EU RISK MANAGEMENT PLAN (RMP) FOR

pembrolizumab IV

RMP version to be assessed as part of this application:

RMP Version number: 42.0

Data lock point for this RMP: 03-SEP-2023

Date of final sign off: 28-FEB-2024

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Rationale for submitting an updated RMP:

Addition of a new indication for pembrolizumab, in combination with platinum-containing chemotherapy as neoadjuvant treatment, and then continued as monotherapy as adjuvant treatment, for the treatment of resectable non-small cell lung carcinoma at high risk of recurrence in adults.

Summary of significant changes in this RMP:

Addition of study KEYNOTE-671 in Modules SIII, SVII, and SVIII; no changes to the risk profile in Modules SIII, SVII, and SVIII.

Other RMP versions under evaluation:

- **RMP Version:** 44.1

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Details of the currently approved RMP:

- **Version number: 41.0**

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Qualified Person for Pharmacovigilance (QPPV) name*:* Peter De Veene, MD

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation holder´s QPPV. The electronic signature is available on file.

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LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
AEOSI	Adverse Events of Special Interest
AJCC	American Joint Committee on Cancer
ALT	Alanine Aminotransferase
APaT	All Patients as Treated
ASaT	All Subjects as Treated
ASCT	Autologous Stem Cell Transplant
ASE	Aggregate Safety Evaluation
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical classification system
AUC	Area Under the Curve
BICR	Blinded Independent Central Review
BTC	Biliary Tract Carcinoma
CCA	Cholangiocarcinoma
cHL	classical Hodgkin Lymphoma
CPS	Combined Positive Score
CR	Complete response
CRC	Colorectal Cancer
CT	Clinical Trial
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	Cytotoxic T-Lymphocyte-Associated Antigen 4
CVD	Cardiovascular Disease
DBL	Database Lock
dMMR	Mismatch Repair Deficient
EC	Endometrial carcinoma
EEA	European Economic Area
EGFR	Epidermal Growth Factor Receptor
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
EPAR	European Public Assessment Report
EU	European Union
GEJ	Gastro-esophageal Junction
GVHD	Graft Versus Host Disease
HCP	Health Care Provider
HGB	Hemoglobin

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HIV	Human Immunodeficiency Virus
HL	Hodgkin Lymphoma
HNSCC	Head and Neck Squamous Cell Carcinoma
HSCT	Hematopoietic Stem Cell Transplant
IgG4	Immunoglobulin G4
IM	Intramuscular(ly)
INN	International Nonproprietary Name
IPI	Ipilimumab
IV	Intravenous(ly)
KN	KEYNOTE
mAb	Humanized monoclonal antibody
MAH	Marketing Authorisation Holder
MNP	Malignant neoplasm progression
MSI-H	Microsatellite Instability-High
MSS	Microsatellite Stable
N/A	Not Applicable
NAFLD	Nonalcoholic fatty liver disease
NASH	Nonalcoholic steatohepatitis
NCI	National Cancer Institute
NED	No Evidence of Disease
NHL	Non-Hodgkin Lymphoma
NSCLC	Non-Small Cell Lung Cancer
ORR	Objective Response Rate
OS	Overall Survival
PAES	Post-Authorisation Efficacy Studies
pCR	Pathological Complete Response
PD	Pharmacodynamics
PD-1	Programmed Cell Death-1
PD-L1	Programmed Cell Death 1 Ligand
PD-L2	Programmed Cell Death 2 Ligand
PFS	Progression Free Survival
PK	Pharmacokinetics
PIP	Pediatric Investigation Plans
PM	Postmarketing
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic Safety Update Report
Q2W	Every 2 weeks
Q3W	Every 3 weeks

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QPPV	Qualified Person for Pharmacovigilance
RCC	Renal Cell Carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RMP	Risk Management Plan
SAE	Serious Adverse Event
SCT	Stem Cell Transplantation
SOC	Standard of Care
SmPC	Summary of Product Characteristics
SMQ	Standardized MedDRA Query
TNBC	Triple-Negative Breast Cancer
TPC	Treatment of Physician's Choice
TPS	Tumor Proportion Score
ULN	Upper Limit of Normal
US	United States
VOD	Veno-occlusive Disease
UC	Urothelial Carcinoma

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PART I: PRODUCT(S) OVERVIEW

Table I.1: Product Overview

Active substance(s) **(International Nonproprietary Name (INN) or common name)**	Pembrolizumab
Pharmacotherapeutic group(s) (Anatomical Therapeutic Chemical classification system (ATC) Code)	L01FF02
Marketing Authorisation	Merck Sharp & Dohme B.V. Waarderweg 39 2031 BN Haarlem The Netherlands
Number of medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	KEYTRUDA®
Marketing authorisation procedure	Centralised
Brief description of the product	Chemical class: Humanized monoclonal anti PD-1 antibody
	Summary of mode of action: Pembrolizumab is a potent and highly-selective humanized monoclonal antibody (mAb) of the Immunoglobulin G4 (IgG4)/kappa isotype directed to the programmed cell death-1 (PD-1) receptor and designed to directly block the interaction between the receptor and its ligands, PD-L1 and PD-L2. The PD-1 pathway represents a major immune control switch which may be engaged by tumor cells to overcome active T-cell immune surveillance.
	Important information about its composition: Pembrolizumab is presented as: - a sterile, preservative-free, clear to slightly opalescent, colourless to slightly yellow solution. Each vial of 4 mL contains 100 mg of pembrolizumab.
Hyperlink to the Prescribing Information	Refer to the proposed Product Information in module 1.3.1.
Indication(s) in the EEA	Current: Melanoma KEYTRUDA as monotherapy is indicated for the treatment of adults and adolescents aged 12 years and older with advanced (unresectable or metastatic) melanoma. KEYTRUDA as monotherapy is indicated for the adjuvant treatment of adults and adolescents aged 12 years and older with Stage IIB, IIC or III melanoma and who have undergone complete resection. Non small cell lung carcinoma (NSCLC) KEYTRUDA in combination with platinum-containing chemotherapy as neoadjuvant treatment, and then continued as monotherapy as adjuvant treatment, is indicated for the treatment of resectable non-small cell lung carcinoma at high risk of recurrence in adults. KEYTRUDA as monotherapy is indicated for the adjuvant treatment of adults with non-small cell lung carcinoma who are at high risk of recurrence following complete resection and platinum based chemotherapy.

Table I.1: Product Overview

	KEYTRUDA as monotherapy is indicated for the first-line treatment of metastatic non-small cell lung carcinoma (NSCLC) in adults whose tumours express PD-L1 with a ≥50% tumour proportion score (TPS) with no EGFR or ALK positive tumour mutations. KEYTRUDA, in combination with pemetrexed and platinum chemotherapy, is indicated for the first-line treatment of metastatic non-squamous NSCLC in adults whose tumours have no EGFR or ALK positive mutations. KEYTRUDA in combination with carboplatin and either paclitaxel or nab-paclitaxel is indicated for the first-line treatment of metastatic squamous NSCLC in adults. KEYTRUDA as monotherapy is indicated for the treatment of locally advanced or metastatic NSCLC in adults whose tumours express PD-L1 with a ≥1% TPS and who have received at least one prior chemotherapy regimen. Patients with EGFR or ALK positive tumour mutations should also have received targeted therapy before receiving KEYTRUDA. <u>Classical Hodgkin lymphoma (cHL)</u> KEYTRUDA as monotherapy is indicated for the treatment of adult and paediatric patients aged 3 years or older with relapsed or refractory classical Hodgkin Lymphoma (cHL) who have failed autologous stem cell transplant (ASCT) or following at least two prior therapies when ASCT is not a treatment option. <u>Urothelial carcinoma</u> KEYTRUDA as monotherapy is indicated for the treatment of locally advanced or metastatic urothelial carcinoma in adults who have received prior platinum-containing chemotherapy. KEYTRUDA as monotherapy is indicated for the treatment of locally advanced or metastatic urothelial carcinoma in adults who are not eligible for cisplatin-containing chemotherapy, and whose tumours express PD L1 with a combined positive score (CPS) ≥ 10. <u>Head and neck squamous cell carcinoma (HNSCC)</u> KEYTRUDA, as monotherapy or in combination with platinum and 5-fluorouracil (5-FU) chemotherapy, is indicated for the first-line treatment of metastatic or unresectable recurrent head and neck squamous cell carcinoma (HNSCC) in adults whose tumours express PD-L1 with a CPS ≥ 1. KEYTRUDA as monotherapy is indicated for the treatment of recurrent or metastatic HNSCC in adults whose tumours express PD-L1 with a ≥ 50% TPS and progressing on or after platinum-containing chemotherapy. <u>Renal cell carcinoma (RCC)</u> KEYTRUDA, in combination with axitinib, is indicated for the first-line treatment of advanced renal cell carcinoma (RCC) in adults. KEYTRUDA, in combination with lenvatinib, is indicated for the first-line treatment of advanced renal cell carcinoma (RCC) in adults. KEYTRUDA as monotherapy is indicated for the adjuvant treatment of adults with renal cell carcinoma at increased risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions.

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Table I.1: Product Overview

	Microsatellite instability high (MSI-H) or mismatch repair deficient (dMMR) cancers Colorectal cancer (CRC) KEYTRUDA as monotherapy is indicated for adults with microsatellite instability high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer in the following settings: - first-line treatment of metastatic colorectal cancer; - treatment of unresectable or metastatic colorectal cancer after previous fluoropyrimidine-based combination therapy. Non-colorectal cancers KEYTRUDA as monotherapy is indicated for the treatment of the following MSI H or dMMR tumours in adults with: - advanced or recurrent endometrial carcinoma, who have disease progression on or following prior treatment with a platinum containing therapy in any setting and who are not candidates for curative surgery or radiation; - unresectable or metastatic gastric, small intestine, or biliary cancer, who have disease progression on or following at least one prior therapy. Oesophageal carcinoma KEYTRUDA, in combination with platinum and fluoropyrimidine based chemotherapy, is indicated for the first-line treatment of patients with locally advanced unresectable or metastatic carcinoma of the oesophagus in adults whose tumours express PD-L1 with a CPS ≥ 10. Triple negative breast cancer (TNBC) KEYTRUDA, in combination with chemotherapy as neoadjuvant treatment, and then continued as monotherapy as adjuvant treatment after surgery, is indicated for the treatment of adults with locally advanced, or early-stage triple-negative breast cancer (TNBC) at high risk of recurrence. KEYTRUDA, in combination with chemotherapy, is indicated for the treatment of locally recurrent unresectable or metastatic triple-negative breast cancer (TNBC) in adults whose tumors express PD-L1 with a CPS ≥10 and who have not received prior chemotherapy for metastatic disease. Endometrial carcinoma (EC) KEYTRUDA, in combination with lenvatinib, is indicated for the treatment of advanced or recurrent endometrial carcinoma in adults who have disease progression on or following prior treatment with a platinum-containing therapy in any setting and who are not candidates for curative surgery or radiation. Cervical cancer 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.Gastric or gastro-oesophageal junction adenocarcinoma KEYTRUDA, in combination with trastuzumab, fluoropyrimidine- and platinum-containing chemotherapy, is indicated for the first-line treatment of locally advanced unresectable or metastatic HER2-positive gastric or gastro-oesophageal junction adenocarcinoma in adults whose tumours express PD-L1 with a CPS ≥ 1. KEYTRUDA, in combination with fluoropyrimidine and platinum -containing chemotherapy, is indicated for the first-line treatment of locally advanced unresectable or metastatic HER2-negative gastric or gastro-oesophageal junction adenocarcinoma in adults whose tumours express PD-L1 with a CPS ≥ 1.

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Table I.1: Product Overview

	Biliary tract carcinoma (BTC) KEYTRUDA, in combination with gemcitabine and cisplatin, is indicated for the first-line treatment of locally advanced unresectable or metastatic biliary tract carcinoma in adults. Proposed: Not applicable
Pharmaceutical form(s) and strengths	Current: 100 mg liquid pembrolizumab in a 10 mL single-use vial
	Proposed: Not applicable
Posology and route of administration in the EEA	The recommended dose of KEYTRUDA in adults is either 200 mg every 3 weeks or 400 mg every 6 weeks administered as an intravenous infusion over 30 minutes. The recommended dose of KEYTRUDA as monotherapy in paediatric patients aged 3 years and older with cHL or patients aged 12 years and older with melanoma is 2 mg/kg bodyweight (bw) (up to a maximum of 200 mg), every 3 weeks administered as an intravenous infusion over 30 minutes. For use in combination, see the Summary of Product Characteristics (SmPC) for the concomitant therapies. Patients should be treated with KEYTRUDA until disease progression or unacceptable toxicity (and up to maximum duration of therapy if specified for an indication). Atypical responses (i.e. an initial transient increase in tumour size or small new lesions within the first few months followed by tumour shrinkage) have been observed. It is recommended to continue treatment for clinically stable patients with initial evidence of disease progression until disease progression is confirmed. For the adjuvant treatment of melanoma, NSCLC, or RCC, KEYTRUDA should be administered until disease recurrence, unacceptable toxicity, or for a duration of up to one year. For the neoadjuvant and adjuvant treatment of TNBC, patients should be treated with neoadjuvant KEYTRUDA in combination with chemotherapy for 8 doses of 200 mg every 3 weeks or 4 doses of 400 mg every 6 weeks or until disease progression that precludes definitive surgery or unacceptable toxicity, followed by adjuvant treatment with KEYTRUDA as monotherapy for 9 doses of 200 mg every 3 weeks or 5 doses of 400 mg every 6 weeks or until disease recurrence or unacceptable toxicity. Patients who experience disease progression that precludes definitive surgery or unacceptable toxicity related to KEYTRUDA as neoadjuvant treatment in combination with chemotherapy should not receive KEYTRUDA monotherapy as adjuvant treatment.
Is/will the product be subject to additional monitoring in the EU?	No

PART II: SAFETY SPECIFICATION

PART II: MODULE SI - EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

Melanoma

Incidence and prevalence:

Over 80% of the world's 287,700 annual new cases of melanoma occur in Australia, Europe, or North America [Ref. 5.4: 05DXHB]. Incidence varies according to geographic latitude, with the highest rates (per 100,000) found in Australia and New Zealand (33.6) and lowest in South-Central Asia (0.3) [Ref. 5.4: 05DXHB]. In Europe, incidence (per 100,000) ranges from 5.3 in the Central/Eastern region to 18.8 in Western countries, with 144,209 incident cases expected in 2018 [Ref. 5.4: 05DXHB]. In the United States (US), incidence is 22.2 per 100,000, corresponding to 96,480 new cases in 2019 [Ref. 5.4: 05DN03]. The 5-year prevalence in Europe is 494,111 cases [Ref. 5.4: 05DXHB].

Demographics of the indication population and risk factors for the disease:

Although melanoma incidence increases by age worldwide with a median age at diagnosis of 65 years [Ref. 5.4: 05DN03], it is one of the most common cancers among adolescents and young adults [Ref. 5.4: 05DR9D]. Incidence is higher for females until age 45-55, after which rates are higher among males [Ref. 5.4: 04KB3D, 03MS03]. Risk factors include fair skin, multiple dysplastic nevi, and family history of melanoma; ultraviolet light also plays a role [Ref. 5.4: 03MS0N].

The main existing treatment options

Most patients with early-stage disease will be cured by excision [Ref. 5.4: 05DLL8]. Adjuvant radiation therapy may be used for select patients with positive nodes or other features predicting high risk of relapse. For metastatic or unresectable melanoma, multiple targeted therapies have been FDA-approved, including immune checkpoint inhibitors, BRAF V600 targeted treatment, and BRAF/MEK combinations. Several drugs within these classes have been approved in the adjuvant setting.

Natural history of the indicated condition, including mortality and morbidity:

Mortality rates (per 100,000) are highest in Australia and New Zealand (3.4) and lowest in South-Central Asia (0.19) [Ref. 5.4: 05DXHB]. In Europe, mortality (per 100,000) ranges from 1.5 in the Southern region to 2.0 in Northern countries, with 27,147 deaths expected in 2018 [Ref. 5.4: 05DXHB]. In the US and Europe, the 5-year relative survival is 92% and 83%, respectively [Ref. 5.4: 04KJJL, 05DN03]. Stage-specific overall survival varies across Europe, as follows: 95%–100% (stage I), 65%–92.8% (stage II), 41%–71% (stage III), and 9%–28% (stage IV) [Ref. 5.4: 05DRW3].

Important co-morbidities

Most melanomas occur among adults over age 50 [Ref. 5.4: 05DN03] for whom there is an increased risk of cardiovascular or cerebrovascular diseases, diabetes, and secondary cancers compared to younger adults [Ref. 5.4: 057XQG]. A higher prevalence of comorbidity may be associated with higher melanoma stage [Ref. 5.4: 05DQKR, 03N0KS].

Non-Small Cell Lung Cancer (NSCLC)

Incidence and prevalence:

Approximately 2,206,771 new lung cancer cases were diagnosed worldwide in 2020 [Ref. 5.4: 07XQ8W], with greater than 80% of all lung cancers being classified as NSCLC [Ref. 5.4: 05HV4Z]. Globally, lung cancer is the second most commonly diagnosed tumor type (11.4%), second only to breast cancer (11.7%) [Ref. 5.4: 07XQ8W] and incidence varies widely with smoking prevalence [Ref. 5.4: 05QDW7]. The age-standardized incidence rate (per 100,000) of NSCLC (with appropriate proportions applied (80%)) [Ref. 5.4: 05QDW7] is highest in Polynesia/Micronesia (29.4), Eastern Asia (27.5), and North America (26.1); rates are lowest in most of Africa (5.0) [Ref. 5.4: 05QDW7]. In Europe, NSCLC incidence ranges from 21.5 in Central/Eastern countries to 26.2 in the Western region, with 382,027 new cases expected in 2020 [Ref. 5.4: 05QDW7]. The 5-year prevalence of NSCLC in Europe is 466,339 cases [Ref. 5.4: 05QDW7]. In the US, NSCLC incidence is 26.5 per 100,000, corresponding to 182,300 new cases in 2020, with a 5-year prevalence of 236,210 cases [Ref. 5.4: 05QDW7].

Demographics of the indication population and risk factors for the disease:

Lung cancer is most frequently diagnosed between the ages of 65 and 74 years [Ref. 5.4: 058TT3]. In both the US and across Europe, incidence and mortality rates are higher in men than women [Ref. 5.4: 05QDW7], with incidence rising in women [Ref. 5.4: 05DQP9]. Tobacco exposure is the primary risk factor for developing lung cancer [Ref. 5.4: 05DQP9] and two-thirds of lung cancer deaths are attributable to smoking [Ref. 5.4: 05QDW7].

The main existing treatment options

Surgery provides the best chance for a cure among patients with stage I or II disease [Ref. 5.4: 05DMDQ]. Chemoradiation may improve survival for locally advanced unresectable disease. Patients with metastatic disease may achieve improved survival and palliation of symptoms with chemotherapy (typically a platinum doublet), targeted agents, checkpoint inhibitors, and other supportive measures combined or alone.

Natural history of the indicated condition, including mortality and morbidity:

Worldwide, lung cancer was the leading cause (18.0%) of all cancer deaths (1.8 million) in 2020 [Ref. 5.4: 05QDW7]. In Europe, the age-standardized mortality rate (per 100,000) of NSCLC (with appropriate proportions applied (80%)) [Ref. 5.4: 05HV4Z] ranged from 16.1 in Northern countries to 19.0 in the Western region [Ref. 5.4: 07XQ8W]. Lung cancer survival is poor in Europe with 1-year and 5-year relative survival of 39% and 13%, respectively [Ref. 5.4: 05DPLK].

Important co-morbidities:

As lung cancer is primarily a disease of the aged and most common among smokers, cardiovascular disease (CVD), chronic obstructive pulmonary (COPD), diabetes, and other malignancies are expected to be the most prevalent comorbidities in NSCLC [Ref. 5.4: 0439J6].

Hodgkin Lymphoma (HL)

Incidence and prevalence:

Hodgkin lymphoma (HL) is a rare lymphoid malignancy of B-cell origin involving the lymph nodes and lymphatic system [Ref. 5.4: 052ZM2]. There are two major variants of HL, the uncommon nodular lymphocyte predominant (NLP) subtype (<10%) and the classical variety divided into four subtypes (lymphocyte-rich, 5%; nodular sclerosis, 70%; mixed cellularity, 20-25%; or lymphocyte-depleted, <1%) [Ref. 5.4: 052ZM2]. The estimated new cases globally 2018 was estimated to be 79,990 (1.0 per 100,000 world populations) [Ref. 5.4: 05DXHB]. Incidence (per 100,000) is highest in Southern (2.8) and Northern (2.6) Europe; rates are lowest in Eastern Asia (0.35) [Ref. 5.4: 05DXHB]. Nearly one quarter of the world's HL cases are diagnosed in Europe, where an estimated 19,193 new cases (2.4 per 100,000) of HL were reported in 2018 [Ref. 5.4: 05DXHB]. The incidence of HL in European children 0-19 years of age is 1.3 per 100,000, yielding 2193 new cases in 2018 [Ref. 5.4: 05DXHB]. In the US, incidence is 2.7 per 100,000, corresponding to 8100 new cases in 2019; 12% of cases occur in persons under age 20 [Ref. 5.4: 05DMHL]. The 5-year overall prevalence in Europe is 77,315 cases, with 6289 children ages 0-19 years [Ref. 5.4: 05DXHB].

Demographics of the indication population and risk factors for the disease:

HL is more common in males and is most frequently diagnosed in young adults ages 20-34 years [Ref. 5.4: 052ZM2]. HL is one of the few malignancies with shared features of biology and natural history for children and adults [Ref. 5.4: 05G5VD]. Risk factors are not well described, but a viral etiology has long been hypothesized [Ref. 5.4: 052ZM2]. Epstein-Barr virus (EBV) is highly prevalent among HL patients and accounts for up to 40-50% of all global cases [Ref. 5.4: 04HTK5]. However, the rate of EBV-positive HL varies considerably by geography with lower a prevalence observed in North America (32%) and Europe (36%) compared to Africa (74%), Central/South America (61%), and Asia (56%) [Ref. 5.4: 04HTK5]. HL in young children is more likely to be EBV-associated compared to adolescents and young adults [Ref. 5.4: 05G5VD].

The main existing treatment options:

Historically, treatment of classical HL in childhood and adults generally utilized the same strategy and agents, with high cure rates of at least 80% of patients overall; 90-95% of children can be cured [Ref. 5.4: 05DMDL, 05G5VD]. Current management of classical HL involves initial treatment with chemotherapy alone or combined with radiation therapy for early stage disease. Several chemotherapy options and brentuximab vedotin are available for stage III-IV disease. High-dose salvage chemotherapy followed by autologous stem cell transplantation and checkpoint inhibitors are options for refractory or relapsed disease. The NLP subtype is

characterized by an indolent course and occasional late relapse; most patients present with early-stage disease. Radiation therapy is the preferred treatment for early stage NLPHL; chemotherapy with or without rituximab/radiation is recommended for stage III-IV NLPHL.

Natural history of the indicated condition, including mortality and morbidity:

In 2018, 26,167 HL deaths (0.3 per 100,000) occurred in the world. Mortality (per 100,000) is highest in Northern Africa (0.63) and lowest in East Asia (0.13); in Europe, mortality ranges from 0.19 in Western countries to 0.43 in Central and Eastern region, resulting in 4307 deaths in 2018 [Ref. 5.4: 05DXHB]. The overall 5-year survival in Europe is 80.3% [Ref. 5.4: 05DPN4]. The overall 5-year survival in the US is 86.6%, with stage-specific survival as follows: 91.6% (stage I), 93.5% (stage II), 82.9% (stage III), and 73.5% (stage IV) [Ref. 5.4: 05DMHL]. Among children and adolescents, 5-year survival is more than 95% [Ref. 5.4: 05G5VD]. Of the 1000 HL deaths expected in 2019 in the US, 0.9% occurred among persons under age 20 [Ref. 5.4: 05DMHL].

Important co-morbidities:

Given the relatively young average age of HL patients, fewer common age-related comorbid conditions would be expected compared to patients with other cancers.

Urothelial Carcinoma

Incidence and prevalence:

Urinary bladder cancer (UBC) comprises 90-95% of all urothelial carcinomas; the remaining are upper tract urothelial cancers [Ref. 5.4: 05DMLD]. Overall, the age standardized incidence of UBC (per 100,000) is 5.7 globally [Ref. 5.4: 05DXHB]. The age standardized incidence per 100,000 persons is highest in Southern Europe (15.2) and lowest in Middle Africa (1.2) [Ref. 5.4: 05DXHB]. Rates are generally declining in developed countries and increasing in less developed regions [Ref. 5.4: 04GXQB]. In the US, there are 80,470 new cases of UCB expected in 2019 [Ref. 5.4: 057K9G]. The 5-year UBC prevalence is 308,011 in North America and 631,337 in Europe [Ref. 5.4: 05DXHB].

Demographics of the indication population and risk factors for the disease:

UBC incidence is 3-5 times higher in males than females [Ref. 5.4: 05DXHB]. UBC usually occurs among older adults; the median age at diagnosis is 73 years in the US [Ref. 5.4: 057K9G]. Tobacco consumption is a significant risk factor for urothelial cancer [Ref. 5.4: 05DMLD].

The main existing treatment options:

Clinically, UBC classified as non-muscle-invasive (NMIBC) represents approximately 75% of newly diagnosed cases, while the remaining 25% are muscle-invasive cancers [Ref. 5.4: 059FM9]. *See section below for NMIBC treatment.* Standard treatment options for muscle-invasive UBC include radical cystectomy with or without neoadjuvant (cisplatin-based) or adjuvant therapies, bladder-preserving approaches, and systemic therapy for

advanced and metastatic disease. The FDA has approved PD-1 inhibitors for locally advanced or metastatic urothelial cancers.

Natural history of the indicated condition, including mortality and morbidity:

Approximately 5% of UBC patients have metastatic disease at the time of diagnosis; however, roughly half of all patients experience relapse after cystectomy, with distant metastases most common [Ref. 5.4: 059FM9]. Mortality rates (per 100,000) are highest in Northern Africa (4.4) and lowest in Central America (0.75); European rates range from 2.6 (Northern) to 3.2 (Southern) [Ref. 5.4: 05DXHB]. The 5-year survival by UBC stage is as follows: in situ: 95.8%, local: 69.5%, regional: 36.3%, distant: 4.6% [Ref. 5.4: 057K9G]. The overall 5-year UBC relative survival in Europe is 68% [Ref. 5.4: 04D76G].

Important co-morbidities:

As bladder cancer is primarily a disease of the aged, CVD, COPD, diabetes and other malignancies are expected to be the most prevalent comorbidities in patients with urothelial cancers [Ref. 5.4: 04H4GM, 04GXN0].

Head and Neck Squamous Cell Carcinoma (HNSCC)

Incidence and prevalence:

Head and neck cancer (HNC) encompasses a heterogeneous group of cancers of the upper aero-digestive tract, including the oral cavity, salivary glands, pharynx, and larynx [Ref. 5.4: 04DP5M]. Cancers of the lip and oral cavity, oropharynx, hypopharynx, and larynx, which are primarily (>90%) comprised of squamous cell carcinoma histology, are collectively termed head and neck squamous cell carcinoma (HNSCC) [Ref. 5.4: 04DGDP, 04DP5M]. Worldwide, HNSCC incidence varies widely by country and tumor site; the most common sites in Europe are lip and oral cavity (42%) and larynx (27%). Across Europe, combined HNSCC age-standardized incidence (per 100,000) ranges by region from 8.5 (Southern Europe) to 11.8 (Central and Eastern Europe), corresponding to approximately 147,000 new cases and 443,000 5-year prevalent cases in 2018 [Ref. 5.4: 05DXHB]. In the US, HNSCC age-standardized incidence is roughly 10 cases per 100,000 with 55,000 new cases expected in 2018 [Ref. 5.4: 05DRVZ, 0565YM].

Demographics of the population in the indication population and risk factors for the disease:

HNC occurs most often among adults over age 60 years [Ref. 5.4: 057SQL, 05DMHM]. However, some oropharyngeal cancer cases are related to human papillomavirus (HPV) and tend to occur in younger adults [Ref. 5.4: 04DGDY]. Males are 2-3 times more likely to have HNSCC compared to females [Ref. 5.4: 05DXHB]. Tobacco and alcohol consumption are the dominant risk factors, particularly for cancers of the oral cavity and larynx, [Ref. 5.4: 04DP5M]. Increased HPV prevalence is largely responsible for a dramatic rise in oropharyngeal cancer in North America and Western Europe [Ref. 5.4: 04DGDY].

The main existing treatment options:

HNSCC treatment is complex with specific site, stage and pathology directing management. Single-modality surgery or radiation therapy is generally recommended for early-stage disease [Ref. 5.4: 05DLLB]. Standard options for locally advanced stage III or IV tumors include surgery plus postoperative radiotherapy. Combined concomitant chemoradiation may be recommended post-operatively for high-risk features or unresectable tumors. Commonly used agents include cisplatin, carboplatin, paclitaxel, docetaxel, 5-FU, methotrexate, capecitabine, and cetuximab. For advanced, unresectable, metastatic or recurrent HNSCC, participation in clinical trials is recommended. Emerging targeted therapies include tyrosine kinase or checkpoint inhibitors.

Natural history of the indicated condition, including mortality and morbidity:

Across European regions, combined HNSCC mortality rates range from 2.8 to 6.6 per 100,000 [Ref. 5.4: 05DXHB]. In Europe, five-year survival ranges from 33-44%, with the majority of cases diagnosed at stage III or IV [Ref. 5.4: 04SRJJ]. Patients with HPV-associated HNC generally have an improved prognosis and respond better to chemotherapy [Ref. 5.4: 05DLLB].

Important co-morbidities:

Studies of HNSCC patients in Europe found the most common co-morbidities to be cardiovascular disease, asthma/COPD, diabetes, liver disease, and depression [Ref. 5.4: 04D0C7, 04DDMM].

Renal Cell Carcinoma (RCC)

Incidence and prevalence:

The age-standardized incidence of kidney cancer (per 100,000) is highest in North America (12.2) and Northern Europe/Australia and New Zealand (10.3); rates are lowest in Middle Africa (1.0) [Ref. 5.4: 06C8B2]. More than one-third of incident cases occur in Europe, with nearly 139,000 incident cases expected in 2020 [Ref. 5.4: 06C86L]. In the US, kidney cancer incidence is anticipated to be 16.4 per 100,000, yielding roughly 76,000 new cases in 2021 [Ref. 5.4: 06C86L]. Approximately 85% of all primary kidney cancers are comprised by RCC, and approximately 70% have clear cell histology, [Ref. 5.4: 05DMDM]. RCC incidence has increased over the last few decades in the US and most of Europe [Ref. 5.4: 05BFQQ, 04BN0K]. The 5-year prevalence of kidney cancer in Europe is 405,983 cases [Ref. 5.4: 06C8B2].

Demographics of the indication population and risk factors for the disease:

Kidney cancer incidence increases by age with a median age at diagnosis of 64 years in the US [Ref. 5.4: 06CL4Y]. In most countries, it is roughly twice as common among males compared to females [Ref. 5.4: 06C8B2]. Established risk factors for RCC include obesity, smoking, hypertension, and chronic kidney disease; other probable risk factors include low physical

activity, diabetes, occupational chemical exposure, radiation exposure, and analgesic use [Ref. 5.4: 05DPRK, 053GXR, 053GXZ, 053GY2].

The main existing treatment options:

Surgical resection is the primary treatment for localized disease [Ref. 5.4: 05DMDM]. There is little evidence of benefit with adjuvant therapy for most patients with locally advanced disease. Approved and emerging targeted therapies for advanced or relapsed RCC include checkpoint inhibitors, anti-vascular endothelial growth factor (VEGF) antibodies, tyrosine kinase inhibitors (TKI), and mammalian target of rapamycin (mTOR) protein inhibitors.

Natural history of the indicated condition, including mortality and morbidity:

Worldwide, kidney cancer age-standardized mortality rates (per 100,000) are highest in Central/Eastern Europe (3.4) and Western Europe (2.8); 54,000 deaths occurred in Europe during 2020 [Ref. 5.4: 06C8B2]. Prognosis has improved significantly in the US and Europe, due in part to the advent of TKI therapy [Ref. 5.4: 053TKZ, 05BFQQ]. The majority (65%) of kidney cancers diagnosed in the US is localized and 16% of tumors are metastatic [Ref. 5.4: 06CL4Y]. The overall 5-year survival in Europe and the US is 60% and 76%, respectively [Ref. 5.4: 06CL4Y, 04D76G]. Clear cell histology, accounting for the majority of RCC, is associated with a better prognosis than non-clear cell RCC [Ref. 5.4: 053GY0].

Important co-morbidities:

Cardiovascular or cerebrovascular diseases, hypertension, chronic obstructive pulmonary disease, diabetes, and other prevalent comorbidities among elderly populations are frequently observed in cancer patients [Ref. 5.4: 04VW4L].

Microsatellite Instability-High (MSI-H)/deficient Mismatch Repair (dMMR) Colorectal Cancer (CRC)

Incidence and prevalence:

The prevalence of MSI-H/dMMR status varies widely by tumor type and disease stage [Ref. 5.4: 04TCGC, 04TCK9]. MSI-H/dMMR is present in approximately 15% of all colorectal cancer [Ref. 5.4: 04TC0P]. MSI-H/dMMR is more common among stage II (~20%) than stage III (~12%) colorectal cancer and is least frequent in stage IV (~4%) disease [Ref. 5.4: 04TC0P].

Demographics of the indication population and risk factors for the disease:

Lynch Syndrome results from germline mutations in mismatch repair (MMR) genes and accounts for a small portion of MSI-H/dMMR colorectal cancers; the majority of MSI-H/dMMR tumors arise in the sporadic form [Ref. 5.4: 04TC0P]. Few consistent differences have been observed for the association between MSI status and lifestyle factors among colorectal cancer patients [Ref. 5.4: 05FB0L]. However, some studies report a higher proportion of MSI-H/dMMR tumors for current smokers [Ref. 5.4: 04W005, 05FB0L] and

those with a family history of colorectal cancer [Ref. 5.4: 04VYPZ, 04W02X]. BRAF mutations are more common in MSI-H/dMMR colorectal patients [Ref. 5.4: 04VWL2].

The main existing treatment options:

Pembrolizumab was approved in the US to treat MSI-H or MMR deficient colorectal cancer following progression on a fluoropyrimidine, oxaliplatin, and irinotecan treatment. Prior to the approval of pembrolizumab, there were no FDA-approved therapies specifically for the treatment of MSI-H/dMMR cancers and the standard of care consisted of chemotherapy regimens and palliative care if response was not achieved. Nivolumab (as a single agent or in combination with ipilimumab) is approved for MSI-H or dMMR metastatic CRC that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan [Ref. 5.4: 05DLL7]. Routine testing for MMR deficiency or MSI status is recommended for all patients with colorectal cancers [Ref. 5.4: 05DLL7].

Natural history of the indicated condition, including mortality and morbidity:

Sporadic MSI-H/dMMR colorectal cancer is generally associated with lower stage at diagnosis, larger tumor size, proximal colon predominance, wildtype p53 status, poor differentiation, mucinous histology, and less metastasis [Ref. 5.4: 04VZ0J, 04VWL8]. MSI-H/dMMR colorectal cancer patients have a survival advantage limited to those with localized disease [Ref. 5.4: 04VZ0J, 043SX8]. In contrast, mCRC patients with MSI-H/dMMR had worse survival and poor prognosis compared to microsatellite stable (MSS) mCRC [Ref. 5.4: 043VF3].

Important co-morbidities:

Co-morbidity prevalence among MSI-H/dMMR cancer patients is unknown. However, co-morbidities are common among cancer patients, particularly with older adults for whom cancer is most common [Ref. 5.4: 04VW4L]. Secondary tumors or multiple primary have been reported among MMR deficient and MSI-H colorectal cancer patients [Ref. 5.4: 04W654, 04VZ03].

Esophageal Cancer

Incidence and prevalence:

Over 77% of the 572,034 new esophageal cancer cases diagnosed worldwide occur in Asia [Ref. 5.4: 05DXHB]. The highest age-standardized incidence rates (per 100,000) are found in Eastern Asia (12.2) and the lowest are in Central America (0.96) [Ref. 5.4: 05DXHB]. In Europe, nearly 53,000 new cases were diagnosed in 2018; incidence rates range from 3.0 in Central/Eastern countries to 5.5 in Northern Europe [Ref. 5.4: 05DXHB]. In the US, incidence is 4.3 per 100,000, with 17,650 new cases in 2019 [Ref. 5.4: 05DMHK]. Squamous cell carcinoma is the predominant histologic subtype worldwide; however, adenocarcinoma is most frequently diagnosed in the US and much of Europe [Ref. 5.4: 054HBS]. The 5-year prevalence in Europe is approximately 56,000 cases [Ref. 5.4: 05DXHB].

Demographics of the indication population and risk factors for the disease:

Esophageal cancer incidence increases with age, with a median age at diagnosis of 68 years in the US [Ref. 5.4: 05DMHK]. In most regions, including the US and Europe, males have a 3- to 5-fold higher incidence compared to females [Ref. 5.4: 05DXHB]. Smoking is the primary risk factor for the squamous cell carcinoma subtype, but alcohol use, poor nutrition, and infectious agents have also been implicated [Ref. 5.4: 054HBS]. Gastroesophageal reflux disease occurs in 10-20% of adults in Western countries and is a major risk factor for adenocarcinoma, either directly or through an intermediate pre-malignant lesion, Barrett's esophagus [Ref. 5.4: 054HBS].

The main existing treatment options:

Surgery is the standard treatment for limited disease [Ref. 5.4: 05DLL9]. For locally advanced disease, preoperative treatment with chemotherapy or chemoradiation therapy is indicated. Patients with unresectable, locally advanced or metastatic disease, particularly those with adenocarcinoma, may consider different palliative treatment options, including brachytherapy or chemotherapy. A trastuzumab-containing regimen may be indicated for some HER2-positive tumors. Other approved or emerging targeted therapies include vascular endothelial growth factor receptor 2 (VEGFR-2) antibodies and checkpoint inhibitors.

Natural history of the indicated condition, including mortality and morbidity:

In Europe, mortality rates (per 100,000) range from 1.5 in Southern Europe to 4.3 in Northern Europe [Ref. 5.4: 05DXHB]. The overall 5-year survival in the US and Europe is 19.9% and 9-21%, respectively [Ref. 5.4: 05DMHK, 054HM8]. Most cases are diagnosed at regional (32%) or distant (40%) stage, contributing to the poor overall survival [Ref. 5.4: 05DMHK].

Important co-morbidities:

Most esophageal cancers occur among adults over age 60 years who have an increased risk of cardiovascular or cerebrovascular diseases, diabetes, and second primary malignancies, such as cancers of the oropharynx, lung and stomach [Ref. 5.4: 054HS0].

Triple Negative Breast Cancer (TNBC)

Incidence and prevalence:

Triple negative breast cancer (TNBC) is an aggressive subtype of breast cancer (BC) defined by an absence of expression of the estrogen receptor and progesterone receptor, and by absence of overexpression or amplification of the human epidermal growth factor receptor 2 [Ref. 5.4: 059X3Q]. TNBC comprises 15-20% of all BC, with infiltrating ductal carcinoma (not otherwise specified) accounting for approximately 92% of TNBC cases [Ref. 5.4: 059PJL]. Data on the incidence and prevalence rates of TNBC are scarce. Based on overall BC incidence (per 100,000) for the world, US and Europe, the estimated number of annual TNBC cases is roughly 365,000, 91,000, and 47,000, respectively [Ref. 5.4: 05DXHB] [Ref. 5.4: 059RH3].

Demographics of the indication population and risk factors for the disease:

TNBC is most common in young, pre-menopausal patients; although BC incidence generally increases with age, the proportion of BC cases categorized with the TNBC subtype decreases with age [Ref. 5.4: 05DNTY]. In the US, women of African ancestry are twice as likely to have the TNBC subtype compared to other women with BC [Ref. 5.4: 05DNTY]. TNBC etiology is not well understood. Compared to other BC subtypes, TNBC has a higher prevalence of BRCA1 or BRCA2 germline mutations. The reproductive factors generally associated with increased BC risk, such as increased parity, younger age at first birth, older age at menarche, and oral contraceptive use, are not strongly linked to TNBC risk [Ref. 5.4: 05DQP0].

The main existing treatment options:

The standard of care for TNBC continues to be conventional chemotherapy and radiation as with BC in general; optimal regimens for TNBC have yet to be established. For women with metastatic breast cancer, including TNBC, who have germline BRCA mutations, PARP inhibitors may be considered. For PD-L1 expressing metastatic TNBC, PD-L1 inhibitors in combination with chemotherapy are newer options.

Management of early-stage breast cancer has been based on use of systemic chemotherapy given prior to (neoadjuvant therapy, NAC) or after (adjuvant therapy) definitive surgery according to NCCN and ESMO guidelines [Ref. 5.4: 05MDND, 05B2QG]. Patients with high-risk, early-stage TNBC who are eligible for NAC are primarily treated with taxane- and anthracycline-based chemotherapy regimens. Until recently, radiation therapy was the only adjuvant treatment option, if clinically indicated, for patients who received chemotherapy prior to surgery. Capecitabine has been added as a recommended adjuvant treatment for patients not achieving pathological complete response (pCR) following NAC.

Natural history of the indicated condition, including mortality and morbidity:

Important characteristics of TNBC are high proliferation and frequent metastasis to visceral organs and brain; TNBC tumors have the highest recurrence rates compared to other BC subtypes [Ref. 5.4: 05DNRG]. Compared to other hormonal and HER2 subtypes, TNBC has the poorest survival and prognosis is consistently lower at each disease stage; TNBC 3-year survival ranges from 94% for stage IA disease to 20% for stage IV [Ref. 5.4: 05DNNW].

Important co-morbidities:

Data describing specific co-morbidities among TNBC patients are scarce. A recent study of more than 50,000 TNBC patients reported 82% with no comorbid conditions [Ref. 5.4: 05DRW2].

Endometrial Carcinoma

Incidence and prevalence:

The incidence (per 100,000) of carcinoma of the uterine corpus, often referred to as endometrial carcinoma, is highest in North America (20.5) and lowest in South-Central Asia

(2.5) [Ref. 5.4: 05DXHB]. In Europe, incidence (per 100,000) ranges from 12.3 in Western countries to 19.0 in the Central/Eastern region, yielding roughly 122,000 new cases in 2018 [Ref. 5.4: 05DXHB]. The incidence in the US is 27.5 per 100,000 women with nearly 62,000 new cases expected in 2019 [Ref. 5.4: 057Y2L]. The 5-year prevalence in Europe is 445,805 cases [Ref. 5.4: 05DXHB].

Demographics of the indication population and risk factors for the disease:

Endometrial carcinoma is most frequently diagnosed among women aged 45-74 years with a median age at diagnosis of 63 years in the US [Ref. 5.4: 057Y2L]. The incidence of endometrial carcinoma in Europe has also been increasing [Ref. 5.4: 04KB2V], and the estimated median age at diagnosis in 2020 was between 64-69 years [Ref. 5.4: 05Q3MX]. The main risk factors for endometrial carcinoma are related to endogenous and exogenous estrogen, including excess weight, abdominal fatness, menopausal estrogen therapy, early age at menarche, late menopause, nulliparity, and diabetes [Ref. 5.4: 04SXYB].

The main existing treatment options:

The main categories for delineating treatment include disease limited to the uterus, involvement of the cervix, and suspected extrauterine disease [Ref. 5.4: 05DMDS]. Minimally invasive surgery is preferred for disease limited to the uterus, whereas radical hysterectomy is recommended for tumors with cervical involvement. Systemic therapy may be considered for those not suitable for surgery and certain adjuvant therapies may be selected based on patient risk factors. Multi-agent chemotherapy regimens are preferred for metastatic, recurrent, or high-risk disease. Targeted therapies are currently under investigation; bevacizumab and temsirolimus are considered appropriate for patients who have progressed on previous cytotoxic chemotherapy.

Natural history of the indicated condition, including mortality and morbidity:

In Europe, mortality (per 100,000) is highest in Central/Eastern countries (3.9) and lowest in the Western region (2.1) [Ref. 5.4: 05DXHB]. In the US, most cases (67%) are diagnosed as localized tumors with 21% having regional disease and 9% diagnosed at distant stage [Ref. 5.4: 057Y2L]. The overall 5-year survival in the US and Europe is 81% and 72-79%, respectively [Ref. 5.4: 057Y2L] [Ref. 5.4: 05F2FK]. Despite early detection, approximately 13% of all endometrial carcinomas recur [Ref. 5.4: 04SJ3G].

Important co-morbidities:

Co-morbidities are common among patients with cancer, particularly in older adults [Ref. 5.4: 057XQG]. Most endometrial carcinoma occurs among women over age 55 for whom comorbidities, such as hypertension, diabetes, and obesity, are common [Ref. 5.4: 057XM4].

MSI-H/ dMMR Solid tumors

Incidence and prevalence:

The prevalence of MSI-H/dMMR status varies widely by tumor type and disease stage [Ref. 5.4: 04TCGC] [Ref. 5.4: 04TCK9]. The highest prevalence of MSI-H/dMMR is found in endometrial (20-30%) and gastric (20%) cancers [Ref. 5.4: 04TCGC] [Ref. 5.4: 04TCK9] [Ref. 5.4: 04Q8R4]. MSI-H/dMMR prevalence in small intestinal cancer is about 10% [Ref. 5.4: 04SRJK] [Ref. 5.4: 05PJBW] [Ref. 5.4: 05P545] [Ref. 5.4: 05PJBJ]. For most other cancers, the prevalence of MSI-H/dMMR is well below 5% [Ref. 5.4: 04TCGC] [Ref. 5.4: 04TCK9] [Ref. 5.4: 04Q8R4]. Both pancreatic cancer and biliary cancer have a very low MSI-H/dMMR prevalence of <3% [Ref. 5.4: 05PJBJ] [Ref. 5.4: 04TCGC] [Ref. 5.4: 04SRJK] [Ref. 5.4: 04SRJK] [Ref. 5.4: 05P545] [Ref. 5.4: 05PJ9H] [Ref. 5.4: 05PJ0F]. MSI-H/dMMR prevalence is generally lower for more advanced stage tumors compared to low stage disease [Ref. 5.4: 04Q8R4].

Demographics of the indication population and risk factors for the disease:

Among patients with solid tumors, MSI-H/dMMR frequency generally increases with age and is higher for females [Ref. 5.4: 04VW8W]. Lynch Syndrome results from germline mutations in mismatch repair genes and accounts for a small portion of MSI-H/dMMR cancers; the majority of MSI-H/dMMR tumors arise in the sporadic form [Ref. 5.4: 04VWCZ]. Few consistent differences are observed for MSI-H/dMMR cancer patients compared to those with low MSI or MSS tumors with regard to common solid tumor risk factors [Ref. 5.4: 04VWCZ] [Ref. 5.4: 04VW73].

The main existing treatment options:

Pembrolizumab was approved in the US to treat unresectable or metastatic MSI-H and dMMR solid tumors that have progressed after prior treatment and for patients with no satisfactory alternative treatment options. Otherwise, MSI-H/dMMR solid tumors are managed with cancer-specific standard-of-care chemotherapeutic treatments regardless of MSI status [Ref. 5.4: 05DMLF]. Routine testing for MMR deficiency or MSI status is recommended for all patients with endometrial (epithelial only) cancers or patients with other select solid tumors who may be candidates for anti-PD-1 treatment [Ref. 5.4: 05DMDS].

Natural history of the indicated condition, including mortality and morbidity:

The prognostic effect of MSI-H/dMMR status varies by tumor type. MSI-H/dMMR gastric cancer patients generally have an overall favorable prognosis including those with advanced disease, possibly due to these tumors having a lower ability to invade serosal layers and spread through the lymphatic system [Ref. 5.4: 04VWCZ]. In contrast, the relationship between MSI/MMR status and disease stage is less consistent for endometrial tumors; MSI-H/dMMR endometrial tumors are often associated with poorer survival [Ref. 5.4: 04FR9W].

Important co-morbidities:

Co-morbidity prevalence among MSI-H/dMMR cancer patients is unknown. However, co-morbidities are common among cancer patients, particularly with older adults for whom cancer is most common [Ref. 5.4: 04VW4L]. Secondary tumors or multiple primary tumors have been reported among MMR deficient and MSI-H endometrial cancer patients [Ref. 5.4: 04W654] [Ref. 5.4: 04VZ03].

Cervical Cancer

Incidence and Prevalence:

Data from GLOBOCAN estimates 58,169 new cases of cervical cancer with an age standardized incidence rate of 10.7 per 100,000 in Europe in 2020 [Ref. 5.4: 06FRP5]. Incidence ranges from 6.8 per 100,000 in the Western European region to 16.0 per 100,000 in Central/Eastern countries [Ref. 5.4: 05DXHB]. The 5-year prevalence in Europe is 190,814 cases [Ref. 5.4: 05DXHB].

Demographics of the indication population and risk factors for the disease:

The global incidence of cervical cancer peaks at ages 50-54 [Ref. 5.4: 06FGNB]. The country with the earliest peak is the UK with incidence peaking between 30-34 years [Ref. 5.4: 06FGNB]. The primary risk factor is persistent infection with certain types of human papillomavirus (HPV) [Ref. 5.4: 04YDD6]. The more recent widespread implementation of the preventive HPV vaccine is expected to contribute to the continuing decline of cervical cancer incidence [Ref. 5.4: 04SXYB]. In contrast, cervical cancer burden remains high in many low and middle-income countries without established vaccination, screening, and treatment programs [Ref. 5.4: 04YDDS].

The main existing treatment options:

The primary treatment of early-stage cervical cancer is surgery or radiotherapy [Ref. 5.4: 05DLL6]. Concurrent chemo-radiotherapy is the standard of care for locally advanced disease. For advanced disease, primary treatment is usually platinum-containing chemotherapy. Targeted therapies, including pembrolizumab (in the US) and bevacizumab (in the EU and US), have an established role for selected metastatic cases.

Natural history of the indicated condition, including mortality and morbidity:

Cervical cancer mortality is highly preventable with access to early screening and treatment [Ref. 5.4: 04YDD6]. In Europe, mortality rates (per 100,000) ranges from 2.1 (Northern) to 6.1 (Central/Eastern) with nearly 26,000 deaths in 2018 [Ref. 5.4: 05DXHB] [Ref. 5.4: 06FGNB]. The 5-year survival in the US and Europe is 65.8% and 62%, respectively [Ref. 5.4: 057SCZ] [Ref. 5.4: 04QRV7].

Important co-morbidities:

The prevalence of co-morbidities among cervical cancer patients is relatively low, possibly due to relatively earlier diagnosis and younger average age at diagnosis compared to other cancers. Cohort studies in Europe reported 80-90% of patients having no recorded comorbidity [Ref. 5.4: 04YVTB] [Ref. 5.4: 04YVTL].

Relevant adverse events in target populations:

Relevant adverse events to be anticipated in the aforementioned target populations exposed to immunotherapy are summarized below. The adverse events selected for inclusion are aligned with the Summary of Product Characteristics (SmPC) section 4.8.

Biliary Tract Carcinoma (BTC)

Incidence and Prevalence:

BTC arises from the epithelial lining of the biliary tree and is comprised by cancers of the intrahepatic or extrahepatic bile ducts (or cholangiocarcinoma, CCA), and gallbladder. Globally, the prevalence of BTC has risen by 35% from 2007 to 2017, resulting in 235,900 prevalent cases [Ref. 5.4: 05FVMP]. In 2017, the global incidence rate for BTC was 2.71 per 100,000 population, with approximately 210,878 new cases [Ref. 5.4: 07Z66G]. Incidence (per 100,000) is highest in Chile (10.38) and generally lowest (<1) in African or Middle Eastern countries. In Europe, incidence (per 100,000) is higher in Eastern (6.3), Southern (5.4), and Central (4.3) regions compared to Northern regions (2.33.4) [Ref. 5.4: 07Z66C]. Intrahepatic CCA is on the rise in the US and Europe (partly due to changes in diagnosis and classification), while gallbladder cancer is declining [Ref. 5.4: 05PFKM, 07Z66H].

Demographics of the indication population and risk factors for the disease:

In Europe and the US, BTC is more common in women; incidence is higher for men in some regions of Asia [Ref. 5.4: 07Z667, 07Z66C, 07Z66G]. Many risk factors have been identified, though the relative strength of these factors varies somewhat by BTC subtype. These include bile duct cysts, cholangitis, cholelithiasis, cirrhosis, HBV/HCV, nonalcoholic fatty livery disease (NAFLD)/nonalcoholic steatohepatitis (NASH), chronic pancreatitis, inflammatory bowel disease, *H pylori* infection, obesity, liver fluke infections, and some occupational exposures or genetic factors; however, roughly half of cases are diagnosed without any identifiable risk factors [Ref. 5.4: 05PFKM, 07Z66H].

The main existing treatment options:

Surgical procedures or radiation may be options for localized BTC [Ref. 5.4: 07Z655]. Liver transplantation is potentially curative for select patients with locally advanced disease. Treatment options for advanced BTC include a combination of durvalumab plus gemcitabine and cisplatin-based chemotherapy, gemcitabine- or fluoropyrimidine-based chemotherapy, pembrolizumab for MSI-H/dMMR tumors, FGFR2 inhibitors, IDH inhibitors fluoropyrimidine-based chemoradiation, or radiation alone. Potential molecular targets for emerging therapies to treat BTC subtypes include NRAS, BAP1, ARID1A, EGFR, NTRK,

BRAF V600E, KRAS, HER2, PIK3C2G, STK11, TP53, and TGFBR2 [Ref. 5.4: 0885WD, 0885WH, 0885WN, 0885WP].

Natural history of the indicated condition, including mortality and morbidity:

Globally, mortality rates (per 100,000) vary widely from 0.8 in South Africa to 21.2 in Chile [Ref. 5.4: 05H5SD]. Survival is similarly poor for CCA and gallbladder cancer with a median survival under 1 year and 5-year survival rates of 10%-20% in Europe and the US [Ref. 5.4: 07Z66C, 07Z653]. Most BTC is diagnosed at a late stage when treatment is less effective [Ref. 5.4: 07Z667].

Important co-morbidities:

Comorbidities are common as most patients are elderly. A study of 86,134 BTC cases found cholelithiasis, liver disease, or diabetes in 18%, 19%, and 33%, respectively [Ref. 5.4: 07Z669].

Gastric Cancer

Incidence and prevalence:

Nearly 75% of the world's 1,089,103 annual new gastric cancer (GC) cases occur in Asia [Ref. 5.4: 06D898]. Incidence varies globally, with the highest age-standardized incidence rates (per 100,000) found in Eastern Asia (22.4); rates are lowest in Southern Africa (3.3) [Ref. 5.4: 06D898]. In Europe, incidence (per 100,000 PY) ranges from 4.6 in Northern countries to 11.3 in the Central/Eastern region, resulting in 136,038 incident cases in 2020 [Ref. 5.4: 06D898]. In the US, age-standardized incidence is 7.1 per 100,000, corresponding to 26,380 new cases expected in 2022 [Ref. 5.4: 08389Q]. The 5-year prevalence in Europe is 213,013 cases [Ref. 5.4: 06D898].

Demographics of the indication population and risk factors for the disease:

Incidence increases with age, with incidence peaking in those over age 70 years [Ref. 5.4: 08097V]. Males have a roughly 2--fold higher incidence compared to females in the US and Europe [Ref. 5.4: 06D8F4] [Ref. 5.4: 06D898]. The primary risk factor for non-cardia (distal) GC (comprising a majority of cases) is Helicobacter pylori gastritis; the reduction in H. pylori prevalence through eradication efforts is significantly contributing to the decline in GC incidence in the US and Europe [Ref. 5.4: 06D8FH]. The less common cardia (proximal) subtype is suspected to be related to obesity, smoking, and gastro-esophageal reflux; incidence is increasing in the US and Europe [Ref. 5.4: 06D8FH].

The main existing treatment options:

Surgery is the primary treatment option for localized disease [Ref. 5.4: 06D8DM]. Combined modality therapy is recommended for locoregional disease; options include peri- or post-operative chemotherapy and pre- or post-operative chemoradiation. For unresectable, locally advanced and metastatic disease, first-line systemic therapy regimens with two cytotoxic drugs are preferred. A fluoropyrimidine combined with oxaliplatin is recommended for most patients

who are HER2-negative, whereas trastuzumab plus chemotherapy is indicated for HER2-positive metastatic disease. Dependent upon local approval, nivolumab with chemotherapy may be an option for first-line treatment, regardless of PD-L1 status; subsequent lines of therapy may include ramucirumab with or without paclitaxel; single-agent chemotherapy; dostarlimab (dMMR tumors); pembrolizumab (MSI-H/dMMR or TMB-high tumors); entrectinib or larotrectinib (NTRK gene fusion-positive tumors); or trifluridine and tipiracil (recurrent/metastatic tumors).

Natural history of the indicated condition, including mortality and morbidity:

Mortality rates (per 100,000) are highest in Eastern Asia (14.6) and lowest in North America (1.8); rates in Europe range from 2.9 in the North to 8.3 in the Central/Eastern region [Ref. 5.4: 06D898]. In Europe, overall 5-year survival ranges from 18.3% to 35.4% [Ref. 5.4: 08097L]. Most US cases are diagnosed at regional (25%) or distant (37%) stage, contributing to a relatively poor 5-year survival (33.3%) [Ref. 5.4: 08389Q].

Important co-morbidities:

A large study of 12,612 GC patients reported a high prevalence of co-morbidities prior to diagnosis; the most common chronic conditions were hypertension (60%), coronary artery disease (30%), diabetes (23.6%), COPD (17%), congestive heart failure (16.4%), and osteoarthritis (13.6%) [Ref. 5.4: 04KCJW].

Table SI.1: Background Frequencies of Relevant Adverse Events in Target Populations

Adverse Event	Frequency*
Immune-mediated Pneumonitis	Pneumonitis occurred in 3.1% of 1994 patients treated with single-agent nivolumab, 6.4% of 1291 patients treated with combined ipilimumab and nivolumab, 3% of 2616 patients treated with atezolizumab, 2% of 1414 patients without prior radiation or 16.6% in 475 patients with radiation and treated with durvalumab, 1.2% of 1738 patients treated with avelumab, 3.2% of 810 patients treated with cemiplimab, and 1.1% of 444 patients receiving dostarlimab.
Immune-mediated Colitis	Colitis occurred in 2.9% of 1994 patients treated with single-agent nivolumab, 21.1% of 982 patients treated with single-agent ipilimumab,9% of 1291 patients treated with combined nivolumab and IPI, 1.6% of 1889 patients treated with durvalumab, 1.5% of 1738 patients treated with avelumab, and 1% of 2616 patients treated with atezolizumab, and 2.2% of 810 patients treated with cemiplimab, and 1.4% of 444 patients receiving dostarlimab.
Immune-mediated Hepatitis	Hepatitis occurred in 1.8% of 1994 patients treated with single-agent nivolumab, 9.3% of 982 patients treated with single-agent ipilimumab 7.9% in 715 patients treated with combined nivolumab and IPI, 1% of 1889 patients treated with durvalumab, 0.9% of 1738 patients treated with avelumab, 1.8% of 2616 patients treated with atezolizumab, 2.0% of 810 patients treated with cemiplimab, and 0.2% of 444 patients receiving dostarlimab.

Public

Table SI.1: Background Frequencies of Relevant Adverse Events in Target Populations

Adverse Event	Frequency*
Immune-mediated Nephritis	Nephritis and renal dysfunction occurred in 1.2% of 1994 patients treated with single-agent nivolumab, 0.1% of 1738 patients treated with avelumab, 0.3% of 1889 patients treated with durvalumab, <1% of 666 patients treated with ipilimumab (IPI), and 0.6% of 810 patients treated with cemiplimab, and 0.5% of 444 patients receiving dostarlimab.
Immune-mediated Endocrinopathies-Hypophysitis (including hypopituitarism)	Hypophysitis occurred in 0.6% of 1994 patients treated with single-agent nivolumab; hypophysitis occurred in 4.4% of 715 patients with combined ipilimumab and nivolumab; hypophysitis occurred in <0.1% of 2616 patients treated with atezolizumab; hypopituitarism occurred in 0.1% of 1738 patients treated with avelumab, and 0.4% in 810 patients treated with cemiplimab.
Immune-mediated Endocrinopathies-Adrenal insufficiency (primary and secondary)	Adrenal insufficiency occurred in 1% of 1994 patients treated with single-agent nivolumab; adrenal insufficiency occurred in 7.8% of 715 patients treated with combined ipilimumab and nivolumab; adrenal insufficiency was reported in 0.4% of 2616 patients treated with atezolizumab; adrenal insufficiency occurred in 0.5% of 1738 patients treated with avelumab; adrenal insufficiency occurred in 0.7% of 1889 patients treated with durvalumab; adrenal insufficiency occurred in 0.4% in 810 patients treated with cemiplimab; and in 0.9% of 444 patients receiving dostarlimab.
Immune-mediated Endocrinopathies-Thyroid Disorder (Hypothyroidism, Hyperthyroidism, Thyroiditis)	Hypothyroidism, hyperthyroidism, and thyroiditis occurred in 8%, 2.7%, and 0.6%, respectively, of 1994 patients treated with single-agent nivolumab; 18.3%, 11.9%, and 2.7% of 715 patients treated with combined IPI and nivolumab; 7.3%, 1.4%, and 0.4%, respectively, of 1889 patients treated with durvalumab; 4.9%, 0.8%, and 0.2%, respectively, of 2616 patients treated with atezolizumab; 5%, 0.4%, and 0.2% respectively, of 1738 patients treated with avelumab; 7%, 3.2%, and 0.6%, respectively, of 810 patients treated with cemiplimab; 5.6%, 1.8%, and 0.5%, respectively, of 444 patients treated with dostarlimab.
Immune-mediated Endocrinopathies-Type 1 Diabetes Mellitus	Diabetes occurred in 0.9% of 1994 patients treated with single-agent nivolumab, 2.7% of 666 patients treated with combined IPI and nivolumab, 0.1% of 1738 patients treated with avelumab; <0.1% of 1889 patients treated with durvalumab, 0.3% of 2616 patients treated with atezolizumab, and 0.1% in 810 patients treated with cemiplimab.
For hematologic malignancies: increased risk of severe complications of allogeneic stem cell transplantation (SCT)	Graft versus host disease (GVHD) • In 18 studies of patients treated with allogeneic transplant, without PD-1 inhibitors, the median and range of incidences (overall or subgroup-specific) reported for Grades 2-4 acute GVHD, Grades 3-4 acute GVHD, and chronic GVHD were 38.2% (11.5%-61%), 15.9% (8%-22%), 41.5% (5%-56%), respectively [Ref. 5.4: 04FF3L, 04FH09, 04FH0G, 04FG37, 04FJTB, 04FF00, 04FF0J, 04FFX4, 04FG2L, 04FF27, 04FGZW, 04FJ33, 04FGZP, 04FG2J, 04FJSZ, 04FJT7, 04FJTD, 04FG08]. Veno-occlusive Disease (VOD) • 8.8% VOD was seen among 843 allogeneic Hematopoietic Stem Cell Transplant (HSCT) procedures in 763 lymphoma/leukemia patients in Spain [Ref. 5.4: 04FKV7]. Hepatic VOD was diagnosed in 2.9% of 1326 patients who received allogeneic HSCT and were included in a nationwide HSCT registry in Taiwan from 2009-14 [Ref. 5.4: 05G7NG]. 1.6% of 1583 patients undergoing reduced-intensity conditioning allogeneic HSCT had developed VOD/sinusoidal obstruction syndrome from 2007-17 at the Dana Farber Cancer Institute [Ref. 5.4: 05G7NH].

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Table SI.1: Background Frequencies of Relevant Adverse Events in Target Populations

Adverse Event	Frequency*
Graft versus host disease (GVHD) in patients with a history of allogeneic stem cell transplant (SCT)	A comprehensive literature review of 13 case reports and 11 original manuscripts described GVHD (acute and chronic) in 283 patients with hematologic malignancies who received checkpoint inhibitors (CPI), including ipilimumab, nivolumab or pembrolizumab, either before or after having failed allogeneic hematopoietic stem cell transplantation (allo-HSCT) [Ref. 5.4: 05G88Y]. Among the 150 patients receiving a CPI after undergoing allo-HSCT (in the original articles), 62 received nivolumab, 85 had ipilimumab, and 4 had pembrolizumab. Of these patients who received CPI post-allo-HSCT, acute GVHD and chronic GVHD developed in 13% and 11%, respectively; 49% had a prior history of GVHD. Among the 26 patients receiving CPI post-allo-HSCT (as part of the case reports and case series), 12 received pembrolizumab and 14 had nivolumab. 19% of these patients developed acute GVHD, and 4% had a flare of existing GVHD.
* Except where otherwise noted, frequencies for the immune-mediated AEs are based on US Prescribing information [Ref. 5.4: 05DMN4, 05DMN5, 05DMN6, 05DNDC, 05DP3H] [Ref. 5.4: 06CLG4] [Ref. 5.4: 06CLG5] for similar class agents.	

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PART II: MODULE SII - NON-CLINICAL PART OF THE SAFETY SPECIFICATION

Key safety findings from non-clinical studies and relevance to human usage:

Table SII.1: Summary of Important Safety Findings from Non-clinical Studies

Key Safety Findings (from non-clinical studies)	Relevance to Human Usage
Repeat-dose toxicity: None Pembrolizumab (MK-3475) was well-tolerated when administered intravenously (IV) to Cynomolgus monkeys at doses of 6, 40 and 200 mg/kg during the 1- and 6-month toxicology studies. There were no findings of toxicological significance and the NOAEL was 200 mg/kg in both studies. The exposure multiple based on a predicted $AUC_{0\text{-}tau}$ of 3607.3 µg.day/mL at the maximum anticipated clinical dose of 10 mg/kg every 2 weeks (Q2W) and/or every 3 weeks (Q3W) was 19-fold at the dose of 200 mg/kg based on the 6-month study.	No safety concerns for repeated administration.
Pregnancy: Based upon data from the literature on the role of the PD-1/PD-L1 pathway in maintaining pregnancy and on experimental results in murine models of allogeneic pregnancy a potential risk with the administration of pembrolizumab to women of childbearing potential has been clearly identified. Because the PD-1/PD-L1 pathway plays a fundamental role in maintaining immune tolerance to the fetus, it is anticipated that the inhibition of PD-1 during pregnancy by treatment with pembrolizumab will have adverse effects on the fetus, including increased risks of abortion and stillbirth [Ref. 5.4: 00VMR9, 02CFKR, 02CFKT, 00VMXH].	Due to its mechanism of action, pembrolizumab may increase the risk of abortion and stillbirths if administered during pregnancy.
Immune-mediated disease: Based on the mechanism of action of pembrolizumab a safety risk for immune-mediated adverse events has been identified. The PD-1/PD-L1 pathway plays an important role in mediating peripheral immune tolerance to self, therefore its inhibition may contribute to the development of immune-mediated adverse events. [Ref. 5.4: 02CFKV, 02CFKW, 02CFKX, 02CFKQ]. However in a T-dependent Antibody Response (TDAR) study in mice, neither immune-mediated toxicity nor effects on the magnitude and kinetics of the primary and recall antibody responses to Hepatitis B vaccine were observed during treatment with anti-PD-1 in comparison to untreated control group [Ref. 4.2.3.7.7: TT151105FIN].	The potential development of immune-mediated adverse events is a known risk with pembrolizumab and is discussed in Section SVII.3.1.

Conclusions on Non-clinical Data

Nonclinical toxicology studies in monkeys of up to 6-months in duration with pembrolizumab demonstrated that there were no adverse effects at exposure multiples of 19-fold over the maximum clinical dose (10 mg/kg) and 94 times the exposure in humans at the dose of 2 mg/kg. The exposure multiple between the NOAEL and a human dose of 200 mg was 74. No reproductive toxicity studies were conducted with pembrolizumab based upon the potential risk to reproduction that is clearly identified from experimental results in the literature. Based on the mechanism of action of pembrolizumab, there is a potential risk of developing immune-mediated adverse events, which is being evaluated in ongoing clinical trials.

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PART II: MODULE SIII - CLINICAL TRIAL EXPOSURE

The clinical trial exposure is presented only for the clinical trial datasets/indications that are included in this RMP.

Clinical Trial Exposure by Duration of Exposure

KEYNOTE-001 (KN001) is a multi-cohort clinical trial evaluating the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD), and anti-tumor activity of pembrolizumab in patients with melanoma (naïve to or previously treated with IPI (IPI)) and Non-Small Cell Lung Cancer (NSCLC). The "All Melanoma" population consisted of cohorts B1 (IPI naïve or IPI treated), B2 (IPI refractory), B3 (IPI naïve or IPI treated), and D (IPI naïve). The NSCLC population consisted of cohort C (2 prior systemic therapy regimens) and cohort F (naïve to treatment, or, had one or more prior systemic treatment regimens). Study visits were every 2 or 3 weeks, dependent on dosing cycles, and patients remained on drug until progressive disease or other protocol defined stopping criteria occurred (e.g., as intercurrent illness that prevented further administration of treatment; or the patient withdrew consent).

KEYNOTE-002 (KN002) is a randomized, Phase II study of pembrolizumab compared to chemotherapy in patients with advanced melanoma. Study visits were every 2 or 3 weeks, dependent on dosing cycles, and patients remained on drug until progressive disease or other protocol defined stopping criteria occurred.

KEYNOTE-006 (KN006) is a multicenter, randomized, controlled, open-label, three-arm, Phase III trial designed to evaluate the safety and efficacy of two dosing regimens of pembrolizumab compared to IPI in patients with unresectable or metastatic advanced melanoma who are IPI-naive. Subjects randomized to either of the pembrolizumab treatment arms received treatment for up to 24 months or until disease progression or other protocol defined stopping criteria occur.

KEYNOTE-671 (KN671) is a multi-center Phase III, randomized, double-blind study of platinum-containing chemotherapy with or without pembrolizumab as neoadjuvant/adjuvant therapy for participants with resectable (American Joint Committee on Cancer [AJCC] 8th edition) Stage II, IIIA, and resectable IIIB (T3-N2) NSCLC. Participants were randomized to receive concomitant neoadjuvant platinum-containing chemotherapy plus pembrolizumab (Q3W × 4 cycles) followed by surgery and adjuvant pembrolizumab (Q3W × 13 cycles) or concomitant neoadjuvant platinum containing chemotherapy plus placebo (Q3W × 4 cycles) followed by surgery and adjuvant placebo (Q3W × 13 cycles), and followed up until death, disease recurrence/progression.

KEYNOTE-091 (KN091) is a multi-center, randomized double blind, placebo-controlled Phase III trial of pembrolizumab monotherapy following resection of stages IB-IIIA non-small cell lung cancer (NSCLC) American Joint Committee on Cancer (AJCC) 7th edition. Adjuvant chemotherapy is not mandatory but considered for patients with stage IB (T ≥ 4 cm) and strongly recommended for stage II and IIIA, according to national and local guidelines. Participants are randomized to receive 18 cycles of pembrolizumab or placebo every 3 weeks

and followed until death, lung cancer recurrence, occurrence of a second primary lung cancer or occurrence of a second primary cancer. KEYNOTE-010 (KN010) is a multi-center, worldwide, randomized, adaptively designed Phase II/III trial of pembrolizumab at two dosing schedules versus docetaxel in subjects with NSCLC with PD-L1 positive tumors who have experienced disease progression after platinum-containing systemic therapy. Subjects randomized to either of the pembrolizumab treatment arms or docetaxel received treatment for up to 24 months or until disease progression or other protocol defined stopping criteria occur.

KEYNOTE-021 (KN021) is a multi-center, open-label, Phase I/II study of pembrolizumab in combination with chemotherapy or immunotherapy in subjects with advanced/metastatic NSCLC. The study consists of two parts with multiple cohorts; cohort A of Part 1 of the study evaluated pembrolizumab in combination with carboplatin-paclitaxel in subjects with metastatic squamous NSCLC who have not previously received systemic therapy for metastatic disease. Subjects were randomized 1:1 to either receive 2mg/kg of pembrolizumab or 10mg/kg combined with carboplatin and paclitaxel. All subjects received up to a maximum of 4 cycles of carboplatin and paclitaxel. Treatment with pembrolizumab continued until a total of 35 treatment administrations or until disease progression or other protocol defined stopping criteria. Cohort C of Part 1 of the study determined the recommended Phase II dosage (RP2D) of pembrolizumab in combination with carboplatin and pemetrexed [standard of care (SOC)]. Part 2 of the study included a randomized comparison of carboplatin and pemetrexed with or without pembrolizumab (Cohort G). Subjects randomized to the combination received 4 cycles of carboplatin and continued maintenance pemetrexed with pembrolizumab for up to 35 cycles or until disease progression or other protocol defined stopping criteria. Subjects randomized to SOC received 4 cycles of carboplatin and continued maintenance pemetrexed until disease progression or other protocol defined stopping criteria.

KEYNOTE-189 (KN189) is a worldwide, multi-site, randomized, double-blind, parallel-group, placebo-controlled study to evaluate intravenous pembrolizumab combined with pemetrexed/platinum chemotherapy versus saline placebo combined with pemetrexed/platinum chemotherapy in subjects with advanced or metastatic non-squamous NSCLC who have not previously received systemic therapy for advanced/metastatic disease. Subjects were randomized 2:1 to either receive pembrolizumab at 200 mg combined with pemetrexed and platinum (investigators choice of cisplatin or carboplatin), or saline placebo, pemetrexed and platinum (investigators choice of cisplatin or carboplatin). Subjects randomized to the combination received 4 cycles of chemotherapy and continued maintenance pemetrexed with pembrolizumab for up to 35 cycles or until disease progression or other protocol defined stopping criteria. Subjects randomized to SOC received 4 cycles of chemotherapy and continued maintenance pemetrexed until disease progression or other protocol defined stopping criteria.

KEYNOTE-024 (KN024) is a multi-center, worldwide, randomized, open label, controlled trial of intravenous (IV) pembrolizumab monotherapy versus the choice of multiple standard of care (SOC) platinum-based chemotherapies in subjects previously untreated for their stage IV, PD-L1 strong, NSCLC. Subjects randomized to pembrolizumab received up to 35 treatments or until disease progression or other protocol defined stopping criteria. Subjects randomized to SOC received the recommended SOC treatments for the selected platinum-based chemotherapies or until disease progression or other protocol defined stopping criteria.

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KEYNOTE-042 (KN042) is a Phase 3 multi-center, international, randomized, open-label, controlled clinical study of pembrolizumab monotherapy versus platinum-based chemotherapy in previously untreated adult subjects with locally advanced or metastatic Tumor Proportion Score (TPS) ≥1% NSCLC, with no EGFR or ALK genomic tumor abberations. Subjects randomized to pembrolizumab received up to 35 treatments or until disease progression or other protocol defined stopping criteria. Subjects randomized to platinum-based chemotherapy received the investigator's choice of carboplatin/paclitaxel or carboplatin/pemetrexed for up to 6 cycles followed by optional pemetrexed maintenance, or until disease progression or other protocol defined stopping criteria. While pemetrexed maintenance was optional, it was strongly recommended for subjects with nonsquamous histologies only.

KEYNOTE-407 (KN407) is a worldwide, multi-site, randomized, double-blind, parallel-group, placebo-controlled study to evaluate intravenous pembrolizumab combined with carboplatin-paclitaxel/nab-paclitaxel chemotherapy versus saline placebo combined with carboplatin-paclitaxel/nab-paclitaxel chemotherapy in subjects with metastatic squamous NSCLC who have not previously received systemic therapy for metastatic disease. Subjects were randomized 1:1 to either receive pembrolizumab combined with carboplatin and investigators choice of paclitaxel or nab-paclitaxel, or saline placebo combined with carboplatin and investigators choice of paclitaxel or nab-paclitaxel. All subjects received up to a maximum of 4 cycles of carboplatin, paclitaxel or nab-paclitaxel and pembrolizumab or saline placebo. Treatment with pembrolizumab or saline placebo continued until a total of 35 treatment administrations or until disease progression or other protocol defined stopping criteria.

KEYNOTE-013 (KN013) is a multi-center, multi-cohort, nonrandomized trial of pembrolizumab in hematologic malignancies. Cohort 3 included subjects with relapsed/refractory nodular sclerosing or mixed cellularity Hodgkin lymphoma (HL) that have failed, are ineligible for, or refused a stem cell transplant and have relapsed after treatment with or failed to respond to brentuximab vedotin. Subjects in Cohort 3 received pembrolizumab 10 mg/kg administered every 2 weeks. Subjects were evaluated at Week 12, then every 8 weeks (± 7 days) to assess response to treatment according to the Revised Response Criteria for Malignant Lymphoma [Ref. 5.4: 03RC2F].

KEYNOTE-087 (KN087) is a multicenter, single arm, multi-cohort, nonrandomized trial of pembrolizumab in subjects with relapsed or refractory classical Hodgkin lymphoma who have failed to achieve a response or progressed after autologous stem cell transplant (ASCT) and have relapsed after treatment with, or failed to respond to, brentuximab vedotin post ASCT (Cohort 1); who were unable to achieve a complete response (CR) or partial response (PR) to salvage chemotherapy and did not receive ASCT, but have relapsed after treatment with, or failed to respond to, brentuximab vedotin (Cohort 2); and subjects who have failed to respond to, or progressed after, ASCT and have not received brentuximab vedotin post ASCT. These subjects may or may not have received brentuximab vedotin as part of primary or salvage treatment (Cohort 3). Subjects received pembrolizumab 200mg every 3 weeks. Subjects were evaluated every 12 weeks (± 7 days) to assess response to treatment according to the Revised Response Criteria for Malignant Lymphoma [Ref. 5.4: 03RC2F].

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KEYNOTE-204 (KN204) is a Phase III, randomized, open-label, multi-national, clinical trial of pembrolizumab compared with brentuximab vedotin (BV) in subjects with relapsed or refractory classical Hodgkin lymphoma (HL). This study enrolled subjects with relapsed or refractory classical HL, who had received at least 1 prior multi-agent chemotherapy regimen. Prior BV or a BV-containing regimen was allowed, provided the subjects responded (partial or complete response) to the BV or BV-containing regimen. Patients received study medication (200mg pembrolizumab or 1.8 mg/kg BV) every 3 weeks. Patients were evaluated every 12 weeks (± 7 days) to assess response to treatment according to the Revised Response Criteria for Malignant Lymphoma [Ref. 5.4: 03RC2F].

KEYNOTE-051 (KN051) is a Phase 1/2, nonrandomized, open-label, single-arm, multicenter study to evaluate the pharmacokinetics, pharmacodynamics, toxicity, safety, and antitumor activity of pembrolizumab in pediatric participants aged 6 months to less than 18 years of age with either advanced melanoma, advanced relapsed or refractory PD-L1 positive malignant solid tumor or other lymphoma, relapsed or refractory classical HL (3 years to 18 years of age), or advanced relapsed or refractory MSI-H solid tumors. Part I objectives are safety, PK, PD, toxicity, and preliminary efficacy in pediatric participants with advanced melanoma or PD-L1-positive advanced, relapsed or refractory solid tumor or other lymphoma. Part 2 objectives are to evaluate safety and efficacy at the established RP2D in pediatric participants within the indications of advanced melanoma; PD-L1-positive advanced, relapsed or refractory solid tumors or other lymphoma; relapsed or refractory classical Hodgkin lymphoma (rrcHL); or advanced, relapsed or refractory microsatellite instability high (MSI-H) solid tumors. Standard RECIST 1.1 criteria were used for assessment of the primary efficacy endpoint in patients with solid tumors and other lymphoma assessments: (every 8 weeks ±7 days through Week 24 and once every 12 weeks ±7 days thereafter) or IWG Revised Response Criteria for patients in the rrcHL Cohort (assessments: every 12 weeks ± 7 days) [Ref. 5.4: 03QY3L].

KEYNOTE-045 (KN045) is a randomized, active-controlled, multi-site, open-label trial of pembrolizumab monotherapy versus investigator's choice of paclitaxel, docetaxel or vinflunine in subjects with locally advanced or metastatic urothelial carcinoma who have received platinum-containing chemotherapy. Subjects randomized to pembrolizumab received up to 24 months of study treatment or until disease progression or other protocol defined stopping criteria. Subjects randomized to chemotherapy received the recommended standard treatment for selected chemotherapy until disease progression or other protocol defined stopping criteria.

KEYNOTE-052 (KN052) is an open-label, single-arm, multi-site trial of pembrolizumab monotherapy in subjects with locally advanced or metastatic UC who have not received prior systemic chemotherapy and who are not eligible to receive cisplatin. Subjects may remain on treatment for 24 months, until disease progression or another protocol-specifid reason for discontinuation from therapy. After discontinuation from treatment, the subject is followed for survival.

KEYNOTE-040 (KN040) is a randomized, active-controlled, multicenter, open-label Phase III clinical trial to examine the efficacy and safety of pembrolizumab versus the choice of 3 different standard treatment options in subjects with recurrent or metastatic (R/M) head and neck squamous cell carcinoma (HNSCC) whose disease has progressed on or after prior

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platinum-containing chemotherapy. Subjects may remain on treatment for 24 months, until disease progression or another protocol-specified reason for discontinuation from therapy. After discontinuation from treatment, the subject is followed for survival.

KEYNOTE-048 (KN048) is a Phase III, randomized, active-controlled, multi-site, open-label trial of pembrolizumab, or pembrolizumab plus chemotherapy (platinum plus 5-FU) versus cetuximab plus chemotherapy in subjects with first line recurrent or metastatic (R/M) head and neck squamous cell carcinoma (HNSCC). Subjects are randomized in a 1:1:1 ratio to one of the three treatment arms in the trial. Randomization is stratified by PD-L1 tumor expression (strongly positive versus not strongly positive) defined by TPS 50% cutpoint, HPV status for oropharyngeal cancer (positive versus negative), and ECOG Performance Scale (0 versus 1). Subjects may remain on treatment for up to 24 months (for those randomized to pembrolizumab arms), until disease progression or another protocol-specified reason for discontinuation from therapy. After discontinuation from treatment, the subject is followed for survival.

KEYNOTE-012 (KN012) is a Phase Ib, nonrandomized, open-label, multicenter, multicohort trial of pembrolizumab in subjects with advanced solid tumors. Subjects were enrolled into Cohort A for triple negative breast cancer (TNBC), Cohort B for the initial head and neck (H/N) cancer cohort and Cohort B2 for the H/N cancer expansion cohort, Cohort C for urothelial tract cancer, or Cohort D for gastric cancer. Only subjects with PD-L1 positive tumors were enrolled in Cohorts A, B, C and D. Subjects in Cohort B2 were enrolled regardless of PD-L1 status. Subjects may remain on treatment for 24 months, until disease progression or another protocol-specified reason for discontinuation from therapy. After discontinuation from treatment, the subject is followed for survival.

KEYNOTE-055 (KN055) is a Phase II, nonrandomized, multicenter, single-cohort trial of pembrolizumab in subjects with recurrent and/or metastatic head and neck squamous cell carcinoma who have progressed on platinum and cetuximab therapy. Subjects may remain on treatment for 24 months, until disease progression or another protocol-specified reason for discontinuation from therapy. After discontinuation from treatment, the subject is followed for survival.

KEYNOTE-054 (KN054) is an international, double-blind, placebo-controlled randomized Phase III trial of pembrolizumab adjuvant treatment in subjects with high-risk stage III melanoma following complete surgical resection compared to placebo. Eligible subjects were randomized into two treatment groups to receive pembrolizumab 200 mg fixed dose or placebo every 3 weeks for one year or up to 18 doses. Subjects were stratified by stage (IIIA [> 1 mm metastasis] versus IIIB versus IIIC 1 to 3 positive lymph nodes versus IIIC >4 positive lymph nodes) and geographical region (North America, European countries, Australia and other countries as designated). After first disease recurrence, subjects have the option to participate in Part 2 of the study; a single treatment group to receive pembrolizumab 200 mg fixed dose every 3 weeks for up to 2 years or until occurrence of a withdrawal criterion. Subjects assigned to the placebo group in Part 1 who experience disease recurrence are offered to crossover to pembrolizumab in Part 2. Subjects randomized to pembrolizumab in Part 1 are considered for re-treatment if their disease recurs >6 months after completing 1 year of adjuvant treatment. Re-challenge is optional and at the discretion of the Investigator.

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KEYNOTE-716 (KN716) is a Phase III, randomized, placebo-controlled, multicenter study of adjuvant pembrolizumab in participants 12 years of age and older with resected Stage IIB or IIC cutaneous melanoma per AJCC eighth edition guidelines. Eligible participants were randomized into two treatment groups to receive pembrolizumab (Adult: 200 mg IV Q3W or Pediatric: 2 mg/kg IV Q3W up to a maximum of 200 mg Q3W) or placebo every 3 weeks for 17 cycles. Participants were stratified as follows: one stratum for pediatric participants (≥12 years of age and <18 years of age) and 3 strata for adult participants (≥18 years of age) based on T-stage tumor thickness and ulceration (T3b, T4a, T4b). After first disease recurrence, participants have the option to participate in Part 2 of the study; a single treatment group to receive up to 17 or 35 cycles of pembrolizumab therapy Q3W per Part 2 eligibility guidelines.

KEYNOTE-426 (KN426) is a Phase III randomized, open-label study to evaluate efficacy and safety of pembrolizumab in combination with axitinib versus sunitinib monotherapy as a first-line treatment for locally advanced or metastatic renal cell carcinoma (mRCC). Eligible subjects were stratified by the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk categories (favorable versus intermediate versus poor) and geographic region (North America versus Western Europe versus "Rest of the World"). Subjects were randomized in a 1:1 ratio to one of the 2 treatment arms in the trial. Study treatments are continued until progressive disease (PD) is BICR-verified or further confirmed by the investigator, unacceptable adverse events (AEs) or intercurrent illness prevents further administration of treatment, death or withdrawal of consent. Following verification or confirmation of PD, all subjects are followed for survival (by phone contact or clinic visit) until death, withdrawal of consent, loss to follow-up, or until the study is concluded or terminated early, whichever comes first.

KEYNOTE-581 (KN581) is a Phase III randomized, open-label study to evaluate efficacy and safety of pembrolizumab plus lenvatinib and lenvatinib plus everolimus versus sunitinib monotherapy as a first-line treatment for advanced or mRCC. Eligible participants were stratified by the Memorial Sloan-Kettering Cancer Center (MSKCC) risk score (favorable, intermediate versus poor risk groups) and geographic region (North America and Western Europe versus Other). Participants were randomized in a 1:1:1 ratio to one of the 3 treatment arms in the trial. Study treatments are continued until confirmed PD by independent review, development of unacceptable toxicity, participant request, withdrawal of consent or study termination by the sponsor. Participants will then enter the follow-up period. The follow up period begins the day after the Off-Treatment Visit and continues as long as the participants is alive, unless the participant withdraws consent, is lost to follow-up, or the sponsor terminates the study.

KEYNOTE-564 (KN564) is a Phase III, randomized, double-blind, placebo-controlled, multicenter, global study to evaluate the efficacy and safety of pembrolizumab in participants with RCC completely resected by nephrectomy and/or metastasectomy with intermediate-high or high risk of recurrence. Eligible patients were randomly assigned in a 1:1 ratio to receive pembrolizumab or placebo as adjuvant therapy following nephrectomy/metastasectomy. Randomization was stratified by metastatic status by investigator review (M0 versus M1 no evidence of disease [NED]). Within the M0 group, randomization was further stratified by ECOG performance status (0 versus 1) and geographic location (United States versus outside of the United States). The study treatment was administered for up to approximately 1 year, or

until disease recurrence, unacceptable toxicity, intercurrent illness preventing further administration of study treatment, investigator's decision, protocol noncompliance, or administrative reasons requiring discontinuation of study treatment. Participants will then enter the follow-up period. After the end of treatment, participants will be followed for the occurrence of AEs. Participants who discontinue for reasons other than disease recurrence will have posttreatment imaging follow-up for disease status until confirmation of disease recurrence, initiating a new anticancer treatment, withdrawing consent, or becoming lost to follow-up. All participants will be followed for OS until death, withdrawal of consent, or the end of the study.

KEYNOTE-177 (KN177) is a 2-arm, multicenter, international, randomized, open-label, Phase III study evaluating the efficacy and safety of pembrolizumab monotherapy versus globally-accepted SOC therapies for CRC in participants with locally confirmed dMMR or MSI-H unresectable or metastatic CRC who have not received prior chemotherapy for unresectable or metastatic CRC. Participants were randomized 1:1 to receive pembrolizumab (200 mg Q3W) or investigator's choice of SOC therapies for CRC (mFOLFOX6 or FOLFIRI with or without combination with bevacizumab or cetuximab). Treatment with pembrolizumab was administered until documented disease progression, patient has received 35 trial treatments (for pembrolizumab), unacceptable toxicity, or other protocol defined stopping criteria. Those subjects that received investigator's choice chemotherapy and have centrally verified progression can crossover and receive pembrolizumab therapy for up to 35 cycles.

KEYNOTE-590 (KN590) is a randomized, double-blind, placebo-controlled, worldwide, Phase III trial to evaluate the efficacy and safety of pembrolizumab in combination with cisplatin and 5-fluorouracil (5-FU) versus placebo in combination with cisplatin and 5-FU as first-line treatment in subjects with locally advanced unresectable or metastatic adenocarcinoma or squamous cell carcinoma of the esophagus or advanced/metastatic Siewert type 1 adenocarcinoma of the esophagogastric junction (GEJ). Subjects were randomized 1:1 to receive pembrolizumab 200 mg intravenous (IV) or saline placebo once every three weeks or chemotherapy (5-fluorouracil 800 mg/m^2 IV on days 1-5 plus cisplatin 80 mg/m^2 IV [for a maximum of 6 cycles]) every 3 weeks. Randomization was stratified by geographic region (Asia vs non-Asia), histology (esophageal squamous cell carcinoma versus adenocarcinoma), and ECOG performance status (0 vs 1). Treatment was continued until confirmed disease progression, completion of 24 months of treatment, or other protocol defined stopping criteria.

KEYNOTE-355 (KN355) is a randomized, double-blind, multi-center, placebo-controlled, Phase III study evaluating the efficacy and safety of pembrolizumab in combination with chemotherapy (paclitaxel, or nab-paclitaxel, or gemcitabine and carboplatin) in subjects with locally recurrent unresectable or metastatic TNBC, regardless of tumor PD-L1 expression, and not previously treated with chemotherapy. Subjects were randomized (2:1) to one of the two treatment arms (pembrolizumab + chemotherapy or placebo + chemotherapy) stratified by chemotherapy treatment (taxane vs. gemcitabine/carboplatin), tumor PD-L1 expression (CPS $\geq$1 vs. CPS<1), and prior treatment with the same class of chemotherapy in the neoadjuvant setting (yes vs. no). Treatment with pembrolizumab or placebo was administered until confirmed disease progression, unacceptable toxicity, or a maximum of 24 months. Administration with pembrolizumab was permitted beyond disease progression if the subject was clinically stable and considered to be deriving clinical benefit.

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KEYNOTE-522 (KN522) is a randomized, double-blind, multi-center, placebo-controlled, Phase III study evaluating pembrolizumab plus chemotherapy (paclitaxel and carboplatin followed by doxorubicin, or epirubicin, and cyclophosphamide) versus placebo plus chemotherapy as neoadjuvant therapy and pembrolizumab versus placebo as adjuvant therapy in patients with previously untreated locally advanced TNBC. Subjects were randomized (2:1) to one of the two treatment arms (pembrolizumab + chemotherapy or placebo + chemotherapy), and stratified by nodal status (positive vs. negative), tumor size (T1/T2 vs. T3/T4) and choice of carboplatin (Q3W vs. weekly). Treatment was continued until completion of study treatment (17 cycles of pembrolizumab/placebo), disease progression in the neoadjuvant phase or recurrence (local or distance) after surgery, or other protocol defined stopping criteria.

KEYNOTE-146 (KN146) is a multi-center, multi-cohort, open-label, Phase Ib/II trial of the combination of lenvatinib and pembrolizumab in patients with advanced/metastatic NSCLC, RCC, endometrial carcinoma, urothelial carcinoma, HNSCC, or melanoma. In KN146, lenvatinib dose is 20 mg orally once daily (the maximum tolerated dose/recommended phase II dose) in combination with pembrolizumab 200 mg administered intravenously every 3 weeks. Patients received study treatment until unacceptable toxicity or disease progression as determined by the investigators. Administration of lenvatinib and pembrolizumab was permitted beyond RECIST-defined disease progression if the patient was clinically stable and considered to be deriving clinical benefit by the investigator. Pembrolizumab dosing was continued up to 35 treatments (approximately 2 years); however, treatment with lenvatinib could be continued beyond 2 years. The primary safety data from KN146 includes all patients with histologically confirmed endometrial carcinoma from Study KN146 who received at least 1 dose of lenvatinib 20 mg/day with pembrolizumab 200 mg Q3W as starting dose, who received 1 or more prior systemic anticancer therapy(ies), who have a median follow-up time of at least 12 months and minimum 6 months follow-up after objective response assessment per investigator (ie, enrolled prior to 01-JUL-2018), and whose tumors are not MSI-H or dMMR.

KEYNOTE-775 (KN775) is a multicenter, randomized, open-label, Phase 3 study to compare the efficacy and safety of lenvatinib in combination with pembrolizumab versus treatment of physician's choice (TPC) in participants with advanced endometrial carcinoma who have been treated with at least one prior platinum-based chemotherapy regimen. In KN775, participants were randomized to one of two treatment arms - Arm A, lenvatinib 20 mg orally once daily plus pembrolizumab 200 mg intravenously every 3 weeks. Arm B, TPC consisting of either doxorubicin 60 mg/m2 by IV bolus injection, 1-hour infusion, or per institutional guidelines every 3 weeks or paclitaxel 80 mg/m2 by 1-hour IV infusion or per institutional guidelines given weekly, 3 weeks on/1 week off. Crossover between treatment arms is not permitted. Prior to randomization, investigators selected and recorded the TPC option in the event the participant was assigned to that arm. Randomization followed a predefined randomization scheme based on specific stratification factors. Each eligible participant is assigned to receive study treatment until disease progression is radiographically documented and verified by blinded independent central review (BICR) per RECIST 1.1, unacceptable adverse event(s), withdrawal of consent, until the participant has received a maximum 35 administrations of pembrolizumab (approximately 2 years), or the participant has received a lifetime cumulative dose of 500 mg/m² of doxorubicin. Participants who stop study treatment after receiving 35

administrations of pembrolizumab for reasons other than disease progression or intolerability, or participants who attain a complete response (CR) and stop study treatment may be eligible for up to 1 year of treatment with pembrolizumab (17 cycles) ± lenvatinib upon experiencing disease progression (Second Course Phase). Participants who complete treatment with pembrolizumab after 35 cycles or CR will continue to receive lenvatinib alone until disease progression is confirmed by BICR, development of unacceptable toxicity, or withdrawal of consent. Participants are permitted to continue study treatment beyond RECIST 1.1-defined disease progression per investigator's assessment as long as the maximum dose of the study drugs have not been reached, if the treating investigator considers that the participant may experience clinical benefit with continued treatment, and the participant is tolerating study treatment.

KEYNOTE-158 (KN158) is a multicenter, global, open-label Phase II study of pembrolizumab monotherapy in multiple types of advanced (unresectable and/or metastatic) rare cancer. All patients enrolled in this study must have a histologically or cytologically documented, advanced solid tumor that is incurable and for which prior standard first-line treatment has failed. Patients must have progressed on or be intolerant to therapies that are known to provide clinical benefit. Treatment with pembrolizumab is administered until documented disease progression, patient has received 35 trial treatments (for pembrolizumab), unacceptable toxicity, or other protocol defined stopping criteria. This multi-histology clinical study has been designed to enroll a "basket" of rare tumor types. Patients with any of the following solid tumor types have been enrolled:

(A) Anal squamous cell carcinoma,
(B) Biliary adenocarcinoma (gallbladder or biliary tree (intrahepatic or extrahepatic cholangiocarcinoma) except ampulla of Vater cancers,
(C) Neuroendocrine tumors (well- and moderately-differentiated), of the lung, appendix, small intestine, colon, rectum, or pancreas,
(D) Endometrial carcinoma (sarcomas and mesenchymal tumors are excluded),
(E) Cervical squamous cell carcinoma,
(F) Vulvar squamous cell carcinoma,
(G) Small cell lung carcinoma,
(H) Mesothelioma (malignant pleural mesothelioma),
(I) Thyroid carcinoma (papillary or follicular subtypes),
(J) Salivary gland carcinoma (sarcomas and mesenchymal tumors are excluded)

OR

(K) Any advanced solid tumor (except CRC) that is MSI-H.
(L) Any advanced solid tumor (including CRC) which is dMMR/MSI-H in subjects from mainland China who are of Chinese descent,
(M) Any advanced solid tumor that has failed at least one systemic line of therapy and is Tumor Mutational Burden-High (TMB-H) (≥10 mut/Mb, F1CDx assay), excluding dMMR/MSI-H tumors.

KEYNOTE-164 (KN164) is a single-arm, multisite, two cohort, Phase II study of pembrolizumab that was designed to evaluate the efficacy of pembrolizumab in patients with locally advanced unresectable or metastatic (Stage IV) MSI-H/dMMR CRC. Treatment with pembrolizumab is administered until documented disease progression, patient has received 35

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trial treatments (for pembrolizumab), unacceptable toxicity, or other protocol defined stopping criteria. Patients who met eligibility criteria have been enrolled in the following 2 cohorts:

- Cohort A: Participants with locally advanced unresectable or metastatic dMMR or MSI-H CRC who had been previously treated with at least 2 lines of standard of care therapies, which must have included fluoropyrimidine, oxaliplatin, and irinotecan.

- Cohort B: Participants with locally advanced unresectable or metastatic dMMR or MSI-H CRC who had been previously treated with at least 1 line of systemic standard of care therapy (fluoropyrimidine + oxaliplatin or fluoropyrimidine + irinotecan ± antivascular endothelial growth factor [anti-VEGF]/ epidermal growth factor receptor [EGFR] monoclonal antibody [mAb]).

KEYNOTE-826 (KN826) is a Phase III, randomized, double-blind, placebo-controlled trial of pembrolizumab plus chemotherapy versus chemotherapy alone in women with persistent, recurrent, or metastatic cervical cancer who are not eligible for treatment with curative intent (such as with surgery and/or radiation) and who have not previously been treated with systemic chemotherapy, with the exception of chemotherapy used as a radio sensitizing agent. Patients were randomized 1:1 to receive pembrolizumab with carboplatin/cisplatin + paclitaxel or placebo with carboplatin/cisplatin + paclitaxel. Bevacizumab was also permitted by investigator choice. Participants received study treatments until disease progression, unacceptable AEs, or other protocol defined stopping criteria.

KEYNOTE-811 (KN811) is a global, randomized, double-blind, Phase III study of pembrolizumab or placebo in combination with trastuzumab and the investigator's choice of chemotherapy with 5-fluorouracil and cisplatin or capecitabine and oxaliplatin in participants with previously untreated unresectable or metastatic, HER2-positive gastric or gastroesophageal junction adenocarcinoma. Patients may remain on treatment for 24 months, until disease progression or another protocol-specified reason for discontinuation from therapy. Patients who complete 35 administrations of pembrolizumab/placebo have the option to receive up to 1 additional year of trastuzumab +capecitabine or 5-fluorouracil (5-FU) or S-1 (tegafur, gimeracil, oteracil) at the discretion of the investigator. After discontinuation from treatment, patients are followed for survival.

KEYNOTE-859 (KN859) is a global, randomized, double-blind, Phase III study of pembrolizumab or placebo in combination with the investigator's choice of chemotherapy with 5-fluorouracil and cisplatin or capecitabine and oxaliplatin in participants with previously untreated unresectable or metastatic, HER2-negative gastric or gastro-oesophageal junction adenocarcinoma. Patients were stratified by geographical region (Europe/Israel/North America/Australia, Asia or Rest of the World), PD-L1 tumor expression status (CPS<1, ≥1) and chemotherapy regimen (FP or CAPOX). Patients may remain on treatment for 24 months, until disease progression or another protocol-specified reason for discontinuation from therapy.

KEYNOTE-966 (KN966) is a global, randomized, double-blinded, multi-site Phase 3 trial of pembrolizumab plus gemcitabine/cisplatin versus placebo plus gemcitabine/cisplatin in patients with locally advanced unresectable or metastatic BTC who have not previously been

treated with systemic chemotherapy, with the exception of adjuvant or neoadjuvant therapy. Prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent or with an agent directed to another stimulatory or coinhibitory T-cell receptor (eg, CTLA-4, OX-40, CD137) was exclusionary. The trial includes patients with BTC diagnosis confirmed by histology, or cytology (small cell cancer, neuroendocrine tumors, lymphoma, sarcoma, and/or mucinous cystic neoplasms are not eligible). To be eligible, patients must have disease not amenable to a curative treatment approach. Patients must also have measurable disease based on RECIST 1.1, as determined by the site investigator, an Eastern Cooperative Oncology Group (ECOG) performance score of 0 or 1 and predicted life expectancy of greater than 3 months. Patients are enrolled regardless of tissue PD-L1 biomarker status. Patients are required to provide a tumor tissue sample for biomarker analysis. Per protocol defined criteria patients with controlled HBV infection on antiviral therapy, as well as patients with past or ongoing HCV infection were eligible for the trial. Participants received study treatments until disease progression, unacceptable AEs, or other protocol defined stopping criteria.

Clinical Trial Summary of Drug Exposure

Table SIII.1 displays duration of exposure for all patients with advanced melanoma who received pembrolizumab monotherapy in the pooled KN001, KN002 and KN006 all patients as treated (APaT) population.

Table SIII.2 displays duration of exposure for all patients with melanoma who received pembrolizumab monotherapy in KN054 and KN716 APaT population. Of note, the median exposure to pembrolizumab in KN054 and KN716 is more than twice as long as the reference safety dataset (8.78 months vs 4.18 months, respectively).

Table SIII.3 displays duration of exposure for all patients with NSCLC who received pembrolizumab monotherapy in the pooled KN001, KN010, KN024, and KN042 APaT population.

Table SIII.4 displays duration of exposure to pembrolizumab for all patients with NSCLC who received pembrolizumab combination therapy in the pooled KN021 (Cohort A, C and G), KN189 and KN407 APaT population.

Table SIII.5 displays duration of exposure for all patients with NSCLC who received pembrolizumab monotherapy in KN091 APaT population. Of note, the median exposure to pembrolizumab in KN091 is more than twice as long as the reference safety dataset (11.7 months vs 4.18 months, respectively).

Table SIII.6 displays duration of exposure to pembrolizumab for all patients with NSCLC who received pembrolizumab in combination with chemotherapy as neoadjuvant treatment followed by continued adjuvant pembrolizumab monotherapy in KN671 APaT population.

Table SIII.7 displays duration of exposure for all patients with HL who received pembrolizumab monotherapy in the pooled KN013 (Cohort 3), KN087, and KN204 APaT population.

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Table SIII.8 displays duration of exposure for all patients with UC who received pembrolizumab monotherapy in the pooled KN045 and KN052 APaT population.

Table SIII.9 displays duration of exposure for all patients with HNSCC who received pembrolizumab monotherapy in the pooled KN012 (B+B2 Cohorts), KN040, KN055, and KN048 APaT population.

Table SIII.10 displays duration of exposure to pembrolizumab for all patients with HNSCC who received pembrolizumab combination therapy in KN048 ASaT Population.

Table SIII.11 displays duration of exposure to pembrolizumab for all patients with RCC who received pembrolizumab combination therapy in the KN426 ASaT population.

Table SIII.12 displays duration of exposure to pembrolizumab for all patients with RCC who received pembrolizumab combination therapy in the KN581 APaT population.

Table SIII.13 displays duration of exposure for all patients with RCC who received pembrolizumab monotherapy in the KN564 APaT population.

Table SIII.14 diplays duration of exposure for the patients with CRC who received pembrolizumab monotherapy in the KN177 ASaT population.

Table SIII.15 displays duration of exposure to pembrolizumab for all patients with esophageal cancer who received pembrolizumab combination therapy in KN590 ASaT population.

Table SIII.16 displays duration of exposure to pembrolizumab for all patients with TNBC who received pembrolizumab combination therapy in KN355 ASaT population.

Table SIII.17 displays duration of exposure to pembrolizumab for all patients with TNBC who received pembrolizumab in combination with neoadjuvant chemotherapy followed by continued adjuvant pembrolizumab monotherapy in the KN522 APaT population.

Table SIII.18 displays duration of exposure to pembrolizumab for all patients with endometrial carcinoma who received pembrolizumab combination therapy in the KN146 and KN775 APaT population.

Table SIII.19 displays duration of exposure for all patients with MSI-H who received pembrolizumab monotherapy in the KN158-Cohort K and KN164-Cohorts A and B ASaT population.

Table SIII.20 displays duration of exposure to pembrolizumab for all patients with cervical cancer who received pembrolizumab combination therapy in the KN826 APaT population.

Table SIII.21 displays duration of exposure to pembrolizumab for all patients with gastric cancer who received pembrolizumab combination therapy in the KN811 APaT population. Of note, the median exposure to pembrolizumab in KN811 is more than twice as long as the pembrolizumab monotherapy reference safety dataset (9.10 months vs 4.18 months, respectively).

Table SIII.22 displays duration of exposure to pembrolizumab for all patients with gastric cancer who received pembrolizumab combination therapy in the KN859 APaT population.

Table SIII.23 displays duration of exposure to pembrolizumab for all patients with BTC who received pembrolizumab combination therapy in the KN966 APaT population.

Table SIII.1: Summary of Drug Exposure Melanoma Subjects KN001, KN002 and KN006 Monotherapy (APaT Population)

	Pembrolizumab 2 mg/kg Q3W	Pembrolizumab 10 mg/kg Q3W	Pembrolizumab 10 mg/kg Q2W	Total
	N=340	N=769	N=458	N=1567
Study Days On-Therapy (days)				
Mean	230.04	224.66	231.36	227.79
Median	129.00	148.00	183.00	155.00
SD	204.06	189.74	185.88	191.74
Range	1.00 to 729.00	1.00 to 759.00	1.00 to 862.00	1.00 to 862.00
Number of Administrations				
Mean	11.43	11.26	16.61	12.86
Median	7.00	8.00	13.00	9.00
SD	9.31	8.69	12.46	10.34
Range	1.00 to 34.00	1.00 to 36.00	1.00 to 59.00	1.00 to 59.00
(pembrolizumab KN001 Database Cutoff Date: 18APR2014). (pembrolizumab KN002 Database Cutoff Date: 28FEB2015). (pembrolizumab KN006 Database Cutoff Date: 03MAR2015).				

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Table SIII.2: Summary of Drug Exposure Melanoma Participants KN054 and KN716 Monotherapy (APaT Population)

	KN716 + KN054 Pembrolizumab Q3W (N=992)
Study Days On-Therapy (Months)	
Mean	8.78
Median	11.07
SD	3.89
Range	0.03 to 15.70
Number of Administrations	
Mean	13.20
Median	17.00
SD	5.47
Range	1.00 to 18.00
Each participant is counted once on each applicable duration category row. Duration of Exposure is calculated as last dose date - first dose date + 1. Database cutoff date for Melanoma (KN054: 02OCT2017, KN716: 04DEC2020)	

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Table SIII.3: Summary of Drug Exposure NSCLC Subjects KN001, KN010, KN024, and KN042 Monotherapy (APaT Population)

	Pembrolizumab 2 mg/kg Q3W (N=400)	Pembrolizumab 10 mg/kg Q3W (N=630)	Pembrolizumab 10 mg/kg Q2W (N=202)	Pembrolizumab 200 mg Q3W (N=790)	Total (N=2022)
Study Days On-Therapy (days)					
Mean	145.01	164.77	176.32	269.07	202.77
Median	106.00	106.00	113.00	176.00	127.00
SD	137.66	165.27	166.20	249.20	205.26
Range	1.00 to 681.00	1.00 to 925.00	1.00 to 601.00	1.00 to 988.00	1.00 to 988.00
Number of Administrations					
Mean	7.56	8.41	12.91	13.23	10.57
Median	6.00	6.00	9.00	9.00	7.00
SD	6.30	7.52	11.38	11.46	9.80
Range	1.00 to 30.00	1.00 to 45.00	1.00 to 42.00	1.00 to 48.00	1.00 to 48.00
Each subject is counted once on each applicable duration category row. Duration of Exposure is calculated as last dose date - first dose date + 1. (pembrolizumab KN001 Database Cutoff Date for Lung: 23JAN2015). (pembrolizumab KN010 Database Cutoff Date: 30SEP2015). (pembrolizumab KN024 Database Cutoff Date: 10JUL2017). (pembrolizumab KN042 Database Cutoff Date: 26FEB2018).					

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Table SIII.4: Summary of Drug Exposure to Pembrolizumab NSCLC Subjects KN021 (Cohorts A, C and G), KN189 and KN407 Combination Therapy (APaT Population)

	Pembrolizumab 10mg/kg Combo **(N=24)**	Pembrolizumab 2mg/kg Combo **(N=25)**	Pembrolizumab 200mg Combo **(N=742)**	Total **(N=791)**
Study Days On-Therapy (days)				
Mean	245.29	386.64	222.62	228.49
Median	172.50	302.00	198.00	199.00
SD	226.91	267.05	151.76	161.55
Range	1.00 to 862.00	29.00 to 785.00	1.00 to 750.00	1.00 to 862.00
Number of Administrations				
Mean	11.21	17.52	10.72	10.95
Median	9.00	15.00	10.00	10.00
SD	9.50	12.18	6.87	7.27
Range	1.00 to 35.00	2.00 to 35.00	1.00 to 35.00	1.00 to 35.00

Each subject is counted once on each applicable duration category row.
Duration of Exposure is calculated as last dose date - first dose date + 1.
MK-3475 Database Cutoff Date for Lung Combination Therapy (KN021 CohortA: 07NOV2016, Cohort G/C: 31MAY2017, KN189: 8NOV2017, KN047: 03APR2018)

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Table SIII.5: Sumary of Drug Exposure NSCLC Participants KN091 Monotherapy (APaT Population)

	Pembrolizumab 200 mg Q3W (N=580)
Study Days On-Therapy (Months)	
Mean	8.66
Median	11.70
SD	4.50
Range	0.03 to 18.86
Number of Administrations	
Mean	12.85
Median	17.00
SD	6.22
Range	1.00 to 18.00

Each participant is counted once on each applicable duration category row.
Duration of Exposure is calculated as last dose date - first dose date + 1.
KN091 Database Cutoff Date: 20SEP2021

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Table SIII.6: Summary of Drug Exposure NSCLC Participants in KN671 Combination Therapy (APaT Population)

	Pembrolizumab 200 mg Q3W (N=396)
Study Days On-Therapy (Months)	
Mean	9.32
Median	10.91
SD	5.35
Range	0.03 to 18.63
Number of Administrations	
Mean	10.92
Median	12.00
SD	5.88
Range	1.00 to 17.00
Each subject is counted once on each applicable duration category row. Duration of Exposure is calculated as last dose date - first dose date + 1. Database Cutoff Date: 29JUL2022	

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Table SIII.7: Summary of Drug Exposure HL Subjects KN013, KN087, and KN204 Monotherapy (APaT Population)

	Pembrolizumab 10 mg/kg Q2W (N=31)	**Pembrolizumab 200 mg Q3W (N=358)**	**Total (N=389)**
Study Days On-Therapy (months)			
Mean	10.74	12.67	12.52
Median	7.85	11.07	10.65
SD	8.97	8.18	8.25
Range	0.03 to 27.93	0.03 to 27.60	0.03 to 27.93
Number of Administrations			
Mean	22.84	18.67	19.01
Median	18.00	16.00	16.00
SD	17.73	11.53	12.16
Range	1.00 to 52.00	1.00 to 36.00	1.00 to 52.00
Each subject is counted once on each applicable duration category row. Duration of Exposure is calculated as last dose date - first dose date + 1. Database Cutoff Date (KN013-Cohort 3: 28SEP2018, KN087: 21MAR2019, KN204: 16JAN2020)			

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Table SIII.8: Summary of Drug Exposure UC Subjects KN045 and KN052 Monotherapy (APaT Population)

	Pembrolizumab 200 mg Q3W	Total
	N=636	N=636
Time on Therapy (days)		
Mean	135.64	135.64
Median	85.00	85.00
SD	131.72	131.72
Range	1.00 to 610.00	1.00 to 610.00
Number of Administrations		
Mean	7.16	7.16
Median	5.00	5.00
SD	6.09	6.09
Range	1.00 to 30.00	1.00 to 30.00
Includes all subjects with urothelial carcinoma who received at least one dose of Pembrolizumab in KN045 and KN052. Pembrolizumab KN045 Database Cutoff Date: 07SEP2016. Pembrolizumab KN052 Database Cutoff Date: 01SEP2016.		

Data on File

Table SIII.9: Summary of Drug Exposure HNSCC Subjects KN012 B+B2 Cohorts, KN040, KN055 and KN048 Monotherapy (ASaT Population)

	Head and Neck Cancer (MK3475 10mg/kg Q2W) (N=60)	Head and Neck Cancer (MK3475 200mg Q3W) (N=849)	Total KN012 B+B2/KN040/KN055/KN048 (N=909)
Study Days On-Therapy (days)			
Mean	208.22	160.18	163.35
Median	100.50	92.00	92.00
SD	236.24	175.01	179.92
Range	1.00 to 778.00	1.00 to 816.00	1.00 to 816.00
Number of Administrations			
Mean	14.87	8.20	8.64
Median	8.00	5.00	5.00
SD	15.63	7.97	8.83
Range	1.00 to 52.00	1.00 to 40.00	1.00 to 52.00
Each subject is counted once on each applicable duration category row. Duration of Exposure is calculated as last dose date - first dose date + 1. MK-3475 Database Cutoff Date for HNSCC (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN048: 13JUN2018, KN055: 22APR2016)			

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Table SIII.10: Summary of Drug Exposure to Pembrolizumab HNSCC Subjects KN048 Combination Therapy (ASaT Population)

	Head and Neck Cancer (MK3475 200mg Q3W) (N=276)
Study Days On-Therapy Pembro (days)	
Mean	223.16
Median	176.00
SD	200.98
Range	1.00 to 736.00
Number of Pembro Administrations	
Mean	10.60
Median	8.00
SD	9.01
Range	1.00 to 35.00
Each subject is counted once on each applicable duration category row. Duration of Exposure is calculated as last dose date - first dose date + 1. MK-3475 Database Cutoff Date for KN048: 13JUN2018.	

Data on File

Table SIII.11: Summary of Drug Exposure to Pembrolizumab RCC Subjects KN426 Combination Therapy (ASaT Population)

	KN426 Data for Pembrolizumab + Axitinib (N=429)
Study Days On-Therapy Pembrolizumab (days)	
Mean	287.04
Median	279.00
SD	175.03
Range	1.00 to 646.00
Number of Pembrolizumab Administrations	
Mean	13.78
Median	14.00
SD	8.04
Range	1.00 to 31.00
Each subject is counted once on each applicable duration category row. Study Days On-Therapy is calculated as last dose date - first dose date + 1 for pembrolizumab in the combo. MK-3475 Database Cutoff Date for KN426: 24AUG2018.	

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Table SIII.12: Summary of Drug Exposure to Pembrolizumab RCC Participants KN581 Combination Therapy (APaT Population)

	Pembrolizumab + Lenvatinib (N=352)
Study Days On-Therapy (days)	
Mean	439.8
Median	459.0
SD	260.60
Range	1 to 901
Number of Pembrolizumab Administrations	
Mean	20.7
Median	22.0
SD	11.86
Range	1 to 39
Study Days On-Therapy is calculated as last dose date - first dose date + 1 for pembrolizumab in the combo. MK-3475 Database Cutoff Date for KN581: 28AUG2020.	

Data on File

Table SIII.13: Summary of Drug Exposure RCC Participants KN564 Monotherapy (APaT Population)

	Pembrolizumab 200 mg Q3W (N=488)
Duration on therapy (months)	
Mean	9.0
Median	11.1
SD	3.70
Range	0.0 to 14.3
Number of Administrations	
Mean	13.5
Median	17.0
SD	5.19
Range	1.0 to 17.0
Each participant is counted once on each applicable duration category row. Duration of Exposure (months) is calculated as (last dose date - first dose date + 1)/30.4367. Includes all participants who received at least one dose of pembrolizumab in KN564. Database cutoff date for RCC (KN564: 14DEC2020)	

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Table SIII.14: Summary of Drug Exposure CRC Subjects KN177 Monotherapy (ASaT Population)

	KN177 Data for Pembrolizumab†† (N=153)
Study Days On-Therapy (Months)	
Mean	13.3
Median	11.1
SD	10.2
Range	0.0 to 30.6
Number of Administrations	
Mean	19.0
Median	16.0
SD	14.1
Range	1.0 to 35.0
Each subject is counted once on each applicable duration category row. Duration of Exposure is calculated as last dose date - first dose date + 1. †† Includes all subjects who received at least one dose of pembrolizumab in KN177. Database cutoff date for CRC (KN177: 19FEB2020)	

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Table SIII.15: Summary of Drug Exposure to Pembrolizumab Esophageal Cancer Subjects KN590 Combination Therapy (ASaT Population)

	KN590 Data for Pembrolizumab (N=370)
Duration On Therapy (month)	
Mean	7.5
Median	5.52
SD	6.86
Range	0.03 to 25.89
Number of Administrations	
Mean	10.8
Median	8.00
SD	9.34
Range	1.00 to 35.00
Each subject is counted once on each applicable duration category row. Duration of Exposure is calculated as (last dose date - first dose date +1)/30.4367 (months). Database Cutoff date for Esophageal (KN590: 02JUL2020)	

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Table SIII.16: Summary of Drug Exposure to Pembrolizumab TNBC Subjects KN355 Combination Therapy (ASaT Population)

	Pembrolizumab (200 mg Q3W) + Chemotherapy (N=596)
Duration of Therapy Pembrolizumab (months)	
Mean	8.2
Median	5.7
SD	7.1
Range	0.0 to 33.0
Number of Pembrolizumab Administrations	
Mean	11.9
Median	9.0
SD	9.5
Range	1.0 to 35.0
Each subject is counted once on each applicable duration category row. Duration on-therapy is calculated as (last dose date - first dose date +1)/30.4367 (months) for pembrolizumab in the combo. Database Cutoff Date for KN355: 11DEC2019.	

Data on File

Table SIII.17: Summary of Drug Exposure to Pembrolizumab TNBC Subjects KN522 Combination Therapy (APaT Population)

	Pembrolizumab 200 mg Q3W (N=783)
Duration of Pembrolizumab Exposure (month)	
Mean	10.9
Median	13.31
SD	5.27
Range	0.03 to 21.91
Number of Pembrolizumab Administrations	
Mean	13.1
Median	17.00
SD	5.41
Range	1.00 to 17.00
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 for pembrolizumab. Database cutoff date for TNBC: (KN522: 23MAR2021)	

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Table SIII.18: Summary of Drug Exposure to Pembrolizumab Endometrial Carcinoma Participants KN146 and KN775 Combination Therapy (APaT Population)

	Pembrolizumab 200mg Q3W (N=530)
Duration of Exposure (day)	
Mean	261.7
Median	211.0
SD	209.40
Range	1.0 to 885.0
Number of Administrations	
Mean	12.6
Median	10.0
SD	9.49
Range	1.0 to 36.0
Duration of exposure (day) is calculated as last dose date - first dose date + 1. Database cutoff date for endometrial carcinoma (KN146: 18AUG2020, KN775: 26OCT2020)	

Data on File

Table SIII.19: Summary of Drug Exposure MSI-H Subjects KN158 Cohort K and KN164 Cohorts A and B Monotherapy (ASaT Population)

	Pembrolizumab 200 mg Q3W (N=475)
Study Days On-Therapy (Months)	
Mean	9.7
Median	5.49
SD	9.30
Range	0.03 to 38.01
Number of Administrations	
Mean	14.3
Median	8.00
SD	12.83
Range	1.00 to 35.00
Each subject is counted once on each applicable duration category row. Duration of Exposure is calculated as last dose date - first dose date + 1. Database cutoff date for MSI-H (KN158-cohort K: 05OCT2020) Database cutoff date for Colorectal (KN164-cohorts A and B: 09SEP2019)	

Data on File

Public

Table SIII.20: Summary of Drug Exposure to Pembrolizumab Cervical Cancer Participants KN826 Combination Therapy (APaT Population)

	Pembrolizumab 200 mg Q3W (N=307)
Duration of Exposure (months)	
Mean	11.42
Median	9.89
SD	7.97
Range	0.03 to 26.02
Number of Cycles	
Mean	15.99
Median	13.00
SD	10.86
Range	1.00 to 35.00
Each participant is counted once on each applicable duration category row. Duration of Exposure is calculated as last dose date - first dose date + 1. Database Cutoff Date: 03MAY2021	

Data on File

Table SIII.21: Summary of Drug Exposure Gastric Cancer Participants in KN811 Combination Therapy (APaT Population)

	Pembrolizumab 200 mg Q3W (N=350)
Study Days On-Therapy (Months)	
Mean	10.80
Median	9.10
SD	7.88
Range	0.03 to 30.29
Number of Administrations	
Mean	15.08
Median	13.00
SD	10.50
Range	1.00 to 35.00
Each subject is counted once on each applicable duration category row. Duration of Exposure is calculated as last dose date - first dose date + 1. Database Cutoff Date: 25MAY2022	

Data on file

Public

Table SIII.22: Summary of Drug Exposure to Pembrolizumab Gastric Cancer Participants in KN859 Combination Therapy (APaT Population)

	Pembrolizumab 200 mg Q3W (N=785)
Duration of Exposure (days)	
Mean	258.5
Median	190.0
SD	227.9
Range	1 to 1025
Number of Pembrolizumab Administrations	
Mean	12.2
Median	9.0
SD	10.1
Range	1 to 35
Each participant is counted once on each applicable duration category row. Duration of exposure is calculated as last dose date - first dose date + 1. Database cutoff date for Gastric (KN859: 03OCT2022)	

Data on File

Table SIII.23: Summary of Drug Exposure to Pembrolizumab BTC Participants in KN966 Combination Therapy (APaT Population)

	KN966 Pembrolizumab (200mg Q3W) + Chemotherapy (N=529)
Duration of Exposure (Days)	
Mean	233.9
Median	184.0
SD	202.86
Range	1.0 to 853.0
Number of Administrations	
Mean	11.1
Median	9.0
SD	8.94
Range	1.0 to 35.0
Each participant is counted once on each applicable duration category row Duration of exposure is calculated as last dose date - first dose date + 1 for pembrolizumab in the combo. (pembrolizumab KN966 Database Cutoff Date: 15DEC2022)	

Data on File

Public

Clinical Trial Exposure by Dose and Duration

Table SIII.24 displays the duration of exposure to pembrolizumab monotherapy in the pooled KN001, KN002 and KN006 melanoma population with respect to time and dose.

Table SIII.25 displays the duration of exposure to pembrolizumab monotherapy in the KN054 and KN716 melanoma population with respect to time and dose.

Table SIII.26 displays the duration of exposure to pembrolizumab monotherapy in the pooled KN001, KN010, KN024, and KN042 NSCLC population with respect to time and dose.

Table SIII.27 displays the duration of exposure to pembrolizumab in the pooled KN021 (Cohorts A, C and G), KN189, and KN407 NSCLC population who received pembrolizumab combination therapy with respect to time and dose.

Table SIII.28 displays the duration of exposure to pembrolizumab monotherapy in KN091 NSCLC population with respect to time and dose.

Table SIII.29 displays the duration of exposure to pembrolizumab in combination with chemotherapy as neoadjuvant treatment followed by continued adjuvant pembrolizumab monotherapy in the KN671 NSCLC population with respect to time and dose.

Table SIII.30 displays the duration of exposure to pembrolizumab monotherapy in the pooled KN013, KN087, and KN204 HL population with respect to time and dose.

Table SIII.31 displays the duration of exposure to pembrolizumab monotherapy in the pooled KN045 and KN052 UC population with respect to time and dose.

Table SIII.32 displays the duration of exposure to pembrolizumab monotherapy in the pooled KN040, KN012, KN055 and KN048 HNSCC population with respect to time and dose.

Table SIII.33 displays the duration of exposure to pembrolizumab in the KN048 HNSCC population who received pembrolizumab combination therapy with respect to time and dose.

Table SIII.34 displays the duration of exposure to pembrolizumab in the KN426 RCC population who received pembrolizumab combination therapy with respect to time and dose.

Table SIII.35 displays the duration of exposure to pembrolizumab in the KN581 RCC population who received pembrolizumab combination therapy with respect to time and dose.

Table SIII.36 displays the duration of exposure to pembrolizumab monotherapy in the KN564 RCC population with respect to time and dose.

Table SIII.37 displays the duration of exposure to pembrolizumab monotherapy in the KN177 CRC population with respect to time and dose.

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Table SIII.38 displays the duration of exposure to pembrolizumab in the KN590 esophageal cancer population who received pembrolizumab combination therapy with respect to time and dose.

Table SIII.39 displays the duration of exposure to pembrolizumab in the KN355 TNBC population who received pembrolizumab combination therapy with respect to time and dose.

Table SIII.40 displays the duration of exposure to pembrolizumab in KN522 TNBC population who received pembrolizumab in combination with neoadjuvant chemotherapy followed by continued adjuvant pembrolizumab monotherapy with respect to time and dose.

Table SIII.41 displays the duration of exposure to pembrolizumab in the KN146 and KN775 endometrial carcinoma population who received pembrolizumab combination therapy with respect to time and dose.

Table SIII.42 displays the duration of exposure to pembrolizumab monotherapy in the KN158 Cohort K and KN164 Cohorts A and B MSI-H population with respect to time and dose.

Table SIII.43 displays the duration of exposure to pembrolizumab in the KN826cervival cancer population who received pembrolizumab combination therapy with respect to time and dose.

Table SIII.44 displays the duration of exposure to pembrolizumab in the KN811 gastric cancer population who received pembrolizumab combination therapy with respect to time and dose.

Table SIII.45 displays the duration of exposure to pembrolizumab in the KN859 gastric cancer population who received pembrolizumab combination therapy with respect to time and dose.

Table SIII.46 displays the duration of exposure to pembrolizumab in the KN966 BTC population who received pembrolizumab combination therapy with respect to time and dose.

Table SIII.24: Clinical Trial Exposure by Dose and Duration Melanoma Subjects KN001, KN002 and KN006 Monotherapy (APaT Population)

Duration of Exposure	Pembrolizumab 2 mg/kg Q3W (N=340)		Pembrolizumab 10 mg/kg Q3W (N=769)		Pembrolizumab 10 mg/kg Q2W (N=458)		Total (N=1567)	
	n	Patient Years	n	Patient Years	n	Patient Years	n	Patient Years
> 0 m	340	214.1	769	473.0	458	290.1	1567	977.2
≥ 1 m	303	213.1	674	469.9	408	288.0	1385	971.0
≥ 3 m	206	196.1	492	437.2	310	270.9	1008	904.2
≥ 6 m	149	176.1	356	388.6	230	241.6	735	806.3
≥ 12 m	96	137.0	215	286.0	124	160.7	435	583.7

Each subject is counted once on each applicable duration category row. Duration of Exposure is calculated as last dose date - first dose date +1.
(pembrolizumab KN001 Database Cutoff Date: 18APR2014).
(pembrolizumab KN002 Database Cutoff Date: 28FEB2015).
(pembrolizumab KN006 Database Cutoff Date: 03MAR2015).

Data on File

Table SIII.25: Clinical Trial Exposure by Dose and Duration Melanoma Participants in KN054 and KN716 Monotherapy (APaT Population)

	KN716 + KN054 Pembrolizumab Q3W (N=992)		
	n	(%)	Person-years
Duration of Exposure			
>0 m	992	(100.0)	(725.4)
>=1 m	944	(95.2)	(723.5)
>=3 m	862	(86.9)	(708.7)
>=6m	724	(73.0)	(656.6)
>=12m	98	(9.9)	(104.2)

Each participant is counted once on each applicable duration category row.
Duration of Exposure is calculated as last dose date - first dose date + 1.
Database cutoff date for Melanoma (KN054: 02OCT2017, KN716: 04DEC2020)

Data on File

Public

Table SIII.26: Clinical Trial Exposure by Dose and Duration NSCLC Subjects KN001, KN010, KN024 and KN042 Monotherapy (APaT Population)

Duration of Exposure	Pembrolizumab 2 mg/kg Q3W (N=400)			Pembrolizumab 10 mg/kg Q3W (N=630)			Pembrolizumab 10 mg/kg Q2W (N=202)			Pembrolizumab 200 mg Q3W (N=790)			Total (N=2022)		
	n	(%)	Person-years	n	(%)	Person-years	n	(%)	Person-years	n	(%)	Person-years	n	(%)	Person-years
>0 m	400	(100.0)	(158.8)	630	(100.0)	(284.2)	202	(100.0)	(97.5)	790	(100.0)	(582.0)	2022	(100.0)	(1122.5)
>=1 m	326	(81.5)	(156.1)	513	(81.4)	(280.1)	170	(84.2)	(96.5)	671	(84.9)	(578.8)	1680	(83.1)	(1111.5)
>=3 m	217	(54.3)	(139.1)	325	(51.6)	(250.1)	106	(52.5)	(86.2)	521	(65.9)	(555.5)	1169	(57.8)	(1030.9)
>=6m	123	(30.8)	(105.2)	220	(34.9)	(211.6)	75	(37.1)	(74.8)	393	(49.7)	(508.4)	811	(40.1)	(900.0)
>=12m	37	(9.3)	(48.3)	91	(14.4)	(120.9)	37	(18.3)	(47.3)	250	(31.6)	(406.3)	415	(20.5)	(622.8)

Each patient is counted once on each applicable duration category row.
Duration of Exposure is calculated as last dose date - first dose date + 1.
(pembrolizumab KN001 Database Cutoff Date for Lung: 23JAN2015).
(pembrolizumab KN010 Database Cutoff Date: 30SEP2015).
(pembrolizumab KN024Database Cutoff Date: 10JUL2017).
(pembrolizumab KN042 Database Cutoff Date: 26FEB2018).

Data on File

Table SIII.27: Clinical Trial Exposure to Pembrolizumab by Dose and Duration NSCLC Subjects KN021 (Cohorts A, C and G), KN189 and KN407 Combination Therapy (APaT Population)

	Pembrolizumab 10mg/kg Combo (N=24)			Pembrolizumab 2mg/kg Combo (N=25)			Pembrolizumab 200mg Combo (N=742)			Total (N=791)		
	n	(%)	Person-years	n	(%)	Person-years	n	(%)	Person-years	n	(%)	Person-years
Duration of Exposure												
>0 m	24	(100.0)	(16.1)	25	(100.0)	(26.5)	742	(100.0)	(452.2)	791	(100.0)	(494.8)
>=1 m	20	(83.3)	(15.9)	24	(96.0)	(26.4)	669	(90.2)	(449.6)	713	(90.1)	(491.9)
>=3 m	17	(70.8)	(15.5)	22	(88.0)	(26.1)	585	(78.8)	(434.7)	624	(78.9)	(476.2)
>=6m	11	(45.8)	(13.1)	17	(68.0)	(24.3)	406	(54.7)	(367.8)	434	(54.9)	(405.3)
>=12m	6	(25.0)	(9.2)	11	(44.0)	(20)	120	(16.2)	(156.8)	137	(17.3)	(186.0)

Each subject is counted once on each applicable duration category row.
Duration of Exposure is calculated as last dose date - first dose date + 1.
MK-3475 Database Cutoff Date for Lung Combination Therapy (KN021 Cohort A: 07NOV2016, Cohort G/C: 31MAY2017, KN189: 8NOV2017, KN407: 03APR2018)

Data on File

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Table SIII.28: Clinical Trial Exposure by Dose and Duration NSCLC Participants KN091 Monotherapy (APaT Population)

	Pembrolizumab 200 mg Q3W (N=580)		
	n	(%)	Person-Years
Duration of Exposure			
>0 m	580	(100.0)	(418.7)
>=1 m	538	(92.8)	(417.4)
>=3 m	461	(79.5)	(403.9)
>=6m	397	(68.4)	(380.1)
>=12m	114	(19.7)	(122.3)

Each participant is counted once on each applicable duration category row.
Duration of Exposure is calculated as last dose date - first dose date + 1.
KN091 Database Cutoff Date: 20SEP2021

Data on File

Table SIII.29: Clinical Trial Exposure by Dose and Duration NSCLC Participants in KN671 Combination Therapy (APaT Population)

	Pembrolizumab 200 mg Q3W (N=396)		
	n	(%)	Person-Years
Duration of Exposure			
>0 m	396	(100.0)	(307.4)
>=1 m	372	(93.9)	(306.5)
>=3 m	292	(73.7)	(293.1)
>=6m	281	(71.0)	(288.7)
>=12m	185	(46.7)	(218.2)

Each subject is counted once on each applicable duration category row.
Duration of Exposure is calculated as last dose date - first dose date + 1.
Database Cutoff Date: 29JUL2022

Data on File

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Table SIII.30: Clinical Trial Exposure by Dose and Duration HL Subjects in KN013, KN087, and KN204 Monotherapy (APaT Population)

	Pembrolizumab 10 mg/kg Q2W (N=31)			Pembrolizumab 200 mg Q3W (N=358)			Total (N=389)		
	n	(%)	Person-years	n	(%)	Person-years	n	(%)	Person-years
Duration of Exposure									
>0 m	31	(100.0)	(27.7)	358	(100.0)	(378.1)	389	(100.0)	(405.8)
>=1 m	29	(93.5)	(27.7)	353	(98.6)	(378.0)	382	(98.2)	(405.7)
>=3 m	25	(80.6)	(27.1)	322	(89.9)	(372.2)	347	(89.2)	(399.3)
>=6m	18	(58.1)	(24.8)	253	(70.7)	(346.5)	271	(69.7)	(371.3)
>=12m	11	(35.5)	(19.7)	171	(47.8)	(288.5)	182	(46.8)	(308.2)
>=18m	8	(25.8)	(16.0)	111	(31.0)	(216.2)	119	(30.6)	(232.2)

Each subject is counted once on each applicable duration category row.
Duration of Exposure is calculated as last dose date - first dose date + 1.
Database Cutoff Date (KN013-Cohort 3: 28SEP2018, KN087: 21MAR2019, KN204: 16JAN2020)

Data on File

Table SIII.31: Clinical Trial Exposure by Dose and Duration UC Subjects KN045 and KN052 Monotherapy (APaT Population)

Duration of Exposure	**Pembrolizumab 200 mg Q3W (N=636)**	
	n	**Patient Years**
> 0 m	636	236.2
≥ 1 m	510	232.0
≥ 3 m	296	195.3
≥ 6 m	167	148.0
≥ 12 m	52	65.1

Each subject is counted once on each applicable duration category row. Duration of Exposure is calculated as last dose date - first dose date +1.
Includes all subjects with urothelial carcinoma who received at least one dose of Pembrolizumab in KN045 and KN052.
Pembrolizumab KN045 Database Cutoff Date: 07SEP2016.
Pembrolizumab KN052 Database Cutoff Date: 01SEP2016.

Data on File

Table SIII.32: Clinical Trial Exposure by Dose and Duration HNSCC Subjects KN012 B+B2 Cohorts, KN040, KN055 and KN048 Monotherapy (ASaT Population)

	Pembrolizumab 10mg/kg Q2W (N=60)			Pembrolizumab 200mg Q3W (N=849)			Total (N=909)		
	n	(%)	Person-years	n	(%)	Person-years	n	(%)	Person-years
Duration of Exposure									
>0 m	60	(100.0)	(34.2)	849	(100.0)	(372.3)	909	(100.0)	(406.5)
>=1 m	53	(88.3)	(34.0)	681	(80.2)	(366.9)	734	(80.7)	(400.9)
>=3 m	34	(56.7)	(31.0)	425	(50.1)	(324.6)	459	(50.5)	(355.5)
>=6m	19	(31.7)	(25.9)	262	(30.9)	(266.0)	281	(30.9)	(291.8)
>=12m	12	(20.0)	(21.1)	106	(12.5)	(161.0)	118	(13.0)	(182.1)

Each subject is counted once on each applicable duration category row.
Duration of Exposure is calculated as last dose date - first dose date + 1.
MK-3475 Database Cutoff Date for HNSCC (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN048: 13JUN2018, KN055: 22APR2016)

Data on File

Public

Table SIII.33: Clinical Trial Exposure to Pembrolizumab by Dose and Duration HNSCC Subjects in KN048 Combination Therapy (ASaT Population)

	Pembrolizumab 200mg Q3W (N=276)		
	n	(%)	Person-years
Duration of Exposure			
>0 m	276	(100.0)	(170.0)
>=1 m	239	(86.6)	(168.9)
>=3 m	198	(71.7)	(161.8)
>=6m	129	(46.7)	(135.2)
>=12m	51	(18.5)	(81.0)

Each subject is counted once on each applicable duration category row.
Duration of Exposure is calculated as last dose date - first dose date + 1.
MK-3475 Database Cutoff Date for KN048: 13JUN2018.

Data on File

Table SIII.34: Clinical Trial Exposure to Pembrolizumab by Dose and Duration RCC Subjects KN426 Combination Therapy (ASaT Population)

	KN426 Data for Pembrolizumab + Axitinib (N=429)		
	n	(%)	Person-years
Duration of Exposure			
>0 m	429	(100.0)	(337.1)
>=1 m	395	(92.1)	(335.7)
>=3 m	346	(80.7)	(327.7)
>=6m	300	(69.9)	(311.0)
>=12m	152	(35.4)	(200.4)
>=18m	32	(7.5)	(50.9)

Each subject is counted once on each applicable duration category row.
Duration of Exposure is calculated as (last dose date - first dose date +1)/30.4367 (months).
Duration of Exposure is calculated as last dose date - first dose date + 1 for pembrolizumab in the combo.
MK-3475 Database Cutoff Date for KN426: 24AUG2018.

Data on File

Table SIII.35: Clinical Trial Exposure to Pembrolizumab by Dose and Duration RCC Participants KN581 Combination Therapy (APaT Population)

Duration of Exposure	Pembrolizumab + Lenvatinib(N=352)		
	n	(%)	Person-years
>0 m	352	(100.0)	(423.9)
>=1 m	326	(92.6)	(423.2)
>=3 m	301	(85.5)	(418.9)
>=6 m	272	(77.3)	(407.7)
>=12 m	213	(60.5)	(363.8)
>=18 m	140	(39.8)	(272.2)

Each participant is counted once on each applicable duration category row.
Duration of Exposure is calculated as last dose date - first dose date + 1 for pembrolizumab in the combo.MK-3475 Database Cutoff Date for KN581: 28AUG2020.

Data on File

Table SIII.36: Clinical Trial Exposure by Dose and Duration RCC Participants KN564 Monotherapy (APaT Population)

	Pembrolizumab 200 mg Q3W (N=488)		
	n	(%)	Person-years
Duration of Exposure			
>0 m	488	(100.0)	(364.3)
>=1 m	463	(94.9)	(363.1)
>=3 m	428	(87.7)	(357.0)
>=6 m	370	(75.8)	(334.4)
>=9 m	325	(66.6)	(306.7)
>=12 m	32	(6.6)	(34.6)

Each participant is counted once on each applicable duration category row.
Duration of Exposure (months) is calculated as (last dose date - first dose date + 1)/30.4367.
Includes all participants who received at least one dose of pembrolizumab in KN564.
Database cutoff date for RCC (KN564: 14DEC2020)

Data on File

Table SIII.37: Clinical Trial Exposure by Dose and Duration CRC Subjects KN177 Monotherapy (ASaT Population)

	KN177 Data for Pembrolizumab†† (N=153)		
	n	(%)	Person-years
Duration of Exposure			
>0 m	153	(100.0)	(169.0)
>=1 m	134	(87.6)	(168.5)
>=3 m	112	(73.2)	(165.0)
>=6m	96	(62.7)	(158.7)
>=12m	73	(47.7)	(141.7)
Each subject is counted once on each applicable duration category row. Duration of Exposure is calculated as last dose date - first dose date + 1. †† Includes all subjects who received at least one dose of pembrolizumab in KN177. Database cutoff date for CRC (KN177: 19FEB2020)			

Data on File

Table SIII.38: Clinical Trial Exposure to Pembrolizumab by Dose and Duration Esophageal Cancer Subjects KN590 Combination Therapy (ASaT Population)

	KN590 Data for Pembrolizumab (N=370)		
	n	(%)	Person-years
Duration of Exposure			
>0 m	370	(100.0)	(231.5)
>=1 m	323	(87.3)	(230.3)
>=3 m	266	(71.9)	(220.6)
>=6m	161	(43.5)	(180.9)
>=12m	76	(20.5)	(122.3)
Each subject is counted once on each applicable duration category row. Duration of Exposure is calculated as (last dose date - first dose date +1)/30.4367 (months). Database Cutoff date for Esophageal (KN590: 02JUL2020)			

Data on File

Public

Table SIII.39: Clinical Trial Exposure to Pembrolizumab by Dose and Duration TNBC Subjects KN355 Combination Therapy (ASaT Population)

	Pembrolizumab (200 mg Q3W) + Chemotherapy (N=596)		
	n	(%)	Person-years
Duration of Pembrolizumab Exposure			
>0 m	596	(100.0)	(405.3)
>=1 m	550	(92.3)	(403.9)
>=3 m	443	(74.3)	(385.8)
>=6 m	291	(48.8)	(331.3)
>=12 m	146	(24.5)	(229.6)

Each subject is counted once on each applicable duration category row.
Duration of exposure is calculated as (last dose date - first dose date +1)/30.4367 (months) for pembrolizumab in the combo.
Database Cutoff Date for KN355: 11DEC2019.

Data on File

Table SIII.40: Clinical Trial Exposure to Pembrolizumab by Dose and Duration TNBC Subjects KN522 Combination Therapy (APaT Population)

	Pembrolizumab 200 mg Q3W (N=783)		
	n	(%)	Person-years
Duration of Pembrolizumab Exposure			
>0 m	778	(99.4)	(709.7)
>=1 m	741	(94.6)	(708.2)
>=3 m	669	(85.4)	(695.2)
>=6 m	560	(71.5)	(653.5)
>=12 m	503	(64.2)	(607.7)

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 for pembrolizumab.
Database cutoff date for TNBC: (KN522: 23MAR2021)

Data on File

Public

Table SIII.41: Clinical Trial Exposure to Pembrolizumab by Dose and Duration Endometrial Carcinoma Participants KN146 and KN775 Combination Therapy (APaT Population)

	Pembrolizumab 200mg Q3W (N=530)		
	n	(%)	Person-years
Duration of Exposure (month)			
> 0 m	530	(100.0)	379.8
≥ 1 m	472	(89.1)	378.1
≥ 3 m	394	(74.3)	364.4
≥ 6 m	301	(56.8)	330.6
≥ 12 m	141	(26.6)	214.6
≥ 18 m	70	(13.2)	127.4
≥ 24 m	8	(1.5)	16.8
Each participant is counted once on each applicable duration category row. Duration of exposure (month) is calculated as (last dose date - first dose date + 1) / 30.4367. Database cutoff date for endometrial carcinoma (KN146: 18AUG2020, KN775: 26OCT2020)			

Data on File

Table SIII.42: Clinical Trial Exposure by Dose and Duration MSI-H Subjects KN158 Cohort K and KN164 Cohorts A and B Monotherapy (ASaT Population)

	Pembrolizumab 200 mg Q3W (N=475)		
	n	(%)	Person-years
Duration of Exposure			
>0 m	475	(100.0)	(384.2)
>=1 m	405	(85.3)	(382.3)
>=3 m	305	(64.2)	(365.5)
>=6m	227	(47.8)	(337.9)
>=12m	161	(33.9)	(290.9)
>=18m	121	(25.5)	(241.1)
Each subject is counted once on each applicable duration category row. Duration of Exposure is calculated as last dose date - first dose date + 1. Database cutoff date for MSI-H (KN158-cohort K: 05OCT2020) Database cutoff date for Colorectal (KN164-cohorts A and B: 09SEP2019)			

Data on File

Public

Table SIII.43: Clinical Trial Exposure to Pembrolizumab by Dose and Duration Cervical Cancer Participants KN826 Combination Therapy (APaT Population)

	Pembrolizumab 200 mg Q3W (N=307)		
	n	(%)	Person-Years
Duration of Exposure			
>0 m	307	(100.0)	(292.3)
>=1 m	277	(90.2)	(291.7)
>=3 m	251	(81.8)	(287.3)
>=6m	206	(67.1)	(269.6)
>=12m	136	(44.3)	(220.2)
Each participant is counted once on each applicable duration category row. Duration of Exposure is calculated as last dose date - first dose date + 1. Database Cutoff Date: 03MAY2021			

Data on File

Table SIII.44: Clinical Trial Exposure to Pembrolizumab by Dose and Duration Gastric Cancer Participants KN811 Combination Therapy (APaT Population)

	Pembrolizumab 200 mg Q3W (N=350)		
	n	(%)	Person-Years
Duration of Exposure			
>0 m	350	(100.0)	(315.0)
>=1 m	323	(92.3)	(314.0)
>=3 m	286	(81.7)	(307.3)
>=6m	231	(66.0)	(286.4)
>=12m	133	(38.0)	(214.1)
Each subject is counted once on each applicable duration category row. Duration of Exposure is calculated as last dose date - first dose date + 1. Database Cutoff Date: 25MAY2022			

Data on file

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Table SIII.45: Clinical Trial Exposure to Pembrolizumab by Dose and Duration Gastric Cancer Participants KN859 Combination Therapy (APaT Population)

	Pembrolizumab 200 mg Q3W (N=785)		
	n	(%)	Person-years
Duration of exposure (month)			
>0	785	(100.0)	555.6
>=1	688	(87.6)	552.9
>=3	589	(75.0)	535.7
>=6	405	(51.6)	467.4
>=12	186	(23.7)	314.0
Each participant is counted once on each applicable duration category row. Duration of exposure (month) is calculated as (last dose date - first dose date + 1) / 30.4367 Database cutoff date for Gastric (KN859: 03OCT2022)			

Data on File

Table SIII.46: Clinical Trial Exposure to Pembrolizumab by Dose and Duration BTC Participants in KN966 Combination Therapy (APaT Population)

	KN966 Pembrolizumab (200mg Q3W) + Chemotherapy (N=529)		
	n	(%)	Person-Years
Duration of Exposure			
> 0 m	529	(100.0)	(338.7)
≥ 1 m	464	(87.7)	(337.0)
≥ 3 m	376	(71.1)	(322.2)
≥ 6 m	267	(50.5)	(282.5)
≥ 12 m	113	(21.4)	(172.9)
≥ 18 m	57	(10.8)	(106.0)
≥ 24 m	20	(3.8)	(41.9)
Each participant is counted once on each applicable duration category row. Duration of exposure is calculated as last dose date - first dose date + 1 (pembrolizumab KN966 Database Cutoff Date: 15DEC2022)			

Data on File

Clinical Trial Exposure by Age and Gender

Clinical trial exposure to pembrolizumab monotherapy by age and gender for all melanoma patients in the pooled KN001, KN002 and KN006 population are summarized in Table SIII.47. Overall, a greater number of patients less than 65 years have been treated compared to 65 years or older (906 vs. 661). Across the age groups, more males have been treated compared to females (951 vs. 616).

Clinical trial exposure to pembrolizumab monotherapy by age and gender for all melanoma patients in KN054 and KN716 is summarized in Table SIII.48. Overall, a greater number of patients less than 65 years (one patient ≥ 12 and ≤ 18 years of age) have been treated compared

to 65 years or older (684 vs. 308). Across the age groups, more males have been treated compared to females (617 vs. 375).

Clinical trial exposure to pembrolizumab monotherapy by age and gender for all NSCLC patients in KN001, KN010, KN024 and KN042 is summarized in Table SIII.49. Overall, a greater number of patients less than 65 years have been treated compared to 65 years or older (1,116 vs. 906). Across the age groups, more males have been treated compared to females (1,249 vs. 773).

Clinical trial exposure to pembrolizumab by age and gender for all NSCLC patients who received pembrolizumab in combination with chemotherapy in KN189, KN021 (Cohorts A, C and G) and KN407 is summarized in Table SIII.50. Overall, a similar number of patients less than 65 years have been treated compared to 65 years or older (382 vs. 409). Across the age groups, more males have been treated compared to females (516 vs. 275).

Clinical trial exposure to pembolizumab monotherapy by age and gender for NSCLC patients in KN091 is summarized in Table SIII.51. Overall, a similar number of patients less than 65 years have been treated compared to 65 years or older (281 vs. 299). Across the age groups, more males have been treated compared to females (394 vs. 186).

Clinical trial exposure to pembrolizumab in combination with chemotherapy as neoadjuvant treatment followed by continued adjuvant pembrolizumab monotherapy by age and gender for all NSCLC patients in KN671 is summarized in Table SIII.52. Overall, a greater number of patients less than 65 years have been treated compared to 65 years or older (221 vs 175). Across the age groups, more males have been treated compared to females (278 vs 118).

Clinical trial exposure to pembrolizumab monotherapy by age and gender for all HL patients in KN013, KN087, and KN204 is summarized in Table SIII.53. Overall, a greater number of patients less than 65 years have been treated compared to 65 years or older (343 vs. 46). Across the age groups, more males have been treated compared to females (212 vs. 177).

Clinical trial exposure to pembrolizumab monotherapy by age and gender for patients under 18 years in KN051, of which 22 were HL patients, is summarized in Table SIII.54. Of the age groups, there were 3 patients 6 months to less than 2 years, 23 patients 2 to 5 years, 25 patients 6 to 9 years, 36 patients 10 to 13 years, and 74 patients 14 to 17 years. Across the age groups, a similar number of males and females have been treated (82 vs. 79).

Clinical trial exposure to pembrolizumab monotherapy by age and gender for all UC patients in KN045 and KN052 is summarized in Table SIII.55. Overall, a greater number of patients 65 years or older have been treated compared to patients less than 65 years (465 vs. 171). Across the age groups, more males have been treated compared to females (484 vs. 152).

Clinical trial exposure to pembrolizumab monotherapy by age and gender for all HNSCC patients in KN012 B+B2 Cohorts, KN040, KN055, and KN048 is summarized in Table SIII.56. Overall, a greater number of patients less than 65 years have been treated compared to 65 years or older (586 vs.323). Across the age groups, more males have been treated compared to females (752 vs.157).

Clinical trial exposure to pembrolizumab by age and gender for HNSCC patients in KN048 who received pembrolizumab combination therapy is summarized in Table SIII.57. Overall, a greater number of patients less than 65 years have been treated compared to 65 years or older (176 vs.100). Across the age groups, more males have been treated compared to females (220 vs.56).

Clinical trial exposure to pembrolizumab by age and gender for all RCC patients in KN426 who received pembrolizumab combination therapy is summarized in Table SIII.58. Overall, a greater number of patients less than 65 years have been treated compared to 65 years or older (257 vs. 172). Across the age groups, more males have been treated compared to females (306 vs. 123).

Clinical trial exposure to pembrolizumab by age and gender for all RCC patients in KN581 who received pembrolizumab combination therapy is summarized in Table SIII.59. Overall, a greater number of patients less than 65 years have been treated compared to 65 years or older (193 vs. 159). Across the age groups, more males have been treated compared to females (252 vs. 100).

Clinical trial exposure to pembrolizumab monotherapy by age and gender for all RCC patients in KN564 is summarized in Table SIII.60. Overall, a greater number of patients less than 65 years have been treated compared to 65 years or older (333 vs. 155). Across the age groups, more males have been treated compared to females (340 vs. 148).

Clinical trial exposure to pembrolizumab monotherapy by age and gender for all CRC patients in KN177 is summarized in Table SIII.61. Overall, a greater number of patients 65 years or older have been treated compared to patients less than 65 years (80 vs. 73). Across the age groups, more females have been treated compared to males (82 vs. 71). Of note, the absolute difference is small as compared to a number of other datasets.

Clinical trial exposure to pembrolizumab by age and gender for all esophageal cancer patients in KN590 who received pembrolizumab combination therapy is summarized in Table SIII.62. Overall, a greater number of patients less than 65 years have been treated compared to patients 65 years or older (201 vs. 169). Across the age groups, more males have been treated compared to females (305 vs. 65).

Clinical trial exposure to pembrolizumab by age and gender for all TNBC patients in KN355 who received pembrolizumab combination therapy is summarized in Table SIII.63. Overall, a greater number of patients less than 65 years have been treated compared to 65 years or older (459 vs. 137). Only female patients were included in KN355.

Clinical trial exposure to pembrolizumab by age and gender for the TNBC patients in KN522 who received pembrolizumab in combination with neoadjuvant chemotherapy followed by continued adjuvant pembrolizumab monotherapy is summarized in Table SIII.64. Overall, a greater number of patients less than 65 years have been treated compared to 65 years or older (695 vs. 83). Across the age groups, more females have been treated compared to males (777 vs. 1).

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Clinical trial exposure to pembrolizumab by age for all endometrial carcinoma patients in KN146 and KN775 who received pembrolizumab combination therapy is summarized in Table SIII.65. Overall, a similar number of patients less than 65 years have been treated compared to 65 years or older (252 vs. 278). Only female patients were included in KN146 and KN775.

Clinical trial exposure to pembrolizumab monotherapy by age and gender for all MSI-H patients in KN158 Cohort K and KN164 Cohorts A and B is summarized in Table SIII.66. Overall, a greater number of patients less than 65 years have been treated compared to patients 65 years or older (305 vs. 170). Across the age groups, more females have been treated compared to males (262 vs. 213).

Clinical trial exposure to pembrolizumab by age and gender for the cervical cancer patients in KN826 who received pembrolizumab combination therapy is summarized in Table SIII.67. Overall, a greater number of patients less than 65 years have been treated compared to patients 65 years or older (259 vs. 48). Only female patients were included in KN826.

Clinical trial exposure to pembrolizumab by age and gender for gastric cancer patients in KN811 who received pembrolizumab combination therapy is summarized in Table SIII.68. Overall, a greater number of patients less than 65 years have been treated compared to 65 years or older (205 vs. 145). Across the age groups, more males have been treated compared to females (284 vs. 66).

Clinical trial exposure to pembrolizumab by age and gender for gastric cancer patients in KN859 who received pembrolizumab combination therapy is summarized in Table SIII.69. Overall, a greater number of patients less than 65 years have been treated compared to 65 years or older (483 vs.302). Across the age groups, more males have been treated compared to females (522 vs. 263).

Clinical trial exposure to pembrolizumab by age and gender for all BTC patients who received pembrolizumab combination therapy in KN966 is summarized in Table SIII.70. Overall, a similar number of patients less than 65 years and patients 65 years or older were treated (266 vs. 263). Across the age groups, more males have been treated compared to females (279 vs. 250).

Table SIII.47: Clinical Trial Exposure by Age and Gender Melanoma Subjects KN001, KN002 and KN006 Monotherapy (APaT Population)

Age Category (years)	Subjects			Mean Duration (days)			Subject Time (years)		
	Male	Female	Total	Male	Female	Total	Male	Female	Total
<65	516	390	906	236.5	213.4	226.6	334.1	227.8	562.0
≥65	435	226	661	242.2	204.8	229.4	288.4	126.7	415.2
Total	951	616	1567	239.1	210.2	227.8	622.6	354.6	977.2

Duration of exposure is calculated assuming one day of dosing = 7 days of exposure.
Duration of Exposure is calculated as last dose date - first dose date +1.
(pembrolizumab KN001 Database Cutoff Date: 18APR2014).
(pembrolizumab KN002 Database Cutoff Date: 28FEB2015).
(pembrolizumab KN006 Database Cutoff Date: 03MAR2015).

Data on File

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Table SIII.48: Clinical Trial Exposure by Age and Gender Melanoma Participants KN054 and KN716 Monotherapy (APaT Population)

Age Category (Years)	Participants			Mean Duration (days)			Participant Time (years)		
	Male	Female	Total	Male	Female	Total	Male	Female	Total
<65 *	412	272	684	271.3	279.1	274.4	306.0	207.8	513.8
≥65	205	103	308	250.9	250.8	250.9	140.8	70.7	211.6
Total	617	375	992	264.5	271.3	267.1	446.8	278.6	725.4

Duration of Exposure is calculated as last dose date - first dose date + 1.
*one patient in KN716 ≥12 and ≤ 18 years of age
Database cutoff date for Melanoma (KN054: 02OCT2017, KN716: 04DEC2020)

Data on File

Table SIII.49: Clinical Trial Exposure by Age and Gender NSCLC Subjects KN001, KN010, KN024 and KN042 Monotherapy (APaT Population)

Age Category (Years)	**Subjects**			**Mean Duration (days)**			**Subject Time (years)**		
	Male	**Female**	**Total**	**Male**	**Female**	**Total**	**Male**	**Female**	**Total**
<65	662	454	1116	207.2	192.1	201.0	375.5	238.7	614.2
≥65	587	319	906	218.9	179.3	204.9	351.7	156.6	508.3
Total	1249	773	2022	212.7	186.8	202.8	727.2	395.3	1122.5

Duration of Exposure is calculated as last dose date - first dose date +1.
(pembrolizumab KN001 Database Cutoff Date for Lung: 23JAN2015).
(pembrolizumab KN010 Database Cutoff Date: 30SEP2015).
(pembrolizumab KN024 Database Cutoff Date: 10JUL2017).
(pembrolizumab KN042 Database Cutoff Date: 26FEB2018).

Data on File

Table SIII.50: Clinical Trial Exposure to Pembrolizumab by Age and Gender NSCLC Subjects KN021 (Cohorts A, C and G), KN189 and KN407 Combination Therapy (APaT Population)

Age Category (Years)	Subjects			Mean Duration (days)			Subject Time (years)		
	Male	Female	Total	Male	Female	Total	Male	Female	Total
<65	231	151	382	207.6	264.7	230.2	131.3	109.4	240.7
≥65	285	124	409	216.1	251.8	226.9	168.6	85.5	254.1
Total	516	275	791	212.3	258.9	228.5	299.9	194.9	494.8

Duration of Exposure is calculated as last dose date - first dose date +1.
MK-3475 Database Cutoff Date for Lung Combination Therapy (KN021 Cohort A: 07NOV2016, Cohort G/C: 31MAY2017, KN189: 8NOV2017, KN407: 03APR2018)

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Table SIII.51: Clinical Trial Exposure by Age and Gender NSCLC Participants KN091 Monotherapy (APaT Population)

Age Category (Years)	Patients			Mean Duration (days)			Patient Time (years)		
	Male	Female	Total	Male	Female	Total	Male	Female	Total
<65	191	90	281	272.3	270.0	271.5	142.4	66.5	208.9
≥65	203	96	299	255.2	258.7	256.3	141.8	68.0	209.8
Total	394	186	580	263.5	264.1	263.7	284.2	134.5	418.7

Duration of Exposure is calculated as last dose date - first dose date + 1.
KN091 Database Cutoff Date: 20SEP2021

Data on File

Table SIII.52: Clinical Trial Exposure to Pembrolizumab by Age and Gender NSCLC Participants in KN671 Combination Therapy (APaT Population)

Age Category (Years)	Patients			Mean Duration (days)			Patient Time (years)		
	Male	Female	Total	Male	Female	Total	Male	Female	Total
<65	150	71	221	285.3	303.7	291.3	117.2	59.0	176.2
≥65	128	47	175	272.9	276.4	273.8	95.6	35.6	131.2
Total	278	118	396	279.6	292.9	283.5	212.8	94.6	307.4

Duration of Exposure is calculated as last dose date - first dose date + 1.
Database Cutoff Date: 29JUL2022

Data on File

Table SIII.53: Clinical Trial Exposure by Age and Gender HL Subjects KN013, KN087, and KN204 Monotherapy (APaT Population)

Age Category (Years)	Subjects			Mean Duration (days)			Subject Time (years)		
	Male	Female	Total	Male	Female	Total	Male	Female	Total
<65	187	156	343	359.9	427.0	390.4	184.3	182.4	366.7
≥65	25	21	46	302.0	321.9	311.1	20.7	18.5	39.2
Total	212	177	389	353.1	414.6	381.1	204.9	200.9	405.8

Duration of Exposure is calculated as last dose date - first dose date + 1.
Database Cutoff Date (KN013-Cohort 3: 28SEP2018, KN087: 21MAR2019, KN204: 16JAN2020)

Data on File

Table SIII.54: Clinical Trial Exposure by Age and Gender KN051 Parts 1 and II Monotherapy (APaT Population)

Age Category (years)	Persons*		Person Time (years)	
	Male	Female	Male	Female
6 months - <2 years	1	2	0.1	0.2
2 - 5 years	10	13	2.8	4.7
6 - 9 years	9	16	2.8	9.2
10 - 13 years	21	15	6.4	3.3
14 - 17 years	41	33	22.0	19.8

(Database Cutoff Date: 10JAN2020).
* HL n=22

Data on File

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Table SIII.55: Clinical Trial Exposure by Age and Gender UC Subjects KN045 and KN052 Monotherapy (APaT Population)

Age Category (years)	Subjects			Mean Duration (days)			Subject Time (years)		
	Male	Female	Total	Male	Female	Total	Male	Female	Total
<65	133	38	171	131.7	143.9	134.4	47.9	15.0	62.9
≥65	351	114	465	136.9	133.6	136.1	131.6	41.7	173.3
Total	484	152	636	135.5	136.2	135.6	179.5	56.7	236.2

Duration of exposure is calculated assuming one day of dosing = 7 days of exposure.
Duration of Exposure is calculated as last dose date - first dose date +1.
Includes all subjects with urothelial carcinoma who received at least one dose of Pembrolizumab in KN045 and KN052.
Pembrolizumab KN045 Database Cutoff Date: 07SEP2016.
Pembrolizumab KN052 Database Cutoff Date: 01SEP2016.

Data on File

Table SIII.56: Clinical Trial Exposure by Age and Gender HNSCC Subjects KN012 B+B2 Cohorts, KN040, KN055 and KN048 Monotherapy (ASaT Population)

Age Category (Years)	Subjects			Mean Duration (days)			Subject Time (years)		
	Male	Female	Total	Male	Female	Total	Male	Female	Total
<65	493	93	586	149.8	174.4	153.7	202.2	44.4	246.6
≥65	259	64	323	179.8	185.4	180.9	127.5	32.5	160.0
Total	752	157	909	160.1	178.9	163.3	329.6	76.9	406.5

Duration of Exposure is calculated as last dose date - first dose date +1.
MK-3475 Database Cutoff Date for HNSCC (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN048: 13JUN2018, KN055: 22APR2016)

Data on File

Table SIII.57: Clinical Trial Exposure to Pembrolizumab by Age and Gender HNSCC Subjects in KN048 Combination Therapy (ASaT Population)

Age Category (Years)	Subjects			Mean Duration (days)			Subject Time (years)		
	Male	Female	Total	Male	Female	Total	Male	Female	Total
<65	136	40	176	209.2	198.4	206.7	77.9	21.7	99.6
≥65	84	16	100	266.0	178.8	252.1	61.2	7.8	69.0
Total	220	56	276	230.9	192.8	223.2	139.1	29.6	168.6

Duration of Exposure is calculated as last dose date - first dose date +1.
MK-3475 Database Cutoff Date for KN048: 13JUN2018.

Data on File

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Table SIII.58: Clinical Trial Exposure to Pembrolizumab by Age and Gender RCC Subjects KN426 Combination Therapy (ASaT Population)

Age Category (Years)	Subjects			Mean Duration (days)			Subject Time (years)		
	Male	Female	Total	Male	Female	Total	Male	Female	Total
<65	189	68	257	298.9	262.7	289.3	154.7	48.9	203.6
≥65	117	55	172	273.2	305.9	283.7	87.5	46.1	133.6
Total	306	123	429	289.0	282.0	287.0	242.2	95.0	337.1

Duration of Exposure is calculated as last dose date - first dose date + 1 for pembrolizumab in the combo.
MK-3475 Database Cutoff Date for KN426: 24AUG2018.

Data on File

Table SIII.59: Clinical Trial Exposure to Pembrolizumab by Age and Gender RCC Participants KN581 Combination Therapy (APaT Population)

Age Category (years)	Participants			Mean Duration (days)			Participant Time (years)		
	Male	Female	Total	Male	Female	Total	Male	Female	Total
<65	142	51	193	479.8	456.0	473.5	186.6	63.7	250.2
≥65	110	49	159	426.1	337.6	398.9	128.3	45.3	173.6
Total	252	100	352	456.4	398.0	439.8	314.9	109.0	423.9

Duration of Exposure is calculated as last dose date – first dose date + 1 for pembrolizumab in the combo.MK-3475 Database Cutoff Date for KN581: 28AUG2020.

Data on File

Table SIII.60: Clinical Trial Exposure by Age and Gender RCC Participants KN564 Monotherapy (APaT Population)

Age Category (Years)	Participants			Mean Duration (days)			Person Time (years)		
	Male	Female	Total	Male	Female	Total	Male	Female	Total
<65	239	94	333	287.0	272.5	282.9	187.8	70.1	258.0
≥65	101	54	155	241.4	267.4	250.5	66.8	39.5	106.3
Total	340	148	488	273.5	270.7	272.6	254.6	109.7	364.3

Duration of Exposure is calculated as last dose date - first dose date + 1.
Database cutoff date for RCC (KN564: 14DEC2020)

Data on File

Table SIII.61: Clinical Trial Exposure by Age and Gender CRC Subjects in KN177 Monotherapy (AsaT Population)

Age Category (Years)	Subjects			Mean Duration (days)			Subject Time (years)		
	Male	Female	Total	Male	Female	Total	Male	Female	Total
<65	46	34	80	490.9	405.4	454.6	61.8	37.7	99.6
≥65	25	48	73	399.0	320.4	347.3	27.3	42.1	69.4
Total	71	82	153	458.5	355.7	403.4	89.1	79.9	169.0

Duration of Exposure is calculated as last dose date – first dose date +1.
Database cutoff date for CRC (KN177: 19FEB2020)

Data on File

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Table SIII.62: Clinical Trial Exposure to Pembrolizumab by Age and Gender Esophageal Cancer Subjects KN590 Combination Therapy (ASaT Population)

Age Category (Years)	Subjects			Mean Duration (days)			Subject Time (years)		
	Male	Female	Total	Male	Female	Total	Male	Female	Total
<65	165	36	201	233.2	225.5	231.9	105.4	22.2	127.6
≥65	140	29	169	238.8	235.9	238.3	91.5	18.7	110.3
Total	305	65	370	235.8	230.1	234.8	196.9	41.0	237.9

Duration of Exposure is calculated as last dose date - first dose date +1.
Database Cutoff date for Esophageal (KN590: 02JUL2020)

Data on File

Table SIII.63: Clinical Trial Exposure to Pembrolizumab by Age and Gender TNBC Subjects KN355 Combination Therapy (ASaT Population)

Age Category (Years)	Subjects		Mean Duration (days)		Subject Time (years)	
	Female	Total	Female	Total	Female	Total
<65	459	459	236.5	236.5	297.3	297.3
≥65	137	137	288.2	288.2	108.1	108.1
Total	596	596	248.4	248.4	405.3	405.3

Duration of Exposure is calculated as last dose date - first dose date +1 for pembrolizumab in the combo.
Database Cutoff Date for KN355: 11DEC2019.

Data on File

Table SIII.64: Clinical Trial Exposure to Pembrolizumab by Age and Gender TNBC Subjects KN522 Combination Therapy (APaT Population)

Age Category (Years)	Participants			Mean Duration (days)			Person Time (years)		
	Male	Female	Total	Male	Female	Total	Male	Female	Total
<65	0	695	695	0.0	338.9	338.9	0.0	644.9	644.9
≥65	1	82	83	388.0	284.0	285.2	1.1	63.8	64.8
Total	1	777	778	388.0	333.1	333.2	1.1	708.6	709.7

Duration of exposure is the time from the first dose date to the last dose date for pembrolizumab.
Database cutoff date for TNBC: (KN522: 23MAR2021)

Data on File

Table SIII.65: Clinical Trial Exposure to Pembrolizumab by Age Endometrial Carcinoma Participants KN146 and KN775 Combination Therapy (APaT Population)

Age Category (year)	Participants	Mean Duration (days)	Participant Time (years)
<65	252	278.9	192.5
≥65	278	246.1	187.3
Total	530	261.7	379.8

Duration of exposure (day) is calculated as last dose date - first dose date + 1.
Database cutoff date for endometrial carcinoma (KN146: 18AUG2020, KN775: 26OCT2020)

Data on File

Public

Table SIII.66: Clinical Trial Exposure by Age and Gender MSI-H Subjects KN158 Cohort K and KN164 Cohorts A and B Monotherapy (ASaT Population)

Age Category	Subjects			Mean Duration (days)			Subject Time (years)		
(Years)	Male	Female	Total	Male	Female	Total	Male	Female	Total
<65	144	161	305	306.2	263.0	283.4	120.7	115.9	236.7
≥65	69	101	170	281.8	341.1	317.0	53.2	94.3	147.6
Total	213	262	475	298.3	293.1	295.4	174.0	210.3	384.2

Duration of Exposure is calculated as last dose date - first dose date + 1.
Database cutoff date for MSI-H (KN158-cohort K: 05OCT2020)
Database cutoff date for Colorectal (KN164-cohorts A and B: 09SEP2019)

Data on File

Table SIII.67: Clinical Trial Exposure to Pembrolizumab by Age Cervical Cancer Participants in KN826 Combination Therapy (APaT Population)

Age Category (year)	Participants	Mean Duration (days)	Patient Time (years)
<65	259	353.4	250.6
>=65	48	317.0	41.7
Total	307	347.7	292.3

Duration of exposure is the time from the first dose date to the last dose date for pembrolizumab in the combo.
Database Cutoff Date: 03MAY2021

Data on File

Table SIII.68: Clinical Trial Exposure to Pembrolizumab by Age and Gender Gastric Cancer Participants KN811 Combination Therapy (APaT Population)

Age Category	Patients			Mean Duration (days)			Patient Time (years)		
(Years)	Male	Female	Total	Male	Female	Total	Male	Female	Total
<65	169	36	205	324.8	395.9	337.3	150.3	39.0	189.3
≥65	115	30	145	304.4	362.9	316.5	95.8	29.8	125.6
Total	284	66	350	316.5	380.9	328.7	246.1	68.8	315.0

Duration of Exposure is calculated as last dose date – first dose date + 1.
Database Cutoff Date: 25MAY2022

Data on file

Public

Table SIII.69: Clinical Trial Exposure to Pembrolizumab by Age and Gender Gastric Cancer Participants KN859 Combination Therapy (APaT Population)

Age Category (years)	Participants			Mean Duration (days)			Participant Time (years)		
	Male	Female	Total	Male	Female	Total	Male	Female	Total
<65	321	162	483	275.1	224.6	258.2	241.8	99.6	341.4
≥65	201	101	302	263.9	249.6	259.1	145.2	69.0	214.2
Total	522	263	785	270.8	234.2	258.5	387.0	168.7	555.6

Each participant is counted once on each applicable duration category row.
Duration of exposure is calculated as last dose date - first dose date + 1.
Database cutoff date for Gastric (KN859: 03OCT2022)

Data on File

Table SIII.70: Clinical Trial Exposure to Pembrolizumab by Age and Gender BTC Participants in KN966 Combination Therapy (APaT Population)

Age Category (Years)	Participants			Mean Duration (days)			Participants Time (years)		
	Male	Female	Total	Male	Female	Total	Male	Female	Total
<65	142	124	266	243.9	209.3	227.8	94.8	71.0	165.9
≥65	137	126	263	234.6	246.0	240.0	88.0	84.9	172.9
Total	279	250	529	239.3	227.8	233.9	182.8	155.9	338.7

Duration of Exposure is calculated as last dose date - first dose date + 1 for pembrolizumab in the combo.
(pembrolizumab KN966 Database Cutoff Date: 15DEC2022)

Data on File

Clinical Trial Exposure by Racial / Ethnic Origin

Clinical trial exposure to pembrolizumab monotherapy by race for all melanoma patients in the pooled KN001, KN002 and KN006 population is summarized in Table SIII.71. The majority of patients treated have been White (1530) followed by Asian (19) and Black or African American (7).

Clinical trial exposure to pembrolizumab monotherapy by race for all melanoma patients in KN054 and KN716 is summarized in Table SIII.72. The majority of patients treated have been White (432) followed by Asian (4), Black or African American (3), American Indian or Alaska Native (1) and Multiracial (1). Race was not reported for 551 patients as the majority of patients were from KN054 where information on race was not collected due to the European Organisation for Research and Treatment of Cancer (EORTC) standards.

Clinical trial exposure to pembrolizumab monotherapy by race for all NSCLC patients in KN001, KN010, KN024 and KN042 is summarized in Table SIII.73. The majority of patients treated have been White (1,466) followed by Asian (428) and Black or African American (53).

Clinical trial exposure to pembrolizumab by race for all NSCLC patients in KN189, KN021 (Cohorts A, C and G) and KN407 who received pembrolizumab in combination with chemotherapy is summarized in Table SIII.74. The majority of patients treated have been White (681) followed by Asian (73), Black or African American (30), American Indian or

Alaska Native (1) and Native Hawaiian or Other Pacific Islander (1). Five (5) patients did not report race.

Clinical trial exposure to pembrolizumab monotherapy by race for all NSCLC patients in KN091 is summarized in Table SIII.75. The majority of patients treated have been White (442) followed by Asian (107), Other (5), Multiracial (4), American Indian or Alaska Native (1). Twenty-one (21) patients did not report race.

Clinical trial exposure to pembrolizumab in combination with chemotherapy as neoadjuvant treatment followed by continued adjuvant pembrolizumab monotherapy by race for all NSCLC patients in KN671 is summarized in Table SIII.76. The majority of patients treated have been White (249), followed by Asian (124), Black or African American (6), Multiracial (3), and American Indian or Alaska Native (1). Thirteen (13) patients did not report race.

Clinical trial exposure to pembrolizumab monotherapy by race for all HL patients in KN013, KN087, and KN204 is summarized in Table SIII.77. The majority of patients treated have been White (330) followed by Asian (25), Black or African American (11), Multiracial (7), American Indian or Alaska Native (2), and Native Hawaiian or Other Pacific Islander (1). Thirteen (13) patients did not report race.

Clinical trial exposure to pembrolizumab monotherapy by race for all UC patients in KN045 and KN052 is summarized in Table SIII.78. The majority of patients treated have been White (512) followed by Asian (90) and Black or African American (13).

Clinical trial exposure to pembrolizumab monotherapy by race for all HNSCC patients in KN012 B+B2 Cohorts, KN040, KN055 and KN048 is summarized in Table SIII.79. The majority of patient treated have been White (723) followed by Asians (109) and Black or African American (28).

Clinical trial exposure to pembrolizumab by race for HNSCC patients in KN048 who received pembrolizumab combination therapy is summarized in Table SIII.80. The majority of patients treated have been White (200) followed by Asian (60) and Black or African American (10).

Clinical trial exposure to pembrolizumab by race for all RCC patients in KN426 who received pembrolizumab combination therapy is summarized in Table SIII.81. The majority of patients treated have been White (342) followed by Asians (66); Black or African American (9); American Indian or Alaska Native (2); Multiracial (1); Native Hawaiian or Other Pacific Islander (1). Race was not reported for 8 patients.

Clinical trial exposure to pembrolizumab by race for all RCC patients in KN581 who received pembrolizumab combination therapy is summarized in Table SIII.82. The majority of the patients treated have been White (260) followed by Asian (81); Other race (4); and Black or African American (2). Five (5) patients did not report race.

Clinical trial exposure to pembrolizumab monotherapy by race for all RCC patients in KN564 is summarized in Table SIII.83. The majority of patients treated have been White (365) followed by Asian (63); American Indian or Alaska Native (10); Multiracial (8); and Black or African American (6). Thirty-six (36) patients did not report race.

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Clinical trial exposure to pembrolizumab monotherapy by race for all CRC patients in KN177 is summarized in Table SIII.84. The majority of patients treated have been White (113), followed by Asian (24), and Black or African American (9). Seven (7) patients did not report race.

Clinical trial exposure to pembrolizumab by race for all esophageal cancer patients in KN590 who received pembrolizumab combination therapy is summarized in Table SIII.85. The majority of patients treated have been Asian (201), followed by White (136) American Indian or Alaska Native (9), Black or African American (5), and Multiracial (5). Fourteen (14) patients did not report race.

Clinical trial exposure to pembrolizumab by race for all TNBC patients in KN355 who received pembrolizumab combination therapy is summarized in Table SIII.86. The majority of patients treated have been White (399), followed by Asian (138), Black or African American (21), Multiracial (11), and American Indian or Alaska Native (10). Seventeen (17) patients did not report race.

Clinical trial exposure to pembrolizumab by race for all TNBC subjects in KN522 who received pembrolizumab in combination with neoadjuvant chemotherapy followed by continued adjuvant pembrolizumab monotherapy is summarized in Table SIII.87. The majority of patients treated have been White (500), followed by Asian (148), Black or African American (38), American Indian or Alaska Native (14), Multiracial (13), Native Hawaiian or Other Pacific Islander (1). Sixty-four (64) patients did not report race.

Clinical trial exposure to pembrolizumab by race for all endometrial carcinoma patients in KN146 and KN775 who received pembrolizumab combination therapy is summarized in Table SIII.88. The majority of patients treated have been White (364), followed by Asian (90), Black or African American (24); Multiracial (7), American Indian or Alaska Native (5), Native Hawaiian or Other Pacific Islander (2), and Other race (2). Thirty-six (36) patients did not report race.

Clinical trial exposure to pembrolizumab monotherapy by race for all MSI-H patients in KN158 Cohort K and KN164 Cohorts A and B is summarized in Table SIII.89. The majority of patients treated have been White (368), followed by Asian (64), American Indian or Alaska Native (18), Black or African American (16) and Multiracial (7). Two (2) patients did not report race.

Clinical trial exposure to pembrolizumab by race for all cervical cancer patients in KN826 who received pembrolizumab combination therapy is summarized in Table SIII.90. The majority of patients treated have been White (169), followed by Asian (65), Multiracial (32), American Indian or Alaska Native (18), and Black or African American (4). Nineteen (19) patients did not report race.

Clinical trial exposure to pembrolizumab by race for gastric cancer patients in KN811 who received pembrolizumab combination therapy is summarized in Table SIII.91. The majority of patients treated have been White (217), followed by Asian (119), Multiple (6), American

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Indian or Alaska Native (5), and Black or African American (2). Race was not reported for one (1) patient.

Clinical trial exposure to pembrolizumab by race for gastric cancer patients in KN859 who received pembrolizumab combination therapy is summarized in Table SIII.92. The majority of patients treated have been White (422), followed by Asian (269), Multiracial (43), American Indian or Alaska Native (31), Black or African American (12) and Native Hawaiian or Other Pacific Islander (1). Race was not reported for seven (7) patients.

Clinical trial exposure to pembrolizumab by race for all BTC patients in KN966 who received pembrolizumab combination therapy is summarized in Table SIII.93. The majority of patients treated have been White (254), followed by Asian (243), Black or African American (11), Multiracial (5), American Indian or Alaska Native (2) and Native Hawaiian or Other Pacific Islander (1). Thirteen (13) patients did not report race.

Table SIII.71: Clinical Trial Exposure by Race Melanoma Subjects KN001, KN002 and KN006 Monotherapy (APaT Population)

Race	Subjects	Mean Duration (days)	Subject Time (years)
American Indian Or Alaska Native	1	267.0	0.7
Asian	19	133.8	7.0
Black Or African American	7	171.0	3.3
Multiple	4	160.5	1.8
Multiracial	2	330.0	1.8
Native Hawaiian Or Other Pacific Islander	1	274.0	0.8
White	1530	229.3	960.4
Null	3	182.3	1.5
Duration of Exposure is calculated as last dose date - first dose date +1. (pembrolizumab KN001 Database Cutoff Date: 18APR2014). (pembrolizumab KN002 Database Cutoff Date: 28FEB2015). (pembrolizumab KN006 Database Cutoff Date: 03MAR2015).			

Data on File

Table SIII.72: Clinical Trial Exposure by Race Melanoma Participants KN054 and KN716 Monotherapy (APaT Population)

Race	Participants	Mean Duration (days)	Participant Time (years)
American Indian Or Alaska Native	1	112.0	0.3
Asian	4	132.2	1.4
Black Or African American	3	230.7	1.9
Multiracial	1	255.0	0.7
White	432	251.2	297.1
NULL	551	281.0	423.9
Total	992	267.1	725.4
Duration of Exposure is calculated as last dose date - first dose date + 1. Race data were not collected for KN054. Database cutoff date for Melanoma (KN054: 02OCT2017, KN716: 04DEC2020)			

Data on File

Table SIII.73: Clinical Trial Exposure by Race NSCLC Subjects KN001, KN010, KN024 and KN042 Monotherapy (APaT Population)

Race	Subjects	Mean Duration (days)	Subject Time (years)
American Indian Or Alaska Native	16	206.6	9.1
Asian	428	197.8	231.8
Black Or African American	53	187.4	27.2
Multiracial	35	292.0	28.0
Native Hawaiian Or Other Pacific Islander	3	57.3	0.5
White	1466	204.1	819.2
NULL	21	117.4	6.8
Total	2022	202.8	1122.5

Duration of Exposure is calculated as last dose date - first dose date +1.
(pembrolizumab KN001 Database Cutoff Date for Lung: 23JAN2015).
(pembrolizumab KN010 Database Cutoff Date: 30SEP2015).
(pembrolizumab KN024 Database Cutoff Date: 10JUL2017).
(pembrolizumab KN042 Database Cutoff Date: 26FEB2018).

Data on File

Table SIII.74: Clinical Trial Exposure to Pembrolizumab by Race NSCLC Subjects KN021 (Cohorts A, C and G), KN189 and KN407 Combination Therapy (APaT Population)

Race	Subjects	Mean Duration (days)	Subject Time (years)
American Indian Or Alaska Native	1	643.0	1.8
Asian	73	159.4	31.9
Black Or African American	30	224.6	18.4
Native Hawaiian Or Other Pacific Islander	1	512.0	1.4
White	681	235.5	439.1
NULL	5	163.0	2.2
Total	791	228.5	494.8

Duration of Exposure is calculated as last dose date - first dose date +1.
MK-3475 Database Cutoff Date for Lung Combination Therapy (KN021 Cohort A: 07NOV2016, Cohort G/C: 31MAY2017, KN189: 8NOV2017; KN407: 03APR2018)

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Table SIII.75: Clinical Trial Exposure to Pembrolizumab by Race NSCLC Participants KN091 Monotherapy Therapy (APaT Population)

Race	Patients	Mean Duration (days)	Patient Time (years)
American Indian Or Alaska Native	1	365.0	1.0
Asian	107	292.6	85.7
Multiracial	4	335.7	3.7
Other	5	313.8	4.3
White	442	255.3	309.0
NULL	21	261.9	15.1
Total	580	263.7	418.7
Duration of Exposure is calculated as last dose date – first dose date + 1. KN091 Database Cutoff Date: 20SEP2021			

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Table SIII.76: Clinical Trial Exposure to Pembrolizumab by Race NSCLC Participants in KN671 Combination Therapy (APaT Population)

Race	Patients	Mean Duration (days)	Patient Time (years)
American Indian Or Alaska Native	1	413.0	1.1
Asian	124	290.5	98.6
Black Or African American	6	268.5	4.4
Multiracial	3	340.0	2.8
White	249	279.4	190.5
NULL	13	281.0	10.0
Total	396	283.5	307.4
Duration of Exposure is calculated as last dose date - first dose date + 1. Database Cutoff Date: 29JUL2022			

Data on File

Table SIII.77: Clinical Trial Exposure by Race HL Subjects KN013, KN087, and KN204 Monotherapy (APaT Population)

Race	Subjects	Mean Duration (days)	Subject Time (years)
American Indian Or Alaska Native	2	596.0	3.3
Asian	25	416.9	28.5
Black Or African American	11	469.0	14.1
Multiracial	7	328.7	6.3
Native Hawaiian Or Other Pacific Islander	1	715.0	2.0
White	330	377.8	341.4
NULL	13	289.5	10.3
Total	389	381.1	405.8
Duration of Exposure is calculated as last dose date - first dose date + 1. Database Cutoff Date (KN013-Cohort 3: 28SEP2018, KN087: 21MAR2019, KN204: 16JAN2020)			

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Table SIII.78: Clinical Trial Exposure by Race UC Subjects KN045 and KN052 Monotherapy (APaT Population)

Race	Subjects	Mean Duration (days)	Subject Time (years)
American Indian Or Alaska Native	2	65.0	0.4
Asian	90	135.8	33.5
Black Or African American	13	73.2	2.6
Multiracial	3	160.0	1.3
White	512	137.1	192.2
NULL	16	142.8	6.3
Total	636	135.6	236.2

Duration of Exposure is calculated as last dose date - first dose date +1.
Includes all subjects with urothelial carcinoma who received at least one dose of Pembrolizumab in KN045 and KN052.
Pembrolizumab KN045 Database Cutoff Date: 07SEP2016.
Pembrolizumab KN052 Database Cutoff Date: 01SEP2016.

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Table SIII.79: Clinical Trial Exposure by Race HNSCC Subjects KN012 B+B2 Cohorts, KN040, KN055 and KN048 Monotherapy (ASaT Population)

Race	Subjects	Mean Duration (days)	Subject Time (years)
American Indian Or Alaska Native	9	185.2	4.6
Asian	109	165.5	49.4
Black Or African American	28	178.0	13.6
Multi-Racial	12	179.3	5.9
Multiracial	6	154.8	2.5
White	723	162.6	321.8
NULL	22	144.4	8.7
Total	909	163.3	406.5

Duration of Exposure is calculated as last dose date - first dose date +1.
MK-3475 Database Cutoff Date for HNSCC (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN048: 13JUN2018, KN055: 22APR2016)

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Table SIII.80: Clinical Trial Exposure to Pembrolizumab by Race HNSCC Subjects in KN048 Combination Therapy (ASaT Population)

Race	Subjects	Mean Duration (days)	Subject Time (years)
American Indian Or Alaska Native	3	244.7	2.0
Asian	60	161.6	26.5
Black Or African American	10	227.5	6.2
Multiracial	3	249.3	2.0
White	200	240.7	131.8
Total	276	223.2	168.6

Duration of Exposure is calculated as last dose date - first dose date +1.
MK-3475 Database Cutoff Date for KN048: 13JUN2018.

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Table SIII.81: Clinical Trial Exposure to Pembrolizumab by Race RCC Subjects KN426 Combination Therapy (ASaT Population)

Race	Subjects	Mean Duration (days)	Subject Time (years)
American Indian Or Alaska Native	2	372.5	2.0
Asian	66	273.6	49.4
Black Or African American	9	222.4	5.5
Missing	8	370.0	8.1
Multiracial	1	358.0	1.0
Native Hawaiian Or Other Pacific Islander	1	347.0	1.0
White	342	288.5	270.1
Total	429	287.0	337.1
Duration of Exposure is calculated as last dose date - first dose date +1.for pembrolizumab in the combo. MK-3475 Database Cutoff Date for KN426: 24AUG2018.			

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Table SIII.82: Clinical Trial Exposure to Pembrolizumab by Race RCC Participants KN581 Combination Therapy (APaT)

Race	Participants	Mean Duration (days)	Participant Time (years)
White	260	445.5	317.1
Black Or African American	2	713.5	3.9
Asian	81	426.2	94.5
American Indian Or Alaska Native	0	---	---
Native Hawaiian Or Other Pacific Islander	0	---	---
Other	4	214.0	2.3
Missing	5	435.4	6.0
Total	352	439.8	423.9
Duration of Exposure is calculated as last dose date - first dose date + 1 for pembrolizumab in the combo.MK-3475 Database Cutoff Date for KN581: 28AUG2020.			

Data on File

Table SIII.83: Clinical Trial Exposure by Race RCC Participants KN564 Monotherapy (APaT Population)

Race	Participants	Mean Duration (days)	Person Time (years)
American Indian Or Alaska Native	10	268.6	7.4
Asian	63	283.4	48.9
Black Or African American	6	279.8	4.6
Multiracial	8	315.3	6.9
White	365	268.7	268.5
Missing	36	283.9	28.0
Total	488	272.6	364.3
Duration of Exposure is calculated as last dose date - first dose date + 1. Database cutoff date for RCC (KN564: 14DEC2020)			

Data on File

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Table SIII.84: Clinical Trial Exposure by Race CRC Subjects KN177 Monotherapy (ASaT Population)

Race	Subjects	Mean Duration (days)	Subject Time (years)
Asian	24	427.5	28.1
Black Or African American	9	303.6	7.5
White	113	406.6	125.8
Missing	7	398.0	7.6
Total	153	403.4	169.0
Duration of Exposure is calculated as last dose date - first dose date +1. Database cutoff date for CRC (KN177: 19FEB2020)			

Data on File

Table SIII.85: Clinical Trial Exposure to Pembrolizumab by Race Esophageal Cancer Subjects KN590 Combination Therapy (ASaT Population)

Race	Subjects	Mean Duration (days)	Subject Time (years)
American Indian Or Alaska Native	9	146.4	3.6
Asian	201	223.3	122.9
Black Or African American	5	258.4	3.5
Multiracial	5	217.0	3.0
White	136	246.0	91.6
Missing	14	346.6	13.3
Total	370	234.8	237.9
Duration of Exposure is calculated as last dose date - first dose date +1. Database Cutoff date for Esophageal (KN590: 02JUL2020)			

Data on File

Table SIII.86: Clinical Trial Exposure to Pembrolizumab by Race TNBC Subjects in KN355 Combination Therapy (ASaT Population)

Race	Subjects	Mean Duration (days)	Subject Time (years)
American Indian Or Alaska Native	10	203.6	5.6
Asian	138	283.2	107.0
Black Or African American	21	237.2	13.6
Multiracial	11	244.3	7.4
White	399	241.1	263.4
Missing	17	180.3	8.4
Total	596	248.4	405.3
Duration of Exposure is calculated as last dose date - first dose date +1 for pembrolizumab in the combo. Database Cutoff Date for KN355: 11DEC2019.			

Data on File

Public

Table SIII.87: Clinical Trial Exposure to Pembrolizumab by Race TNBC Subjects in KN522 Combination Therapy (APaT Population)

Race	Participants	Mean Duration (days)	Person Time (years)
American Indian Or Alaska Native	14	328.8	12.6
Asian	148	358.4	145.2
Black Or African American	38	325.3	33.8
Multiracial	13	343.2	12.2
Native Hawaiian Or Other Pacific Islander	1	397.0	1.1
White	500	325.3	445.3
Missing	64	339.2	59.4
Total	778	333.2	709.7
Duration of exposure is the time from the first dose date to the last dose date for pembrolizumab. Database cutoff date for TNBC: (KN522: 23MAR2021)			

Data on File

Table SIII.88: Clinical Trial Exposure to Pembrolizumab by Race Endometrial Carcinoma Participants KN146 and KN775 Combination Therapy (APaT Population)

Race	Participants	Mean Duration (days)	Participants Time (years)
American Indian Or Alaska Native	5	329.0	4.5
Asian	90	256.1	63.1
Black Or African American	24	236.0	15.5
Multiracial	7	196.7	3.8
Native Hawaiian Or Other Pacific Islander	2	11.0	0.1
Other	2	69.5	0.4
White	364	265.8	264.9
Missing	36	279.8	27.6
Total	530	261.7	379.8
Duration of exposure (day) is calculated as last dose date - first dose date + 1. Database cutoff date for endometrial carcinoma (KN146: 18AUG2020, KN775: 26OCT2020)			

Data on File

Table SIII.89: Clinical Trial Exposure by Race MSI-H Subjects in KN158 Cohort K and KN164 Cohorts A and B Monotherapy (ASaT Population)

Race	Subjects	Mean Duration (days)	Subject Time (years)
American Indian Or Alaska Native	18	286.8	14.1
Asian	64	315.0	55.2
Black Or African American	16	432.1	18.9
Multiracial	7	152.0	2.9
White	368	288.3	290.5
NULL	2	465.5	2.5
Total	475	295.4	384.2
Duration of Exposure is calculated as last dose date - first dose date + 1. Database cutoff date for MSI-H (KN158-cohort K: 05OCT2020) Database cutoff date for Colorectal (KN164-cohorts A and B: 09SEP2019)			

Data on File

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Table SIII.90: Clinical Trial Exposure to Pembrolizumab by Race Cervical Cancer Participants KN826 Combination Therapy (APaT Population)

Race	Participants	Mean Duration (days)	Participant Time (years)
American Indian Or Alaska Native	18	260.5	12.8
Asian	65	383.0	68.2
Black Or African American	4	381.5	4.2
Multiracial	32	334.2	29.3
White	169	348.9	161.4
NULL	19	314.7	16.4
Total	307	347.7	292.3
Duration of exposure is the time from the first dose date to the last dose date for pembrolizumab in the combo. Database Cutoff Date: 03MAY2021			

Data on File

Table SIII.91: Clinical Trial Exposure to Pembrolizumab by Race in Gastric Cancer Participants KN811 Combination Therapy (APaT Population)

Race	Patients	Mean Duration (days)	Patient Time (years)
American Indian Or Alaska Native	5	282.6	3.9
Asian	119	336.8	109.7
Black Or African American	2	478.0	2.6
Multiple	6	342.3	5.6
White	217	323.7	192.3
NULL	1	304.0	0.8
Total	350	328.7	315.0
Duration of Exposure is calculated as last dose date - first dose date + 1. Database Cutoff Date: 25MAY2022			

Data on File

Table SIII.92: Clinical Trial Exposure to Pembrolizumab by Race in Gastric Cancer Participants KN859 Combination Therapy (APaT Population)

Race	Participants	Mean Duration (days)	Participant Time (years)
American Indian Or Alaska Native	31	220.2	18.7
Asian	269	272.3	200.6
Black Or African American	12	235.9	7.8
Multiracial	43	314.0	37.0
Native Hawaiian Or Other Pacific Islander	1	28.0	0.1
White	422	249.1	287.8
NULL	7	197.0	3.8
Total	785	258.5	555.6

Each participant is counted once on each applicable duration category row.
Duration of exposure is calculated as last dose date - first dose date + 1.
Database cutoff date for Gastric (KN859: 03OCT2022)

Data on File

Table SIII.93: Clinical Trial Exposure to Pembrolizumab by Race BTC Participants in KN966 Combination Therapy (APaT Population)

Race	Participants	Mean Duration (days)	Participant Time (years)
American Indian Or Alaska Native	2	417.0	2.3
Asian	243	229.3	152.5
Black Or African American	11	175.9	5.3
Multiracial	5	122.6	1.7
Native Hawaiian Or Other Pacific Islander	1	279.0	0.8
White	254	238.2	165.7
Missing	13	294.5	10.5
Total	529	233.9	338.7

Duration of exposure is calculated as last dose date - first dose date + 1 for pembrolizumab in the combo.
(pembrolizumab KN966 Database Cutoff Date: 15DEC2022)

Data on File

PART II: MODULE SIV - POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1 Exclusion Criteria in Pivotal Clinical Studies Within the Development Program

Table SIV.1.1: Exclusion Criteria in Pivotal Clinical Studies Within the Development Program

Exclusion Criterion	Reason for Exclusion	Is it Considered to be Missing Information?	Rationale (if not Included as Missing Information)
Hypersensitivity to the active substance or to any of the excipients	Avoid potential harm to the patient	No	Pembrolizumab should not be administered to persons with known hypersensitivity to the active substance or to any of the excipients.
Severe renal or moderate to severe hepatic impairment	No clinical trials have been conducted in subjects with severe renal or moderate or severe hepatic comorbidities	No	Adequately reflected in the SmPC (sections 4.2, 4.4 and 5.2)
Diagnosis of immunosuppression or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days	May confound understanding of drug efficacy or safety profile. Use of immunosuppressive agents may negatively affect efficacy	No	Adequately reflected in the SmPC (sections 4.4, 4.5)
Active infection requiring therapy	Avoid factors that may confound understanding of drug safety profile needed for subsequent drug development and use.	No	Patients that have an active infection should have the infection treated prior to starting.
Autoimmune disease requiring systemic treatment in past 2 years. Replacement therapy allowed.	Avoid factors that may confound understanding of drug efficacy or safety profile needed for subsequent drug development and use.	No	Adequately reflected in the SmPC (section 4.4)
Known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies). Patient is positive for active Hepatitis B (HBsAg reactive) or Hepatitis C (HCV RNA) [qualitative] is detected). Patients with negative Hepatitis C antibody testing may not require RNA testing if deemed appropriate by treating physician	The impact of this agent on HIV or Hepatitis B or C remains unknown. These subjects were excluded given the theoretical safety concern. Hepatitis is an identified adverse event of anti-PD-1 antibody treatment	No	Adequately reflected in the SmPC (section 4.4)

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Table SIV.1.1: Exclusion Criteria in Pivotal Clinical Studies Within the Development Program

Exclusion Criterion	Reason for Exclusion	Is it Considered to be Missing Information?	Rationale (if not Included as Missing Information)
History of non-infectious pneumonitis that required steroids	Avoid increasing risk of pneumonitis from pembrolizumab	No	Pneumonitis is a known risk and is included as an important identified risk for pembrolizumab. Patients with a history of pneumonitis may experience pneumonitis during treatment. However, given the life- threatening nature of the indication and the ability to reverse pneumonitis should it occur during treatment with pembrolizumab, these patients should still have the option of treatment.
Known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.	Avoid factors that may confound understanding of drug efficacy or safety profile needed for subsequent drug development and use.	No	Exclusion is specific to requirements of clinical trial participation rather than real world use.
Prior treatment with IPI or other anti-CTLA-4 agent, any anti-PD-1, anti-PD-L1, or anti-PD-L2 agent.	Avoid factors that may confound understanding drug efficacy and safety	No	Exclusion is specific to understanding of efficacy and safety in clinical trial environment rather than real world use.
Being pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the study, starting with the Pre-screening or Screening visit through 120 days after the last dose of study medication.	Avoid potential harm to the unborn fetus or breastfeeding newborn.	No	Adequately reflected in the SmPC (section 4.6)
Clinically active CNS involvement	High risk patients where active CNS involvement portends poor prognosis and symptoms of the disease. To ensure patients are receiving optimal treatment, per their physician's discretion for their co- morbid conditions which may not always be possible within the confines of a clinical trial.	No	Patients with treated brain metastases were shown to have similar safety and activity of pembrolizumab. Given the fatal nature of their cancer, physicians should be allowed to use discretion on the management of brain metastases with systemic and local treatment options.

Table SIV.1.1: Exclusion Criteria in Pivotal Clinical Studies Within the Development Program

Exclusion Criterion	Reason for Exclusion	Is it Considered to be Missing Information?	Rationale (if not Included as Missing Information)
Having had chemotherapy, radioactive, or biological cancer therapy within 2 weeks prior to the first dose of study therapy	Avoid factors that may confound understanding of drug safety profile and efficacy needed for subsequent drug development and use. To ensure patients are receiving optimal treatment, per their physician's discretion for their co-morbid conditions which may not always be possible within the confines of a clinical trial.	No	Experience to date demonstrates that pembrolizumab is well tolerated for oncology patients. Substantial documented benefits of treatment in life threatening, or otherwise lethal disease may outweigh risks.
Currently participating or participated in a study of an investigational agent or using an investigational device within 30 days of administration of pembrolizumab	Avoid factors that may confound understanding of the efficacy and safety of pembrolizumab in a clinical trial	No	This will not be applicable in the post-marketing environment as the appropriate population will be defined in the SmPC.
Known additional malignancy that is progressing or requires active treatment	To ensure patients are receiving optimal treatment, per their physician's discretion for their co-morbid conditions which may not always be possible within the confines of a clinical trial.	No	Physicians should be allowed to determine which tumor posess the greatest risk and is the highest priority for treatment.
Received a live vaccine within 30 days prior to first dose	Avoid factors that may confound understanding of the efficacy of pembrolizumab in a clinical trial	No	Exclusion is specific to understanding of efficacy and safety in clinical trial environment.
History or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the patient's participation for the full duration of the study, or is not in the best interest of the patient to participate, in the opinion of the treating investigator	Avoid factors that may confound understanding of drug efficacy or safety profile needed for subsequent drug development and use.	No	Information on the conditions are known risks and may be included in other sections of the SmPC.

Public

SIV.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Program

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

SIV.3 Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Program

Those populations detailed in Section SIV will require additional investigation during the development of pembrolizumab. Areas of missing information remain and will be assessed through the clinical development program and post marketing safety surveillance. The European Medicines Agency (EMA) Decision for the first paediatric investigation plan (PIP) covering the condition 'Treatment of all conditions included in the category of malignant neoplasms (except nervous system, haematopoietic and lymphoid tissue)' has been adopted on March 7, 2014. The first PIP was subsequently modified and the EMA decision for the modifications was adopted on February 16, 2018. The EMA Decision for the second PIP covering the condition 'Treatment of Hodgkin Lymphoma' has been adopted on August 1, 2016. The second PIP was subsequently modified and the EMA decision for the modification was adopted on January 30, 2018, and December 6, 2021, respectively. The marketing authorisation holder (MAH) will follow the PIP plans that have been adopted.

The first clinical study in paediatric patients, KEYNOTE-051, began enrollment in March 2015 and a clinical study report was prepared and submitted to the Agency in February 2019, resulting in adoption of an opinion for a PI update on June 27, 2019.

With RMP version 30.0, an updated clinical study report for KEYNOTE-051, with an additional 16 months of follow-up, was included to support the indication in relapsed or refractory classical HL in the paediatric population.

Table SIV.3.1: Exposure of Special Populations Included or not in Clinical Trial Development Programs

Type of Special Population	Exposure
Pregnant and breastfeeding women	Pregnant and breastfeeding women were not included in the pre-authorisation clinical development program. There have been no trials evaluating pembrolizumab in pregnant or lactating women. In clinical trials, women of childbearing potential have been advised to avoid pregnancy and to use effective contraception during the dosing period and for a period of at least 120 days thereafter. A pregnancy test was conducted on each pre-menopausal female of childbearing potential within 72 hours prior to administration of pembrolizumab. If pregnancy was confirmed during the course of the trial, study drug administration was discontinued. Any subject who became pregnant while in a study was followed to the completion/termination of the pregnancy. If the pregnancy continued to term, the outcome (health of infant) was to be reported to the MAH.
Patients with relevant comorbidities: • Patients with hepatic impairment • Patients with renal impairment • Patients with cardiovascular impairment • Immunocompromised patients • Patients with a disease severity different from inclusion criteria in clinical trials	Patients with the following conditions were excluded from clinical trials: active CNS metastases; ECOG PS ≥ 2 (except for urothelial carcinoma and RCC); HIV, hepatitis B or hepatitis C infection; active systemic autoimmune disease; interstitial lung disease; prior pneumonitis requiring systemic corticosteroid therapy; a history of severe hypersensitivity to another monoclonal antibody; receiving immunosuppressive therapy and a history of severe immune-related adverse reactions from treatment with ipilimumab, defined as any Grade 4 toxicity or Grade 3 toxicity requiring corticosteroid treatment (> 10 mg/day prednisone or equivalent) for greater than 12 weeks. Patients with active infections were excluded from clinical trials and were required to have their infection treated prior to receiving pembrolizumab. Patients with active infections occurring during treatment with pembrolizumab were managed with appropriate medical therapy. Patients with clinically significant renal (creatinine > 1.5 x Upper Limit of Normal (ULN)) or hepatic (bilirubin > 1.5 x ULN, alanine aminotransferase (ALT), aspartate aminotransferase (AST) > 2.5 x ULN in the absence of liver metastases) abnormalities at baseline were excluded from clinical trials, therefore information is limited in patients with severe renal and moderate to severe hepatic impairment. These exclusion criteria were applied to ensure that the population under study had adequate organ function in order to have a homogeneous patient population and to avoid potential confounding variables in the interpretation of safety data from the studies.
Population with relevant different ethnic origin	Clinical trials (included in this RMP) exposure by race is presented in PART II: MODULE SIII.
Subpopulations carrying relevant genetic polymorphisms	Subpopulations carrying relevant genetic polymorphisms were not included in the pre-authorisation clinical development program.

Public

PART II: MODULE SV - POST-AUTHORISATION EXPERIENCE

SV.1 Post-Authorisation Exposure

SV.1.1 Method Used to Calculate Exposure

A summary of the worldwide distribution of pembrolizumab for the cumulative period from market introduction to 03-SEP-2023 is presented below based on the available data.

Patient exposure estimates were calculated from our Company's internal distribution data from the Worldwide Financial Reporting System (WFRS), and the Financial Sharing Area databases. This data provides a more complete and consistent methodology for the estimate of patient exposure worldwide for current Company products. Patient exposure estimates were calculated from expanded distribution categories to provide a more accurate estimate of patient exposure worldwide. The effects of this update (starting 01-AUG-2018) may be apparent when comparing current estimates of patient exposure to those of prior reporting periods.

Pembrolizumab is available in 20 mg, 50 mg, and 100 mg vials. The dosing recommendation in adults is either 200 mg every 3 weeks or 400 mg every 6 weeks. Since patient exposure for the doses of 200 mg every 3 weeks or 400 mg every 6 weeks are essentially equivalent, standard dosing of 200 mg every 3 weeks was used for patient exposure estimation.

- The total number of vials for 20 mg vial, 50 mg vial, and 100 mg vial was divided by the average number of vials required to formulate a standard dose of 200mg. Specifically, the number of units utilized when dosing with 20 mg vials was on average 10 units; 50 mg vials was on average 4 units; and 100 mg vials was on average 2 units. Therefore, the total number of vials for the 20 mg strength was divided by 10, the total number of vials for the 50 mg strength was divided by 4, and the total number of vials for the 100 mg strength was divided by 2, to determine the number of doses (cycles).

- The estimated number of doses (cycles) per vial was then divided by the average number of doses estimated per patient per year of treatment with pembrolizumab. The average number of doses estimated per year of treatment with approximately 23 days between doses (recommended 21 days with 2-day allowance for weekends), or an average of 15.9 doses per patient regardless of strength (365 days/23 days).

SV.1.2 Exposure

The estimated number of doses of pembrolizumab distributed worldwide from product launch through 03-SEP-2023 is 37,452,0934. This corresponds to 1,146,866 patient years of treatment.

PART II: MODULE SVI - ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

Potential for Misuse for Illegal Purposes

Pembrolizumab is a potent and highly selective humanized mAb of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Neither pembrolizumab nor its components are known to possess addictive properties.

Public

PART II: MODULE SVII - IDENTIFIED AND POTENTIAL RISKS

SVII.1 Identification of Safety Concerns in the Initial RMP Submission

Not applicable

SVII.1.1 Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Not applicable

SVII.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Not applicable

SVII.2 New Safety Concerns and Reclassification With a Submission of an Updated RMP

Not applicable.

SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

SVII.3.1 Presentation of Important Identified Risks and Important Potential Risks

The characterization of the risk profile of pembrolizumab is presented based on four data sets (n=2799), the melanoma and NSCLC patient populations in KN001, the melanoma patient population in KN002, the melanoma patient population in KN006, and the previously treated NSCLC patient population in KN010, and is considered as the reference safety dataset for pembrolizumab. The reference safety dataset serves as the locked dataset for the characterization of each risk associated with pembrolizumab and is presented in tabular format.

Safety data related to the previously untreated NSCLC population in KN024 (database cutoff date 10-JUL-2017) and KN042 (database cutoff date 26-FEB-2018) (total n=790) was evaluated and is presented in text for each risk. Overall, the safety profile from the NSCLC population in KN024 and KN042 was generally similar to the observed safety profile from the reference safety dataset.

Safety data related to the NSCLC population in KN189 (database cutoff date 08-NOV-2017) and KN021 (Cohorts C and G) pembrolizumab plus chemotherapy (database cutoff date 31-MAY-2017) (total n=488) were evaluated and are presented in text for each risk. Overall, the safety profile from the NSCLC population in KN189 and KN021 (Cohorts C and G) pembrolizumab plus chemotherapy was generally similar to the observed safety profile from the reference safety dataset.

Safety data related to the Hodgkin Lymphoma (HL) populations in KN013 (database cutoff date 28-SEP-2018), KN087 (database cutoff date 21-MAR-2019), and KN204 (database cutoff date 16-JAN-2020) (total n=389) were evaluated and are presented in text for each risk. Overall, the safety profile from the HL population was generally similar to the observed safety profile in the reference safety dataset, with the exception of a higher incidence of pneumonitis (8% versus 3.4%) and hypothyroidism (17% versus 8.5%). The higher incidence of pneumonitis was likely reflective of high rates of prior exposure to radiation and/or chemotherapy; agents with a known association of pulmonary toxicity. The majority of pneumonitis events were Grade 3 and below and resolved with systemic corticosteroids. There were no fatal events of pneumonitis. All reported events of hypothyroidism were Grade 1 and 2 and resolved with standard therapeutic measures. The observed incidence of hypothyroidism was considered attributable to a prior history of regional radiation and to a higher rate of pre-existing hypothyroidism among participants in this group at baseline.

Safety data related to the urothelial carcinoma (UC) indication in KN052 (database cutoff date 01-SEP-2016) (n=370) and KN045 (database cutoff date 07-SEP-2016) (n=266) were evaluated and are presented in text for each risk. Overall, the safety profile from the UC population in KN052 and in KN045 was generally similar to the observed safety profile in the reference safety dataset.

Safety data related to the HNSCC population in KN040 (database cutoff date 15-MAY-2017), KN012 (database cutoff date 26-APR-2016), and KN055 (database cutoff date 22-APR-2016) (total n=609) were evaluated and are presented in text for each risk. Overall, the safety profile from the HNSCC population was generally similar to the reference safety dataset.

Safety data related to the HNSCC population in KN048 (database cutoff date13-JUN-2018) (pembrolizumab monotherapy n=300; pembrolizumab plus chemotherapy n=276) were evaluated and are presented in text for each risk. Overall, the safety profile of pembrolizumab monotherapy from the HNSCC population in KN048 was generally similar to the reference safety dataset. The AE profile observed in pembrolizumab plus chemotherapy was generally similar to the known safety profiles of either pembrolizumab monotherapy or platinum/5-FU chemotherapy.

Safety data related to the melanoma indication in KN054 (database cutoff date 02-OCT-2017) (n= 509) was evaluated and is presented in text for each risk. Overall, the safety profile from the melanoma population in KN054 was generally similar to the observed safety profile from the reference safety dataset. Higher frequencies of some immune-mediated AEs, mostly mild to moderate in severity and manageable with treatment interruption or discontinuation and/or corticosteroid therapy were observed in KN054 in comparison to the reference safety dataset. This could be a reflection of the >2-fold longer exposure to pembrolizumab in KN054 subjects compared to subjects in the reference safety dataset.

Safety data related to the NSCLC population in KN021 Cohort A (database cutoff date 07-NOV-2016) and KN407 (database cutoff 03-APR-2018) (total n=303) were evaluated and are presented in text for each risk. Overall, the risk profile from the NSCLC population observed in the pooled KN407 and KN021 Cohort A combo was generally similar to the risk profile for pembrolizumab as characterized in the reference safety dataset, and the AE summary profile

observed was generally similar to the known safety profiles of either pembrolizumab monotherapy or carboplatin/paclitaxel (or nab-paclitaxel) chemotherapy.

Safety data related to the RCC population in KN426 who received pembrolizumab plus axitinib (database cutoff date 24-AUG-2018), were evaluated and are presented in text for each risk. The AE profile observed in pembrolizumab plus axitinib was generally similar to the known safety profiles of the combined safety profiles of pembrolizumab monotherapy (both in the reference safety dataset and in 1L RCC) and axitinib monotherapy in 1L RCC, with the exception of a higher than expected incidence of Grade 3-4 transaminase elevations. In KN426, Grades 3 and 4 ALT increased (20%) and AST increased (13%) were observed in the pembrolizumab plus axitinib group. The median time to onset of ALT ≥3 times ULN was 2.3 months (range: 7 days to 19.8 months). In patients with ALT ≥3 times ULN (Grade 2-4, n=116), ALT resolved to Grade 0-1 in 94%. Sixty-one percent of the patients with increased ALT received systemic corticosteroids. Of the patients who recovered, 92 (84%) were rechallenged with either pembrolizumab (3%) or axitinib (31%) monotherapy or with both (50%). Of these patients, 55% had no recurrence of ALT >3 times ULN, and of those patients with recurrence of ALT >3 times ULN, all recovered. There were no Grade 5 hepatic events.

Safety data related to the CRC population in KN177 (database cutoff 19-FEB-2020) (n=153) were evaluated and are presented in text for each risk. Overall, the safety profile of pembrolizumab monotherapy in the CRC population in KN177 was generally similar to the observed safety profile in the reference safety dataset.

Safety data related to the esophageal cancer population in KN590 (database cutoff 02-JUL-2020) who received pembrolizumab plus chemotherapy (total n=370) were evaluated and are presented in text for each risk. The AE profile observed in pembrolizumab plus chemotherapy group was generally similar to the known safety profiles of either pembrolizumab monotherapy or platinum/5-FU chemotherapy.

Safety data related to the TNBC population in KN355 (database cutoff 11-DEC-2019) who received pembrolizumab plus chemotherapy (total n=596) were evaluated and are presented in text for each risk. Overall, the observed safety profile of pembrolizumab in combination with chemotherapy in TNBC was generally similar to the known safety profiles of pembrolizumab monotherapy and the chemotherapy administered.

Safety data related to the RCC population in KN581 who received pembrolizumab plus lenvatinib (database cutoff 28-AUG-2020) (n=352) were evaluated and are presented in text for each risk. Overall, the safety profile observed in pembrolizumab in combination with lenvatinib in the RCC population in KN581 was generally similar to the known safety profiles of pembrolizumab monotherapy (reference safety dataset) and lenvatinib monotherapy, except for a higher incidence of immune-mediated AEs primarily due to hypothyroidism (47.2%), mostly grade 1 and 2 events. Smaller increases in some immune- mediated AEs were also observed. The nature (severity, management, and outcome) of the immune-mediated AEs observed with the pembrolizumab and lenvatinib combination was similar to the nature of immune-mediated AEs previously seen with pembrolizumab monotherapy.

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Safety data related to the endometrial carcinoma population in KN146 (database cutoff 18-AUG-2020) and KN775 (database cutoff 26-OCT-2020) (total n=530) who received pembrolizumab plus lenvatinib, were evaluated and are presented in text for each risk. Overall, the safety profile observed in pembrolizumab in combination with lenvatinib in endometrial carcinoma was generally similar to the known safety profiles of pembrolizumab monotherapy (reference safety dataset) and lenvatinib monotherapy, except for a higher incidence of hypothyroidism (55.8%), mostly due to grade 1 and 2 events. Smaller increases in some immune-mediated AEs were observed, including colitis (4.9%) and hyperthyroidism (10.2%). The nature (severity, management, and outcome) of the immune-mediated AEs observed with the pembrolizumab and lenvatinib combination was similar to the nature of immune-mediated AEs previously seen with pembrolizumab monotherapy.

Safety data related to the RCC population in KN564 (database cutoff 14-DEC-2020) (n=488) were evaluated and are presented in text for each risk. Overall, the safety profile of pembrolizumab monotherapy in the RCC population in KN564 was generally similar to the observed safety profile in the reference safety dataset, except for a higher incidence of immune mediated events primarily due to hypothyroidism (21.1%) and hyperthyroidism (11.9%), due to grade 1 and 2 events. The nature (severity, management, and outcome) of the immune-mediated AEs was similar to the nature of immune-mediated AEs previously seen with pembrolizumab monotherapy.

Safety data related to the MSI-H population in KN158 Cohort K (database cutoff 05-OCT-2020) and KN164 Cohorts A and B (database cutoff 09-SEP-2019) (n=475) were evaluated and are presented in text for each risk. Overall, the safety profile of pembrolizumab monotherapy in the MSI-H population in KN158 Cohort K and KN164 Cohorts A and B was generally similar to the observed safety profile in the reference safety dataset.

Safety data related to the cervical cancer population in KN826 (database cutoff 03-MAY-2021) who received pembrolizumab plus chemotherapy ± bevacizumab (total n=307) were evaluated and are presented in text for each risk. Overall, the observed safety profile of pembrolizumab in combination with chemotherapy ± bevacizumab in cervical cancer was generally similar to the known safety profiles of pembrolizumab monotherapy and bevacizumab or the chemotherapy administered. The overall exposure-adjusted incidence of AEOSIs was higher in the pembrolizumab + chemotherapy ± bevacizumab group compared with the pembrolizumab monotherapy reference safety dataset. Most AEOSIs reported in the pembrolizumab + chemotherapy ± bevacizumab group were mild to moderate in severity (Grade 1 or 2). The higher incidence of exposure-adjusted AEOSIs in the pembrolizumab + chemotherapy ± bevacizumab group was driven primarily by infusion reactions (13.4%), reflecting the contribution of pembrolizumab, chemotherapy and bevacizumab.

Safety data related to the TNBC population in KN522 (database cutoff 23-MAR-2021) (n=783) were evaluated and are presented in text for each risk. Overall, the safety profile of pembrolizumab in combination with neoadjuvant chemotherapy followed by continued adjuvant pembrolizumab monotherapy in TNBC in KN522 was generally similar to the known safety profiles of pembrolizumab monotherapy and the chemotherapy administered. A higher frequency of immune-mediated events was observed in the pembrolizumab in combination with neoadjuvant chemotherapy group followed by continued adjuvant pembrolizumab

monotherapy treatment group in comparison to the reference safety dataset. This was primarily driven by hypothyroidism (15.1%), infusion reactions (18%), and severe skin reactions (5.7%), reflecting the contribution of both pembrolizumab and the neoadjuvant chemotherapy administered. Most AEOSIs were grade 1 and 2. The nature (type, severity, management, and outcome) of the immune-mediated AEs observed with pembrolizumab in combination with neoadjuvant chemotherapy followed by continued adjuvant pembrolizumab monotherapy in KN522 was similar to the nature of immune-mediated AEs previously seen with pembrolizumab monotherapy.

Safety data related to the melanoma population in KN716 (database cutoff 04-DEC-2020) (total n=483) were evaluated and are presented in text for each risk. Overall, the safety profile of pembrolizumab monotherapy in the melanoma population in KN716 was generally similar to the observed safety profile in the reference safety dataset. Increases in some immune-mediated AEs were observed. The nature (type, severity, management, and outcome) of the immune-mediated AEs observed with pembrolizumab in KN716 was similar to the nature of immune-mediated AEs previously seen with pembrolizumab monotherapy. The increases in some immune-mediated AEs observed in KN716 could be a reflection of the >2-fold longer duration of exposure to pembrolizumab in KN716 subjects compared to subjects in the reference safety dataset.

Safety data related to the gastric cancer population in KN811 (database cutoff 25-MAY-2022) who received pembrolizumab plus chemotherapy and trastuzumab (n=350) were evaluated and are presented in text for each risk. Overall, the safety profile of pembrolizumab combination therapy in the gastric cancer population in KN811 was generally similar to the observed safety profile in the reference safety dataset, except for a higher incidence of immune-mediated events primarily due to infusion-related reactions (16.0%) and pneumonitis (6.0%). The higher incidence of these events may be driven by the addition of trastuzumab and chemotherapy, since these are known risks for the SOC regimen. The longer duration of exposure compared to the reference safety dataset may also have contributed to the observed higher incidence of these AEOSIs. The nature (severity, management, and outcome) of the immune- mediated AEs was similar to the nature of immune-mediated AEs previously seen with pembrolizumab monotherapy.

Safety data related to the NSCLC population in KN091 (database cutoff date 20-Sep-2021) (total n=580 in pembrolizumab group) were evaluated and are presented in text for each risk. Overall, the safety and tolerability of pembrolizumab administered in KN091 is generally consistent with the known safety profile of pembrolizumab in the advanced cancer setting, except for a higher incidence of immune-mediated events primarily due to a higher cumulative frequency of hypothyroidism (20.7%) and hyperthyroidism (10.7%), due to grade 1 and 2 events. However, the incidences of hyperthyroidism and hypothyroidism in the KN091 pembrolizumab group are consistent with those reported in other adjuvant studies with pembrolizumab monotherapy in melanoma (KN716) and RCC (KN564) populations. The incidence of pneumonitis (6.9%) in pembrolizumab group was higher than in the pembrolizumab reference safety dataset but, consistent with the incidence of pneumonitis (3.8 to 8.3%) reported in individual studies of patients with NSCLC treated with pembrolizumab monotherapy. The increases in some immune-mediated AEs in KN091 could be a reflection of the >2-fold longer duration of exposure to pembrolizumab compared to subjects in the

reference safety dataset. The nature (severity, management, and outcome) of the immune-mediated AEs was similar to the nature of immune-mediated AEs previously seen with pembrolizumab monotherapy.

Safety data related to the gastric cancer population in KN859 (database cutoff 03-OCT-2022) who received pembrolizumab plus chemotherapy (n=785) were evaluated and are presented in text for each risk. Overall, the safety profile of pembrolizumab combination therapy in the gastric cancer population in KN859 was generally similar to the observed safety profiles of pembrolizumab monotherapy and the chemotherapy administered, except for a higher incidence of immune-mediated event of hypothyroidism (15.3%) as compared to the RSD. After adjustment for exposure the event rates for hypothyroidism were similar to the RSD. The events of hypothyroidism in KN859, were mostly Grade 1 and 2 events and are generally consistent in nature with the events of hypothyroidism previously reported for pembrolizumab.

Safety data related to the BTC population in KN966 (database cutoff date: 15-Dec-2022) (total n=529) were evaluated and presented in text for each risk. Overall, safety and tolerability of pembrolizumab in combination with chemotherapy in the BTC population in KN966 was generally similar to the known safety profile of pembrolizumab monotherapy and the safety profile of chemotherapy. The AEOSI severity in most participants were Grade 1 or 2. The nature (type, severity, management, and outcome) of the immune-related AEs observed with pembrolizumab in combination with chemotherapy was similar to the nature of immune-related AEs previously observed with pembrolizumab monotherapy in the reference safety dataset.

Safety data related to the NSCLC population in KN671 (database cutoff date 29-Jul-2022) (total n=396) were evaluated and are presented in text for each risk. Overall, the safety and tolerability of pembrolizumab in combination with chemotherapy as neoadjuvant treatment followed by continued adjuvant pembrolizumab monotherapy administered in KN671 is generally consistent with the known safety profile of pembrolizumab monotherapy and the known safety profile of the individual chemotherapy components.

All identified and potential risks for pembrolizumab are reviewed routinely for a change in characterization (including severity, frequency and risk factors) in accordance with the EMA Guideline on good pharmacovigilance practices (GVP) Module V Risk management systems and Module IX Signal Management. Per this process, data regarding reports of immune-mediated AEOSIs with a fatal outcome were reviewed. Review of the data revealed that a number of AEOSIs had at least 1 event with a reported fatal outcome.

A series of database queries was done to identify all CT and postmarketing AEOSIs with a fatal outcome.

Clinical Trial (CT) Data:

The Aggregate Safety Evaluation (ASE) dataset, which is a locked aggregate CT safety database, was queried. The current 3Q2017 dataset contains all safety data for subjects who received pembrolizumab monotherapy in an open-label or unmasked, completed randomized trial for which there has been a database lock (DBL) on or before 30-Sep-2017 (n=7730). The

ASE was queried to identify any CT AEOSI with a reported Common Terminology Criteria for Adverse Events (CTCAE) Grade 5 (fatal outcome) severity.

Global Safety Database and Postmarketing (PM) Data:

The global safety database contains clinical trial (including MAH sponsored clinical trials, Investigator Initiated Study Programs, MAH Sponsored Individual Patient Use, Business Partner Cases, and Academic Collaboration Studies) information for all serious events as well as other reportable events such as cancer, overdose, pregnancy, lactation, and protocol-specified events of clinical interest. The global safety database also contains all cases from postmarketing sources including health care providers, consumers and scientific literature as well as competent authorities worldwide. The safety database was queried as of 31-Dec-2017 to identify all Grade 5 CT AEOSIs from interventional, pembrolizumab monotherapy trials.

The global safety database was also queried as of 31-Dec-2017, to identify all PM and non-interventional reports containing a reported immune-mediated AEOSI with a fatal outcome. Two separate queries were done: one to identify reports with a fatal AEOSI only, excluding those with other fatal events due to disease progression/related terms, and another query including cases with other reported causes of death including those due to disease progression.

The results indicated that even with the broader global safety database analysis that included cases in which fatal AEOSIs were reported in the setting of disease progression, the number of cases with fatal immune-mediated AEOSIs remains low.

While the frequency of fatal immune-mediated AEOSIs is low, and while there remain some immune-mediated AEOSIs for which there are no reports of fatal outcome, based on the totality of data and medical importance of the information, the MAH updated the Warning and Precautions section of the prescribing information to add language to further qualify and communicate that immune-mediated AEOSIs may be fatal.

The immune-mediated adverse reactions are presumed to have a common aetiology. Of these immune-mediated adverse reactions, information on severity and frequency data for pneumonitis, colitis, hepatitis, nephritis and endocrinopathies is presented, in the risk tables below as part of the important identified risk.

Table SVII.3.1.1: Details of Important Identified Risk: Immune-Mediated Adverse Reactions-Pneumonitis

Important Identified Risk:	**Immune-mediated Pneumonitis**
Potential Mechanisms:	Pembrolizumab is a potent and highly-selective humanized monoclonal antibody (mAb) of the Immunoglobulin G4 (IgG4)/kappa isotype directed to the programmed cell death-1 (PD-1) receptor and designed to directly block the interaction between the receptor and its ligands, PD-L1 and PD-L2. The PD-1 pathway represents a major immune control switch which may be engaged by tumor cells to overcome active T-cell immune surveillance. T-cell activation in proximity to normal tissue may lead to inflammation and injury to normal lung tissue.
Evidence Source(s) and Strength of Evidence:	Review of pembrolizumab clinical trial data, post-marketing experience and literature regarding pneumonitis represent sufficient evidence of a causal association with pembrolizumab exposure. CTD 2.7.4

Table SVII.3.1.1: Details of Important Identified Risk: Immune-Mediated Adverse Reactions-Pneumonitis

	pembrolizumab KN001 Database Cutoff Date: 18APR2014 pembrolizumab KN001 Database Cutoff Date for Lung: 23JAN2015 pembrolizumab KN002 Database Cutoff Date: 28FEB2015 pembrolizumab KN006 Database Cutoff Date: 03MAR2015 pembrolizumab KN010 Database Cutoff Date: 30SEP2015 pembrolizumab KN013 Database Cutoff Date for Hodgkin Lymphoma: 28SEP2018 pembrolizumab KN024 Database Cutoff Date: 10JUL2017 pembrolizumab KN087 Database Cutoff Date: 21MAR2019 pembrolizumab KN045 Database Cutoff Date: 07SEP2016 pembrolizumab KN052 Database Cutoff Date: 01SEP2016 pembrolizumab KN021 Database Cutoff Date Cohort A: 07NOV2016, Cohort G/C: 31MAY2017 pembrolizumab KN189 Database Cutoff Date: 08NOV2017 pembrolizumab KN040 Database Cutoff Date: 15MAY2017 pembrolizumab KN012 Database Cutoff Date: 26APR2016 pembrolizumab KN055 Database Cutoff Date: 22APR2016 pembrolizumab KN054 Database Cutoff Date: 02OCT2017 pembrolizumab KN407 Database Cutoff Date: 03APR2018 pembrolizumab KN426 Database Cutoff Date: 24AUG2018 pembrolizumab KN048 Database Cutoff Date: 13JUN2018 pembrolizumab KN042 Database Cutoff Date: 26FEB2018 pembrolizumab KN177 Database Cutoff Date: 19FEB2020 pembrolizumab KN204 Database Cutoff Date: 16JAN2020 pembrolizumab KN590 Database Cutoff Date: 02JUL2020 pembrolizumab KN355 Database Cutoff Date: 11DEC2019 pembrolizumab KN581 Database Cutoff Date: 28AUG2020 pembrolizumab KN146 Database Cutoff Date: 18AUG2020 pembrolizumab KN775 Database Cutoff Date: 26OCT2020 pembrolizumab KN564 Database Cutoff Date: 14DEC2020 pembrolizumab KN158 Database Cutoff Date Cohort K: 05OCT2020 pembrolizumab KN164 Database Cutoff Date Cohorts A and B: 09SEP2019 pembrolizumab KN826 Database Cutoff Date: 03MAY2021 pembrolizumab KN522 Database Cutoff Date: 23MAR2021 pembrolizumab KN716 Database Cutoff Date: 04DEC2020 pembrolizumab KN811 Database Cutoff Date: 25MAY2022 pembrolizumab KN091 Database Cutoff Date: 20SEP2021 pembrolizumab KN859 Database Cutoff Date: 03OCT2022 pembrolizumab KN966 Database Cutoff Date: 15DEC2022 pembrolizumab KN671 Database Cutoff Date: 29JUL2022

Table SVII.3.1.1: Details of Important Identified Risk: Immune-Mediated Adverse Reactions-Pneumonitis

Characterisation of the Risk: Immune-mediated Pneumonitis

Frequency with 95%CI

95% Confidence Interval for the Overall Incidence (%) of Pneumonitis

KN001, KN002 and KN006 Melanoma Subjects and KN001 and KN010 NSCLC Subjects Treated with Pembrolizumab

	Cumulative MEL 001/002/006 + NSCLC 001/010	
	n (%)	95% CI
Pneumonitis	94 (3.4)	(2.7,4.1)

The overall number and proportion of patients with of pneumonitis in the NSCLC population in KN024 and KN042 (n=790) was 65 (8.2%) (95% CI- 6.4, 10.4). In individual studies of patients with NSCLC (total n=2022), the incidence of pneumonitis (all Grades) ranged from 3.8% to 8.3%. The proportion of patients with events of pneumonitis in KN024 and KN042, although somewhat more common than in the reference safety dataset, were generally consistent in nature with the proportion of events of pneumonitis previously reported for pembrolizumab.

The overall number and proportion of patients with pneumonitis in the NSCLC population in KN189 and KN021 (Cohorts C and G) pembrolizumab plus chemotherapy (n=488) was 22 (4.5%) (95% CI- 2.8, 6.7), which is generally similar to the proportion of patients with the event of pneumonitis in the reference safety dataset for melanoma and NSCLC.

The overall number and proportion of patients with pneumonitis in the HL population in KN013, KN087, and KN204 (n=389) was 31 (8.0%) (95% CI-5.5, 11.1). These proportion of patients with events of pneumonitis, although somewhat more common than the reference safety dataset, were generally consistent in nature with the proportion of events of pneumonitis previously reported for pembrolizumab.

The overall number and proportion of patients with pneumonitis in the UC population in KN052 (n=370) was 7 (1.9%) (95%CI-0.8,3.9) and in KN045 (n=266) was 11 (4.1%) (95%CI-2.1,7.3), which is generally similar to the proportion of patients with the event of pneumonitis in the reference safety dataset for melanoma and NSCLC.

The overall number and proportion of patients with pneumonitis in the HNSCC population in KN040, KN012 and KN055 (n=609) was 23 (3.8%) (95% CI- 2.4,5.6), which is generally similar to the proportion of patients with the event of pneumonitis in the reference safety dataset for melanoma and NSCLC.

The overall number and proportion of patients with pneumonitis in the HNSCC population in KN048 pembrolizumab monotherapy (n=300) and pembrolizumab plus chemotherapy (n=276) groups were 18 (6.0%) (95% CI- 3.6, 9.3) and 15 (5.4%) (95% CI-3.1,8.8) respectively, which is generally similar to the overall proportion of patients with the event of pneumonitis in the reference safety dataset for melanoma and NSCLC.

The overall number and proportion of patients with pneumonitis in the melanoma population in KN054 (n=509) was 17 (3.3%) (95% CI-2.0, 5.3), which is generally similar to the proportion of patients with the events of pneumonitis in the reference safety dataset for melanoma and NSCLC.

The overall number and proportion of patients with pneumonitis in the NSCLC population in KN407 and KN021 (Cohort A) (n=303) was 19 (6.3%) (95% CI-3.8, 9.6). The proportion of patients with events of pneumonitis in KN407 and KN021 (Cohort A), although somewhat more common than in the reference safety dataset, were generally consistent in nature with the proportion of events of pneumonitis previously reported for pembrolizumab.

The overall number and proportion of patients with pneumonitis in the RCC population in KN426 pembrolizumab plus axitinib (n=429) was 12 (2.8%) (95% CI-1.5,4.8), which is similar to the proportion of patients with the event of pneumonitis in the reference safety dataset for melanoma and NSCLC.

Public

Table SVII.3.1.1: Details of Important Identified Risk: Immune-Mediated Adverse Reactions-Pneumonitis

	The overall number and proportion of patients with pneumonitis in the CRC population in KN177 (n=153) was 6 (3.9%) (95% CI-1.5, 8.3) which is generally similar to the proportion of patients with the event of pneumonitis in the reference safety dataset. The overall number and proportion of patients with pneumonitis in the esophageal cancer population in KN590 pembrolizumab plus chemotherapy (n=370) was 23 (6.2%) (95% CI-4,9.2), which is similar to the proportion of patients with the event of pneumonitis reported for the reference safety dataset. The proportion of patients with events of pneumonitis in KN590 were generally consistent in nature with the proportion of events of pneumonitis previously reported for pembrolizumab. The overall number and proportions of patients with pneumonitis in the TNBC population in KN355 pembrolizumab plus chemotherapy group (n=596) was 15 (2.5%) (95% CI-1.4,4.1), which is generally similar to the proportion of patients with the event of pneumonitis in the reference safety dataset for melanoma and NSCLC. The overall number and proportion of patients with pneumonitis in the RCC population in KN581 pembrolizumab plus lenvatinib (n=352) was 19 (5.4%) (95% CI-3.3,8.3), which is generally similar to the proportion of patients with the event of pneumonitis in the reference safety dataset. The overall number and proportion of patients with pneumonitis in the endometrial carcinoma population in KN146 and KN775 pembrolizumab plus lenvatinib (n=530) was 9 (1.7%) (95% CI-0.8, 3.2), which is generally similar to the proportion of patients with the event of pneumonitis in the reference safety dataset. The overall number and proportion of patients with pneumonitis in the RCC population in KN564 pembrolizumab monotherapy (n=488) was 11 (2.3%) (95% CI-1.1,4), which is generally similar to the proportion of patients with the event of pneumonitis in the reference safety dataset for melanoma and NSCLC. The overall number and proportion of patients with pneumonitis in the MSI-H population in KN158 Cohort K and KN164 Cohorts A and B (n=475) was 15 (3.2%) (95% CI-1.8, 5.2) which is generally similar to the proportion of patients with the event of pneumonitis in the reference safety dataset. The overall number and proportion of patients with pneumonitis in the cervical cancer population in KN826 pembrolizumab plus chemotherapy (n=307) was 6 (2.0%) (95% CI-0.7,4.2), which is generally similar to the proportion of patients with the event of pneumonitis in the reference safety dataset. The overall number and proportion of pneumonitis in the TNBC population in KN522 pembrolizumab in combination with neoadjuvant chemotherapy followed by continued adjuvant pembrolizumab monotherapy group (n=783) was 17 (2.2%) (95% CI-1.3,3.5), which is generally similar to the proportion of patients with the event of pneumonitis in the reference safety dataset. The overall number and proportion of patients with pneumonitis in the melanoma population in KN716 pembrolizumab monotherapy (n=483) was 9 (1.9%) (95% CI-0.9, 3.5), which is generally similar to the proportion of patients with the event of pneumonitis in the reference safety dataset for melanoma and NSCLC. The overall number and proportion of patients with of pneumonitis in the gastric cancer population in KN811 pembrolizumab combination therapy (n=350) was 21 (6.0%) (95% CI-3.8, 9.0), which is generally similar to the proportion of patients with events of pneumonitis in the reference safety database. The overall number and proportion of patients with pneumonitis in the NSCLC population in KN091 pembrolizumab monotherapy (n=580) was 40 (6.9%) (95% CI-5.0,9.3), The proportion of patients with the event of pneumonitis in KN091, although somewhat more common than the reference safety dataset, was consistent with the proportion of events of pneumonitis previously reported for pembrolizumab monotherapy NSCLC studies. The overall number and proportion of patients with pneumonitis in the gastric cancer population in KN859 pembrolizumab plus chemotherapy (n=785) was 25 (3.2%) (95% CI-2.1,4.7), which is generally similar to the proportion of patients with the events of pneumonitis in the reference safety dataset.

Table SVII.3.1.1: Details of Important Identified Risk: Immune-Mediated Adverse Reactions-Pneumonitis

<table>
<tr><td></td><td>The overall number and proportion of patients with pneumonitis in the BTC population in KN966 pembrolizumab plus chemotherapy (n=529) was 26 (4.9%) (95% CI-3.2, 7.1), which is generally similar to the proportion of patients with the events of pneumonitis in the reference safety dataset.

The overall number and proportion of patients with pneumonitis in the NSCLC population in KN671 pembrolizumab in combination with chemotherapy as neoadjuvant treatment followed by continued adjuvant pembrolizumab monotherapy (n=396) was 22 (5.6%) (95% CI-3.5, 8.3), which is more common than in the reference safety dataset. However, after adjusting for exposure, the rates for pneumonitis were similar to those reported in the reference dataset.</td></tr>
<tr><td>Outcomes</td><td>Percent overall, fatal, not resolved, resolved, and unknown for identified risk of pneumonitis – pembrolizumab (AEs for 30 days after discontinuation were included)

Pneumonitis (AEOSI)

KN001, KN002 and KN006 Melanoma Subjects and KN001 and KN010 NSCLC Subjects Treated with Pembrolizumab (Treatment-Emergent)

<table>
<tr><td></td><td></td><td colspan="2">Cumulative NSCLC 001/010 + MEL 001/002/006</td></tr>
<tr><td></td><td>Outcome</td><td>n</td><td>(%)</td></tr>
<tr><td>Subjects in population</td><td></td><td>2,799</td><td></td></tr>
<tr><td>With one or more adverse events</td><td>Overall</td><td>94</td><td>(3.4)</td></tr>
<tr><td></td><td>Fatal</td><td>4</td><td>(0.1)</td></tr>
<tr><td></td><td>Not Resolved</td><td>30</td><td>(1.1)</td></tr>
<tr><td></td><td>Resolved</td><td>54</td><td>(2.0)</td></tr>
<tr><td></td><td>Resolving</td><td>5</td><td>(0.2)</td></tr>
<tr><td></td><td>Sequelae</td><td>1</td><td>(0.0)</td></tr>
<tr><td></td><td>Unknown</td><td>0</td><td>(0.0)</td></tr>
<tr><td colspan="4">Every subject is counted once on each applicable row.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns is greater than or equal to the percent incidence specified in the report title, after rounding. Outcome: Resolved = RECOVERED/RESOLVED, Not resolved = NOT RECOVERED/NOT RESOLVED.</td></tr>
</table>

In the NSCLC population in KN024 and KN042 (n=790), the outcomes for the 65 patients with events of pneumonitis were as follows: 33 (4.2%) resolved, 11 (1.4%) resolving, 18 (2.3%) not resolved, and 1 (0.1%) unknown. There were 2 (0.3%) patients with events of pneumonitis with a fatal outcome.

In the NSCLC population in KN189 and KN021(Cohorts C and G) pembrolizumab plus chemotherapy (n=488), the outcomes for the 22 (4.5%) patients with events of pneumonitis were as follows: 13 (2.7%) resolved, 1 (0.2%) resolving, 1 (0.2%) resolved with sequelae, 4 (0.8%) not resolved. There were 3 (0.6%) patients with events of pneumonitis with a fatal outcome reported in KN189.

In the HL population in KN013, KN087, and KN204 (n=389), the outcomes for the 31 (8.0%) patients with events of pneumonitis were as follows: 24 (6.2%) resolved, 1 (0.3%) resolving, and 6 (1.5%) not resolved. There were no patients with events of pneumonitis with a fatal outcome.

In the UC population in KN052 (n=370), the outcomes for the 7 (1.9%) patients with events of pneumonitis were as follows: 3 (0.8%) resolved and 4 (1.1%) not resolved and in KN045 (n=266), the outcomes for the 11 (4.1%) patients with events of pneumonitis were as follows: 5 (1.9%) resolved, 1 (0.4%) resolving, 4 (1.5%) not resolved. There was 1 (0.4%) patient with an event of pneumonitis with a fatal outcome reported in KN045.

In the HNSCC population in KN040, KN012 and KN055 (n=609), the outcomes for the 23 patients with events of pneumonitis were as follows: In the HNSCC population in KN040, KN012 and KN055 (n=609), the outcomes for the 23 patients with events of pneumonitis were as follows: 11 (1.8%) resolved, 3 (0.5%) resolving, 1 (0.2%) resolving with sequelae, 7 (1.1%) not resolved. There was 1 (0.2%) patient with an event of pneumonitis with a fatal outcome reported in KN055.

In the HNSCC population in KN048 pembrolizumab monotherapy group (n=300), the outcomes for the 18 patients with events of pneumonitis were as follows: 11 (3.7%) resolved, 3 (1.0%)</td></tr>
</table>

Table SVII.3.1.1: Details of Important Identified Risk: Immune-Mediated Adverse Reactions-Pneumonitis

	resolving, and 3 (1.0%) not resolved. There was 1 (0.3%) patient with an event of pneumonitis with a fatal outcome. In the HNSCC population in KN048 pembrolizumab plus chemotherapy group (n=276), the outcomes for the 15 patients with events of pneumonitis were as follows: 10 (3.6%) resolved, 2 (0.7%) resolving, 2 (0.7%) resolved with sequelae. There was 1 (0.4%) patient with an event of pneumonitis with a fatal outcome. In the melanoma population in KN054 (n=509), the outcome of the 17 patients with events of pneumonitis were as follows: 8 (1.6%) resolved and 9 (1.8%) not resolved. There were no patients with events of pneumonitis with a fatal outcome. In the NSCLC population in KN407 and KN021 (Cohort A) (n=303), the outcomes for the 19 patients with events of pneumonitis were as follows: 11 (3.6%) resolved, 2 (0.6%) resolving, 1 (0.3%) resolved with sequelae, 4 (1.3%) not resolved. There was 1 (0.3%) patient with an event of pneumonitis with a fatal outcome. In the RCC population in KN426 pembrolizumab plus axitinib (n=429), the outcomes for the 12 patients with events of pneumonitis were as follows: 1 (0.2%) fatal, 7 (1.6%) resolved, 2 (0.5%) not resolved and 2 (0.5%) resolving. In the CRC population in KN177 (n=153), the outcomes for the 6 patients with events of pneumonitis were as follows: 2 (1.3%) resolved, 1 (0.7%) resolving, 1 (0.7%) resolved with sequelae and 2 (1.3%) not resolved. There were no patients with events of pneumonitis with a fatal outcome. In the esophageal cancer population in KN590 pembrolizumab plus chemotherapy (n=370), the outcomes for the 23 patients with events of pneumonitis were as follows: 11 (3%) resolved, 5 (1.4%) resolving, and 5 (1.4%) not resolved. There were 2 (0.5%) patients with events of pneumonitis with a fatal outcome. In the TNBC population in KN355 pembrolizumab plus chemotherapy group (n=596), the outcomes for the 15 patients with events of pneumonitis were as follows: 11 (1.8%) resolved, 1 (0.2%) resolving, and 3 (0.5%) not resolved. There were no patients with events of pneumonitis with a fatal outcome. In the RCC population in KN581 pembrolizumab plus lenvatinib (n=352), the outcomes for the 19 patients with events of pneumonitis were as follows: 7 (2%) resolved, 2 (0.6%) resolved with sequelae, 2 (0.6%) resolving, and 7 (2%) not resolved. There was 1 (0.3%) patient with an event of pneumonitis with a fatal outcome. In the endometrial carcinoma population in KN146 and KN775 pembrolizumab plus lenvatinib (n=530), the outcome for the 9 patients with events of pneumonitis was as follows: 5 (0.9%) resolved, 3 (0.6%) not resolved, and 1 (0.2%) resolving. There were no patients with events of pneumonitis with a fatal outcome. In the RCC population in KN564 pembrolizumab monotherapy (n=488), the outcomes for the 11 patients with events of pneumonitis were as follows: 10 (2%) resolved and 1 (0.2%) not resolved. There were no patients with events of pneumonitis with a fatal outcome. In the MSI-H population in KN158 Cohort K and KN164 Cohorts A and B (n=475), the outcomes for the 15 patients with events of pneumonitis were as follows: 7 (1.5%) resolved, 3 (0.6%) resolving, 2 (0.4%) resolved with sequelae and 3 (0.6%) not resolved. There were no patients with events of pneumonitis with a fatal outcome. In the cervical cancer population in KN826 pembrolizumab plus chemotherapy (n=307), the outcomes for the 6 patients with events of pneumonitis were as follows: 2 (0.7%) not resolved, 2 (0.7%) resolving, and 2 (0.7%) resolved. There were no patients with events of pneumonitis with a fatal outcome. In the TNBC population in KN522 pembrolizumab in combination with neoadjuvant chemotherapy followed by continued adjuvant pembrolizumab monotherapy group (n=783), the outcomes for the 17 patients with events of pneumonitis were as follows: 13 (1.7%) resolved, 2 (0.3%) not resolved, and 1 (0.1%) resolving. There was 1 (0.1%) patient with an event of pneumonitis with a fatal outcome. In the melanoma population in KN716 pembrolizumab monotherapy (n=483). The outcomes for the 9 patients with events of pneumonitis were as follows: 5 (1%) resolved, 2 (0.4%) not resolved, and 2 (0.4%) resolving. There were no patients with events of pneumonitis with a fatal outcome.

Table SVII.3.1.1: Details of Important Identified Risk: Immune-Mediated Adverse Reactions-Pneumonitis

<table>
<tr><td></td><td>
In the gastric cancer population in KN811 pembrolizumab combination therapy (n=350), the outcomes for the 21 patients with events of pneumonitis were as follows: 13 (3.7%) resolved, 5 (1.4%) not resolved, and 1 (0.3%) resolving. There were 2 (0.6%) patients with events of pneumonitis with a fatal outcome.

In the NSCLC population in KN091 pembrolizumab monotherapy (n=580), the outcomes for the 40 patients with events of pneumonitis were as follows: 27 (4.7%) resolved, 11 (1.9%) not resolved, and 2 (0.3%) resolved with sequelae. There were no patients with events of pneumonitis with a fatal outcome.

In the gastric cancer population in KN859 pembrolizumab plus chemotherapy (n=785), the outcomes for the 25 patients with events of pneumonitis were as follows: 13 (1.7%) not resolved, 8 (1.0%) resolved, 2 (0.3%) resolving, and 1 (0.1%) resolved with sequelae. There was 1 (0.1%) patient with a fatal event of pneumonitis.

In the BTC population in KN966 pembrolizumab plus chemotherapy (n=529), the worst reported outcomes for the 26 patients with events of pneumonitis were as follows: 9 (1.7%) resolved, 9 (1.7%) not resolved, 6 (1.1%) resolving and 1 (0.2%) resolved with sequelae. There was 1 (0.2%) patient with an event of pneumonitis with a fatal outcome.

In the NSCLC population in KN671 pembrolizumab in combination with chemotherapy as neoadjuvant treatment followed by continued adjuvant pembrolizumab monotherapy group (n=396), the outcomes for the 22 patients with events of pneumonitis were as follows: 10 (2.5%) resolved, 6 (1.5%) not resolved, 4 (1.0%) resolving, and 1 (0.3%) resolved with sequelae. There was 1 (0.3%) patient with an event of pneumonitis with a fatal outcome.

Aggregate Review

Review of the ASE dataset (n=7730) yielded 12 fatal cases of pneumonitis. Review of the global safety database yielded the following: 31 fatal cases from ongoing interventional monotherapy clinical trials (including the 12 cases from ASE) and 100 fatal cases from the PM or non-interventional environment. Of the 100, there were 84 cases in which fatal pneumonitis was the only grade 5 event and 16 cases that reported a grade 5 pneumonitis, as well as a grade 5 malignant neoplasm progression (MNP) or other related fatal event(s).
</td></tr>
<tr><td>Seriousness</td><td>
Percent serious for identified risk of pneumonitis - pembrolizumab (Serious AEs for 90 days after discontinuation were included.)

Pneumonitis - Serious (AEOSI)
KN001, KN002 and KN006 Melanoma Subjects and KN001 and KN010 NSCLC Subjects Treated with Pembrolizumab
(Treatment Emergent)
<table>
<tr><td></td><td colspan="2">Cumulative NSCLC 001/010 + MEL 001/002/006</td></tr>
<tr><td></td><td>n</td><td>(%)</td></tr>
<tr><td>Subjects in population</td><td>2,799</td><td></td></tr>
<tr><td>with one or more adverse events</td><td>49</td><td>(1.8)</td></tr>
<tr><td></td><td></td><td></td></tr>
<tr><td>Interstitial lung disease</td><td>3</td><td>(0.1)</td></tr>
<tr><td>Pneumonitis</td><td>46</td><td>(1.6)</td></tr>
<tr><td colspan="3">Every subject 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.
Include all treated subjects in KN001 Part B1, B2, B3, D, C, F1, F2, F3 and all subjects in KN002 treated with Pembrolizumab in the original phase and all subjects in KN006 and KN010 treated with Pembrolizumab.</td></tr>
</table>

Of the 65 patients with events of pneumonitis in the NSCLC population in KN024 and KN042 (n=790), 37 (4.7%) experienced serious events of pneumonitis.

Of the 22 patients with events of pneumonitis in the NSCLC population in KN189 and KN021 (Cohorts C and G) pembrolizumab plus chemotherapy (n=488), 13 (2.7%) experienced serious events of pneumonitis.
</td></tr>
</table>

Public

Table SVII.3.1.1: Details of Important Identified Risk: Immune-Mediated Adverse Reactions-Pneumonitis

	Of the 31 patients with events of pneumonitis in the HL population in KN013, KN087, and KN204 (n=389), 15 (3.9%) experienced serious events of pneumonitis. Of the 7 patients with events of pneumonitis in the UC population in KN052 (n=370), 3 (0.8%) experienced serious events of pneumonitis and of the 11 patients with events of pneumonitis in the UC population in KN045 (n=266), 7 (2.6%) experienced serious events of pneumonitis. Of the 23 patients with events of pneumonitis in the HNSCC population in KN040, KN012 and KN055 (n=609), 12 (2%) experienced serious events of pneumonitis. Of the 18 patients with events of pneumonitis in the HNSCC population in KN048 pembrolizumab monotherapy group (n=300), 4 (1.3%) were serious. Of the 15 events of pneumonitis in the HNSCC pembrolizumab plus chemotherapy group (n=276), 5 (1.8%) experiencedserious events of pneumonitis. Of the 17 patients with events of pneumonitis in the melanoma population in KN054 (n=509), 8 (1.6%) experienced serious events of pneumonitis. Of the 19 patients with events of pneumonitis in the NSCLC population in KN407 and KN021 (Cohort A) (n=303), 9 (3.0%) experienced serious events of pneumonitis. Of the 12 patients with events of pneumonitis in the RCC population in KN426 pembrolizumab plus axitinib (n=429), 6 (1.4%) experienced serious events of pneumonitis. Of the 6 patients with events of pneumonitis in the CRC population in KN177 (n=153), 1 (0.7%) experienced a serious event of pneumonitis. Of the 23 patients with events of pneumonitis in the esophageal cancer population in KN590 pembrolizumab plus chemotherapy (n=370) 14 (3.8%) experienced serious events of pneumonitis. Of the 15 patients with events of pneumonitis in the TNBC population in KN355 pembrolizumab plus chemotherapy group (n=596), 7 (1.2%) experienced serious events of pneumonitis. Of the 19 patients with events of pneumonitis in the RCC population in KN581 pembrolizumab plus lenvatinib (n=352), 9 (2.6%) experienced serious events of pneumonitis. There were 4 (0.8%) patients with serious events of pneumonitis reported in the endometrial carcinoma population in KN146 and KN775 pembrolizumab plus lenvatinib (n=530). Of the 11 patients with events of pneumonitis in the RCC population in KN564 pembrolizumab monotherapy (n=488), 5 (1%) experienced serious events of pneumonitis. Of the 15 patients with events of pneumonitis in the MSI-H population in KN158 Cohort K and KN164 Cohorts A and B (n=475) 6 (1.3%) experienced serious events of pneumonitis. Of the 6 patients with events of pneumonitis in the cervical cancer population in KN826 pembrolizumab plus chemotherapy (n=307), 1 (0.3%) experienced a serious event of pneumonitis. Of the 17 patients with events of pneumonitis in the TNBC population in KN522 pembrolizumab in combination with neoadjuvant chemotherapy followed by continued adjuvant pembrolizumab monotherapy group (n=783), 9 (1.1%) experienced serious events of pneumonitis. Of the patients with 9 events of pneumonitis in the melanoma population in KN716 pembrolizumab monotherapy (n=483), 3 (0.6%) experienced serious events of pneumonitis. Of the 21 patients with events of pneumonitis in the gastric cancer population in KN811 pembrolizumab combination therapy (n=350), 8 (2.3%) experienced serious events of pneumonitis. Of the 40 patients with events of pneumonitis in the NSCLC population in KN091 pembrolizumab monotherapy (n=580), 16 (2.8%) experienced serious events of pneumonitis. Of the 25 patients with events of pneumonitis in the gastric cancer population in KN859 pembrolizumab plus chemotherapy (n=785), 12 (1.5%) experienced a serious event of pneumonitis. Of the 26 patients with events of pneumonitis in the BTC population in KN966 pembrolizumab plus chemotherapy (n=529), 8 (1.5%) experienced serious events of pneumonitis. Of the 22 patients with events of pneumonitis in the NSCLC population in KN671 pembrolizumab in combination with chemotherapy as neoadjuvant treatment followed by continued adjuvant pembrolizumab monotherapy (n=396), 11 (2.8%) experienced serious events of pneumonitis.

Table SVII.3.1.1: Details of Important Identified Risk: Immune-Mediated Adverse Reactions-Pneumonitis

Severity and Nature of the Risk

Identified treatment emergent adverse events (AE) of pneumonitis (all events) in participants summarized by grade– pembrolizumab (Table includes events for 30 days after discontinuation)

Pneumonitis (AEOSI)
KN001, KN002 and KN006 Melanoma Subjects and KN001 and KN010 NSCLC Subjects Treated with Pembrolizumab
(Treatment Emergent)

	Cumulative NSCLC 001/010 + MEL 001/002/006	
	n	(%)
Subjects in population	2,799	
with one or more adverse events	94	(3.4)
Interstitial lung disease	7	(0.3)
Grade 1	3	(0.1)
Grade 2	2	(0.1)
Grade 3	1	(0.0)
Grade 5	1	(0.0)
Pneumonitis	87	(3.1)
Grade 1	19	(0.7)
Grade 2	34	(1.2)
Grade 3	24	(0.9)
Grade 4	7	(0.3)
Grade 5	3	(0.1)

Every subject is counted a single time for each applicable specific adverse event. A subject with multiple adverse events within a system organ class is counted a single time for that system organ class.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns is greater than or equal to the incidence specified in the report title, after rounding.
Only the highest reported grade of a given adverse event is counted for the individual subject.
Grades are based on National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

In the NSCLC population in KN024 and KN042 (n=790), there were 19 (2.4%) patients with Grade 3, 6 (0.8%) patients with Grade 4 and 2 (0.3%) patients with Grade 5 events of pneumonitis.

In the NSCLC population in KN189 and KN021 (Cohorts C and G) pembrolizumab plus chemotherapy (n=488), there were 8 (1.6%) patients with Grade 3, 1 (0.2%) patient with Grade 4, and 3 (0.6%) patients with Grade 5 events of pneumonitis.

In the HL population in KN013, KN087, and KN204 (n=389), there were 6 (1.5%) patients with Grade 3, 3 (0.8%) patients with Grade 4 and no patients with Grade 5 events of pneumonitis.

In the UC population in KN052 (n=370), there were 3 (0.8%) patients with Grade 3 events and no patients with Grade 4 or 5 events of pneumonitis; in the UC population in KN045 (n=266), there were 5 (1.9%) patients with Grade 3 events, no patients with Grade 4 events, and 1 (0.4%) patient with a Grade 5 event of pneumonitis.

In the HNSCC population in KN040, KN012 and KN055 (n=609), there were 6 (1.0%) patients with Grade 3 events and 1 (0.2%) patient with a Grade 5 event of pneumonitis.

In the HNSCC population in KN048 pembrolizumab monotherapy group (n=300), there were 4 (1.3%) patients with Grade 3 events and 1 (0.3%) patient with a Grade 5 event of pneumonitis; in the pembrolizumab plus chemotherapy group (n=276), there were 3 (1.1%) patients with Grade 3 events and 1 (0.4%) patient with a Grade 5 events of pneumonitis.

In the melanoma population in KN054 (n=509), there were 4 (0.8%) patients with Grade 3 events of pneumonitis reported. There were no patients with Grade 4 or 5 events of pneumonitis.

In the NSCLC population in KN407 and KN021 (Cohort A) (n=303), there were 6 (2.0%) patients with Grade 3, no patients with Grade 4, and 1 (0.3%) patient with a Grade 5 event of pneumonitis.

In the RCC population in KN426 pembrolizumab plus axitinib (n=429), there was 1 (0.2%) patient with a Grade 3 event and 1 (0.2%) patient with a Grade 5 event of pneumonitis reported.

Table SVII.3.1.1: Details of Important Identified Risk: Immune-Mediated Adverse Reactions-Pneumonitis

	In the CRC population in KN177 (n=153) there were no Grade 3-5 events of pneumonitis reported. In the esophageal cancer population in KN590 pembrolizumab plus chemotherapy (n=370) there were 7 (1.9%) patients with Grade 3 events, no patients with Grade 4 events, and 2 (0.5%) patients with Grade 5 events of pneumonitis reported. In the TNBC population in KN355 pembrolizumab plus chemotherapy group (n=596), there were 5 (0.8%) patients with Grade 3 events, and 1 (0.2%) patients with a Grade 4 event. There were no patients with Grade 5 events of pneumonitis reported. In the RCC population in KN581 pembrolizumab plus lenvatinib (n=352) there were 5 (1.4%) patients with Grade 3 events, 1 (0.3%) patient with a Grade 4 event, and 1 (0.3%) patient with a Grade 5 event of pneumonitis reported. In the endometrial carcinoma population in KN146 and KN775 pembrolizumab plus lenvatinib (n=530) there were 4 (0.8%) patients with Grade 3 and no patients with Grade 4 or 5 events of pneumonitis reported. In the RCC population in KN564 pembrolizumab monotherapy (n=488) there were 2 (0.4%) patients with Grade 3, 2 (0.4%) patients with Grade 4, and no patients with Grade 5 events of pneumonitis reported. In the MSI-H population in KN158 Cohort K and KN164 Cohorts A and B (n=475), there were 5 (1.1%) patients with Grade 3 events of pneumonitis. There were no patients with Grade 4 or 5 events of pneumonitis reported. In the cervical cancer population in KN826 pembrolizumab plus chemotherapy (n=307), there was 1 (0.3%) patient with a Grade 3 and no patients with Grade 4 or 5 events of pneumonitis reported. In the TNBC population in KN522 pembrolizumab in combination with neoadjuvant chemotherapy followed by continued adjuvant pembrolizumab monotherapy group (n=783) there were 6 (0.8%) patients with Grade 3 events, no patients with Grade 4 events, and 1 (0.1%) patient with a Grade 5 event of pneumonitis reported. In the melanoma population in KN716 pembrolizumab monotherapy (n=483) there was 1 (0.2%) patient with a Grade 3 and no patients with Grade 4 or 5 events of pneumonitis reported. In the gastric cancer population in KN811 pembrolizumab combination therapy (n=350) there were 3 (0.9%) patients with a Grade 3, 1 (0.3%) patient with a Grade 4, and 2 (0.6%) patients with Grade 5 events of pneumonitis reported. In the NSCLC population in KN091 pembrolizumab monotherapy (n=580), there were 6 (1.0%) patients with Grade 3, 2 (0.3%) patients with Grade 4, and no patients with Grade 5 events of pneumonitis reported. In the gastric cancer population in KN859 pembrolizumab plus chemotherapy (n=785), there were 8 (1.0%) patients with a Grade 3, 1 (0.1%) patient with a Grade 4, and 1 (0.1%) patient with a Grade 5 event of pneumonitis reported. In the BTC population in KN966 pembrolizumab plus chemotherapy (n=529, there were 5 (0.9%) patients with Grade 3 events, no patients with Grade 4 events, and 1 (0.2%) patient with a Grade 5 event of pneumonitis reported. In the NSCLC population in KN671 pembrolizumab in combination with chemotherapy as neoadjuvant treatment followed by continued adjuvant pembrolizumab monotherapy (n=396) there were 6 (1.5%) patients with Grade 3, 1 (0.3%) patient with a Grade 4, and 1 (0.3%) patient with a Grade 5 event of pneumonitis reported. In the global safety database through 31-DEC-2017, (pembrolizumab monotherapy trials only), there were 31 Grade 5 clinical trial reports of pneumonitis. Review of pembrolizumab clinical trial data from ongoing studies and postmarketing data regarding immune-mediated pneumonitis, including fatal cases, is consistent with the risk as characterized in the RMP

Table SVII.3.1.1: Details of Important Identified Risk: Immune-Mediated Adverse Reactions-Pneumonitis

Risk Factors and Risk Groups:	Patients with a history of non-infectious pneumonitis that required steroids or current pneumonitis were excluded from the clinical trials. These patients are considered to be a risk group for the development of pneumonitis; in the interim analysis of the KN001 NSCLC cohort, possible risk factors identified that might predispose subjects to pneumonitis were a documented history of prior thoracic radiation to the chest (≥30Gy). According to the literature, risk factors for interstitial lung disease may include occupational exposure to toxins, chest irradiation, some chemotherapies, smoking and advanced age.
Preventability:	Although the development of pneumonitis cannot be completely prevented; patients should be monitored for signs and symptoms of pneumonitis. Suspected pneumonitis should be confirmed with radiographic imaging and other causes excluded. Withholding/discontinuation of pembrolizumab and appropriate medical intervention including corticosteroids following the onset of pneumonitis may result in recovery.
Impact on the Risk-Benefit Balance of the Product:	Severe pneumonitis may be life-threatening or fatal in individual patients. However, given the fatal outcome of untreated cancer, the risk of pneumonitis which generally can be managed, is outweighed by the potential benefit.
Public Health Impact:	This risk has minimal public health impact outside its effect on individual patients.

Table SVII.3.1.2: Details of Important Identified Risk: Immune-Mediated Adverse Reactions- Colitis

Important Identified Risk:	Immune-mediated Colitis
Potential Mechanisms:	Pembrolizumab is a potent and highly-selective humanized monoclonal antibody (mAb) of the Immunoglobulin G4 (IgG4)/kappa isotype directed to the programmed cell death-1 (PD-1) receptor and designed to directly block the interaction between the receptor and its ligands, PD-L1 and PD-L2. The PD-1 pathway represents a major immune control switch which may be engaged by tumor cells to overcome active T-cell immune surveillance. A potential mechanism of action is T-cell activation in proximity to normal tissue resulting in inflammation and injury to normal GI tissue.
Evidence Source(s) and Strength of Evidence:	Review of pembrolizumab clinical trial data, post-marketing experience and literature regarding colitis represent sufficient evidence of a causal association with pembrolizumab exposure. CTD 2.7.4 Please reference evidence source cited in Table SVII.3.1.1; Details of Important Identified Risk: Immune-Mediated Pneumonitis
Characterisation of the Risk: Immune-mediated Colitis	
Frequency with 95%CI	95% Confidence Interval for the Overall Incidence (%) of Colitis KN001, KN002 and KN006 Melanoma Subjects and KN001 and KN010 NSCLC Subjects Treated with Pembrolizumab

	Cumulative MEL 001/002/006 + NSCLC 001/010	
	n (%)	95% CI
Colitis	48 (1.7)	(1.3,2.3)

The overall number and proportion of patients with colitis in the NSCLC population in KN024 and KN042 (n=790) was 13 (1.6%) (95% CI-0.9, 2.8), which is generally similar to the proportion of patients with the event of colitis in the reference safety dataset for melanoma and NSCLC.

The overall number and proportion of patients with colitis in the NSCLC population in KN189 and KN021 (Cohorts C and G) pembrolizumab plus chemotherapy (n=488) was 14 (2.9%) (95% CI-

Table SVII.3.1.2: Details of Important Identified Risk: Immune-Mediated Adverse Reactions- Colitis

	1.6, 4.8), which is generally similar to the proportion of patients with the event of colitis in the reference safety dataset for melanoma and NSCLC. The overall number and proportion of patients with colitis in the HL population in KN013, KN087, and KN204 (n=389) was 6 (1.5%) (95%CI-0.6, 3.3), which is generally similar to the proportion of patients with the event of colitis in the reference safety dataset for melanoma and NSCLC. The overall number and proportion of patients with colitis in the UC population in KN052 (n=370) was 9 (2.4%) (95%CI-1.1,4.6) and in KN045 (n=266) was 6 (2.3%) (95%CI-0.8,4.8), which is generally similar to the proportion of patients with the event of colitis in the reference safety dataset for melanoma and NSCLC. The overall number and proportion of patients with colitis in the HNSCC population in KN040, KN012 and KN055 (n=609) was 4 (0.7%) (95% CI- 0.2,1.7), which is generally similar to the proportion of patients with the event of colitis in the reference safety dataset for melanoma and NSCLC. The overall number and proportion of patients with colitis in the HNSCC population in KN048 pembrolizumab monotherapy (n=300) and pembrolizumab plus chemotherapy (n=276) groups were 3 (1.0%) (95% CI- 0.2, 2.9) and 7 (2.5) (95% CI- 1,5.2) respectively, which is generally similar to the proportion of patients with the event of colitis in the reference safety dataset for melanoma and NSCLC. The overall number and proportion of patients with colitis in the melanoma population in KN054 (n=509) was 19 (3.7%) (95% CI-2.3, 5.8). The proportion of patients with events of colitis in KN054 although somewhat more common than in the reference safety dataset were generally consistent in nature with the proportion of patients with events of colitis previously reported for pembrolizumab. The overall number and proportion of patients with colitis in the NSCLC population in KN407 and KN021 (Cohort A) (n=303) was 9 (3.0%) (95% CI-1.4, 5.6), which is generally similar to the proportion of patients with the event of colitis in the reference safety dataset for melanoma and NSCLC. The overall number and proportion of patients with colitis in the RCC population in KN426 pembrolizumab plus axitinib (n=429) was 11 (2.6%) (95% CI-1.3,4.5), which is generally similar to the proportion of patients with the event of colitis in the reference safety dataset for melanoma and NSCLC. The overall number and proportion of patients with colitis in the CRC population in KN177 (n=153) was 10 (6.5%) (95% CI-3.2,11.7). Colitis was reported more frequently in the KN177 pembrolizumab safety dataset compared with the RSD (6.5% vs 1.7%, respectively); however, when adjusted for exposure, the incidences were similar (6.1 vs 4.1 events per 100 person-years) and the proportion of events were generally consistent in nature with the proportion of events of colitis previously reported for pembrolizumab. The overall number and proportion of patients with colitis in the esophageal cancer population in KN590 pembrolizumab plus chemotherapy (n=370) was 8 (2.2%) (95%CI-0.9,4.2), which is generally similar to the proportion of patients with the event of colitis in the reference safety dataset for melanoma and NSCLC. The overall number and proportion of patients with colitis in the TNBC population in KN355 pembrolizumab plus chemotherapy group (n=596) was 11 (1.8) (95% CI- 0.9,3.3), which is generally similar to the proportion of patients with the event of colitis in the reference safety dataset for melanoma and NSCLC. The overall number and proportion of patients with colitis in the RCC population in KN581 pembrolizumab plus lenvatinib (n=352) was 9 (2.6%) (95% CI-1.2, 4.8), which is generally similar to the proportion of patients with the event of colitis in the reference safety dataset. The overall number and proportion of patients with colitis in the endometrial carcinoma population in KN146 and KN775 pembrolizumab plus lenvatinib (n=530) was 26 (4.9%) (95% CI-3.2, 7.1). The proportion of patients with events of colitis in KN146 and KN775, although higher in

Table SVII.3.1.2: Details of Important Identified Risk: Immune-Mediated Adverse Reactions- Colitis

	frequency than in the reference safety dataset, were generally consistent in nature with the proportion of events of colitis previously reported for pembrolizumab. The overall number and proportion of patients with colitis in the RCC population in KN564 pembrolizumab monotherapy (n=488) was 8 (1.6%) (95% CI-0.7,3.2), which is generally similar to the proportion of patients with the event of colitis in the reference safety dataset for melanoma and NSCLC. The overall number and proportion of patients with colitis in the MSI-H population in KN158 Cohort K and KN164 Cohorts A and B (n=475) was 10 (2.1%) (95% CI-1.0, 3.8) which is generally similar to the proportion of patients with the event of colitis in the reference safety dataset. The overall number and proportion of patients with colitis in the cervical cancer population in KN826 pembrolizumab plus chemotherapy (n=307) was 16 (5.2%) (95% CI-3.0, 8.3). Although more common than in the reference safety dataset, the proportion of events of colitis were generally consistent in nature with the proportion of events of colitis previously reported for pembrolizumab. The overall number and proportion of patients with colitis in the TNBC population in KN522 pembrolizumab in combination with neoadjuvant chemotherapy followed by continued adjuvant pembrolizumab monotherapy group (n=783) was 13 (1.7%) (95% CI-0.9,2.8), which is generally similar to the proportion of patients with the event of colitis in the reference safety dataset. The overall number and proportion of patients with colitis in the melanoma population in KN716 pembrolizumab monotherapy (n=483) was 17 (3.5%) (95% CI-2.1, 5.6), which is generally similar to the proportion of patients with the event of colitis in the reference safety dataset for melanoma and NSCLC. The overall number and proportion of patients with colitis in the gastric cancer population in KN811 pembrolizumab combination therapy (n=350) was 17 (4.9%) (95% CI 2.9, 7.7). Colitis was reported more frequently in the KN811 pembrolizumab safety dataset compared with the RSD, however when adjusted for exposure, the incidences were similar (0.5 vs 0.3 events per 100 person-months) and the proportion of patients with events of colitis were generally consistent in nature with the proportion of patients with events of colitis previously reported for pembrolizumab. The overall number and proportion of patients with colitis in the NSCLC population in KN091 pembrolizumab monotherapy (n=580) was 14 (2.4%) (95% CI-1.3,4.0), which is generally similar to the proportion of patients with the event of colitis in the reference safety dataset. The overall number and proportion of patients with colitis in the gastric cancer population in KN859 pembrolizumab plus chemotherapy (n=785) was 26 (3.3%) (95% CI-2.2, 4.8) which is generally similar to the proportion of patients with the event of colitis in the reference safety dataset. The overall number and proportion of patients with colitis in the BTC population in KN966 pembrolizumab plus chemotherapy (n=529) was 9 (1.7%) (95% CI-0.8,3.2), which is the same as the proportion of patients with events of colitis in the reference safety dataset. The overall number and proportion of patients with colitis in the NSCLC population in KN671 pembrolizumab in combination with chemotherapy neoadjuvant treatment followed by continued adjuvant pembrolizumab monotherapy (n=396) was 5 (1.3%) (95% CI-0.4,2.9), which is generally similar to the overall proportion of patients with events of colitits in the reference safety dataset.

Table SVII.3.1.2: Details of Important Identified Risk: Immune-Mediated Adverse Reactions- Colitis

Outcomes

Percent overall, fatal, not resolved, resolved, and unknown for identified risk of colitis - pembrolizumab (Table includes events for 30 days after discontinuation.)

Colitis (AEOSI)
KN001, KN002 and KN006 Melanoma Subjects and KN001 and KN010 NSCLC Subjects Treated with Pembrolizumab (Treatment Emergent)

		Cumulative NSCLC 001/010 + MEL 001/002/006	
	Outcome	n	(%)
Subjects in population		2,799	
With one or more adverse events	Overall	48	(1.7)
	Fatal	0	(0.0)
	Not Resolved	6	(0.2)
	Resolved	41	(1.5)
	Resolving	1	(0.0)
	Unknown	0	(0.0)

Every subject is counted once on each applicable row.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns is greater than or equal to the percent incidence specified in the report title, after rounding.
Outcome: Resolved = RECOVERED/RESOLVED, Not resolved = NOT RECOVERED/NOT RESOLVED.

In the NSCLC population in KN024 and KN042 (n=790), the outcomes of the 13 patients with events of colitis were as follows: 11 (1.4%) resolved, 2 (0.3%) not resolved. There were no patients with events of colitis with a fatal outcome.

In the NSCLC population in KN189 and KN021 (Cohorts C and G) pembrolizumab plus chemotherapy (n=488), the outcomes of the 14 patients with events of colitis were as follows: 10 (2.1%) resolved, 4 (0.8%) not resolved. There were no patients with events of colitis with a fatal outcome.

In the HL population in KN013, KN087, and KN204 (n=389), the outcomes of the 6 (1.5%) patients with events of colitis were as follows: 6 (1.5%) resolved. There were no patients with events of colitis with a fatal outcome.

In the UC population in KN052 (n=370), the outcomes for the 9 (2.4%) patients with events of colitis were as follows: 5 (1.4%) resolved, 3 (0.8%) not resolved, 1 (0.3%) resolving and in KN045 (n=266), the outcomes for the 6 (2.3%) patients with events of colitis were as follows: 6 (2.3%) resolved. There were no patients with events of colitis with a fatal outcome.

In the HNSCC population in KN040, KN012 and KN055 (n=609), the outcomes for the 4 patients with events were as follows: 3 (0.5%) resolved and 1 (0.2%) not resolved. There were no patients with events of colitis with a fatal outcome.

In the HNSCC population in KN048 pembrolizumab monotherapy group (n=300), the outcomes for the 3 patients with events of colitis were as follows: 1 (0.3%) resolved, 1 (0.3%) resolved with sequalae and 1 (0.3%) resolving. There were no fatal outcomes. In the HNSCC population in KN048 pembrolizumab plus chemotherapy group (n=276), the outcomes for the 7 patients with events of colitis were as follows: 5 (1.8%) resolved and 2 (0.7%) not resolved. There were no patients with events of colitis with a fatal outcome.

In the melanoma population in KN054 (n=509), the outcomes for the 19 patients with events of colitis were as follows: 10 (2.0%) not resolved, 8 (1.6%) resolved, and 1 (0.2%) resolved with sequelae. There were no patients with events of colitis with a fatal outcome.

In the NSCLC population in KN407 and KN021 (Cohort A) (n=303), the outcomes of the 9 patients with events of colitis were as follows: 8 (2.6%) resolved, 1 (0.3%) resolving. There were no patients with events of colitis with a fatal outcome.

In the RCC population in KN426 pembrolizumab plus axitinib (n=429), the outcomes for the 11 patients with events of colitis were as follows: 8 (1.9%) resolved, 1 (0.2%) not resolved, 1 (0.2%)

Table SVII.3.1.2: Details of Important Identified Risk: Immune-Mediated Adverse Reactions- Colitis

	resolving and 1 (0.2%) resolved with sequelae. There were no patients with events of colitis with a fatal outcome. In the CRC population in KN177 (n=153), the outcomes for the 10 patients with events of colitis were as follows: 9 (5.9%) resolved, and 1 (0.7%) not resolved. There were no patients with events of colitis with a fatal outcome. In the esophageal cancer population in KN590 pembrolizumab plus chemotherapy (n=370), the outcomes of the 8 patients with events of colitis were as follows: 6 (1.6%) resolved and 2 (0.5%) resolving. In the TNBC population in KN355 pembrolizumab plus chemotherapy group (n=596), the outcomes for the 11 patients with events of colitis were as follows: 8 (1.3%) resolved, 2 (0.3%) not resolved, and 1 (0.2%) resolved with sequelae. There were no patients with events of colitis with a fatal outcome. In the RCC population in KN581 pembrolizumab plus lenvatinib (n=352), the outcomes for the 9 patients with events of colitis were as follows: 6 (1.7%) resolved, 2 (0.6%) not resolved, and 1 (0.3%) resolving. There were no patients with events of colitis with a fatal outcome. In the endometrial carcinoma population in KN146 and KN775 pembrolizumab plus lenvatinib (n=530), the outcomes for the 26 patients with events of colitis were as follows: 16 (3.0%) resolved, 7 (1.3%) not resolved, 1 (0.2%) resolving and 1 (0.2%) resolved with sequelae. There was 1 (0.2%) patient with an event of colitis with a fatal outcome. In the RCC population in KN564 pembrolizumab monotherapy (n=488), the outcomes for the 8 patients with events of colitis were as follows: 6 (1.2%) resolved, 1 (0.2%) resolved with sequelae, and 1 (0.2%) not resolved. There were no patients with events of colitis with a fatal outcome. In the MSI-H population in KN158 Cohort K and KN164 Cohorts A and B (n=475), the outcome for the 10 (2.1%) patients with events of colitis was resolved. There were no patients with events of colitis with a fatal outcome. In the cervical cancer population in KN826 pembrolizumab plus chemotherapy (n=307), the outcomes for the 16 patients with events of colitis were as follows: 11 (3.6%) resolved, 2 (0.7%) resolving, and 3 (1.0%) not resolved. There were no patients with events of colitis with a fatal outcome. In the TNBC population in KN522 pembrolizumab in combination with neoadjuvant chemotherapy followed by continued adjuvant pembrolizumab monotherapy group (n=783), the outcomes for the 13 patients with events of colitis were as follows: 12 (1.5%) resolved, and 1 (0.1%) not resolved. There were no patients with events of colitis with a fatal outcome. In the melanoma population in KN716 pembrolizumab monotherapy (n=483), the outcome for the 17 patients with events of colitis were as follows: 12 (2.5%) resolved, 2 (0.4%) not resolved, 2 (0.4%) resolving, and 1 (0.2%) resolved with sequelae. There were no patients with events of colitis with a fatal outcome. In the gastric cancer population in KN811 pembrolizumab combination therapy (n=350), the outcomes for the 17 patients with events of colitis were as follows: 12 (3.4%) resolved, 3 (0.9%) not resolved. 1 (0.3%) resolving and 1 (0.3%) resolved with sequelae. There were no patients with events of colitis with a fatal outcome. In the NSCLC population in KN091 pembrolizumab monotherapy (n=580), the outcomes for the 14 patients with events of colitis were as follows: 12 (2.1%) resolved, 1 (0.2%) resolved with sequelae, and 1 (0.2%) not resolved. There were no patients with events of colitis with a fatal outcome. In the gastric cancer population in KN859 pembrolizumab plus chemotherapy (n=785), the outcomes for the 26 patients with events of colitis were as follows: 22 (2.8%) resolved, 2 (0.3%) not resolved, and 2 (0.3%) resolving. There were no patients with an event of colitis with a fatal outcome. In the BTC population in KN966 pembrolizumab plus chemotherapy (n=529), the worst reported outcomes for the 9 patients with events of colitis were as follows: 7 (1.3%) resolved, 1 (0.2%) not resolved and 1 (0.2%) resolving. There were no patients with events of colitis with a fatal outcome.

Table SVII.3.1.2: Details of Important Identified Risk: Immune-Mediated Adverse Reactions- Colitis

<table>
<tr><td></td><td>In the NSCLC population in KN671 pembrolizumab in combination with chemotherapy as neoadjuvant treatment followed by continued adjuvant pembrolizumab monotherapy group (n=396), the outcomes for the 5 patients with events of colitits were as follows: 4 (1.0%) resolved, and 1 (0.3%) resolving. There were no patients with events of colitis with a fatal outcome.
Aggregate Review
Review of the ASE dataset (n=7730) yielded 2 fatal cases of colitis. Review of the global safety database yielded the following: 2 fatal cases from ongoing interventional monotherapy clinical trials (corresponding to the 2 cases from ASE) and 11 fatal cases from the PM or non-interventional environment. Of the 11, there were 10 cases in which fatal colitis was the only Grade 5 event and 1 case that reported a Grade 5 colitis, as well as a Grade 5 MNP or other related fatal event(s).</td></tr>
<tr><td>Seriousness</td><td>Percent serious for identified risk of colitis - Pembrolizumab (All Serious AEs for 90 days after discontinuation were included.)
Colitis – Serious (AEOSI)
KN001, KN002 and KN006 Melanoma Subjects and KN001 and KN010 NSCLC Patients Treated with Pembrolizumab (Treatment Emergent)
<table>
<tr><td></td><td colspan="2">Cumulative NSCLC 001/010 + MEL 001/002/006</td></tr>
<tr><td></td><td>n</td><td>(%)</td></tr>
<tr><td>Subjects in population</td><td>2,799</td><td></td></tr>
<tr><td>with one or more adverse events</td><td>32</td><td>(1.1)</td></tr>
<tr><td></td><td></td><td></td></tr>
<tr><td>Colitis</td><td>30</td><td>(1.1)</td></tr>
<tr><td>Colitis microscopic</td><td>1</td><td>(0.0)</td></tr>
<tr><td>Enterocolitis</td><td>1</td><td>(0.0)</td></tr>
<tr><td colspan="3">Every subject 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.
Include all treated subjects in KN001 Part B1, B2, B3, D, C, F1, F2, F3 and all subjects in KN002 treated with Pembrolizumab in the original phase, and all subjects in KN006 and KN010 treated with Pembrolizumab.</td></tr>
</table>
Of the 13 patients with events of colitis in the NSCLC population in KN024 and KN042 (n=790), 8 (1.0%) experienced serious events of colitis.
Of the 14 patients with events of colitis in the NSCLC population in KN189 and KN021 (Cohorts C and G) pembrolizumab plus chemotherapy (n=488), 5 (1.0%) experienced serious events of colitis.
Of the 6 patients with events of colitis in the HL population in KN013, KN087, and KN204 (n=389), 2 (0.5%) experienced serious events of colitis.
Of the 9 patients with events of colitis in the UC population in KN052 (n=370), 2 (0.5%) experienced serious events of colitis and of the 6 patients with events of colitis in the UC population in KN045 (n=266), 5 (1.9%) experienced serious events of colitis.
Of the 4 patients with events of colitis in the HNSCC population (n=609), all 4 (0.7%) events of colitis experienced serious events of colitis.
Of the 3 patients with events of colitis in the HNSCC population in KN048 pembrolizumab monotherapy group (n=300), 2 (0.7%) experienced serious events of colitis. Of the 7 patients with events of colitis in the HNSCC population in KN048 pembrolizumab plus chemotherapy group (n=276), 2 (0.7%) experienced serious events of colitis s.
Of the 19 patients with events of colitis in the melanoma population in KN054 (n=509), 10 (2.0%) experienced serious events of colitis.
Of the 9 patients with events of colitis in the NSCLC population in KN407 and KN021 (Cohort A) (n=303), 7 (2.3%) experienced serious events of colitis.
Of the 11 patients with events of colitis in the RCC population in KN426 pembrolizumab plus axitinib (n=429), 6 (1.4%) experienced serious events of colitis.
Of the 10 patients with events of colitis in the CRC population in KN177 (n=153), 5 (3.3%) experienced serious events of colitis.</td></tr>
</table>

Table SVII.3.1.2: Details of Important Identified Risk: Immune-Mediated Adverse Reactions- Colitis

	Of the 8 patients with events of colitis in the esophageal cancer population in KN590 pembrolizumab plus chemotherapy (n=370), 6 (1.6%) experienced serious events of colitis. Of the 11 patients with events of colitis in the TNBC population in KN355 pembrolizumab plus chemotherapy group (n=596), 1 (0.2%) experienced a serious event of colitis. Of the 9 patients with events of colitis in the RCC population in KN581 pembrolizumab plus lenvatinib (n=352), 4 (1.1%) experienced serious events of colitis. Of the 26 patients with events of colitis in the endometrial carcinoma population in KN146 and KN775 pembrolizumab plus lenvatinib (n=530), 10 (1.9%) experienced serious events of colitis. Of the 8 patients with events of colitis in the RCC population in KN564 pembrolizumab monotherapy (n=488), 6 (1.2%) experienced serious events of colitis. Of the 10 patients with events of colitis in the MSI-H population in KN158 Cohort K and KN164 Cohorts A and B (n=475), 2 (0.4%) experienced serious events of colitis. Of the 16 patients with events of colitis in the cervical cancer population in KN826 pembrolizumab plus chemotherapy (n=307), 5 (1.6%) experienced serious events of colitis. Of the 13 patients with events of colitis in the TNBC population in KN522 pembrolizumab in combination with neoadjuvant chemotherapy followed by continued adjuvant pembrolizumab monotherapy group (n=783), 7 (0.9%) experienced serious events of colitis. Of the 17 patients with events of colitis in the melanoma population in KN716 pembrolizumab monotherapy (n=483), 7 (1.4%) experienced serious events of colitis. Of the 17 patients with events of colitis in gastric cancer population in KN811 pembrolizumab combination therapy (n=350), 6 (1.7%) experienced serious events of colitis. Of the 14 patients with events of colitis in the NSCLC population in KN091 pembrolizumab monotherapy (n=580), 4 (0.7%) experienced serious events of colitis. Of the 26 patients with events of colitis in the gastric cancer population in KN859 pembrolizumab plus chemotherapy (n=785), 21 (2.7%) experienced a serious event of colitis. Of the 9 patients with events of colitis in the BTC population in KN966 pembrolizumab plus chemotherapy (n=529), 6 (1.1%) experienced serious events of colitis. Of the 5 patients with events of colitis in the NSCLC population in KN671 pembrolizumab in combination with chemotherapy as neoadjuvant treatment followed by continued adjuvant pembrolizumab monotherapy (n=396), 2 (0.5%) experienced serious events of colitis.

Table SVII.3.1.2: Details of Important Identified Risk: Immune-Mediated Adverse Reactions- Colitis

Severity and Nature of the Risk

Identified treatment emergent adverse events (AE) of colitis (all events) in participants summarized by grade– pembrolizumab. (AEs for 30 days after discontinuation were included)

Colitis (AEOSI)
KN001, KN002 and KN006 Melanoma Subjects and KN001 and KN010 NSCLC Patients Treated with Pembrolizumab (Treatment Emergent)

	Cumulative NSCLC 001/010 + MEL 001/002/006	
	n	(%)
Subjects in population	2,799	
with one or more adverse events	48	(1.7)
Colitis	45	(1.6)
Grade 1	5	(0.2)
Grade 2	9	(0.3)
Grade 3	29	(1.0)
Grade 4	2	(0.1)
Colitis microscopic	2	(0.1)
Grade 1	1	(0.0)
Grade 2	1	(0.0)
Enterocolitis	1	(0.0)
Grade 3	1	(0.0)
Autoimmune colitis	1	(0.0)
Grade 2	1	(0.0)

Every subject is counted a single time for each applicable specific adverse event. A subject with multiple adverse events within a system organ class is counted a single time for that system organ class.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns is greater than or equal to the incidence specified in the report title, after rounding.
Only the highest reported grade of a given adverse event is counted for the individual subject.
Grades are based on NCI CTCAE version 4.0.

In the NSCLC population in KN024 and KN042 (n=790), there were 7 (0.9%) patients with Grade 3 events of colitis. There were no patients with Grade 4 or 5 events of colitis.

In the NSCLC population in KN189 and KN021 (Cohorts C and G) pembrolizumab plus chemotherapy (n=488), there were 5 (1.0%) patients with Grade 3 events of colitis. There were no patients with Grade 4 or 5 events of colitis.

In the HL population in KN013, KN087, and KN204 (n=389), there were 3 (0.8%) patients with Grade 3 events of colitis. There were no patients with Grade 4 or 5 events of colitis.

In the UC population in KN052 (n=370), there were 3 (0.8%) patients with Grade 3 events, 1 (0.3%) patient with a Grade 4 event, and no patients with Grade 5 events of colitis; in the UC population in KN045 (n=266), there were 3 (1.1%) patients with Grade 3 events and no patients with Grade 4 or 5 events of colitis.

In the HNSCC population in KN040, KN012 and KN055 (n=609), there was 1 (0.2%) patient with a Grade 3 event of colitis. There were no patients with Grade 4 or 5 events of colitis.

In the HNSCC population in KN048 pembrolizumab monotherapy group (n=300), there were 2 (0.7%) patients with Grade 3 events of colitis. There were no patients with Grade 4 or 5 events of colitis. In the pembrolizumab plus chemotherapy group (n=276), there were 2 (0.7%) patients with Grade 3 events of colitis. There were no patients with Grade 4 or 5 events of colitis.

In the melanoma population in KN054 (n=509), there were 10 (2.0%) patients with Grade 3 events of colitis. There were no patients with Grade 4 or 5 events of colitis.

In the NSCLC population in KN407 and KN021 (Cohort A) (n=303), there were 4 (1.3%) patients with Grade 3 events and 2 (0.7%) patients with Grade 4 events. There were no patients with Grade 5 events of colitis.

In the RCC population in KN426 pembrolizumab plus axitinib (n=429), there were 8 (1.9%) patients with Grade 3 events of colitis. There were no patients with Grade 4 or 5 events of colitis.

Table SVII.3.1.2: Details of Important Identified Risk: Immune-Mediated Adverse Reactions- Colitis

	In the CRC population in KN177 (n=153) there were 3 (2.0%) patients with Grade 3 events and 2 (1.3%) patients with Grade 4 events of colitis. There were no patients with Grade 5 events of colitis reported. In the esophageal cancer population in KN590 pembrolizumab plus chemotherapy (n=370), there were 4 (1.1%) patients with Grade 3 events of colitis. There were no patients with Grade 4 or 5 events of colitis. In the TNBC population in KN355 pembrolizumab plus chemotherapy group (n=596), there were 2 (0.3%) patients with Grade 3 events of colitis. There were no patients with Grade 4 or 5 events of colitis. In the RCC population in KN581 pembrolizumab plus lenvatinib (n=352) there were 4 (1.1%) patients with Grade 3 events of colitis. There were no patients with Grade 4 or 5 events of colitis. In the endometrial carcinoma population in KN146 and KN775 pembrolizumab plus lenvatinib (n=530) there were 8 (1.5%) patients with Grade 3, 1 (0.2%) patient with a Grade 4, and 1 (0.2%) patient with a Grade 5 events of colitis. In the RCC population in KN564 pembrolizumab monotherapy (n=488) there were 5 (1.0%) patients with Grade 3 events of colitis. There were no patients with Grade 4 or 5 events of colitis. In the MSI-H population in KN158 Cohort K and KN164 Cohorts A and B (n=475), there was 1 (0.2%) patient with a Grade 3 and 1 (0.2%) patient with a Grade 4 event of colitis. There were no patients with Grade 5 events of colitis reported. In the cervical cancer population in KN826 pembrolizumab plus chemotherapy (n=307), there were 5 (1.6%) patients with Grade 3 and no patients with Grade 4 or 5 events of colitis reported. In the TNBC population in KN522 pembrolizumab in combination with neoadjuvant chemotherapy followed by continued adjuvant pembrolizumab monotherapy group (n=783) there were 5 (0.6%) patients with Grade 3 events, and 1 (0.1%) patient with a Grade 4 event of colitis. There were no patients with Grade 5 events of colitis reported. In the melanoma population in KN716 pembrolizumab monotherapy (n=483), there were 8 (1.7%) patients with Grade 3 events of colitis. There were no patients with Grade 4 or 5 events of colitis. In the gastric cancer population in KN811 pembrolizumab combination therapy (n=350), there were 9 (2.6%) patients with Grade 3 events of colitis. There were no patients with Grade 4 and 5 events of colitis. In the NSCLC population in KN091 pembrolizumab monotherapy (n=580) there were 4 (0.7%) patients with Grade 3 events of colitis. There were no patients with Grade 4 or 5 events of colitis. In the gastric cancer population in KN859 pembrolizumab plus chemotherapy (n=785), there were 18 (2.3%) patients with a Grade 3, and 1 (0.1%) patient with a Grade 4 event of colitis reported. There were no patients with a Grade 5 event of colitis reported. In the BTC population in KN966 pembrolizumab plus chemotherapy (n=529), there were 4 (0.8%) patients with Grade 3 events and 1 (0.2%) patient with a Grade 4 event of colitis. There were no patients with Grade 5 events of colitis. In the NSCLC population in KN671 pembrolizumab in combination with chemotherapy as neoadjuvant treatment followed by continued adjuvant pembrolizumab monotherapy (n=396) there were 3 (0.8%) patients with Grade 3 events of colitis, there were no patients with Grade 4 or 5 events of colitis reported. In the global safety database through 31-DEC-2017, (pembrolizumab monotherapy trials only), there were 2 Grade 5 clinical trial reports of colitis. Review of pembrolizumab clinical trial data from ongoing studies and postmarketing data regarding immune-mediated colitis, including fatal cases, is consistent with the risk as characterized in this RMP.
Risk Factors and Risk Groups:	No specific risk factors for colitis and diarrhea associated with pembrolizumab were identified.
Preventability:	Although the development of colitis cannot be completely prevented; patients should be monitored for signs and symptoms of colitis and if they develop, other causes excluded. Withholding/discontinuation of pembrolizumab and appropriate medical intervention including corticosteroids following the onset of colitis may result in recovery.

Table SVII.3.1.2: Details of Important Identified Risk: Immune-Mediated Adverse Reactions- Colitis

Impact on the Risk-Benefit Balance of the Product:	Severe colitis may be life-threatening or fatal in individual patients. However, given the fatal outcome of untreated cancer, the risk of colitis which generally can be managed, is outweighed by the potential benefit of pembrolizumab treatment.
Public Health Impact:	This risk has minimal public health impact outside its effect on individual patients.

Table SVII.3.1.3: Details of Important Identified Risk: Immune-Mediated Adverse Reactions- Hepatitis

Important Identified Risk:	Immune-mediated Hepatitis
Potential Mechanisms:	Pembrolizumab is a potent and highly-selective humanized monoclonal antibody (mAb) of the Immunoglobulin G4 (IgG4)/kappa isotype directed to the programmed cell death-1 (PD-1) receptor and designed to directly block the interaction between the receptor and its ligands, PD-L1 and PD-L2. The PD-1 pathway represents a major immune control switch which may be engaged by tumor cells to overcome active T-cell immune surveillance. A potential mechanism of action is T-cell activation in proximity to normal tissue resulting inflammation and injury to normal liver tissue.
Evidence Source(s) and Strength of Evidence:	Review of pembrolizumab clinical trial data, post-marketing experience and literature regarding hepatitis represent sufficient evidence of a causal association with pembrolizumab exposure. CTD 2.7.4 Please reference evidence source cited in Table SVII.3.1.1; Details of Important Identified Risk: Immune-Mediated Pneumonitis
Characterisation of the Risk: Immune-mediated Hepatitis	
Frequency with 95%CI	95% Confidence Interval for the Overall Incidence (%) of Hepatitis KN001, KN002 and KN006 Melanoma Subjects and KN001 and KN010 NSCLC Subjects Treated with Pembrolizumab

	Cumulative MEL 001/002/006 + NSCLC 001/010	
	n (%)	95% CI
Hepatitis	18 (0.6)	(0.4,1.0)

The overall number and proportion of patients with hepatitis reported in the NSCLC population in KN024 and KN042 (n=790) was 10 (1.3%) (95% CI-. (0.6, 2.3), which is generally similar to the proportion of patients with the event of hepatitis in the reference safety dataset for melanoma and NSCLC.

The overall number and proportion of patients with hepatitis in the NSCLC population in KN189 and KN021 (Cohorts C and G) pembrolizumab plus chemotherapy (n=488) was 5 (1%) (95% CI-0.3, 2.4), which is generally similar to the proportion of patients with the event of hepatitis in the reference safety dataset for melanoma and NSCLC.

The overall number and proportion of patients with hepatitis in the HL population in KN013, KN087, and KN204 (n=389) was 2 (0.5%) (95%CI-0.1, 1.8), which is generally similar to the overall proportion of patients with the event of hepatitis in the reference safety dataset for melanoma and NSCLC.

The overall number and proportion of patients with hepatitis in the UC population in KN052 (n=370) was 4 (1.1%) (95%CI-0.3,2.7), which is generally similar to the proportion of patients with the event of hepatitis in the reference safety dataset for melanoma and NSCLC.

There were no patients with events of hepatitis reported in the UC population in KN045.

The overall number and proportion of patients with hepatitis in the HNSCC population in KN040, KN012 and KN055 (n=609) was 6 (1.0%) (95% CI- 0.4,2.1), which is generally similar to the

Table SVII.3.1.3: Details of Important Identified Risk: Immune-Mediated Adverse Reactions- Hepatitis

	proportion of patients with the event of hepatitis in the reference safety dataset for melanoma and NSCLC. The overall number and proportion of patients with hepatitis in the HNSCC population in KN048 pembrolizumab monotherapy (n=300) and pembrolizumab plus chemotherapy (n=276) groups were 2 (0.7%) (95% CI- 0.1,2.4) and 0 (0) (95% CI-0, 1.3) respectively, which is generally similar to the proportion of patients with the event of hepatitis in the reference safety dataset for melanoma and NSCLC. The overall number and proportion of patients with hepatitis in the melanoma population in KN054 (n=509) was 9 (1.8%) (95% CI-0.8, 3.3). The proportion of patients with events of hepatitis in KN054 although somewhat more common than in the reference safety dataset were generally consistent in nature with the proportion of events of hepatitis previously reported for pembrolizumab. The overall number and proportion of patients with hepatitis in the NSCLC population in KN407 and KN021 (Cohort A) (n=303), was 5 (1.7%) (95% CI-0.5, 3.8), which is generally similar to the proportion of patients with the event of hepatitis in the reference safety dataset for melanoma and NSCLC. The overall number and proportion of patients with hepatitis in the RCC population in KN426 pembrolizumab plus axitinib (n=429) was 12 (2.8%) (95% CI-1.5,4.8), which is higher than the proportion of patients with the event of hepatitis in the reference safety dataset for melanoma and NSCLC. The overall number and proportion of patients with hepatitis in the CRC population in KN177 (n=153) was 4 (2.6%) (95% CI-(0.7,6.6)) which is generally similar to the proportion of patients with the event of hepatitis in the reference safety dataset. The overall number and proportion of patients with hepatitis in the esophageal cancer population in KN590 pembrolizumab plus chemotherapy (n=370) was 5 (1.4%) (95% CI-0.4,3.1), which is generally similar to the proportion of patients with the event of hepatitis in the reference safety dataset for melanoma and NSCLC. The overall number and proportion of patients with hepatitis in the TNBC population in KN355 pembrolizumab plus chemotherapy group (n=596) was 5 (0.8%) (95% CI-0.3,1.9), which is generally similar to the proportion of patients with the event of hepatitis in the reference data set for melanoma and NSCLC. The overall number and proportion of patients with hepatitis in the RCC population in KN581 pembrolizumab plus lenvatinib (n=352) was 7 (2.0%) (95% CI-0.8,4.1), which is generally similar to the proportion of patients with the event of hepatitis in the reference safety dataset. The overall number and proportion of patients with hepatitis in the endometrial carcinoma population in KN146 and KN775 pembrolizumab plus lenvatinib (n=530) was 8 (1.5%) (95% CI-0.7, 3.0) which is generally similar to the proportion of patients with the event of hepatitis in the reference safety dataset. The overall number and proportion of patients with hepatitis in the RCC population in KN564 pembrolizumab monotherapy (n=488) was 5 (1%) (95% CI-0.3,2.4), which is generally similar to the proportion of patients with the event of hepatitis in the reference safety dataset for melanoma and NSCLC. The overall number and proportion of patients with hepatitis in the MSI-H population in KN158 Cohort K and KN164 Cohorts A and B (n=475) was 4 (0.8%) (95% CI-0.2,2.1) which is generally similar to the proportion of patients with the event of hepatitis in the reference safety dataset. The overall number and proportion of patients with hepatitis in the cervical cancer population in KN826 pembrolizumab plus chemotherapy (n=307) was 5 (1.6%) (95% CI-0.5, 3.8), which is generally similar to the proportion of patients with the event of hepatitis in the reference safety dataset. The overall number and proportion of patients with hepatitis in the TNBC population in KN522 pembrolizumab in combination with neoadjuvant chemotherapy followed by continued adjuvant pembrolizumab monotherapy group (n=783) was 11 (1.4%) (95% CI-0.7,2.5), which is generally similar to the proportion of patients with the event of hepatitis in the reference safety dataset. The overall number and proportion of patients with hepatitis in the melanoma population in KN716 pembrolizumab monotherapy (n=483) was 10 (2.1%) (95% CI-1.0, 3.8), which is generally similar

Table SVII.3.1.3: Details of Important Identified Risk: Immune-Mediated Adverse Reactions- Hepatitis

<table>
<tr><td></td><td>to the proportion of patients with the event of hepatitis in the reference safety dataset for melanoma and NSCLC.

The overall number and proportion of patients with hepatitis in the gastric cancer population in KN811 pembrolizumab combination therapy (n=350) was 2 (0.6%) (95% CI-0.1, 2.1), which is the same as the proportion of patients with the event of hepatitis in the reference safety dataset.

The overall number and proportion of patients with hepatitis in the NSCLC population in KN091 pembrolizumab monotherapy (n=580) was 10 (1.7%) (95% CI-0.8,3.1), which is generally similar to the proportion of patients with the event of hepatitis in the reference safety dataset

The overall number and proportion of patients with hepatitis in the gastric cancer population in KN859 pembrolizumab plus chemotherapy (n=785) was 9 (1.1%) (95% CI-0.5, 2.2), which is generally similar to the proportion of patients with the events of hepatitis in the reference safety dataset.

The overall number and proportion of patients with hepatitis in the BTC population in KN966 pembrolizumab plus chemotherapy (n=529) was 9 (1.7%) (95% CI-0.8, 3.2), which is generally similar to the proportion of patients with the events of hepatitis in the reference safety dataset.

The overall number and proportion of patients with hepatitis in the NSCLC population in KN671 pembrolizumab in combination with chemotherapy neoadjuvant treatment followed by continued adjuvant pembrolizumab monotherapy (n=396) was 3 (0.8%) (95% CI-0.2, 2.2), which is generally similar to the overall proportion of patients with events of hepatitis in the reference safety dataset.</td></tr>
<tr><td>Outcomes</td><td>Percent overall, fatal, not resolved, resolved, and unknown for identified risk of hepatitis - pembrolizumab. (Table includes events for 30 days after discontinuation.)

Hepatitis (AEOSI)
KN001, KN002 and KN006 Melanoma Subjects and KN001 and KN010 NSCLC Subjects Treated with Pembrolizumab
(Treatment Emergent)

<table>
<tr><td></td><td></td><td colspan="2">Cumulative NSCLC 001/010 + MEL 001/002/006</td></tr>
<tr><td></td><td>Outcome</td><td>n</td><td>(%)</td></tr>
<tr><td>Subjects in population</td><td></td><td>2,799</td><td></td></tr>
<tr><td>With one or more adverse events</td><td>Overall</td><td>18</td><td>(0.6)</td></tr>
<tr><td></td><td>Fatal</td><td>0</td><td>(0.0)</td></tr>
<tr><td></td><td>Not Resolved</td><td>2</td><td>(0.1)</td></tr>
<tr><td></td><td>Resolved</td><td>14</td><td>(0.5)</td></tr>
<tr><td></td><td>Resolving</td><td>2</td><td>(0.1)</td></tr>
<tr><td></td><td>Unknown</td><td>0</td><td>(0.0)</td></tr>
<tr><td colspan="4">Every subject is counted once on each applicable row.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns is greater than or equal to the percent incidence specified in the report title, after rounding.
Outcome: Resolved = RECOVERED/RESOLVED, Not resolved = NOT RECOVERED/NOT RESOLVED.</td></tr>
</table>

In the NSCLC population in KN024 and KN042, the outcomes of the 10 patients with events of hepatitis were as follows: 9 (1.1%) resolved, 1 (0.1%) resolving. There were no patients with events of hepatitis with a fatal outcome.

In the NSCLC population in KN189 and KN021 (Cohorts C and G) pembrolizumab plus chemotherapy (n=488), the outcomes of the 5 patients with events were as follows: 3 (0.6%) resolved, 1 (0.2%) not resolved, 1 (0.2%) unknown. There were no patients with events of hepatitis with a fatal outcome.

In the HL population in KN013, KN087, and KN204 (n=389), the outcome of the 2 patients with events of hepatitis were as follows: 1 resolved (0.3%) and 1 not resolved (0.3%). There were no patients with events of hepatitis with a fatal outcome.

In the UC population in KN052 (n=370), the outcomes for the 4 patients with events of hepatitis were as follows: 4 (1.1%) resolved. There were no patients with events of hepatitis with a fatal outcome.</td></tr>
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Table SVII.3.1.3: Details of Important Identified Risk: Immune-Mediated Adverse Reactions- Hepatitis

	In the HNSCC population in KN040, KN012 and KN055 (n=609), the outcomes for the 6 patients with events of hepatitis were as follows: 4 (0.7%) resolved, 1 (0.2%) resolving and 1 (0.2%) not resolved. There were no patients with events of hepatitis with a fatal outcome. In the HNSCC population in KN048 pembrolizumab monotherapy group (n=300), the outcomes for the 2 patients with events of hepatitis were as follows: 1 (0.3%) resolved and 1 (0.3%) resolving. There were no patients with events of hepatitis with a fatal outcome. In the HNSCC population in KN048 pembrolizumab plus chemotherapy group (n=276), there were no patients with events of hepatitis. In the melanoma population in KN054 (n=509), the outcomes for the 9 patients with events of hepatitis were as follows: 6 (1.2%) not resolved and 3 (0.6%) resolved. There were no patients with events of hepatitis with a fatal outcome. In the NSCLC population in KN407 and KN021 (Cohort A) (n=303), the outcomes of the 5 patients with events of hepatitis were as follows: 3 (1.0%) resolved, 1 (0.3%) not resolved and 1 (0.3%) resolving. There were no patients with events of hepatitis with a fatal outcome. In the RCC population in KN426 pembrolizumab plus axitinib (n=429), the outcomes for the 12 patients with events of hepatitis were as follows: 9 (2.1%) resolved, 2 (0.5%) resolving and 1 (0.2%) resolved with sequelae. There were no patients with events of hepatitis with a fatal outcome. In the CRC population in KN177 (n=153), the outcomes for the 4 patients with events of hepatitis were as follows: 4 (2.6%) resolved. There were no patients with events of hepatitis with a fatal outcome. In the esophageal cancer population in KN590 pembrolizumab plus chemotherapy (n=370), the outcomes for the 5 patients with events of hepatitis were as follows: 2 (0.5%) resolved and 3 (0.8%) not resolved. There were no patients with events of hepatitis with a fatal outcome. In the TNBC population in KN355 pembrolizumab plus chemotherapy group (n=596), the outcomes for the 5 patients with events of hepatitis were as follows: 2 (0.3%) resolved, 2 (0.3%) not resolved, and 1 (0.2%) resolving. There were no patients with events of hepatitis with a fatal outcome. In the RCC population in KN581 pembrolizumab plus lenvatinib (n=352), the outcomes for the 7 patients with events of hepatitis were as follows: 3 resolved (0.9%), 2 (0.6%) resolving, 1 (0.3%) not resolved. There was 1 (0.3%) patient with an event of hepatitis that resulted in a fatal outcome. In the endometrial carcinoma population in KN146 and KN775 pembrolizumab plus lenvatinib (n=530), the outcomes for the 8 patients with events of hepatitis were as follows: 4 (0.8%) resolved, 3 (0.6%) not resolved, and 1 (0.2%) resolved with sequelae. There were no patients with events of hepatitis with a fatal outcome. In the RCC population in KN564 pembrolizumab monotherapy (n=488), the outcomes for the 5 patients with events of hepatitis were as follows: 5 (1%) resolved. There were no events of hepatitis with a fatal outcome. In the MSI-H population in KN158 Cohort K and KN164 Cohorts A and B (n=475), the outcomes for the 4 (0.8%) patients with events of hepatitis were as follows: 3 (0.6%) resolved and 1 (0.2%) not resolved. There were no patients with events of hepatitis with a fatal outcome. In the cervical cancer population in KN826 pembrolizumab plus chemotherapy (n=307), the outcomes for the 5 patients with events of hepatitis were as follows: 1 (0.3%) resolving, and 4 (1.3%) resolved. There were no patients with events of hepatitis with a fatal outcome. In the TNBC population in KN522 pembrolizumab in combination with neoadjuvant chemotherapy followed by continued adjuvant pembrolizumab monotherapy group (n=783), the outcomes for the 11 patients with events of hepatitis were as follows: 8 (1.0%) resolved, and 3 (0.4%) not resolved. There were no patients with events of hepatitis with a fatal outcome. In the melanoma population in KN716 pembrolizumab monotherapy (n=483), the outcomes for the 10 patients with events of hepatitis were as follows: 6 (1.2%) resolved, 2 (0.4%) resolving, 1 (0.2%) not resolved, and 1 (0.2%) resolved with sequelae. There were no patients with events of hepatitis with a fatal outcome.

Table SVII.3.1.3: Details of Important Identified Risk: Immune-Mediated Adverse Reactions- Hepatitis

<table>
<tr><td></td><td>In the gastric cancer population in KN811 pembrolizumab combination therapy (n=350), the outcome for the 2 events of hepatitis was as follows: 1 (0.3%) resolved. There was 1 (0.3%) patient with an event of hepatitis that resulted in a fatal outcome.

In the NSCLC population in KN091 pembrolizumab monotherapy (n=580), the outcomes for the 10 patients with events of hepatitis were as follows: 7 (1.2%) resolved, 2 (0.3%) not resolved, and 1 (0.2%) resolved with sequelae. There were no patients with events of hepatitis with a fatal outcome.

In the gastric cancer population in KN859 pembrolizumab plus chemotherapy (n=785), the outcomes for the 9 patients with events of hepatitis were as follows: 6 (0.8%) resolved, 1 (0.1%) not resolved, 1 (0.1%) resolving, and 1 (0.1%) unknown. There were no patients with an event of hepatitis with a fatal outcome.

In the BTC population in KN966 pembrolizumab plus chemotherapy (n=529), the worst reported outcomes for the 9 patients with events of hepatitis were as follows: 8 (1.5%) resolved and 1 (0.2%) not resolved. There were no patients with events of hepatitis with a fatal outcome.

In the NSCLC population in KN671 pembrolizumab in combination with chemotherapy as neoadjuvant treatment followed by continued adjuvant pembrolizumab monotherapy group (n=396), the outcomes for the 3 patients with events of hepatitis were as follows: 2 (0.5%) resolved, and 1 (0.3%) resolved with sequelae. There were no patients with events of hepatitis with a fatal outcome.

Aggregate Review

Review of the ASE dataset (n=7730) yielded no fatal cases of hepatitis. Review of the global safety database yielded the following: 4 fatal cases from ongoing interventional monotherapy clinical trials and 9 fatal cases from the PM or non-interventional environment. Of the 9, all were cases in which fatal hepatitis was the only Grade 5 event.</td></tr>
<tr><td>Seriousness</td><td>Percent serious for identified risk of hepatitis - Pembrolizumab. (Serious AEs for 90 days after discontinuation were included.)

Hepatitis - Serious (AEOSI)
KN001, KN002 and KN006 Melanoma Subjects and KN001 and KN010 NSCLC Subjects Treated with Pembrolizumab
(Treatment Emergent)

<table>
<tr><td></td><td colspan="2">Cumulative NSCLC 001/010 + MEL 001/002/006</td></tr>
<tr><td></td><td>n</td><td>(%)</td></tr>
<tr><td>Subjects in population</td><td>2,799</td><td></td></tr>
<tr><td>with one or more adverse events</td><td>11</td><td>(0.4)</td></tr>
<tr><td></td><td></td><td></td></tr>
<tr><td>Autoimmune hepatitis</td><td>8</td><td>(0.3)</td></tr>
<tr><td>Drug-induced liver injury</td><td>2</td><td>(0.1)</td></tr>
<tr><td>Hepatitis</td><td>2</td><td>(0.1)</td></tr>
<tr><td colspan="3">Every subject 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.
Include all treated subjects in KN001 Part B1, B2, B3, D, C, F1, F2, F3 and all subjects in KN002 treated with Pembrolizumab in the original phase, and all subjects in KN006 and KN010 treated with Pembrolizumab.</td></tr>
</table>

Of the 10 patients with events of hepatitis in the NSCLC population in KN024 and KN042, 6 (0.8%) experienced serious events of hepatitis.

Of the 5 patients with events of hepatitis in the NSCLC population in KN189 and KN021 (Cohorts C and G) pembrolizumab plus chemotherapy (n=488), 3 (0.6%) experienced serious events of hepatitis.

Of the 2 patients with events of hepatitis in the HL population in KN013, KN087, and KN204 (n=389), 2 (0.5%) experienced serious events of hepatitis.

Of the 4 patients with events of hepatitis in the UC population in KN052 (n=370), 3 (0.8%) experienced serious events of hepatitis.</td></tr>
</table>

Table SVII.3.1.3: Details of Important Identified Risk: Immune-Mediated Adverse Reactions- Hepatitis

	Of the 6 patients with events of hepatitis in the HNSCC population in KN040, KN012 and KN055 (n=609), 2 (0.3%) experienced serious events of hepatitis. Of the 2 patients with events of hepatitis in the HNSCC population in KN048 pembrolizumab monotherapy group (n=300), 2 (0.7%) experienced serious events of hepatitis. There were no patients with serious events of hepatitis reported in the pembrolizumab plus chemotherapy group (n=276). Of the 9 patients with events of hepatitis in the melanoma population in KN054 (n=509), 4 (0.8%) experienced serious events of hepatitis. Of the 5 patients with events of hepatitis in the NSCLC population in KN407 and KN021 (Cohort A) (n=303), 2 (0.7%) experienced serious. events of hepatitis Of the 12 patients with events of hepatitis in the RCC population in KN426 pembrolizumab plus axitinib (n=429), 7 (1.6%) experienced serious events of hepatitis. Of the 4 patients with events of hepatitis in the CRC population in KN177 (n=153), 4 (2.6%) experienced serious events of hepatitis. Of the 5 patients with events of hepatitis in the esophageal cancer population in KN590 pembrolizumab plus chemotherapy (n=370), 3 (0.8%) experienced serious events of hepatitis. Of the 5 patients with events of hepatitis in TNBC population in KN355 pembrolizumab plus chemotherapy group (n=596), 4 (0.7%) experienced serious events of hepatitis. Of the 7 patients with events of hepatitis in the RCC population in KN581 pembrolizumab plus lenvatinib (n=352), 6 (1.7%) experienced serious events of hepatitis. Of the 8 patients with events of hepatitis in the endometrial carcinoma population in KN146 and KN775 pembrolizumab plus lenvatinib (n=530), 4 (0.8%) experienced serious events of hepatitis. Of the 5 patients with events of hepatitis in the RCC population in KN564 pembrolizumab monotherapy (n=488), 3 (0.6%) experienced serious events of hepatitis. Of the 4 patients with events of hepatitis in the MSI-H population in KN158 Cohort K and KN164 Cohorts A and B (n=475), 1 (0.2%) experienced a serious event of hepatitis. Of the 5 patients with events of hepatitis in the cervical cancer population in KN826 pembrolizumab plus chemotherapy (n=307), 3 (1.0%) experienced serious events of hepatitis. Of the 11 patients with events of hepatitis in the TNBC population in KN522 pembrolizumab in combination with neoadjuvant chemotherapy followed by continued adjuvant pembrolizumab monotherapy group (n=783), 7 (0.9%) experienced serious events of hepatitis. Of the 10 patients with events of hepatitis in the melanoma population in KN716 pembrolizumab monotherapy (n=483), 2 (0.4%) experienced serious events of hepatitis. Of the 2 patients with events of hepatitis in gastric cancer population in KN811 pembrolizumab combination therapy (n=350), 2 (0.6%) experienced serious events of hepatitis. Of the 10 patients with events of hepatitis in the NSCLC population in KN091 pembrolizumab monotherapy (n=580), 9 (1.6%) experienced serious events of hepatitis. Of the 9 patients with events of hepatitis in the gastric cancer population in KN859 pembrolizumab plus chemotherapy (n=785), 4 (0.5%) experienced serious events of hepatitis. Of the 9 patients with events of hepatitis in the BTC population in KN966 pembrolizumab plus chemotherapy (n=529), 3 (0.6%) were serious. Of the 3 patients with events of hepatitis in the NSCLC population in KN671 pembrolizumab in combination with chemotherapy as neoadjuvant treatment followed by continued adjuvant pembrolizumab monotherapy (n=396), 2 (0.5%) experienced serious events of hepatitis.

Table SVII.3.1.3: Details of Important Identified Risk: Immune-Mediated Adverse Reactions- Hepatitis

Severity and Nature of the Risk

Identified treatment emergent adverse events (AE) of hepatitis (all events) in participants summarized by grade – Pembrolizumab. (AEs for 30 days after discontinuation were included)

Hepatitis (AEOSI)
KN001, KN002 and KN006 Melanoma Subjects and KN001 and KN010 NSCLC Subjects Treated with Pembrolizumab
(Treatment Emergent)

	Cumulative NSCLC 001/010 + MEL 001/002/006	
	n	(%)
Subjects in population	2,799	
with one or more adverse events	18	(0.6)
Autoimmune hepatitis	12	(0.4)
Grade 2	4	(0.1)
Grade 3	7	(0.3)
Grade 4	1	(0.0)
Drug-induced liver injury	2	(0.1)
Grade 3	1	(0.0)
Grade 4	1	(0.0)
Hepatitis	5	(0.2)
Grade 1	1	(0.0)
Grade 3	4	(0.1)

Every subject is counted a single time for each applicable specific adverse event. A subject with multiple adverse events within a system organ class is counted a single time for that system organ class.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns is greater than or equal to the incidence specified in the report title, after rounding.
Only the highest reported grade of a given adverse event is counted for the individual subject.
Grades are based on NCI CTCAE version 4.0.

In the NSCLC population in KN024 and KN042, (n=790), there were 6 (0.8%) patients with Grade 3 events, 2 (0.3%) patients with Grade 4 events, and no patients with Grade 5 events of hepatitis.

In the NSCLC population in KN189 and KN021 (Cohorts C and G) pembrolizumab plus chemotherapy (n=488), there were 3 (0.6%) patients with Grade 3 events, 1 (0.2%) patient with a Grade 4 event, and no patients with Grade 5 events of hepatitis.

In the HL population in KN013, KN087, and KN204 (n=389), there were 2 (0.5%) patients with Grade 3 events and no patients with Grade 4 or 5 events of hepatitis reported.

In the UC population in KN052 (n=370), there were 4 (1.1%) patients with Grade 3 events and there were no patients with Grade 4 or 5 events of hepatitis.

In the HNSCC population in KN040, KN012 and KN055 (n=609), there were 3 (0.5%) patients with Grade 3 events and 1 (0.2%) patient with a Grade 4 event of hepatitis.

In the HNSCC population in KN048 pembrolizumab monotherapy group (n=300), there were 2 (0.7%) patients with Grade 4 events; there were no patients with Grade 5 events of hepatitis; in the pembrolizumab plus chemotherapy group (n=276), there were no patients with events of hepatitis.

In the melanoma population in KN054 (n=509), there were 6 (1.2%) patients with Grade 3 events and 1 (0.2%) patient with a Grade 4 event of hepatitis. There were no patients with Grade 5 events of hepatitis.

In the NSCLC population in KN407 and KN021 (Cohort A) (n=303), there were 4 (1.3%) patients with Grade 3 events, 1 (0.3%) patient with a Grade 4 event and no patients with Grade 5 events of hepatitis.

In the RCC population in KN426 pembrolizumab plus axitinib (n=429), there were 7 (1.6%) patients with Grade 3 events and 3 (0.7%) patients with Grade 4 events of hepatitis. There were no patients with Grade 5 events of hepatitis.

In the CRC population in KN177 (n=153) there were 4 (2.6%) patients with Grade 3 events. There were no patients with Grade 4 or 5 events of hepatitis.

In the esophageal cancer population in KN590 pembrolizumab plus chemotherapy (n=370), there were 5 (1.4%) patients with Grade 3 events of hepatitis. There were no patients with Grade 4 or 5 events of hepatitis.

Table SVII.3.1.3: Details of Important Identified Risk: Immune-Mediated Adverse Reactions- Hepatitis

	In the TNBC population in KN355 pembrolizumab plus chemotherapy group (n=596), there were 3 (0.5%) patients with Grade 3 and 1 (0.2%) patient with a Grade 4 event of hepatitis. There were no patients with Grade 5 events of hepatitis. In the RCC population in KN581 pembrolizumab plus lenvatinib (n=352) there were 3 (0.9%) patients with Grade 3, 1 (0.3%) patient with a Grade 4, and 1 (0.3%) patient with a Grade 5 events of hepatitis. In the endometrial carcinoma population in KN146 and KN775 pembrolizumab plus lenvatinib (n=530), there were 7 (1.3%) patients with Grade 3 and no patients with Grade 4 or 5 events of hepatitis. In the RCC population in KN564 pembrolizumab monotherapy (n=488) there were 4 (0.8%) patients with Grade 3 events of hepatitis. There were no patients with Grade 4 or 5 events of hepatitis. In the MSI-H population in KN158 Cohort K and KN164 Cohorts A and B (n=475), there were 2 (0.4%) patients with Grade 3 events of hepatitis. There were no patients with Grade 4 or 5 events of hepatitis reported. In the cervical cancer population in KN826 pembrolizumab plus chemotherapy (n=307), there were 3 (1.0%) patients with Grade 3 and 1 (0.3%) patient with a Grade 4 events of hepatitis reported. There were no Grade 5 events of hepatitis. In the TNBC population in KN522 pembrolizumab in combination with neoadjuvant chemotherapy followed by continued adjuvant pembrolizumab monotherapy group (n=783) there were 6 (0.8%) patients with Grade 3 events, and 3 (0.4%) patients with Grade 4 events of hepatitis. There were no patients with Grade 5 events of hepatitis reported. In the melanoma population in KN716 pembrolizumab monotherapy (n=483), there were 8 (1.7%) patients with Grade 3 events of hepatitis. There were no patients with Grade 4 or 5 events of hepatitis. In the gastric cancer population in KN811 pembrolizumab combination therapy (n=350), there was 1 (0.3%) patient with a Grade 4 event and 1 (0.3%) patient with a Grade 5 event of hepatitis. In the NSCLC population in KN091 pembrolizumab monotherapy (n=580) there were 5 (0.9%) patients with Grade 3 and 4 (0.7%) patients with Grade 4 events of hepatitis. There were no patients with Grade 5 events of hepatitis. In the gastric cancer population in KN859 pembrolizumab plus chemotherapy (n=785), there were 3 (0.4%) patients with a Grade 3 event of hepatitis reported. There were no patients with Grade 4 or 5 events of hepatitis reported. In the BTC population in KN966 pembrolizumab plus chemotherapy (n=529), there were 5 (0.9%) patients with Grade 3 events of hepatitis reported. There were no patients with Grade 4 or 5 events of hepatitis. In the NSCLC population in KN671 pembrolizumab in combination with chemotherapy as neoadjuvant treatment followed by continued adjuvant pembrolizumab monotherapy (n=396) there was 1 (0.3%) patient with a Grade 4 event of hepatitis, there were no patients with Grade 3 or 5 events of hepatitis reported. In the global safety database through 31-DEC-2017, (pembrolizumab monotherapy trials only), there were 4 Grade 5 clinical trial reports of hepatitis. Review of pembrolizumab clinical trial data from ongoing studies and postmarketing data regarding immune-mediated hepatitis, including fatal cases, is consistent with the risk as characterized in this RMP.
Risk Factors and Risk Groups:	Patients with moderate to severe liver dysfunction were excluded from clinical trials. No analysis of specific risk factors for immune-mediated hepatitis associated with pembrolizumab has been undertaken.
Preventability:	Although the development of hepatitis cannot be completely prevented; patients should be monitored for signs and symptoms of hepatitis and if they develop, other causes excluded. Withholding/discontinuation of pembrolizumab and appropriate medical intervention including corticosteroids following the onset of hepatitis may result in recovery.

Table SVII.3.1.3: Details of Important Identified Risk: Immune-Mediated Adverse Reactions- Hepatitis

Impact on the Risk-Benefit Balance of the Product:	Hepatic failure may be life-threatening or fatal in individual patients; however, the event can be managed with cessation of pembrolizumab and immunosuppression with corticosteroids. Given the fatal outcome of untreated cancer, the risk of immune-mediated hepatitis is outweighed by the potential benefit.
Public Health Impact:	This risk has minimal public health impact outside its effect on individual patients.

Table SVII.3.1.4: Details of Important Identified Risk: Immune-Mediated Adverse Reactions- Nephritis

Important Identified Risk:	Immune-mediated Nephritis
Potential Mechanisms:	Pembrolizumab is a potent and highly-selective humanized monoclonal antibody (mAb) of the Immunoglobulin G4 (IgG4)/kappa isotype directed to the programmed cell death-1 (PD-1) receptor and designed to directly block the interaction between the receptor and its ligands, PD-L1 and PD-L2. The PD-1 pathway represents a major immune control switch which may be engaged by tumor cells to overcome active T-cell immune surveillance. T-cell activation in proximity to normal tissue may lead to inflammation and injury to normal tissue.
Evidence Source(s) and Strength of Evidence:	Review of pembrolizumab clinical trial data, post-marketing experience and literature regarding nephritis represent sufficient evidence of a causal association with pembrolizumab exposure. CTD 2.7.4 Please reference evidence source cited in Table SVII.3.1.1; Details of Important Identified Risk: Immune-Mediated Pneumonitis
Characterisation of the Risk: Immune-mediated Nephritis	
Frequency with 95%CI	95% Confidence Interval for the Overall Incidence (%) of Nephritis KN001, KN002 and KN006 Melanoma Subjects and KN001 and KN010 NSCLC Subjects Treated with Pembrolizumab

	Cumulative MEL 001/002/006 + NSCLC 001/010	
	n (%)	95% CI
Nephritis	9 (0.3)	(0.1,0.6)

The overall number and proportion of patients with nephritis in the NSCLC population in KN024 and KN042 (n=790) was 4 (0.5%) (95%CI- 0.1, 1.3), which is generally similar to the proportion of patients with the event of nephritis in the reference safety dataset for melanoma and NSCLC.

The overall number and proportion of patients with nephritis in the NSCLC population in KN189 and KN021 (Cohorts C and G) pembrolizumab plus chemotherapy (n=488) was 7 (1.4%) (95% CI-0.6, 2.9), which is marginally higher than the proportion of patients with the event of nephritis in the reference safety dataset for melanoma and NSCLC.

The overall number and proportion of patients with nephritis in the HL population in KN013, KN087, and KN204 (n=389) was 2 (0.5%) (95%CI-0.1, 1.8), which is generally similar to the proportion of patients with the event of nephritis in the reference safety dataset for melanoma and NSCLC.

The overall number and proportion of patients with nephritis in the UC population in KN052 (n=370) was 1 (0.3%) (95%CI-0,1.5) and in KN045 (n=266) was 2 (0.8%) (95%CI-0.1,2.7), which is generally similar to the proportion of patients with the event of nephritis in the reference safety dataset for melanoma and NSCLC.

There were no patients with events of nephritis reported in the HNSCC population in KN040, KN012 and KN055.

Table SVII.3.1.4: Details of Important Identified Risk: Immune-Mediated Adverse Reactions- Nephritis

	The overall number and proportion of patients with nephritis in the HNSCC population in KN048 pembrolizumab monotherapy (n=300) and pembrolizumab plus chemotherapy (n=276) groups were 2 (0.7%) (95%CI-0.1, 2.4) and 2 (0.7%) (95%CI-0.1, 2.6) respectively, which is generally similar to the proportion of patients with the event of nephritis in the reference safety dataset for melanoma and NSCLC. The overall number and proportion of patients with nephritis in the melanoma population in KN054 (n=509) was 2 (0.4%) (95% CI-0,1.4), which is generally similar to the proportion of patients with the event of nephritis in the reference safety dataset for melanoma and NSCLC. The overall number and proportion of patients with nephritis in the NSCLC population in KN407 and KN021 (Cohort A) (n=303), was 2 (0.7%) (95%CI-0.1, 2.4), which is generally similar to the proportion of patients with the event of nephritis in the reference safety dataset for melanoma and NSCLC. The overall number and proportion of patients with nephritis in the RCC population in KN426 pembrolizumab plus axitinib (n=429) was 6 (1.4%) (95% CI-0.5,3), which is generally similar to the proportion of patients with the event of nephritis in the reference safety dataset for melanoma and NSCLC. The overall number and proportion of patients with nephritis in the CRC population in KN177 (n=153) was 1 (0.7%) (95% CI-0,3.6) which is generally similar to the proportion of patients with the event of nephritis in the reference safety dataset for melanoma and NSCLC. The overall number and proportion of patients with nephritis in the esophageal cancer population in KN590 pembrolizumab plus chemotherapy (n=370) was 1 (0.3%) (95% CI-0,1.5), which is generally similar to the proportion of patients with the event of nephritis in the reference safety dataset for melanoma and NSCLC. The overall number and proportion of patients with nephritis in the TNBC population in KN355 pembrolizumab plus chemotherapy group (n=596) was 4 (0.7%) (95% CI-0.2,1.7), which is generally similar to the overall frequency in the reference safety dataset for melanoma and NSCLC. The overall number and proportion of patients with nephritis in the RCC population in KN581 pembrolizumab plus lenvatinib (n=352) was 6 (1.7%) (95% CI-0.6, 3.7), which is generally similar to the proportion of patients with the event of nephritis in the reference safety dataset. The overall number and proportion of patients with nephritis in the endometrial carcinoma population in KN146 and KN775 pembrolizumab plus lenvatinib (n=530) was 5 (0.9%) (95% CI-0.3, 2.2), which is generally similar to the proportion of patients with the event of nephritis in the reference safety dataset. The overall number and proportion of patients with nephritis in the RCC population in KN564 pembrolizumab monotherapy (n=488) was 3 (0.6%) (95% CI-0.1,1.8), which is generally similar to the proportion of patients with the event of nephritis in the reference safety dataset for melanoma and NSCLC. The overall number and proportion of patients with nephritis in the MSI-H population in KN158 Cohort K and KN164 Cohorts A and B (n=475) was 2 (0.4%) (95% CI-0.1,1.5) which is generally similar to the proportion of patients with the event of nephritis in the reference safety dataset. The overall number and proportion of patients with nephritis in the cervical cancer population in KN826 pembrolizumab plus chemotherapy (n=307) was 1 (0.3%) (95% CI-0.0, 1.8), which is generally similar to the proportion of patients with the event of nephritis in the reference safety dataset. The overall number and proportion of patients with nephritis in the TNBC population in KN522 pembrolizumab in combination with neoadjuvant chemotherapy followed by continued adjuvant pembrolizumab monotherapy group (n=783) was 7 (0.9%) (95% CI-0.4,1.8), which is generally similar to the proportion of patients with the event of nephritis in the reference safety dataset. The overall number and proportion of patients with nephritis in the melanoma population in KN716 pembrolizumab monotherapy (n=483) was 7 (1.4%) (95% CI-0.6, 3.0), which is generally similar

Table SVII.3.1.4: Details of Important Identified Risk: Immune-Mediated Adverse Reactions- Nephritis

<table>
<tr><td></td><td>to the proportion of patients with the event of nephritis in the reference safety dataset for melanoma and NSCLC.

The overall number and proportion of patients with nephritis in the gastric cancer population in KN811 pembrolizumab combination therapy (n=350) was 4 (1.1%) (95% CI-0.3, 2.9), which is generally similar to the proportion of patients with the event of nephritis in the reference safety dataset.

The overall number and proportion of patients with nephritis in the NSCLC population in KN091 pembrolizumab monotherapy (n=580) was 4 (0.7%) (95% CI-0.2, 1.8), which is generally similar to the proportion of patients with the event of nephritis in the reference safety dataset.

The overall number and proportion of patients with nephritis in the gastric cancer population in KN859 pembrolizumab plus chemotherapy (n=785) was 4 (0.5%) (95% CI-0.1, 1.3), which is generally similar to the proportion of patients with the event of nephritis in the reference safety dataset.

The overall number and proportion of patients with nephritis in the BTC population in KN966 pembrolizumab plus chemotherapy (n=529) was 2 (0.4%) (95% CI-0.0, 1.4), which is generally similar to the proportion of patients with the events of nephritis in the reference safety dataset.

There were no events of nephritis reported in the NSCLC population in KN671 pembrolizumab in combination with chemotherapy as neoadjuvant treatment followed by continued adjuvant pembrolizumab monotherapy (n=396).</td></tr>
<tr><td>Outcomes</td><td>Percent overall, fatal, not resolved, resolved, and unknown for identified risk of nephritis as assessed by the Sponsor - pembrolizumab. (Table includes events for 30 days after discontinuation.)

Nephritis (AEOSI)
KN001, KN002 and KN006 Melanoma Subjects and KN001 and KN010 NSCLC Subjects Treated with Pembrolizumab
(Treatment Emergent)

<table>
<tr><td></td><td></td><td colspan="2">Cumulative NSCLC 001/010 + MEL 001/002/006</td></tr>
<tr><td></td><td>Outcome</td><td>n</td><td>(%)</td></tr>
<tr><td>Subjects in population</td><td></td><td>2,799</td><td></td></tr>
<tr><td></td><td></td><td></td><td></td></tr>
<tr><td>With one or more adverse events</td><td>Overall</td><td>9</td><td>(0.3)</td></tr>
<tr><td></td><td>Fatal</td><td>0</td><td>(0.0)</td></tr>
<tr><td></td><td>Not Resolved</td><td>3</td><td>(0.1)</td></tr>
<tr><td></td><td>Resolved</td><td>5</td><td>(0.2)</td></tr>
<tr><td></td><td>Resolving</td><td>1</td><td>(0.0)</td></tr>
<tr><td></td><td>Unknown</td><td>0</td><td>(0.0)</td></tr>
<tr><td colspan="4">Outcome: Resolved = RECOVERED/RESOLVED, Not resolved = NOT RECOVERED/NOT RESOLVED
Every subject is counted once for the AE outcome, with the order: Fatal>Not Resolved>Resolving>Unknown>Sequelae>Resolved.</td></tr>
</table>

In the NSCLC population in KN024 and KN042 (n=790), the outcomes of the 4 patients with events of nephritis were as follows: 2 (0.3%) resolved, 1 (0.1%) resolving, 1 (0.1%) resolved with sequelae.

In the NSCLC population in KN189 and KN021 (Cohorts C and G) pembrolizumab plus chemotherapy (n=488), the outcomes of the 7 patients with events of nephritis were as follows: 2 (0.4%) resolved, 3 (0.6%) resolving, 2 (0.4%) not resolved. There were no patients with events of nephritis with a fatal outcome.

In the HL population in KN013, KN087, and KN204 (n=389), the outcome of the 2 (0.5%) patients with events of nephritis were as follows: 1 (0.3%) not resolved and 1 (0.3%) resolved. There were no fatal outcomes.

In the UC population in KN052 (n=370), the outcome for the 1 patient with an event of nephritis was: 1 (0.3%) resolved and in the UC population in KN045 (n=266), the outcomes for the 2 patients</td></tr>
</table>

Table SVII.3.1.4: Details of Important Identified Risk: Immune-Mediated Adverse Reactions- Nephritis

	with events of nephritis were as follows: 2 (0.8%) resolved. There were no patients with events of nephritis with a fatal outcome. In the HNSCC population in KN048 pembrolizumab monotherapy group (n=300), the outcomes for the 2 patients with events of nephritis were as follows: 1 (0.3%) not resolved and 1 (0.3%) resolved with sequelae. There were no fatal outcomes. In the HNSCC population in KN048 pembrolizumab plus chemotherapy group (n=276), the outcome for the 2 patients with events of nephritis were as follows: 1 (0.4%) resolved and 1 (0.4%) not resolved. There were no patients with events of nephritis with a fatal outcome. In the melanoma population in KN054 (n=509), the outcome of the 2 patients with events of nephritis were as follows: 1 (0.2%) not resolved and 1 (0.2%) resolved with sequelae. There were no patients with events of nephritis with a fatal outcome. In the NSCLC population in KN407 and KN021 (Cohort A) (n=303), the outcomes of the 2 patients with events of nephritis were as follows: 1 (0.3%) resolved, 1 (0.3%) resolving. There were no patients with events of nephritis with a fatal outcome. In the RCC population in KN426 pembrolizumab plus axitinib (n=429), the outcomes for the 6 patients with events of nephritis were as follows: 4 (0.9%) resolved and 2 (0.5%) not resolved. There were no patients with events of nephritis with a fatal outcome. In the CRC population in KN177 (n=153), the outcome of the 1 (0.7%) patient with an event of nephritis was not resolved. There were no patients with events of nephritis with a fatal outcome. In the esophageal cancer population in KN590 pembrolizumab plus chemotherapy (n=370), the outcome of the 1 patient with an event of nephritis was as follows: 1 (0.3%) not resolved. There were no patients with events of nephritis with a fatal outcome. In the TNBC population in KN355 pembrolizumab plus chemotherapy group (n=596), the outcomes for the patients with events of nephritis were as follows: 2 (0.3%) resolved, 1 (0.2%) not resolved, and 1 (0.2%) resolved with sequelae. There were no patients with events of nephritis with a fatal outcome. In the RCC population in KN581 pembrolizumab plus lenvatinib (n=352), the outcome of the 6 (1.7%) patients with events of nephritis were as follows: 2 (0.6%) resolved, 1 (0.3%) resolving, 1 (0.3%) resolved with sequelae, and 1 (0.3%) not resolved. There was 1 (0.3%) patient with an event of nephritis that resulted in a fatal outcome. In the endometrial carcinoma population in KN146 and KN775 pembrolizumab plus lenvatinib (n=530), the outcomes for the 5 patients with events of nephritis were as follows: 4 (0.8%) resolved and 1 (0.2%) not resolved. There were no patients with events of nephritis with a fatal outcome. In the RCC population in KN564 pembrolizumab monotherapy (n=488), the outcomes for the 3 patients with events of nephritis were as follows: 1 (0.2%) resolved, 1 (0.2%) resolving, and 1 (0.2%) resolved with sequelae. There were no patients with events of nephritis with a fatal outcome. In the MSI-H population in KN158 Cohort K and KN164 Cohorts A and B (n=475), the outcomes for the 2 (0.4%) patients with events of nephritis were as follows: 1 (0.2%) resolved and 1 (0.2%) resolving. There were no patients with events of nephritis with a fatal outcome. In the cervical cancer population in KN826 pembrolizumab plus chemotherapy (n=307), the outcome of the 1 patient with an event of nephritis was as follows: 1 (0.3%) not resolved. There were no patients with events of nephritis with a fatal outcome. In the TNBC population in KN522 pembrolizumab in combination with neoadjuvant chemotherapy followed by continued adjuvant pembrolizumab monotherapy group (n=783), the outcomes for the 7 patients with events of nephritis were as follows: 5 (0.6%) resolved, 1 (0.1%) not resolved, and 1 (0.1%) unknown. There were no patients with events of nephritis with a fatal outcome. In the melanoma population in KN716 pembrolizumab monotherapy (n=483), the outcomes of the 7 patients with events of nephritis were as follows: 6 (1.2%) resolved, and 1 (0.2%) not resolved. There were no patients with events of nephritis with a fatal outcome.

Table SVII.3.1.4: Details of Important Identified Risk: Immune-Mediated Adverse Reactions- Nephritis

<table>
<tr><td></td><td>In the gastric cancer population in KN811 pembrolizumab combination therapy (n=350), the outcomes for the 4 patients with events of nephritis were as follows: 2 (0.6%) resolving and 2 (0.6%) not resolved. There were no patients with events of nephritis with a fatal outcome.

In the NSCLC population in KN091 pembrolizumab monotherapy (n=580), the outcomes for the 4 patients with events of nephritis were as follows: 3 (0.5%) resolved and 1 (0.2%) not resolved. There were no patients with events of nephritis with a fatal outcome.

In the gastric cancer population in KN859 pembrolizumab plus chemotherapy (n=785), the outcomes for the 4 patients with events of nephritis were as follows: 3 (0.4%) not resolved, and 1 (0.1%) resolved. There were no patients with events of nephritis with a fatal outcome.

In the BTC population in KN966 pembrolizumab plus chemotherapy (n=529), the worst reported outcomes for the 2 patients with events of nephritis were as follows: 1 (0.2%) resolved and 1 (0.2%) not resolved. There were no patients with events of nephritis with a fatal outcome.

Aggregate Review

Review of the ASE dataset (n=7730) yielded no fatal cases of nephritis. Review of the global safety database also yielded no fatal cases from ongoing interventional monotherapy clinical trials and no fatal cases from the PM or non-interventional environment.</td></tr>
<tr><td>Seriousness</td><td>Percent serious for identified risk of nephritis- pembrolizumab (Serious AEs for 90 days after discontinuation were included.)

Nephritis - Serious (AEOSI)
KN001, KN002 and KN006 Melanoma Subjects and KN001 and KN010 NSCLC Subjects Treated with Pembrolizumab
(Treatment Emergent)

<table>
<tr><td></td><td colspan="2">Cumulative NSCLC 001/010 + MEL 001/002/006</td></tr>
<tr><td></td><td>n</td><td>(%)</td></tr>
<tr><td>Subjects in population</td><td>2,799</td><td></td></tr>
<tr><td>with one or more adverse events</td><td>8</td><td>(0.3)</td></tr>
<tr><td></td><td></td><td></td></tr>
<tr><td>Acute kidney injury</td><td>2</td><td>(0.1)</td></tr>
<tr><td>Autoimmune nephritis</td><td>1</td><td>(0.0)</td></tr>
<tr><td>Renal failure</td><td>2</td><td>(0.1)</td></tr>
<tr><td>Tubulointerstitial nephritis</td><td>3</td><td>(0.1)</td></tr>
<tr><td colspan="3">Every subject 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.
Include all treated subjects in KN001 Part B1, B2, B3, D, C, F1, F2, F3 and all subjects in KN002 treated with Pembrolizumab in the original phase, and all subjects in KN006 and KN010 treated with Pembrolizumab.</td></tr>
</table>

The 4 patients with events of nephritis reported in the NSCLC population in KN024 and KN042 (n=790) 3(0.4%) experienced serious events of nephritis.

Of the 7 patients with events of nephritis in the NSCLC population in KN189 and KN021 (Cohorts C and G) pembrolizumab plus chemotherapy (n=488), 5 (1.0%) experienced serious events of nephritis.

There was 1 (0.3%) patient with a serious event of nephritis reported in the HL population in KN013, KN087, and KN204 (n=389).

The 1 (0.3%) patient with an event of nephritis in the UC population in KN052 (n=370) experienced a serious event of nephritis and the 2 (0.8%) patients with events of nephritis in the UC population in KN045 (n=266) experienced serious events of nephritis.

Of the 2 patients with events of nephritis reported in the HNSCC pembrolizumab monotherapy population in KN048 (n=300), 1 (0.3%) experienced a serious event of nephritis. Of the 2 patients with events of nephritis reported in the HNSCC pembrolizumab plus chemotherapy group in KN048 (n=276), none experienced serious events of nephritis.</td></tr>
</table>

Table SVII.3.1.4: Details of Important Identified Risk: Immune-Mediated Adverse Reactions- Nephritis

	The 2 patients with events of nephritis reported in the melanoma population in KN054 (n=509) experienced serious events of nephritis (0.4%). Of the 2 patients with events (0.7%) of nephritis in the NSCLC population in KN407 and KN021 (Cohort A) (n=303), both experienced serious events of nephritis. Of the 6 patients with events of nephritis in the RCC population in KN426 pembrolizumab plus axitinib (n=429), 2 (0.5%) experienced serious events of nephritis. The one patient with an event of nephritis in the CRC population in KN177 (n=153) experienced a serious event of nephritis (0.7%). There were no patients with serious events of nephritis in the esophageal cancer population in KN590 pembrolizumab plus chemotherapy (n=370). Of the 4 patients with events of nephritis in the TNBC population in KN355 pembrolizumab plus chemotherapy group (n=596), 1 (0.2%) experienced a serious event of nephritis. Of the 6 (1.7%) patients with events of nephritis in the RCC population in KN581 pembrolizumab plus lenvatinib (n=352), 3 (0.9%) experienced serious events of nephritis. Of the 5 patients with events of nephritis in the endometrial carcinoma population in KN146 and KN775 pembrolizumab plus lenvatinib (n=530), 3 (0.6%) experienced serious events of nephritis. Of the 3 patients with events of nephritis in the RCC population in KN564 pembrolizumab monotherapy (n=488), 1 (0.2%) experienced a serious event of nephritis. There were no patients with serious events of nephritis reported in the MSI-H population in KN158 Cohort K and KN164 Cohorts A and B (n=475). There were no patients with serious events of nephritis in the cervical cancer population in KN826 pembrolizumab plus chemotherapy (n=307). Of the 7 patients with events of nephritis in the TNBC population in KN522 pembrolizumab in combination with neoadjuvant chemotherapy followed by continued adjuvant pembrolizumab monotherapy group (n=783), 6 (0.8%) experienced serious events of nephritis. Of the 7 patients with events of nephritis in the melanoma population in KN716 pembrolizumab monotherapy (n=483), 4 (0.8%) experienced serious events of nephritis. Of the 4 patients with events of nephritis in the gastric cancer population in KN811 pembrolizumab combination therapy (n=350), 2 (0.6%) experienced serious events of nephritis. There were no patients with serious events of nephritis in the NSCLC population in KN091 pembrolizumab monotherapy (n=580). Of the 4 patients with events of nephritis in the gastric cancer population in KN859 pembrolizumab plus chemotherapy (n=785), 4 (0.5%) experienced serious events of nephritis. There were no patients with serious events of nephritis in the BTC population in KN966 pembrolizumab plus chemotherapy (n=529).

Table SVII.3.1.4: Details of Important Identified Risk: Immune-Mediated Adverse Reactions- Nephritis

Severity and Nature of the Risk

Nephritis (AEOSI)
KN001, KN002 and KN006 Melanoma Subjects and KN001 and KN010 NSCLC Subjects Treated with Pembrolizumab
(Treatment Emergent)

	Cumulative NSCLC 001/010 + MEL 001/002/006	
	n	(%)
Subjects in population	2,799	
with one or more adverse events	9	(0.3)
Acute kidney injury	2	(0.1)
Grade 3	1	(0.0)
Grade 4	1	(0.0)
Autoimmune nephritis	1	(0.0)
Grade 2	1	(0.0)
Renal failure	2	(0.1)
Grade 3	2	(0.1)
Tubulointerstitial nephritis	4	(0.1)
Grade 1	1	(0.0)
Grade 2	2	(0.1)
Grade 3	1	(0.0)

Every subject is counted a single time for each applicable specific adverse event. A subject with multiple adverse events within a system organ class is counted a single time for that system organ class.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns is greater than or equal to the incidence specified in the report title, after rounding.
Only the highest reported grade of a given adverse event is counted for the individual subject.
Grades are based on NCI CTCAE version 4.0.

In the NSCLC population in KN024 and KN042 (n=790), there were 2 (0.3%) patients with Grade 3 events of nephritis. There were no patients with Grade 4 or 5 events of nephritis.

In the NSCLC population in KN189 and KN021 (Cohorts C and G) pembrolizumab plus chemotherapy (n=488), there was 4 (0.8%) patients with Grade 3 events, 2 (0.4) patients with Grade 4 events and no patients with Grade 5 events of nephritis.

In the HL population in KN013, KN087, and KN204 (n=389), there was 1 (0.3%) patient with a Grade 3 and 1 (0.3%) patient with a Grade 4 event of nephritis. There were no patients with Grade 5 events of nephritis.

In the UC population in KN052 (n=370), there was 1 (0.3%) patient with a Grade 3 event and no patients with Grade 4 or 5 events of nephritis; in the UC population in KN045 (n=266), there were 2 (0.8%) patients with Grade 3 events and no patients with Grade 4 or 5 events of nephritis.

In the HNSCC population in KN048 pembrolizumab monotherapy group (n=300), there was 1 (0.3%) patient with a Grade 3 event of nephritis. There were no patients with Grade 4 or 5 events of nephritis; in the pembrolizumab plus chemotherapy group (n=276), there were no patients with Grade 3-5 events of nephritis.

In the melanoma population in KN054 (n=509), there were 2 (0.4%) patients with Grade 3 event of nephritis. There were no patients with Grade 4 or 5 events of nephritis.

In the NSCLC population in KN407 and KN021 (Cohort A) (n=303), there were 2 (0.7%) patients with a Grade 3 events. There were no patients with Grade 4 or 5 events of nephritis.

In the RCC population in KN426 pembrolizumab plus axitinib (n=429), there was 1 (0.3%) patient with Grade 3 event of nephritis. There were no patients with Grade 4 or 5 events of nephritis.

In the CRC population in KN177 (n=153) there were no patients with Grade 3-5 events of nephritis reported.

Table SVII.3.1.4: Details of Important Identified Risk: Immune-Mediated Adverse Reactions- Nephritis

	In the esophageal cancer population in KN590 pembrolizumab plus chemotherapy (n=370), there were no patients with Grade 3-5 events of nephritis. In the TNBC population in KN355 pembrolizumab plus chemotherapy group (n=596), there were no patients with Grade 3-5 events of nephritis. In the RCC population in KN581 pembrolizumab plus lenvatinib (n=352) there were 3 (0.9%) patients with Grade 3, no patients with Grade 4, and 1 (0.3%) patient with a Grade 5 events of nephritis. In the endometrial carcinoma population in KN146 and KN775 pembrolizumab plus lenvatinib (n=530), there were 3 (0.6%) patients with Grade 3 events of nephritis. There were no patients with Grade 4 or 5 events of nephritis. In the RCC population in KN564 pembrolizumab monotherapy (n=488) there was 1 (0.2%) patient with a Grade 3 event of nephritis. There were no patients with Grade 4 or 5 events of nephritis. In the MSI-H population in KN158 Cohort K and KN164 Cohorts A and B (n=475), there were no patients with Grade 3-5 events of nephritis. In the cervical cancer population in KN826 pembrolizumab plus chemotherapy (n=307), there were no patients with Grade 3-5 events of nephritis. In the TNBC population in KN522 pembrolizumab in combination with neoadjuvant chemotherapy followed by continued adjuvant pembrolizumab monotherapy group (n=783) there were 4 (0.5%) patients with Grade 3 events, and 2 (0.3%) patients with Grade 4 event of nephritis. There were no patients with Grade 5 events of nephritis reported. In the melanoma population in KN716 pembrolizumab monotherapy (n=483), there were 2 (0.4%) patients with Grade 3 events of nephritis. There were no patients with Grade 4 or 5 events of nephritis. In the gastric cancer population in KN811 pembrolizumab combination therapy (n=350), there was 1 (0.3%) patient with a Grade 3 event of nephritis. There were no patients with Grade 4 or 5 events of nephritis. In the NSCLC population in KN091 pembrolizumab monotherapy (n=580) there were no patients with Grade 3, 4, or 5 events of nephritis. In the gastric cancer population in KN859 pembrolizumab plus chemotherapy (n=785), there were 4 (0.5%) patients with Grade 3 events of nephritis reported. There were no patients with Grade 4 or 5 events of nephritis. In the BTC population in KN966 pembrolizumab plus chemotherapy (n=529), there were no patients with Grade 3, 4 or 5 events of nephritis. Review of other pembrolizumab clinical trial data from ongoing studies regarding immune-mediated nephritis is consistent with the risk as characterized in this RMP.
Risk Factors and Risk Groups:	Patients with severe renal dysfunction were excluded from clinical trials. No specific risk factors for nephritis associated with pembrolizumab have been identified.
Preventability:	Although the development of nephritis cannot be completely prevented; patients should be monitored for signs and symptoms of nephritis and if they develop, other causes excluded. Withholding/discontinuation of pembrolizumab and appropriate medical intervention including corticosteroids following the onset of nephritis may result in recovery.
Impact on the Risk-Benefit Balance of the Product:	Nephritis can potentially lead to severe or life threatening renal injury. Given the fatal outcome of untreated cancer, the risk of nephritis which generally can be managed is outweighed by the potential benefit.
Public Health Impact:	This risk has minimal public health impact outside its effect on individual patients.

Table SVII.3.1.5: Details of Important Identified Risk: Immune-Mediated Adverse Reactions- Endocrinopathies – Hypophysitis (Including Hypopituitarism)

<table>
<tr><td>Important Identified Risk:</td><td>Immune-mediated Endocrinopathies- Hypophysitis (including hypopituitarism)</td></tr>
<tr><td><u>Potential Mechanisms:</u></td><td>Pembrolizumab is a potent and highly-selective humanized monoclonal antibody (mAb) of the Immunoglobulin G4 (IgG4)/kappa isotype directed to the programmed cell death-1 (PD-1) receptor and designed to directly block the interaction between the receptor and its ligands, PD-L1 and PD-L2. The PD-1 pathway represents a major immune control switch which may be engaged by tumor cells to overcome active T-cell immune surveillance. T-cell activation in proximity to normal tissue may lead to inflammation and injury to normal tissue.</td></tr>
<tr><td><u>Evidence Source(s) and Strength of Evidence:</u></td><td>Review of pembrolizumab clinical trial data, post-marketing experience and literature regarding endocrinopathies- hypophysitis represent sufficient evidence of a causal association with pembrolizumab exposure.

CTD 2.7.4

Please reference evidence source cited in Table SVII.3.1.1; Details of Important Identified Risk: Immune-Mediated Pneumonitis</td></tr>
<tr><td colspan="2"><u>Characterisation of the Risk:</u> Immune-mediated Endocrinopathies- Hypophysitis (including hypopituitarism)</td></tr>
<tr><td>Frequency with 95%CI</td><td>95% Confidence Interval for the Overall Incidence (%) of Hypophysitis
KN001, KN002 and KN006 Melanoma and KN001 and KN010 NSCLC Subjects Treated with Pembrolizumab

<table>
<tr><td></td><td colspan="2">Cumulative MEL 001/002/006 + NSCLC 001/010</td></tr>
<tr><td></td><td>n (%)</td><td>95% CI</td></tr>
<tr><td>Hypophysitis*</td><td>17 (0.6)</td><td>(0.4,1)</td></tr>
<tr><td colspan="3">* includes hypopituitarism</td></tr>
</table>

The overall number and proportion of patients with hypophysitis in the NSCLC population in KN024 and KN042 (n=790) was 4 (0.5%) (95% CI-0.1, 1.3), which is generally similar to the proportion of patients with the event of hypophysitis in the reference safety dataset for melanoma and NSCLC.

The overall number and proportion of patients with hypophysitis in the NSCLC population in KN189 and KN021 (Cohorts C and G) pembrolizumab plus chemotherapy (n=488) was 3 (0.6%) (95% CI- 0.1, 1.8), which is generally similar to the proportion of patients with the event of hypophysitis in the reference safety dataset for melanoma and NSCLC.

There were no patients with events of patients with hypophysitis reported in the HL population in KN013, KN087, and KN204.

The overall number and proportion of patients with hypophysitis in the UC population in KN052 (n=370) was 2 (0.5%) (95%CI-0.1,1.9) which is generally similar to the proportion of patients with the event of hypophysitis in the reference safety dataset for melanoma and NSCLC. There were no patients with events of hypophysitis reported in the UC population in KN045.

There were no patients with events of hypophysitis reported in the HNSCC population in KN040, KN012 and KN055.

The overall number and proportion of patients with hypophysitis in the HNSCC population in KN048 pembrolizumab monotherapy(n=300) and pembrolizumab plus chemotherapy (n=276) groups, were 1 (0.3%) (95% CI-0,1.8) and 1 (0.4%) (95% CI-0,2) respectively, which is generally similar to the proportion of patients with the event of hypophysitis in the reference safety dataset for melanoma and NSCLC.

The overall number and proportion of patients with hypophysitis in the melanoma population in KN054 (n=509) was 11 (2.2%) (95% CI-1.1,3.8). The proportion of patients with events of hypophysitis in KN054 although somewhat more common than in the reference safety dataset were</td></tr>
</table>

Table SVII.3.1.5: Details of Important Identified Risk: Immune-Mediated Adverse Reactions- Endocrinopathies – Hypophysitis (Including Hypopituitarism)

	generally consistent in nature with the proportion of events of hypophysitis previously reported for pembrolizumab. The overall number and proportion of patients with hypophysitis in the NSCLC population in KN407 and KN021 (Cohort A) (n=303), was 3 (1.0%) (95% CI-0.2, 2.9), which is generally similar to the proportion of patients with the event of hypophysitis in the reference safety dataset for melanoma and NSCLC. The overall number and proportion of patients with hypophysitis in the RCC population in KN426 pembrolizumab plus axitinib (n=429) was 5 (1.2%) (95% CI-0.4,2.7), which is generally similar to the proportion of patients with the event of hypophysitis in the reference safety dataset for melanoma and NSCLC. The overall number and proportion of patients with hypophysitis in the CRC population in KN177 (n=153) was 2 (1.3%) (95% CI-0.2,4.6) which is generally similar to the proportion of patients with the event of hypophysitis in the reference safety dataset for melanoma and NSCLC. The overall number and proportion of patients with hypophysitis in the esophageal cancer population in KN590 pembrolizumab plus chemotherapy (n=370) was 3 (0.8%) (95% CI-0.2,2.4), which is generally similar to the proportion of patients with the event of hypophysitis in the reference safety dataset for melanoma and NSCLC. The overall number and proportion of patients with hypophysitis in the TNBC population in KN355 pembrolizumab plus chemotherapy group (n=596) was 1 (0.2%) (95% CI-0, 0.9), which is generally similar to the proportion of patients with the event of hypophysitis in the reference safety dataset for melanoma and NSCLC. The overall number and proportion of patients with hypophysitis in the RCC population in KN581 pembrolizumab plus lenvatinib (n=352) was 3 (0.9%) (95% CI-0.2,2.5) which is generally similar to the proportion of patients with the event of hypophysitis in the reference safety dataset. The overall number and proportion of patients with hypophysitis in the endometrial carcinoma population in KN146 and KN775 pembrolizumab plus lenvatinib (n=530) was 3 (0.6%) (95% CI-0.1,1.6), which is generally similar to the proportion of patients with the event of hypophysitis in the reference safety dataset. The overall number and proportion of patients with hypophysitis in the RCC population in KN564 pembrolizumab monotherapy (n=488) was 2 (0.4%) (95% CI-0,1.5), which is generally similar to the proportion of patients with the event of hypophysitis in the reference safety dataset for melanoma and NSCLC. There were no patients with events of hypophysitis reported in the MSI-H population in KN158 Cohort K and KN164 Cohorts A and B. The overall number and proportion of patients with hypophysitis in the cervical cancer population in KN826 pembrolizumab plus chemotherapy (n=307) was 1 (0.3%) (95% CI-0.0, 1.8), which is generally similar to the proportion of patients with the event of hypophysitis in the reference safety dataset. The overall number and proportion of patients with hypophysitis in the TNBC population in KN522 pembrolizumab in combination with neoadjuvant chemotherapy followed by continued adjuvant pembrolizumab monotherapy group (n=783) was 15 (1.9%) (95% CI-1.1,3.1), which is generally similar to the proportion of patients with the event of hypophysitis in the reference safety dataset. The overall number and proportion of patients with hypophysitis in the melanoma population in KN716 pembrolizumab monotherapy (n=483) was 10 (2.1%) (95% CI-1.0, 3.8), which is generally similar to the proportion of patients with the event of hypophysitis in the reference safety dataset for melanoma and NSCLC. The overall number and proportion of patients with hypophysitis in the gastric cancer population in KN811 pembrolizumab combination therapy (n=350) was 4 (1.1%) (95% CI-0.3,2.9), which is

Table SVII.3.1.5: Details of Important Identified Risk: Immune-Mediated Adverse Reactions- Endocrinopathies – Hypophysitis (Including Hypopituitarism)

generally similar to the proportion of patients with the event of hypophysitis in the reference safety dataset.

The overall number and proportion of patients with hypophysitis in the NSCLC population in KN091 pembrolizumab monotherapy (n=580) was 7 (1.2%) (95% CI-0.5,2.5), which is generally similar to the proportion of patients with the event of hypophysitis in the reference safety dataset.

The overall number and proportion of patients with hypophysitis in the gastric cancer population in KN859 pembrolizumab plus chemotherapy (n=785) was 3 (0.4%) (95% CI-0.1, 1.1), which is generally similar to the proportion of patients with the event of hypophysitis in the reference safety dataset.

The overall number and proportion of patients with hypophysitis in the BTC population in KN966 pembrolizumab plus chemotherapy (n=529) was 2 (0.4%) (95% CI-0.0, 1.4), which is generally similar to the proportion of patients with the event of hypophysitis in the reference safety dataset.

The overall number and proportion of patients with hypophysitis in the NSCLC population in KN671 pembrolizumab in combination with chemotherapy neoadjuvant treatment followed by continued adjuvant pembrolizumab monotherapy (n=396) was 2 (0.5%) (95% CI-0.1, 1.8), which is generally similar to the overall proportion of patients with events of hypophysitis in the reference safety dataset.

Outcomes

Percent overall, fatal, not resolved, resolved, and unknown for identified risk of hypopituitarism, hypophysitis - pembrolizumab. (AEs for 30 days after discontinuation were included)

Hypopituitarism and Hypophysitis (AEOSI)
KN001, KN002 and KN006 Melanoma and KN001 and KN010 NSCLC Subjects Treated with Pembrolizumab (Treatment-Emergent)

		Cumulative NSCLC 001/010 + MEL 001/002/006	
	Outcome	n	(%)
Subjects in population		2,799	
With one or more adverse events	Overall	17	(0.6)
	Fatal	0	(0.0)
	Not Resolved	10	(0.4)
	Resolved	5	(0.2)
	Sequelae	2	(0.1)
	Unknown	0	(0.0)

Every subject is counted once on each applicable row.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns is greater than or equal to the percent incidence specified in the report title, after rounding.
Outcome: Resolved = RECOVERED/RESOLVED, Not resolved = NOT RECOVERED/NOT RESOLVED.

In the NSCLC population in KN024 and KN042 (n=790), the outcome of the 4 (0.5%) patients with events of hypophysitis. were as follows: 2 (0.3%) resolved, 2 (0.3%) not resolved. There were no patients with events of hypophysitis with a fatal outcome.

In the NSCLC population in KN189 and KN021 (Cohorts C and G) pembrolizumab plus chemotherapy (n=488), the outcome of the 3 patients with events of hypophysitis were as follows: 1 (0.2%) resolved, 1 (0.2%) resolving, and 1 (0.2%) resolved with sequelae. There were no patients with events of hypophysitis with a fatal outcome.

In the UC population in KN052 (n=370), the outcomes for the 2 patients with events of hypophysitis were as follows: 2 (0.5%) resolved. There were no patients with events of hypophysitis with a fatal outcome.

In the HNSCC population in KN048 pembrolizumab monotherapy group (n=300), the outcome for the 1 (0.3%) patient with an event of hypophysitis was resolved with sequelae. There were no fatal outcomes. In the HNSCC population in KN048 pembrolizumab plus chemotherapy group (n=276),

Table SVII.3.1.5: Details of Important Identified Risk: Immune-Mediated Adverse Reactions- Endocrinopathies – Hypophysitis (Including Hypopituitarism)

	the outcome for the 1 (0.4%) patient with an event of hypophysitis was not resolved. There were no patients with events of hypophysitis with a fatal outcome. In the melanoma population in KN054 (n=509), the outcomes for the 11 patients with events of hypophysitis were as follows: 1 (0.2%) resolved, 5 (1%) not resolved and 5 (1%) resolved with sequelae. There were no patients with events of hypophysitis with a fatal outcome. In the NSCLC population in KN407 and KN021 (Cohort A) (n=303), the outcomes for the 3 patients with events of hypophysitis were as follows: 2 (0.7%) resolving, 1 (0.3%) resolved. There were no patients with events of hypophysitis with a fatal outcome. In the RCC population in KN426 pembrolizumab plus axitinib (n=429) the outcomes for the 5 patients with events of hypophysitis were as follows: 2 (0.5%) resolved, 2 (0.5%) not resolved and 1 (0.2%) resolving. There were no patients with events of hypophysitis with a fatal outcome. In the CRC population in KN177 (n=153), the outcomes for the 2 patients with events of hypophysitis were as follows: 2 (1.3%) not resolved. There were no patients with events of hypophysitis with a fatal outcome. In the esophageal cancer population in KN590 pembrolizumab plus chemotherapy (n=370), the outcomes for the 3 patients with events of hypophysitis were as follows: 2 (0.5%) resolved with sequelae and 1 (0.3%) not resolved. There were no patients with events of hypophysitis with a fatal outcome. In the TNBC population in KN355 pembrolizumab plus chemotherapy group (n=596), the outcome for the 1 (0.2%) patient with an event of hypophysitis was resolved. In the RCC population in KN581 pembrolizumab plus lenvatinib (n=352), the outcomes for the 3 (0.9%) patients with events of hypophysitis were as follows: 2 (0.6%) not resolved, and 1 (0.3%) resolving. There were no patients with events of hypophysitis with a fatal outcome. In the endometrial carcinoma population in KN146 and KN775 pembrolizumab plus lenvatinib (n=530) the outcomes for the 3 patients with events of hypophysitis were as follows: 2 (0.4%) not resolved, and 1 (0.2%) resolved. There were no patients with events of hypophysitis with a fatal outcome. In the RCC population in KN564 pembrolizumab monotherapy (n=488), the outcomes for the 2 patients with events of hypophysitis were as follows: 2 (0.4%) resolved. There were no patients with events of hypophysitis with a fatal outcome. In the cervical cancer population in KN826 pembrolizumab plus chemotherapy (n=307), the outcome for the 1 (0.3%) patient with an event of hypophysitis was resolving. There were no patients with events of hypophysitis with a fatal outcome. In the TNBC population in KN522 pembrolizumab in combination with neoadjuvant chemotherapy followed by continued adjuvant pembrolizumab monotherapy group (n=783), the outcomes for the 15 patients with events of hypophysitis were as follows: 3 (0.4%) resolved, 6 (0.8%) not resolved, 5 (0.6%) resolved with sequelae, and 1 (0.1%) resolving. There were no patients with events of hypophysitis with a fatal outcome. In the melanoma population in KN716 pembrolizumab monotherapy (n=483), the outcomes for the 10 patients with events of hypophysitis were as follows: 5 (1%) not resolved, 3 (0.6%) resolving, 2 (0.4%) resolved. There were no patients with events of hypophysitis with a fatal outcome. In the gastric cancer population in KN811 pembrolizumab combination therapy (n=350), the outcome for the 4 patients with events of hypophysitis were as follows: 2 (0.6%) resolved, 1 (0.3%) not resolved and 1 (0.3%) resolving. There were no patients with events of hypophysitis with a fatal outcome. In the NSCLC population in KN091 pembrolizumab monotherapy (n=580), the outcomes for the 7 patients with events of hypophysitis were as follows: 6 (1%) not resolved and 1 (0.2%) resolved. There were no patients with events of hypophysitis with a fatal outcome.

Table SVII.3.1.5: Details of Important Identified Risk: Immune-Mediated Adverse Reactions- Endocrinopathies – Hypophysitis (Including Hypopituitarism)

<table>
<tr><td></td><td>In the gastric cancer population in KN859 pembrolizumab plus chemotherapy (n=785), the outcomes for the 3 patients with events of hypophysitis were as follows: 2 (0.3%) not resolved, and 1 (0.1%) resolved with sequelae. There were no patients with events of hypophysitis with a fatal outcome.

In the BTC population in KN966 pembrolizumab plus chemotherapy (n=529), the worst reported outcomes for the 2 (0.4%) patients with events of hypophysitis were not resolved. There were no patients with events of hypophysitis with a fatal outcome.

In the NSCLC population in KN671 pembrolizumab in combination with chemotherapy as neoadjuvant treatment followed by continued adjuvant pembrolizumab monotherapy group (n=396), the outcomes for the 2 patients with events of hypophysitis were as follows: 1 (0.3%) resolved, and 1 (0.3%) resolving. There were no patients with events of hypophysitis with a fatal outcome.

Aggregate Review

Review of the ASE dataset (n=7730) yielded no fatal cases of hypophysitis. Review of the global safety database also yielded no fatal cases from ongoing interventional monotherapy clinical trials and no fatal cases from the PM or non-interventional environment.</td></tr>
<tr><td>Seriousness</td><td>Percent serious for identified risk of hypopituitarism, hypophysitis – pembrolizumab (Serious AEs for 90 days after discontinuation were included.)

Hypopituitarism and Hypophysitis - Serious (AEOSI)
KN001, KN002 and KN006 Melanoma and KN001 and KN010 NSCLC Subjects Treated with Pembrolizumab
(Treatment-Emergent)

<table>
<tr><td></td><td colspan="2">Cumulative NSCLC 001/010 + MEL 001/002/006</td></tr>
<tr><td></td><td>n</td><td>(%)</td></tr>
<tr><td>Subjects in population</td><td>2,799</td><td></td></tr>
<tr><td>with one or more adverse events</td><td>10</td><td>(0.4)</td></tr>
<tr><td></td><td></td><td></td></tr>
<tr><td>Hypophysitis</td><td>5</td><td>(0.2)</td></tr>
<tr><td>Hypopituitarism</td><td>5</td><td>(0.2)</td></tr>
<tr><td colspan="3">Every subject 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.
Include all treated subjects in KN001 Part B1, B2, B3, D, C, F1, F2, F3 and all subjects in KN002 treated with Pembrolizumab in the original phase , and all subjects in KN006 and KN010 treated with Pembrolizumab.</td></tr>
</table>

The 4 patients with events of hypophysitis reported in the NSCLC population in KN024 and KN042 (n=790) experienced serious (0.5%) events of hypophysitis.

There were no patients with serious events of hypophysitis reported in the NSCLC population in KN189 or KN021 (Cohorts C and G) pembrolizumab plus chemotherapy.

The 2 (0.5%) patients with events of hypophysitis reported in the UC population in KN052 (n=370) experienced serious events of hypophysitis.

The 1 (0.3%) patient with an event of hypophysitis reported in the HNSCC population in KN048 pembrolizumab monotherapy group (n=300) was serious. The 1 (0.4%) patient with an event of hypophysitis reported in the HNSCC population in KN048 pembrolizumab plus chemotherapy group (n=276) experienced a serious event of hypophysitis.

Of the 11 patients with events of hypophysitis reported in the melanoma population in KN054 (n=509), 4 (0.8%) experienced serious events of hypophysitis.</td></tr>
</table>

Table SVII.3.1.5: Details of Important Identified Risk: Immune-Mediated Adverse Reactions- Endocrinopathies – Hypophysitis (Including Hypopituitarism)

	Of the 3 patients with events of hypophysitis reported in the NSCLC population in KN407 and KN021 (Cohort A) (n=303), 2 (0.7%) experienced serious events of hypophysitis. Of the 5 patients with events of hypophysitis in the RCC population in KN426 pembrolizumab plus axitinib (n=429), 2 (0.5%) experienced serious events of hypophysitis. There were no patients with serious adverse events of hypophysitis in the CRC population in KN177 (n=153). Of the 3 patients with events of hypophysitis in the esophageal cancer population in KN590 pembrolizumab plus chemotherapy (n=370), 2 experienced serious events of hypophysitis. There were no patients with serious events of hypophysitis in the TNBC population in KN355 pembrolizumab plus chemotherapy group (n=596). Of the 3 patients with events of hypophysitis in the RCC population in KN581 pembrolizumab plus lenvatinib (n=352), 2 (0.6%) experienced serious events of hypophysitis. Of the 3 patients with events of hypophysitis in the endometrial carcinoma population in KN146 and KN775 pembrolizumab plus lenvatinib (n=530), 1 (0.2%) experienced a serious event of hypophysitis. Of the 2 patients with events of hypophysitis in the RCC population in KN564 pembrolizumab monotherapy (n=488), 1 (0.2%) experienced a serious event of hypophysitis. The 1 (0.3%) patient with an event of hypophysitis reported in the cervical cancer population in KN826 pembrolizumab plus chemotherapy (n=307) experienced a serious event of hypophysitis. Of the 15 patients with events of hypophysitis in the TNBC population in KN522 pembrolizumab in combination with neoadjuvant chemotherapy followed by continued adjuvant pembrolizumab monotherapy group (n=783), 10 (1.3%) experienced serious events of hypophysitis. Of the 10 patients with events of hypophysitis in the melanoma population in KN716 (n=483), 4 (0.8%) experienced serious events of hypophysitis. Of the 4 patients with events of hypophysitis in gastric cancer population in KN811 pembrolizumab combination therapy (n=350), 3 (0.9%) experienced serious events of hypophysitis. Of the 4 patients with events of hypophysitis in the NSCLC population in KN091 pembrolizumab monotherapy (n=580), 4 (0.7%) experienced serious events of hypophysitis. Of the 3 patients with events of hypophysitis in the gastric cancer population in KN859 pembrolizumab plus chemotherapy (n=785), 1 (0.1%) experienced a serious event of hypophysitis. Of the 2 patients with events of hypophysitis in the BTC population in KN966 (n=529), 1 (0.2%) experienced a serious event of hypophysitis. Of the 2 patients with events of hypophysitis in the NSCLC population in KN671 pembrolizumab in combination with chemotherapy as neoadjuvant treatment followed by continued adjuvant pembrolizumab monotherapy (n=396), 1 (0.3%) experienced a serious event of hypophysitis.

Table SVII.3.1.5: Details of Important Identified Risk: Immune-Mediated Adverse Reactions- Endocrinopathies – Hypophysitis (Including Hypopituitarism)

Severity and Nature of the Risk

Identified treatment emergent adverse events (AE) of hypopituitarism, hypophysitis (all events) in participants summarized by grade– pembrolizumab. (Table includes events for 30 days after discontinuation.)

Hypopituitarism and Hypophysitis (AEOSI)
KN001, KN002 and KN006 Melanoma and KN001 and KN010 NSCLC Subjects Treated with Pembrolizumab (Treatment-Emergent)

	Cumulative NSCLC 001/010 + MEL 001/002/006	
	n	(%)
Subjects in population	2,799	
with one or more adverse events	17	(0.6)
Hypophysitis	9	(0.3)
Grade 2	5	(0.2)
Grade 3	3	(0.1)
Grade 4	1	(0.0)

Hypopituitarism	8	(0.3)
Grade 1	2	(0.1)
Grade 2	1	(0.0)
Grade 3	5	(0.2)

Every subject is counted a single time for each applicable specific adverse event. A subject with multiple adverse events within a system organ class is counted a single time for that system organ class.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns is greater than or equal to the incidence specified in the report title, after rounding.
Only the highest reported grade of a given adverse event is counted for the individual subject.
Grades are based on NCI CTCAE version 4.0.

In the NSCLC population in KN024 and KN042 (n=790), there were 4 patients with Grade 3 events of hypophysitis (0.5%). There were no patients with Grade 4 or 5 events of hypophysitis.

In the NSCLC population in KN189 and KN021 (Cohorts C and G) pembrolizumab plus chemotherapy (n=488), there were no patients with Grade 3, 4 or 5 events of hypophysitis.

In the UC population in KN052 (n=370), there were 2 (0.5%) patients with Grade 3 events and no patients with Grade 4 or 5 events of hypophysitis.

In the HNSCC population in KN048 pembrolizumab monotherapy group (n=300), there was 1 patient with a Grade 3 event of hypophysitis (0.3%). There were no patients with Grade 4 or 5 events of hypophysitis. In the HNSCC population in KN048 pembrolizumab plus chemotherapy group (n=276), there was 1 patient with a Grade 3 event of hypophysitis (0.4%). There were no patients with Grade 4 or 5 events of hypophysitis.

In the melanoma population in KN054 (n=509), there were 3 (0.6%) patients with Grade 3 events and no patients with Grade 4 or 5 events of hypophysitis.

In the NSCLC population in KN407 and KN021 (Cohort A) (n=303), there was 1 (0.3%) patient with a Grade 3 event and 1 (0.3%) patient with a Grade 4 event. There were no patients with Grade 5 events of hypophysitis.

In the RCC population in KN426 pembrolizumab plus axitinib (n=429), there were 4 (0.9%) patients with Grade 3 events of hypophysitis. There were no patients with Grade 4 or 5 events of hypophysitis.

In the CRC population in KN177 (n=153) there were no patients with Grade 3-5 events of hypophysitis reported.

Table SVII.3.1.5: Details of Important Identified Risk: Immune-Mediated Adverse Reactions- Endocrinopathies – Hypophysitis (Including Hypopituitarism)

	In the esophageal cancer population in KN590 pembrolizumab plus chemotherapy (n=370), there was 1 (0.3%) patient with a Grade 3 event of hypophysitis. There were no patients with Grade 4 or 5 events of hypophysitis. In the TNBC population in KN355 pembrolizumab plus chemotherapy group (n=596), there were no patients with Grade 3-5 events of hypophysitis. In the RCC population in KN581 pembrolizumab plus lenvatinib (n=352), there were 2 (0.6%) patients with Grade 3 events of hypophysitis. There were no patients with Grade 4 or 5 events of hypophysitis. In the endometrial carcinoma population in KN146 and KN775 pembrolizumab plus lenvatinib (n=530), there were 2 (0.4%) patients with Grade 3 events of hypophysitis. There were no patients with Grade 4 or 5 events of hypophysitis. In the RCC population in KN564 pembrolizumab monotherapy (n=488) there were 2 (0.4%) patients with Grade 3 events of hypophysitis. There were no patients with Grade 4 or 5 events of hypophysitis. In the cervical cancer population in KN826 pembrolizumab plus chemotherapy (n=307), there was 1 (0.3%) patient with a Grade 3 event of hypophysitis. There were no patients with Grade 4 or 5 events of hypophysitis. In the TNBC population in KN522 pembrolizumab in combination with neoadjuvant chemotherapy followed by continued adjuvant pembrolizumab monotherapy group (n=783) there were 10 (1.3%) patients with Grade 3 events of hypophysitis. There were no patients with Grade 4 or 5 events of hypophysitis reported. In the melanoma population in KN716 pembrolizumab monotherapy (n=483), there were 3 (0.6%) patients with Grade 3 events of hypophysitis. There were no patients with Grade 4 or 5 events of hypophysitis. In the gastric cancer population in KN811 pembrolizumab combination therapy (n=350), there were 2 (0.6%) patients with Grade 3 events of hypophysitis. There were no patients with Grade 4 or 5 events of hypophysitis. In the NSCLC population in KN091 pembrolizumab monotherapy (n=580) there were 3 (0.5%) patients with Grade 3 events of hypophysitis. There were no patients with Grade 4 or 5 events of hypophysitis. In the gastric cancer population in KN859 pembrolizumab plus chemotherapy (n=785), there was 1 (0.1%) patient with a Grade 3 event of hypophysitis reported. There were no patients with Grade 4 or 5 events of hypophysitis. In the BTC population in KN966 pembrolizumab plus chemotherapy (n=529), there was 1 (0.2%) patient with a Grade 3 event of hypophysitis reported. There were no patients with Grade 4 or 5 events of hypophysitis. In the NSCLC population in KN671 pembrolizumab in combination with chemotherapy as neoadjuvant treatment followed by continued adjuvant pembrolizumab monotherapy (n=396) there was 1 (0.3%) patient with a Grade 3 event of hypophysitis, there were no patients with Grade 4 or 5 events of hypophysitis reported.
Risk Factors and Risk Groups:	No specific risk factors for hypophysitis (including hypopituitarism) associated with pembrolizumab have been identified.

Table SVII.3.1.5: Details of Important Identified Risk: Immune-Mediated Adverse Reactions- Endocrinopathies – Hypophysitis (Including Hypopituitarism)

Preventability:	Although the development of hypophysitis (including hypopituitarism) cannot be completely prevented; patients should be monitored for signs and symptoms of hypophysitis (including hypopituitarism) and if they develop, other causes excluded. Withholding/discontinuation of pembrolizumab and appropriate medical intervention including corticosteroids following the onset of hypophysitis (including hypopituitarism) may result in recovery.
Impact on the Risk-Benefit Balance of the Product:	Hypophysitis and hypopituitarism have the potential to become severe or life-threatening due to hormone deficiencies in individual patients. Given the fatal outcome of untreated cancer, the risk of hypophysitis (including hypopituitarism) is outweighed by the potential benefit.
Public Health Impact:	This risk has minimal public health impact outside its effect on individual patients.

Table SVII.3.1.6: Details of Important Identified Risk: Immune-Mediated Adverse Reactions- Endocrinopathies –Adrenal Insufficiency (Primary and Secondary)

Important Identified Risk:	Immune-mediated Endocrinopathies- Adrenal Insufficiency (primary and secondary)
Potential Mechanisms:	Pembrolizumab is a potent and highly-selective humanized monoclonal antibody (mAb) of the Immunoglobulin G4 (IgG4)/kappa isotype directed to the programmed cell death-1 (PD-1) receptor and designed to directly block the interaction between the receptor and its ligands, PD-L1 and PD-L2. The PD-1 pathway represents a major immune control switch which may be engaged by tumor cells to overcome active T-cell immune surveillance. T-cell activation in proximity to normal tissue may lead to inflammation and injury to normal tissue.
Evidence Source(s) and Strength of Evidence:	Review of pembrolizumab clinical trial data, post-marketing experience and literature regarding endocrinopathies- Adrenal insufficiency (primary and secondary) represent sufficient evidence of a causal association with pembrolizumab exposure. CTD 2.7.4 Please reference evidence source cited in Table SVII.3.1.1; Details of Important Identified Risk: Immune-Mediated Pneumonitis
Characterisation of the Risk: Immune-mediated Endocrinopathies- Adrenal Insufficiency (primary and secondary)	
Frequency with 95%CI	95% Confidence Interval for the Overall Incidence (%) of AEOSI- Adrenal Insufficiency KN001, KN002 and KN006 Melanoma and KN001 and KN010 NSCLC Subjects Treated with Pembrolizumab

	Cumulative MEL 001/002/006 + NSCLC 001/010	
	n (%)	95% CI
Adrenal Insufficiency*	22 (0.8)	(0.5, 1.2)

*Includes adrenocortical insufficiency acute, secondary adrenocortical insufficiency, primary adrenal insufficiency and Addison's disease

The overall number and proportion of patients with adrenal insufficiency in the NSCLC population in KN024 and KN042 (n=790), was 4 (0.5%) (95% CI-0.1,1.3), which is generally similar to the proportion of patients with the event of adrenal insufficiency in the reference safety dataset for melanoma and NSCLC.

The overall number and proportion of patients with adrenal insufficiency in the NSCLC population in KN189 and KN021 (Cohorts C and G) (n=488) was 3 (0.6%) (95% CI- 0.1, 1.8), which is generally similar to the proportion of patients with the event of adrenal insufficiency in the reference safety dataset for melanoma and NSCLC.

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Table SVII.3.1.6: Details of Important Identified Risk: Immune-Mediated Adverse Reactions- Endocrinopathies –Adrenal Insufficiency (Primary and Secondary)

	The overall number and proportion of patients with adrenal insufficiency reported in the HL population in KN013, KN087, and KN204 (n=389) was 1 (0.3%) (95%CI-0.0, 1.4), which is generally similar to the proportion of patients with the event of adrenal insufficiency in the reference safety dataset for melanoma and NSCLC. The overall number and proportion of patients with adrenal insufficiency in the UC population in KN052 (n=370) was 6 (1.6%) (95%CI-0.6, 3.5) and in KN045 (n=266) was 1 (0.4%) (95%CI-0, 2.1), which is generally similar to the proportion of patients with the event of adrenal insufficiency in the reference safety dataset for melanoma and NSCLC. The overall number and proportion of patients with adrenal insufficiency in the HNSCC population in KN040, KN012 and KN055 (n=609) was 4 (0.7%) (95%CI-0.2, 1.7), which is generally similar to the proportion of patients with the event of adrenal insufficiency in the reference safety dataset for melanoma and NSCLC. The overall number and proportion of patients with adrenal insufficiency in the HNSCC population in KN048 pembrolizumab monotherapy (n=300) and pembrolizumab plus chemotherapy (n=276) groups, were 1 (0.3%) (95% CI-0,1.8) and 0 (0%) (95% CI-0,1.3) respectively, which is generally similar to the proportion of patients with the event of adrenal insufficiency in the reference safety dataset for melanoma and NSCLC. The overall number and proportion of patients with adrenal insufficiency in the melanoma population in KN054 (n=509) was 5 (1%) (95% CI-0.3, 2.3) which is generally similar to the overall frequency in the reference safety dataset for melanoma and NSCLC. There were no patients with events of adrenal insufficiency in the NSCLC population in KN407 and KN021 (Cohort A). The overall number and proportion of patients with adrenal insufficiency in the RCC population in KN426 pembrolizumab plus axitinib (n=429) was 13 (3.0%) (95% CI-1.6,5.1). The proportion of patients with events of adrenal insufficiency, in the RCC population in KN426 pembrolizumab plus axitinib, although somewhat more common than in the reference safety dataset were generally consistent in nature with the proportion of patients with events of adrenal insufficiency previously reported for pembrolizumab. The overall number and proportion of patients with adrenal insufficiency in the CRC population in KN177 (n=153) was 4 (2.6%) (95% CI-0.7,6.6) which is generally similar to the proportion of patients with the event of adrenal insufficiency in the reference safety dataset. The overall number and proportion of patients with adrenal insufficiency in the esophageal cancer population in KN590 pembrolizumab plus chemotherapy (n=370) was 4 (1.1%) (95% CI-0.3,2.7), which is generally similar to the proportion of patients with the event of adrenal insufficiency in the reference safety dataset for melanoma and NSCLC. The overall number and proportion of patients with adrenal insufficiency in the TNBC population in KN355 pembrolizumab plus chemotherapy group (n=596) was 7 (1.2%) (95% CI-0.5,2.4), which is generally similar to the proportion of patients with the event of adrenal insufficiency in the reference safety dataset for melanoma and NSCLC. The overall number and proportion of patients with adrenal insufficiency in the RCC population in KN581 pembrolizumab plus lenvatinib (n=352) was 18 (5.1%) (95% CI-3.1,8.0). The proportion of patients with events of adrenal insufficiency, although higher than the reference safety dataset, were generally consistent in nature with the proportion of patients with events of adrenal insufficiency previously reported for pembrolizumab. The overall number and proportion of patients with adrenal insufficiency in the endometrial carcinoma population in KN146 and KN775 pembrolizumab plus lenvatinib (n=530) was 9 (1.7%) (95% CI-0.8, 3.2), which is generally similar to the proportion of patients with the event of adrenal insufficiency in the reference safety dataset. The overall number and proportion of patients with adrenal insufficiency in the RCC population in KN564 pembrolizumab monotherapy (n=488) was 10 (2%) (95% CI-1,3.7), which is generally similar to the proportion of patients with the event of adrenal insufficiency in the reference safety dataset for melanoma and NSCLC.

Table SVII.3.1.6: Details of Important Identified Risk: Immune-Mediated Adverse Reactions- Endocrinopathies –Adrenal Insufficiency (Primary and Secondary)

	There were no patients with events of adrenal insufficiency reported in the MSI-H population in KN158 Cohort K and KN164 Cohorts A and B. The overall number and proportion of patients with adrenal insufficiency in the cervical cancer population in KN826 pembrolizumab plus chemotherapy (n=307) was 4 (1.3%) (95% CI-0.4, 3.3), which is generally similar to the proportion of patients with the event of adrenal insufficiency in the reference safety dataset. The overall number and proportion of patients with adrenal insufficiency in the TNBC population in KN522 pembrolizumab in combination with neoadjuvant chemotherapy followed by continued adjuvant pembrolizumab monotherapy group (n=783) was 20 (2.6%) (95% CI-1.6,3.9), which is generally similar to the proportion of patients with the event of adrenal insufficiency in the reference safety dataset. The overall number and proportion of patients with adrenal insufficiency in the melanoma population in KN716 pembrolizumab monotherapy (n=483) was 11 (2.3%) (95% CI-1.1, 4.0), which is generally similar to the proportion of patients with the event of adrenal insufficiency in the reference safety dataset for melanoma and NSCLC. The overall number and proportion of patients with adrenal insufficiency in the gastric cancer population in KN811 pembrolizumab combination therapy (n=350) was 4 (1.1%) (95% CI-0.3, 2.9), which is generally similar to the proportion of patients with the event of adrenal insufficiency in the reference safety dataset. The overall number and proportion of patients with adrenal insufficiency in the NSCLC population in KN091 pembrolizumab monotherapy (n=580) was 10 (1.7%) (95% CI- 0.8, 3.1), which is generally similar to the proportion of patients with the event of adrenal insufficiency in the reference safety dataset. The overall number and proportion of patients with adrenal insufficiency in the gastric cancer population in KN859 pembrolizumab plus chemotherapy (n=785) was 10 (1.3%) (95% CI-0.6, 2.3), which is generally similar to the proportion of patients with the event of adrenal insufficiency in the reference safety dataset. The overall number and proportion of patients with adrenal insufficiency in the BTC population in KN966 pembrolizumab plus chemotherapy (n=529) was 3 (0.6%) (95% CI-0.1, 1.6), which is generally similar to the proportion of patients with the event of adrenal insufficiency in the reference safety dataset. The overall number and proportion of patients with adrenal insufficiency in the NSCLC population in KN671 pembrolizumab in combination with chemotherapy neoadjuvant treatment followed by continued adjuvant pembrolizumab monotherapy (n=396) was 1 (0.3%) (95% CI-0.0, 1.4), which is generally similar to the overall proportion of patients with events of adrenal insufficiency in the reference safety dataset.

Table SVII.3.1.6: Details of Important Identified Risk: Immune-Mediated Adverse Reactions- Endocrinopathies –Adrenal Insufficiency (Primary and Secondary)

Outcomes

Percent overall, fatal, not resolved, resolved, and unknown for identified risk of adrenal insufficiency (primary and secondary) - pembrolizumab. (AEs for 30 days after discontinuation were included)

Adrenal Insufficiency (AEOSI)
KN001, KN002 and KN006 Melanoma and KN001 and KN010 NSCLC Subjects Treated with Pembrolizumab (Treatment-Emergent)

		Cumulative NSCLC 001/010 + MEL 001/002/006	
	Outcome	n	(%)
Subjects in population		2,799	
With one or more adverse events	Overall	22	(0.8)
	Fatal	0	(0.0)
	Not Resolved	17	(0.6)
	Resolved	5	(0.2)
	Sequelae	0	(0.0)
	Unknown	0	(0.0)

Every subject is counted once on each applicable row.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns is greater than or equal to the percent incidence specified in the report title, after rounding.
Outcome: Resolved = RECOVERED/RESOLVED, Not resolved = NOT RECOVERED/NOT RESOLVED.

In the NSCLC population in KN024 and KN042 (n=790), the outcome of the 4 (0.5%) patients with events of adrenal insufficiency were as follows: 2 (0.3%) resolved, 2 (0.3%) not resolved. There were no patients with events of adrenal insufficiency with a fatal outcome.

In the NSCLC population in KN189 and KN021 (Cohorts C and G) (n=488), the outcome of the 3 patients with events of adrenal insufficiency were as follows: 1 (0.2%) resolved, 1 (0.2%) not resolved, and 1 (0.2%) unknown. There were no patients with events of adrenal insufficiency with a fatal outcome.

In the HL population in KN013, KN087, and KN204 (n=389), the outcome for the 1 (0.3%) patient with an event of adrenal insufficiency was not recovered. There were no patients with events of adrenal insufficiency with a fatal outcome.

In the UC population in KN052 (n=370), the outcomes for the 6 patients with events of adrenal insufficiency were as follows: 3 (0.8%) not resolved, 1 (0.3%) resolved with sequelae and 2 (0.5%) resolved and in the UC population in KN045 (n=266), the outcome for the 1 (0.4%) patient with an event of adrenal insufficiency was not resolved. There were no patients with events of adrenal insufficiency with a fatal outcome.

In the HNSCC population in KN040, KN012 and KN055 (n=609), the outcomes for the 4 patients with events of adrenal insufficiency were as follows: 2 (0.3%) not resolved, 1 (0.2%) resolving and 1 (0.2%) resolved with sequelae. There were no patients with events of adrenal insufficiency with a fatal outcome.

In the HNSCC population in KN048 pembrolizumab monotherapy group (n=300), the outcome for the 1 (0.3%) patient with an event of adrenal insufficiency was resolved with sequelae. There were no patients with events of adrenal insufficiency with a fatal outcome.

In the melanoma population in KN054 (n=509), the outcomes for the 5 patients with events of adrenal insufficiency were as follows: 3 (0.6%) not resolved and 2 (0.4%) resolved with sequelae. There were no patients with events of adrenal insufficiency with a fatal outcome.

In the RCC population in KN426 pembrolizumab plus axitinib (n=429) the outcomes for the 13 patients with events of adrenal insufficiency were as follows: 2 (0.5%) resolved, 4 (0.9%) not

Table SVII.3.1.6: Details of Important Identified Risk: Immune-Mediated Adverse Reactions- Endocrinopathies –Adrenal Insufficiency (Primary and Secondary)

	resolved, 2 (0.5%) resolving and 5 (1.2%) resolved with sequelae. There were no patients with events of adrenal insufficiency with a fatal outcome. In the CRC population in KN177 (n=153), the outcomes for the 4 patients with events of adrenal insufficiency were as follows: 2 (1.3%) not resolved, 1 (0.7% resolved, and 1 (0.7%) resolved with sequelae. There were no patients with events of adrenal insufficiency with a fatal outcome. In the RCC population in KN581 pembrolizumab plus lenvatinib (n=352), the outcomes for the 18 patients with events of adrenal insufficiency were as follows: 15 (4.3%) not resolved, 2 (0.6%) resolving, and 1 (0.3%) resolved. There were no patients with events of adrenal insufficiency with a fatal outcome. In the esophageal cancer population in KN590 pembrolizumab plus chemotherapy (n=370), the outcomes for the 4 patients with events of adrenal insufficiency were as follows: 1 (0.3%) resolved, 2 (0.5%) not resolved, and 1 (0.3%) resolving. There were no patients with events of adrenal insufficiency with a fatal outcome. In the TNBC population in KN355 pembrolizumab plus chemotherapy group (n=596) the outcomes for the 7 patients with events of adrenal insufficiency were as follows: 2 (0.3%) resolved, 4 (0.7%) not resolved, and 1 (0.2%) resolved with sequelae. There were no patients with events of adrenal insufficiency with a fatal outcome. In the endometrial carcinoma population in KN146 and KN775 pembrolizumab plus lenvatinib (n=530) the outcomes for the 9 patients with events of adrenal insufficiency were as follows: 5 (0.9%) not resolved, 2 (0.4%) resolving, 1 (0.2%) resolved, and 1 (0.2%) resolved with sequelae. There were no patients with events of adrenal insufficiency with a fatal outcome. In the RCC population in KN564 pembrolizumab monotherapy (n=488), the outcomes for the 10 patients with events of adrenal insufficiency were as follows: 1 (0.2%) resolved, 2 (0.4%) resolving, 3 (0.6%) not resolved and 4 (0.8%) resolved with sequelae. There were no patients with events of adrenal insufficiency with a fatal outcome. In the cervical cancer population in KN826 pembrolizumab plus chemotherapy (n=307), the outcomes for the 4 patients with events of adrenal insufficiency were as follows: 1 (0.3%) not resolved, 1 (0.3%) resolving, and 2 (0.7%) resolved with sequelae. There were no patients with events of adrenal insufficiency with a fatal outcome. In the TNBC population in KN522 pembrolizumab in combination with neoadjuvant chemotherapy followed by continued adjuvant pembrolizumab monotherapy group (n=783), the outcomes for the 20 patients with events of adrenal insufficiency were as follows: 1 (0.1%) resolved, 9 (1.1%) not resolved, 5 (0.6%) resolving, and 5 (0.6%) resolved with sequelae. There were no patients with events of adrenal insufficiency with a fatal outcome. In the melanoma population in KN716 pembrolizumab monotherapy (n=483), the outcomes for the 11 patients with events of adrenal insufficiency were as follows: 5 (1%) not resolved, 3 (0.6%) resolving, and 3 (0.6%) resolved. There were no patients with events of adrenal insufficiency with a fatal outcome. In the gastric cancer population in KN811 pembrolizumab combination therapy (n=350), the outcome for the 4 patients with events of adrenal insufficiency were as follows: 2 (0.6%) not resolved, 1 (0.3%) resolving and 1 (0.3%) resolved with sequelae. There were no patients with events of adrenal insufficiency with a fatal outcome. In the NSCLC population in KN091 pembrolizumab monotherapy (n=580), the outcomes for the 10 patients with events of adrenal insufficiency were as follows: 1 (0.2%) resolved, 1 (0.2%) resolved with sequelae, and 8 (1.4%) not resolved. There were no patients with events of adrenal insufficiency with a fatal outcome. In the gastric cancer population in KN859 pembrolizumab plus chemotherapy (n=785), the outcomes for the 10 patients with events of adrenal insufficiency were as follows: 6 (0.8%) not resolved, and 4 (0.5%) resolving. There were no patients with events of adrenal insufficiency with a fatal outcome.

Table SVII.3.1.6: Details of Important Identified Risk: Immune-Mediated Adverse Reactions- Endocrinopathies –Adrenal Insufficiency (Primary and Secondary)

<table>
<tr><td></td><td>In the BTC population in KN966 pembrolizumab plus chemotherapy (n=529), the worst reported outcomes for the 3 patients with events of adrenal insufficiency were as follows: 1 (0.2%) resolving, 1 (0.2%) not resolved and 1 (0.2%) resolved with sequelae. There were no patients with events of adrenal insufficiency with a fatal outcome.

In the NSCLC population in KN671 pembrolizumab in combination with chemotherapy as neoadjuvant treatment followed by continued adjuvant pembrolizumab monotherapy group (n=396), the outcome for the 1 (0.3%) patient with an event of adrenal insufficiency was resolving. There were no patients with events of hypophysitis with a fatal outcome.

Aggregate Review

Review of the ASE dataset (n=7730) yielded no fatal cases of adrenal insufficiency. Review of the global safety database also yielded no fatal cases from ongoing interventional monotherapy clinical trials and no fatal cases from the PM or non-interventional environment.</td></tr>
<tr><td>Seriousness</td><td>Percent serious for identified risk of adrenal insufficiency (primary and secondary) – pembrolizumab (Serious AEs for 90 days after discontinuation were included.)

Adrenal Insufficiency - Serious (AEOSI)
KN001, KN002 and KN006 Melanoma and KN001 and KN010 NSCLC Subjects Treated with Pembrolizumab
(Treatment-Emergent)

<table>
<tr><td></td><td colspan="2">Cumulative NSCLC 001/010 + MEL 001/002/006</td></tr>
<tr><td></td><td>n</td><td>(%)</td></tr>
<tr><td>Subjects in population</td><td>2,799</td><td></td></tr>
<tr><td>with one or more adverse events</td><td>10</td><td>(0.4)</td></tr>
<tr><td></td><td></td><td></td></tr>
<tr><td>Adrenal insufficiency</td><td>8</td><td>(0.3)</td></tr>
<tr><td>Adrenocortical insufficiency acute</td><td>1</td><td>(0.0)</td></tr>
<tr><td>Secondary adrenocortical insufficiency</td><td>1</td><td>(0.0)</td></tr>
<tr><td colspan="3">Every subject 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.
Include all treated subjects in KN001 Part B1, B2, B3, D, C, F1, F2, F3 and all subjects in KN002 treated with Pembrolizumab in the original phase, and all subjects in KN006 and KN010 treated with Pembrolizumab.</td></tr>
</table>

Of the 4 patients with events of adrenal insufficiency reported in the NSCLC population in KN024 and KN042 (n=790), 2 (0.3%) experienced serious events of adrenal insufficiency.

Of the 3 patients with events of adrenal insufficiency reported in the NSCLC population in KN189 and KN021 (Cohorts C and G), 1 (0.2%) experienced a serious event of adrenal insufficiency.

There were no patients with serious events of adrenal insufficiency reported in the HL population in KN013, KN087, and KN204 (n=389).

Of the 6 (1.6%) patients with events of adrenal insufficiency reported in the UC population in KN052 (n=370), all 6 experienced serious events of adrenal insufficiency and the 1 (0.4%) patient with an event of adrenal insufficiency reported in the UC population in KN045 (n=266) experienced a serious event of adrenal insufficiency.

Of the 4 patients with events of adrenal insufficiency reported in the HNSCC population in KN040, KN012 and KN055 (n=609), 1 (0.2%) experienced a serious event of adrenal insufficiency.

The 1 (0.3%) patient with an event of adrenal insufficiency reported in the HNSCC population in KN048 pembrolizumab monotherapy group (n=300) experienced a serious event of adrenal insufficiency.

Of the 5 patients with events of adrenal insufficiency reported in the melanoma population in KN054 (n=509), 1 (0.2%) experienced a serious event of adrenal insufficiency.</td></tr>
</table>

Table SVII.3.1.6: Details of Important Identified Risk: Immune-Mediated Adverse Reactions- Endocrinopathies –Adrenal Insufficiency (Primary and Secondary)

	Of the 13 patients with events of adrenal insufficiency in the RCC population in KN426 pembrolizumab plus axitinib (n=429), 5 (1.2%) experienced serious events of adrenal insufficiency. Of the 4 patients with events of adrenal insufficiency in the CRC population in KN177 (n=153), 2 (1.3%) experienced serious events of adrenal insufficiency. Of the 4 patients with events of adrenal insufficiency in the esophageal cancer population in KN590 pembrolizumab plus chemotherapy (n=370), 1 (0.3%) experienced a serious event of adrenal insufficiency. Of the 7 patients with events of adrenal insufficiency in the TNBC population in KN355 pembrolizumab plus chemotherapy group (n=596), 3 (0.5%) experienced serious events of adrenal insufficiency. Of the 18 patients with events of adrenal insufficiency in the RCC population in KN581 pembrolizumab plus lenvatinib (n=352), 7 (2.0%) experienced serious events of adrenal insufficiency. Of the 9 patients with events of adrenal insufficiency in the endometrial carcinoma population in KN146 and KN775 pembrolizumab plus lenvatinib (n=530), 6 (1.1%) experienced serious events of adrenal insufficiency. Of the 10 patients with events of adrenal insufficiency in the RCC population in KN564 pembrolizumab monotherapy (n=488), 6 (1.2%) experienced serious events of adrenal insufficiency. Of the 4 patients with events of adrenal insufficiency in the cervical cancer population in KN826 pembrolizumab plus chemotherapy (n=307), 3 (1.0%) experienced serious events of adrenal insufficiency. Of the 20 patients with events of adrenal insufficiency in the TNBC population in KN522 pembrolizumab in combination with neoadjuvant chemotherapy followed by continued adjuvant pembrolizumab monotherapy group (n=783), 8 (1.0%) experienced serious events of adrenal insufficiency. Of the 11 patients with events of adrenal insufficiency in the melanoma population in KN716 pembrolizumab monotherapy (n=483), 4 (0.8%) experienced serious events of adrenal insufficiency. Of the 4 patients with events of adrenal insufficiency in gastric cancer population in KN811 pembrolizumab combination therapy (n=350), 1 (0.3%) experienced a serious event of adrenal insufficiency. Of the 10 patients with events of adrenal insufficiency in the NSCLC population of KN091 pembrolizumab monotherapy (n=580), 2 (0.3%) experienced serious events of adrenal insufficiency. Of the 10 patients with events of adrenal insufficiency in the gastric cancer population in KN859 pembrolizumab plus chemotherapy (n=785), 4 (0.5%) experienced serious events of adrenal insufficiency. Of the 3 patients with events of adrenal insufficiency in the BTC population in KN966 pembrolizumab plus chemotherapy (n=529), 1 (0.2%) experienced a serious event of adrenal insufficiency. The 1 (0.3%) patient with an event of adrenal insufficiency in the NSCLC population in KN671 pembrolizumab in combination with chemotherapy as neoadjuvant treatment followed by continued adjuvant pembrolizumab monotherapy (n=396), experienced a serious event of adrenal insufficiency.
Severity and Nature of the Risk	Identified treatment emergent adverse events (AE) of adrenal insufficiency (primary and secondary) (all events) in participants summarized by grade– pembrolizumab. (Table includes events for 30 days after discontinuation.)

Table SVII.3.1.6: Details of Important Identified Risk: Immune-Mediated Adverse Reactions- Endocrinopathies –Adrenal Insufficiency (Primary and Secondary)

Adrenal Insufficiency (AEOSI)
KN001, KN002 and KN006 Melanoma and KN001 and KN010 NSCLC Subjects Treated with Pembrolizumab (Treatment-Emergent)

	Cumulative NSCLC 001/010 + MEL 001/002/006	
	n	(%)
Subjects in population	2,799	
with one or more adverse events	22	(0.8)
Adrenal insufficiency	20	(0.7)
Grade 1	3	(0.1)
Grade 2	9	(0.3)
Grade 3	7	(0.3)
Grade 4	1	(0.0)
Adrenocortical insufficiency acute	1	(0.0)
Grade 3	1	(0.0)
Secondary adrenocortical insufficiency	1	(0.0)
Grade 3	1	(0.0)

Every subject is counted a single time for each applicable specific adverse event. A subject with multiple adverse events within a system organ class is counted a single time for that system organ class.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns is greater than or equal to the incidence specified in the report title, after rounding.
Only the highest reported grade of a given adverse event is counted for the individual subject.
Grades are based on NCI CTCAE version 4.0.

In the NSCLC population in KN024 and KN042 (n=790), there was 1 (0.2%) patient with a Grade 3 event and 1 (0.2%) patient with a Grade 4 event of adrenal insufficiency. There were no patients with Grade 5 events of adrenal insufficiency.

In the NSCLC population in KN189 and KN021 (Cohorts C and G) (n=488), there was 1 (0.2%) patient with a Grade 3 event and no patients with Grade 4 or 5 events of adrenal insufficiency.

In the HL population in KN013, KN087, and KN204 (n=389), there were no patients with Grade 3-5 events of adrenal insufficiency.

In the UC population in KN052 (n=370), there were 5 (1.4%) patients with Grade 3 events and 1 (0.3%) patient with a Grade 4 event of adrenal insufficiency. There were no patients with Grade 5 events of adrenal insufficiency. In the UC population in KN045 (n=266), there was 1 (0.4) patient with a Grade 3 event and patients with no Grade 4 or 5 events of adrenal insufficiency.

In the HNSCC population in KN040, KN012 and KN055 (n=609), there was 1 (0.2%) patient with a Grade 3 event and no patients with Grade 4 or 5 events of adrenal insufficiency.

In the HNSCC population in KN048 pembrolizumab monotherapy group (n=300), there was 1 patient with a Grade 3 event of adrenal insufficiency (0.3%). There were no patients with Grade 4 or 5 events of adrenal insufficiency.

In the melanoma population in KN054 (n=509), there was 1 (0.2%) patient with a Grade 3 event and no patients with Grade 4 or 5 events of adrenal insufficiency.

In the RCC population in KN426 pembrolizumab plus axitinib (n=429), there were 10 (2.3%) patients with Grade 2 events and 3 (0.7%) patients with Grade 3 events of adrenal insufficiency. There were no patients with Grade 4 or 5 events of adrenal insufficiency.

In the CRC population in KN177 (n=153) there were 2 (1.3%) patients with Grade 3 events of adrenal insufficiency. There were no patients with Grade 4 or 5 events of adrenal insufficiency.

Table SVII.3.1.6: Details of Important Identified Risk: Immune-Mediated Adverse Reactions- Endocrinopathies –Adrenal Insufficiency (Primary and Secondary)

	In the esophageal cancer population in KN590 pembrolizumab plus chemotherapy (n=370), there were 2 (0.5%) patients with Grade 3 events of adrenal insufficiency. There were no patients with Grade 4 or 5 events of adrenal insufficiency. In the TNBC population in KN355 pembrolizumab plus chemotherapy group (n=596), there were 2 (0.3%) patients with Grade 3 events, and 1 (0.2%) patient with a Grade 4 event of adrenal insufficiency. There were no patients with Grade 5 events of adrenal insufficiency. In the RCC population in KN581 pembrolizumab plus lenvatinib (n=352), there were 4 (1.1%) patients with Grade 3 events of adrenal insufficiency. There were no patients with Grade 4 or 5 events of adrenal insufficiency. In the endometrial carcinoma population in KN146 and KN775 pembrolizumab plus lenvatinib (n=530), there were 6 (1.1%) patients with Grade 3 events of adrenal insufficiency. There were no patients with Grade 4 or 5 events of adrenal insufficiency. In the RCC population in KN564 pembrolizumab monotherapy (n=488) there were 6 (1.2%) patients with Grade 3 events of adrenal insufficiency. There were no patients with Grade 4 or 5 events of adrenal insufficiency. In the cervical cancer population in KN826 pembrolizumab plus chemotherapy (n=307), there were 3 (1.0%) patients with Grade 3 events of adrenal insufficiency. There were no patients with Grade 4 or 5 events of adrenal insufficiency. In the TNBC population in KN522 pembrolizumab in combination with neoadjuvant chemotherapy followed by continued adjuvant pembrolizumab monotherapy group (n=783) there were 7 (0.9%) patients with Grade 3 events and 1 (0.1%) patient with a Grade 4 event of adrenal insufficiency. There were no patients with Grade 5 events of adrenal insufficiency reported. In the melanoma population in KN716 pembrolizumab monotherapy (n=483), there were 4 (0.8%) patients with Grade 3 events of adrenal insufficiency. There were no patients with Grade 4 or 5 events of adrenal insufficiency. In the gastric cancer population in KN811 pembrolizumab combination therapy (n=350), there was 1 (0.3%) patient with a Grade 3 event of adrenal insufficiency. There were no patients with Grade 4 or 5 events of adrenal insufficiency. In the NSCLC population in KN091 pembrolizumab monotherapy (n=580) there were 4 (0.7%) patients with Grade 3 events of adrenal insufficiency. There were no patients with Grade 4 or 5 events of adrenal insufficiency. In the gastric cancer population in KN859 pembrolizumab plus chemotherapy (n=785), there were 3 (0.4%) patients with a Grade 3, and 1 (0.1%) patient with a Grade 4 event of adrenal insufficiency reported. There were no patients with Grade 5 events of adrenal insufficiency. In the BTC population in KN966 pembrolizumab plus chemotherapy (n=529), there was 1 (0.2%) patient with a Grade 3 event of adrenal insufficiency reported. There were no patients with Grade 4 or 5 events of adrenal insufficiency. In the NSCLC population in KN671 pembrolizumab in combination with chemotherapy as neoadjuvant treatment followed by continued adjuvant pembrolizumab monotherapy (n=396) there was 1 (0.3%) patient with a Grade 3 event of adrenal insufficiency, there were no patients with Grade 4 or 5 events of adrenal insufficiency reported.
Risk Factors and Risk Groups:	No specific risk factors for adrenal insufficiency (primary and secondary) associated with pembrolizumab have been identified.
Preventability:	Although the development of adrenal insufficiency (primary and secondary) cannot be completely prevented; patients should be monitored for signs and symptoms of adrenal insufficiency (primary and secondary) and if they develop, other causes excluded. Withholding/discontinuation of pembrolizumab and appropriate medical intervention including corticosteroids following the onset of adrenal insufficiency (primary and secondary) may result in recovery.

Table SVII.3.1.6: Details of Important Identified Risk: Immune-Mediated Adverse Reactions- Endocrinopathies –Adrenal Insufficiency (Primary and Secondary)

Impact on the Risk-Benefit Balance of the Product:	Adrenal insufficiency (primary and secondary) has the potential to become severe or life-threatening due to hormone deficiencies, in individual patients. Given the fatal outcome of untreated cancer, the risk of adrenal insufficiency (primary and secondary) is outweighed by the potential benefit.
Public Health Impact:	This risk has minimal public health impact outside its effect on individual patients.

Table SVII.3.1.7: Details of Important Identified Risk: Immune-Mediated Adverse Reactions- Endocrinopathies - Thyroid Disorder (Hypothyroidism, Hyperthyroidism, Thyroiditis)

Important Identified Risk:	Immune-mediated Endocrinopathies- Thyroid Disorder (Hypothyroidism, Hyperthyroidism, Thyroiditis)
Potential Mechanisms:	Pembrolizumab is a potent and highly-selective humanized monoclonal antibody (mAb) of the Immunoglobulin G4 (IgG4)/kappa isotype directed to the programmed cell death-1 (PD-1) receptor and designed to directly block the interaction between the receptor and its ligands, PD-L1 and PD-L2. The PD-1 pathway represents a major immune control switch which may be engaged by tumor cells to overcome active T-cell immune surveillance. The specific mechanism of thyroid disorders associated with pembrolizumab is unknown, but it is likely that immune mediated adverse events, including thyroid disorders, is due to immune mediated reaction to certain normal tissues.
Evidence Source(s) and Strength of Evidence:	Review of pembrolizumab clinical trial data, post-marketing experience and literature regarding endocrinopathies- thyroid disorder represent sufficient evidence of a causal association with pembrolizumab exposure. CTD 2.7.4 Please reference evidence source cited in Table SVII.3.1.1; Details of Important Identified Risk: Immune-Mediated Pneumonitis
Characterisation of the Risk: Immune-mediated Endocrinopathies- Thyroid Disorder (Hypothyroidism, Hyperthyroidism, Thyroiditis)	
Frequency with 95%CI	95% Confidence Interval for the Overall Incidence (%) of Hypothyroidism, Hyperthyroidism, Thyroiditis KN001, KN002 and KN006 Melanoma Subjects and KN001 and KN010 NSCLC Subjects Treated with Pembrolizumab

	Cumulative MEL 001/002/006 + NSCLC 001/010	
	n (%)	95% CI
Hypothyroidism	237 (8.5)	(7.5,9.6)
Hyperthyroidism	96 (3.4)	(2.8,4.2)
Thyroiditis	16 (0.6)	(0.3,0.9)

In the NSCLC population in KN189 and KN021 (Cohorts C and G) pembrolizumab plus chemotherapy (n=488), the overall number and proportion of patients with hypothyroidism was 39 (8%) (95% CI- 5.7, 10.8); of hyperthyroidism was 21 (4.3%) (95% CI- 2.7, 6.5); and of thyroiditis was 1 (0.2%) (95% CI- 0, 1.1), which was generally similar to the proportion of patients with the events of hypothyroidism, hyperthyroidism, and thyroiditis in the reference safety dataset for melanoma and NSCLC.

Table SVII.3.1.7: Details of Important Identified Risk: Immune-Mediated Adverse Reactions- Endocrinopathies - Thyroid Disorder (Hypothyroidism, Hyperthyroidism, Thyroiditis)

	The overall number and proportion of patients with hyperthyroidism in the HL population in KN013, KN087, and KN204 (n=389) was 17 (4.4%) (95%CI-2.6, 6.9); and of thyroiditis was 5 (1.3%) (95% CI-0.4, 3.0), which are generally similar to the proportion of patients with the events of hyperthyroidism and thyroiditis in the reference safety dataset for melanoma and NSCLC. The overall number and proportion of patients with hypothyroidism in the HL population in KN013, KN087, and KN204 (n=389) was 66 (17%) (95% CI-13.4, 21.1); all events of hypothyroidism were Grade 1 and 2. The rate of hypothyroidism seen in HL subjects is likely to be secondary to the significant proportion of subjects with a history of radiation to the neck and/or mediastinum, and to a higher rate of pre-existing hypothyroidism among participants in this group at baseline. The overall number and proportion of patients with hypothyroidism in the UC population in KN052 (n=370) was 24 (6.5%) (95%CI-4.2,9.5) and in KN045 (n=266) was 17 (6.4%) (95%CI-3.8,10); of hyperthyroidism in the UC population in KN052 (n=370) was 9 (2.4%) (95%CI-1.1,4.6) and in KN045 (n=266) was 10 (3.8%) (95%CI-1.8,6.8); and of thyroiditis in the UC population in KN052 (n=370) was 3 (0.8%) (95%CI-0.2,2.4) and in KN045 (n=266) was 2 (0.8%) (95%CI-0.1,2.7), which is generally similar to the proportion of patients with the events of hypothyroidism, hyperthyroidism, and thyroiditis in the reference safety dataset for melanoma and NSCLC. The overall number and proportion of patients with hypothyroidism in the HNSCC population in KN040, KN012 and KN055 (n=609) was 92 (15.1%) (95% CI-12.4, 18.2); the majority of these events were Grade 1 and 2. In view of the history of these subjects and the known risk of hypothyroidism in the HNSCC population, the higher rate of hypothyroidism in the HNSCC population when compared with the reference safety dataset largely reflects disease-related risk factors. The overall number and proportion of patients with hyperthyroidism in the HNSCC population in KN040, KN012 and KN055 (n=609) was 10 (1.6%) (95% CI-0.8, 3), which is generally similar to the proportion of patients with the events of hyperthyroidism in the reference safety dataset for melanoma and NSCLC. The number and proportion of patients with thyroiditis in the HNSCC population in KN040, KN012 and KN055 (n=609) was 3 (0.5%) (95% CI-0.1, 1.4), which are generally similar to the proportion of patients with the events of hyperthyroidism in the reference safety dataset for melanoma and NSCLC. The overall number and proportion of patients with hypothyroidism in the HNSCC population in KN048 pembrolizumab monotherapy group (n=300), was 54 (18%) (95% CI-13.8,22.8); of hyperthyroidism was 8 (2.7%) (95% CI-1.2,5.2); there were no cases of thyroiditis reported. The overall number and proportion of patients with hypothyroidism in the HNSCC population in KN048 pembrolizumab plus chemotherapy group (n=276), was 42 (15.2%) (95% CI-11.2,20); of hyperthyroidism was 13 (4.7%) (95% CI-2.5,7.9); and of thyroiditis was 1 (0.4%) (95% CI-0,2) in the HNSCC population in KN048 pembrolizumab plus chemotherapy group (n=276).The proportion of patients with events of hypothyroidism in KN048 although somewhat more common than in the reference safety dataset were generally consistent in nature with the proportion of events of hypothyroidism previously reported for pembrolizumab use in the HNSCC population. In the melanoma population in KN054 (n=509), the overall number and proportion of patients with events hypothyroidism was 75 (14.7%) (95% CI-11.8,18.1); of hyperthyroidism was 53 (10.4%) (95% CI-7.9,13.4); and of thyroiditis was 16 (3.1%) (95% CI-1.8, 5.1). The proportion of patients with events of hypothyroidism, hyperthyroidism and thyroiditis in KN054 although somewhat more common than in the reference safety dataset were generally consistent in nature with the proportion of events of hypothyroidism, hyperthyroidism and thyroiditis previously reported for pembrolizumab. The overall number and proportion of patients with hypothyroidism in the NSCLC population in KN407 and KN021 (Cohort A) (n=303), was 24 (7.9%) (95%CI-5.1, 11.6), the overall number and proportion of patients with hyperthyroidism was 20 (6.6%) (95% CI- 4.1,10), and the overall number and proportion of patients with thyroiditis was 3 (1%) (95%CI-0.2,2.9), which is generally similar to the proportion of patients with the events of hypothyroidism, hyperthyroidism, and thyroiditis in the reference safety dataset for melanoma and NSCLC.

Table SVII.3.1.7: Details of Important Identified Risk: Immune-Mediated Adverse Reactions- Endocrinopathies - Thyroid Disorder (Hypothyroidism, Hyperthyroidism, Thyroiditis)

	In the RCC population in KN426 pembrolizumab plus axitinib (n=429) the overall number and proportion of patients with hypothyroidism was 152 (35.4%) (95% CI-30.9,40.2); of hyperthyroidism was 55 (12.8%) (95% CI-9.8,16.4); and of thyroiditis was 12 (2.8%) (95% CI-1.5,4.8). Hypothyroidism is a known ADR of axitinib therapy, and axitinib contributes to the incidence of hypothyroidism in this combination. The proportion of patients with events of hypothyroidism, hyperthyroidism and thyroiditis in KN426 although more common than in the reference safety dataset were generally consistent in nature with the proportion of events of hypothyroidism, hyperthyroidism and thyroiditis previously reported for pembrolizumab. In the in the CRC population in KN177 (n=153) the overall number and proportion of patients with hypothyroidism was 19 (12.4%) (95% CI-7.6,18.7); of hyperthyroidism was 6 (3.9%) (95% CI-1.5,8.3); and of thyroiditis was 2 (1.3%) (95% CI-0.2,4.6). Hypothyroidism was reported more frequently in the KN177 pembrolizumab safety dataset compared with the RSD (12.4% vs 8.5%, respectively); however, when adjusted for exposure, the incidences were similar. The proportion of patients with events of hypothyroidism, hyperthyroidism and thyroiditis in KN177 were generally consistent in nature with the proportion of events of hypothyroidism, hyperthyroidism and thyroiditis previously reported for pembrolizumab. In the esophageal cancer population in KN590 pembrolizumab plus chemotherapy (n=370), the overall number and proportion of patients with hypothyroidism was 40 (10.8%) (95% CI-7.8,14.4); of hyperthyroidism was 21 (5.7%) (95% CI-3.5,8.5); and of thyroiditis 1 (0.3%) (95% CI-0,1.5), which are generally similar to the proportion of patients with the events of hypothyroidism, hyperthyroidism, and thyroiditis in the reference safety dataset for melanoma and NSCLC. In the TNBC population in KN355 pembrolizumab plus chemotherapy group (n=596) the overall number and proportion of patients with hyperthyroidism was 31 (5.2%) (95% CI-3.6,7.3); and of thyroiditis was 8 (1.3%) (95% CI-0.6,2.6), which are generally similar to the proportion of patients with the events of hyperthyroidism and thyroiditis in the reference safety dataset for melanoma and NSCLC. The overall number and proportion of patients with hypothyroidism was 95 (15.9%) (95% CI-13.1,19.1), although higher than in the reference safety dataset, the events were generally consistent in nature with the proportion of events of hypothyroidism previously reported for pembrolizumab. In the RCC population in KN581 pembrolizumab plus lenvatinib (n=352), the number and proportion of patients with thyroiditis was 2 (0.6%) (95% CI-0.1,2.0), which is generally similar to the proportion of patients with the events of thyroiditis in the reference safety dataset. The overall number and proportion of patients with hypothyroidism was 166 (47.2%) (95% CI- 41.8,52.5), which although higher than hypothyroidism in the reference safety dataset, was generally consistent in nature with the proportion of events of hypothyroidism previously reported for pembrolizumab. The overall number and proportion of patients with hyperthyroidism was 28 (8.0%) (95% CI-5.4,11.3), which although higher than hyperthyroidism in the reference safety dataset, was generally consistent in nature with the proportion of events of hyperthyroidism previously reported for pembrolizumab. In the endometrial carcinoma population in KN146 and KN775 pembrolizumab plus lenvatinib (n=530) the overall number and proportion of patients with thyroiditis was 12 (2.3%) (95% CI-1.2, 3.9), which is generally similar to the proportion of patients with the event of thyroiditis in the reference safety dataset. The overall number and proportion of patients with hypothyroidism was 296 (55.8%) (95% CI-51.5, 60.1); and of hyperthyroidism was 54 (10.2%) (95% CI-7.7, 13.1). The proportion of patients with events of hypothyroidism and hyperthyroidism in KN146 and KN775, although higher in frequency than in the reference safety dataset, were generally consistent in nature with the proportion of events of hypothyroidism and hyperthyroidism previously reported for pembrolizumab. The overall number and proportion of patients with hypothyroidism in the RCC population in KN564 pembrolizumab monotherapy (n=488) was 103 (21.1%) (95% CI-17.6,25); of hyperthyroidism was 58 (11.9%) (95% CI- 9.1,15.1). The overall number and proportion of patients with thyroiditis was 6 (1.2%) (95% CI-0.5,2.7), which was generally consistent to the overall proportion of patients with the events of hypothyroidism, hyperthyroidism, and thyroiditis in the

Table SVII.3.1.7: Details of Important Identified Risk: Immune-Mediated Adverse Reactions- Endocrinopathies - Thyroid Disorder (Hypothyroidism, Hyperthyroidism, Thyroiditis)

	reference safety dataset. The proportion of patients with events of hypothyroidism and hyperthyroidism in KN564 although more common than in the reference safety dataset were generally consistent in nature with the proportion of events of hypothyroidism and hyperthyroidism previously reported for pembrolizumab. In the MSI-H population in KN158 Cohort K and KN164 Cohorts A and B (n=475), the overall number and proportion of patients with hypothyroidism was 53 (11.2%) (95% CI-8.5, 14.3) and of hyperthyroidism was 25 (5.3%) (95% CI-3.4, 7.7), which is generally similar to the proportion of patients with the events of hypothyroidism and hyperthyroidism in the reference safety dataset. There were no patients with events of thyroiditis reported in the MSI-H population in KN158 Cohort K and KN164 Cohorts A and B. In the cervical cancer population in KN826 pembrolizumab plus chemotherapy (n=307), the overall number and proportion of patients with hypothyroidism was 56 (18.2%) (95% CI-14.1, 23.0); of hyperthyroidism was 23 (7.5%) (95% CI-4.8, 11.0); and of thyroiditis 11 (3.6%) (95% CI-1.8, 6.3). The proportion of patients with events of hypothyroidism, hyperthyroidism and thyroiditis although more common than in the reference safety dataset were generally consistent in nature with the proportion of events of hypothyroidism, hyperthyroidism and thyroiditis previously reported for pembrolizumab. In the TNBC population in KN522 pembrolizumab in combination with neoadjuvant chemotherapy followed by continued adjuvant pembrolizumab monotherapy group (n=783) the number and proportion of patients with hyperthyroidism was 41 (5.2%) (95% CI-3.8,7.0); and of thyroiditis was 16 (2.0%) (95% CI- 1.2,3.3), which are generally consistent to the proportion of patients with events of hyperthyroidism and thyroiditis in the reference safety dataset. The overall number and proportion of patients with hypothyroidism was 118 (15.1%) (95% CI-12.6,17.8), although higher than in the reference safety dataset, the proportion of patients with events were generally consistent in nature with the proportion of events of hypothyroidism previously reported for pembrolizumab. In the melanoma population in KN716 (n=483), the overall number and proportion of patients with hypothyroidism was 76 (15.7%) (95% CI-12.6, 19.3); of hyperthyroidism was 50 (10.4%) (95% CI-7.8, 13.4); of thyroiditis was 8 (1.7%) (95% CI-0.7, 3.2). The proportion of patients with events of hypothyroidism and hyperthyroidism in KN716 although more common than in the reference safety dataset were generally consistent in nature with the proportion of events of hypothyroidism and hyperthyroidism previously reported for pembrolizumab in advanced cancer. The overall number and proportion of patients with hypothyroidism in the gastric cancer population in KN811 pembrolizumab combination therapy (n=350) was 37 (10.6%) (95% CI-7.6, 14.3); with hyperthyroidism was 14 (4.0%) (95% CI-2.2, 6.6); and with thyroiditis was 4 (1.1%) (95% CI-0.3, 2.9), which were generally similar to the proportion of patients with events of hypothyroidism, hyperthyroidism, and thyroiditis in the reference safety dataset. The overall number and proportion of patients with hypothyroidism in the NSCLC population in KN091 pembrolizumab monotherapy (n=580) was 120 (20.7%) (95% CI-17.5,24.2); of hyperthyroidism was 62 (10.7%) (95% CI-8.3,13.5). The proportion of patients with events of hypothyroidism and hyperthyroidism in KN091 although more common than in the reference safety dataset, was generally consistent with the proportion of events of hypothyroidism and hyperthyroidism reported in adjuvant studies with pembrolizumab monotherapy. The proportion of patients with events of thyroiditis was 6 (1%) (95% CI-0.4,2.2) in KN091 which was similar to the proportion of patients with the events of thyroiditis in the reference safety dataset. In the gastric cancer population in KN859 pembrolizumab plus chemotherapy (n=785), the overall number and proportion of patients with hypothyroidism was 120 (15.3%) (95% CI-12.8, 18.0); of hyperthyroidism was 44 (5.6%) (95% CI-4.1, 7.5); and of thyroiditis was 9 (1.1%) (95% CI-0.5, 2.2). The proportion of patients with events of hypothyroidism, although more common than in the reference safety dataset, were generally consistent in nature with the proportion of patients with events of hypothyroidism previously reported for pembrolizumab. The proportions of patients with hyperthyroidism and thyroiditis were generally similar to the overall frequency in the reference safety dataset.

Table SVII.3.1.7: Details of Important Identified Risk: Immune-Mediated Adverse Reactions- Endocrinopathies - Thyroid Disorder (Hypothyroidism, Hyperthyroidism, Thyroiditis)

<table>
<tr><td></td><td>In the BTC population in KN966 (n=529) pembrolizumab plus chemotherapy, the overall number and proportion of patients with hypothyroidism was 46 (8.7%) (95% CI-6.4, 11.4); of hyperthyroidism was 19 (3.6%) (95% CI 2.2, 5.6); and thyroiditis was 3 (0.6%) (95% CI-0.1, 1.6), whichis generally similar to the proportion of patients with the events of hypothyroidism, hyperthyroidism, and thyroiditis in the reference safety dataset.

In the NSCLC population in KN671 pembrolizumab in combination with chemotherapy neoadjuvant treatment followed by continued adjuvant pembrolizumab monotherapy (n=396) the overall number and proportion of patients with hypothyroidism was 44 (11.1%) (95% CI-8.2, 14.6), with hyperthyroidism was 22 (5.6%) (95% CI-3.5, 8.3), and with thyroiditis was 4 (1.0) (95% CI 0.3, 2.6). The events of hypothyroidism and hyperthyroidism in KN671 were more common than in the reference safety dataset. However, after adjusting for exposure, the rates for hypothyroidism and hyperthyroidism were similar to those reported in the reference dataset. The overall number and proportion of patients with thyroiditis were similar to the reference safety dataset.</td></tr>
<tr><td>Outcomes</td><td>Percent overall, fatal, not resolved, resolved, and unknown for identified risk of thyroid disorder–pembrolizumab (Table includes events for 30 days after discontinuation.)

Hypothyroidism (AEOSI)

KN001, KN002 and KN006 Melanoma Subjects and KN001 and KN010 NSCLC Subjects Treated with Pembrolizumab (Treatment Emergent).
<table>
<tr><td></td><td></td><td colspan="2">Cumulative NSCLC 001/010 + MEL 001/002/006</td></tr>
<tr><td></td><td>Outcome</td><td>n</td><td>(%)</td></tr>
<tr><td>Subjects in population</td><td></td><td>2,799</td><td></td></tr>
<tr><td>With one or more adverse events</td><td>Overall</td><td>237</td><td>(8.5)</td></tr>
<tr><td></td><td>Fatal</td><td>0</td><td>(0.0)</td></tr>
<tr><td></td><td>Not Resolved</td><td>176</td><td>(6.3)</td></tr>
<tr><td></td><td>Resolved</td><td>46</td><td>(1.6)</td></tr>
<tr><td></td><td>Resolving</td><td>6</td><td>(0.2)</td></tr>
<tr><td></td><td>Sequelae</td><td>2</td><td>(0.1)</td></tr>
<tr><td></td><td>Unknown</td><td>7</td><td>(0.3)</td></tr>
<tr><td colspan="4">Every subject is counted once on each applicable row.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns is greater than or equal to the percent incidence specified in the report title, after rounding.
Outcome: Resolved = RECOVERED/RESOLVED, Not resolved = NOT RECOVERED/NOT RESOLVED.</td></tr>
</table>

In the NSCLC population in KN024 and KN042 (n=790), the outcomes of the 93 patients with events of hypothyroidism were as follows: 25 (3.2%) resolved, 12 (1.5%) resolving, 52 (6.6%) not resolved, 2 (0.3%) resolved with sequelae, 2 (0.3%) unknown. There were no patients with events of hypothyroidism with a fatal outcome.

In the NSCLC population in KN189 and KN021 (Cohorts C and G) pembrolizumab plus chemotherapy (n=488), the outcomes of the 39 patients with events of hypothyroidism were as follows: 12 (2.5%) resolved, 5 (1%) resolving, 21 (4.3%) not resolved, 1 (0.2%) unknown. There were no patients with events of hypothyroidism with a fatal outcome.

In the HL population in KN013, KN087, and KN204 (n=389), the outcomes of the 66 patients with events of hypothyroidism were as follows: 27 (6.9%) resolved, 8 (2.1%) resolving, 27 (6.9%) not resolved, and 4 (1.0%) resolved with sequelae. There were no patients with events of hypothyroidism with a fatal outcome.

In the UC population in KN052 (n=370), the outcomes for the 24 patients with events of hypothyroidism were as follows: 1 (0.3%) resolved, 3(0.8%) resolving, 17 (4.6%) not resolved, and 3 (0.8%) unknown and in KN045 (n=266), the outcomes for the 17 patients with events of</td></tr>
</table>

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Table SVII.3.1.7: Details of Important Identified Risk: Immune-Mediated Adverse Reactions- Endocrinopathies - Thyroid Disorder (Hypothyroidism, Hyperthyroidism, Thyroiditis)

	hypothyroidism were as follows: 4 (1.5%) resolved, 2 (0.8%) resolved with sequelae, 11 (4.1%) not resolved. There were no patients with events of hypothyroidism with a fatal outcome. In the HNSCC population in KN040, KN012 and KN055 (n=609), the outcomes of the 92 patients with events of hypothyroidism were as follows: 12 (2.0%) resolved, 8 (1.3%) resolving, 66 (10.8%) not resolved and 6 (1.0%) unknown. There were no patients with events of hypothyroidism with a fatal outcome. In the HNSCC population in KN048 pembrolizumab monotherapy group (n=300), the outcomes of the 54 (18%) patients with events of hypothyroidism were as follows: 14 (4.7%) resolved, 12 (4.0%) resolving, 27 (9.0%) not resolved and 1 (0.3%) unknown. There were no fatal outcomes. In the HNSCC population in KN048 pembrolizumab plus chemotherapy group (n=276), the outcomes of the 42 (15.2%) patients with events of hypothyroidism were as follows: 10 (3.6%) resolved, 5 (1.8%) resolving and 27 (9.8%) not resolved. There were no patients with events of hypothyroidism with a fatal outcome. In the melanoma population in KN054 (n=509), the outcomes of the 75 patients with events of hypothyroidism were as follows: 20 (3.9%) resolved, 2 (0.4%) resolved with sequelae, and 53 (10.4%) not resolved. There were no patients with events of hypothyroidism with a fatal outcome. In the NSCLC population in KN407 and KN021 (Cohort A) (n=303), the outcomes of the 24 patients with events of hypothyroidism were as follows: 13 (4.3%) not resolved, 8 (2.6%) resolving, and 3 (1.0%) resolved. There were no patients with events of hypothyroidism with a fatal outcome. In the RCC population in KN426 pembrolizumab plus axitinib (n=429), the outcomes for the 152 patients with events of hypothyroidism were as follows: 38 (8.9%) resolved, 95 (22.1%) not resolved, and 19 (4.4%) resolving. There were no patients with events of hypothyroidism with a fatal outcome. In the CRC population in KN177 (n=153), the outcomes for the 19 patients with events of hypothyroidism were as follows: 5 (3.3%) resolved, 1 (0.7%) resolving and 13 (8.5%) not resolved. There were no patients with events of hypothyroidism with a fatal outcome. In the esophageal cancer population in KN590 pembrolizumab plus chemotherapy (n=370), the outcomes for the 40 patients with events of hypothyroidism were as follows: 11 (3%) resolved, 23 (6.2%) not resolved, 5 (1.4%) resolving and 1 (0.3%) resolved with sequelae. There were no patients with events of hypothyroidism with a fatal outcome. In the TNBC population in KN355 pembrolizumab plus chemotherapy group (n=596), the outcomes for the 95 patients with events of hypothyroidism were as follows: 26 (4.4%) resolved, 47 (7.9%) not resolved, 21 (3.5%) resolving, and 1 (0.2%) resolved with sequelae. There were no patients with events of hypothyroidism with a fatal outcome. In the RCC population in KN581 pembrolizumab plus lenvatinib (n=352), the outcomes for the 166 patients with events of hypothyroidism were as follows: 118 (33.5%) not resolved, 33 (9.4%) resolved, 14 (4.0%) resolving, and 1 (0.3%) resolved with sequelae. There were no patients with events of hypothyroidism with a fatal outcome. In the endometrial carcinoma population in KN146 and KN775 pembrolizumab plus lenvatinib (n=530), the outcomes for the 296 patients with events of hypothyroidism were as follows: 197 (37.2%) not resolved, 54 (10.2%) resolved, 38 (7.2%) resolving, 6 (1.1%) resolved with sequelae, and 1 (0.2%) unknown. There were no patients with events of hypothyroidism with a fatal outcome. In the RCC population in KN564 pembrolizumab monotherapy (n=488), the outcomes for the 103 patients with events of hypothyroidism were as follows: 15 (3.1%) resolved, 60 (12.3%) not resolved, 26 (5.3%) resolving, and 2 (0.4%) resolved with sequelae. There were no patients with events of hypothyroidism with a fatal outcome. In the MSI-H population in KN158 Cohort K and KN164 Cohorts A and B (n=475), the outcomes for the 53 (11.2%) patients with events of hypothyroidism were as follows: 15 (3.2%) resolved, 8 (1.7%) resolving, 1 (0.2%) unknown and 29 (6.1%) not resolved. There were no patients with events of hypothyroidism with a fatal outcome. In the cervical cancer population in KN826 pembrolizumab plus chemotherapy (n=307), the outcomes for the 56 patients with events of hypothyroidism were as follows: 32 (10.4%) not

Table SVII.3.1.7: Details of Important Identified Risk: Immune-Mediated Adverse Reactions- Endocrinopathies - Thyroid Disorder (Hypothyroidism, Hyperthyroidism, Thyroiditis)

	resolved, 16 (5.2%) resolving, and 8 (2.6%) resolved. There were no patients with events of hypothyroidism with a fatal outcome.In the TNBC population in KN522 pembrolizumab in combination with neoadjuvant chemotherapy followed by continued adjuvant pembrolizumab monotherapy group (n=783), the outcomes for the 118 patients with events of hypothyroidism were as follows: 33 (4.2%) resolved, 64 (8.2%) not resolved, 19 (2.4%) resolving, and 2 (0.3%) resolved with sequelae. There were no patients with events of hypothyroidism with a fatal outcome. In the melanoma population in KN716 pembrolizumab monotherapy (n=483), the outcomes for the 76 patients with events of hypothyroidism were as follows: 43 (8.9%) not resolved, 24 (5%) resolving, and 9 (1.9%) resolved. There were no patients with events of hypothyroidism with a fatal outcome. In the gastric cancer population in KN811 pembrolizumab combination therapy (n=350), the outcome for the 37 patients with events of hypothyroidism were as follows: 17 (4.9%) not resolved 12 (3.4%) resolved, and 8 (2.3%) resolving. There were no patients with events of hypothyroidism with a fatal outcome. In the NSCLC population in KN091 pembrolizumab monotherapy (n=580), the outcomes for the 120 patients with events of hypothyroidism were as follows: 21 (3.6%) resolved and 99 (17.1%) not resolved. There were no patients with events of hypothyroidism with a fatal outcome. In the gastric cancer population in KN859 pembrolizumab plus chemotherapy (n=785), the outcomes for the 120 patients with events of hypothyroidism were as follows: 69 (8.8%) not resolved, 28 (3.6%) resolving, 20 (2.5%) resolved, and 3 (0.4%) resolved with sequelae. There were no patients with events of hypothyroidism with a fatal outcome. In the BTC population in KN966 pembrolizumab plus chemotherapy (n=529), the worst reported outcomes for the 46 patients with events of hypothyroidism were as follows: 26 (4.9%) not resolved, 14 (2.6%) resolving and 6 (1.1%) resolved. There were no patients with events of hypothyroidism with a fatal outcome. In the NSCLC population in KN671 pembrolizumab in combination with chemotherapy as neoadjuvant treatment followed by continued adjuvant pembrolizumab monotherapy group (n=396), the outcome for the 44 patients with events of hypothyroidism were as follows: 26 (6.6%) not resolved, 8 (2.0%) resolving, 9 (2.3%) resolved, and 1 (0.3%) resolved with sequele. There were no patients with events of hypothyroidism with a fatal outcome.

Hyperthyroidism (AEOSI)
KN001, KN002 and KN006 Melanoma Subjects and KN001 and KN010 NSCLC Subjects Treated with Pembrolizumab
(Treatment Emergent)

		Cumulative NSCLC 001/010 + MEL 001/002/006	
	Outcome	n	(%)
Subjects in population		2,799	
With one or more adverse events	Overall	96	(3.4)
	Fatal	0	(0.0)
	Not Resolved	23	(0.8)
	Resolved	71	(2.5)
	Unknown	2	(0.1)

Every subject is counted once on each applicable row.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns is greater than or equal to the percent incidence specified in the report title, after rounding.
Outcome: Resolved = RECOVERED/RESOLVED, Not resolved = NOT RECOVERED/NOT RESOLVED.

In the NSCLC population in KN024 and KN042 (n=790), the outcomes of the 50 patients with events of hyperthyroidism were as follows: 40 (5.1%) resolved, 3 (4%) resolving (0.9%) not resolved. There were no patients with events of hyperthyroidism with a fatal outcome.

In the NSCLC population in KN189 and KN021 (Cohorts C and G) pembrolizumab plus chemotherapy (n=488), the outcomes of the 21 patients with events of hyperthyroidisim were as follows: 16 (3.3%) resolved, 3 (0.6%) resolving, 2 (0.4%) not resolved. There were no patients with events of hyperthyroidism with a fatal outcome.

In the HL population in KN013, KN087, and KN204 (n=389), the outcomes of the 17 patients with events of hyperthyroidism were as follows: 15 (3.9%) resolved, 1 (0.3%) not resolved, and 1 (0.3%) resolved with sequelae. There were no patients with events of hyperthyroidism with a fatal outcome.

In the UC population in KN052 (n=370), the outcomes for the 9 patients with events of hyperthyroidism were as follows: 6 (1.6%) resolved, 1 (0.3%) resolving, 1 (0.3%) not resolved, and 1 (0.3%) unknown and in KN045 (n=266), the outcomes for the 10 patients with events of hyperthyroidism were as follows: 7(2.6%) resolved, 2 (0.8%) not resolved, and 1 (0.4%) unknown. There were no patients with events of hyperthyroidism with a fatal outcome.

In the HNSCC population in KN040, KN012 and KN055 (n=609), the outcomes of the 10 patients with events of hyperthyroidism were as follows: 6 (1.0%) resolved, 2 (0.3%) resolving, 1 (0.2%) not resolved and 1(0.2%) unknown. There were no patients with events of hyperthyroidism with a fatal outcome.

In the HNSCC population in KN048 pembrolizumab monotherapy group (n=300), the outcomes of the 8 (2.7%) patients with events of hyperthyroidism were as follows: 4 (1.3%) resolved, 1 (0.3%) resolving, 1 (0.3%) resolved with sequelae, and 2 (0.7%) not resolved. There were no fatal outcomes. In the HNSCC population in KN048 pembrolizumab plus chemotherapy group (n=276), the outcomes of the 13 (4.7%) patients with events of hyperthyroidism were as follows: 9 (3.3%) resolved, 2 (0.7%) resolving and 2 (0.7%) not resolved. There were no patients with events of hyperthyroidism with a fatal outcome.

In the melanoma population in KN054 (n=509), the outcomes of the 53 patients with events of hyperthyroidism were as follows: 44 (8.6%) resolved, 6 (1.2%) not resolved and 3 (0.6%) recovered with sequelae. There were no patients with events of hyperthyroidism with a fatal outcome.

In the NSCLC population in KN407 and KN021 (Cohort A) (n=303), the outcomes of the 20 patients with events of hyperthyroidism were as follows: 12 (4.0%) resolved, 5 (1.7%) not resolved, 3 (1.0%) resolving. There were no patients with events of hyperthyroidism with a fatal outcome.

In the RCC population in KN426 pembrolizumab plus axitinib (n=429) the outcomes for the 55 patients with events of hyperthyroidism were as follows: 47 (11.0%) resolved, 7 (1.6%) not resolved, and 1 (0.2%) resolving. There were no patients with events of hyperthyroidism with a fatal outcome.

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Table SVII.3.1.7: Details of Important Identified Risk: Immune-Mediated Adverse Reactions- Endocrinopathies - Thyroid Disorder (Hypothyroidism, Hyperthyroidism, Thyroiditis)

	In the CRC population in KN177 (n=153), the outcomes for the 6 patients with events of hyperthyroidism were as follows: 5 (3.3%) resolved and 1 (0.7%) not resolved. There were no patients with events of hyperthyroidism with a fatal outcome. In the esophageal cancer population in KN590 pembrolizumab plus chemotherapy (n=370), the outcomes for the 21 patients with events of hyperthyroidism were as follows: 14 (3.8%) resolved, 6 (1.6%) not resolved, and 1 (0.3%) resolving. There were no patients with events of hyperthyroidism with a fatal outcome. In the TNBC population in KN355 pembrolizumab plus chemotherapy group (n=596) the outcomes for the 31 patients with events of hyperthyroidism were as follows: 21 (3.5%) resolved, 7 (1.2%) not resolved, 1 (0.2%) resolving, 1 (0.2%) resolved with sequelae and 1 (0.2%) unknown. There were no patients with events of hyperthyroidism with a fatal outcome. In the RCC population in KN581 pembrolizumab plus lenvatinib (n=352), the outcomes for the 28 patients with events of hyperthyroidism were as follows: 20 (5.7%) resolved, 4 (1.1%) resolving, 3 (0.9%) not resolved, 1 (0.3%) resolved with sequelae. There were no events of hyperthyroidism with a fatal outcome. In the endometrial carcinoma population in KN146 and KN775 pembrolizumab plus lenvatinib (n=530) the outcomes for the 54 patients with events of hyperthyroidism were as follows: 46 (8.7%) resolved, 7 (1.3%) not resolved, and 1 (0.2%) resolved with sequelae. There were no patients with events of hyperthyroidism with a fatal outcome.In the RCC population in KN564 pembrolizumab monotherapy (n=488), the outcomes for the 58 patients with events of hyperthyroidism were as follows: 47 (9.6%) resolved, 3 (0.6%) not resolved, 3 (0.6%) resolving, and 5 (1%) resolved with sequelae. There were no patients with events of hyperthyroidism with a fatal outcome. In the MSI-H population in KN158 Cohort K and KN164 Cohorts A and B (n=475), the outcomes for the 25 (5.3%) patients with events of hyperthyroidism were as follows: 21 (4.4%) resolved, 1 (0.2%) resolved with sequelae, and 3 (0.6%) not resolved. There were no patients with events of hyperthyroidism with a fatal outcome. In the cervical cancer population in KN826 pembrolizumab plus chemotherapy (n=307), the outcomes for the 23 patients with events of hyperthyroidism were as follows: 19 (6.2%) resolved, 3 (1.0%) not resolved and 1 (0.3%) resolved with sequelae. There were no patients with events of hyperthyroidism with a fatal outcome. In the TNBC population in KN522 pembrolizumab in combination with neoadjuvant chemotherapy followed by continued adjuvant pembrolizumab monotherapy group (n=783), the outcomes for the 41 patients with events of hyperthyroidism were as follows: 35 (4.5%) resolved, 3 (0.4%) not resolved, 2 (0.3%) resolving, and 1 (0.1%) resolved with sequelae. There were no patients with events of hyperthyroidism with a fatal outcome. In the melanoma population in KN716 pembrolizumab monotherapy (n=483), the outcomes for the 50 patients with events of hyperthyroidism were as follows: 43 (8.9%) resolved, 5 (1%) not resolved, 1 (0.2%) resolving, and 1 (0.2%) resolved with sequelae. There were no patients with events of hyperthyroidism with a fatal outcome. In the gastric cancer population in KN811 pembrolizumab combination therapy (n=350), the outcome for the 14 patients with events of hyperthyroidism were as follows: 6 (1.7%) resolved, 6 (1.7%) not resolved and 2 (0.6%) resolving. There were no patients with events of hyperthyroidism with a fatal outcome. In the NSCLC population in KN091 pembrolizumab monotherapy (n=580), the outcomes for the 62 patients with events of hyperthyroidism were as follows: 60 (10.3%) resolved and 2 (0.3%) not resolved. There were no patients with events of hyperthyroidism with a fatal outcome. In the gastric cancer population in KN859 pembrolizumab plus chemotherapy (n=785), the outcomes for the 44 patients with events of hyperthyroidism were as follows: 33 (4.2%) resolved, 7 (0.9%) not resolved, 2 (0.3%) resolving, and 2 (0.3%) resolved with sequelae. There were no patients with events of hyperthyroidism with a fatal outcome.

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Table SVII.3.1.7: Details of Important Identified Risk: Immune-Mediated Adverse Reactions- Endocrinopathies - Thyroid Disorder (Hypothyroidism, Hyperthyroidism, Thyroiditis)

In the BTC population in KN966 pembrolizumab plus chemotherapy (n=529), the worst reported outcomes for the 19 patients with events of hyperthyroidism were as follows: 15 (2.8%) resolved, 2 (0.4%) not resolved and 2 (0.4%) resolving. There were no patients with events of hyperthyroidism with a fatal outcome.

In the NSCLC population in KN671 pembrolizumab in combination with chemotherapy as neoadjuvant treatment followed by continued adjuvant pembrolizumab monotherapy group (n=396), the outcome for the 22 patients with events of hyperthyroidism were as follows: 3 (0.8%) not resolved, 2 (0.5%) resolving, and 17 (4.3%) resolved. There were no patients with events of hyperthyroidism with a fatal outcome.

Thyroiditis (AEOSI)
KN001, KN002 and KN006 Melanoma Subjects and KN001 and KN010 NSCLC Subjects Treated with Pembrolizumab
(Treatment Emergent)

		Cumulative NSCLC 001/010 + MEL 001/002/006	
	Outcome	n	(%)
Subjects in population		2,799	
With one or more adverse events	Overall	16	(0.6)
	Fatal	0	(0.0)
	Not Resolved	8	(0.3)
	Resolved	7	(0.3)
	Resolving	1	(0.0)
	Unknown	0	(0.0)

Every subject is counted once on each applicable row.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns is greater than or equal to the percent incidence specified in the report title, after rounding.
Outcome: Resolved = RECOVERED/RESOLVED, Not resolved = NOT RECOVERED/NOT RESOLVED.

In the NSCLC population in KN024 and KN042 (n=790), the outcomes of the 14 patients with events of thyroiditis were as follows: 7 (0.9%) not resolved, 6 (0.8%) resolved and 1 (0.1%) recovered with sequelae. There were no patients with events of thyroiditis with a fatal outcome.

In the NSCLC population in KN189 and KN021 (Cohorts C and G) pembrolizumab plus chemotherapy (n=488), the outcome of the 1 (0.2%) patient with an event of thyroiditis was not resolved.

In the HL population in KN013, KN087, and KN204 (n=389), the outcomes of the 5 patients with events of thyroiditis were as follows: 2 (0.5%) not resolved, 2 (0.5%) resolved, and 1 (0.3%) recovered with sequelae. There were no patients with events of thyroiditis with a fatal outcome.

In the UC population in KN052 (n=370), the outcomes for the 3 patients with events of thyroiditis were as follows: 1 (0.3%) resolving and 2 (0.5%) not resolved and in KN045 (n=266), the outcomes for the 2 patients with events of thyroiditis were as follows: 2 (0.8%) resolving. There were no patients with events of thyroiditis with a fatal outcome. In the HNSCC population in KN040, KN012 and KN055 (n=609), the outcomes of the 3 patients with events of thyroiditis were as follows: 1 (0.2%) resolved, 1 (0.2%) resolving and 1 (0.2%) not resolved. There were no patients with events of thyroiditis with a fatal outcome.

In the HNSCC population in KN048 pembrolizumab monotherapy group (n=300), there were no events of thyroiditis. In the HNSCC population in KN048 pembrolizumab plus chemotherapy group (n=276), the outcome of the 1 (0.4%) patient with an event of thyroiditis was resolved. There were no patients with events of thyroiditis with a fatal outcome.

Table SVII.3.1.7: Details of Important Identified Risk: Immune-Mediated Adverse Reactions- Endocrinopathies - Thyroid Disorder (Hypothyroidism, Hyperthyroidism, Thyroiditis)

	In the melanoma population in KN054 (n=509), the outcomes of the 16 patients with events of thyroiditis were as follows: 6 (1.2%) not resolved, 9 (1.8%) resolved, and 1(0.2%) recovered with sequelae. There were no patients with events of thyroiditis with a fatal outcome. In the NSCLC population in KN407 and KN021 (Cohort A) (n=303), the outcomes of the 3 patients with events of thyroiditis were as follows: 2 (0.7%) not resolved, 1 (0.3%) resolved. There were no patients with events of thyroiditis with a fatal outcome. In the RCC population in KN426 pembrolizumab plus axitinib (n=429) the outcomes for the 12 patients with events of thyroiditis were as follows: 4 (0.9%) resolved, 7 (1.6%) not resolved, and 1 (0.2%) resolving. There were no patients with events of thyroiditis with a fatal outcome. In the CRC population in KN177 (n=153), the outcomes for the 2 patients with events of thyroiditis were as follows: 1 (0.7%) resolved and 1 (0.7%) resolved with sequelae. There were no patients with events of thyroiditis with a fatal outcome. In the esophageal cancer population in KN590 pembrolizumab plus chemotherapy (n=370), the outcome for the 1 patient with an event of thyroiditis was as follows: 1 (0.3%) not resolved. There were no patients with events of thyroiditis with a fatal outcome. In the TNBC population in KN355 pembrolizumab plus chemotherapy group (n=596), the outcomes for the 8 patients with events of thyroiditis were as follows: 4 (0.7%) resolved, 2 (0.3%) not resolved, and 2 (0.3%) resolving. There were no fatal outcomes. In the RCC population in KN581 pembrolizumab plus lenvatinib (n=352), the outcomes for the 2 patients with events of thyroiditis there were as follows: 1 (0.3%) resolved, and 1 (0.3%) not resolved. There were no patients with events of thyroiditis with a fatal outcome. In the endometrial carcinoma population in KN146 and KN775 pembrolizumab plus lenvatinib (n=530) the outcomes for the 12 patients with events of thyroiditis were as follows: 6 (1.1%) not resolved, 4 (0.8%) resolved, 1 (0.2%) resolved with sequelae, and 1 (0.2%) resolving. There were no patients with events of thyroiditis with a fatal outcome. In the RCC population in KN564 pembrolizumab monotherapy (n=488), the outcomes for the 6 patients with events of thyroiditis were as follows: 3 (0.6%) resolved and 3 (0.6%) not resolved. There were no patients with events of thyroiditis with a fatal outcome. In the cervical cancer population in KN826 pembrolizumab plus chemotherapy (n=307), the outcomes for the 11 patients with events of thyroiditis were as follows: 6 (2.0%) not resolved, 4 (1.3%) resolved and 1 (0.3%) resolving. There were no patients with events of thyroiditis with a fatal outcome. In the TNBC population in KN522 pembrolizumab in combination with neoadjuvant chemotherapy followed by continued adjuvant pembrolizumab monotherapy group (n=783), the outcomes for the 16 patients with events of thyroiditis were as follows: 7 (0.9%) resolved, 8 (1.0%) not resolved, and 1 (0.1%) resolved with sequelae. There were no patients with events of thyroiditis with a fatal outcome. In the melanoma population in KN716 pembrolizumab monotherapy (n=483), the outcome for the 8 patients with events of thyroiditis was as follows: 5 (1%) not resolved, 2 (0.4%) resolving, and 1 (0.2%) resolved. There were no patients with events of thyroiditis with a fatal outcome. In the gastric cancer population in KN811 pembrolizumab combination therapy (n=350), the outcome for the 4 patients with events of thyroiditis were as follows: 2 (0.6%) not resolved, 1 (0.3%) resolving and 1 (0.3%) resolved. There were no patients with events of thyroiditis with a fatal outcome. In the NSCLC population in KN091 pembrolizumab monotherapy (n=580), the outcomes for the 6 patients with events of thyroiditis were as follows: 1 (0.2%) resolved, 1 (0.2%) resolved with sequelae, and 4 (0.7%) not resolved. There were no patients with events of thyroiditis with a fatal outcome. In the gastric cancer population in KN859 pembrolizumab plus chemotherapy (n=785), the outcomes for the 9 patients with events of thyroiditis were as follows: 3 (0.4%) not resolved, 3 (0.4%) resolving, 2 (0.3%) resolved, and 1 (0.1%) resolved with sequelae. There were no patients with events of thyroiditis with a fatal outcome.

Table SVII.3.1.7: Details of Important Identified Risk: Immune-Mediated Adverse Reactions- Endocrinopathies - Thyroid Disorder (Hypothyroidism, Hyperthyroidism, Thyroiditis)

<table>
<tr><td></td><td>In the BTC population in KN966 pembrolizumab plus chemotherapy (n=529), the worst reported outcomes for the 3 (0.6%) patients with events of thyroiditis were not resolved. There were no patients with events of thyroiditis with a fatal outcome.

In the NSCLC population in KN671 pembrolizumab in combination with chemotherapy as neoadjuvant treatment followed by continued adjuvant pembrolizumab monotherapy group (n=396), the outcome for the 4 patients with events of thyroiditis were as follows: 3 (0.8%) not resolved, and 1 (0.3%) resolved. There were no patients with events of thyroiditis with a fatal outcome.

Aggregate Review
Review of the ASE dataset (n=7730) yielded no fatal cases of thyroid disorders. Review of the global safety database yielded the following: no fatal cases from ongoing interventional monotherapy clinical trials and 1 fatal case of thyroiditis and 1 fatal case of hypothyroidism reported from the PM or non-interventional environment. In both cases, the thyroid disorder event was the only Grade 5 event.</td></tr>
<tr><td>Seriousness</td><td>Percent serious for identified risk of thyroid disorder - pembrolizumab. (Serious AEs for 90 days after discontinuation were included.)

Hypothyroidism - Serious (AEOSI)
KN001, KN002 and KN006 Melanoma Subjects and KN001 and KN010 NSCLC Subjects Treated with Pembrolizumab
(Treatment-Emergent)

<table>
<tr><td></td><td colspan="2">Cumulative NSCLC 001/010 + MEL 001/002/006</td></tr>
<tr><td></td><td>n</td><td>(%)</td></tr>
<tr><td>Subjects in population</td><td>2,799</td><td></td></tr>
<tr><td>with one or more adverse events</td><td>5</td><td>(0.2)</td></tr>
<tr><td></td><td></td><td></td></tr>
<tr><td>Hypothyroidism</td><td>5</td><td>(0.2)</td></tr>
<tr><td colspan="3">Every subject 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.
Include all treated subjects in KN001 Part B1, B2, B3, D, C, F1, F2, F3 and all subjects in KN002 treated with Pembrolizumab in the original phase and all subjects in KN006 and KN010 treated with Pembrolizumab.</td></tr>
</table>

Of the 93 patients with events of hypothyroidism in the NSCLC population in KN024 and KN042 (n=790), 1 (0.1%) experienced a serious event of hypothyroidism.

Of the 39 patients with events of hypothyroidism in the NSCLC population in KN189 and KN021 (Cohorts C and G) pembrolizumab plus chemotherapy (n=488), 1 (0.2%) of the events experienced a serious event of hypothyroidism.

Of the 66 patients with events of hypothyroidism in the HL population in KN013, KN087, and KN204 (n=389), none of the patients experienced events serious events of hypothyroidism.

Of the 24 patients with events of hypothyroidism in the UC population in KN052 (n=370) and the 17 events of hypothyroidism in the UC population in KN045 (n=266), none of the patients experienced serious events of hypothyroidism.

Of the 92 patients with events of hypothyroidism in the HNSCC population in KN040, KN012 and KN055 (n=609), none of the patients experienced serious events of hypothyroidism.

Of the 54 patients with events of hypothyroidism in the HNSCC population in KN048 pembrolizumab monotherapy group (n=300), none of the patients experienced serious events of hypothyroidism. Of the 42 patients with events of hypothyroidism in the HNSCC population in KN048 pembrolizumab plus chemotherapy group (n=276), none of the patients experienced serious events of hypothyroidism.</td></tr>
</table>

Table SVII.3.1.7: Details of Important Identified Risk: Immune-Mediated Adverse Reactions- Endocrinopathies - Thyroid Disorder (Hypothyroidism, Hyperthyroidism, Thyroiditis)

	Of the 75 patients with events of hypothyroidism in the melanoma population in KN054 (n=509), none of the patients experienced serious events of hypothyroidism. Of the 24 patients with events of hypothyroidism in the NSCLC population in KN407 and KN021 (Cohort A) (n=303), 1 (0.3%) experienced a serious event of hypothyroidism. Of the 152 patients with events of hypothyroidism in the RCC population in KN426 pembrolizumab plus axitinib (n=429), 1 (0.2%) experienced a serious event of hypothyroidism. Of the 19 patients with events of hypothyroidism in the CRC population in KN177 (n=153), none of the patients experienced serious events of hypothyroidism. There were no patients with serious events of hypothyroidism in the esophageal cancer population in KN590 pembrolizumab plus chemotherapy (n=370). Of the 95 patients with events of hypothyroidism in the TNBC population in KN355 pembrolizumab plus chemotherapy group (n=596), 1 (0.2%) experienced a serious event of hypothyroidism. Of the 166 patients with events of hypothyroidism in the RCC population in KN581 pembrolizumab plus lenvatinib (n=352), 3 (0.9%) experienced serious events of hypothyroidism. Of the 296 patients with events of hypothyroidism in the endometrial carcinoma population in KN146 and KN775 pembrolizumab plus lenvatinib (n=530), 3 (0.6%) experienced serious events of hypothyroidism. Of the 103 patients with events of hypothyroidism in the RCC population in KN564 pembrolizumab monotherapy (n=488), none of the patients experienced serious events of hypothyroidism. Of the 53 patients with events of hypothyroidism in the MSI-H population in KN158 Cohort K and KN164 Cohorts A and B (n=475), none of the patients experienced serious events of hypothyroidism. There were no patients with serious events of hypothyroidism in the cervical cancer population in KN826 pembrolizumab plus chemotherapy (n=307). Of the 118 patients with events of hypothyroidism in the TNBC population in KN522 pembrolizumab in combination with neoadjuvant chemotherapy followed by continued adjuvant pembrolizumab monotherapy group (n=783), 3 (0.4%) experienced serious events of hypothyroidism. There were no patients with serious events of hypothyroidism in the melanoma population in KN716 pembrolizumab monotherapy (n=483). Of the 37 patients with events of hypothyroidism in gastric cancer population in KN811 pembrolizumab combination therapy (n=350), 1 (0.3%) experienced a serious event of hypothyroidism. Of the 120 patients with events of hypothyroidism in the NSCLC population in KN091 pembrolizumab monotherapy (n=580), 2 (0.3%) experienced serious events of hypothyroidism. There were no serious events of hypothyroidism in the gastric population in KN859 pembrolizumab monotherapy (n=785). Of the 46 patients with events of hypothyroidism in the BTC population in KN966 pembrolizumab plus chemotherapy (n=529), 1 (0.2%) experienced a serious event of hypothyroidism. Of the 44 patients with events of hypothyroidism in the NSCLC population in KN671 pembrolizumab in combination with chemotherapy as neoadjuvant treatment followed by continued adjuvant pembrolizumab monotherapy (n=396), 1 (0.3%) experienced a serious event of hypothyroidism.

Table SVII.3.1.7: Details of Important Identified Risk: Immune-Mediated Adverse Reactions- Endocrinopathies - Thyroid Disorder (Hypothyroidism, Hyperthyroidism, Thyroiditis)

Hyperthyroidism - Serious (AEOSI)
KN001, KN002 and KN006 Melanoma Subjects and KN001 and KN010 NSCLC Subjects Treated with Pembrolizumab
(Treatment-Emergent)

	Cumulative NSCLC 001/010 + MEL 001/002/006	
	n	(%)
Subjects in population	2,799	
with one or more adverse events	6	(0.2)
Hyperthyroidism	6	(0.2)

Every subject 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.
Include all treated subjects in KN001 Part B1, B2, B3, D, C, F1, F2, F3 and all subjects in KN002 treated with Pembrolizumab in the original phase and all subjects in KN006 and KN010 treated with Pembrolizumab.

Of the 50 patients with events of hyperthyroidism in the NSCLC population in KN024 and KN042 (n=790), 2 (0.3%) experienced serious events of hyperthyroidism.

Of the 21 patients with events of hyperthyroidism in the NSCLC population in KN189 and KN021 (Cohorts C and G) pembrolizumab plus chemotherapy (n=488), none of the patients experienced serious events of hyperthyroidism.

Of the 17 patients with events of hyperthyroidism in the HL population in KN013, KN087, and KN204 (n=389), none of the patients experienced serious events of hyperthyroidism.

Of the 9 patients with events of hyperthyroidism in the UC population in KN052 (n=370) and the 10 events of hyperthyroidism in the UC population in KN045 (n=266), none of the of the patients experienced serious events of hyperthyroidism.

Of the 10 patients with events of hyperthyroidism in the HNSCC population in KN040, KN012 and KN055 (n=609), 1 (0.2%) experienced a serious event of hyperthyroidism.

Of the 8 patients with events of hyperthyroidism in the HNSCC population in KN048 pembrolizumab monotherapy group (n=300), 1 (0.3%) experienced a serious event of hyperthyroidism. Of the 13 patients with events of hyperthyroidism in the HNSCC pembrolizumab plus chemotherapy group (n=276), none of the patients experienced serious events of hyperthyroidism.

Of the 53 patients with events of hyperthyroidism in the melanoma population in KN054 (n=509), 1 (0.2%) experienced a serious event of hyperthyroidism.

Of the 20 patients with events of hyperthyroidism in the NSCLC population in KN407 and KN021 (Cohort A) (n=303), 1 (0.3%) experienced a serious event of hyperthyroidism.

Of the 55 patients with events of hyperthyroidism in the RCC population in KN426 pembrolizumab plus axitinib (n=429), 2 (0.5%) experienced serious events of hyperthyroidism.

Of the 6 patients with events of hyperthyroidism in the CRC population in KN177 (n=153), none of the patients experienced serious events of hyperthyroidism.

Of the 21 patients with events of hyperthyroidism in the esophageal cancer population in KN590 pembrolizumab plus chemotherapy (n=370), 2 (0.5%) experienced serious events of hyperthyroidism.

Of the 31 patients with events of hyperthyroidism in the TNBC population in KN355 pembrolizumab plus chemotherapy group (n=596), none of the patients experienced serious events of hyperthyroidism.

Of the 28 patients with events of hyperthyroidism in the RCC population in KN581 pembrolizumab plus lenvatinib (n=352), none of the patients experienced serious events of hyperthyroidism.

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Table SVII.3.1.7: Details of Important Identified Risk: Immune-Mediated Adverse Reactions- Endocrinopathies - Thyroid Disorder (Hypothyroidism, Hyperthyroidism, Thyroiditis)

Of the 54 patients with events of hyperthyroidism in the endometrial carcinoma population in KN146 and KN775 pembrolizumab plus lenvatinib (n=530), 3 (0.6%) experienced serious events of hyperthyroidism.

Of the 58 patients with events of hyperthyroidism in the RCC population in KN564 pembrolizumab monotherapy (n=488), 2 (0.4%) experienced serious events of hyperthyroidism.

Of the 25 patients with events of hyperthyroidism in the MSI-H population in KN158 Cohort K and KN164 Cohorts A and B (n=475), 1 (0.2%) experienced a serious event of hyperthyroidism.

There were no patients with serious events of hyperthyroidism in the cervical cancer population in KN826 pembrolizumab plus chemotherapy (n=307).

Of the 41 patients with events of hyperthyroidism in the TNBC population in KN522 pembrolizumab combination with neoadjuvant chemotherapy followed by continued adjuvant pembrolizumab monotherapy group (n=783), 2 (0.3%) experienced serious events of hyperthyroidism.

There were no patients with serious events of hyperthyroidism in the melanoma population in KN716 pembrolizumab monotherapy (n=483).

Of the 14 patients with events of hyperthyroidism in the gastric cancer population in KN811 pembrolizumab combination therapy (n=350), none of the patients experienced serious events of hyperthyroidism.

Of the 62 patients with events of hyperthyroidism in the NSCLC population in KN091 pembrolizumab monotherapy (n=580), 2 (0.3%) experienced serious events of hyperthyroidism.

Of the 44 patients with events of hyperthyroidism in the gastric population in KN859 pembrolizumab monotherapy (n=785), none of the patients experienced serious events of hyperthyroidism.

Of the 19 patients with events of hyperthyroidism in the BTC population in KN966 pembrolizumab plus chemotherapy (n=529), 1 (0.2%) experienced a serious event of hyperthyroidism.

Of the 22 patients with events of hyperthyroidism in the NSCLC population in KN671 pembrolizumab in combination with chemotherapy as neoadjuvant treatment followed by continued adjuvant pembrolizumab monotherapy (n=396), 1 (0.3%) experienced a serious event of hyperthyroidism.

Thyroiditis - Serious (AEOSI)
KN001, KN002 and KN006 Melanoma Subjects and KN001 and KN010 NSCLC Subjects Treated with Pembrolizumab
(Treatment-Emergent)

	Cumulative NSCLC 001/010 + MEL 001/002/006	
	n	(%)
Subjects in population	2,799	
with one or more adverse events	1	(0.0)
Thyroiditis	1	(0.0)

Every subject 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.
Include all treated subjects in KN001 Part B1, B2, B3, D, C, F1, F2, F3 and all subjects in KN002 treated with Pembrolizumab in the original phase and all subjects in KN006 and KN010 treated with Pembrolizumab.

The 1 patient with an event of thyroiditis in the NSCLC population in KN024 and KN042 (n=790), did not experience a serious event of thyroiditis.

The 1 patient with an event of thyroiditis in the NSCLC population in KN189 and KN021 (Cohorts C and G) pembrolizumab plus chemotherapy (n=488), did not experience a serious event of thyroiditis.

Table SVII.3.1.7: Details of Important Identified Risk: Immune-Mediated Adverse Reactions- Endocrinopathies - Thyroid Disorder (Hypothyroidism, Hyperthyroidism, Thyroiditis)

	Of the 5 patients with events of thyroiditis in the HL population in KN013, KN087, and KN204 (n=389), none of the patients experienced serious events of thyroiditis. Of the 3 patients with events of thyroiditis in the UC population in KN052 (n=370), 1 (0.3%) was serious. There were no patients with serious events of thyroiditis reported in the UC population in KN045. Of the 3 patients with events of thyroiditis in the HNSCC population in KN040, KN012 and KN055 (n=609), none of the patients experienced serious events of thyroiditis. There were no patients with events of thyroiditis in the HNSCC population in KN048 monotherapy group (n=300). The 1 patient with an event of thyroiditis in the HNSCC population in KN048 pembrolizumab plus chemotherapy group (n=278) did not experience a serious event of thyroiditis. Of the 16 patients with events of thyroiditis in the melanoma population in KN054 (n=509), 2 (0.4%) experienced serious events of thyroiditis. Of the 3 patients with events of thyroiditis in the NSCLC population in KN407 and KN021 (Cohort A) (n=303), 1 (0.3%) experienced a serious event of thyroiditis. Of the 12 patients with events of thyroiditis in the RCC population in KN426 pembrolizumab plus axitinib (n=429), none of the patients experienced serious events of thyroiditis. Of the 2 patients with events of thyroiditis in the CRC population in KN177 (n=153), 1 (0.7%) experienced a serious event of thyroiditis. There were no patients with serious events of thyroiditis in the esophageal cancer population in KN590 pembrolizumab plus chemotherapy (n=370). Of the 8 patients with events of thyroiditis in the TNBC population in KN355 pembrolizumab plus chemotherapy group (n=596), none of the patients experienced serious events of thyroiditis. Of the 2 patients with events of thyroiditis in the RCC population in KN581 pembrolizumab plus lenvatinib (n=352), none of the patients experienced serious events of thyroiditis. Of the 12 patients with events of thyroiditis in the endometrial carcinoma population in KN146 and KN775 pembrolizumab plus lenvatinib (n=530), none of the patients experienced serious events of thyroiditis. Of the 6 patients with events of thyroiditis in the RCC population in KN564 pembrolizumab monotherapy (n=488), 2 (0.4%) experienced serious events of thyroiditis. There were no patients with serious events of thyroiditis in the cervical cancer population in KN826 pembrolizumab plus chemotherapy (n=307). Of the 16 patients with events of thyroiditis in the TNBC population in KN522 pembrolizumab in combination with neoadjuvant chemotherapy followed by continued adjuvant pembrolizumab monotherapy group (n=783), 2 (0.3%) experienced serious events of thyroiditis. There were no patients with serious events of thyroiditis in the melanoma population in KN716 pembrolizumab monotherapy (n=483). Of the 4 patients with events of thyroiditis in the gastric cancer population in KN811 pembrolizumab combination therapy (n=350), none of the patients experienced serious events of thyroiditis. Of the 6 patients with events of thyroiditis in the NSCLC population in KN091 pembrolizumab monotherapy (n=580), none of the patients experienced serious events of thyroiditis. Of the 9 patients with events of thyroiditis in the gastric population in KN859 pembrolizumab monotherapy (n=785), none of the patients experienced serious events of thyroiditis. Of the 3 patients with events of thyroiditis in the BTC population in KN966 pembrolizumab plus chemotherapy (n=529), none of the patients experienced serious events of thyroiditis.

Table SVII.3.1.7: Details of Important Identified Risk: Immune-Mediated Adverse Reactions- Endocrinopathies - Thyroid Disorder (Hypothyroidism, Hyperthyroiditis)

<table>
<tr><td></td><td>Of the 4 patients with events of thyroiditis in the NSCLC population in KN671 pembrolizumab in combination with chemotherapy as neoadjuvant treatment followed by continued adjuvant pembrolizumab monotherapy (n=396), there were no serious events of thyroiditis.</td></tr>
<tr><td>Severity and Nature of the Risk</td><td>Identified treatment emergent adverse events (AE) of thyroid disorder (all events) in participants summarized by grade– pembrolizumab (AEs for 30 days after discontinuation were included)

Hypothyroidism (AEOSI)
KN001, KN002 and KN006 Melanoma Subjects and KN001 and KN010 NSCLC Subjects Treated with Pembrolizumab
(Treatment-Emergent)

<table>
<tr><td></td><td colspan="2">Cumulative NSCLC 001/010 + MEL 001/002/006</td></tr>
<tr><td></td><td>n</td><td>(%)</td></tr>
<tr><td>Subjects in population</td><td>2,799</td><td></td></tr>
<tr><td>with one or more adverse events</td><td>237</td><td>(8.5)</td></tr>
<tr><td></td><td></td><td></td></tr>
<tr><td>Hypothyroidism</td><td>236</td><td>(8.4)</td></tr>
<tr><td>Grade 1</td><td>60</td><td>(2.1)</td></tr>
<tr><td>Grade 2</td><td>173</td><td>(6.2)</td></tr>
<tr><td>Grade 3</td><td>3</td><td>(0.1)</td></tr>
<tr><td>Myxoedema</td><td>1</td><td>(0.0)</td></tr>
<tr><td>Grade 2</td><td>1</td><td>(0.0)</td></tr>
<tr><td>Primary hypothyroidism</td><td>1</td><td>(0.0)</td></tr>
<tr><td>Grade 2</td><td>1</td><td>(0.0)</td></tr>
<tr><td colspan="3">Every subject is counted a single time for each applicable specific adverse event. A subject with multiple adverse events within a system organ class is counted a single time for that system organ class.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns is greater than or equal to the incidence specified in the report title, after rounding.
Only the highest reported grade of a given adverse event is counted for the individual subject.
Grades are based on NCI CTCAE version 4.0</td></tr>
</table>

In the NSCLC population in KN024 and KN042 (n=790), there was 1 (0.1%) patient with a Grade 3 event and no patients with Grade 4-5 events of hypothyroidism.

In the NSCLC population in KN189 and KN021 (Cohorts C and G) pembrolizumab plus chemotherapy (n=488), there were 2 (0.4%) patients with Grade 3 events and no patients with Grade 4-5 events of hypothyroidism.

In the HL population in KN013, KN087, and KN204 (n=389), there were no patients with Grade 3-5 events of hypothyroidism.

In the UC population in KN052 (n=370) and KN045 (n=266), there were no patients with Grade 3-5 events of hypothyroidism.

In the HNSCC population in KN040, KN012 and KN055 (n=609), there were 3 (0.5%) patients with Grade 3 events and no patients with Grade 4-5 events of hypothyroidism.

In the HNSCC population in KN048 pembrolizumab monotherapy group (n=300), there were no patients with Grade 3-5 events of hypothyroidism. In the HNSCC population in KN048 pembrolizumab plus chemotherapy group (n=276), there were no patients with Grade 3-5 events of hypothyroidism.

In the melanoma population in KN054 (n=509), there were no patients with Grade 3-5 events of hypothyroidism.

In the NSCLC population in KN407 and KN021 (Cohort A) (n=303), there was 1 (0.3%) patient with a Grade 3 event of hypothyroidism. There were no patients with Grade 4 or Grade 5 events of hypothyroidism.</td></tr>
</table>

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Table SVII.3.1.7: Details of Important Identified Risk: Immune-Mediated Adverse Reactions- Endocrinopathies - Thyroid Disorder (Hypothyroidism, Hyperthyroidism, Thyroiditis)

	In the RCC population in KN426 pembrolizumab plus axitinib (n=429), there was 1 (0.2%) patient with a Grade 3 event of hypothyroidism. There were no patients with Grade 4 or 5 events of hypothyroidism. In the CRC population in KN177 (n=153) there were no patients with Grade 3-5 events of hypothyroidism reported. In the esophageal cancer population in KN590 pembrolizumab plus chemotherapy (n=370), there were no patients with Grade 3-5 events of hypothyroidism. In the TNBC population in KN355 pembrolizumab plus chemotherapy group (n=596), there were 2 (0.3%) patients with Grade 3 events of hypothyroidism. There were no patients with Grade 4 or 5 events of hypothyroidism. In the RCC population in KN581 pembrolizumab plus lenvatinib (n=352), there were 5 (1.4%) patients with Grade 3 events of hypothyroidism. There were no patients with Grade 4 or 5 events of hypothyroidism. In the endometrial carcinoma population in KN146 and KN775 pembrolizumab plus lenvatinib (n=530), there were 5 (0.9%) patients with Grade 3, and 1 (0.2%) patient with a Grade 4 events of hypothyroidism. There were no patients with Grade 5 events of hypothyroidism. In the RCC population in KN564 pembrolizumab monotherapy (n=488) there was 1 (0.2%) patient with a Grade 3 event of hypothyroidism. There were no patients with Grade 4 or 5 events of hypothyroidism. In the MSI-H population in KN158 Cohort K and KN164 Cohorts A and B (n=475), there were no patients with Grade 3-5 events of hypothyroidism reported. In the cervical cancer population in KN826 pembrolizumab plus chemotherapy (n=307), there were 4 (1.3%) patients with Grade 3 events of hypothyroidism. There were no patients with Grade 4 or 5 events of hypothyroidism reported. In the TNBC population in KN522 pembrolizumab in combination with neoadjuvant chemotherapy followed by continued adjuvant pembrolizumab monotherapy group (n=783) there were 4 (0.5%) patients with Grade 3 events of hypothyroidism. There were no patients with Grade 4 or 5 events of hypothyroidism reported. In the melanoma population in KN716 pembrolizumab monotherapy (n=483), there were no patients with Grade 3-5 events of hypothyroidism. In the gastric cancer population in KN811 pembrolizumab combination therapy (n=350), there was 1 (0.3%) patient with a Grade 3 event of hypothyroidism. There were no patients with Grade 4 or 5 events of hypothyroidism. In the NSCLC population in KN091 pembrolizumab monotherapy (n=580) there was 1 (0.2%) patient with a Grade 3 event of hypothyroidism. There were no patients with Grade 4 or 5 events of hypothyroidism. In the BTC population in KN966 pembrolizumab plus chemotherapy (n=529), there was 1 (0.2%) patient with a Grade 3 event of hypothyroidism reported. There were no patients with Grade 4 or 5 events of hypothyroidism. In the gastric cancer population in KN859 pembrolizumab plus chemotherapy (n=785), there was 1 (0.1%) patient with a Grade 3 event of hypothyroidism reported. There were no patients with Grade 4 or 5 events of hypothyroidism reported. In the NSCLC population in KN671 pembrolizumab in combination with chemotherapy as neoadjuvant treatment followed by continued adjuvant pembrolizumab monotherapy (n=396) there were no patients with Grade 3, 4, or 5 events of hypothyroidism reported.

Table SVII.3.1.7: Details of Important Identified Risk: Immune-Mediated Adverse Reactions- Endocrinopathies - Thyroid Disorder (Hypothyroidism, Hyperthyroidism, Thyroiditis)

Hyperthyroidism (AEOSI)
KN001, KN002 and KN006 Melanoma Subjects and KN001 and KN010 NSCLC Subjects Treated with Pembrolizumab
(Treatment-Emergent)

	Cumulative NSCLC 001/010 + MEL 001/002/006	
	n	(%)
Subjects in population	2,799	
with one or more adverse events	96	(3.4)
Hyperthyroidism	96	(3.4)
Grade 1	70	(2.5)
Grade 2	22	(0.8)
Grade 3	4	(0.1)

Every subject is counted a single time for each applicable specific adverse event. A subject with multiple adverse events within a system organ class is counted a single time for that system organ class.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns is greater than or equal to the incidence specified in the report title, after rounding.
Only the highest reported grade of a given adverse event is counted for the individual subject.
Grades are based on NCI CTCAE version 4.0.

In the NSCLC population in KN024 and KN042 (n=790), there was 1 (0.1%) patient with a Grade 3 and no patients with Grade 4-5 events of hyperthyroidism.

In the NSCLC population in KN189 and KN021 (Cohorts C and G) pembrolizumab plus chemotherapy (n=488), there were no patients with Grade 3-5 events of hyperthyroidism.

In the HL population in KN013, KN087, and KN204 (n=389), there were no patients with Grade 3-5 events of hyperthyroidism reported.

In the UC population in KN052 (n=370) and KN045 (n=266), there were no patients with Grade 3-5 events of hyperthyroidism.

In the HNSCC population in KN040, KN012 and KN055 (n=609), there were no patients with Grade 3-5 events of hyperthyroidism.

In the HNSCC population in KN048 pembrolizumab monotherapy group (n=300), there was 1 (0.3%) patient with a Grade 3 event of hyperthyroidism. There were no patients with Grade 4 or 5 events of hyperthyroidism.

In the HNSCC population in KN048 pembrolizumab plus chemotherapy group (n=276), there were no patients with Grade 3-5 events of hyperthyroidism.

In the melanoma population in KN054 (n=509), there was 1 patient with a Grade 3 (0.2%) event of hyperthyroidism. There were no patients with Grade 4 or 5 events of hyperthyroidism.

In the NSCLC population in KN407 and KN021 (Cohort A) (n=303), there was 1 (0.3%) patient with a Grade 3 event of hyperthyroidism. There were no patients with Grade 4 or 5 events of hyperthyroidism.

In the RCC population in KN426 pembrolizumab plus axitinib (n=429), there were 5 (1.2%) patients with Grade 3 events of hyperthyroidism. There were no patients with Grade 4 or 5 events of hyperthyroidism.

In the CRC population in KN177 (n=153) there were no patients with Grade 3-5 events of hyperthyroidism. reported.

In the esophageal cancer population in KN590 pembrolizumab plus chemotherapy (n=370), there was 1 (0.3%) patient with a Grade 3 event of hyperthyroidism. There were no patients with Grade 4 or 5 events of hyperthyroidism.

In the TNBC population in KN355 pembrolizumab plus chemotherapy group (n=596), there was 1 (0.2%) patient with a Grade 3 event of hyperthyroidism. There were no patients with Grade 4 or 5 events of hyperthyroidism.

Table SVII.3.1.7: Details of Important Identified Risk: Immune-Mediated Adverse Reactions- Endocrinopathies - Thyroid Disorder (Hypothyroidism, Hyperthyroidism, Thyroiditis)

	In the RCC population in KN581 pembrolizumab plus lenvatinib (n=352), there were no patients with Grade 3-5 events of hyperthyroidism. In the endometrial carcinoma population in KN146 and KN775 pembrolizumab plus lenvatinib (n=530), there were 3 (0.6%) patients with Grade 3 events of hyperthyroidism. There were no patients with Grade 4 or 5 events of hyperthyroidism. In the RCC population in KN564 pembrolizumab monotherapy (n=488) there was 1 (0.2%) patient with a Grade 3 event of hyperthyroidism. There were no patients with Grade 4 or 5 events of hyperthyroidism. In the MSI-H population in KN158 Cohort K and KN164 Cohorts A and B (n=475), there was 1 (0.2%) patient with a Grade 3 event of hyperthyroidism. There were no patients with Grade 4 or 5 events of hyperthyroidism reported. In the cervical cancer population in KN826 pembrolizumab plus chemotherapy (n=307), there were no patients with Grade 3-5 events of hyperthyroidism reported. In the TNBC population in KN522 pembrolizumab in combination with neoadjuvant chemotherapy followed by continued adjuvant pembrolizumab monotherapy group (n=783) there were 2 (0.3%) patients with Grade 3 events of hyperthyroidism. There were no patients with Grade 4 or 5 events of hyperthyroidism reported. In the melanoma population in KN716 pembrolizumab monotherapy (n=483), there was 1 (0.2%) patient with a Grade 3 event of hyperthyroidism. There were no patients with Grade 4 or 5 events of hyperthyroidism. In the gastric cancer population in KN811 pembrolizumab combination therapy (n=350), there were no patients with Grade 3-5 events of hyperthyroidism. In the NSCLC population in KN091 pembrolizumab monotherapy (n=580) there was 1 (0.2%) patient with a Grade 3 event of hyperthyroidism. There were no patients with Grade 4 or 5 events of hyperthyroidism. In the gastric cancer population in KN859 pembrolizumab plus chemotherapy (n=785), there were no patients with Grade 3-5 events of hyperthyroidism reported. In the BTC population in KN966 pembrolizumab plus chemotherapy (n=529), there was 1 (0.2%) patient with a Grade 3 event of hyperthyroidism reported. There were no patients with Grade 4 or 5 events of hyperthyroidism. In the NSCLC population in KN671 pembrolizumab in combination with chemotherapy as neoadjuvant treatment followed by continued adjuvant pembrolizumab monotherapy (n=396) there were no patients with Grade 3, 4, or 5 events of hyperthyroidism reported.

Table SVII.3.1.7: Details of Important Identified Risk: Immune-Mediated Adverse Reactions- Endocrinopathies - Thyroid Disorder (Hypothyroidism, Hyperthyroidism, Thyroiditis)

Thyroiditis (AEOSI)
KN001, KN002 and KN006 Melanoma Subjects and KN001 and KN010 NSCLC Subjects Treated with Pembrolizumab
(Treatment-Emergent)

	Cumulative NSCLC 001/010 + MEL 001/002/006	
	n	(%)
Subjects in population	2,799	
with one or more adverse events	16	(0.6)
Autoimmune thyroiditis	5	(0.2)
Grade 1	2	(0.1)
Grade 2	3	(0.1)
Thyroiditis	11	(0.4)
Grade 1	7	(0.3)
Grade 2	4	(0.1)

Every subject is counted a single time for each applicable specific adverse event. A subject with multiple adverse events within a system organ class is counted a single time for that system organ class.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns is greater than or equal to the incidence specified in the report title, after rounding.
Only the highest reported grade of a given adverse event is counted for the individual subject.
Grades are based on NCI CTCAE version 4.0.

In the NSCLC population in KN024 and KN042 (n=790), there were no patients with Grade 3-5 events of thyroiditis.

In the NSCLC population in KN189 and KN021 (Cohorts C and G) pembrolizumab plus chemotherapy (n=488), there were no patients with Grade 3-5 events of thyroiditis.

In the HL population in KN013, KN087, and KN204 (n=389), there were no patients with Grade 3-5 events of thyroiditis reported.

In the UC population in KN052 (n=370), there was 1 (0.3%) patient with a Grade 3 event of thyroiditis and no patients with Grade 4 or Grade 5 events and in the UC population in KN045 (n=266), there were no patients with Grade 3-5 events of thyroiditis.

In the HNSCC population in KN040, KN012 and KN055 (n=609), there were no patients with Grade 3-5 events of thyroiditis.

In the HNSCC population in KN048 within both the pembrolizumab monotherapy (n=300) and pembrolizumab plus chemotherapy (n=276) groups, there were no patients with Grade 3-5 events of thyroiditis.

In the melanoma population in KN054 (n=509), there were no patients with Grade 3-5 events of thyroiditis.

In the NSCLC population in KN407 and KN021 (Cohort A) (n=303), there was 1 (0.3%) patient with a Grade 3 event of thyroiditis reported. There were no patients with Grade 4 or Grade 5 events of thyroiditis.

In the RCC population in KN426 pembrolizumab plus axitinib (n=429), there was 1 (0.2%) patient with a Grade 3 event of thyroiditis. There were no patients with Grade 4 or 5 events of thyroiditis.

In the CRC population in KN177 (n=153) there were no patients with Grade 3-5 events of thyroiditis reported.

In the esophageal cancer population in KN590 pembrolizumab plus chemotherapy (n=370), there were no patients with Grade 3-5 events of thyroiditis.

In the TNBC population in KN355 pembrolizumab plus chemotherapy group (n=596), there was 1 (0.2%) patient with a Grade 3 event of thyroiditis. There were no patients with Grade 4 or 5 events of thyroiditis.

In the RCC population in KN581 pembrolizumab plus lenvatinib (n=352), there were no patients with Grade 3-5 events of thyroiditis.

Table SVII.3.1.7: Details of Important Identified Risk: Immune-Mediated Adverse Reactions- Endocrinopathies - Thyroid Disorder (Hypothyroidism, Hyperthyroidism, Thyroiditis)

	In the endometrial carcinoma population in KN146 and KN775 pembrolizumab plus lenvatinib (n=530), there were no patients with Grade 3-5 events of thyroiditis reported. In the RCC population in KN564 pembrolizumab monotherapy (n=488) there were 2 (0.4%) Grade 3 events of thyroiditis. There were no patients with Grade 4 or 5 events of thyroiditis. In the cervical cancer population in KN826 pembrolizumab plus chemotherapy (n=307), there were 2 (0.7%) patients with Grade 3 and no patients with Grade 4 or 5 events of thyroiditis reported. In the TNBC population in KN522 pembrolizumab in combination with neoadjuvant chemotherapy followed by continued adjuvant pembrolizumab monotherapy group (n=783) there were 2 (0.3%) patients with Grade 3 events of thyroiditis. There were no patients with Grade 4 or 5 events of thyroiditis reported. In the melanoma population in KN716 pembrolizumab monotherapy (n=483), there were no patients with Grade 3-5 events of thyroiditis. In the gastric cancer population in KN811 pembrolizumab combination therapy (n=350), there were no patients with Grade 3-5 events of thyroiditis. In the NSCLC population in KN091 pembrolizumab monotherapy (n-580) there were no patients with Grade 3, 4 or 5 events of thyroiditis. In the gastric cancer population in KN859 pembrolizumab plus chemotherapy (n=785), there were no patients with Grade 3-5 events of thyroiditis reported. In the BTC population in KN966 pembrolizumab plus chemotherapy (n=529), there were no patients with Grade 3, 4, or 5 events of thyroiditis. In the NSCLC population in KN671 pembrolizumab in combination with chemotherapy as neoadjuvant treatment followed by continued adjuvant pembrolizumab monotherapy (n=396) there were no patients with Grade 3, 4, or 5 events of thyroiditis reported. In the global safety database through 31-DEC-2017, (pembrolizumab monotherapy trials only), there were no Grade 5 clinical trial reports of thyroid disorders. Review of pembrolizumab clinical trial data from ongoing studies and postmarketing data regarding immune-mediated endocrinopathies- thyroid disorder (hypothyroidism, hyperthyroidism, thyroiditis), including reports of fatal cases of hypothyroidism and thyroiditis, is consistent with the risk as characterized in this RMP.
Risk Factors and Risk Groups:	No specific risk factors for thyroid disorders (hyperthyroidism, hypothyroidism, thyroiditis) associated with pembrolizumab have been identified.
Preventability:	Although the development of thyroid disorders (hypothyroidism, hyperthyroidism, thyroiditis) cannot be completely prevented; patients should be monitored for signs and symptoms of thyroid disorders (hypothyroidism, hyperthyroidism, thyroiditis) and if they develop, other causes excluded. Withholding/discontinuation of pembrolizumab and appropriate medical intervention including corticosteroids following the onset of thyroid disorders (hypothyroidism, hyperthyroidism, thyroiditis) may result in recovery.
Impact on the Risk-Benefit Balance of the Product:	Severe thyroid disorders (hypothyroidism, hyperthyroidism, and thyroiditis) may be reported to be life-threating or fatal in individual patients. However, given the fatal outcome of untreated cancer, the risk of thyroid disorders which generally can be managed, is outweighed by the potential benefit of pembrolizumab treatment.
Public Health Impact:	This risk has minimal public health impact outside its effect on individual patients.

Table SVII.3.1.8: Details of Important Identified Risk: Immune-Mediated Adverse Reactions- Endocrinopathies -Type 1 Diabetes Mellitus

<table>
<tr><td>Important Identified Risk:</td><td>Immune-mediated Endocrinopathies-Type 1 Diabetes Mellitus (T1DM)</td></tr>
<tr><td><u>Potential Mechanisms:</u></td><td>Pembrolizumab is a potent and highly-selective humanized monoclonal antibody (mAb) of the Immunoglobulin G4 (IgG4)/kappa isotype directed to the programmed cell death-1 (PD-1) receptor and designed to directly block the interaction between the receptor and its ligands, PD-L1 and PD-L2. The PD-1 pathway represents a major immune control switch which may be engaged by tumor cells to overcome active T-cell immune surveillance. T-cell activation in proximity to normal tissue may lead to inflammation and injury to normal tissue.</td></tr>
<tr><td><u>Evidence Source(s) and Strength of Evidence:</u></td><td>Review of pembrolizumab clinical trial data, post-marketing experience and literature regarding endocrinopathies- type 1 diabetes mellitus represent sufficient evidence of a causal association with pembrolizumab exposure.

CTD 2.7.4

Please reference evidence source cited in Table SVII.3.1.1; Details of Important Identified Risk:

Immune-Mediated Pneumonitis</td></tr>
<tr><td colspan="2"><u>Characterisation of the Risk:</u> Immune-mediated Endocrinopathies-Type 1 Diabetes Mellitus (T1DM)</td></tr>
<tr><td>Frequency with 95%CI</td><td>95% Confidence Interval for the Overall Incidence (%) of Type 1 Diabetes Mellitus
KN001, KN002 and KN006 Melanoma Subjects and KN001 and 010 NSCLC Subjects Treated with Pembrolizumab
<table>
<tr><td></td><td colspan="2">Cumulative MEL 001/002/006 + NSCLC 001/010</td></tr>
<tr><td></td><td>n (%)</td><td>95% CI</td></tr>
<tr><td>Type 1 Diabetes Mellitus</td><td>6 (0.2)</td><td>(0.1,0.5)</td></tr>
</table>

The overall number and proportion of patients with T1DM in the NSCLC population in KN024 and KN042 (n=790) was 1 (0.1%) (95%CI-0, 0.7), which is generally similar to the proportion of patients with the event of T1DM in the reference safety dataset for melanoma and NSCLC.

The overall number and proportion of patients with T1DM in the NSCLC population in KN189 and KN021 (Cohorts C and G) pembrolizumab plus chemotherapy (n=488) was 1 (0.2%) (95% CI-0, 1.1), which is generally similar to the proportion of patients with the event of T1DM in the reference safety dataset for melanoma and NSCLC.

There were no patients with events of T1DM reported in the HL population in KN013, KN087, and KN204 (n=389).

The overall number and proportion of patients with T1DM in the UC population in KN052 (n=370) was 4 (1.1%) (95%CI-0.3,2.7), which is generally similar to the proportion of patients with the event of T1DMin the reference safety dataset for melanoma and NSCLC. There were no patients with events of T1DM in the UC population in KN045.

The overall number and proportion of patients with T1DM in the HNSCC population in KN040, KN012 and KN055 (n=609) was 3 (0.5%) (95%CI-0.1,1.4), which is generally similar to the proportion of patients with the event of T1DM in the reference safety dataset for melanoma and NSCLC.

There were no patients with events of T1DM reported in the HNSCC population in KN048 pembrolizumab monotherapy group (n=300) or pembrolizumab plus chemotherapy group (n=276).

The overall number and proportion of patients with T1DM in the melanoma population in KN054 (n=509) was 5 (1.0%) (95%CI-0.3,2.3). The proportion of patients with events of T1DM in KN054 although somewhat more common than in the reference safety dataset were generally consistent in nature with the proportion of events of T1DM previously reported for pembrolizumab.

There were no patients with events of T1DM reported in the NSCLC population in KN407 and KN021 (Cohort A) (n=303).

The overall number and proportion of patients with T1DM in the RCC population in KN426 pembrolizumab plus axitinib (n=429) was 1 (0.2%) (95% CI-0,1.3), which is generally similar to the overall frequency in the reference safety dataset for melanoma and NSCLC.</td></tr>
</table>

Table SVII.3.1.8: Details of Important Identified Risk: Immune-Mediated Adverse Reactions- Endocrinopathies -Type 1 Diabetes Mellitus

	The overall number and proportion of patients with T1DM in the CRC population in KN177 (n=153) was 1 (0.7%) (95% CI-0, 3.6) which is generally similar to the overall frequency in the reference safety dataset for melanoma and NSCLC. The overall number and proportion of patients with T1DM in the esophageal cancer population in KN590 pembrolizumab plus chemotherapy (n=370) was 1 (0.3%) (95% CI-0,1.5), which is generally similar to the proportion of patients with the event of T1DM in the reference safety dataset for melanoma and NSCLC. The overall number and proportion of patients with T1DM in the TNBC population in KN355 pembrolizumab plus chemotherapy group (n=596) was 2 (0.3%) (95% CI-0,1.2), which is generally similar to the proportion of patients with the event of T1DM in the reference dataset for melanoma and NSCLC. The overall number and proportion of patients with T1DM in the RCC population in KN581 pembrolizumab plus lenvatinib (n=352) was 2 (0.6%), which is generally similar to the proportion of patients with the event of T1DM in the reference safety dataset. The overall number and proportion of patients with T1DM in the endometrial carcinoma population in KN146 and KN775 pembrolizumab plus lenvatinib (n=530) was 4 (0.8%) (95% CI-0.2, 1.9), which is generally similar to the proportion of patients with the event of T1DM in the reference safety dataset. The overall number and proportion of patients with T1DM in the RCC population in KN564 pembrolizumab monotherapy (n=488) was 9 (1.8%) (95% CI-0.8,3.5). The proportion of patients with events of T1DM in KN564 although somewhat more common than in the reference safety dataset were generally consistent in nature with the proportion of patients with events of T1DM previously reported for pembrolizumab. The overall number and proportion of patients with T1DM in the MSI-H population in KN158 Cohort K and KN164 Cohorts A and B (n=475) was 2 (0.4%) (95% CI-0.1,1.5) which is generally similar to the proportion of patients with the event of T1DM in the reference safety dataset. The overall number and proportion of patients with T1DM in the cervical cancer population in KN826 pembrolizumab plus chemotherapy (n=307) was 2 (0.7%) (95% CI-0.1, 2.3), which is generally similar to the proportion of patients with the event of T1DM in the reference safety dataset. The overall number and proportion of patients with T1DM in the TNBC population in KN522 pembrolizumab in combination with neoadjuvant chemotherapy followed by continued adjuvant pembrolizumab monotherapy group (n=783) was 4 (0.5%) (95% CI-0.1,1.3), which is generally similar to the proportion of patients with the event of T1DM in the reference safety dataset. The overall number and proportion of patients with T1DM in the melanoma population in KN716 pembrolizumab monotherapy (n=483) was 2 (0.4%) (95% CI-0.1, 1.5), which is generally similar to the proportion of patients with the event of T1DM in the reference safety dataset for melanoma and NSCLC. The overall number and proportion of patients with T1DM in the gastric cancer population in KN811 pembrolizumab combination therapy (n=350) was 1 (0.3%) (95% CI-0.0, 1.6), which is generally similar to the proportion of patients with events of T1DM in the reference safety dataset. The overall number and proportion of patients with T1DM in the NSCLC population in KN091 pembrolizumab monotherapy (n=580) was 1 (0.2%) (95% CI-0.0,1.0), which is generally similar to the proportion of patients with the event of T1DM in the reference safety dataset. The overall number and proportion of patients with T1DM in the gastric cancer population in KN859 pembrolizumab plus chemotherapy (n=785) was 5 (0.6%) (95% CI-0.2, 1.5), which is generally similar to the proportion of patients with the events of T1DM in the reference safety dataset. There were no patients with events of T1DM reported in the BTC population in KN966 pembrolizumab plus chemotherapy group (n=529). There were no events of T1DM reported in the NSCLC population in KN671 pembrolizumab in combination with chemotherapy as neoadjuvant treatment followed by continued adjuvant pembrolizumab monotherapy (n=396).

Table SVII.3.1.8: Details of Important Identified Risk: Immune-Mediated Adverse Reactions- Endocrinopathies -Type 1 Diabetes Mellitus

Outcomes

Percent overall, fatal, not resolved, resolved, and unknown for identified risk of Type 1 Diabetes Mellitus - pembrolizumab (Table includes events for 30 days after discontinuation.)

Type 1 Diabetes Mellitus (AEOSI)
KN001, KN002 and KN006 Melanoma Subjects and KN001 and 010 NSCLC Subjects Treated with Pembrolizumab
(Treatment Emergent)

		Cumulative NSCLC 001/010 + MEL 001/002/006	
	Outcome	n	(%)
Subjects in population		2,799	
With one or more adverse events	Overall	6	(0.2)
	Fatal	0	(0.0)
	Not Resolved	4	(0.1)
	Resolved	2	(0.1)
	Unknown	0	(0.0)

Every subject is counted once on each applicable row.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns is greater than or equal to the percent incidence specified in the report title, after rounding.
Outcome: Resolved = RECOVERED/RESOLVED, Not resolved = NOT RECOVERED/NOT RESOLVED.

In the NSCLC population in KN024 and KN042 (n=790), the outcome of the 1 (0.1%) patient with an event of T1DM was resolved. There were no patients with events of T1DM with a fatal outcome.

In the NSCLC population in KN189 and KN021 (Cohorts C and G) pembrolizumb plus chemotherapy (n=488), the outcome of the 1 (0.2%) patient with an event of T1DM was not resolved. There were no patients with events of T1DM with a fatal outcome.

In the UC population in KN052 (n=370), the outcomes for the 4 patients with events of T1DM were as follows: 1 (0.3%) resolved, 1 (0.3%) resolved with sequelae, and 2 (0.5%) not resolved. There were no patients with events of T1DM with a fatal outcome.

In the HNSCC population in KN040, KN012 and KN055 (n=609), the outcomes of the 3 patients with events of T1DM were as follows: 3 (0.5%) not resolved. There were no fatal outcomes.

In the melanoma population in KN054 (n=509), the outcome of the 5 patients with events of T1DM were as follows: 5 (1.0%) not resolved. There were no patients with events of T1DM with a fatal outcome.

In the RCC population in KN426 pembrolizumab plus axitinib (n=429), the outcome for the 1 (0.2%) patient with an event of T1DM was resolved with sequelae. There were no fatal outcomes.

In the CRC population in KN177 (n=153), the outcome for the 1 patient with an event of T1DM was as follows: 1 (0.7%) not resolved. There were no patients with events of T1DM with a fatal outcome.

In the esophageal cancer population in KN590 pembrolizumab plus chemotherapy (n=370), the outcome for the 1 (0.3%) patient with an event of T1DM was not resolved. There were no patients with events of T1DM with a fatal outcome. In the TNBC population in KN355 pembrolizumab plus chemotherapy group (n=596), the outcome for the 2 patients with events of T1DM were as follows: 1 (0.2%) not resolved, and 1 (0.2%) resolved with sequelae. There were no patients with events of T1DM with a fatal outcome.

In the RCC population in KN581 pembrolizumab plus lenvatinib (n=352), the outcome for the 2 patients with events of T1DM were as follows: 2 (0.6%) not resolved. There were no patients with events of T1DM with a fatal outcome.

In the endometrial carcinoma population in KN146 and KN775 pembrolizumab plus lenvatinib (n=530), the outcome for the 4 (0.8%) patients with events of T1DM were as follows: 1 (0.2%) resolved, 2 (0.4%) resolved with sequelae, and 1 (0.2%) resolving. There were no patients with events of T1DM with a fatal outcome.

Table SVII.3.1.8: Details of Important Identified Risk: Immune-Mediated Adverse Reactions- Endocrinopathies -Type 1 Diabetes Mellitus

<table>
<tr><td></td><td>
In the RCC population in KN564 pembrolizumab monotherapy (n=488), the outcomes for the 9 patients with events of T1DM were as follows: 8 (1.6%) resolved with sequelae and 1 (0.2%) resolving. There were no patients with events of T1DM with a fatal outcome.

In the MSI-H population in KN158 Cohort K and KN164 Cohorts A and B (n=475), the outcomes for the 2 (0.4%) patients with events of T1DM were as follows: 1 (0.2%) resolved and 1 (0.2%) not resolved. There were no patients with events of T1DM with a fatal outcome.

In the cervical cancer population in KN826 pembrolizumab plus chemotherapy (n=307), the outcomes for the 2 patients with events of T1DM were as follows: 2 (0.7%) resolved. There were no patients with events of T1DM with a fatal outcome.

In the TNBC population in KN522 pembrolizumab in combination with neoadjuvant chemotherapy followed by continued adjuvant pembrolizumab monotherapy group (n=783), the outcomes for the 4 patients with events of T1DM were as follows: 3 (0.4%) not resolved, and 1 (0.1%) resolved with sequelae. There were no patients with events of T1DM with a fatal outcome.

In the melanoma population in KN716 pembrolizumab monotherapy (n=483), the outcomes of the 2 patients with events of T1DM were as follows: 1 (0.2%) not resolved, and 1 (0.2%) resolved with sequelae. There were no patients with events of T1DM with a fatal outcome.

In the gastric cancer population in KN811 pembrolizumab combination therapy (n=350), the outcome for the 1 (0.3%) patient with the event of T1DM was resolved. There were no patients with events of T1DM with a fatal outcome.

In the NSCLC population in KN091 pembrolizumab monotherapy (n=580), the outcomes for the 1 patient with an event of T1DM was as follows: 1 (0.2%) not resolved. There were no patients with events of T1DM with a fatal outcome.

In the gastric cancer population in KN859 pembrolizumab plus chemotherapy (n=785), the outcomes for the 5 patients with events of T1DM were as follows: 2 (0.3%) not resolved, 2 (0.3%) resolved, and 1 (0.1%) resolved with sequelae. There were no patients with events of T1DM with a fatal outcome.

Aggregate Review

Review of the ASE dataset (n=7730) yielded no fatal cases of T1DM. Review of the global safety database yielded the following: 1 fatal case from ongoing interventional monotherapy clinical trials and no fatal cases from the PM or non-interventional environment.
</td></tr>
<tr><td>Seriousness</td><td>
Percent serious for identified risk of Type 1 Diabetes Mellitus - Pembrolizumab (Serious AEs for 90 days after discontinuation were included.)

Type 1 Diabetes Mellitus - Serious (AEOSI)
KN001, KN002 and KN006 Melanoma Subjects and KN001 and 010 NSCLC Subjects Treated with Pembrolizumab
(Treatment Emergent)
<table>
<tr><td></td><td colspan="2">Cumulative NSCLC 001/010 + MEL 001/002/006</td></tr>
<tr><td></td><td>n</td><td>(%)</td></tr>
<tr><td>Subjects in population</td><td>2,799</td><td></td></tr>
<tr><td>with one or more adverse events</td><td>6</td><td>(0.2)</td></tr>
<tr><td></td><td></td><td></td></tr>
<tr><td>Diabetic ketoacidosis</td><td>2</td><td>(0.1)</td></tr>
<tr><td>Type 1 diabetes mellitus</td><td>4</td><td>(0.1)</td></tr>
<tr><td colspan="3">Every subject 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.
Include all treated subjects in KN001 Part B1, B2, B3, D, C, F1, F2, F3 and all subjects in KN002 treated with Pembrolizumab in the original phase and all subjects in KN006 and KN010 treated with Pembrolizumab.</td></tr>
</table>

The 1 patient with an event of T1DM reported in the NSCLC population in KN024 and KN042 (n=790) experienced a serious event of T1DM (0.1%).

The 1 patient with an event of T1DM reported in the NSCLC population in KN189 and KN021 (Cohorts C and G) pembrolizumab plus chemotherapy (n=488) experienced a serious event of T1DM (0.2%).
</td></tr>
</table>

Table SVII.3.1.8: Details of Important Identified Risk: Immune-Mediated Adverse Reactions- Endocrinopathies -Type 1 Diabetes Mellitus

	Of the 4 patients with events of T1DM reported in the UC population in KN052 (n=370), all experienced serious events of T1DM (1.1%). Of the 3 patients with events of T1DM reported in the HNSCC population in KN040, KN012 and KN055 (n=609), all experienced serious events of T1DM (0.5%). Of the 5 patients with events of T1DM reported in the melanoma population in KN054 (n=509), all experienced serious events of T1DM (1.0%). The 1 patient with an event of T1DM reported in the RCC population in KN426 pembrolizumab plus axitinib (n=429) experienced a serious event of T1DM (0.2%). There were no patients with serious events of T1DM reported in the CRC population in KN177 (n=153). There were no patients with serious events of T1DM in the esophageal cancer population in KN590 pembrolizumab plus chemotherapy (n=370). Of the 2 patients with events of T1DM reported in the TNBC population in KN355 pembrolizumab plus chemotherapy group (n=596), 1 (0.2%) experienced a serious event of T1DM. Of the 2 patients with events of T1DM reported in the RCC population in KN581 pembrolizumab plus lenvatinib (n=352), 1 (0.3%) experienced a serious event of T1DM. All 4 patients with events of T1DM reported in the endometrial carcinoma population in KN146 and KN775 pembrolizumab plus lenvatinib (n=530) experienced serious events of T1DM (0.8%). Of the 9 patients with events of T1DM in the RCC population in KN564 pembrolizumab monotherapy (n=488), all experienced serious events of T1DM (1.8%). Of the 2 patients with events of T1DM in the MSI-H population in KN158 Cohort K and KN164 Cohorts A and B (n=475), 1 (0.2%) experienced a serious event of T1DM. The 2 patients with events of T1DM reported in the cervical cancer population in KN826 pembrolizumab plus chemotherapy (n=307) experienced serious events of T1DM (0.7%). Of the 4 patients with events of T1DM in the TNBC population in KN522 pembrolizumab in combination with neoadjuvant chemotherapy followed by continued adjuvant pembrolizumab monotherapy group (n=783), 3 (0.4%) experienced serious events of T1DM. Of the 2 patients with events of T1DM reported in the melanoma population in KN716 pembrolizumab monotherapy (n=483), both experienced serious events of T1DM (0.4%). The 1 patient with the event of T1DM reported in the gastric cancer population in KN811 pembrolizumab combination therapy (n=350) experienced a serious (0.3%) event. The 1 patient with an event of T1DM reported in the NSCLC population in KN091 pembrolizumab monotherapy (n=580) experienced a serious event of T1DM (0.2%). Of the 5 patients with events of T1DM in the gastric cancer population in KN859 pembrolizumab plus chemotherapy (n=785), all 5 (0.6%) experienced a serious event of T1DM.

Table SVII.3.1.8: Details of Important Identified Risk: Immune-Mediated Adverse Reactions- Endocrinopathies -Type 1 Diabetes Mellitus

Severity and Nature of the Risk

Identified treatment emergent adverse events (AE) of Type 1 Diabetes Mellitus (all events) in participants summarized by grade–pembrolizumab (AEs for 30 days after discontinuation were included)

Type 1 Diabetes Mellitus (AEOSI)
KN001, KN002 and KN006 Melanoma Subjects and KN001 and 010 NSCLC Subjects Treated with Pembrolizumab
(Treatment Emergent)

	Cumulative NSCLC 001/010 + MEL 001/002/006	
	n	(%)
Subjects in population	2,799	
with one or more adverse events	6	(0.2)
Diabetic ketoacidosis	2	(0.1)
Grade 3	1	(0.0)
Grade 4	1	(0.0)
Type 1 diabetes mellitus	5	(0.2)
Grade 2	2	(0.1)
Grade 3	2	(0.1)
Grade 4	1	(0.0)

Every subject is counted a single time for each applicable specific adverse event. A subject with multiple adverse events within a system organ class is counted a single time for that system organ class.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns is greater than or equal to the incidence specified in the report title, after rounding.
Only the highest reported grade of a given adverse event is counted for the individual subject.
Grades are based on NCI CTCAE version 4.0.

In the NSCLC population in KN024 and KN042 (n=790), there was 1 (0.1%) patient with a Grade 4 event of T1DM. There were no patients with Grade 3 or 5 events of T1DM.

In the NSCLC population in KN189 and KN021 (Cohorts C and G) pembrolizumab plus chemotherapy (n=488), there was 1 (0.2%) patient with a Grade 4 event of T1DM. There were no patients with Grade 3 or 5 events of T1DM.

In the UC population in KN052 (n=370), there were 2 (0.5%) patients with Grade 3 events and 2 (0.5%) patients with Grade 4 events of T1DM.

In the HNSCC population in KN040, KN012 and KN055 (n=609), there were 3 (0.5%) patients with Grade 4 events of T1DM.

In the melanoma population in KN054 (n=509), there were 4 (0.8%) patients with Grade 3 events and 1 (0.2%) patient with a Grade 4 event of T1DM.

In the RCC population in KN426 pembrolizumab plus axitinib (n=429), there was 1 (0.2%) patient with a Grade 4 event of T1DM. There were no patients with Grade 5 events of T1DM.

In the CRC population in KN177 (n=153) there was 1 (0.7%) patient with a Grade 3 event of T1DM. There were no patients with Grade 4 or 5 events of T1DM reported.

In the esophageal cancer population in KN590 pembrolizumab plus chemotherapy (n=370), there was 1 (0.3%) patient with a Grade 3 event of T1DM. There were no patients with Grade 4 or 5 events of T1DM.

In the TNBC population in KN355 pembrolizumab plus chemotherapy group (n=596), there was 1 (0.2%) patient with a Grade 3 event of T1DM. There were no patients with Grade 4 or 5 events of T1DM.

In the RCC population in KN581 pembrolizumab plus lenvatinib (n=352), there was 1 (0.3%) patient with a Grade 4 event of T1DM. There were no patients with Grade 3 or 5 events of T1DM.

In the endometrial carcinoma population in KN146 and KN775 pembrolizumab plus lenvatinib (n=530), there were 2 (0.4%) patients with Grade 3 and 2 (0.4%) patients with Grade 4 events of T1DM. There were no patients with Grade 5 events of T1DM.

In the RCC population in KN564 pembrolizumab monotherapy (n=488) there were 7 (1.4%) patients with Grade 3 and 2 (0.4%) patients with Grade 4 events of T1DM. There were no patients with Grade 5 events of T1DM.

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Table SVII.3.1.8: Details of Important Identified Risk: Immune-Mediated Adverse Reactions- Endocrinopathies -Type 1 Diabetes Mellitus

	In the MSI-H population in KN158 Cohort K and KN164 Cohorts A and B (n=475), there was 1 (0.2%) patient with a Grade 3 event of T1DM. There were no patients with Grade 4 or 5 events of T1DM reported. In the cervical cancer population in KN826 pembrolizumab plus chemotherapy (n=307), there were 2 (0.7%) patients with Grade 4 events of T1DM. There were no patients with Grade 3 or 5 events of T1DM. In the TNBC population in KN522 pembrolizumab in combination with neoadjuvant chemotherapy followed by continued adjuvant pembrolizumab monotherapy group (n=783) there were 2 (0.3%) patients with Grade 3 events and 2 (0.3%) patients with Grade 4 events of T1DM. There were no patients with Grade 5 events of T1DM reported. In the melanoma population in KN716 pembrolizumab monotherapy (n=483), there was 1 (0.2%) patient with a Grade 3 and 1 (0.2%) patient with a Grade 4 event of T1DM. There were no patients with Grade 5 events of T1DM. In the gastric cancer population in KN811 pembrolizumab combination therapy (n=350), there was 1 (0.3%) patient with a Grade 3 event of T1DM. There were no patients with Grade 4 or Grade 5 events of T1DM. In the NSCLC population in KN091 pembrolizumab monotherapy (n=580) there was 1 (0.2%) patient with a Grade 3 event of T1DM. There were no patients with Grade 4 or 5 events of T1DM. In the gastric cancer population in KN859 pembrolizumab plus chemotherapy (n=785), there were 4 (0.5%) patients with a Grade 3 and 1 (0.1%) patient with a Grade 4 event of T1DM reported. There were no patients with a Grade 5 events of T1DM. In the global safety database through 31-DEC-2017, (pembrolizumab monotherapy trials only), there was 1 Grade 5 clinical trial report of T1DM. Review of pembrolizumab clinical trial data from ongoing studies and postmarketing data regarding immune-mediated endocrinopathies- Type I diabetes mellitus, including fatal cases, is consistent with the risk as characterized in this RMP.
Risk Factors and Risk Groups:	No specific risk factors for Type I DM associated with pembrolizumab have been identified.
Preventability:	Although the development of Type I DM cannot be completely prevented; patients should be monitored for hyperglycemia or other signs and symptoms of diabetes. Insulin should be administered for type 1 diabetes, and pembrolizumab should be withheld in cases of Grade 3 hyperglycaemia until metabolic control is achieved.
Impact on the Risk-Benefit Balance of the Product:	Diabetes mellitus and diabetic ketoacidosis can be life-threatening or fatal in individual patients. Given the fatal outcome of untreated cancer, the risk of TIDM is outweighed by the potential benefit of pembrolizumab treatment.
Public Health Impact:	This risk has minimal public health impact outside its effect on individual patients.

Table SVII.3.1.9: Details of Important Potential Risk: For Hematologic Malignancies: Increased Risk of Severe Complications of Allogeneic Stem Cell Transplantation (SCT) in Patients Who Have Previously Received Pembrolizumab

Important Potential Risk:	For hematologic malignancies: increased risk of severe complications of allogeneic stem cell transplantation (SCT) in patients who have previously received pembrolizumab
Potential Mechanisms:	The safety and efficacy of HSCT may be different in patients previously exposed to PD-1 inhibitors, given their immunomodulatory mechanism and their prolonged clinical activity. Specifically, residual PD-1 inhibition peri- and post-SCT could enhance allogeneic T-cell responses, which could augment the graft-versus-tumor (GVT) effect but also increase the incidence or severity of graft-versus-host disease (GVHD) and other immune complications of SCT.
Evidence Source(s) and Strength of Evidence:	Review of pembrolizumab literature regarding increased risk of severe complications of allogeneic stem cell transplantation in patients who have previously received pembrolizumab represents scientific evidence of a possible causal association with pembrolizumab exposure. Abstract [Ref. 5.4: 04FG2Z] CTD 2.7.4
Characterisation of the Risk: For hematologic malignancies: increased risk of severe complications of allogeneic stem cell transplantation (SCT) in patients who have previously received pembrolizumab	
Frequency with 95%CI	Unknown
Seriousness / Outcomes	A case series has been presented in the literature [Ref. 5.4: 04FG2Z] that describes a cohort of patients who received PD-1 inhibitors and went on to receive allogeneic SCT. An increased risk of severe complications, including graft versus host disease (GVHD) and veno-occlusive disease of the liver was noted. In addition, the US product circular for nivolumab [Ref. 5.4: 04GJ9J] describes severe complications of allogeneic SCT following prior nivolumab therapy. Fatal outcomes have been reported.
Severity and Nature of the Risk	Hepatic VOD and severe GVHD (which can include skin, liver and gastrointestinal symptoms), including fatal reports, have been reported in patients who have undergone allogeneic stem cell transplant following pembrolizumab therapy. Review of the reports does not provide sufficient evidence for a causal relationship between an increased risk of severe complications of allogeneic transplant and prior pembrolizumab therapy. Therefore, this is presented as a potential risk in this RMP.
Risk Factors and Risk Groups:	Patients with hematologic malignancies undergoing allogeneic SCT who were previously treated with a PD-inhibitor.
Preventability:	These complications are preventable if patients do not undergo allogeneic SCT following PD-1 therapy; however, hematologic malignancy patients who are candidates for allogeneic SCT have generally exhausted other treatment options.
Impact on the Risk-Benefit Balance of the Product:	These complications may be fatal in individual patients. However, given the fatal outcome of untreated lymphoma in patients who have exhausted other treatment alternatives and that the limited data available suggests that these complications can be medically managed in the majority of cases, the risk is outweighed by the potential benefit.
Public Health Impact:	This risk has minimal public health impact outside its effect on individual patients.

Table SVII.3.1.10: Details of Important Potential Risk: Graft Versus Host Disease (GVHD) After Pembrolizumab Administration in Patients With a History of Allogeneic Stem Cell Transplant (SCT)

Important Potential Risk:	GVHD after pembrolizumab administration in patients with a history of allogeneic SCT
Potential Mechanisms:	The anti-tumor effect of allogeneic SCT is based upon donor stem cells reconstituting an immune system, thereby allowing for a potent graft versus tumor (GVT) effect, but also creating a significant risk of GVHD. GVHD occurs due to the donor's immune system recognizing recipient major (MHC) or minor histocompatibility antigens, exacerbated by tissue damage caused by conditioning regimens. One of the major physiologic mechanisms responsible for maintaining immune tolerance in this setting is the attenuation of donor T-cell response caused by ligation of the PD1 receptor on donor T lymphocytes to its ligands on recipient tissue. Disruption of this immune axis by PD1 inhibition, while promoting GVT effect, may also increase the risk of GVHD.
Evidence Source(s) and Strength of Evidence:	Published literature [Ref. 5.4: 04PSFD] Postmarketing data
Characterisation of the Risk: GVHD after pembrolizumab administration in patients with a history of allogeneic SCT	
Frequency with 95%CI	Unknown
Seriousness / Outcomes	Published literature has suggested that a PD-1 inhibitor (nivolumab) may have induced fatal and serious GVHD given post-allogeneic SCT. Two case series, primarily involving nivolumab, have been published in the literature, suggesting that PD-1 therapy in patients who have undergone allogeneic SCT are at risk of developing GVHD. Importantly, these case series identify a risk factor of a history of GVHD after allogeneic SCT. Furthermore, it was observed that those patients who developed GVHD following PD-1-inhibitor therapy were, on average, closer to their allogeneic SCT than those who did not develop GVHD following treatment with PD-1-inhibitors.
Severity and Nature of the Risk	Currently there is very little direct experience with pembrolizumab in this setting by which to estimate any potential effect. In the clinical trial database, there are 5 subjects who received an allogeneic SCT 5 or more years before pembrolizumab treatment. Three of these had a history of GVHD with the allogeneic SCT; however, none developed GVHD after receiving pembrolizumab. Therefore, this is presented as a potential risk in this RMP.
Risk Factors and Risk Groups:	Patients with a history of allogeneic SCT treated with a PD-1 inhibitor.
Preventability:	These complications are preventable if patients do not undergo allogeneic SCT prior to PD-1 therapy. However, hematologic malignancy patients who have undergone allogeneic SCT and subsequently relapse or develop a secondary malignancy and may be candidates for pembrolizumab therapy have generally exhausted other treatment options.
Impact on the Risk-Benefit Balance of the Product:	These complications may be fatal in individual patients. However, given the fatal outcome of untreated lymphoma in patients who have exhausted other treatment alternatives and that the limited data available suggests that these complications can be medically managed in the majority of cases, as well as the need for therapeutic alternatives in patients who have a medical history of allogeneic SCT and then develop secondary malignancy, the risk is outweighed by the potential benefit.
Public Health Impact:	This risk has minimal public health impact outside its effect on individual patients.

SVII.3.2 Presentation of the Missing Information

Not applicable

PART II: MODULE SVIII - SUMMARY OF THE SAFETY CONCERNS

Table SVIII.1: Summary of Safety Concerns

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

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PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

III.1 Routine Pharmacovigilance Activities

The MAH maintains systems and standard practices for routine pharmacovigilance activities to collect reports of suspected adverse reactions (including spontaneous reports, reports from clinical studies, reports of pregnancy/lactation exposures, overdoses and medication errors); prepare reports for regulatory authorities (e.g. individual case safety reports, Periodic Safety Update Reports (PSURs), etc.), and maintain continuous monitoring of the safety profile of approved products (including signal detection, issue evaluation, updating of labeling, and liaison with regulatory authorities). The MAH maintains a Pharmacovigilance System Master File which contains details of these systems and standard practices.

MAH-sponsored clinical trials are being conducted in multiple different tumor types including but not limited to: melanoma, non-small cell lung cancer, hematologic malignancies, bladder tumors, and multiple other solid tumor types that will continue to inform the safety profile of pembrolizumab. All of these on-going and planned clinical trials will continue to provide valuable data and help to inform the MAH regarding ongoing safety concerns and to identify future safety signals.

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Routine Pharmacovigilance Activities Beyond Adverse Reactions Reporting and Signal Detection:

Table III.1.1: Overview of Pharmacovigilance Actions

Areas Requiring Further Investigation	Proposed Routine and Additional Pharmacovigilance Activities	Objectives
Important Identified risk: Immune-Mediated Adverse Reactions		
In order to monitor for and better characterize the occurrence of immune-mediated adverse reactions the MAH monitors and evaluates reports of immune-mediated adverse reactions received in the postmarketing and clinical environment.	Routine pharmacovigilance Additional pharmacovigilance including: • Safety monitoring in all ongoing MAH-sponsored clinical trials for pembrolizumab in various tumor types	To monitor, identify and evaluate reports of immune-mediated adverse reactions in patients treated with pembrolizumab
Important Potential Risk: For hematologic malignancies: increased risk of severe complications of allogeneic SCT in patients who have previously received pembrolizumab		
In order to monitor for and better characterize the occurrence (for hematologic malignancies) of an increased risk of severe complications of allogeneic SCT in patients who have previously received pembrolizumab, the MAH monitors and evaluates reports of severe complications of allogeneic SCT in patients who have previously received pembrolizumab from both the postmarketing and clinical environment.	Routine pharmacovigilance Additional pharmacovigilance including: • Safety monitoring in the ongoing HL trial (KN204)	To monitor, identify and evaluate for hematologic malignancies: reports of severe complications of allogeneic SCT in patients who have previously received pembrolizumab
Important Potential Risk: Graft versus host disease (GVHD) after pembrolizumab administration in patients with a history of allogeneic stem cell transplant (SCT)		
In order to monitor for and better characterize the occurrence of GVHD after pembrolizumab administration in patients with a history of allogeneic SCT, the MAH monitors and evaluates reports of GVHD after pembrolizumab administration in patients with a history of allogeneic SCT from both the postmarketing and clinical trial environment.	Routine pharmacovigilance Additional pharmacovigilance including: ▪ Safety monitoring in all ongoing MAH-sponsored clinical trials for pembrolizumab in various tumor types	To monitor, identify and evaluate reports of GVHD after pembrolizumab administration in patients with a history of allogeneic SCT

Other Forms of Routine Pharmacovigilance Activities for Safety Concerns:

Not applicable.

III.2 Additional Pharmacovigilance Activities

All ongoing and planned additional pharmacovigilance activities are described below.

III.3 Summary Table of Additional Pharmacovigilance Activities

On-Going and Planned Additional Pharmacovigilance Activities

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

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PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

Table IV.1: Planned and On-Going Post-Authorisation Efficacy Studies that are Conditions of the Marketing Authorisation or that are Specific Obligations

Study Status	Summary of Objectives	Efficacy Uncertainties Addressed	Milestones	Due Date
Efficacy studies which are conditions of the marketing authorization				
A randomized, placebo-controlled, parallel-group, crossover/rechallenge, multi-center study of adjuvant pembrolizumab in participants 12 years of age and older with resected Stage IIB and IIC cutaneous melanoma (KN716) (on-going)	The value of biomarkers to predict the efficacy of pembrolizumab should be further explored, specifically Additional biomarkers other than PD-L1 expression status by Immunohistochemistry (IHC) (e.g. PD-L2, RNA signature, etc.) predictive of pembrolizumab efficacy should be investigated together with more information regarding the pattern of expression of PD L1 obtained in the resected Stage II melanoma adjuvant study (KN716): • Genomic analyses using whole exome sequencing and/or RNAseq (e.g. Nanostring RNA gene signature) • IHC staining for PD-L2 • Data on RNA and proteomic serum profiling	Explore additional biomarkers	Final report (melanoma adjuvant study)	4Q 2024
A Phase III, Randomized, Open-label, Clinical Trial to Compare Pembrolizumab with Brentuximab Vedotin in Subjects with Relapsed or Refractory Classical Hodgkin Lymphoma (KN204) (on-going)	To compare overall survival (OS), progression free survival (PFS) and objective response rate (ORR) of pembrolizumab when compared to Brentuximab Vedotin in subjects with relapsed or refractory cHL and to examine the safety and tolerability between treatment groups.	Long term efficacy and safety	Final study report	4Q 2025

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Table IV.1: Planned and On-Going Post-Authorisation Efficacy Studies that are Conditions of the Marketing Authorisation or that are Specific Obligations

Study Status	Summary of Objectives	Efficacy Uncertainties Addressed	Milestones	Due Date
Adjuvant immunotherapy with anti-PD-1 monoclonal antibody Pembrolizumab (MK-3475) versus placebo after complete resection of high-risk Stage III melanoma: A randomized, double-blind Phase 3 trial of the EORTC Melanoma Group (KN054) (on-going)	To prospectively assess whether post-operative adjuvant therapy with pembrolizumab improves recurrence-free survival (RFS) as compared to placebo in high-risk patients with complete resection of Stage IIIA (> 1 mm metastasis), IIIB and IIIC melanoma. To prospectively assess whether in the subgroup of patients with PD-L1- positive tumor expression, pembrolizumab improves recurrence-free survival as compared to placebo (primary endpoints); distant metastasis free survival (DMFS) and overall survival (OS) in all-subjects and subjects with PD-L1-positive tumors (secondary endpoints for final study report)	Long term efficacy and safety	Final Study Report	4Q 2027
A Phase II study of pembrolizumab (MK-3475) in previously treated participants with advanced solid tumors (KN158) (on-going)	To evaluate the antitumor activity of pembrolizumab in participants with MSI-H/dMMR gastric, biliary or small intestine cancer	Additional efficacy	Clinical Study Report	1Q 2025
A randomized, placebo-controlled, parallel-group, crossover/rechallenge, multi-center study of adjuvant pembrolizumab in participants 12 years of age and older with resected Stage IIB or IIC cutaneous melanoma (KN716) (on-going)	To compare RFS, DMFS and OS between pembrolizumab and placebo in patients with resected Stage IIB or IIC cutaneous melanoma	Long term efficacy and safety	Clinical Study Report	2Q 2023 4Q 2028
A randomized, Phase 3 trial with pembrolizumab versus placebo for patients with early stage NSCLC after resection and completion of standard adjuvant therapy (KN091) (on-going)	To compare OS between pembrolizumab and placebo in patients with early stage NSCLC after resection and completion of standard adjuvant therapy To assess data on treatment post-progression, and particularly on the uptake and activity of anti-PD(L)1 in patients previously treated with adjuvant pembrolizumab	Long term efficacy and safety	Final Study Report	3Q2026

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PART V: RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

Risk Minimisation Plan

V.1 Routine Risk Minimisation Measures

Table V.1.1: Description of Routine Risk Minimisation Measures by Safety Concern

Safety Concern	Routine Risk Minimisation Activities
Immune-Mediated Adverse Reactions	**Objective of the Risk Minimisation Measures:** The objective is to inform prescribers of the risk of immune-mediated adverse reactions and to provide appropriate advice to minimize the risk in clinical practice. **Text in SmPC:** Sections 4.2, 4.4, 4.8 of the SmPC: Immune-mediated adverse reactions
For Hematologic Malignancies: Increased risk of severe complications of allogeneic stem cell transplantation (SCT) in patients who have previously received pembrolizumab	**Objective of the Risk Minimisation Measures:** The objective is to inform prescribers of the potential risk of: For hematologic malignancies: Increased risk of severe complications of allogeneic SCT in patients who have previously received pembrolizumab and to provide appropriate advice to minimize the risk in clinical practice. **Text in SmPC:** Sections 4.4, 4.8 of the SmPC
Graft versus host disease (GVHD) after pembrolizumab administration in patients with a history of allogenic stem cell transplantation (SCT)	**Objective of the Risk Minimisation Measures:** The objective is to inform prescribers of the potential risk of GVHD after pembrolizumab administration in patients with a history of allogeneic SCT and to provide appropriate information to assist in early recognition and treatment in clinical practice. **Text in SmPC:** Section 4.4 of the SmPC

V.2 Additional Risk Minimisation Measures

Table V.2.1: Description of Additional Risk Minimisation Measures by Safety Concern

Safety Concern	Additional Risk Minimisation Activities
Immune-Mediated Adverse Reactions	**Objective and Rationale:** Receipt of educational material will reinforce communication of the information in the SmPC from prescribers to their patients and are intended to help minimize the risk of immune-mediated reactions in clinical practice. Patient educational material in the form of patient card will enable patient awareness of side effects and early recognition of immune mediated events supporting risk Minimisation. **Proposed Actions:** Educational materials: • Patient Card Healthcare providers will distribute the Patient Card to the patients/caregivers to educate them about symptoms of immune-mediated adverse reactions. Patients will receive: • Information about key symptoms that need to be reported immediately to the physician/nurse. • Instruction on the importance of carrying the wallet-sized Patient Card at all times, to show it at medical visits to healthcare professionals other than the prescriber.
	How Effectiveness of the Risk Minimisation Measures for the Safety Concern Will be Measured: Implementation: • Communication via direct mail to oncologists, oncology nurses and oncology pharmacists who treat patients with the approved indication(s). The records of the mailer will be used to track the risk Minimisation activity. • Training of the local country staff on the patient card and on the need to provide the material to new prescribers will be completed. Records of the training will be maintained. Clinical outcomes: • The MAH's educational plan will encourage patients to report signs and symptoms associated with immune-mediated reactions to their HCPs. • Information from ongoing pharmacovigilance activities will assess appropriate recognition and management of immune-mediated adverse reactions and that the events observed in real world use are consistent with the cases observed in the clinical trial program and characterized in the SmPC and patient card. **Criteria for Judging the Success of the Proposed Risk Minimisation Measure(s):** Clinical features of reported Adverse Drug Reactions (ADRs) are reviewed to ensure consistency with both the known safety profile of pembrolizumab and also with appropriate medical management guidelines in the SmPC. Upon review of the data, appropriate measures will be considered if new information is obtained that indicates that additional risk minimisation measures are warranted. **Planned Date(s) for Assessment:** Proposed review period: • Data will be reviewed as part of routine pharmacovigilance processes and will be presented in the PSUR if clinically meaningful new safety information is identified.

Table V.2.1: Description of Additional Risk Minimisation Measures by Safety Concern

Safety Concern	Additional Risk Minimisation Activities
For Hematologic Malignancies: Increased risk of severe complications of allogeneic stem cell transplantation (SCT) in patients who have previously received pembrolizumab	Not applicable
Graft versus host disease (GVHD) after pembrolizumab administration in patients with a history of allogeneic stem cell transplant (SCT)	Not applicable

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V.3 Summary of Risk Minimisation Measures

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

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

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN BY PRODUCT

Summary of risk management plan for pembrolizumab

This is a summary of the risk management plan (RMP) for pembrolizumab. The RMP details important risks of pembrolizumab, how these risks can be minimised, and how more information will be obtained about pembrolizumab's risks and uncertainties (missing information).

Pembrolizumab's Summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how pembrolizumab should be used.

I. The Medicine and What it is Used For

Melanoma

Pembrolizumab as monotherapy is indicated for the treatment of adults and adolescents aged 12 years and older with advanced (unresectable or metastatic) melanoma.

Pembrolizumab as monotherapy is indicated for the adjuvant treatment of adults and adolescents aged 12 years and older with Stage IIB, IIC or III melanoma and who have undergone complete resection.

Non-small cell lung carcinoma (NSCLC)

Pembrolizumab in combination with platinum-containing chemotherapy as neoadjuvant treatment, and then continued as monotherapy as adjuvant treatment, is indicated for the treatment of resectable non-small cell lung carcinoma at high risk of recurrence in adults.

Pembrolizumab as monotherapy is indicated for the adjuvant treatment of adults with non-small cell lung carcinoma who are at high risk of recurrence following complete resection and platinum-based chemotherapy.

Pembrolizumab as monotherapy is indicated for the first-line treatment of metastatic non-small cell lung carcinoma (NSCLC) in adults whose tumours express PD-L1 with a ≥50% tumour proportion score (TPS) with no EGFR or ALK positive tumour mutations.

Pembrolizumab, in combination with pemetrexed and platinum chemotherapy, is indicated for the first-line treatment of metastatic non-squamous NSCLC in adults whose tumours have no EGFR or ALK positive mutations.

Pembrolizumab, in combination with carboplatin and either paclitaxel or nab-paclitaxel, is indicated for the first-line treatment of metastatic squamous NSCLC in adults.

Pembrolizumab as monotherapy is indicated for the treatment of locally advanced or metastatic NSCLC in adults whose tumours express PD-L1 with a ≥1% TPS and who have received at

least one prior chemotherapy regimen. Patients with EGFR or ALK positive tumour mutations should also have received targeted therapy before receiving pembrolizumab.

Classical Hodgkin lymphoma (cHL)

Pembrolizumab as monotherapy is indicated for the treatment of adult and paediatric patients aged 3 years and older with relapsed or refractory classical Hodgkin Lymphoma (cHL) who have failed autologous stem cell transplant (ASCT) or following at least two prior therapies when ASCT is not a treatment option.

Urothelial carcinoma

Pembrolizumab as monotherapy is indicated for the treatment of locally advanced or metastatic urothelial carcinoma in adults who have received prior platinum-containing chemotherapy.

Pembrolizumab as monotherapy is indicated for the treatment of locally advanced or metastatic urothelial carcinoma in adults who are not eligible for cisplatin-containing chemotherapy and whose tumours express PD-L1 with a combined positive score (CPS) ≥ 10.

Head and neck squamous cell carcinoma (HNSCC)

Pembrolizumab, as monotherapy or in combination with platinum and 5-fluorouracil (5-FU) chemotherapy, is indicated for the first-line treatment of metastatic or unresectable recurrent head and neck squamous cell carcinoma (HNSCC) in adults whose tumours express PD-L1 with a CPS ≥ 1.

Pembrolizumab as monotherapy is indicated for the treatment of recurrent or metastatic HNSCC in adults whose tumours express PD-L1 with a ≥ 50% TPS and progressing on or after platinum-containing chemotherapy.

Renal cell carcinoma (RCC)

Pembrolizumab, in combination with axitinib, is indicated for the first-line treatment of advanced renal cell carcinoma (RCC) in adults.

Pembrolizumab, in combination with lenvatinib, is indicated for the first-line treatment of advanced renal cell carcinoma (RCC) in adults.

Pembrolizumab as monotherapy is indicated for the adjuvant treatment of adults with renal cell carcinoma at increased risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions.

Microsatellite instability high (MSI-H) or mismatch repair deficient (dMMR) cancers

Colorectal cancer (CRC)
Pembrolizumab as monotherapy is indicated for adults with MSI-H or dMMR colorectal cancer in the following settings:

- first-line treatment of metastatic colorectal cancer;

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- treatment of unresectable or metastatic colorectal cancer after previous fluoropyrimidine-based combination therapy.

Non-colorectal cancers
Pembrolizumab as monotherapy is indicated for the treatment of the following MSI-H or dMMR tumours in adults with:

- advanced or recurrent endometrial carcinoma, who have disease progression on or following prior treatment with a platinum-containing therapy in any setting and who are not candidates for curative surgery or radiation;
- unresectable or metastatic gastric, small intestine, or biliary cancer, who have disease progression on or following at least one prior therapy.

Oesophageal carcinoma

Pembrolizumab, in combination with platinum and fluoropyrimidine based chemotherapy, is indicated for the first-line treatment of locally advanced unresectable or metastatic carcinoma of the oesophagus in adults whose tumours express PD-L1 with a CPS ≥ 10

Triple negative breast cancer (TNBC)

Pembrolizumab, in combination with chemotherapy as neoadjuvant treatment, and then continued as monotherapy as adjuvant treatment after surgery, is indicated for the treatment of adults with locally advanced, or early-stage triple-negative breast cancer (TNBC) at high risk of recurrence.

Pembrolizumab, in combination with chemotherapy, is indicated for the treatment of locally recurrent unresectable or metastatic triple-negative breast cancer (TNBC) in adults whose tumors express PD-L1 with a CPS ≥10 and who have not received prior chemotherapy for metastatic disease.

Endometrial carcinoma (EC)

Pembrolizumab, in combination with lenvatinib, is indicated for the treatment of advanced or recurrent endometrial carcinoma in adults who have disease progression on or following prior treatment with a platinum-containing therapy in any setting and who are not candidates for curative surgery or radiation.

Cervical cancer

Pembrolizumab, 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.

Gastric or gastro-oesophageal junction adenocarcinoma

Pembrolizumab, in combination with trastuzumab, fluoropyrimidine- and platinum-containing chemotherapy, is indicated for the first-line treatment of locally advanced unresectable or

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metastatic HER2-positive gastric or gastro-oesophageal junction adenocarcinoma in adults whose tumours express PD-L1 with a CPS ≥ 1.

Pembrolizumab, in combination with fluoropyrimidine- and platinum-containing chemotherapy, is indicated for the first-line treatment of locally advanced unresectable or metastatic HER2-negative gastric or gastro-oesophageal junction adenocarcinoma in adults whose tumours express PD-L1 with a CPS ≥ 1.

Biliary tract carcinoma (BTC)

Pembrolizumab, in combination with gemcitabine and cisplatin, is indicated for the first-line treatment of locally advanced unresectable or metastatic biliary tract carcinoma in adults.
It contains 100 mg liquid pembrolizumab in a 10 mL single-use vial as the active substance and it is given by intravenous infusion.

The Recommended Dose of Pembrolizumab is:

- 200 mg every 3 weeks or 400 mg every 6 weeks administered as an intravenous infusion over 30 minutes.

Further information about the evaluation of pembrolizumab's benefits can be found in pembrolizumab's European Public Assessment Report (EPAR), including in its plain-language summary, available on the EMA website, under the medicine's webpage link to product's EPAR summary landing page on the EMA webpage at the following link:

https://www.ema.europa.eu/en/medicines/human/EPAR/keytruda

II. Risks Associated With the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of pembrolizumab, together with measures to minimise such risks and the proposed studies for learning more about pembrolizumab's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size - the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status - the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In the case of pembrolizumab, these measures are supplemented with *additional risk minimisation measures* mentioned under relevant important risks, below. In addition to these

measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment - so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*. If important information that may affect the safe use of pembrolizumab is not yet available, it is listed under 'missing information' below.

II.A List of Important Risks and Missing Information

Important risks of pembrolizumab are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of pembrolizumab. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

Pembrolizumab has been on the market since July of 2015. Risk minimization activities recommending specific clinical measures to address the risks have become fully integrated into standard clinical practice, such as inclusion into treatment protocols or clinical guidelines. The identified risks in the EU RMP are: Immune-mediated adverse reactions.

The potential risks in the EU RMP include: an increased risk of severe complications of allogeneic stem cell transplantation (SCT) in patients who have previously received pembrolizumab and Graft versus host disease (GVHD) after pembrolizumab administration in patients with a history of allogeneic stem cell transplant (SCT).

Table II.A.1: List of Important Risks and Missing Information

List of Important Risks and Missing Information	
Important identified risks	Immune-mediated adverse reactions
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

II.B Summary of Important Risks

Table II.B.1: Important Identified Risk: Immune-Mediated Adverse Reactions

Evidence for linking the risk to the medicine	Review of pembrolizumab clinical trial data, post-marketing experience and literature regarding immune-mediated adverse reactions represent sufficient evidence of a causal association with pembrolizumab exposure. pembrolizumab KN001 Database Cutoff Date: 18APR2014 pembrolizumab KN001 Database Cutoff Date for Lung: 23JAN2015 pembrolizumab KN002 Database Cutoff Date: 28FEB2015 pembrolizumab KN006 Database Cutoff Date: 03MAR2015 pembrolizumab KN010 Database Cutoff Date: 30SEP2015 pembrolizumab KN013 Database Cutoff Date for Hodgkin Lymphoma: 28SEP2018 pembrolizumab KN024 Database Cutoff Date: 10JUL2017 pembrolizumab KN087 Database Cutoff Date: 21MAR2019 pembrolizumab KN045 Database Cutoff Date: 07SEP2016 pembrolizumab KN052 Database Cutoff Date: 01SEP2016 pembrolizumab KN021 Database Cutoff Date Cohort A: 07NOV2016, Cohort G/C: 31MAY2017 pembrolizumab KN189 Database Cutoff Date: 08NOV2017 pembrolizumab KN040 Database Cutoff Date: 15MAY2017 pembrolizumab KN012 Database Cutoff Date: 26APR2016 pembrolizumab KN055 Database Cutoff Date: 22APR2016 pembrolizumab KN054 Database Cutoff Date: 02OCT2017 pembrolizumab KN407 Database Cutoff Date: 03APR2018 pembrolizumab KN426 Database Cutoff Date: 24AUG2018 pembrolizumab KN048 Database Cutoff Date: 13JUN2018 pembrolizumab KN042 Database Cutoff Date: 26FEB2018 pembrolizumab KN177 Database Cutoff Date: 19FEB2020 pembrolizumab KN204 Database Cutoff Date: 16JAN2020 pembrolizumab KN590 Database Cutoff Date: 02JUL2020 pembrolizumab KN355 Database Cutoff Date: 11DEC2019 pembrolizumab KN581 Database Cutoff Date: 28AUG2020 pembrolizumab KN146 Database Cutoff Date: 18AUG2020 pembrolizumab KN775 Database Cutoff Date: 26OCT2020 pembrolizumab KN564 Database Cutoff Date: 14DEC2020 pembrolizumab KN158 Database Cutoff Date Cohort K: 05OCT2020 pembrolizumab KN164 Database Cutoff Date Cohorts A and B: 09SEP2019 pembrolizumab KN826 Database Cutoff Date: 03MAY2021 pembrolizumab KN522 Database Cutoff Date: 23MAR2021 pembrolizumab KN716 Database Cutoff Date: 04DEC2020 pembrolizumab KN811 Database Cutoff Date: 25MAY2022 pembrolizumab KN091 Database Cutoff Date: 20SEP2021 pembrolizumab KN859 Database Cutoff Date: 03OCT2022 pembrolizumab KN966 Database Cutoff Date: 15DEC2022 pembrolizumab KN671 Database Cutoff Date: 29JUL2022

Table II.B.1: Important Identified Risk: Immune-Mediated Adverse Reactions

Risk factors and risk groups	**Pneumonitis** Patients with a history of non-infectious pneumonitis that required steroids or current pneumonitis were excluded from the clinical trials. These patients are considered to be a risk group for the development of pneumonitis; in the interim analysis of the KN001 NSCLC cohort, possible risk factors identified that might predispose subjects to pneumonitis were a documented history of prior thoracic radiation to the chest (≥30Gy). According to the literature, risk factors for interstitial lung disease may include occupational exposure to toxins, chest irradiation, some chemotherapies, smoking and advanced age. **Colitis** No specific risk factors for colitis and diarrhea associated with pembrolizumab were identified. **Hepatitis** Patients with moderate to severe liver dysfunction were excluded from clinical trials. No analysis of specific risk factors for immune-mediated hepatitis associated with pembrolizumab has been undertaken. **Nephritis** Patients with severe renal dysfunction were excluded from clinical trials. No specific risk factors for nephritis associated with pembrolizumab have been identified. **Endocrinopathies** No specific risk factors for endocrinopathies associated with pembrolizumab have been identified.
Risk minimisation measures	Routine risk minimisation measures: ▪ The risk of the immune-mediated adverse reactions associated with the use of pembrolizumab is described in the SmPC, Section 4.2, 4.4, 4.8 and appropriate advice is provided to the prescriber to minimize the risk. Additional risk minimisation measures: ▪ Patient card
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Safety monitoring in all ongoing MAH-sponsored clinical trials for pembrolizumab in various tumor types.

Table II.B.2: Important Potential Risk: For Hematologic Malignancies: Increased Risk of Severe Complications of Allogeneic Stem Cell Transplantation (SCT) in Patients Who Have Previously Received Pembrolizumab

Evidence for linking the risk to the medicine	Review of pembrolizumab literature regarding increased risk of severe complications of allogeneic stem cell transplantation in patients who have previously received pembrolizumab represents scientific evidence of a possible causal association with pembrolizumab exposure.
Risk factors and risk groups	Patients with hematologic malignancies undergoing allogeneic SCT who were previously treated with a PD-1 inhibitor.
Risk minimisation measures	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.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: ▪ Safety monitoring in the ongoing HL trial (KN204)

Table II.B.3: Important Potential Risk: Graft Versus Host Disease (GVHD) After Pembrolizumab Administration in Patients With a History of Allogeneic Stem Cell Transplant (SCT)

Evidence for linking the risk to the medicine	Published literature Postmarketing data
Risk factors and risk groups	Patients with a history of allogeneic SCT treated with a PD-1 inhibitor.
Risk minimisation measures	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.
Additional pharmacovigilance activities	Routine pharmacovigilance activities Additional pharmacovigilance including: ▪ Safety monitoring in all other ongoing MAH-sponsored clinical trials for pembrolizumab in various tumor types

II.C Post-Authorisation Development Plan

II.C.1 Studies Which are Conditions of the Marketing Authorisation

The following studies are conditions of the marketing authorisation:

Table II.C.1.1: Studies Which are Conditions of the Marketing Authorisation

Study Title	Objectives
Efficacy studies which are conditions of the marketing authorisation	
A randomized, placebo-controlled, parallel-group, crossover/rechallenge, multi-center study of adjuvant pembrolizumab in participants 12 years of age and older with resected Stage IIB and IIC cutaneous melanoma (KN716) (on-going)	The value of biomarkers to predict the efficacy of pembrolizumab should be further explored, specifically: Additional biomarkers other than PD-L1 expression status by Immunohistochemistry (IHC) (e.g. PD-L2, RNA signature, etc.) predictive of pembrolizumab efficacy should be investigated together with more information regarding the pattern of expression of PD L1 obtained in the resected Stage II melanoma adjuvant study (KN716): • Genomic analyses using whole exome sequencing and/or RNAseq (e.g. Nanostring RNA gene signature) • IHC staining for PD-L2 • Data on RNA and proteomic serum profiling
A Phase III, Randomized, Open-label, Clinical Trial to Compare Pembrolizumab with Brentuximab Vedotin in Subjects with Relapsed or Refractory Classical Hodgkin Lymphoma (KN204) (on-going)	To compare overall survival (OS), progression free survival (PFS) and objective response rate (ORR) of pembrolizumab when compared to Brentuximab Vedotin in subjects with relapsed or refractory cHL and to examine the safety and tolerability between treatment groups.
Adjuvant immunotherapy with anti-PD-1 monoclonal antibody Pembrolizumab (MK-3475) versus placebo after complete resection of high-risk Stage III melanoma: A randomized, double-blind Phase 3 trial of the EORTC Melanoma Group (KN054) (on-going)	To prospectively assess whether post-operative adjuvant therapy with pembrolizumab improves recurrence-free survival (RFS) as compared to placebo in high-risk patients with complete resection of Stage IIIA (> 1 mm metastasis), IIIB and IIIC melanoma. To prospectively assess whether in the subgroup of patients with PD-L1- positive tumor expression, pembrolizumab improves recurrence-free survival as compared to placebo (primary endpoint); distant metastasis free survival (DMFS) and overall survival (OS) in all-subjects and subjects with PD-L1-positive tumors (secondary endpoints for final study report).
A Phase II study of pembrolizumab (MK-3475) in previously treated participants with advanced solid tumors (KN158) (on-going)	To evaluate the antitumor activity of pembrolizumab in participants with MSI-H/dMMR gastric, biliary and small intestine cancer.
A randomized, placebo-controlled, parallel-group, crossover/rechallenge, multi-center study of adjuvant pembrolizumab in participants 12 years of age and older with resected Stage IIB or IIC cutaneous melanoma (KN716) (on-going)	To compare RFS, DMFS and OS between pembrolizumab and placebo in patients with resected Stage IIB or IIC melanoma.

Table II.C.1.1: Studies Which are Conditions of the Marketing Authorisation

Study Title	Objectives
A randomized, Phase 3 trial with pembrolizumab versus placebo for patients with early stage NSCLC after resection and completion of standard adjuvant therapy (KN091) (on-going)	To compare OS between pembrolizumab and placebo in patients with early stage NSCLC after resection and completion of standard adjuvant therapy To assess data on treatment post-progression, and particularly on the uptake and activity of anti-PD(L)1 in patients previously treated with adjuvant pembrolizumab

II.C.2 Other Studies in Post-Authorisation Development Plan

There are no studies required for pembrolizumab.

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ANNEXES

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ANNEX 4 – SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

This RMP annex is not applicable.

Public

ANNEX 6 – DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES

Risk Minimisation Activity: Educational material

The Marketing Authorisation Holder (MAH) shall ensure that all physicians who are expected to prescribe pembrolizumab are provided with the *Patient Cards*.

Overview of Implementation

- The MAH will ensure distribution of the educational material; details on the exact target audience for the communications/materials and the specifics of the risk minimisation materials will be agreed with the National Competent Authorities.
- In addition, the MAH will train the local MSD country staff on the patient card and on the need to provide the material to new prescribers. Records of the training will be maintained. The records of the mailer will be tracked and be used to report on the implementation of the risk minimization activity.
- Information from ongoing pharmacovigilance activities (routine pharmacovigilance) will assess appropriate recognition and management of immune-mediated adverse reactions and that the events observed in real world use are consistent with the cases observed in the clinical trial program and characterized in the SmPC and patient educational material.

Patient Card

Key elements:

- Information that pembrolizumab can cause serious side effects in many parts of the body that can get worse, can sometimes become life-threatening and lead to death, and need to be addressed immediately by the patient communicating with the treating physician
- Description of the main symptoms of immune-mediated adverse reactions and the importance of notifying their treating physician immediately if symptoms occur, persist, or worsen:
    - Lungs: shortness of breath, chest pain, or coughing)
    - Intestines: diarrhoea or more bowel movements than usual, black, tarry, sticky stools or stools with blood or mucus, or severe stomach pain or tenderness
    - Liver: nausea or vomiting, pain on the right side of stomach, yellowing of skin or whites of eyes, dark urine, or bleeding or bruising more easily than normal
    - Kidneys: changes in the amount or colour of your urine

- Hormone glands (especially the thyroid, pituitary, and adrenal glands): rapid heartbeat, weight loss, increased sweating, weight gain, hair loss, feeling cold, constipation, deeper voice, muscle aches, dizziness or fainting, headaches that will not go away
- Type 1 diabetes, including diabetic ketoacidosis (acid in the blood produced from diabetes): feeling more hungry or thirsty, needing to urinate more often, weight loss, feeling tired or feeling sick, stomach pain, fast and deep breathing, confusion, unusual sleepiness, a sweet smell to your breath, a sweet or metallic taste in your mouth, or a different odour to your urine or sweat

- The importance of not attempting to self-treat any symptoms without consulting their Healthcare Professional first
- Placeholder including the weblink of the Package Leaflet on the EMA website
- The importance of carrying the wallet-sized Patient Card at all times, to show it at all medical visits to healthcare professionals other than the prescriber (e.g. emergency healthcare professionals). The Card reminds patients about key symptoms that need to be reported immediately to the physician/ nurse. It also contains prompts to enter contact details of the treating physician and to alert other physicians that the patient is treated with pembrolizumab.

The MAH shall agree to the format and content of the above material with the National Competent Authority prior to launch in the Member State.