15.4)	4	(4.5)	2	(9.1)	11	(6.7)	0	(0.0)	3	(3.3)	2	(8.3)	301	(8.4)	297	(11.4)
discontinued all drugs	10	(5.9)	3	(11.5)	3	(3.4)	1	(4.5)	6	(3.6)	0	(0.0)	3	(3.3)	2	(8.3)	301	(8.4)	297	(11.4)
discontinued any drug due to a serious drug-related adverse event	27	(15.9)	4	(15.4)	6	(6.7)	2	(9.1)	17	(10.3)	3	(10.7)	2	(2.2)	1	(4.2)	135	(3.8)	130	(5.0)
discontinued pembrolizumab or placebo	16	(9.4)	3	(11.5)	2	(2.2)	1	(4.5)	6	(3.6)	0	(0.0)	1	(1.1)	1	(4.2)	135	(3.8)	130	(5.0)
discontinued all drugs	5	(2.9)	3	(11.5)	1	(1.1)	1	(4.5)	2	(1.2)	0	(0.0)	1	(1.1)	1	(4.2)	135	(3.8)	130	(5.0)

[a] Determined by the investigator to be related to the drug.
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 preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.
Grades are based on NCI CTCAE version 4.0.
[e] 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, KN012 cohort B and B2, KN013 cohort 3, KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN087, KN177, and KN204.
Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 03APR2020)
Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEP2018)
Database cutoff date for HNSCC (KN012 cohort B and B2: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)
Database cutoff date for cHL (KN013 cohort 3: 28SEP2018, KN087: 21MAR2019, KN204: 16JAN2020)
Database cutoff date for Bladder (KN045: 26OCT2017, KN052: 26SEP2018)
Database cutoff date for CRC (KN177: 19FEB2020)
Database cutoff date for Cervical (KN826: 03MAY2021)

Source: [ISS: adam-adsl; adae]

Upon request, exposure-adjusted AE summaries in participants by age (age <65 years and ≥ 65 years were provided. The AE profile in the pembrolizumab + chemotherapy + bevacizumab group was

generally similar between participants who were <65 years and ≥65 years. The small sample size for the ≥65 years age subgroup in KEYNOTE-826 should be considered when comparing the AE data by age.

Table 85. Exposure-Adjusted Adverse Event Summary by Bevacizumab Use (Including Multiple Occurrences of Events) (Participants Age <65 Years) (APaT Population)

	Event Count and Rate (Events/100 person-years)[†]			
	Pembrolizumab + Chemotherapy w/ Bevacizumab	Pembrolizumab + Chemotherapy w/o Bevacizuma	Placebo + Chemotherapy w/ Bevacizumab	Placebo + Chemotherapy w/o Bevacizumab
Number of Participants exposed	170	89	165	92
Total exposure[‡] in person-years	202.97	73.67	159.16	56.94
Total events (rate)				
adverse events	3,939 (1940.67)	1,436 (1949.18)	3,275 (2057.66)	1,388 (2437.86)
drug-related[§] adverse events	2,286 (1126.27)	829 (1125.26)	1,841 (1156.69)	765 (1343.63)
toxicity grade 3-5 adverse events	570 (280.83)	253 (343.41)	478 (300.32)	249 (437.34)
toxicity grade 3-5 drug-related adverse events	371 (182.79)	151 (204.96)	290 (182.21)	133 (233.60)
serious adverse events	200 (98.54)	85 (115.38)	145 (91.10)	75 (131.73)
serious drug-related adverse events	96 (47.30)	30 (40.72)	60 (37.70)	24 (42.15)
adverse events leading to death	7 (3.45)	2 (2.71)	10 (6.28)	2 (3.51)
drug-related adverse events leading to death	1 (0.49)	0 (0.00)	3 (1.88)	1 (1.76)
adverse events resulting in drug discontinuation	99 (48.78)	22 (29.86)	66 (41.47)	22 (38.64)
drug-related adverse events resulting in drug discontinuation	85 (41.88)	18 (24.43)	58 (36.44)	15 (26.35)
serious adverse events resulting in drug discontinuation	40 (19.71)	8 (10.86)	28 (17.59)	4 (7.03)
serious drug-related adverse events resulting in drug discontinuation	30 (14.78)	6 (8.14)	22 (13.82)	2 (3.51)

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

MedDRA V24.0 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: 03MAY2021

Table 86. Exposure-Adjusted Adverse Event Summary by Bevacizumab Use (Including Multiple Occurrences of Events) (Participants Age ≥65 Years) (APaT Population)

	Event Count and Rate (Events/100 person-years)[†]							
	Pembrolizumab + Chemotherapy w/ Bevacizumab		Pembrolizumab + Chemotherapy w/o Bevacizuma		Placebo + Chemotherapy w/ Bevacizumab		Placebo + Chemotherapy w/o Bevacizumab	
Number of Participants exposed	26		22		28		24	
Total exposure[‡] in person-years	27.75		17.72		32.50		16.75	
Total events (rate)								
adverse events	471	(1697.37)	414	(2336.00)	587	(1805.90)	378	(2256.26)
drug-related[§] adverse events	290	(1045.09)	256	(1444.48)	324	(996.78)	222	(1325.11)
toxicity grade 3-5 adverse events	100	(360.37)	86	(485.26)	82	(252.27)	42	(250.70)
toxicity grade 3-5 drug-related adverse events	73	(263.07)	65	(366.76)	52	(159.98)	30	(179.07)
serious adverse events	27	(97.30)	28	(157.99)	35	(107.68)	11	(65.66)
serious drug-related adverse events	10	(36.04)	15	(84.64)	16	(49.22)	6	(35.81)
adverse events leading to death	3	(10.81)	2	(11.29)	1	(3.08)	1	(5.97)
drug-related adverse events leading to death	0	(0.00)	1	(5.64)	0	(0.00)	0	(0.00)
adverse events resulting in drug discontinuation	19	(68.47)	11	(62.07)	13	(39.99)	3	(17.91)
drug-related adverse events resulting in drug discontinuation	11	(39.64)	8	(45.14)	12	(36.92)	2	(11.94)
serious adverse events resulting in drug discontinuation	7	(25.23)	3	(16.93)	4	(12.31)	2	(11.94)
serious drug-related adverse events resulting in drug discontinuation	4	(14.41)	2	(11.29)	4	(12.31)	1	(5.97)

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

MedDRA V24.0 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: 03MAY2021

Sex

Table 87. Adverse Event Summary by Sex (Male, Female) (APaT Population)

	KN826 Pembrolizumab + Chemotherapy				KN826 Placebo + Chemotherapy				Pooled Safety Dataset for Pembrolizumab + Chemotherapy[f]				Cervical Safety Dataset for Pembrolizumab Monotherapy[d]				Pembrolizumab Monotherapy Reference Safety Dataset[e]			
	M		F		M		F		M		F		M		F		M		F	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	0		307		0		309		1,041		992		0		122		4,039		2,146	
with one or more adverse events	0	(0.0)	305	(99.3)	0	(0.0)	307	(99.4)	1,034	(99.3)	981	(98.9)	0	(0.0)	119	(97.5)	3,908	(96.8)	2,081	(97.0)
with no adverse event	0	(0.0)	2	(0.7)	0	(0.0)	2	(0.6)	7	(0.7)	11	(1.1)	0	(0.0)	3	(2.5)	131	(3.2)	65	(3.0)
with drug-related[†] adverse events	0	(0.0)	298	(97.1)	0	(0.0)	300	(97.1)	995	(95.6)	953	(96.1)	0	(0.0)	82	(67.2)	2,826	(70.0)	1,540	(71.8)
with toxicity grade 3-5 adverse events	0	(0.0)	251	(81.8)	0	(0.0)	232	(75.1)	813	(78.1)	770	(77.6)	0	(0.0)	65	(53.3)	1,965	(48.7)	1,019	(47.5)
with toxicity grade 3-5 drug-related adverse events	0	(0.0)	210	(68.4)	0	(0.0)	198	(64.1)	640	(61.5)	645	(65.0)	0	(0.0)	17	(13.9)	662	(16.4)	313	(14.6)
with serious adverse events	0	(0.0)	153	(49.8)	0	(0.0)	131	(42.4)	562	(54.0)	400	(40.3)	0	(0.0)	52	(42.6)	1,580	(39.1)	791	(36.9)
with serious drug-related adverse events	0	(0.0)	93	(30.3)	0	(0.0)	71	(23.0)	320	(30.7)	230	(23.2)	0	(0.0)	12	(9.8)	473	(11.7)	228	(10.6)
who died	0	(0.0)	14	(4.6)	0	(0.0)	14	(4.5)	98	(9.4)	41	(4.1)	0	(0.0)	4	(3.3)	224	(5.5)	97	(4.5)
who died due to a drug-related adverse event	0	(0.0)	2	(0.7)	0	(0.0)	4	(1.3)	32	(3.1)	11	(1.1)	0	(0.0)	0	(0.0)	24	(0.6)	15	(0.7)
discontinued any drug due to an adverse event	0	(0.0)	115	(37.5)	0	(0.0)	82	(26.5)	307	(29.5)	244	(24.6)	0	(0.0)	11	(9.0)	544	(13.5)	288	(13.4)
discontinued pembrolizumab or placebo	0	(0.0)	46	(15.0)	0	(0.0)	25	(8.1)	198	(19.0)	147	(14.8)	0	(0.0)	11	(9.0)	544	(13.5)	288	(13.4)
discontinued all drugs	0	(0.0)	18	(5.9)	0	(0.0)	15	(4.9)	76	(7.3)	49	(4.9)	0	(0.0)	11	(9.0)	544	(13.5)	288	(13.4)
discontinued any drug due to a drug-related adverse event	0	(0.0)	96	(31.3)	0	(0.0)	69	(22.3)	230	(22.1)	204	(20.6)	0	(0.0)	6	(4.9)	292	(7.2)	152	(7.1)
discontinued pembrolizumab or placebo	0	(0.0)	31	(10.1)	0	(0.0)	12	(3.9)	121	(11.6)	113	(11.4)	0	(0.0)	6	(4.9)	292	(7.2)	152	(7.1)
discontinued all drugs	0	(0.0)	10	(3.3)	0	(0.0)	6	(1.9)	44	(4.2)	32	(3.2)	0	(0.0)	6	(4.9)	292	(7.2)	152	(7.1)
discontinued any drug due to a serious adverse event	0	(0.0)	51	(16.6)	0	(0.0)	32	(10.4)	199	(19.1)	128	(12.9)	0	(0.0)	9	(7.4)	397	(9.8)	201	(9.4)
discontinued pembrolizumab or placebo	0	(0.0)	33	(10.7)	0	(0.0)	16	(5.2)	157	(15.1)	111	(11.2)	0	(0.0)	9	(7.4)	397	(9.8)	201	(9.4)
discontinued all drugs	0	(0.0)	17	(5.5)	0	(0.0)	11	(3.6)	71	(6.8)	39	(3.9)	0	(0.0)	9	(7.4)	397	(9.8)	201	(9.4)
discontinued any drug due to a serious drug-related adverse event	0	(0.0)	39	(12.7)	0	(0.0)	23	(7.4)	125	(12.0)	95	(9.6)	0	(0.0)	4	(3.3)	177	(4.4)	88	(4.1)
discontinued pembrolizumab or placebo	0	(0.0)	22	(7.2)	0	(0.0)	8	(2.6)	87	(8.4)	80	(8.1)	0	(0.0)	4	(3.3)	177	(4.4)	88	(4.1)
discontinued all drugs	0	(0.0)	10	(3.3)	0	(0.0)	4	(1.3)	40	(3.8)	23	(2.3)	0	(0.0)	4	(3.3)	177	(4.4)	88	(4.1)

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

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

Grades are based on NCI CTCAE version 4.0.

[d] Includes all participants who received at least one dose of pembrolizumab in KN028 cohort B4 and KN158 cohort E.

[e] 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, KN012 cohort B and B2, KN013 cohort 3, KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN087, KN177, and KN204.

[f] Includes all subjects who received at least one dose of pembrolizumab combo therapy in KN021 cohort A/C/G, KN048, KN189, KN355, KN407, and KN590.

Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 03APR2020)

Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEP2018, KN021: 19AUG2019, KN189: 20MAY2019, KN407: 09MAY2019)

Database cutoff date for HNSCC (KN012 cohort B and B2: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)

Database cutoff date for cHL (KN013 cohort 3: 28SEP2018, KN087: 21MAR2019, KN204: 16JAN2020)

Database cutoff date for Bladder (KN045: 26OCT2017, KN052: 26SEP2018)

Database cutoff date for Esophageal (KN590: 02JUL2020)

Database cutoff date for CRC (KN177: 19FEB2020)

Database cutoff date for TNBC (KN355: 11DEC2019)

Database cutoff date for Cervical (KN826: 03MAY2021, KN028 cohort B4: 20FEB2017, KN158 cohort E: 27JUN2019)

Source: [ISS: adam-adsl; adae]

ECOG

Table 88. Adverse Event Summary by ECOG (APaT Population)

	KN826 Pembrolizumab + Chemotherapy				KN826 Placebo + Chemotherapy				Pooled Safety Dataset for Pembrolizumab + Chemotherapy[f]				Cervical Safety Dataset for Pembrolizumab Monotherapy[d]				Pembrolizumab Monotherapy Reference Safety Dataset[e]			
	[0] Normal Activity		[1] Symptoms, but ambulatory		[0] Normal Activity		[1] Symptoms, but ambulatory		[0] Normal Activity		[1] Symptoms, but ambulatory		[0] Normal Activity		[1] Symptoms, but ambulatory		[0] Normal Activity		[1] Symptoms, but ambulatory	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	178		127		170		139		913		1,116		40		82		2,942		3,069	
with one or more adverse events	177	(99.4)	126	(99.2)	168	(98.8)	139	(100.0)	908	(99.5)	1,103	(98.8)	39	(97.5)	80	(97.6)	2,852	(96.9)	2,970	(96.8)
with no adverse event	1	(0.6)	1	(0.8)	2	(1.2)	0	(0.0)	5	(0.5)	13	(1.2)	1	(2.5)	2	(2.4)	90	(3.1)	99	(3.2)
with drug-related[†] adverse events	175	(98.3)	121	(95.3)	164	(96.5)	136	(97.8)	883	(96.7)	1,061	(95.1)	33	(82.5)	49	(59.8)	2,223	(75.6)	2,048	(66.7)
with toxicity grade 3-5 adverse events	151	(84.8)	98	(77.2)	123	(72.4)	109	(78.4)	689	(75.5)	890	(79.7)	18	(45.0)	47	(57.3)	1,196	(40.7)	1,680	(54.7)
with toxicity grade 3-5 drug-related adverse events	129	(72.5)	80	(63.0)	109	(64.1)	89	(64.0)	583	(63.9)	699	(62.6)	8	(20.0)	9	(11.0)	446	(15.2)	499	(16.3)
with serious adverse events	91	(51.1)	60	(47.2)	62	(36.5)	69	(49.6)	368	(40.3)	590	(52.9)	12	(30.0)	40	(48.8)	930	(31.6)	1,347	(43.9)
with serious drug-related adverse events	59	(33.1)	32	(25.2)	36	(21.2)	35	(25.2)	205	(22.5)	344	(30.8)	3	(7.5)	9	(11.0)	336	(11.4)	348	(11.3)
who died	5	(2.8)	8	(6.3)	3	(1.8)	11	(7.9)	40	(4.4)	99	(8.9)	0	(0.0)	4	(4.9)	83	(2.8)	222	(7.2)
who died due to a drug-related adverse event	1	(0.6)	1	(0.8)	1	(0.6)	3	(2.2)	18	(2.0)	25	(2.2)	0	(0.0)	0	(0.0)	13	(0.4)	26	(0.8)
discontinued any drug due to an adverse event	72	(40.4)	43	(33.9)	41	(24.1)	41	(29.5)	238	(26.1)	312	(28.0)	3	(7.5)	8	(9.8)	333	(11.3)	470	(15.3)
discontinued pembrolizumab or placebo	31	(17.4)	15	(11.8)	14	(8.2)	11	(7.9)	134	(14.7)	210	(18.8)	3	(7.5)	8	(9.8)	333	(11.3)	470	(15.3)
discontinued all drugs	8	(4.5)	10	(7.9)	7	(4.1)	8	(5.8)	36	(3.9)	89	(8.0)	3	(7.5)	8	(9.8)	333	(11.3)	470	(15.3)
discontinued any drug due to a drug-related adverse event	65	(36.5)	31	(24.4)	36	(21.2)	33	(23.7)	204	(22.3)	230	(20.6)	2	(5.0)	4	(4.9)	217	(7.4)	214	(7.0)
discontinued pembrolizumab or placebo	25	(14.0)	6	(4.7)	9	(5.3)	3	(2.2)	103	(11.3)	131	(11.7)	2	(5.0)	4	(4.9)	217	(7.4)	214	(7.0)
discontinued all drugs	7	(3.9)	3	(2.4)	3	(1.8)	3	(2.2)	27	(3.0)	49	(4.4)	2	(5.0)	4	(4.9)	217	(7.4)	214	(7.0)
discontinued any drug due to a serious adverse event	32	(18.0)	19	(15.0)	18	(10.6)	14	(10.1)	125	(13.7)	201	(18.0)	2	(5.0)	7	(8.5)	214	(7.3)	363	(11.8)
discontinued pembrolizumab or placebo	19	(10.7)	14	(11.0)	9	(5.3)	7	(5.0)	100	(11.0)	167	(15.0)	2	(5.0)	7	(8.5)	214	(7.3)	363	(11.8)
discontinued all drugs	8	(4.5)	9	(7.1)	5	(2.9)	6	(4.3)	29	(3.2)	81	(7.3)	2	(5.0)	7	(8.5)	214	(7.3)	363	(11.8)
discontinued any drug due to a serious drug-related adverse event	28	(15.7)	11	(8.7)	14	(8.2)	9	(6.5)	95	(10.4)	125	(11.2)	1	(2.5)	3	(3.7)	118	(4.0)	140	(4.6)
discontinued pembrolizumab or placebo	16	(9.0)	6	(4.7)	6	(3.5)	2	(1.4)	73	(8.0)	94	(8.4)	1	(2.5)	3	(3.7)	118	(4.0)	140	(4.6)
discontinued all drugs	7	(3.9)	3	(2.4)	2	(1.2)	2	(1.4)	21	(2.3)	42	(3.8)	1	(2.5)	3	(3.7)	118	(4.0)	140	(4.6)

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

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

Grades are based on NCI CTCAE version 4.0.

[d] Includes all participants who received at least one dose of pembrolizumab in KN028 cohort B4 and KN158 cohort E.

[e] 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, KN012 cohort B and B2, KN013 cohort 3, KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN087, KN177, and KN204.

[f] Includes all subjects who received at least one dose of pembrolizumab combo therapy in KN021 cohort A/C/G, KN048, KN189, KN355, KN407, and KN590.

Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 03APR2020)

Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEP2018, KN021: 19AUG2019, KN189: 20MAY2019, KN407: 09MAY2019)

Database cutoff date for HNSCC (KN012 cohort B and B2: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)

Database cutoff date for cHL (KN013 cohort 3: 28SEP2018, KN087: 21MAR2019, KN204: 16JAN2020)

Database cutoff date for Bladder (KN045: 26OCT2017, KN052: 26SEP2018)

Database cutoff date for Esophageal (KN590: 02JUL2020)

Database cutoff date for CRC (KN177: 19FEB2020)

Database cutoff date for TNBC (KN355: 11DEC2019)

Database cutoff date for Cervical (KN826: 03MAY2021, KN028 cohort B4: 20FEB2017, KN158 cohort E: 27JUN2019)

Source: [ISS: adam-adsl; adae]

Region

Table 89. Adverse Event summary by Region (EU, ex-EU) (APaT Population)

	KN826 Pembrolizumab + Chemotherapy				KN826 Placebo + Chemotherapy				Pooled Safety Dataset for Pembrolizumab + Chemotherapy[f]				Cervical Safety Dataset for Pembrolizumab Monotherapy[d]				Pembrolizumab Monotherapy Reference Safety Dataset[e]			
	EU		Ex-EU		EU		Ex-EU		EU		Ex-EU		EU		Ex-EU		EU		Ex-EU	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	103		204		108		201		690		1,343		61		61		2,217		3,968	
with one or more adverse events	101	(98.1)	204	(100.0)	107	(99.1)	200	(99.5)	681	(98.7)	1,334	(99.3)	60	(98.4)	59	(96.7)	2,135	(96.3)	3,854	(97.1)
with no adverse event	2	(1.9)	0	(0.0)	1	(0.9)	1	(0.5)	9	(1.3)	9	(0.7)	1	(1.6)	2	(3.3)	82	(3.7)	114	(2.9)
with drug-related[†] adverse events	101	(98.1)	197	(96.6)	105	(97.2)	195	(97.0)	647	(93.8)	1,301	(96.9)	44	(72.1)	38	(62.3)	1,526	(68.8)	2,840	(71.6)
with toxicity grade 3-5 adverse events	79	(76.7)	172	(84.3)	74	(68.5)	158	(78.6)	515	(74.6)	1,068	(79.5)	35	(57.4)	30	(49.2)	1,022	(46.1)	1,962	(49.4)
with toxicity grade 3-5 drug-related adverse events	67	(65.0)	143	(70.1)	63	(58.3)	135	(67.2)	395	(57.2)	890	(66.3)	10	(16.4)	7	(11.5)	341	(15.4)	634	(16.0)
with serious adverse events	50	(48.5)	103	(50.5)	36	(33.3)	95	(47.3)	348	(50.4)	614	(45.7)	32	(52.5)	20	(32.8)	846	(38.2)	1,525	(38.4)
with serious drug-related adverse events	27	(26.2)	66	(32.4)	22	(20.4)	49	(24.4)	192	(27.8)	358	(26.7)	9	(14.8)	3	(4.9)	260	(11.7)	441	(11.1)
who died	3	(2.9)	11	(5.4)	6	(5.6)	8	(4.0)	49	(7.1)	90	(6.7)	2	(3.3)	2	(3.3)	113	(5.1)	208	(5.2)
who died due to a drug-related adverse event	1	(1.0)	1	(0.5)	3	(2.8)	1	(0.5)	9	(1.3)	34	(2.5)	0	(0.0)	0	(0.0)	11	(0.5)	28	(0.7)
discontinued any drug due to an adverse event	37	(35.9)	78	(38.2)	25	(23.1)	57	(28.4)	225	(32.6)	326	(24.3)	6	(9.8)	5	(8.2)	287	(12.9)	545	(13.7)
discontinued pembrolizumab or placebo	14	(13.6)	32	(15.7)	9	(8.3)	16	(8.0)	138	(20.0)	207	(15.4)	6	(9.8)	5	(8.2)	287	(12.9)	545	(13.7)
discontinued all drugs	6	(5.8)	12	(5.9)	6	(5.6)	9	(4.5)	46	(6.7)	79	(5.9)	6	(9.8)	5	(8.2)	287	(12.9)	545	(13.7)
discontinued any drug due to a drug-related adverse event	32	(31.1)	64	(31.4)	22	(20.4)	47	(23.4)	175	(25.4)	259	(19.3)	4	(6.6)	2	(3.3)	166	(7.5)	278	(7.0)
discontinued pembrolizumab or placebo	9	(8.7)	22	(10.8)	5	(4.6)	7	(3.5)	87	(12.6)	147	(10.9)	4	(6.6)	2	(3.3)	166	(7.5)	278	(7.0)
discontinued all drugs	5	(4.9)	5	(2.5)	4	(3.7)	2	(1.0)	24	(3.5)	52	(3.9)	4	(6.6)	2	(3.3)	166	(7.5)	278	(7.0)
discontinued any drug due to a serious adverse event	16	(15.5)	35	(17.2)	15	(13.9)	17	(8.5)	133	(19.3)	194	(14.4)	5	(8.2)	4	(6.6)	205	(9.2)	393	(9.9)
discontinued pembrolizumab or placebo	11	(10.7)	22	(10.8)	8	(7.4)	8	(4.0)	107	(15.5)	161	(12.0)	5	(8.2)	4	(6.6)	205	(9.2)	393	(9.9)
discontinued all drugs	6	(5.8)	11	(5.4)	6	(5.6)	5	(2.5)	43	(6.2)	67	(5.0)	5	(8.2)	4	(6.6)	205	(9.2)	393	(9.9)
discontinued any drug due to a serious drug-related adverse event	13	(12.6)	26	(12.7)	12	(11.1)	11	(5.5)	85	(12.3)	135	(10.1)	3	(4.9)	1	(1.6)	98	(4.4)	167	(4.2)
discontinued pembrolizumab or placebo	7	(6.8)	15	(7.4)	5	(4.6)	3	(1.5)	59	(8.6)	108	(8.0)	3	(4.9)	1	(1.6)	98	(4.4)	167	(4.2)
discontinued all drugs	5	(4.9)	5	(2.5)	4	(3.7)	0	(0.0)	21	(3.0)	42	(3.1)	3	(4.9)	1	(1.6)	98	(4.4)	167	(4.2)

[a] Determined by the investigator to be related to the drug.
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 preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.
Grades are based on NCI CTCAE version 4.0.
[d] Includes all participants who received at least one dose of pembrolizumab in KN028 cohort B4 and KN158 cohort E.
[e] 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, KN012 cohort B and B2, KN013 cohort 3, KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN087, KN177, and KN204.
[f] Includes all subjects who received at least one dose of pembrolizumab combo therapy in KN021 cohort A/C/G, KN048, KN189, KN355, KN407, and KN590.
Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 03APR2020)
Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEP2018, KN021: 19AUG2019, KN189: 20MAY2019, KN407: 09MAY2019)
Database cutoff date for HNSCC (KN012 cohort B and B2: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)
Database cutoff date for cHL (KN013 cohort 3: 28SEP2018, KN087: 21MAR2019, KN204: 16JAN2020)
Database cutoff date for Bladder (KN045: 26OCT2017, KN052: 26SEP2018)
Database cutoff date for Esophageal (KN590: 02JUL2020)
Database cutoff date for CRC (KN177: 19FEB2020)
Database cutoff date for TNBC (KN355: 11DEC2019)
Database cutoff date for Cervical (KN826: 03MAY2021, KN028 cohort B4: 20FEB2017, KN158 cohort E: 27JUN2019)

Source: [ISS: adam-adsl; adae]

Safety related to drug-drug interactions and other interactions

Please refer to the Discussion on clinical pharmacology.

Immunogenicity

No new immunogenicity data are available.

Discontinuation due to adverse events

Table 90. Participants With Adverse Events Resulting in Discontinuation of Any Treatment by System Organ Class and Preferred Term (Incidence >0% in One or More Treatment Groups) (APaT Population)

	KN826 Pembrolizumab + Chemotherapy		KN826 Placebo + Chemotherapy		Pooled Safety Dataset for Pembrolizumab + Chemotherapy[f]		Cervical Safety Dataset for Pembrolizumab Monotherapy[d]		Pembrolizumab Monotherapy Reference Safety Dataset[e]	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	307		309		2,033		122		6,185	
with one or more adverse events	115	(37.5)	82	(26.5)	551	(27.1)	11	(9.0)	832	(13.5)
with no adverse events	192	(62.5)	227	(73.5)	1,482	(72.9)	111	(91.0)	5,353	(86.5)
Blood and lymphatic system disorders	**12**	**(3.9)**	**10**	**(3.2)**	**60**	**(3.0)**	**0**	**(0.0)**	**12**	**(0.2)**
Anaemia	7	(2.3)	4	(1.3)	11	(0.5)	0	(0.0)	3	(0.0)
Autoimmune haemolytic anaemia	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Disseminated intravascular coagulation	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Febrile neutropenia	1	(0.3)	1	(0.3)	14	(0.7)	0	(0.0)	0	(0.0)
Haemolytic anaemia	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Immune thrombocytopenia	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Leukopenia	0	(0.0)	0	(0.0)	2	(0.1)	0	(0.0)	0	(0.0)
Neutropenia	3	(1.0)	3	(1.0)	24	(1.2)	0	(0.0)	1	(0.0)
Pancytopenia	1	(0.3)	0	(0.0)	3	(0.1)	0	(0.0)	0	(0.0)
Thrombocytopenia	2	(0.7)	2	(0.6)	9	(0.4)	0	(0.0)	3	(0.0)
Thrombotic microangiopathy	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)	0	(0.0)
Cardiac disorders	**4**	**(1.3)**	**1**	**(0.3)**	**30**	**(1.5)**	**0**	**(0.0)**	**36**	**(0.6)**
Acute coronary syndrome	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)	1	(0.0)
Acute myocardial infarction	1	(0.3)	0	(0.0)	1	(0.0)	0	(0.0)	2	(0.0)
Angina unstable	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)	0	(0.0)
Arrhythmia	0	(0.0)	0	(0.0)	2	(0.1)	0	(0.0)	0	(0.0)
Arteriospasm coronary	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)	0	(0.0)
Atrial fibrillation	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	3	(0.0)

	KN826 Pembrolizumab + Chemotherapy		KN826 Placebo + Chemotherapy		Pooled Safety Dataset for Pembrolizumab + Chemotherapy[f]		Cervical Safety Dataset for Pembrolizumab Monotherapy[d]		Pembrolizumab Monotherapy Reference Safety Dataset[e]	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Ear and labyrinth disorders	**1**	**(0.3)**	**1**	**(0.3)**	**11**	**(0.5)**	**0**	**(0.0)**	**0**	**(0.0)**
Deafness	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)	0	(0.0)
Hypoacusis	0	(0.0)	0	(0.0)	3	(0.1)	0	(0.0)	0	(0.0)
Ototoxicity	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)	0	(0.0)
Tinnitus	1	(0.3)	1	(0.3)	6	(0.3)	0	(0.0)	0	(0.0)
Endocrine disorders	**1**	**(0.3)**	**0**	**(0.0)**	**4**	**(0.2)**	**0**	**(0.0)**	**18**	**(0.3)**
Addison's disease	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Adrenal insufficiency	1	(0.3)	0	(0.0)	2	(0.1)	0	(0.0)	4	(0.1)
Hyperthyroidism	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	3	(0.0)
Hypophysitis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	5	(0.1)
Hypopituitarism	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	4	(0.1)
Hypothyroidism	0	(0.0)	0	(0.0)	2	(0.1)	0	(0.0)	2	(0.0)
Eye disorders	**1**	**(0.3)**	**0**	**(0.0)**	**2**	**(0.1)**	**0**	**(0.0)**	**3**	**(0.0)**
Cystoid macular oedema	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)	0	(0.0)
Iridocyclitis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Lacrimation increased	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)	0	(0.0)
Optic neuropathy	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Uveitis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Gastrointestinal disorders	**23**	**(7.5)**	**10**	**(3.2)**	**56**	**(2.8)**	**5**	**(4.1)**	**88**	**(1.4)**
Abdominal distension	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Abdominal pain	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)	1	(0.0)

	KN826 Pembrolizumab + Chemotherapy		KN826 Placebo + Chemotherapy		Pooled Safety Dataset for Pembrolizumab + Chemotherapy[f]		Cervical Safety Dataset for Pembrolizumab Monotherapy[d]		Pembrolizumab Monotherapy Reference Safety Dataset[e]	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
General disorders and administration site conditions	**8**	**(2.6)**	**7**	**(2.3)**	**49**	**(2.4)**	**0**	**(0.0)**	**87**	**(1.4)**
Localised oedema	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Malaise	1	(0.3)	0	(0.0)	2	(0.1)	0	(0.0)	2	(0.0)
Mucosal inflammation	0	(0.0)	0	(0.0)	8	(0.4)	0	(0.0)	1	(0.0)
Multiple organ dysfunction syndrome	0	(0.0)	0	(0.0)	2	(0.1)	0	(0.0)	2	(0.0)
Oedema	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	3	(0.0)
Oedema peripheral	0	(0.0)	0	(0.0)	4	(0.2)	0	(0.0)	0	(0.0)
Pain	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	7	(0.1)
Performance status decreased	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Physical deconditioning	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)	0	(0.0)
Prosthetic cardiac valve thrombosis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Pyrexia	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)	1	(0.0)
Sudden cardiac death	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)	0	(0.0)
Sudden death	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)	2	(0.0)
Swelling face	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Systemic inflammatory response syndrome	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Hepatobiliary disorders	**4**	**(1.3)**	**0**	**(0.0)**	**26**	**(1.3)**	**3**	**(2.5)**	**34**	**(0.5)**
Autoimmune hepatitis	1	(0.3)	0	(0.0)	11	(0.5)	0	(0.0)	12	(0.2)
Biliary obstruction	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Cholangitis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Cholangitis sclerosing	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)	0	(0.0)
Cholestasis	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)	0	(0.0)
Drug-induced liver injury	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)

	KN826 Pembrolizumab + Chemotherapy		KN826 Placebo + Chemotherapy		Pooled Safety Dataset for Pembrolizumab + Chemotherapy[f]		Cervical Safety Dataset for Pembrolizumab Monotherapy[d]		Pembrolizumab Monotherapy Reference Safety Dataset[e]	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Hepatobiliary disorders	**4**	**(1.3)**	**0**	**(0.0)**	**26**	**(1.3)**	**3**	**(2.5)**	**34**	**(0.5)**
Hepatic failure	0	(0.0)	0	(0.0)	2	(0.1)	0	(0.0)	3	(0.0)
Hepatic function abnormal	0	(0.0)	0	(0.0)	3	(0.1)	0	(0.0)	2	(0.0)
Hepatitis	0	(0.0)	0	(0.0)	6	(0.3)	2	(1.6)	9	(0.1)
Hepatitis toxic	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Hepatotoxicity	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Hyperbilirubinaemia	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.8)	1	(0.0)
Immune-mediated hepatitis	2	(0.7)	0	(0.0)	2	(0.1)	0	(0.0)	2	(0.0)
Liver disorder	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)	0	(0.0)
Liver injury	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Immune system disorders	**8**	**(2.6)**	**8**	**(2.6)**	**7**	**(0.3)**	**0**	**(0.0)**	**9**	**(0.1)**
Anaphylactic reaction	1	(0.3)	0	(0.0)	1	(0.0)	0	(0.0)	0	(0.0)
Anaphylactic shock	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Anaphylactoid reaction	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Autoimmune disorder	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Autoinflammatory disease	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Cytokine release syndrome	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Drug hypersensitivity	2	(0.7)	3	(1.0)	2	(0.1)	0	(0.0)	1	(0.0)
Hypersensitivity	4	(1.3)	4	(1.3)	4	(0.2)	0	(0.0)	0	(0.0)
Sarcoidosis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	3	(0.0)
Serum sickness	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Infections and infestations	**7**	**(2.3)**	**3**	**(1.0)**	**63**	**(3.1)**	**1**	**(0.8)**	**85**	**(1.4)**

	KN826 Pembrolizumab + Chemotherapy		KN826 Placebo + Chemotherapy		Pooled Safety Dataset for Pembrolizumab + Chemotherapy[f]		Cervical Safety Dataset for Pembrolizumab Monotherapy[d]		Pembrolizumab Monotherapy Reference Safety Dataset[e]	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Infections and infestations	**7**	**(2.3)**	**3**	**(1.0)**	**63**	**(3.1)**	**1**	**(0.8)**	**85**	**(1.4)**
Thrombophlebitis septic	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Tracheitis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Tuberculosis	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)	0	(0.0)
Urinary tract infection	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	3	(0.0)
Urosepsis	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)	5	(0.1)
Injury, poisoning and procedural complications	**5**	**(1.6)**	**3**	**(1.0)**	**10**	**(0.5)**	**0**	**(0.0)**	**12**	**(0.2)**
Alcohol poisoning	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)	0	(0.0)
Arterial injury	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Facial bones fracture	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Fall	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Femur fracture	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Infusion related reaction	3	(1.0)	3	(1.0)	7	(0.3)	0	(0.0)	3	(0.0)
Pneumonitis chemical	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Post procedural haemorrhage	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)	1	(0.0)
Radiation pneumonitis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Radiation proctitis	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Spinal fracture	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)	0	(0.0)
Traumatic intracranial haemorrhage	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Wound decomposition	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Wound haemorrhage	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Investigations	**11**	**(3.6)**	**5**	**(1.6)**	**69**	**(3.4)**	**0**	**(0.0)**	**49**	**(0.8)**

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.

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

[d] Includes all participants who received at least one dose of pembrolizumab in KN028 cohort B4 and KN158 cohort E.

[e] 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, KN012 cohort B and B2, KN013 cohort 3, KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN087, KN177, and KN204.

[f] Includes all subjects who received at least one dose of pembrolizumab combo therapy in KN021 cohort A/C/G, KN048, KN189, KN355, KN407, and KN590.

Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 03APR2020)

Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEP2018, KN021: 19AUG2019, KN189: 20MAY2019, KN407: 09MAY2019)

Database cutoff date for HNSCC (KN012 cohort B and B2: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)

Database cutoff date for cHL (KN013 cohort 3: 28SEP2018, KN087: 21MAR2019, KN204: 16JAN2020)

Database cutoff date for Bladder (KN045: 26OCT2017, KN052: 26SEP2018)

Database cutoff date for Esophageal (KN590: 02JUL2020)

Database cutoff date for CRC (KN177: 19FEB2020)

Database cutoff date for TNBC (KN355: 11DEC2019)

Database cutoff date for Cervical (KN826: 03MAY2021, KN028 cohort B4: 20FEB2017, KN158 cohort E: 27JUN2019)

Table 91. Participants With Adverse Events Resulting in Discontinuation of Any Treatment by System Organ Class and Preferred Term by Bevacizumab Use (Incidence >0% in One or More Treatment Groups) (APaT Population)

	KN826 Pembrolizumab + Chemotherapy w/ Bevacizumab		KN826 Pembrolizumab + Chemotherapy w/o Bevacizumab		KN826 Placebo + Chemotherapy w/ Bevacizumab		KN826 Placebo + Chemotherapy w/o Bevacizumab		Pembrolizumab Monotherapy Reference Safety Dataset[e]	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	196		111		193		116		6,185	
with one or more adverse events	88	(44.9)	27	(24.3)	61	(31.6)	21	(18.1)	832	(13.5)
with no adverse events	108	(55.1)	84	(75.7)	132	(68.4)	95	(81.9)	5,353	(86.5)
Blood and lymphatic system disorders	**8**	**(4.1)**	**4**	**(3.6)**	**8**	**(4.1)**	**2**	**(1.7)**	**12**	**(0.2)**
Anaemia	6	(3.1)	1	(0.9)	3	(1.6)	1	(0.9)	3	(0.0)
Autoimmune haemolytic anaemia	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Disseminated intravascular coagulation	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Febrile neutropenia	0	(0.0)	1	(0.9)	1	(0.5)	0	(0.0)	0	(0.0)
Haemolytic anaemia	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Immune thrombocytopenia	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Neutropenia	2	(1.0)	1	(0.9)	2	(1.0)	1	(0.9)	1	(0.0)
Pancytopenia	0	(0.0)	1	(0.9)	0	(0.0)	0	(0.0)	0	(0.0)
Thrombocytopenia	2	(1.0)	0	(0.0)	2	(1.0)	0	(0.0)	3	(0.0)
Cardiac disorders	**4**	**(2.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(0.9)**	**36**	**(0.6)**
Acute coronary syndrome	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Acute myocardial infarction	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Atrial fibrillation	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	3	(0.0)
Atrioventricular block complete	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Autoimmune pericarditis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Cardiac arrest	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)	7	(0.1)
Cardiac failure	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Cardiac failure acute	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Cardiac failure congestive	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Cardiac ventricular disorder	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Cardio-respiratory arrest	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	4	(0.1)
Ischaemic cardiomyopathy	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Left ventricular failure	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Myocardial infarction	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.9)	6	(0.1)
Myocardial necrosis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Myocarditis	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)	4	(0.1)
Pericardial effusion	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Stress cardiomyopathy	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

	KN826 Pembrolizumab + Chemotherapy w/ Bevacizumab		KN826 Pembrolizumab + Chemotherapy w/o Bevacizumab		KN826 Placebo + Chemotherapy w/ Bevacizumab		KN826 Placebo + Chemotherapy w/o Bevacizumab		Pembrolizumab Monotherapy Reference Safety Dataset[e]	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Ear and labyrinth disorders	**1**	**(0.5)**	**0**	**(0.0)**	**1**	**(0.5)**	**0**	**(0.0)**	**0**	**(0.0)**
Tinnitus	1	(0.5)	0	(0.0)	1	(0.5)	0	(0.0)	0	(0.0)
Endocrine disorders	**0**	**(0.0)**	**1**	**(0.9)**	**0**	**(0.0)**	**0**	**(0.0)**	**18**	**(0.3)**
Addison's disease	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Adrenal insufficiency	0	(0.0)	1	(0.9)	0	(0.0)	0	(0.0)	4	(0.1)
Hyperthyroidism	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	3	(0.0)
Hypophysitis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	5	(0.1)
Hypopituitarism	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	4	(0.1)
Hypothyroidism	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Eye disorders	**1**	**(0.5)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**3**	**(0.0)**
Iridocyclitis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Optic neuropathy	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Uveitis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Gastrointestinal disorders	**17**	**(8.7)**	**6**	**(5.4)**	**9**	**(4.7)**	**1**	**(0.9)**	**88**	**(1.4)**
Abdominal distension	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Abdominal pain	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Abdominal pain upper	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Anal fistula	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)	0	(0.0)
Anal haemorrhage	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Aptyalism	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Ascites	0	(0.0)	1	(0.9)	0	(0.0)	0	(0.0)	2	(0.0)
Autoimmune colitis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Autoimmune pancreatitis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Chronic gastritis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Colitis	1	(0.5)	2	(1.8)	0	(0.0)	0	(0.0)	29	(0.5)
Colitis microscopic	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Diarrhoea	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	13	(0.2)
Duodenal obstruction	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Duodenal perforation	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Enteritis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Enterocolitis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Enterocutaneous fistula	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)	0	(0.0)
Enterovesical fistula	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)	0	(0.0)
Gastric disorder	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Gastric haemorrhage	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)

	KN826 Pembrolizumab + Chemotherapy w/ Bevacizumab		KN826 Pembrolizumab + Chemotherapy w/o Bevacizumab		KN826 Placebo + Chemotherapy w/ Bevacizumab		KN826 Placebo + Chemotherapy w/o Bevacizumab		Pembrolizumab Monotherapy Reference Safety Dataset[e]	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
General disorders and administration site conditions	**7**	**(3.6)**	**1**	**(0.9)**	**5**	**(2.6)**	**2**	**(1.7)**	**87**	**(1.4)**
General physical health deterioration	1	(0.5)	0	(0.0)	1	(0.5)	0	(0.0)	10	(0.2)
Generalised oedema	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	4	(0.1)
Infusion site reaction	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)	0	(0.0)
Localised oedema	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Malaise	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Mucosal inflammation	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Multiple organ dysfunction syndrome	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Oedema	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	3	(0.0)
Pain	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	7	(0.1)
Performance status decreased	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Prosthetic cardiac valve thrombosis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Pyrexia	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Sudden death	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Swelling face	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Systemic inflammatory response syndrome	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Hepatobiliary disorders	**4**	**(2.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**34**	**(0.5)**
Autoimmune hepatitis	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)	12	(0.2)
Biliary obstruction	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Cholangitis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Drug-induced liver injury	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Hepatic failure	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	3	(0.0)
Hepatic function abnormal	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Hepatitis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	9	(0.1)
Hepatitis toxic	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Hepatotoxicity	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Hyperbilirubinaemia	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Immune-mediated hepatitis	2	(1.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Liver injury	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Immune system disorders	**6**	**(3.1)**	**2**	**(1.8)**	**7**	**(3.6)**	**1**	**(0.9)**	**9**	**(0.1)**
Anaphylactic reaction	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

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	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Infections and infestations	**5**	**(2.6)**	**2**	**(1.8)**	**3**	**(1.6)**	**0**	**(0.0)**	**85**	**(1.4)**
Septic shock	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	8	(0.1)
Soft tissue infection	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Staphylococcal bacteraemia	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Thrombophlebitis septic	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Tracheitis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Urinary tract infection	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	3	(0.0)
Urosepsis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	5	(0.1)
Injury, poisoning and procedural complications	**4**	**(2.0)**	**1**	**(0.9)**	**2**	**(1.0)**	**1**	**(0.9)**	**12**	**(0.2)**
Arterial injury	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Facial bones fracture	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Fall	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Femur fracture	0	(0.0)	1	(0.9)	0	(0.0)	0	(0.0)	0	(0.0)
Infusion related reaction	3	(1.5)	0	(0.0)	2	(1.0)	1	(0.9)	3	(0.0)
Pneumonitis chemical	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Post procedural haemorrhage	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Radiation pneumonitis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Radiation proctitis	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Traumatic intracranial haemorrhage	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Wound decomposition	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Wound haemorrhage	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Investigations	**8**	**(4.1)**	**3**	**(2.7)**	**3**	**(1.6)**	**2**	**(1.7)**	**49**	**(0.8)**
Alanine aminotransferase increased	2	(1.0)	0	(0.0)	0	(0.0)	2	(1.7)	21	(0.3)
Amylase increased	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Aspartate aminotransferase increased	2	(1.0)	0	(0.0)	0	(0.0)	1	(0.9)	20	(0.3)
Blood alkaline phosphatase increased	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Blood bilirubin increased	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	5	(0.1)
Blood creatine phosphokinase increased	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Blood creatinine increased	0	(0.0)	2	(1.8)	0	(0.0)	0	(0.0)	1	(0.0)
Blood uric acid increased	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Nervous system disorders	**10**	**(5.1)**	**5**	**(4.5)**	**14**	**(7.3)**	**6**	**(5.2)**	**52**	**(0.8)**
Ataxia	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Autoimmune neuropathy	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Axonal neuropathy	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Brain oedema	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Cerebral ischaemia	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)	1	(0.0)
Cerebrovascular accident	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	7	(0.1)
Cognitive disorder	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Coma	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Dementia	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Demyelinating polyneuropathy	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Embolic stroke	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Encephalitis autoimmune	0	(0.0)	1	(0.9)	0	(0.0)	0	(0.0)	1	(0.0)
Encephalopathy	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Epilepsy	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)

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	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Renal and urinary disorders	**12**	**(6.1)**	**0**	**(0.0)**	**9**	**(4.7)**	**3**	**(2.6)**	**28**	**(0.5)**
Acute kidney injury	5	(2.6)	0	(0.0)	1	(0.5)	2	(1.7)	8	(0.1)
Autoimmune nephritis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Azotaemia	2	(1.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Bladder diverticulum	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Chronic kidney disease	1	(0.5)	0	(0.0)	0	(0.0)	1	(0.9)	0	(0.0)
Glomerulonephritis membranous	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Haematuria	0	(0.0)	0	(0.0)	3	(1.6)	0	(0.0)	1	(0.0)
Hydronephrosis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Nephritis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Nephropathy	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Nephrotic syndrome	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Postrenal failure	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)	0	(0.0)
Proteinuria	5	(2.6)	0	(0.0)	2	(1.0)	0	(0.0)	0	(0.0)
Renal failure	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)	6	(0.1)
Renal impairment	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Tubulointerstitial nephritis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	4	(0.1)
Urinary tract obstruction	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Urogenital fistula	0	(0.0)	0	(0.0)	2	(1.0)	0	(0.0)	0	(0.0)
Reproductive system and breast disorders	**7**	**(3.6)**	**3**	**(2.7)**	**12**	**(6.2)**	**0**	**(0.0)**	**0**	**(0.0)**
Female genital tract fistula	4	(2.0)	2	(1.8)	7	(3.6)	0	(0.0)	0	(0.0)
Uterine haemorrhage	0	(0.0)	1	(0.9)	0	(0.0)	0	(0.0)	0	(0.0)
Vaginal fistula	2	(1.0)	0	(0.0)	2	(1.0)	0	(0.0)	0	(0.0)
Vaginal haemorrhage	1	(0.5)	0	(0.0)	3	(1.6)	0	(0.0)	0	(0.0)
Vulval ulceration	0	(0.0)	0	(0.0)	1	(0.5)	0	(0.0)	0	(0.0)
Respiratory, thoracic and mediastinal disorders	**3**	**(1.5)**	**0**	**(0.0)**	**1**	**(0.5)**	**2**	**(1.7)**	**201**	**(3.2)**
Acute respiratory failure	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	4	(0.1)
Aspiration	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Bronchostenosis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Chronic obstructive pulmonary disease	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	4	(0.1)
Cough	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Diffuse alveolar damage	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Dyspnoea	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	16	(0.3)

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.

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

[e] 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, KN012 cohort B and B2, KN013 cohort 3, KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN087, KN177, and KN204.

Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 03APR2020)

Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEP2018)

Database cutoff date for HNSCC (KN012 cohort B and B2: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)

Database cutoff date for cHL (KN013 cohort 3: 28SEP2018, KN087: 21MAR2019, KN204: 16JAN2020)
Database cutoff date for Bladder (KN045: 26OCT2017, KN052: 26SEP2018)
Database cutoff date for CRC (KN177: 19FEB2020)
Database cutoff date for Cervical (KN826: 03MAY2021)

Post marketing experience

The safety profile of pembrolizumab was summarized in the Periodic Safety Update Report covering the period 04-SEP-2019 through 03-SEP-2020, specifically Appendix 20.3 (Numbers of Adverse Reactions and Events by Preferred Term from Postauthorization Sources).

2.5.1. Discussion on clinical safety

The safety profile of pembrolizumab (KEYTRUDA®, MK-3475) in combination with chemotherapy with/without bevacizumab for the treatment of cervical tumours in adults is derived from the pivotal study KEYNOTE-826. In order to contextualise the study results with respect to the overall toxicity of pembrolizumab given as add-on to chemotherapeutic agents, the trial was analysed in comparison with a pooled safety dataset for pembrolizumab+chemotherapy including all indications for which pembrolizumab drug combinations are currently approved in the EU (n=2033). Moreover, to better characterise the contribution of pembrolizumab to the adverse events associated with the backbone therapy, the MAH also presented data by bevacizumab use. Supportive data were also submitted attaining the use of pembrolizumab as monotherapy in the intended indication, which derive from the Phase I and II studies KN028 (cohort B4) and KN158 (cohort E) (n=122); these populations were separately analysed from the large pembrolizumab monotherapy reference safety database (RSD=6185) that was also presented as comparative group.

With a cut-off date of 03 May 2021, KEYNOTE-826 includes a total of 616 participants allocated with a 1:1 randomisation scheme to the active and control arm. The majority of the study population received bevacizumab (196 patients, 63.8% in the pembrolizumab+chemotherapy group; 193 patients, 62.4% in the placebo+chemotherapy group). Overall, exposure in the placebo group was shorter than in pembrolizumab: 54.6% and 28.5% of total patients in the group of pembrolizumab+chemotherapy with and without bevacizumab had >12-month exposure vs 40.9% and 14.7% in the group of placebo+chemotherapy with and without bevacizumab, respectively. Of note, the use of bevacizumab was associated with a longer exposure to treatment in both arms (13.91 months in median vs 6.31 in the counterpart in the pembrolizumab arm and 9.69 vs 5.39 months in median in the placebo), likely due to a more favourable disease progression conferred by this treatment.

However, unlike the placebo arm, the pembrolizumab group showed a worse baseline performance score in patients not receiving bevacizumab (53.2% with ECOG 1 vs 34.7% with ECOG score 1 in the group with bevacizumab), which also could have concurred to the observed shorter length of treatment in this subgroup. Assignment of patients to bevacizumab was an investigator decision driven by the clinical conditions at baseline and the expected patient drug tolerability. It is therefore recognised that a poorer performance status in patients not receiving bevacizumab compared to those assigned to bevacizumab likely reflects the typology of patients generally excluded from treatment. The comparative datasets including pembrolizumab monotherapy in both participants with cervical tumour and RSD showed a more limited exposure length than study KEYNOTE-826 (>12-month exposure was in the 14.8% and 23.1% of the dataset, respectively); similarly, the pooled pembrolizumab+chemotherapy database provided data for a 12-month exposure in 27.1% of the recruited population.

According with disease epidemiology and clinical features, cervical tumour patients were younger (above 80% were aged <65-years compared to 59.9% and 58%) and with better ECOG score (above 50% with ECOG score 1 compared to 44.9% and 47.6%) than the pooled pembrolizumab+chemotherapy dataset and RSD.

The analysis of **overall adverse events** revealed an unfavourable outcome for the experimental therapy compared to placebo as demonstrated by increased frequency in grade 3-5 AEs (81.8% vs 75.1%), drug-related SAEs (30.3% vs 23%) and drug discontinuations (37.5%vs 26.5%) compared to control. Of note, fatalities were similar between groups (4.6% vs 4.5%). The rate of AE across all the different categories was overall consistent with the pooled dataset of pembrolizumab+chemotherapy. As expected, the drug combination tested in KEYNOTE-826 appeared worse than pembrolizumab monotherapy relatively to either the specific indication (cervical monotherapy) or the totality of treated patients across all different clinical settings (RSD); the only exception was for the rate of fatalities that was higher in the RSD, likely due to the older age and different tumour-specific clinical course of the RSD database. Exposure adjusted results confirmed a potentiating effect of pembrolizumab on chemotherapy-related AEs for what concerns the incidence of grade 3-5 drug-related AEs, drug-related SAEs and drug discontinuations due to AEs, all of them occurring with a similar incidence compared to the historical data on combined therapies as defined by the pooled pembrolizumab+chemotherapy dataset. The contribution of the individual component of the drug combination administrated in study KEYNOTE-826 varied, with the addition of bevacizumab worsening the safety profile of placebo+chemotherapy, which was further compromised by the addition of pembrolizumab particularly for the category of drug discontinuations. Overall, pembrolizumab+chemotherapy without bevacizumab appeared similarly tolerated than placebo+chemotherapy with bevacizumab.

The **pattern of AEs** was consistent with the known safety profiles of pembrolizumab, chemotherapy and bevacizumab. Specifically, alopecia, anaemia, nausea, diarrhea, fatigue, and system nervous disorders were among the most common (>20% of incidence) side effects across all chemotherapy subgroups regardless of the use of bevacizumab or pembrolizumab; in patients receiving bevacizumab, hypertension, rash, ALT increase and epistaxis occurred more frequently than in the absence of bevacizumab; pembrolizumab was associated with a higher rate of endocrine disturbances. Compared to the control arm, treatment with pembrolizumab enhanced the incidence of blood and lymphatic system disorders (72.3% vs 67.7%), endocrine disturbances (25.7% vs 12.65%), hepatobiliary disorders (6.2% vs 4.9%) that were also reflected in the higher incidence of laboratory investigation abnormalities mainly related to myelosuppression and liver dysfunction. The majority of these AEs were judged drug-related by Investigators. The rate of all these AEs was more frequent than previously reported in the pooled dataset of pembrolizumab+chemotherapy, likely because of the longer exposure of study KEYNOTE-826. However, the exposure-adjusted analysis by bevacizumab showed that pembrolizumab mainly contributed to the endocrine disturbances, while no impact of immunotherapy was apparent for the events in the other SOC categories.

In terms of severity, pembrolizumab mainly increased **Grade 3-5 AEs** (81.8% vs 75.1%) within the SOC category of blood and lymphatic system disorders (i.e. anaemia, neutrophil count decrease, trombocytopenia, febrile neutropenia) that are typically associated with the use of chemotherapeutic agents, while toxicity classically related to bevacizumab (i.e. hypertension) was not worsen. Among fatal AEs, however, the group treated with pembrolizumab+chemotherapy+bevacizumab more frequently presented events of cardiac and hemorragic nature in addition to sepsis, relatively to placebo.

As regards **SAEs** (50.5% vs 48.6%), events included febrile neutropenia (6.8% vs 4.2%), and anaemia (4.6% vs 3.9%) among those that were impaired by pembrolizumab treatment.

As expected, the incidence of **AEOSIs** was more frequent in the pembrolizumab group compared to placebo (69.23% vs 40.70%). The pattern of events was typical of pembrolizumab monotherapy as

colitis (6.5% vs 1.9%), hepatitis (1.6% vs 0.4%), hyperthyroidism (7.1% vs 3.8%), hypothyroidism (19.2% vs 12.1%), severe skin reactions (5% vs 0.4%), and pneumonitis (1.9% vs 0.4%) were among the most frequently reported events. There was one death related to AEOSIs in the experimental arm (0.3%).

The rate of AEOSIs (41% vs 26.5%), grade 3-5 AEOSIs (13.4% vs 5.2%), drug-related grade 3-5 AEOSIs (11.7% vs 4.2%) and any study drug dose discontinuation due to AESOIs (8.8% vs 3.6%) was above the previously reported experience of the pooled pembrolizumab+chemotherapy dataset. These data were confirmed by the exposure-adjusted analysis showing added toxicities for each drug component, with the combination of pembrolizumab+chemotherapy+bevacizumab displaying the worst safety profile, although the only AEOSI-related death occurred in the group of pembrolizumab-treated patients not receiving bevacizumab.

The data show added toxicities for each drug component and the different comparisons might be also impacted by different baseline characteristics (with generally younger and fitter patients in the EC indication compared to the pooled pembro+chemo dataset and with also generally more favourable baseline characteristics for the patients attributed to bevacizumab compared to those without bevacizumab).

The rate of **drug discontinuations** was higher in the pembrolizumab group compared to control, particularly in association with bevacizumab. The same trend was observable in the control arm.

Analysis by subgroups

Age: unlike the placebo arm, tolerability within the pembrolizumab treated patient group in combination with chemotherapy with/without bevacizumab worsened by age, as demonstrated by an increased incidence of events across all categories in patients aged >65 years compared to the <65-years of age counterpart. However, the requested exposure-adjusted analysis did not reveal significant differences between the two categories. The limited numerosity of the sample size for ages >75 years (n=10/arm) hampers definitive conclusion in this patient subgroup that, however, has been historically characterised by the worse pembrolizumab toxicity when administrated as add-on to chemotherapy.

Sex: considering that the totality of recruited patients were women, a sex-dependent analysis of toxicity is of scarce value.

ECOG score: Participants with a higher (1 vs 0) **ECOG** PS at baseline reported higher frequencies of fatalities in both treatment arms; pembrolizumab slightly augmented the toxicity of therapy in both ECOG score categories.

Race: Race does not seem to influence the toxicity profile of either regimens since similar rate of events is observable in white and non-white across all AEs categories; pembrolizumab worsened the toxicity of chemotherapy regardless of race.

Region: ex-EU showed a higher incidence of AEs than EU across all categories. No specific causes related to different patient management or study conduct between the two geographic areas could be identified.

2.5.2. Conclusions on clinical safety

Pembrolizumab as add-on to chemotherapy with/without bevacizumab impaired the overall toxicity of the backbone therapy with an increased frequency of adverse events than previously reported in other indications for which pembrolizumab+chemotherapy was licenced. The safety profile of the experimental treatment used in study KEYNOTE-826 reflected the established toxicity of the individual components of the drug combination. No new safety signals emerged. AEOSI were more frequent than previously registered in other chemotherapy/pembrolizumab associations, mainly with the concomitant use of bevacizumab. As expected, an age-dependent reduction in tolerability was observed.

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 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 35 is acceptable.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 35 with the following content:

Safety concerns

Table SVIII.1:Summary of Safety Concerns

Summary of safety concerns	
Important identified risks	Immune-related adverse reactions (including immune related pneumonitis, colitis, hepatitis, nephritis, and endocrinopathies)
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

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-Related Adverse Reactions		
Immune-related adverse reactions (including immune-related pneumonitis, colitis, hepatitis, nephritis and endocrinopathies)	Routine risk minimisation measures: The risk of the immune-related adverse reactions (including immune-related pneumonitis colitis, hepatitis, nephritis, and endocrinopathies) 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 Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted questionnaire for spontaneous postmarketing reports of all adverse events
	Additional risk minimisation measures: Patient educational materials	Additional pharmacovigilance including: • Safety monitoring in all ongoing MAH-sponsored clinical trials for pembrolizumab in various tumor types

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

Safety Concern	Risk minimisation Measures	Pharmacovigilance Activities
Important Potential Risks		
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. No additional risk minimisation measures warranted	Routine pharmacovigilance activities 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, 4.8, 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:

there are only minor changes in the leaflet section 1, currently no changes of the package leaflet are foreseen impacting the safe use of the medicinal product, moreover, no changes are foreseen in the design, layout and format of the package leaflet.

2.7.2. Additional monitoring

Pursuant to Article 23(3) of Regulation No (EU) 726/2004, Keytruda (pembrolizumab) has been removed from the additional monitoring list with the renewal procedure five years after the Union reference date.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Persistent, recurrent or metastatic cervical cancer not amenable to curative treatment, first line.

The adopted indication is "KEYTRUDA, in combination with chemotherapy with or without bevacizumab, is indicated for the treatment of persistent, recurrent, or metastatic cervical cancer in adults whose tumours express PD-L1 with a CPS ≥ 1".

3.1.2. Available therapies and unmet medical need

Cisplatin-based doublets with topotecan or paclitaxel have demonstrated superiority to cisplatin monotherapy as first line treatment of advanced/metastatic cancer, with cisplatin plus paclitaxel the preferred regimen based on the balance between efficacy and toxicity profile (ESMO GL; Monk BJ, 2009). The combination of paclitaxel and carboplatin could be considered an alternative for patients that are not candidates for cisplatin. The addition of bevacizumab to chemotherapy significantly prolonged overall survival as compared chemotherapy alone, at the expenses of higher toxicity (Tewari KS, 2014). The triplet combination bevacizumab-cisplatin-paclitaxel is considered the preferred first-line regimen in metastatic or recurrent cervical cancer (ESMO, NCCN).

3.1.3. Main clinical studies

KEYNOTE-826: a phase 3 randomized, double-blind, placebo-controlled trial of pembrolizumab plus chemotherapy (cisplatin or carboplatin plus paclitaxel) with or without bevacizumab vs placebo plus chemotherapy with or without bevacizumab for the 1L treatment of persistent, recurrent, or metastatic cervical cancer. Results of interim analysis 1 support the extension of indication application.

3.2. Favourable effects

- Statistically significant and clinically relevant improvement in OS in all the populations analysed (all-comers, CPS≥1, CPS≥10: in CPS≥1 OS HR 0.64, median OS NR (19.8, NR) vs 16.3 (14.5, 19.4) (gain in median OS of 8 months in the all-comers population), KM curves separated at month 3 and remain in favour of pembrolizumab combination.
- Statistically significant improvement in PFS by investigator for the addition of pembrolizumab to chemotherapy +/- bevacizumab in all the populations analysed (all-comers, CPS≥1, CPS≥10): in CPS≥1 PFS HR 0.62, gain in median PFS of 2 months.
- Supportive ORR and DOR trends: 18% increase in ORR, median DOR 18 vs 10.4 months in the CPS≥1 population.

3.3. Uncertainties and limitations about favourable effects

- Acknowledging the small number of subjects (34 vs 34), apparent lack of benefit in CPS<1 population: OS HR 1, PFS HR 0.94, ORR difference -6.4%, DOR 10.7 vs 8.5. This lack of benefit of

pembrolizumab in PD-L1 CPS<1 is supported by biological plausibility and external data (KEYNOTE-158). As a result, the MAH restricted the indication to CPS≥1 population.

3.4. Unfavourable effects

- increased frequency in grade 3-5 AEs (81.8% vs 75.1%), drug-related SAEs (30.3% vs 23%) and drug discontinuations (37.5% vs 26.5%) in the group of pembrolizumab+chemotherapy with/without bevacizumab compared to the control arm
- alopecia, anaemia, nausea, diarrhea, fatigue, and neuropathies were among the most common (>20% of incidence) side effects across all chemotherapy subgroups regardless of the use of bevacizumab or pembrolizumab
- in patients receiving bevacizumab, hypertension, rash, ALT increase and hepixtasis occurred more frequently than in the absence of bevacizumab in both treatment arms
- Compared to the control arm, treatment with pembrolizumab enhanced the incidence of blood and lymphatic system disorders (72.3% vs 67.7%), endocrine disturbances (25.7% vs 12.65%), hepatobiliary disorders (6.2% vs 4.9%)
- Pembrolizumab mainly increased **Grade 3-5 AEs** (81.8% vs 75.1%) within the SOC category of blood and lymphatic system disorders (i.e. anaemia, neutrophil count decrease, trombocytopenia, febrile neutropenia)
- As regards **SAEs** (50.5% vs 48.6%), events included febrile neutropenia (6.8% vs 4.2%), and anaemia (4.6% vs 3.9%) among those impaired by pembrolizumab treatment
- the incidence of **AEOSIs** was more frequent in the pembrolizumab group compared to placebo (69.23% vs 40.70%). The pattern of events is typical of pembrolizumab monotherapy as colitis (6.5% vs 1.9%), hepatitis (1.6% vs 0.4%), hyperthyroidism (7.1% vs 3.8%), hypothyroidism (19.2% vs 12.1%), severe skin reactions (5% vs 0.4%), and pneumonitis (1.9% vs 0.4%) were among the most frequently reported events.
- The rate of AEOSIs (41% vs 26.5%), grade 3-5 AEs (13.4% vs 5.2%), drug-related grade 3-5 AEs (11.7% vs 4.2%) and any study drug dose discontinuation due to AESOIs (8.8% vs 3.6%) was above the previously reported experience of the pooled pembrolizumab+chemotherapy dataset. These data were confirmed by the exposure-adjusted analysis and with the combination of pembrolizumab+chemotherapy+bevacizumab displaying the worst safety profile.

3.5. Uncertainties and limitations about unfavourable effects

None.

3.6. Effects Table

Table 92. Effects Table for Keytruda in persistent, recurrent, or metastatic cervical cancer in adults (study KEYNOTE-826, data cut-off: 03 May 2021)

Effect	Short description	Unit	Treatment Pembro + chemo +/- beva	Control Placebo + chemo +/- beva	Uncertainties / Strength of evidence	References
Favourable Effects in PD-L1 CPS⩾1 population						
PFS (by inv	Time from randomization to first documented	months (95% CI)	CPS≥1: 10.4 (9.7, 12.3)	CPS≥1: 8.2 (6.3, 8.5)	Statistically significant and clinically relevant	CSR KN-826

Effect	Short description	Unit	Treatment Pembro + chemo +/- beva	Control Placebo + chemo +/- beva	Uncertainties / Strength of evidence	References
per RECIST 1.1)	disease progression per RECIST 1.1 based on investigator or death due to any cause, whichever occurs first		CPS≥1: 0.62 (0.50, 0.77), p<0.0001		survival advantage in all populations analysed (all-comers, CPS≥1, CPS≥10)/ supportive ORR and DOR/due to the lack of benefit in CPS<1 population indication was restricted to CPS ⩾1	
OS	Time from randomization to death due to any cause	months (95% CI)	CPS≥1: NR (19.8, NR)	CPS≥1: 16.3 (14.5, 19.4)		
			CPS≥1: 0.64 (0.50, 0.81), p<0.0001			
ORR	Confirmed CR or PR (by inv per RECIST 1.1)	% (95% CI)	CPS≥1: 68.1 (62.2, 73.6)	CPS≥1: 50.2 (44.1, 56.2)		
DOR	Time from first response to PD or death due to any cause, whichever occurs first, in subjects who achieve a PR or CR	months (range)	CPS≥1: 18 (1.3+, 24.2+)	CPS≥1: 10.4 (1.5+, 22+)		
PFS by BICR	Time from randomization to first documented disease progression per RECIST 1.1 based on BICR or death due to any cause, whichever occurs first	months (95% CI)	CPS≥1: 12.8 (10.4, 20.6)	CPS≥1: 8.3 (7.7, 9.2)	PFS by BICR consistent with PFS by investigator	
			CPS≥1: 0.60 (0.48, 0.75)			
Unfavourable Effects						
AE summary	AE	%	99.3	99.4	Pembrolizumab increased the toxicity of the SoC. AEOSI were higher compared to other pembrolizumab+chemotherapy combination, mostly in the presence of bevacizumab.	CSR KN-826
	drug related AE	%	97.1	97.1		
	G3-5 AE	%	81.8	75.1		
	drug related G3-5 AE	%	68.4	64.1		
	SAE	%	49.8	42.4		
	drug related SAE	%	30.3	23		
	death due to AE	%	3.9	4.9		
	death due to drug related AE	%	0.7	1.3		
	discontinuation due to AE	%	37.5	26.5		
	discontinuation due to drug related AE	%	31.3	22.3		
AEOSI	hypothyroidism	%	12.4	2.1		
	Hyperthyroidism	%	7.1	3.8		
	colitis	%	6.5	1.9		

Effect	Short description	Unit	Treatment Pembro + chemo +/- beva	Control Placebo + chemo +/- beva	Uncertainties / Strength of evidence	References
	Severe skin reactions	%	5	0.4		
	Pneumonitis	%	1.9	0.4		

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Pembrolizumab as add-on to chemotherapy with/without bevacizumab in the pivotal study KEYNOTE-826 demonstrated statistically significant and clinically meaningful improvement in OS at the interim analysis, supported by statistically significant PFS and positive ORR and DOR trends as compared to placebo+chemotherapy with/without bevacizumab. Such results were observed consistently in all the populations analysed (all-comers, CPS≥1 and CPS≥10). However, the results in the all-comers population are driven by PD-L1 positive disease, as apparent lack of benefit is observed in patients with PD-L1 negative tumours (CPS<1). Acknowledging that this represent only a small subgroup not included in the multiplicity strategy, biological plausibility is supported by the results of pembrolizumab monotherapy in 2L cervical cancer. The MAH has restricted the indication to CPS≥1 population. Although results were from interim analysis, the median follow up, number of events and subjects who had discontinued treatment are considered sufficient to conclude on the B/R in the sought indication in view of the overall data provided. All the populations analysed for efficacy impaired the overall toxicity of the backbone therapy with an increased frequency of adverse events than previously reported in other indications for which pembrolizumab+chemotherapy was licenced. The safety profile of the experimental treatment used in study KEYNOTE-826 reflected the established toxicity of the individual components of the drug combination. No new safety signals emerged. AEOSI were more frequent than previously reported in other chemotherapy/pembrolizumab associations, mainly observed with the concomitant use of bevacizumab. As expected, an age-dependent reduction in tolerability was observed.

3.7.2. Balance of benefits and risks

Relevant benefit is observed from the experimental therapy as compared to standard treatment for first line treatment of persistent, recurrent or metastatic cervical cancer. However, the CPS<1 population did not appear to benefit from the addition of pembrolizumab to standard treatment. Despite the add-on toxicity, the benefit outweighs the risks in the PD-L1 CPS≥1 population.

3.7.3. Additional considerations on the benefit-risk balance

According to data utilization provided by the MAH, the use of platinum doublet in 1L +/- bevacizumab is the standard of care globally, and platinum-paclitaxel doublet is the most used chemotherapy doublet worldwide. The use of topotecan in 1L (which can be associated with paclitaxel and bevacizumab in 1L cervical cancer as per bevacizumab label) appears limited and this drug tends to be used as monotherapy in 2L or 3L.

Based on prior experience for pembrolizumab in combination with chemotherapy, it has been observed that safety of combination regimens usually reflects the established toxicity of the individual components of the combined drug. As a result, physicians experienced in the use of anticancer drugs might be expected to be able to manage side effect of a combination with anti-PD(L)1.

On the other hand, uncertainties might be raised due to the lack of safety data for the combination with any topotecan-based regimens, along with difficulties to conclude on the possibility to extrapolate from irinotecan to topotecan. However, any combination with topotecan-based treatment might be expected to be limited in clinical practice, as discussed above.

With regard to efficacy aspects, it seems unlikely that the added benefit of pembrolizumab would change if added to one or another regimen considered active in a certain disease/setting.

To conclude, the B/R can be considered positive for general use "in combination with chemotherapy" as in the sought indication.

3.8. Conclusions

The overall B/R of Keytruda in combination with chemotherapy, with or without bevacizumab, for the treatment of persistent, recurrent, or metastatic cervical cancer in adults in PD-L1 CPS≥1 population is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends 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, II and IIIB

Extension of indication to include a new indication for Keytruda, in combination with chemotherapy, with or without bevacizumab, for the treatment of persistent, recurrent, or metastatic cervical cancer in adults; as a consequence, sections 4.1, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 35 of the RMP has also been submitted.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I, II and IIIB and to the Risk Management Plan are recommended.

5. EPAR changes

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

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion ‘Keytruda-H-C-3820-II-0117’