16 SIGNAL AND RISK EVALUATION

16.1 Summary of Safety Concerns

The list of safety concerns in the PSUR conforms to the guidance in ICH E2C (R2) and GVP Module VII/ Annex I and may differ from the list of safety concerns in the Core RMP.

The product-specific safety concerns (important identified and potential risks, and missing information) at the beginning of the PSUR reporting interval are tabulated in Table 16.1.1.

Table 16.1.1 Summary of Safety Concerns (Beginning of the Reporting Interval)

Important identified risks	• Immune-Mediated Adverse Reactions • Immune-Mediated pneumonitis* • Immune-Mediated colitis • Immune-Mediated hepatitis • Immune-Mediated nephritis • Immune-Mediated endocrinopathies - Hypophysitis (including hypopituitarism)) - Thyroid Disorder (hypothyroidism, hyperthyroidism, thyroiditis) - Type 1 diabetes mellitus - Adrenal insufficiency (primary and secondary) • Severe skin reactions, including Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) • Other Immune-Mediated Adverse Reactions • Uveitis • Myositis • Guillain-Barre Syndrome • Pancreatitis • Myocarditis • Solid organ transplant rejection following pembrolizumab treatment in donor organ recipients • Encephalitis • Sarcoidosis • Myasthenic Syndrome • Myelitis • Vasculitis • Sclerosing cholangitis • Hypoparathyroidism • Gastritis • Infusion-Related Reactions
Important potential risks	• Immune-Mediated Adverse Events • 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	• Safety in patients with severe hepatic impairment • Safety in patients with severe renal impairment • Safety in patients with active systemic autoimmune disease • Safety in patients with HIV • Reproductive and lactation data • Potential pharmacodynamic interaction with systemic immunosuppressants

*Safety concern is also included in the Core RMP

For the list of EU Safety Concerns, see the EU Regional Appendix.

16.2 Signal Evaluation

This section summarizes the results of evaluations of safety signals that were closed during the reporting interval.

16.2.1 Autoimmune haemolytic anemia

Table 16.2.1.1 Signal Evaluation for Autoimmune haemolytic anemia

Source / Trigger of Signal	Health Authority Request (Swissmedic)
Background	In the literature, autoimmune hemolytic anemia (AIHA) is broadly defined as the immune-mediated destruction of red blood cells. It is a rare and diverse group of diseases, with approximately half of the cases being idiopathic and the remaining cases are often associated with underlying malignancy, autoimmune disorders, drugs, and infections. This group of diseases can be differentiated into five types: warm AIHA (wAIHA), cold agglutinin disease (CAD), drug-induced immune hemolytic anemia (DIIHA), paroxysmal cold hemoglobinuria (PCH), and mixed AIHA [08DS7G]. Drug-induced immune hemolytic anemia (DIIHA) has been described with a wide variety of therapeutics including antibiotics, antiviral drugs, platinum chemotherapy, methyldopa, and nonsteroidal anti-inflammatory drugs (NSAIDs). The antibodies formed can be IgG, IgM and can activate complement, causing overlap with other AIHA types and can make definitive diagnosis challenging [08DS74]. The cornerstone of treatment for DIIHA is the removal of the offending drug. For severe cases, administration of steroids, regardless of etiology, intravenous immune globulins (IVIG), plasma-exchange, and rituximab can be indicated. [08DS7G].
Method(s) of Evaluation	Pre-Clinical/ Biologic Plausibility Epidemiology/Literature Review: Background incidence rates of autoimmune hemolytic anemia in general population and cancer patients treated with immune checkpoint inhibitor (ICI). A comprehensive search in Embase & Medline cumulative to 01-Aug-2023 for studies evaluating AIHA among patients with the use of an ICI. Clinical trial data analysis: The aggregate safety evaluation dataset (ASE), and the cumulative safety dataset (CSD) were searched using the HLTs of Anaemias haemolytic immune and Anaemias haemolytic NEC (MedDRA version 26.0). Review of the Company Global Safety Database and EudraVigilance Data Analysis System (EVDAS) cumulative to 30-Jun-2023 using the High Level Terms (HLTs) of Anaemias haemolytic immune and Anaemias haemolytic NEC (MedDRA v26.0). **Case Definition** **Abrupt decrease in hemoglobin ≥2 g/dL** **AND** **<u>At least two</u> of the below features of hemolysis**: ✓ Elevated lactate dehydrogenase (without other explanation) ✓ Elevated reticulocyte count (or %) ✓ Presence of spherocytes on peripheral blood smear ✓ Low or undetectable serum haptoglobin **AND** **Evidence for immune-mediated mechanism excluding other alternative etiology** ✓ Positive direct antiglobulin test (DAT) without alternative cause **OR** Negative DAT with evidence for immune-mediated mechanism (e.g., anti-erythrocyte antibody), without alternative cause

Table 16.2.1.1 Signal Evaluation for Autoimmune haemolytic anemia

Results	**Pre-clinical/Biologic Plausibility:** Pembrolizumab therapy is known to be associated with immune-mediated reactions, and these events are clearly described in product labeling. Based on pembrolizumab's mechanism of action, there is biologic plausibility that immune-mediated hemolytic anemia could be associated with pembrolizumab use. There are no specific toxicology or other pre-clinical data relating to immune-mediated hemolytic anemia. **Epidemiology/Literature Review:** The epidemiology of AIHA varies by etiology and type [08D6GJ] [08D57H]. The incidence of AIHA ranged from 1.8-5.0 per 100,000 person-years based on large-scale studies in the US and Denmark [00WD58] [08D5C7]. To our knowledge, there are no estimates of incidence or prevalence reported for AIHA across all cancer types. Most observational studies focused on patients with chronic lymphocytic leukemia (CLL) and lymphoma, reporting that the prevalence of AIHA ranged between 4.3-5.1% among patients with CLL [08D5DH] [08D5GP] and the prevalence of AIHA ranged between 0.19-0.24% among patients with non-Hodgkin's lymphoma and Hodgkin's lymphoma [08D6JD]. The real-world data from large-scale cohort studies of cancer patients receiving ICI treatment consistently show that AIHA is a rare potentially life-threatening event with incidence consistently in the range from 0.04-1.16%. The literature search did not yield any real-world studies that evaluated the association between AIHA and ICI treatment in patients with cancer. **Review of aggregate data from clinical trials:** A search of the ASE dataset (n=9,118) identified 3 (0.03%) patients who experienced the event of Autoimmune haemolytic anaemia and 1 (0.01%) patient who experienced Haemolytic anemia. No events were reported in comparator arms placebo, chemotherapy, ipilimumab, and cetuximab. Findings from the CSD (n=10,997) identified 3 (0.03%) cases of Autoimmune hemolytic anemia and 2 (0.02%) cases of Haemolytic anemia. **Company Global Safety Database Review** A total of 201 cases, containing 205 events, were identified from the company's global safety database. Of the 201 cases identified, 165 cases did not meet the case definition for immune-mediated hemolytic anemia (described in case definition section above). Of the remaining 36 cases that met the case definition, 13 cases had insufficient information to fully assess causality (critical components of medical history, concomitant medications, clinical course, and/or physical/laboratory findings were missing). Of the remaining 23 cases, 20 cases had evidence of a more likely alternative etiology based on plausible temporal relationship and review of full clinical details (nine (9) cases had evidence of underlying medical conditions including underlying malignancies, hematological disorders, and infection and ten (10) cases had concomitant medications/procedures with known risk of hemolytic anemia). The remaining 3 cases that met the case definition without a clear more likely alternative etiology [08DQS9]. These 3 cases had clinical presentations consistent with immune-mediated hemolytic anemia, had plausible temporal relationships with pembrolizumab treatment, biologic plausibility associated with pembrolizumab's mechanism of action, and lacked definitive alternative etiologies, the most likely etiology for the events in these 3 cases was assessed as pembrolizumab use. **EudraVigilance Data Analysis System Review** The data from the review of EVDAS yielded no additional information to alter the conclusions of this review. Please refer to Appendix 21.10.2.1 for further details

Table 16.2.1.1 Signal Evaluation for Autoimmune haemolytic anemia

Discussion	Immune-mediated hemolytic anemia is a rare and diverse group of diseases, with approximately half the cases being idiopathic and the remaining cases often associated with underlying malignancy, autoimmune disorders, drugs, and infections.
	While review of preclinical pembrolizumab data did not identify any specific toxicology related to hemolytic anemia; there is biologic plausibility based on pembrolizumab's mechanism of action. The real-world data from large-scale cohort studies of cancer patients receiving ICI treatment consistently show that AIHA is a rare, but potentially serious, immune-related adverse event, with the incidence ranging from 0.04-1.16%. The incidence (0.04%-0.05%) of immune-mediated hemolytic anemia with pembrolizumab use in the clinical databases was consistent with that observed in literature. Comprehensive review of the 201 cases (205 events) identified in the company's global safety database yielded 36 cases meeting the case definition for immune-mediated hemolytic anemia; Thirteen (13) of these 36 cases lacked necessary information for fully assess the case (such as medical history, concomitant medications, clinical course, and laboratory work up). In 20 of the 36 cases there was a more likely alternative etiology (i.e. underlying malignancies, hematological disorders, infection, concomitant medications, or transfusions). based on plausible temporal relationship and full review of cases details. The 3 remaining cases met case definition and had no clear alternative etiologies. Based on review of the available information provided in these 3 cases, biologic plausibility, and temporal relationship with pembrolizumab use, the events were assessed as most likely related to pembrolizumab use.
Conclusion	Signal Confirmed. Based on the totality of the information reviewed and presented above, the Company considers that there is sufficient evidence to support a causal association between the event of immune-mediated hemolytic anemia and pembrolizumab use. CCDS will be updated with the inclusion of hemolytic anemia under Warnings & Precautions. The Company will continue to monitor immune-mediated hemolytic anemia and the general safety profile of pembrolizumab use through its routine pharmacovigilance activities.

16.2.2 Risk of severe skin reactions with pembrolizumab in combination with enfortumab vedotin

Table 16.2.2.1 Signal Evaluation of Risk of severe skin reactions with pembrolizumab in combination with enfortumab vedotin

Source / Trigger of Signal	Clinical study results
Background	Skin reactions, including SCAR and fatal events, are a well-characterized, important identified risk of enfortumab vedotin (EV) therapy, and as such, are described in product labeling, including the approved United States Prescribing Information (USPI) and in the Investigator's Brochure. Furthermore, severe skin reactions (SSR) are known to occur in association with pembrolizumab and immune-mediated dermatologic adverse reactions are described in the Warnings and Precautions section of the USPI. The US EV (PADCEV®) Prescribing Information includes a boxed warning for severe skin reactions and states, "PADCEV can cause severe and fatal cutaneous adverse reactions, including Stevens-Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN)." On 16 December 2021, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a marketing authorization for the medicinal product Padcev, intended for the treatment of adult patients with urothelial cancer. However, on 24 December 2021, the French Health Authority (ANSM), suspended enrollment in the expanded access program for EV monotherapy in urothelial carcinoma (*An expanded access treatment protocol of enfortumab vedotin in subjects with locally advanced or metastatic urothelial carcinoma*; EV-902) in France due to 6 cases of severe cutaneous adverse reactions (SCAR), 3 of which were fatal. ANSM notified the European Medicines
	Agency (EMA) of the cases and suspension of EV-902 in France, and EMA notified the remaining member state health authorities. Our Company was subsequently contacted by European health authorities concerning EV plus pembrolizumab trials being conducted by our Company following the ANSM request. The CHMP subsequently readopted its positive opinion on 24 February 2022, taking into account additional safety information. EV is being co-developed by Astellas Pharma Inc. and Seagen, Inc. In addition, our Company, Seagen, and Astellas are parties to clinical trial collaboration and supply agreements to study EV in combination with pembrolizumab for the treatment of muscle invasive bladder cancer. Seagen and Astellas have conducted a review of the cases observed in the EV-902 expanded access program and do not believe these events constitute a new safety signal. It is the position of Seagen and Astellas that based on the totality of data available from all EV clinical trials, the favorable benefit-risk profile for EV has not changed.
Method(s) of Evaluation	Our Company performed a review of available data in participants enrolled in KN-869/EV-103 Cohorts A and K, as well as preliminary safety data from our Company studies KN-905 and KN-B15, focusing on skin events within the pembrolizumab adverse events of special interest (AEOSI) methodology. The data was reviewed with the pembrolizumab RMST on 21-Jan-2022. Our Company performed a review of safety data from KN-A39/EV-302, including the pembrolizumab adverse events of special interest (AEOSI) category 'Severe skin reactions'. The data was reviewed by the internal pembrolizumab/EV RMST on 28-Sep-2023

Table 16.2.2.1 Signal Evaluation of Risk of severe skin reactions with pembrolizumab in combination with enfortumab vedotin

Results	Data from the 45 participants in the safety dataset for KN-869/EV-103 Cohort A (EV plus pembrolizumab) and 60 participants in the safety dataset for Cohort K EV plus pembrolizumab group were examined utilizing the July 2021 data cut. The proportion of participants with events within the pembrolizumab Adverse Event of Special Interest (AEOSI) category of Severe skin reactions with enfortumab vedotin (EV) administered in combination with pembrolizumab was noted to potentially be higher than that of pembrolizumab monotherapy in preliminary data from KN-869/EV-103. Case reports of events of skin toxicity from KN-905 were consistent with findings from KN-869/EV-103. EV plus pembrolizumab data from the 440 participants in that treatment arm of KN-A39/EV-302 (data cut 08-AUG-2023) were reviewed. No new patterns were identified for the events of skin toxicity compared to the previous evaluation; KN-A39/EV-302 safety data were generally consistent with KN-869/EV-103. The proportion of participants with events within the AEOSI category 'Severe skin reactions' was consistent with KN-869/EV-103 (17.0% vs 26.4%, respectively). The incidence of grade ≥3 AEOSI 'Severe skin reactions' was consistent with KN-869/EV-103 (11.8% vs 20.7%, respectively). Overall, AEOSI events of severe skin reactions primarily consisted of nonserious Grade 3 rash maculopapular events. There were no fatal events of severe skin reactions.
Discussion	Our Company considered there is very limited information about the safety of EV with pembrolizumab based on the analysis KN-869/EV-103. There is not enough evidence to support an enhanced frequency of severe skin reactions with EV in combination with pembrolizumab as compared to EV monotherapy. Skin reactions, including fatal events, are in the product labeling for both EV and pembrolizumab. The data suggests a similar frequency of severe skin reactions of EV in combination with pembrolizumab compared to EV only. Our Company concluded that based on the analysis of KN- A39/EV-302 data, the incidence, nature, and severity of SSR were consistent with KN- 869/EV-103. No new patterns were identified. SSR events were effectively managed by dose modifications and/or treatment with corticosteroids as applicable. A majority of severe skin reactions resolved with treatment. SSR events do not require additional instructions to the prescribers or investigators
Conclusion	The signal is refuted. Overall, safety findings for SSR with pembrolizumab in combination with enfortumab vedotin do not represent a significant change to the core risk profile of pembrolizumab and do not warrant a change to core product labeling based on the data available at the time of evaluation. The MAH monitors the safety of pembrolizumab on an ongoing basis and will continue to monitor the safety of pembrolizumab when administered in combination with EV.

16.2.3 Pancreatic failure/exocrine pancreatic insufficiency

Table 16.2.3.1 Signal Evaluation for Pancreatic failure/exocrine pancreatic insufficiency

Source / Trigger of Signal	Health Authority Request (PRAC)
Background	Exocrine Pancreatic Insufficiency (EPI) is characterized by the inadequate secretion of pancreatic enzymes into the duodenum leading to maldigestion of dietary fat. This can manifest as steatorrhea/diarrhea, bloating, weight loss and malabsorption of key nutrients which can lead to osteoporosis, increased risk of infection and cardiovascular events. EPI can be caused by pancreatic disorders which lead to reduced parenchymal cell mass such as pancreatitis (most notably chronic), pancreatic cancer, surgery involving the pancreas, and cystic fibrosis. Additionally, it can be caused by reduced signaling and feedback to the pancreas in patients who have had surgeries of the upper GI tract, celiac disease, and inflammatory bowel disease. Patients with poorly controlled Type I or II diabetes will often have laboratory tests that suggest EPI, but rarely exhibit symptoms consistent with severe EPI [08F6RL] [08F605]. EPI is a distinct clinical entity from pancreatitis. EPI presents with bloating and discomfort but infrequently is painful, appetite is intact, and pancreatic enzymes (such as lipase and amylase) in the blood are found to be normal or low, compared to pancreatitis which has elevated enzymes. The condition can be diagnosed clinically in high-risk patients, and there are several diagnostic tests available when the diagnosis is in question. The simplest and most widely available is Fecal Elastase-1 (FE-1). A cutoff of 200 µg /g is generally accepted as the cutoff under which EPI is diagnosed. False positives are possible in patients with watery stool due to dilution. Other, less commonly used, tests are included in our case definition to represent accepted diagnostic criteria from the literature [08F604]. EPI is generally irreversible (apart from reversal of duct obstruction) but manageable by oral pancreatic enzyme replacement therapy (PERT), which is well tolerated by patients [08F606]. Prompt diagnosis and management is essential to prevent complications of malnutrition.
Method(s) of Evaluation	Pre-clinical/toxicology data review Epidemiology/Literature Review: Background rates of EPI in general population, cancer population, and pts treated with ICI. A comprehensive search in Embase & Medline cumulative to 14-SEP-2023 for studies evaluating EPI among pts treated with ICI. Review of the Aggregate Safety Evaluation (ASE) database and Cumulative Safety Dataset (CSD) using PTs of Pancreatic failure, Pancreatic atrophy, Pancreatic toxicity, Steatorrhoea, Exocrine pancreatic function test abnormal. Examination of the Company Global Safety Database using above PTs cumulative to 15-AUG-2023 and EudraVigilance Data Analysis System cumulative to 15-AUG-2023 using the PT pancreatic failure and MedDRA version 26

Table 16.2.3.1 Signal Evaluation for Pancreatic failure/exocrine pancreatic insufficiency

Results	**Preclinical/Toxicology** There is no specific toxicology or pre-clinical data relating to pancreatic failure and pembrolizumab. **Epidemiology/Literature Review:** A variety of pancreatic or extrapancreatic disorders can cause pancreatic failure/exocrine pancreatic insufficiency, of which the prevalence varies by the underlying condition [08F605]. Data on the burden of pancreatic failure/exocrine pancreatic insufficiency in the general population is sparse. To our knowledge, there are no estimates of incidence or prevalence reported for pancreatic failure/exocrine pancreatic insufficiency across all cancer types. Observational studies focused on patients with pancreatic cancer, reporting that the prevalence of exocrine pancreatic insufficiency ranged between 50-66% at diagnosis. The real-world data from large-scale cohort studies of cancer patients receiving ICI treatment show that immune-related pancreatic failure/exocrine pancreatic insufficiency is rare with the rates ranging from 0.05-1.16%. A search of the published literature describing EPI in patients treated with ICIs was performed to identify evidence of the proposed pathophysiology and class effect. The results yielded 10 relevant publications supporting a causal association between ICI exposure and EPI. EPI clinical manifestation and treatment differ from the clinical presentation of other immune mediated adverse events (e.g., colitis, pancreatitis, T1DM). **Review of aggregate data from clinical trials:** Search of the ASE database retrieved 4 cases with the PT Pancreatic failure in the pembrolizumab monotherapy group (n=9,118). The ASE revealed generally comparable frequencies for the number of cases with pembrolizumab (0.04%) versus chemotherapy (0.08%). As the numbers are low, overall generalizations based on these frequencies are limited. No meaningful imbalance between the pembrolizumab arm and comparator arms was identified. A search of the CSD (n=10,997) revealed 6 cases (0.05%) with the PT Pancreatic failure. The rate is consistent with ASE findings. **Review of data from the Company Global Safety Database** A total of 43 individual case safety reports (ICSRs), containing 47 events, were identified from the company's global safety database. Of the 43 cases, 4 were from interventional trials, 9 from noninterventional studies and 30 from spontaneous reports. Thirty-nine (39) cases were serious, 4 were nonserious. Outcome was reported in 23 of the 47 events: recovered (8), recovered/resolved with sequelae (3), recovering (3), or not recovered (9). There were no fatal outcomes. Age was reported in 28 cases with age at event onset ranging from 19 to 83 years, with a median age of 67 years. Of the 43 cases, 42 reported gender, with 18 females and 24 males. Time to onset was reported in 18 cases for 21 events, ranging from 35 to 1448 days, (median 486). There were 5 cases in the Company Global Safety Dataset including 2 cases published in the literature that describe cases of EPI that meet case definition, do not have clear alternative etiology, and have a time to onset that is consistent with what is described in the literature. **Search of EVDAS database:** The data from the review of EVDAS yielded no additional information to alter the conclusions of this review. Please refer to Appendix 21.10.2.2 for further details.
Discussion	EPI is a rare disorder, characterized by the loss of pancreatic enzymes necessary for digestion of fat and absorption of fat-soluble vitamins. It can lead to serious sequela if not promptly diagnosed and managed. EPI has many causes, most notably disorders of the pancreas such as

Table 16.2.3.1 Signal Evaluation for Pancreatic failure/exocrine pancreatic insufficiency

	chronic pancreatitis, pancreatic cancer, and pancreatic surgery. An immune-mediated mechanism is plausible due to activation of CD8+ T cells in the pancreas. Rates of moderate to severe EPI in the general population are unknown as population-level studies have relied on laboratory testing of asymptomatic patients. Rates of EPI among patients with pancreatic cancer are high (50-66% at time of diagnosis), however rates in the general cancer population have not been studied. There is a growing body of literature describing EPI in patients treated with ICIs. Rates of EPI in these studies range from 0.05-1.16%. The incidence rate of EPI in the clinical safety databases for pembrolizumab ranges from 0.04% to 0.05%. This rate is comparable between pembrolizumab monotherapy and chemotherapy, despite being limited by the small number of reported cases. Comprehensive literature review revealed 10 relevant publications supporting a causal association between ICI exposure and EPI. Studies and case reports consistently show EPI to be a late-onset event, with a median TTO of 13 months as reported in the largest retrospective study on the topic. There was no significant difference noted in the type of ICI received, indicating a class effect. In a majority of the cases described, EPI occurs in patients without predisposing risk factors or prior pancreatitis. In a large retrospective review of the FAERS database, pancreatic failure was disproportionately described with ICIs compared to other cancer therapies. A cumulative review of the company global safety database identified 43 potential cases of EPI based on the search strategy. We focused our attention on cases that met case definition of immune mediated EPI in the absence of alternative or labeled etiologies. We highlighted five cases which all describe clinically significant EPI without evidence of alternative diagnoses. Time to onset (TTO) is in the range of that described in the literature for ICI associated EPI**.**
Conclusion	Signal confirmed Based on the totality of the information reviewed and presented above, the Company considers that there is sufficient evidence to support a causal association of exocrine pancreatic insufficiency with exposure to pembrolizumab. The Company will update the Warnings and Precautions of the CCDS to include exocrine pancreatic insufficiency. In addition, subsequent to the safety label update to the CCDS, the Company proposes an update to the local label to include exocrine pancreatic insufficiency. The Company will continue to monitor reports of exocrine insufficiency temporally associated with pembrolizumab exposure through routine pharmacovigilance activity

16.2.4 Coeliac disease

Table 16.2.4.1 Signal Evaluation for Coeliac disease

Source / Trigger of Signal	Health Authority Request (PRAC)
Background	Coeliac disease (CD) is a chronic, multiorgan autoimmune disease that affects the small intestine in genetically susceptible individuals precipitated by the ingestion of gluten and characterized by malabsorption resulting from mucosal injury after ingestion of wheat gluten or related rye and barley proteins [08FD5Z] [08FD63]. In western countries, the prevalence is around 0.6% histologically confirmed and 1% in serological screening of the general population [08FD5Z]. Among adults, two to three times as many women have the disease as men. The clinical manifestations of CD vary greatly according to age group. The classic presentation in adults is diarrhea, which may be accompanied by abdominal pain or discomfort. Other silent presentations in adults include iron-deficiency anemia, osteoporosis, and incidental recognition at endoscopy performed for other reasons, such as symptoms of gastroesophageal reflux [08FD66]. The most important serological investigations in the diagnosis of CD are IgA class anti-transglutaminase antibodies
	(TTGA; anti-TG2) with the highest sensitivity (98%) and specificity estimated at around 90%, and IgA class anti-endomysial antibodies (EMA), this test having a lower sensitivity compared to IgA-class TTGA (90% vs. 98%) but showing an almost absolute specificity for CD [08FD63]. Therefore, serological testing for CD relies on anti- TG2 (TTGA) as the first step and IgA-EMA as a confirmatory test, particularly when TG2 has a low titre (<2 times the upper normal limit (ULN)) [08FD5Z]. Endoscopic features of CD include a paucity or loss of mucosal folds, effacement of folds with oedema, presence of a mosaic pattern, scalloping, nodularity, and increased visibility of the vasculature [08FD63]. Regarding events arising in the gastrointestinal tract, CD and CD-like conditions have rarely been described and their real incidence among immune checkpoint inhibitors (ICIs) related immune-related adverse events is unknown, with only a very small number of cases reported to date [08FD63].
Method(s) of Evaluation	Preclinical/Toxicology Data Review Epidemiology/Literature Review Examination of Clinical Trial Data including Aggregate Safety Evaluation (ASE) and Cumulative Safety Dataset (CSD) using the MedDRA version 26.0 and Preferred Terms (PTs) of Coeliac disease, Malabsorption, Gluten sensitivity, Autoimmune enteropathy, Gluten ataxia, and Microvillous inclusion disease. Examination of the Company global safety database to identify all cases involving pembrolizumab and events of coeliac disease through 15-AUG-2023 using a search of cases with the PTs of Coeliac disease, Malabsorption, Gluten sensitivity, Autoimmune enteropathy, Gluten ataxia, and Microvillous inclusion disease was performed (MedDRA v.26.0). Review of data available in EudraVigilance Data Analysis System (EVDAS for cases involving pembrolizumab and events of coeliac disease through 15-AUG-2023 using the PTs of Coeliac disease, Malabsorption, Gluten sensitivity, Autoimmune enteropathy, Gluten ataxia, and Microvillous inclusion disease (MedDRA v.26.0). **Case Definition** After excluding alternative etiologies or diagnosis, the presence of malabsorption resulting in classic symptoms of diarrhea, weight loss, or failure to thrive accompanied by vague abdominal symptoms confirmed by the combination of: positive serologic markers such as anti-tissue transglutaminase (anti-TG2), anti- endomysial antibodies (anti-EMA), small intestinal (especially, duodenal) biopsy while on gluten-containing diet with histopathologic evidence of villous flattening/atrophy (Marsh classification, if available), presence of diffuse villi infiltration of intraepithelial lymphocytes (IELs), plasma cells, eosinophils, and crypt hyperplasia, endoscopic features that include mucosal fissuring, nodular mucosa (mosaicism), bulb atrophy with visible sub-mucosal vessels and loss, and reduction or scalloping of Kerckring folds, genetic profiling (if available) such as HLA-DQ2/8

Table 16.2.4.1 Signal Evaluation for Coeliac disease

	genotyping, and/or improvement with gluten-free diet (GFD).
Results	**Preclinical/Toxicology** There were no findings (e.g., no pembrolizumab-related diarrhea or histomorphological findings in the gastrointestinal tract) indicative of coeliac disease in monkeys dosed with pembrolizumab for up to 6 months. **Epidemiology/Literature Review:** The prevalence of coeliac disease in the general population varies by different diagnostic criteria used and across geographic regions [08FBYT]. When a biopsy was used to confirm the diagnosis of coeliac disease, the pooled prevalence was 0.6-0.7% globally with a narrow range of 0.4-0.8% across geographic regions [08FBYT] [08FBCN]. To our knowledge, there are no estimates of incidence or prevalence reported for coeliac disease across all cancer types. Two observational studies that were identified, both large-scale database studies in the US, focused on patients with cancers of small and large intestines and reported that the prevalence of coeliac disease ranged from 1-3%
	[08FBCL][08FBCM]. In summary, the real-world data on coeliac disease among patients with cancer receiving ICI is limited. The identified cohort studies reported rates of immune-related coeliac disease, based on a few observed cases, ranging from 0.04-1.06%. The literature search did not yield any real-world studies that evaluated the association between coeliac disease and ICI treatment in patients with cancer. **Literature Review:** A comprehensive literature search identified two articles that described celiac disease or celiac- disease-like conditions in ICI treated patients. A retrospective review of medical records characterized clinicopathological and immunophenotypic features of immune checkpoint inhibitor associated celiac disease (ICI-CeD) in comparison to ICI-associated duodenitis (ICI-Duo) and usual celiac disease (CeD). This article of interest shows similar clinicopathological and immunophenotypic features between ICI-CeD and ICI-Duo. It was concluded that in the absence of pretreatment tTG-IgA titers, pretreatment histological confirmation, and HLA genotyping, definitive decision if de novo CeD (asymptomatic or subclinical) that progressed to symptomatic CeD in the setting of ICIs, especially for the cases with family history, cannot be made. In another article of interest based on an electronic literature search original reports in which CD or pathological CD-like conditions were documented histologically in patients treated with ICIs. It was acknowledged that limitations include few papers, case reports, and case series reported in the literature with an absence of controlled studies. Furthermore, the papers published lacked relevant data (serology and genetics) useful for validating a correct diagnosis of CD. **Review of aggregate data from clinical trials:** A search of the ASE database did not identify any participants with the PTs of Coeliac disease, Gluten sensitivity, Autoimmune enteropathy, Gluten ataxia, or Microvillous inclusion disease. The only PT identified was Malabsorption (n=1; 0.01%) in a participant exposed to pembrolizumab monotherapy. As the numbers are generally low, overall generalizations based on these frequencies are limited. No meaningful imbalances between the pembrolizumab arm and comparator arms were identified. **Review of the Cumulative Safety Database:** A search of the CSD identified participants with the PTs of Coeliac disease (n=1; 0.01%) and Malabsorption (n=2; 0.02%); these small numbers of patients with events limit any generalizations to be made. **Review of data from the Company Global Safety Database** A total of 31 individual case safety reports (ICSRs) containing 32 events, were identified

Table 16.2.4.1 Signal Evaluation for Coeliac disease

	from the Company's global safety database. Of the 31 cases identified from the Company's global safety database, 4 were from interventional trials, 8 from non-interventional studies, and 19 were spontaneous reports, of which 8 cases were from the literature. Twenty-two events were serious and 10 were non- serious. Outcome was reported in 17 of the 32 events: 1 event of malabsorption had a fatal outcome. The remaining 16 events were reported as either recovering/resolving (6), not recovered/not resolved (5), recovered/resolved (4), or recovered/resolved with sequelae (1). Age was reported in 26/31 cases with age at event onset ranging from 43 to 71 years, with a median age of 63 years. Of the 31 cases, 30 reported patient gender: 15 females and 15 males. Time to onset (TTO) was reported in 16 cases, ranging from 3 days to 1,387 days (median 118 days). In the remaining cases, TTO was unknown or unavailable based on the reported therapy and adverse event information. Of the 31 cases, 24 cases included reports that were medically unconfirmed, lacked key diagnostic criteria (i.e., no coeliac serology evaluation, no biopsy) to satisfy the case definition, and/or were missing necessary information needed for assessment of a complete and scientific assessment (i.e., medical history, concomitant medications, and/or detailed physical/laboratory findings).
	The remaining seven literature case reports or abstract presentations included variable features of the case definition. The seven cases either were missing important clinical information to confirm the clinical diagnosis of CD or biopsy findings were inconclusive and suggest possible alternative etiology. **Search of EVDAS database:** The data from the review of EVDAS yielded no additional information to alter the conclusions of this review. Please refer to Appendix 21.10.2.3 for further details.
Discussion	Review of preclinical data did not identify any findings indicative of coeliac disease in animal studies when dosed with pembrolizumab. Estimated prevalence in the general population varies by different diagnostic criteria and across geographic regions. Pooled prevalence reported to be 0.6–0.7% globally with a narrow range of 0.4–0.8% across geographic regions with biopsy confirmed diagnosis of CD. Two observational studies that focused on patients with cancers of small and large intestines reported prevalence of CD ranging from 1-3%. Literature review reported a low rate (0.04-1.06%) of immune-related CD among patients treated with ICI. There are overlapping clinical and histopathological similarities between CD and other inflammatory/autoimmune enteropathies however, there is a paucity of data to support a causal association of CD with ICI given the few papers, case reports, and case series that are reported in the literature and an absence of controlled studies. Overall, based on the totality of the evidence including variable reporting of features meeting the Coeliac disease case definition criteria, very low event rate from the pembrolizumab clinical trial data, no meaningful imbalance of rate of CD in clinical trial data, lack of real-world data for the association between CD and ICI treated cancer patients combined with the experience of 831,758 patient-years of exposure to pembrolizumab, there is insufficient evidence for a causal link between pembrolizumab therapy and Coeliac disease

Table 16.2.4.1 Signal Evaluation for Coeliac disease

Conclusion	Signal was refuted. Based on the totality of the information reviewed and presented above, the Company considers that there is currently insufficient evidence to support a causal association of Coeliac disease with exposure to pembrolizumab. The available data does not support an update to the CCDS or RMP. The Company will continue to monitor Coeliac disease temporally associated with pembrolizumab exposure through routine pharmacovigilance activity.

16.2.5 Tuberculosis

Table 16.2.5.1 Signal Evaluation for Tuberculosis

Source / Trigger of Signal	Health Authority request (SFDA).
Background	Previously, a request was made to all Market Authorisation Holders (MAHs) of Immune Checkpoint Inhibitors as part of a Pharmacovigilance Risk Assessment Committee (PRAC) signal assessment report to provide a cumulative review of all cases of tuberculosis (including tuberculosis reactivation). The Company conducted a comprehensive evaluation of this topic and provided a report to PRAC on 04-Nov-2019. To avoid duplication, the response to the SFDA evaluated all relevant information from 16-Sep-2019 (following the data cut-off for the PRAC response). Any follow-up information received after 16-Sep-2019 from previously reviewed cases was also evaluated. Mycobacterium tuberculosis causes tuberculosis (TB) and is a leading infectious cause of death in adults worldwide. It is estimated that approximately a quarter of the world's population is infected with M. tuberculosis, with about 10 million people developing active TB disease and 1.5 million dying from it every year. According to the World Health Organization (WHO), around 5 to 10 percent of individuals infected with M. tuberculosis will develop active TB disease in their lifetime if left untreated. Approximately half of those who progress to active disease do so within the first two to three years following infection. [08FYJD] [08FYKG] Among individuals with latent infection and no underlying medical problems, reactivation disease occurs in approximately 5 to 10 percent of cases. The risk of reactivation is markedly increased in patients with HIV and other medical conditions. Many new cases of TB are attributable to five risk factors: undernutrition, HIV infection, alcohol use disorders, smoking (especially among men), and diabetes. [08FYJD] Immunosuppression is clearly associated with reactivation TB, although it is not clear what specific host factors maintain the infection in a latent state and what triggers the latent infection to break containment and become active. [07Z68Y] [07Z68Z]
Method(s) of Evaluation	Preclinical/Toxicology data review Epidemiology/Literature Review: Background rates of TB in general population, cancer population and patients treated with Immune Checkpoint Inhibitors (ICI). A comprehensive search in Embase & Medline from 01-Jan-2019 to 16-Oct-2023 for studies evaluating TB among patients treated with ICI. Review of Aggregate Safety Evaluation (ASE) database and Cumulative Safety Dataset (CSD) using HLT of Tuberculous infections. Examination of the Company global safety database to identify all cases involving pembrolizumab and events of Tuberculosis for 16-Sept-2019 through 30 Sept-2023 using a search strategy of HLT of Tuberculous infections (MedDRA version 26.0).

Table 16.2.5.1 Signal Evaluation for Tuberculosis

Results	**Aggregate Clinical Trial Data** Unblinded Aggregate Safety Evaluation (ASE) and Cumulative Safety Dataset (CSD) datasets identified similar frequencies for TB in pembrolizumab treated patients, other immune checkpoint inhibitors, and placebo. As the numbers are generally low, overall generalizations based on these frequencies are limited. No meaningful imbalances between the pembrolizumab arm and comparator arms were identified. **Company Global Safety Database**: Cases were retrieved utilizing the search strategy described above and evaluated to assess a possible association between the administration of pembrolizumab and Tuberculosis (tuberculosis reactivation) A total of 98 case reports (containing 101 events) were identified from the Company's Global Safety Database (16-Sep-2019 through 30-Sep-2023). There is no MedDRA Preferred Term (PT) of Tuberculosis reactivated; however, the Lower Level Term (LLT) Tuberculosis reactivated maps to the PT Tuberculosis ensuring all potential cases of Tuberculosis reactivated were captured. A total of 49 of the 98 cases, which includes 5 cases of latent tuberculosis, lacked sufficient information (e.g., medical history, concurrent conditions and/or medications, treatment information, laboratory results, time to onset) needed for
	adequate medical assessment and will not be discussed further. Additionally, during review, one case from Japan was found to be a duplicate report. Of the remaining 49 cases with adequate information for medical assessment, there were confounding factors present in all 49 cases. These confounding factors included preexisting conditions (e.g., history of TB, diabetes), recent use of concomitant medications (including carboplatin, cisplatin, entecavir, tenofovir, live Bacillus Calmette-Guerin (BCG) vaccine, pemetrexed, prednisolone) that can increase the risk of immunosuppression and subsequent TB infection or reactivation of latent TB. Upon reviewing the 98 cases, four potential cases of tuberculosis reactivation, which were coded as Tuberculosis in the preferred term (PT) category, were identified. However, one of the cases lacked sufficient information for a meaningful evaluation. In another case, the evaluation was confounded by several factors, including prior chemotherapy with immunosuppressive agents (carboplatin and pemetrexed) and the fact that the case was from an endemic region. The details for the remaining 2 cases are discussed in Appendix 21.10.2.4. Please refer to Appendix 21.10.2.4 for further details.
Discussion	Tuberculosis is a leading infectious cause of death in adults worldwide. Reactivation of disease, i.e onset of active disease many years following a period of latent infection occurs in approximately 5 to 10 percent of cases. Immunosuppression is clearly associated with reactivated TB, although it is not clear what specific host factors maintain the infection in a latent state and what triggers the latent infection to break containment and become active. Many immunosuppressive medical conditions are known to be associated with reactivation of TB [07Z68Y] [07Z68Z]. Preclinical data suggestive of findings related to TB in animal studies with pembrolizumab are unclear, as conflicting results have been noted. Based on the mechanism of action, there is biological plausibility supporting a risk of immune mediated events during pembrolizumab therapy. In summary, the patients who are candidates for pembrolizumab therapy are in an immunocompromised state due to the underlying malignancy and recent or concomitant immunomodulatory therapies and as such are susceptible to infections such as TB. Review of available literature did not identify new safety concerns about tuberculosis with immune checkpoint inhibitors. The review of clinical trial safety data indicates that the rates of TB reported with the use of pembrolizumab is low compared with the background rates in general or cancer population. Additionally, all identified cases from the global safety database were either confounded or without sufficient information for further assessment.

Table 16.2.5.1 Signal Evaluation for Tuberculosis

Conclusion	Signal was refuted. Based on the totality of the information reviewed and presented above, including data covered in PRAC response on 4-NOV-2019, the Company considered that there is not sufficient evidence to support a causal association of tuberculosis (including tuberculosis reactivation) with exposure to pembrolizumab. The Company will continue to monitor tuberculosis related events associated with pembrolizumab exposure through routine pharmacovigilance activity.

16.2.6 Aplastic anemia

Table 16.2.6.1 Signal Evaluation for Aplastic anemia

Source / Trigger of Signal	Health Authority Request (Swissmedic)
Background	**Introduction** The Company has performed a review and evaluation of safety data related to Aplastic Anemia (AA) and the administration of pembrolizumab for the interval 01-APR-2022 through 31-DEC-2023. Two prior reviews of AA have been performed, one cumulative (through 31-JAN-2021) and one incremental (01-FEB-2021 to 31-MAR-2022). Based on the review of the totality of data at the time of those reviews, there was insufficient evidence to support a causal association between AA and pembrolizumab use. For consistency, the methodology including search strategies used in this assessment aligns with those in the previous assessments. The overall analysis is based on totality of the data including information presented from the prior two assessments. **Background information** Aplastic anemia (AA) is a rare and heterogeneous disorder. Most cases of AA have no identifying cause and are classified as idiopathic. The three primary mechanisms leading to hypocellular bone marrow characteristic of AA include direct chemical and physical damage to hematopoietic stem cells (HSC) (e.g., cytotoxic drugs, radiation), genetic deficits (e.g., telomere disease, Fanconi anemia), and immune destruction of HSCs (e.g. seronegative hepatitis, idiopathic). [05R4WB] [05R6C6] In addition to a bone marrow aspiration and biopsy, a comprehensive evaluation must rule out other causes of marrow failure, such as megaloblastic anemia, metastatic bone marrow infiltration, myelodysplastic syndrome, and paroxysmal nocturnal hemoglobinuria. The evaluation should include a peripheral blood count and microscopic evaluation, reticulocyte count, cytogenic testing, viral testing (e.g., cultures or serology), flow cytometry, nutritional status (e.g., folate), and antinuclear antibody. [05R6C6] **Biological Plausibility** Pembrolizumab therapy is known to be associated with immune-mediated reactions, and these events are clearly described in product labeling. Based on pembrolizumab's mechanism of action, there is biological plausibility that AA could be associated with pembrolizumab use.

Table 16.2.6.1 Signal Evaluation for Aplastic anemia

Method(s) of Evaluation	Review of the aplastic anemia with the use of pembrolizumab included the following: Pre-clinical/toxicology data review Epidemiology/Literature Review: Background rates of AA in the general population and patients treated with ICI, and a comprehensive search in Embase and Medline in the interval 01-APR-2022 through 31-DEC-2023 for studies evaluating AA among patients treated with ICI. Clinical trial data analysis: The aggregate safety evaluation dataset (ASE) and the cumulative safety dataset (CSD) were searched using the preferred terms (PT): Aplastic anemia, Autoimmune aplastic anemia, Pancytopenia, Autoimmune pancytopenia, Cytopenia, Immune-mediated cytopenia, Myelosuppression, Panmyelopathy and Bone marrow failure (MedDRA v26.1). Review of the Company Global Safety Database and EudraVigilance Data Analysis System (EVDAS) for the interval 01-APR-2022 through 31-DEC-2023 with the same PTs and MedDRA listed prior. **Case Definition:** The following case definition for AA was used for this evaluation: AA is defined as the presence of pancytopenia with a hypocellular bone marrow in the absence of an abnormal marrow infiltrate or marrow fibrosis. The case definition requires the following:
	Bone marrow aspiration and biopsy are required to establish the diagnosis of AA and to exclude other causes of pancytopenia. AND There must be at least two of the following: hemoglobin concentration (Hb) <100 g/l platelet count <50 x 10^9/l neutrophil count <1.5 x 10^9/l Evidence for an immune-mediated mechanism, with the exclusion of other etiologies.
Results	**Preclinical/Toxicology:** Toxicology studies with pembrolizumab in cynomolgus monkeys, including a chronic study with 6-months of dosing up to 200 mg/kg every other week followed by 4-months of treatment-free period, did not detect any effects of pembrolizumab on red blood cells or bone marrow. **Epidemiology and Literature Review:** Due to the rarity of the disease, data on the burden of aplastic anemia in the general population is sparse. Per the expert review of global epidemiologic studies, the incidence of aplastic anemia in the general population was estimated to be 2-3 cases per million persons in the United States and Europe and up to 7.4 cases per million persons in East Asia [05R4WB]. The incidence of aplastic anemia across all cancer types is not available. New evidence shows that the incidence of aplastic anemia in ICI-treated patients ranges from 0.09% to 0.9%, and this finding is consistent with the incidence from previous assessments (0.01% to 0.9%). An observational study using the US Food and Drug Administration Adverse Event Reporting System (FAERS) from January 2011 to June 2022 identified 38 cases of AA related to ICI treatment. A disproportionality analyses in this study showed a statistically significant reporting odds ratio of ICI use as a class for AA [08HTY4]. **Review of aggregate data from clinical trials:** A search of the ASE for AA related PTs in the pembrolizumab monotherapy data (n=9118) revealed frequencies for Pancytopenia and Bone marrow failure of 0.1% (n=8) and 0.0% (n=1) respectively. The comparator arms of chemotherapy (n=1324) and ipilimumab (n=256) had frequencies of Pancytopenia (0.8% and 0.4%) and Bone marrow failure (0.0% and 0.0%) respectively.

Table 16.2.6.1 Signal Evaluation for Aplastic anemia

	A search of the CSD for AA related PTs revealed 5 (0.05%) incidences of pancytopenia, with no events reported for the other PTs in the AA term selection strategy. The overall rate of pancytopenia and all AA related PTs in the CSD was consistent with that observed in the ASE Database**.** **Review of data from the Company Global Safety Database:** A total of 552 individual case safety reports (ICSRs), containing 569 events, were identified from the company's global safety database. There were 30 cases from interventional trials, 51 from noninterventional studies, and 471 from spontaneous reports; 550 cases were serious, 2 cases were nonserious. Outcome was reported in all 569 events: 555 events were reported as either recovered (164), recovered/resolved with sequelae (4), recovering (135), not recovered (33), unknown (219), and fatal (14). Time to onset was reported in 388 cases, ranging from 1 to 1546 days, (median 27.5 days). There were 13 cases that included 14 events with fatal outcomes: AA (n=1 event), bone marrow failure (n=2 events), myelosuppression (n=4 events), and pancytopenia (n=7 events). Of the 13 fatal cases, 11 did not meet the case definition: 1 had a bone marrow biopsy with results that were not consistent with a hypocellular marrow, and 10 did not have bone marrow biopsies (BMB) reported. Of the two fatal cases that met the case definition, both had a more likely alternative etiology for AA based on plausible temporal relationship and full review of clinical details (1 with concomitant chemotherapy medication, and 1 with recent SARS-CoV-2 infection and concurrent sepsis). From the total of 552 identified cases, 536 cases did not report a bone marrow biopsy and or aspiration having been performed and thus do not meet the case criteria requirement as stated
	above. Of the remaining 16 cases that did report a confirmed bone marrow biopsy: one case recorded a normal bone marrow biopsy result, one case reported a hypercellular bone marrow, 2 cases were missing important information needed for full case assessment (medical history, concomitant medications, bone marrow biopsy result), 2 cases reported an alternative diagnosis of chronic lymphocytic leukemia (CLL)/small lymphocytic leukemia (SLL) and acute promyelocytic leukemia, and 8 cases reported the use of concurrent myelosuppressive chemotherapy as a more likely etiology for AA. The two remaining cases, which met the case definition, lacked sufficient information to assess causality. **Search of EVDAS database:** Additionally, the EVDAS database was searched, and a total of 469 cases were identified of which 396 cases were included in the Company safety database review. The remaining 73 cases were reviewed and yielded no additional information to alter the conclusions of this review. Please refer to Appendix 21.10.2.5 for further details.
Discussion	AA is a rare and heterogeneous disorder of bone marrow failure in which most cases are idiopathic in nature. Review of preclinical data did not identify any findings relating AA to pembrolizumab use in animal studies. Recent observational studies estimate the incidence of aplastic anemia in patients with cancer receiving ICI treatment to be 0.09% to 0.9%. However, to our knowledge, there is no information regarding the incidence of AA among patients with cancer to assess whether there may be an increased incidence among cancer patients treated with ICIs. A recent analysis of FAERS data indicated that there was disproportionate reporting of aplastic anemia in patients following ICI treatment. However, important limitations exist for studies based on data from the passive surveillance systems that include inability to evaluate true incidence due to lack of denominators for use in ICI-treated patients, potential reporting bias, and lack of standardized case definition for AA. This analysis also had the limitation of reliance on reported preferred terms without the ability to confirm diagnoses and the absence of case level detail to assess causality. In the ASE database, the frequency of AA related PTs reported with pembrolizumab monotherapy use was generally low, and therefore overall generalizations based on these frequencies are limited. No meaningful imbalance between the pembrolizumab arm and comparator arms was identified. The results in CSD were consistent with ASE database. During interval review of the Company's global safety database, 552 cases were identified using the search strategy described above, and of the 552 cases, 536 did not report a bone

Table 16.2.6.1 Signal Evaluation for Aplastic anemia

	marrow biopsy and/or aspiration having been performed and thus did not meet the case definition for further review. Of the 16 cases that did report a confirmed bone marrow biopsy, 2 cases had hematologic parameters and bone marrow biopsy results that met the case criteria and were further described. Both cases lacked sufficient information to assess causality.
Conclusion	Signal was refuted. Based on the totality of the information reviewed and presented above, the Company considers that there is not sufficient evidence to support a causal association of AA with exposure to pembrolizumab, and no updates are required to the CCDS or RMP at this time. The Company will continue to monitor AA temporally associated with pembrolizumab exposure through its robust routine pharmacovigilance activities.

16.2.7 Tuberculosis, including reactivation

Table 16.2.7.1 Signal evaluation for Tuberculosis (tuberculosis reactivation)

Source / Trigger of Signal	Health Authority Request (Hong Kong)
Background	The Company acknowledged the request by the Drug Office (DO) of the Department of Health, Hong Kong to obtain follow-up information regarding a new case of tuberculosis received by the Hong Kong DO in FEB-2024. The Hong Kong DO note that a global assessment report on the relationship between the event Tuberculosis (TB) (TB reactivation) and the use of Pembrolizumab had been provided by the Company on March 2022; and requested an updated global assessment report on the relationship between the event TB (TB reactivation) and the use of pembrolizumab based on global PV data. To meet the request for an updated global assessment report for TB (TB reactivation), the Company submitted the comprehensive evaluation submitted to the Saudi Food and Drug Authority (SFDA) (Response to Agency Questions Received 8-Oct-2023 - Saudi Arabia SFDA- Tuberculosis, Doc ID: 08FDLQ) in November 2023 that covered the period from 15-SEP-2019 through 30-SEP-2023. An incremental review of the Company Global Safety Database covering the period after 30-SEP-2023 was also submitted. Please refer to Appendix 21.10.2.6 for further details
Method(s) of Evaluation	Review of the Company Global Safety Database from 01-OCT-2023 to 08-FEB-2024, time from the SFDA response and receipt of the new case by the Hong Kong DO (MedDRA v26.1; HLT Tuberculosis infections).
Results	Two cases [08JFGJ] of TB were identified and are described below. • Case of a [redacted] patient in [redacted] 50s who started neoadjuvant therapy with pembrolizumab, paclitaxel, carboplatin, and doxorubicin for treatment of right side, triple negative invasive ductal breast carcinoma; followed by radiotherapy (RT) and breast conserving surgery. The patient experienced “pneumonia or tuberculosis” and primary adrenal insufficiency (PAI). Treatment for PAI included hydrocortisone and rapison. Information regarding relevant tests for the diagnosis of “pneumonia or tuberculosis”, clinical course of events, treatment for “pneumonia or tuberculosis”, outcome of events, and action taken with pembrolizumab in response to the events was not reported. Information regarding medical history, concurrent conditions, and concomitant medication was not reported • Case of a 70-year-old [redacted] who started therapy with pembrolizumab for the treatment of left lung adenocarcinoma, non-small cell lung cancer. Approximately 9 months after starting therapy with pembrolizumab, CT scan revealed distal atelectasis and severe inflammation in bilateral lung. Respiratory pathogen testing revealed mycobacterium tuberculosis complex. The patient was hospitalized for treatment and was discharged approximately 45 days later but readmitted the next day due to hepatitis. Symptomatic treatment was given outside hospital. The outcome of mycobacterium tuberculosis pneumonia was not recovered. The action taken with pembrolizumab in response to the events hepatitis and Mycobacterium tuberculosis pneumonia

Table 16.2.7.1 Signal evaluation for Tuberculosis (tuberculosis reactivation)

	was reported as withdrawn. Information regarding clinical course of events, treatment of events and time of final discharge was not reported. The outcome of the event hepatitis and distal atelectasis was unknown. Please refer to Appendix 21.10.2.6 for further details
Discussion	A summary of the review performed in November 2023 and submitted to the SFDA, concluded that patients who are candidates for pembrolizumab therapy are in an immunocompromised state due to the underlying malignancy and recent or concomitant immunomodulatory therapies and as such are susceptible to infections such as TB. As stated in the SFDA response, review of available literature did not identify new safety concerns about tuberculosis with immune checkpoint inhibitors; and review of clinical trial safety data indicated that the rates of TB reported with the use of pembrolizumab was low compared with the background rates in general or cancer population. A comprehensive review of all identified cases from global safety database were either confounded or without sufficient information for further assessment. The two cases reported to the Company safety database since the data lock date of the evaluation for SFDA did not identify any new meaningful safety information.
Conclusion	Signal was refuted. The available scientific evidence does not support an association between pembrolizumab and tuberculosis (tuberculosis reactivation).

16.2.8 Polymyalgia Rheumatica

Table 16.2.8.1 Signal Evaluation for Polymyalgia Rheumatica

Source / Trigger of Signal	Health Authority Request (TGA)
Background	TGA requested the Company (MAH) "to make safety-related changes to the Product Information (PI) of Keytruda/Pembrolizumab." Polymyalgia rheumatica (PMR) is a common inflammatory rheumatic disease of older individuals, characterized clinically by aching and morning stiffness about the shoulders, hip girdle, and neck. It can be associated with giant cell arteritis (GCA, also known as Horton disease, Horton giant cell arteritis, and temporal arteritis); the two disorders may represent different manifestations of a shared disease process. The etiology of polymyalgia rheumatica is not well understood. Familial aggregation of PMR has suggested a genetic predisposition. [08JX4T] Diagnostic criteria for polymyalgia rheumatica were developed by the European League Against Rheumatism (EULAR) / American College of Rheumatology (ACR) panel in 2012 [08JP0H].
Method(s) of Evaluation	Review of polymyalgia rheumatica with pembrolizumab, included the following: • Preclinical/Toxicology Data Review • Epidemiology/Literature Review: background rates of PMR in the general population. A comprehensive search of Embase and Medline cumulative to 29-Feb-2024 for studies evaluating PMR among patients with the use of an immune checkpoint inhibitor (ICI, including PD-1, PD-L1, or CTLA-4 inhibitors). • Clinical trial data analysis: the aggregate safety evaluation (ASE) database and the cumulative safety dataset (CSD) were searched using a strategy of 'PT Polymyalgia Rheumatica' (MedDRA version 26.1). • Examination of Company global safety database to review all cases from interventional studies, noninterventional studies, and spontaneous cases with pembrolizumab using a search strategy of PT of polymyalgia rheumatica (MedDRA version 26.1) from 16-Aug-2020 through 31-Jan-2024. • Review of data available in Eudravigilance Data Analysis System (EDVAS). Search of the EVDAS database was performed for cases involving pembrolizumab and the PMR events from 16-Aug-2020 through 31-Jan-2024 using the PT of polymyalgia rheumatica (MedDRA version 26.1).

Table 16.2.8.1 Signal Evaluation for Polymyalgia Rheumatica

	Case definition: The presence of clinical presentation and laboratory findings consistent with the EULAR/ACR diagnostic criteria, in the absence of an identifiable alternative cause [08JP0H].
Results	**Preclinical/Toxicology Data Review** There is no specific toxicology or pre-clinical data relating to 'polymyalgia rheumatica' and pembrolizumab. **Epidemiology/Literature Review:** Polymyalgia rheumatica (PMR) is a common inflammatory rheumatic disease, and people who are older than 50 years or women are more likely to develop PMR. PMR has been reported as the second most common inflammatory autoimmune rheumatic disease after rheumatoid arthritis in people 50 years and older. The global incidence of PMR highly varies across geographic area, ranging from 2 cases per 100,000 persons in Korea to 113 cases per 100,000 persons in Norway in the age group 50 years or older [08JS46]; [08JS44]. While different study design and diagnostic criteria may contribute to the wide range of the incidence estimates, PMR appears more common in populations of Northern European ancestry but is less common in non-Caucasian population [08JS46]. In addition to genetic factors, environmental agents, such as viral infections and ultraviolet radiation, might be the etiologic causes for PMR [08JS44]. Sporadic cases of PMR have been reported in published observational studies among patient treated with ICI. As there is no population-based incidence estimate for PMR in the general cancer population, it is not clear if ICI-treated patients have a higher risk of developing PMR compared to general cancer patients. **Review of aggregate data from clinical trials:** The incidence of participants with adverse events of polymyalgia rheumatica when treated with pembrolizumab monotherapy is 0.1% (n=13). There were no participants with AE of polymyalgia rheumatica in the comparator arms including placebo, chemotherapy, ipilimumab, and cetuximab. A search of the CSD revealed 15 (0.1%) adverse events of polymyalgia rheumatica. The overall incidence of participants with AE of polymyalgia rheumatica in the CSD was consistent with that observed in the ASE Database. **Review of data from the Company Global Safety Database:** A total of 91 individual case safety reports (ICSRs), containing 93 events, were identified from the company's global safety database from 16-AUG-2020 to 31-Jan-2024. Of the 91 cases retrieved, 13 were from interventional trials, 3 from noninterventional studies and 75 from spontaneous reports. Of the total of 91 identified cases, 76/91 cases did not meet the case definition for polymyalgia rheumatica due to insufficient information regarding clinical symptoms or comprehensive assessment to exclude alternate etiology as per the case definition. Of the remaining 15/91 cases that met the case definition, 12/15 cases were confounded by one or more of the following: anti-nuclear antibodies (ANA) elevated, history of rheumatoid arthritis, concurrent use of nivolumab and ipilimumab, psoriatic arthropathy, concurrent infection, polymyositis, history of polymyalgia rheumatica, treatment of arthritis with tocilizumab, and concurrent condition of arthritis and gout. The available information in another 3/15 cases was insufficient to allow meaningful medical assessment of the association between polymyalgia rheumatica and pembrolizumab. **Search of EVDAS database:** The EVDAS database search for the PT of polymyalgia rheumatica identified 79 cases. Of those cases, 76 cases were included in the total number of cases in the Company safety database review. The remaining 3 additional cases contained insufficient information for a complete medical assessment (e.g., medical history, concurrent conditions, concomitant medications, time to onset, laboratory results, treatment information, etc.). The data from the review of EVDAS yielded no additional information to alter the conclusions of this review.
Discussion	PMR is a common chronic inflammatory condition of unknown etiology that affects elderly individuals. There is no specific diagnostic laboratory test and inflammatory markers for PMR. PMR is a diagnosis of exclusion. Diagnostic criteria for PMR were developed by EULAR / ACR were used identify patients for the purpose of this assessment. There were no specific toxicology or pre-clinical findings for pembrolizumab related to polymyalgia rheumatica. Literature review revealed sporadic cases of PMR reported in published observational studies among patients treated with ICI. As there is no population-based incidence estimate for PMR in patients with cancer, it is not clear if ICI-treated patients have a higher risk of developing PMR than general cancer patients. A review of the clinical trial data revealed low incidence of participants with AEs of PMR (0.1%) in pembrolizumab arm.

Table 16.2.8.1 Signal Evaluation for Polymyalgia Rheumatica

	The current review of the Company Global Safety Database identified 91 potential cases of PMR based on the search strategy, of which 76/91 cases did not meet the case definition for polymyalgia rheumatica. Of the 15/91 cases that met the case definition, 12/15 cases contained confounded factors in concomitant medication or comorbid conditions. The available information in another 3/15 cases was insufficient to allow meaningful medical assessment of the association between polymyalgia rheumatica and pembrolizumab. The data from the review of EVDAS yielded no additional information to alter the conclusions of this review. Please refer to Appendix 21.10.2.7 for further details.
Conclusion	Signal refuted Based on the totality of the information reviewed and presented above, the Company considers that there is insufficient evidence to support a causal association of polymyalgia rheumatica with exposure to pembrolizumab and therefore, an update to the product label is not required. The Company will continue to monitor polymyalgia rheumatica temporally associated with pembrolizumab exposure through routine pharmacovigilance activity.

16.2.9 Tenosynovitis

Table 16.2.9.1 Signal Evaluation for Tenosynovitis

Source / Trigger of Signal	Health Authority Request (TGA)
Background	This assessment is in response to the Request by the Therapeutic Goods Administration (TGA) for the marketing Authorization Holder (MAH) to make safety-related changes to the Product Information (PI) of Keytruda/Pembrolizumab. The TGA specifically requested to add Tenosynovitis to Section 4.4 Special Warnings and Precautions for Use under Other immune-mediated adverse reactions in addition to where it is already included in Section 4.8 (Adverse Effects/Undesirable Effects) under Post-marketing Experience. Tenosynovitis is the inflammation of the fluid-filled synovium within the tendon sheath. It may present with a variety of non-specific clinical manifestations including swelling, pain, erythema, and difficulty in moving the affected tendon. The condition can affect any tendon surrounded by a sheath but has a predilection for the hand, wrist, and foot [08JN4W]. A detailed history and physical examination to identify possible etiologies (injury, fever, purulence, longstanding arthritis, or autoimmune disorder, nodules) is essential. Laboratory tests can confirm certain etiologies, such as infections or rheumatological conditions. Ultrasound can aid in diagnosis and when ultrasound is limited or additional fine detail evaluation is required, further evaluation with MRI is an option. Tenosynovitis can be due to infectious or non-infectious causes (autoimmune, overuse, and idiopathic). Tenosynovitis is also frequently observed in the clinical setting of autoimmune conditions such as rheumatoid arthritis with up to 87% of patients with rheumatoid arthritis displaying objective evidence of tenosynovitis on MRI studies[08JN4F]. Other chronic conditions, particularly diabetes, has been associated with stenosing tenosynovitis; a longitudinal cohort study over 20 years showed that DM is an important risk factor for developing stenosing tenosynovitis. [08JSWH]. Tenosynovitis, has also been attributed with occupational repetitive use and may affect any of the tendons of the forearm and hand. Examples include trigger finger and de Quervain's tenosynovitis[08JSWL]. This is the first assessment of Tenosynovitis for pembrolizumab.

Table 16.2.9.1 Signal Evaluation for Tenosynovitis

Method(s) of Evaluation	**Case Definition** . Each report was reviewed to determine whether the report met the following case definition of tenosynovitis. 1)Clinical symptoms and Physical exam findings consistent with tenosynovitis including swelling, pain, erythema, and difficulty moving the affected joint; laboratory findings may additionally be used to support exclusion of alternative etiologies; AND 2) Confirmation of inflammation of tendon sheath by radiographic evaluation (ultrasound/ MRI). **Examination of Clinical Trial Data** o The Clinical Datasets were searched using the Preferred Terms (PT) Tenosynovitis and Tenosynovitis stenosans, MedDRA version 26.1. o Aggregate Safety Evaluation (ASE) database, which is an aggregate clinical trial dataset containing safety data for pembrolizumab. The most recent dataset contains all safety data for subjects in an open-label or unmasked, completed randomized trial with a pembrolizumab monotherapy arm for which there has been a database lock on or before 31-MAR-2018 (n=9118). Comparator safety data from these trials is also included in the ASE. At present, comparators include ipilimumab, cetuximab, cytotoxic chemotherapy (all treatments combined) and placebo. o Cumulative Safety Dataset (CSD): The CSD for this response (n=10,997) includes pembrolizumab monotherapy safety data aggregated across trials that included a pembrolizumab monotherapy arm and were submitted to a health authority with a data cutoff on or prior to 20-SEP-2021. **Examination of the Company global safety database** to identify all cases including interventional study cases, noninterventional study cases, and spontaneous cases involving pembrolizumab and events of tenosynovitis through 31 January 2024 using the same search strategy of Preferred Terms (PT) Tenosynovitis and Tenosynovitis stenosans, MedDRA version 26.1. **Review of data available in EudraVigilance Data Analysis System (EVDAS): Search of the EVDAS database** for cases involving pembrolizumab and events of tenosynovitis through 31-JAN-2024 using the same search strategy of Preferred Terms (PT) Tenosynovitis and Tenosynovitis stenosans, MedDRA version 26.1 **Epidemiology/Literature review:** A search of the published literature (Embase®, MEDLINE®) describing tenosynovitis in patients treated with pembrolizumab was performed. The following search strategies were used for this review: (tenosynovitis and (pembrolizumab OR mk 3475 OR mk3475 OR lambrolizumab)) and (ud(<20240229)). Please refer to Appendix 21.10.2.8 for further details
Results	**Pre-clinical/Toxiology** There is no specific toxicology or pre-clinical data relating to tenosynovitis and pembrolizumab. **Epidemiology** No observational real-world studies of tenosynovitis incidence in pembrolizumab-treated patients were found in the published literature. One pharmacovigilance (PV) study was identified which was conducted using the U.S. Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) to assess the relationship between ICI therapies and musculoskeletal adverse events [08JS4P].

Table 16.2.9.1 Signal Evaluation for Tenosynovitis

	While significant RORs between ICIs, including pembrolizumab, and tenosynovitis were reported, disproportionality analyses are hypothesis-generating in nature to assess the statistical association between a certain drug and an adverse event, as a ROR only evaluates an increased risk of AE reporting and it does not quantify the true risk of developing an AE in patients who used the drug. Reporting bias and the lack of standard definition of tenosynovitis across different reporting sources may also affect the results. Thus, the causal inference between pembrolizumab and tenosynovitis cannot be determined based on findings of disproportionality analysis alone. **Aggregate Clinical Trial Data** 1. Unblinded Aggregate Safety Evaluation (ASE) Search of the ASE retrieved 7 cases (0.1%) of tenosynovitis in pembrolizumab monotherapy (n=9,118) versus no incidences (0.0%) in the comparator arms including chemotherapy (n=1,324), ipilimumab (n=256), cetuximab (n=71), and placebo (n=502). The incidences of Tenosynovitis stenosans were zero in all the arms. As the numbers are generally low, overall generalizations based on these frequencies are limited. No meaningful imbalance between the pembrolizumab arm and comparator arms was identified. 2. *Cumulative Safety Dataset* A search of the CSD revealed 9 subjects (0.1 %) with events of tenosynovitis The overall rate of tenosynovitis in the CSD was consistent with that observed in the ASE Database. No cases with event of Tenosynovitis stenosans were observed. **Company Global Safety Database Review** As of 03-SEP-2023, there was a total of 67,086 patients treated with pembrolizumab in the Company sponsored clinical trial program and approximately 1,146,866 patient years of exposure to pembrolizumab in the post marketing setting. A total of 28 individual case safety reports (ICSRs), containing tenosynovitis events, were identified from the company's global safety database. There were 25 reports of the PT of tenosynovitis and 3 reports of the event of tenosynovitis stenosans. Four cases were from interventional trials, 6 from noninterventional studies and 18 from spontaneous reports. Twenty-five (cases)were serious, and 3 were nonserious. Outcome was reported in 18 of the 28 events: No events had fatal outcomes or outcomes of recovered/resolved with sequelae. The remaining 18 events were reported as either recovered (13), recovering (4), or not recovered (1). Age was reported in 25 cases with age at event onset ranging from 38 to 82 years, with a median age of 63 years. All 28 cases reported gender, with 12 females and 16 males. Time to onset was reported in 14 cases, ranging from 9 to 463 days (median 86.5 days). From the total of 28 identified cases, 26 cases did not have a confirmation of inflammation of tendon sheath by radiographic evaluation (ultrasound/ MRI) and did not meet the prespecified case definition for tenosynovitis. The 2 remaining cases that met the case definition; 1 case showed ultrasound findings of tenosynovitis, more likely related to a past medical history of type 2 diabetes mellitus and polymyalgia rheumatica. The second case MRI demonstrates myositis, and fasciitis likely representing any of the spectrum of rheumatologic disorders frequently encountered in the elderly population. **EVDAS Database** The data from the review of EVDAS yielded no additional information to alter the conclusions of this review.
Discussion	. Examination of the aggregate clinical trial data (ASE and CSD) did not reveal an imbalance of tenosynovitis events between pembrolizumab exposure versus comparator arms; in addition the event rate observed in clinical trial is consistent with the background rate of tenosynovitis in cancer

Table 16.2.9.1 Signal Evaluation for Tenosynovitis

	patients. The data from the review of the Company safety database and EVDAS yielded no additional information There were no toxicology or pre-clinical data related to tenosynovitis. No observational real-world studies of tenosynovitis incidence in pembrolizumab-treated patients were found in the published literature Based on the totality of the information reviewed and presented above, the Company considers that there is not sufficient evidence to support a causal association of tenosynovitis with exposure to pembrolizumab and no update to the current product labelling is required at this time. The Company will continue to monitor tenosynovitis temporally associated with pembrolizumab exposure through routine pharmacovigilance activity.
Conclusion	Signal was refuted. The available scientific evidence does not support an association between pembrolizumab and tenosynovitis.

16.2.10 Sjogren's Syndrome

Table 16.2.10.1 Signal Evaluation for Sjogren's Syndrome

Source / Trigger of Signal	Health Authority Request (TGA)
Background	This assessment is in response to the Request by the Therapeutic Goods Administration (TGA) for the marketing Authorization Holder (MAH) to make safety-related changes to the Product Information (PI) of Keytruda/Pembrolizumab. The TGA requested to add Sjogren's syndrome to Section 4.4 Special Warnings and Precautions for Use under Other immune-mediated adverse reactions in addition to where it is already included in Section 4.8 (Adverse Effects/Undesirable Effects) under Post-marketing Experience. Prior assessments of Sjogren's syndrome were performed based on a PRAC request in 2020 with a review period cumulative to 15-MAY-2020, and subsequently through bi-annual aggregate safety data review with the last performed 31-MAR-2022 and included in the PSUR (Reporting interval 04-SEP-2021 to 03-SEP-2022). [085M77] The results of these reviews noted insufficient evidence to support a causal association between pembrolizumab and the event of Sjogren's syndrome. Although the results of the prior reviews noted insufficient evidence to support a causal association, Sjogren's Syndrome was added to section 4.8 of the EU SmPC following PRAC mandate. Sjogren's syndrome is a chronic autoimmune inflammatory disorder characterized by diminished lacrimal and salivary gland function with resultant dryness of the eyes and mouth. In addition, a variety of other disease manifestations affecting multiple organs and organ systems may occur, and the clinical features of Sjogren's syndrome can be divided into the two broad categories of exocrine glandular features and extraglandular features. Sjogren's syndrome occurs in a primary form not associated with other diseases and in a secondary form that complicates other rheumatic conditions. The most common diseases associated with Sjogren's syndrome are rheumatoid arthritis and systemic lupus erythematosus. Sjogren's syndrome is most common in women in their 50s and 60s but can affect adolescents and young adults, as well as men. [08JSWM]

Table 16.2.10.1 Signal Evaluation for Sjogren's Syndrome

Method(s) of Evaluation	• **Biological Plausibility/Preclinical Data** • **Literature review:** A literature review describing Sjogren's Syndrome in patients treated with pembrolizumab and other approved immune checkpoints inhibitors. The search of relevant literature was conducted from 9-JUN-2022 through 29-FEB-2024 using Embase and Medline, those published prior to 9-JUN-2024 were previously reviewed and summarized in the prior assessment reports provided in 2020 and 2022. (ema-responses-PRAC-recommendation-Sjögren's Syndrome, Doc ID: 05HM3J), [085M77] • **Epidemiology:** Background rates of Sjogren's Syndrome in the general population and in patients with cancer. • **Examination of Clinical Trial Data:** The Clinical Datasets were searched using the PT of Sjogren's Syndrome (MedDRA version 26.1). o Aggregate Safety Evaluation (ASE) database: The ASE is an aggregate clinical trial dataset containing safety data for pembrolizumab. The most recent dataset contains all safety data for subjects in an open-label or unmasked, completed randomized trial with a pembrolizumab monotherapy arm for which there has been a database lock on or before 31-MAR-2018 (n=9118). Comparator safety data from these trials is also included in the ASE. At present, comparators include ipilimumab, cetuximab, cytotoxic chemotherapy (all treatments combined) and placebo. o Cumulative Safety Dataset (CSD): The CSD for this response (N=10,997) includes pembrolizumab monotherapy safety data aggregated across trials that included a pembrolizumab monotherapy arm and were submitted to a health authority with a data cutoff on or prior to 20-SEP-2021. • **Company global safety database**: Review of the Company global safety database to identify all cases including interventional study cases, noninterventional study cases, and spontaneous cases involving pembrolizumab and PT of Sjogren's Syndrome from 01-APR-2022 through 31-JAN-2024 using MedDRA version 26.1. • **EudraVigilance Data Analysis System (EVDAS):** Review of data available in EVDAS for cases involving pembrolizumab and the preferred term (PT) Sjogren's Syndrome for the review period of from 01-APR-2022 through 31-JAN-2024 using MedDRA version 26.1. **Case Definition:** ACR-EULAR* Classification Criteria for primary Sjogren's syndrome The case definition used for this assessment was based on a weighted scoring system per the 2016 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria for primary Sjogren's syndrome based on several criteria, including number of mononuclear-cell infiltrates in labial salivary gland biopsy, presence of anti-SSA antibodies, SICCA ocular staining score, Schirmer test, and unstimulated whole salivary flow. Please refer to Appendix 21.10.2.9 for further details. Individuals were classified as having primary Sjogren's syndrome if they had a total score of ≥4. A history of head and neck radiation treatment, active hepatitis C infection, acquired immunodeficiency syndrome (AIDS), sarcoidosis, amyloidosis, graft-versus-host disease, and IgG4-related disease (IgG4-RD) exclude a diagnosis of primary Sjogren's syndrome [05JNHC]. Please refer to Appendix 21.10.2.9 for further details.

Table 16.2.10.1 Signal Evaluation for Sjogren's Syndrome

Results	**Biological Plausibility/Preclinical Data** There is no specific toxicology or pre-clinical data relating to Sjogren's Syndrome and pembrolizumab administration. **Epidemiology and Literature Review** Limited studies have estimated the incidence of Sjogren's syndrome in the general population, and the reported incidence highly varies across studies due to different diagnostic criteria (or case definition) and study design. A recent comprehensive review has summarized that the incidence of Sjogren's syndrome in the general population likely ranges from 1 to 10 cases per 100,000 person-year (PY), with multiple studies reporting the incidence estimates around 5 cases per 100,000 PY [08JS42]. There is no population-based data reporting the background rates of Sjogren's syndrome in general cancer population. According to the two previous assessments (ema-responses-PRAC-recommendation-Sjögren's Syndrome, Doc ID: 05HM3J), [085M77], sporadic cases of Sjogren's syndrome had been reported in ICI-treated patients, where its incidence ranged from 0.22% in 465 ICI-treated pan-tumor patients to 3.13% in 32 patients with advanced renal cell carcinoma who received nivolumab. **Aggregate Clinical Trial Data** • **Unblinded Aggregate Safety Evaluation (ASE)** Review of the ASE data did not reveal an imbalance in the different treatment groups. Search of the ASE dataset revealed the overall frequency for Sjogren's Syndrome was 0.4% (4 events) out of 9,118 patients exposed to pembrolizumab monotherapy versus no cases in other comparator arms including chemotherapy, ipilimumab, cetuximab, and placebo. As the numbers are generally low, overall generalizations based on these frequencies are limited. • **Cumulative Running Safety Dataset** Search of the CSD (n=10,997) revealed 9 (0.1%) patients exposed to pembrolizumab monotherapy reported the event of Sjogren's syndrome. The overall rate of Sjogren's syndrome in the CSD was generally consistent with that observed in the ASE Database. **Company Global Safety Database Review** Of the 27 identified cases (4 from interventional trials, 3 from non-interventional studies, and 20 from spontaneous reports), 22 cases contained insufficient information to meet the case definition of Sjogren's syndrome and 3 cases had evidence of a more likely alternative etiology. The remaining 2 cases contained sufficient information for diagnostic confirmation of Sjogren's syndrome. In one case, a literature article described a 66-year-old [redacted] with a history of right upper lobectomy. Prior to the diagnosis of Sjogren's syndrome, [redacted] experienced circular lesions that were diagnosed as suspected cutaneous lupus. Following that, [redacted] experienced painful palpation near the salivary glands with ultrasound noting a heterogeneous echostructure with fibrosis and cysts, dry eyes with deterioration in vision quality, and antibody titers against SS-A (Ro) and SS-B (La). The diagnosis of cutaneous lupus prior to Sjogren's syndrome symptoms, the patient's gender and age all confound the temporal association with pembrolizumab. In the second case, a literature article described a 71-year-old [redacted] with a history of breast cancer treated with adjuvant radiotherapy and tamoxifen. Subsequently, [redacted] was diagnosed with pulmonary adenocarcinoma, underwent a thoracoscopic lobectomy and initiated pembrolizumab monotherapy. Approximately 6 months after starting pembrolizumab, symptoms of burning in the throat began and progressed to extreme mucosal dryness. [redacted] was hospitalized and clinical evaluation noted buccal dryness, oral ulcers, dark brown tongue, and a markedly positive antinuclear antibody of 1/160 with positive anti-Ro52-SSA differentiation. Ophthalmological investigation confirmed xerophthalmia with Schirmer test of <1 mm after 3 min, and corneal erosions had been objectified upon examination. The patient's historical and current conditions of breast cancer and pulmonary adenocarcinoma as well as the related prior use of

Table 16.2.10.1 Signal Evaluation for Sjogren's Syndrome

	chemotherapy and radiation to the chest, [redacted] gender and age all confound the temporal association with pembrolizumab. **Search of EVDAS database** The data from the review of EVDAS yielded no additional information to alter the conclusions of this review. Please refer to Appendix 21.10.2.9 for further details.
Discussion	Taken as a whole, the safety information reviewed for this analysis and presented above is not considered to provide sufficient evidence for a causal association between pembrolizumab and Sjogren's syndrome. There are no specific toxicology or pre-clinical data relating to Sjogren's Syndrome and pembrolizumab and review of epidemiology data and published literature did not reveal any new information. The data from the clinical trial pembrolizumab monotherapy ASE and CSD databases revealed a low incidence of Sjogren's Syndrome and the absence of an imbalance between pembrolizumab and chemotherapy. Reports in the Company safety database, contained insufficient information to meet the case definition of Sjogren's Syndrome, had evidence of a more likely alternative etiology, or were confounded by an atypical clinical presentation in which alternative etiologies were reported and the causal role of pembrolizumab and the event of Sjogren's syndrome was considered to be indeterminate. Please refer to Appendix 21.10.2.9 for further details
Conclusion	Signal was refuted. The available scientific evidence does not support an association between pembrolizumab and Sjogren's syndrome. Based on the totality of the information reviewed and presented above, the Company considers that there is insufficient evidence to support a causal association of Sjogren's syndrome with exposure to pembrolizumab. Therefore, the company does not consider an update to the pembrolizumab product labeling, nor the addition of Sjogren's syndrome to section 4.4 (special warnings and precautions) of the pembrolizumab Australian Prescribing information to be warranted at this time. The Company will continue to monitor Sjogren's syndrome through routine pharmacovigilance activity.

16.2.11 Tumour lysis syndrome

Table 16.2.11.1 Signal Evaluation for Tumour lysis syndrome

Source / Trigger of Signal	Health Authority Request (Medsafe)
Background	Tumour lysis syndrome (TLS) occurs when the intracellular contents of tumor cells are released into the systemic circulation as a result of massive destruction of malignant cells, either spontaneously, or more often, following treatment with antineoplastic agents. TLS is characterized by metabolic disturbances of hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia, which can overwhelm the body's ability to maintain homeostasis, and may lead to organ dysfunction, including acute renal failure, cardiac arrhythmia, seizure, or sudden death. Patients with a large "tumor burden" of cancer cells and/or tumors that typically have rapidly dividing cells, such as acute leukemia or high-grade lymphoma, as well as tumors that are highly responsive to therapy, are at greatest risk of developing TLS, although solid tumors have also been associated with TLS [06GB2B]. TLS can occur spontaneously or after initiation of cytoreductive chemotherapy [06GB2B]. The Company previously performed an assessment of TLS cumulatively through 03-SEP-2021, at the request of the United States Food and Drug Administration (FDA) (BLA 125514 FDA IR tumor lysis syndrome, Doc ID: 06G0B2) . In this current assessment, the Company performed an

Table 16.2.11.1 Signal Evaluation for Tumour lysis syndrome

	incremental review and evaluation of safety data related to TLS and the administration of pembrolizumab from 04-SEP-2021 through 31-JAN-2024. The overall analysis is based on the totality of the data.
Method(s) of Evaluation	• Preclinical Data review • Epidemiology/ Literature for background rates in the cancer population. A review for updates and/or new literature since 04-SEP-2021 for studies evaluating TLS among patients with the use of an immune checkpoint inhibitor (ICI), including PD-1, PD-L1, or CTLA-4 inhibitors. • Examination of Clinical Trial Data, including Aggregate Safety Evaluation (ASE) database and Cumulative Safety Dataset (CSD) using the Preferred Term (PT) of "Tumour lysis syndrome" (MedDRA version 26.1) • Examination of the Company global safety database to identify all cases involving pembrolizumab and events of TLS from 04-SEP-2021 to 31-JAN-2024 using a search of cases with the PT of "Tumour lysis syndrome" (MedDRA version 26.1) • Review of data available in EudraVigilance Data Analysis System (EVDAS) for cases involving pembrolizumab and events of TLS from 01-SEP-2021 to 31-JAN-2024 using a search of cases with the PT of "Tumour lysis syndrome" (MedDRA version 26.1) (previous review of EVDAS data was cumulative to 31-AUG-2021) Case Definition The presence of laboratory and clinical manifestations consistent with the Cairo and Bishop criteria, in the absence of an identifiable alternative cause. [00TSKB] Laboratory TLS (LTLS) was defined as 2 or more serum levels of the following within 3 days before or 7 days after treatment initiation: • elevated uric acid (≥ 476µmol/L [8mg/dL]), or a 25 % increase in the serum value over baseline • elevated potassium (≥ 6.0 mmol/L [6mEq/L]), or a 25 % increase in the serum value over baseline • elevated phosphate (≥ 2.1 mmol/L [6.5mg/dL] for children or ≥ 1.45mmol/L [4.5mg/dL] for adults), or a 25 % increase in the serum value over baseline • decreased calcium (≤ 1.75mmol/L [7 mg/dL]), or a 25% decrease in the serum value over baseline Clinical TLS (CTLS) was defined as laboratory TLS plus one or more of the following that was not directly or probably attributable to a therapeutic agent: • Acute kidney injury indicated by increased serum creatinine concentration (≥1.5x upper limit of normal [ULN]) • cardiac arrhythmia • sudden death • seizure Please refer to Appendix 21.10.2.10 for further details.
Results	**Preclinical data** There is no specific toxicology or pre-clinical data relating to TLS and pembrolizumab. **Epidemiology Review** The incidence of TLS in cancer patients is unknown, as the incidence from published studies varies by cancer type and cancer treatment and may also be impacted by the distinction between LTLS and CTLS with symptoms [08JLHJ] [06GB63]. TLS is more common in patients with hematologic malignancies, and the reported incidence of TLS ranged from 0.33% in patients with low-risk chronic lymphocytic leukemia, to 30.7% in patients with aggressive hematologic malignancies and high tumor burden [08JKMH] [08JLHJ]. The incidence of TLS in patients with solid tumors is difficult to determine due to the scarcity of data. In addition, spontaneous LTLS has been reported to occur in patients with solid tumors, with the most common sites of primary lesions being the lungs, colon, or liver, however, multiple other primary sites have also

Table 16.2.11.1 Signal Evaluation for Tumour lysis syndrome

	been described [08JLV7]. Most patients who experienced spontaneous TLS had been diagnosed with metastatic disease, mainly in the liver and/or lungs. **Literature Review** A comprehensive literature search identified case reports of TLS in patients treated with ICIs; however, in the identified case reports all patients had underlying risk factors for TLS. **Review of aggregate data from clinical trials** A search of the ASE database revealed a similar frequency for TLS with pembrolizumab monotherapy (2 cases, 0.02%) as compared to other therapies (chemotherapy 0%, ipilimumab 0%, cetuximab 0%) and to placebo (0%). No meaningful imbalance between the pembrolizumab arm and the comparator arms were identified. The small number of patients that experienced TLS limit any generalizations. A search of the CSD identified 2 participants (0.02%) with the PT of "tumour lysis syndrome". The overall prevalence of TLS in the CSD is consistent with that observed in the ASE database. The small number of patients that experienced TLS limit any generalizations. **Review of data from the Company global safety database** A total of 32 individual case safety reports (ICSRs), containing 32 events, were identified from the Company's global safety database. [08JLTZ] Four cases were from interventional trials, one case was from a noninterventional study, and 27 cases were from spontaneous reports. Twenty of the 32 cases, including 3 fatal cases, lacked sufficient information regarding initiation and/or discontinuation dates, concomitant medications, concurrent medical conditions, medical history, and/or limited details/ supporting data [including missing or partial laboratory values, units, and/or dates] of the event of TLS, precluding a complete medical assessment. Five of the 32 cases did not have laboratory values or clinical criteria consistent with the case definition of TLS. Of the remaining 7 cases, 4 cases met the strict Cairo-Bishop diagnostic criteria for TLS (including occurring within the "3 days before to 7 days after treatment initiation" window specified in the Cairo-Bishop diagnostic criteria), while 3 cases occurred greater than 7 days after treatment initiation but met the laboratory TLS and/or clinical TLS criteria. All 7 cases had compelling alternative etiologies for TLS, including underlying metastatic disease with high tumor burden, as well as pre-existing conditions and/or concurrent conditions that constitute risk factors for acute kidney injury, including underlying renal dysfunction, exposure to nephrotoxic agents, tumor occlusion of the kidney, dehydration, and active infection. **Search of the EVDAS database** The data from the review of EVDAS yielded no additional information to alter the conclusions of this review. A total of 31 cases were identified; 26 cases were included in the total number of cases in the Company global safety database review, of which 2 cases were captured in the previous review cumulative through 31-AUG-2021, and the remaining 5 cases lacked sufficient evidence to assess the event of TLS. Please refer to Appendix 21.10.2.10 for further details.
Discussion	Review of preclinical data did not identify any findings related to TLS in animal studies with pembrolizumab. Per literature reports, the precise incidence of tumor lysis syndrome in the general cancer population is unknown. The incidence of TLS following immune checkpoint inhibitor (ICI) exposure is also unknown; several cases of TLS following ICI use have been reported in the published literature and occurred mostly in patients with solid tumors with widespread metastases and all cases had risk factors, including underlying conditions with high tumor or metastatic burden or concomitant renal dysfunction, which provided plausible alternative explanations for TLS. There are several factors that increase the risk of developing TLS including renal insufficiency, dehydration, highly proliferating malignancies, sensitivity of the tumor cells to cancer therapy, baseline elevations in uric acid and phosphorus, and exposure to nephrotoxic substances. Liver metastasis is known to be a strong risk factor for the development of TLS in solid tumors. TLS in solid tumor patients on cancer targeted therapy may not only indicate an adverse treatment effect, but could rather be indicative of disease progression, especially if it occurs after several cycles of therapy. [08JJFR]

Table 16.2.11.1 Signal Evaluation for Tumour lysis syndrome

	A review of the clinical trial data revealed a low incidence of TLS in the pembrolizumab arm. Evaluation of the cases from the Company global safety database of the 4 cases that met the case definition including onset within 7 days of pembrolizumab exposure and the 3 cases that met partial case definition criteria revealed that TLS occurred mostly in patients with solid tumors with widespread metastases or with high tumor burden. However, all cases had compelling alternative etiologies for TLS, including underlying metastatic disease with high tumor burden, as well as pre-existing conditions and/or concurrent conditions that constitute risk factors for acute kidney injury, including underlying renal dysfunction, exposure to nephrotoxic agents, tumor occlusion of the kidney, dehydration, and active infection. The data from the review of EVDAS yielded no additional information. Please refer to Appendix 21.10.2.10 for further details
Conclusion	Signal refuted. Based on the totality of the information reviewed and presented above, the Company considers that there is insufficient evidence to support a causal association of TLS with exposure to pembrolizumab and therefore, an update to the product label is not required. The Company will continue to monitor TLS temporally associated with pembrolizumab exposure through routine pharmacovigilance activity.

16.2.12 Type 2 Diabetes Mellitus and increased risk of immune related adverse events

Table 16.2.12.1 Signal Evaluation for Type 2 Diabetes Mellitus and increased risk of immune related adverse events

Source / Trigger of Signal	Pre-publication abstract and manuscript from the European Organisation for Research and Treatment of Cancer (EORTC).
Background	The Company received a draft version of a EORTC abstract, and manuscript entitled “Prognostic and predictive importance of body mass index and type 2 diabetes in the European Organisation for Research and Treatment of Cancer 1325/KEYNOTE-054 phase III trial of pembrolizumab versus placebo in resected high-risk stage III melanoma”. The abstract conclusion included the following statement: “The hazard ratio for the association between type 2 diabetes mellitus and immune related adverse events among patients receiving pembrolizumab was 1.64 (95% CI 1.00-2.70).” Based on this conclusion from the abstract, the Company performed an independent evaluation of the association between type 2 diabetes mellitus (T2DM) and immune related adverse events (irAEs) in patients receiving pembrolizumab in larger datasets to evaluate for any potential association.
Method(s) of Evaluation	Clinical trial data included in Cumulative Safety Dataset (CSD) for pembrolizumab monotherapy were examined to identify irAEs by utilizing the preferred terms (PTs) contained in the adverse event of special interest (AEOSI) list. Data was reviewed and compared between subjects with T2DM and subjects without T2DM from KN054, aggregated adjuvant studies (including KN054, KN091, KN564, and KN716), and across all studies contained in the CSD. T2DM subjects were defined as subjects having at least one of the following PTs in their medical history: diabetes mellitus, diabetes mellitus inadequate control, insulin-requiring type 2 diabetes mellitus, type 2 diabetes mellitus, and insulin resistant diabetes.
Results	Findings of the KN054 analysis performed by EORTC about potential association between T2DM and AEOSIs after adjusting for covariates was replicated. However, a similar analysis of Our Company’s larger clinical trial dataset (CSD with N=10,879) comprised of study participants who received pembrolizumab monotherapy, showed no meaningful association between T2DM and the incidence of AEOSIs.

Table 16.2.12.1 Signal Evaluation for Type 2 Diabetes Mellitus and increased risk of immune related adverse events

	The respective calculated hazard ratios (HRs) for AEOSIs when adjusted for age, sex, ECOG, and region for KN054, the aggregated adjuvant study data, and for the CSD of subjects with T2DM versus subjects without T2DM indicated no difference in risk of AEOSI (or irAEs). Adjustments for baseline characteristics (age, sex, ECOG and region) had minimal impact on the association between T2DM and AEOSI analysis. **Hazard Ratios for TREATMENT** **Model** / **Comparisons** / **HR Point Estimate** / **95% CI** Adjusted Models (adjusted for age, sex, ECOG, region) — CSD: T2DM vs. non-T2DM: 1.11 (0.99, 1.25) Adjusted Models (adjusted for age, sex, ECOG, region) — Adjuvant: T2DM vs. non-T2DM: 1.09 (0.88, 1.35) Adjusted Models (adjusted for age, sex, ECOG, region) — KN054: T2DM vs. non-T2DM: 1.66 (0.99, 2.79)
Discussion	The Company performed its own assessment on the incidence of AEOSI in subjects with T2DM versus subjects without T2DM, reviewing data from the original KN054 study cited in the received abstract and manuscript, as well as data from larger datasets including the pembrolizumab aggregated adjuvant studies dataset and the CSD. Larger dataset analyses did not support findings from KN054 and did not show increased risk of AEOSIs in subjects with T2DM. The findings from KN054 may be due to chance or small sample size. Based on analysis results, no association between T2DM and AEOSI for pembrolizumab use can be established.
Conclusion	Signal was refuted. Based on the totality of the information reviewed and presented above, the Company considers that there is insufficient evidence to support an association between T2DM and an increased risk of AEOSI (or irAEs) in patients who receive pembrolizumab. The Company will continue to monitor irAE in T2DM patients receiving pembrolizumab through routine pharmacovigilance activity.

16.2.13 Pericarditis

Table 16.2.13.1 Signal Evaluation for Pericarditis

Source / Trigger of Signal	Bi-annual Aggregate Review
Background	On 19-Dec-2023, the signal review for immune-mediated pericarditis was initiated following bi-annual aggregate review (AR) for pembrolizumab. There have been previous health authority requests to review this topic. The most recent review evaluated data through 31-Jan-2018. These prior reviews did not have well-documented cases for proper evaluation and had cases with significant confounding factors or alternate etiologies for causal association; therefore, these signal reviews were previously refuted with a recommendation to continue to monitor. Of note, “pericarditis” has been included in all immune checkpoint inhibitor USPIs, including pembrolizumab (Warnings & Precautions section), as part of an FDA Class Labeling initiative. Pericarditis was also mandated by the PRAC for inclusion in the pembrolizumab EU SmPC (Section 4.8, Undesirable Effects). Based on the discussion of cases identified from AR, the Company performed an interval review (01-Feb-2018 through 31-Dec-2023) of the event immune-mediated pericarditis with pembrolizumab use to assess if there was sufficient evidence of a causal association between the event and pembrolizumab and evaluate if an update of the pembrolizumab Company Core Data Sheet (CCDS) was deemed necessary.
Method(s) of Evaluation	• Pre-Clinical/Toxicology Data Review • Epidemiology/Literature review: Background rates of pericarditis in general population and in patients with cancer. A comprehensive search in Embase and Medline cumulative up to 31-Jan-2024 for studies evaluating immune-mediated pericarditis in patients treated with pembrolizumab and other approved immune checkpoint inhibitors (ICI).

Table 16.2.13.1 Signal Evaluation for Pericarditis

	• Clinical trial data analysis: The Aggregate Safety Evaluation (ASE) dataset is an aggregate clinical trial safety database for pembrolizumab. The most recent dataset contains all safety data for patients in an open-label or unmasked, completed randomized trial with a pembrolizumab monotherapy arm for which there has been a database lock on or before 31-Mar-2018 (n=9118). Additionally, the MK-3475 Cumulative Safety Database (CSD) includes pembrolizumab monotherapy safety data aggregated across trials that included a pembrolizumab monotherapy arm and were submitted to a health authority prior to the database lock date of 20-Sep-2021 (n=10,997). The ASE and CSD databases were searched for PTs from the MedDRA (version 26.1): Autoimmune pericarditis, Cardiac tamponade, Immune-mediated pericarditis, Pericarditis, Pericarditis adhesive, Pericarditis constrictive, Pleuropericarditis, and Myopericarditis. • Company safety database and Eudravigilance (EVDAS) database review: Databases were queried to identify all cases including interventional study cases, noninterventional study cases and spontaneous cases involving pembrolizumab and events of pericarditis. Prior company pericarditis reviews were conducted cumulatively through 31-Jan-2018, therefore an interval review was performed 01-Feb-2018 through 31-Dec-2023 using MedDRA (version 26.1): PTs: Autoimmune pericarditis, Cardiac tamponade, Immune-mediated pericarditis, Pericarditis, Pericarditis adhesive, Pericarditis constrictive, and Pleuropericarditis. In addition, a cumulative search through 31-Dec-2023 was performed using MedDRA (version 26.1) for PT: Myopericarditis. **Case Definition** Pericarditis can be defined as inflammation of the pericardial sac, which includes the visceral and parietal pericardial layers. Pericarditis can be clinically diagnosed when ≥ 2 of following 4 criteria are present (ESC 2015 Guidelines): • Classic chest pain – sharp, pleuritic, positional (exacerbated in supine position, alleviated leaning forward) • Pericardial friction rub on auscultation • Classic EKG findings – most common is diffuse ST elevation with associated PR depression • New or worsening pericardial effusion (assessed by echocardiography, CT or cardiac MRI) Therefore, evaluation of safety data related to immune-mediated pericarditis is based on the case definition described below: Compatible clinical presentation that is not associated with alternate etiologies including malignancy (definitely excluded with pathological data, i.e., cytology), infection, recent radiation therapy and/or chemotherapy, other concurrent illness or concomitant medication.
Results	**Pre-clinical/Toxicology:** There are no specific toxicology or pre-clinical data relating to pericarditis. However, there is biological plausibility by which pembrolizumab can be associated to immune mediated events. **Epidemiology:** The overall cumulative incidence of pericarditis in ICI-treated cancer patients ranged from 0.06% to 2.2%, based on review of the published literature. One study reported a higher risk of developing pericardial disease in ICI-treated patients compared to non-ICI-treated patients. However, important limitations need to be acknowledged when interpreting findings from retrospective, observational studies. Confounding factors, such as prior cancer therapy (radiation or other systemic anti-cancer treatments) or traditional cardiovascular disease risk factors (hypertension, smoking, diabetes mellitus, and prior history of cardiovascular diseases) were common in ICI-treated patients. Additionally, some patients did not have complete echocardiogram data to confirm the diagnosis of pericarditis or only the ICD codes were used to identify patients with pericarditis. Thus, the causality between ICI treatment and pericarditis should be evaluated based on the totality of evidence.

Table 16.2.13.1 Signal Evaluation for Pericarditis

	Company Product Literature Database Review: A search was conducted for literature articles from the Company Product Literature Database to identify literature related to immune-mediated pericarditis with pembrolizumab treated patients. Through this literature search three articles were identified as articles of interest, including cases series and a pharmacovigilance study. **Aggregate Clinical Trial Data:** Search of the ASE and CSD datasets identified comparable frequencies for pericarditis events with pembrolizumab monotherapy versus comparator therapy (chemotherapy). Frequency of pericarditis-related adverse events were less than 0.25% in the aforementioned groups. **Company Safety Database Review:** A total of 275 cases were identified in the company safety database with a total of 290 events that were coded to the following PTs: Cardiac tamponade (130), Pericarditis (105), Myopericarditis (26), Immune-mediated pericarditis (9), Autoimmune pericarditis (5), Pericarditis constrictive (4), Pleuropericarditis (4), and Pericarditis adhesive (1). Among the 275 identified cases one case was determined to be a duplicate. All events were reported as serious; case categories: Spontaneous (142), Interventional (111), Non-Interventional (21); Gender: Male (157), Female (113), Not reported (4); Age range 20-92 years (median 63 years); time to onset (TTO) reported for 200 events with range of 1-1473 days (median 97 days). Of the 274 cases: 224 cases did not meet the case definition; 18 cases were confounded by alternative etiologies (positive atypical/malignant cytology (6), myocarditis (1)); 15 cases lacked the necessary information needed for medical assessment (including labs, diagnostics, cytology, or full clinical course); 7 cases in which the patients did not receive pembrolizumab; and 2 cases were confounded by use of other concomitant medications (Covid-19 vaccine, Doxorubicin). The remaining 8 cases provided details with adequate diagnostic evaluation and case history, and lack of a more plausible explanation. **Cases Identified in EVDAS Review:** The EudraVigilance Data Analysis System (EVDAS) was searched, using the strategy described previously and yielded five additional cases. Four of the five cases were confounded (septic shock, Covid-19 vaccination, acute myocardial infarction, and concomitant doxorubicin). The remaining case had inadequate information provided and did not allow for meaningful assessment. The data from the review of cases obtained from EVDAS yielded no additional information to alter the conclusions of this review. Please refer to Appendix 21.10.2.11 for further details.
Discussion	In summary, there were no toxicology or pre-clinical data related to immune-mediated pericarditis, however immune-mediated adverse events are biologically plausible with pembrolizumab use. Literature review identified an observational pharmacovigilance study and case reports of immune-mediated pericarditis with most of the anti-PD1/PD-L1 therapies including pembrolizumab. Pembrolizumab monotherapy safety data (CSD) (n=10,997) has 27 patients (0.25%) reporting pericarditis-related terms. Of the 274 cases reviewed from Global Safety database, eight cases had adequate diagnostic evaluation and case history to perform a thorough assessment. After review, these eight cases met diagnostic criteria for pericarditis, responded appropriately to corticosteroid therapy, and lacked any alterative etiology or significant clinical confounding factor, thereby fulfilling our case definition of immune-mediated pericarditis.

Table 16.2.13.1 Signal Evaluation for Pericarditis

Conclusion	Signal is confirmed. Based on the totality of the information in this review, the Company considers there is sufficient evidence to support a causal association of immune-mediated pericarditis with exposure to pembrolizumab. The MAH has updated the CCDS Warnings and Precautions section to include the risk of immune-mediated pericarditis with pembrolizumab.

16.2.14 Risk for immune-mediated adverse reactions in patients with pre-existing autoimmune disease

Table 16.2.14.1 Signal evaluation for Risk for immune-mediated adverse reactions in patients with pre-existing autoimmune disease

Source / Trigger of Signal	Health Authority Request (Swissmedic)
Background	Autoimmune disease (AID) is defined as a pathologic state in which there is an aberrant immune response directed at normal tissue leading to inflammation, cell injury, or a functional disturbance with clinical manifestations [03RCG9]. These conditions represent a relatively common and diverse set of clinical syndromes caused by the immune activation of T cells, B cells, or both, in the absence of an ongoing infection or other discernible cause. An autoimmune disease usually can be generalized or tissue- or organ-specific and either acute or chronic. This clinically heterogenous group of diseases can involve essentially any organ system and affect individuals of any age but are especially prevalent in women. [08MFXY] The PD-1 pathway, as an inhibitory signal, controls the induction and maintenance of tolerance to self-antigens in the context of autoimmunity and has been implicated in the pathogenesis of inflammatory bowel disease, systemic lupus erythematosus, Type 1 diabetes, systemic vasculitis, and others. Some patients who receive immune checkpoint inhibitors (ICIs) develop severe immune-mediated adverse events (imAEs) that mimic the presentation of autoimmune diseases [08D082]. It is believed that imAEs occur due to disruption of immunologic self-tolerance, a mechanism that also seems to explain autoimmune diseases. Activation of the immune system with ICIs also poses a potential risk of pre-existing auto-immune disease (AID) worsening/flare. As such, patients with autoimmune diseases were historically excluded from trials with ICIS, including pembrolizumab, resulting in scarcity of information in this patient population and is therefore initially classified as Missing Information in the pembrolizumab PSUR.
Method(s) of Evaluation	• Preclinical Data review • Epidemiology/Literature review of studies evaluating safety data related to patients with a medical history of autoimmune diseases with the use of an immune checkpoint inhibitors (ICIs), including PD-1, PD-L1, or CTLA-4 inhibitors. • Clinical Trial Dataset – Review of the Cumulative Safety Dataset (CSD) (n=10,997) using the PTs contained within the HLGT of autoimmune disease to identify patients who had a past medical history of autoimmune disease. Adverse Events (AEs) and Adverse Events of Special Interest (AEOSI) were reviewed and summarized for subjects who had a pre-existing autoimmune condition and compared with those in patients who did not have a history of AID. • Company Global Safety Database – Review of the company's global safety database using the HLGT term autoimmune disease cumulative to 30-JUN-2023. Then the AE profile was summarized in the identified patients. To identify the patients who had a flare of their autoimmune disease following pembrolizumab therapy, the cases were searched for the same autoimmune PTs reported as both an adverse event and medical history. In addition, verbatim terms were searched for words suggesting a flare (i.e. flare, exacerbation, aggravation, worsening, reactivation). • EVDAS was not queried due to an inability to search by a patient's medical history.

Table 16.2.14.1 Signal evaluation for Risk for immune-mediated adverse reactions in patients with pre-existing autoimmune disease

	Case definition The definition of an autoimmune disease used in this review is derived from Witebsky's postulates which include 1) the presence of an immune reaction specific to some self-antigen or self-tissue, 2) evidence that such reaction is not secondary to tissue damage but is of primary pathologic significance, and 3) the absence of another well-defined cause of the disease [08D07W].
Results	**Pre-clinical data** There is no specific toxicology or pre-clinical data relating to the risk of immune-mediated adverse reactions in patients with pre-existing autoimmune disease and pembrolizumab. **Epidemiology/Literature Review** Population-based estimates of imAE incidence in people with pre-existing AID is limited. One large, prospective study with >2,000 patients with pre-existing AID conducted in Belgium during the COVID era reported that the cumulative incidence of AID flare-ups was 39.1% before COVID vaccination (10.7% required systemic steroids) and 29.1% after COVID vaccination (5.7% needed systemic steroids), respectively. To our knowledge, the incidence of imAE in the general cancer patients with pre-existing AID is not available. Thirty-three observational studies including retrospective cohort studies and case series were identified that reported imAEs observed among patients with pre-existing AIDs who received ICI treatment. A total of 2,570 patients were included in these published studies, for whom the most common cancer types were melanoma and lung cancer. The most common pre-existing AIDs were rheumatologic, dermatologic, and endocrine AIDs. While some studies provided relevant information regarding AID symptoms and therapy at ICI initiation, it remains unclear for most studies how many patients had any active systemic AID when they received an ICI treatment, defined as having received treatment for AIDs within two years prior to the ICI initiation. The reported rates of pre-existing AID flares varied considerably by study, ranging from 7.5% to 52% based on studies with a sample size of greater than 10 patients. In one study that reported stratified results based on whether the pre-existing AID was clinically active at ICI initiation, the rates of flares were comparable between clinically active (46.7%) and inactive (47.1%) AIDs. But in another study, the rate of flares was higher in patients with active AIDs (60%) than in patients with latent AIDs (22.1%). However, the numbers of patients with active AIDs in both studies were small (< 30 patients). In a study comparing safety outcomes between combination (N=64) and monotherapy (N=69) with ICIs in patients with pre-existing AIDs [08MV73], there was no difference in the incidence rate of pre-existing AID flares (0.27 vs. 0,30 event per person-year) between the two groups. Flares of pre-existing AIDs often required treatment, some of which led to discontinuation of the ICI treatment. The incidence rates of new imAEs unrelated to pre-existing AID also highly varied across studies, ranging from 21.1% to 67% based on studies with a sample size of greater than 10 patients. Commonly reported new imAEs included dermatologic and GI toxicity, arthritis, thyroid dysfunction, and pneumonitis. A recent retrospective study included 197 patients with melanoma, genitourinary, and other cancers who received an ICI treatment between October 2014 and April 2021 and had a confirmed AID diagnosis prior to the ICI initiation. The results showed that 25.3% patients developed new imAEs after starting the ICI treatment, and patients with Hashimoto hypothyroidism and neurologic AIDs had a higher incidence of new imAEs. Another retrospective cohort study evaluated 813 patients exposed to ICI treatments, of which 8.2% had a pre-existing AID. The study did not observe a significant difference in the incidence rates of new imAE between AID group and non-AID group, suggesting that the pre-existing AID status may be not associated with enhanced toxicity in patients treated with ICIs. However, another study reported that patients with combination ICI therapy (N=64) had a significantly higher incidence rate of all-grade de novo imAEs compared to patients treated with anti-PD-1 monotherapy (N=69) (0.52 vs. 0.26 event per person-year, HR=2.27, p-value=0.002) Han et al. examined 1,822 patients who received ICI therapy for the treatment of solid tumors and identified 147 patients who had a medical history of an AID. The authors concluded that the safety and efficacy of ICIs in patients with and without autoimmune disease seems to be similar with the caveat that patients with active AID seem to have poorer outcomes. The literature suggests that the incidence of flares in oncology patients with a history of AID is between 16.7%

Table 16.2.14.1 Signal evaluation for Risk for immune-mediated adverse reactions in patients with pre-existing autoimmune disease

	to 52%. **Clinical Trial Dataset** A total of 351 patients out of 10,997 patients in the CSD had a medical history of AID. Of the 351 patients with a medical history of an autoimmune condition, the medical history most commonly (>5%) included chronic gastritis (31.1%), vitiligo (15.4%), rheumatoid arthritis (11.1%), autoimmune thyroiditis (9.1%) and type 1 diabetes mellitus (8.3%). There was a generally similar incidence of all AE categories, except for a higher incidence of grade 3-5 AEs (53.6 vs. 46.9%) in the population with autoimmune disease compared with the population without autoimmune disease. There was no clinically significant difference in the incidence of overall AEOSIs across all categories between the two groups. Additionally, the occurrence of death and discontinuation due to AEs was minimal within both groups. **Company Global Safety Database Review** A search of the Company's global safety database yielded a total of 1,699 cases with a medical history of one or more AIDs. The most frequently reported adverse events in the 1,699 patients with a medical history of AID were: malignant neoplasm progression (239 cases), diarrhoea (99 cases), fatigue (90 cases), hypothyroidism (89 cases), rheumatoid arthritis (88 cases), death (87 cases), and arthralgia (85 cases). No new safety issues or patterns were observed in these cases. Of the 1,699 cases with a medical history of one or more AIDs, 159 cases reported a flare of the AID. In 7 cases the patient experienced a flare of more than one AID, hence the number of outcomes is greater than the number of cases. Some of the symptoms of AID flare reported could also mimic symptoms of disease progression (e.g., weakness, pain, and difficulty of swallowing in the patient with tongue cancer, dyspnea and orthopnea in patient with stage III melanoma with lung metastasis, and progressive weakness in a patient with metastatic bone cancer). Please refer to Appendix 21.10.2.12 for further details.
Discussion	A review of literature and epidemiologic data showed a broad-spectrum incidence of AID flares and immune-mediated AEs in this patient population with pre-existing AID. The literature reports a wide range for the incidence of AID flares in patients receiving ICI therapy, ranging from 7.5% to 52%. The review by Han et al. concluded that 13.6% of patients experienced a flare of an AID and that no safety concerns were identified as a result of these flares. The incidence rates of new imAEs unrelated to pre-existing AID also highly varied across studies, ranging from 21.1% to 67%. A cumulative search of the clinical trial database involving 10,997 subjects identified 351 (3.2%) subjects with a medical history of an AID. It was observed that 32.5% of patients with a medical history of an AID experienced an AEOSI. A review of the AEs reported in these populations indicated that the types of events were either generally consistent with the established safety profile of pembrolizumab monotherapy or most likely related to the underlying diseases. There was no evidence suggesting any new patterns of immune mediated AEs with pembrolizumab use in patients with pre-existing AIDs. A cumulative search of the safety database identified 1,699 post-marketing cases from non-interventional trials or spontaneous reports in subjects with pre-existing AIDs. A review of the AEs and AEOSI in current available data did not provide evidence suggesting any new safety concerns. A review of the reports of worsening of pre-existing AIDs showed insufficient information in the majority of the cases precluding an assessment of the most likely etiology including nature of the flare, severity, treatment received, action taken with pembrolizumab or outcome of the flare. In the reports that provided additional case details, no pattern with regard to timing, severity, and the role of pembrolizumab could be established. This assessment had several limitations. Patients with active autoimmune diseases were historically excluded from clinical trials. The exacerbation of pre-existing AID, or flare, is not described in case narratives for non-serious cases of AID in clinical trial data as these usually do not include narratives and therefore limits clinical interpretation about events of AID flare. In addition, the status of AID (active versus latent disease) is not typically captured in the medical history. As such, patients with active AID (a population identified as missing information) are not identifiable. It is possible that a disease in a latent phase was captured as an active condition in the patient's medical history.

Table 16.2.14.1 Signal evaluation for Risk for immune-mediated adverse reactions in patients with pre-existing autoimmune disease

Conclusion	Signal was refuted. The review of the available data in patients with a history of an autoimmune disorder did not reveal new safety concerns with pembrolizumab use in this subpopulation. However, the quality of available data is not sufficient to fully characterize whether or not there are differences in the safety profile between the patient population with and without autoimmune disorders. As such the population will remain categorized as missing information in the pembrolizumab PSUR. There was no clinical information identified in our review that would warrant an update in the product information. Current labeling adequately reflects the known safety profile of pembrolizumab. The Company will continue monitoring this topic through robust routine pharmacovigilance activities.

16.2.15 Capillary Leak Syndrome

Table 16.2.15.1 Signal evaluation for Capillary Leak Syndrome

Source / Trigger of Signal	Health Authority Request (SFDA)
Background	Capillary leak syndrome (CLS) is often used to reference a constellation of pathologic manifestations associated with an increased capillary permeability to proteins that leads to hypoalbuminemia in the absence of albuminuria, as well as the leaking of plasma from the blood circulatory system to surrounding tissues, muscle, organs, or body cavities. As a result, patients develop hemoconcentration, hypotension, and segmental or generalized edema. [088MQQ] A common complication of CLS is acute kidney injury, which can occur in 28%- 62% of patients. The most classic form of CLS is represented by primary CLS, which can also be referred to as systemic CLS (SCLS), idiopathic SCLS (ISCLS), or Clarkson's disease. This rare and potentially fatal condition is characterized by recurrent, acute self-reversing episodes of capillary leak. The etiology of SCLS is unknown. It is likely that it involves a defective and reversible cellular phenomenon in the capillaries leading to albumin leak. Monoclonal Ig, predominantly of the IgG-κ type, is present in most patients with SCLS. Capillary leaks, presenting in an acute form similar to SCLS or in a more chronic form, are described in other conditions, such as sepsis, autoimmunity, hematologic diseases, after stem cell transplantation, differentiation syndrome following the treatment of acute promyelocytic leukemia, ovarian hyperstimulation syndrome, viral infections, snakebite envenomation, and adverse drug reactions. In cancer-treated patients, CLS can be related to the cancer itself (43.6%) or occur after bone marrow transplantation (4.8%) but is most frequently associated with anticancer agents (51.6%). Anticancer drug induced CLS has a variable incidence depending on the diagnostic criteria used and the specific drug studied. The median delay between start of the suspected medication and occurrence of the event of CLS was 8 days in this large study (interquartile range, 2.25-31.7). [088MQQ], [088MQT] Treatment of CLS is generally supportive. Specific treatment measures that have been reported with secondary CLS include corticosteroids, beta2 agonists, thalidomide, antihistamines, plasmapheresis, and intravenous immunoglobulin (IVIG). There have been varying degrees of efficacy reported for these agents and no clear treatment guidelines exist. The Company previously performed an assessment of CLS cumulatively through 30-JAN-2023, at the request of the European Medicines Agency's Pharmacovigilance Risk Assessment Committee (PRAC) (ema-responses-prac-recommendation-capillary-leak-syndrome, Doc ID: 087VMM). In this current assessment, the Company performed an incremental review and evaluation of safety data related to CLS and the administration of pembrolizumab from 31-JAN-2023 through 04-JUN-2024. The overall analysis is based on the totality of the data.

Table 16.2.15.1 Signal evaluation for Capillary Leak Syndrome

Method(s) of Evaluation	• Preclinical Data review • Epidemiology/ Literature for background rates of CLS in the general population and patients treated with an immune checkpoint inhibitor (ICI). A comprehensive search in Embase & Medline from 22-FEB-2023 to 24-JUN-2024 for studies evaluating CLS among patients treated with an ICI. • Clinical trial data analysis: The aggregate safety evaluation dataset (ASE), and the cumulative safety dataset (CSD) were searched using the Preferred Term (PT) of "Capillary leak syndrome" (MedDRA version 27.0). • Review of the Company global safety database from 31-JAN-2023 to 04-JUN-2024 using the PT of "Capillary leak syndrome" or 2 of the 3 key diagnostic triad PTs of "hypotension", "hypoalbuminemia", and "hemoconcentration" (MedDRA version 27.0). • Review of data available in EudraVigilance Data Analysis System (EVDAS) from 31-JAN-2023 to 04-JUN-2024 using the PT of "Capillary leak syndrome" (MedDRA version 27.0). **Case Definition** The presence of intravascular hypovolemia and/or generalized edema with a diagnostic triad of hypotension, hemoconcentration, and hypoalbuminemia as key supporting evidence, in the absence of an identifiable alternative cause. The presence of a monoclonal gammopathy supports the diagnosis, but it is not required.
Results	**Preclinical data** Based on the mechanism of action for pembrolizumab, there is biological plausibility for an immune-mediated etiology. No new information is available since the 2023 assessment. **Epidemiology/Literature Review** The epidemiology of CLS varies by etiology. Idiopathic CLS, also known as Clarkson's disease, is an exceedingly rare condition. There is no population-based incidence of idiopathic CLS available [088PCH] [088P26]. While the data on CLS with the use of ICIs in real-world settings are limited, the few available studies identified from the previous review cumulative to 21-FEB-2023 reported a rate of 0.06-0.8% based on small numbers of observed cases [088PDL], [088PWX], [085JVB]. No new observational real-world studies in the updated literature review from 22-FEB-2023 to 24-JUN-2024 were found to report CLS incidence in ICI-treated patients. **Review of aggregate data from clinical trials** A search of the ASE dataset identified no cases with the PT of "Capillary leak syndrome". The findings from the CSD revealed one case of 'CLS' (<0.01%) in which the patient developed grade 3 nonserious CLS. Therapy with pembrolizumab continued and the outcome of the AE was reported as resolved. **Review of data from the Company global safety database** A total of 6 individual case safety reports containing 6 events were identified from the Company's global safety database from 31-JAN-2023 through 04-JUN-2024 utilizing the PT "capillary leak syndrome"; there were no reports identified that had at least 2 of 3 of the key diagnostic triad PTs. Upon comprehensive review of these 6 cases, 2 cases lacked sufficient information to make a meaningful medical assessment, 1 case was confounded by a concomitant IL-2A agent, and 1 case failed to provide sufficient evidence to support CLS diagnosis and rule out alternative causes, e.g., infection, which was the cause of patient's death. The remaining 2 cases met the case definition for CLS, however both cases lacked sufficient diagnostic work-up to reasonably rule out confounding factors or alternate etiologies. Moreover, in one of the two cases, the patient had recurring CLS after the discontinuation of pembrolizumab, which could point towards a possibility of an etiology alternative to immune-mediated CLS. The additional search and review of follow-up information received for the previously reviewed cases for the period through 30-JAN-2023 did not identify new medically significant information and did not alter the disposition of these cases. There were 2 cases that received updates after the prior review to either contain the PT of "capillary leak syndrome" or meet at least 2 of the 3 diagnostic criteria for CLS. Both cases were confounded by the concomitant use of an IL-2 agent, and progression of underlying malignancy which was more likely the cause for the patient's

Table 16.2.15.1 Signal evaluation for Capillary Leak Syndrome

	presentation with hypotension and hypoalbuminemia, respectively. **Search of the EVDAS database** The data from the review of EVDAS yielded no additional information to alter the conclusion of this review. A total of 6 cases were identified, and all 6 cases were included in the Company global safety database review. Please refer to Appendix 21.10.2.13 for further details
Discussion	CLS is a rare and potentially life-threatening disorder. CLS can occur idiopathically or secondary to a variety of causes, including anticancer drugs. The pathophysiology behind drug induced CLS is not fully understood and could be different than that of idiopathic. No standard of care in regard to specific treatment for drug induced CLS currently exists. Multiple potential causes of CLS have been reported. Based on the mechanism of action for pembrolizumab, there is biological plausibility for an immune-mediated etiology. The limited data available for studies of CLS with the use of ICIs in real-world settings reported a rate of 0.06-0.8%. Review of the pembrolizumab clinical trial data identified a single case of CLS (<0.01%) in patients receiving pembrolizumab. The interval review of literature up to 24-JUN-2024 yielded no new information regarding CLS and pembrolizumab. The interval review of the global safety database revealed no compelling evidence for a causal relationship between pembrolizumab exposure and CLS. A review of EVDAS did not contribute any new information. In summary, taking totality of data into consideration (including data assessed in prior PRAC assessment and the interval review since last data cut through 04-JUN-2024), all cases identified from company global safety database either lacked sufficient information for diagnosing potential drug induced CLS, suggested clear alternative etiology, or had a strong confounding factor based on medical assessment.
Conclusion	Signal was refuted. Based on the totality of the information reviewed and presented above, the Company considers that there is not sufficient evidence to support a causal association of CLS with exposure to pembrolizumab and an update to the product label is not warranted at this time. The Company will continue to monitor CLS temporally associated with pembrolizumab exposure through routine pharmacovigilance activity.

16.2.16 Evaluating immune-mediated adverse events in infants following in utero exposure to pembrolizumab to check the appropriateness of current labeling/risk minimization measures

Table 16.2.16.1 Signal evaluation for immune-mediated adverse events in infants following in utero exposure to pembrolizumab to check the appropriateness of current labeling/risk minimization measures

Source / Trigger of Signal	Health Authority Request (PRAC)
Background	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. Human IgG4 (immunoglobulin) is known to cross the placental barrier and pembrolizumab is an IgG4. Based on pembrolizumab mechanism of action and its ability to cross the placenta barrier, there is potential risk to the fetus. Thus, pregnant women are excluded from all pembrolizumab clinical trials. The CCDS states that its use in the marketed setting is “not recommended during pregnancy unless the clinical benefit outweighs the potential risk to the fetus”. The EU SmPC states that "women of childbearing potential should use effective contraception during treatment with pembrolizumab and for at least 4 months after the last dose of pembrolizumab”, and “pembrolizumab should not be used during pregnancy unless the clinical condition of the woman requires treatment with pembrolizumab.” The Company performed a review and evaluation of safety data related to immune-mediated adverse events (irAEs) in infants following in utero exposure to pembrolizumab. The review is based on a request by PRAC: “Within future PSURs, the MAH should provide a cumulative review of all immune-mediated adverse events in infants following in utero exposure to pembrolizumab.” This signal evaluation examined the available information on irAEs following in utero exposure to pembrolizumab to determine if current risk minimization measures are adequate. As part of a PRAC assessment report, in PSUR #12 (04-Sep-2022 to 03-Sep-2023), the MAH was asked to discuss new information regarding the populations categorized as missing information in the summary of safety concerns. This included reproductive and lactation data. The conclusion was that the reproductive and lactating subpopulation will remain as missing information and be monitored through routine pharmacovigilance activities. Please refer to Appendix 21.10.2.14 for further details

Method(s) of Evaluation	• Preclinical Data Review
	• Epidemiology/Literature Review:
	  ○ A literature review of Medline database was conducted cumulative to 15-JUL-2024 for studies evaluating irAEs among infants following in utero exposure to pembrolizumab.
	• Evaluation of safety data related to irAEs in infants are based on the following case definition:
	  • Any immune-mediated adverse events in infants following in utero exposure to pembrolizumab. Infant is defined as ≤ 1 year of age.
	Review of the topic includes the following:
	• Cumulative examination of the Company global safety database to identify all cases including interventional study serious cases, noninterventional study cases, and spontaneous cases involving pembrolizumab and immune-related adverse events in patients less than or equal to one year of age using MedDRA version 27.0 through 15JUL2024.
	• Review of data available in EudraVigilance Data Analysis System (EVDAS): Cumulative search of the EVDAS database for cases involving pembrolizumab and immune-related adverse events in patients less than or equal to one year of age using MedDRA version 27.0 through 15JUL2024.
	
	Please refer to Appendix 21.10.2.14 for further details

Table 16.2.16.1 Signal evaluation for immune-mediated adverse events in infants following in utero exposure to pembrolizumab to check the appropriateness of current labeling/risk minimization measures

Results	**Literature** There are limited number of studies identified investigating the rate of irAEs among infants following in utero exposure to pembrolizumab or other ICI treatments. Two pharmacovigilance studies utilized the World Health Organization's VigiBase, a global database of adverse event reports of medicines and vaccines, to identify reported maternal, fetal, or newborn adverse outcomes following ICI treatment during pregnancy [08NC4R] [08N6RB]. Two additional reviews of the published literature and studies from the FDA Adverse Events Reporting System Public Dashboard described infant outcomes after in utero exposure to ICIs [08CSWN] [08NC53]; the only reported irAE cited in each review was a case report describing hypothyroidism in a newborn after first trimester nivolumab exposure [08NC58]. Thyroid replacement therapy was then administered at 50/25 µg on alternate days, and the infant met all developmental milestones at the 6-month follow-up. Routine monitoring had been planned to evaluate hormonal and immunological function. The MAH reviewed this case as part of its review of the Company's Global Safety Database described below as case [redacted] [08N4MT]. A recently published literature case report identified a case of necrotizing enterocolitis occurring following in utero exposure to pembrolizumab [08N6RF] [08NBTK] [08NBTR]. While the event is complicated with Klebsiella infection, the possible causal relationship between in-utero exposure of pembrolizumab and enterocolitis cannot be excluded. This case report further referenced three other case reports of in utero exposure to pembrolizumab, one of which reported an adverse event [08KJSJ]. This referenced event is discussed below as part of our review of the Company's Global Safety Database. **Company Global Safety Database Review** From the total of 53 identified cases, 44 cases did not meet the case definition for in utero exposure to pembrolizumab in an infant patient less than or equal to one year of age. Of the 44 cases, 30 cases did not report both patient age and in utero exposure, 13 cases reported infant patient age but did not report in utero exposure and 1 case reported paternal in utero-exposure; however, the case did not result in a live birth due to an elective abortion. Of the remaining 9 cases (all following maternal exposure) that met the case definition, 5 cases had an AE suggestive of an irAE while 4 cases had events not related to an irAE. Of the five cases suggestive of an irAE in infants (age <=1 year) and having history of in utero pembrolizumab exposure, all were serious and only two cases had adequate information for detailed review [08N4MT]: • [redacted]: This is the spontaneous report of a 3-day-old [redacted] child. The mother has a past medical history significant for tobacco use and was found to have triple negative breast cancer, which was initially treated with a lumpectomy. Also in the same year, the child's mother started pembrolizumab 200 mg IV Q3W in addition to paclitaxel and carboplatin (dose, route and frequency not provided). Carboplatin was discontinued approximately 1 month later due to an unspecified hematological malignancy. The mother was amenorrheic and found that she was 23.6 weeks pregnant and further treatment with pembrolizumab was not continued. The mother had received 6 cycles of pembrolizumab during the first and second trimester. The course of the pregnancy was unremarkable, and the infant patient was born at 37 weeks and 6 days by planned Cesarian-section. At birth, the infant patient weighed 3690 grams and their physical exam was unremarkable. Three days following birth, the infant patient was found to have hypothyroidism. Laboratory values demonstrated low free T3 (2.1 pmol/L), low free T4 (5.1 pmol/L) and high TSH (>100,000 mIU/L), negative anti-TPO, anti-thyroglobin, anti-TSH receptor antibodies. Thyroid ultrasound demonstrated normal size thyroid with normal vascularization. Thyroid scintigraphy demonstrated absence of fixation in the thyroid compartment or ectopic fixation. The infant patient was treated with L-thyroxine with gradual normalization of laboratory values. At the time of reporting, the infant patient had not recovered from hypothyroidism. • [redacted]: This is the literature case of a 3-month-old [redacted] with immune-related enterocolitis. The patient's mother is a 26-year-old female who was diagnosed on an unknown date with stage IIIB superficial spreading melanoma on

Table 16.2.16.1 Signal evaluation for immune-mediated adverse events in infants following in utero exposure to pembrolizumab to check the appropriateness of current labeling/risk minimization measures

	the right thigh. After excision and lymph node dissection, an ultrasound revealed that the mother was 9 weeks pregnant. At 16 weeks gestation, it was decided by the multidisciplinary team that the clinical benefit to the mother outweighed the potential risk to the fetus and the mother started pembrolizumab 400 mg IV Q6 weeks. At 37 weeks gestation and three weeks since the last pembrolizumab administration, due to maternal cholestasis, labor was induced and resulted in a healthy, 3300 gram [redacted] via uncomplicated vaginal delivery. Up until the age of 4 months the developmental milestones were reached, and the infant was in good health. It is not noted whether the mother was breastfeeding or not. At 4 months of age, the infant patient developed watery diarrhea, decreased oral intake and vomiting. After ruling out cow's milk allergy, infant patient was started on total parenteral nutrition (TPN). The infant patient was found to be Covid positive. The infant patient developed hypoalbuminemia and hypogammaglobulinemia. An upper and lower endoscopy demonstrated hyperemic mucosa in the stomach and colon. The infant patient was found to have a positive anti-Harmonin but negative FOXP3 genetic mutation testing. Histological analysis demonstrated total villous atrophy, chronic inflammation, and increased apoptosis in the duodenal crypts without loss of goblet or Panneth cells. Blood sample analysis demonstrated a hyperactivated phenotype of the CD4+ and CD8+ cells. The serum concentration of pembrolizumab in the infant patient at 16.5 weeks of age was 0.5 ng/ml. The infant patient was started on prednisolone 2 mg/kg with subsequent tapering, followed by infliximab 5 mg/kg on weeks 0, 2, and 6 and azathioprine. Ten weeks after admission, the infant patient was discharged on continued therapy with complete enteral feeding and normal weight gain. After three doses of infliximab, T-cell activation was normalized, and duodenal mucosa showed only partial villous atrophy. Gastric mucosa was normalized without evidence of inflammation on an endoscopy at 2 years. The investigator considered the event to be recovering. **EVDAS:** The data from the review of EVDAS yielded no additional information to alter the conclusions of this review. Please refer to Appendix 21.10.2.14 for further details
Discussion	A review of the medical literature discussing irAEs following in-utero exposure to any ICI identified two pharmacovigilance studies that queried the WHO Vigibase. The authors concluded that no pattern of specific fetal/neonatal irAEs could be ascertained from the available data. There was one recently published case report identified of necrotizing enterocolitis where the possible role of in-utero pembrolizumab exposure cannot be ruled out. A review of our Company's Global Safety Database identified 53 ICSRs in infants of which 9 cases met the case definition. Following medical review, there were two well-documented reports of irAEs following in-utero exposure to pembrolizumab. In both cases, one case of congenital hypothyroidism and the other case of ir-enterocolitis, the possible role of in-utero pembrolizumab exposure cannot be ruled out. Based on pembrolizumab mechanism of action and its ability to cross the placenta barrier, the potential to cause fetal harm is clearly stated in pembrolizumab's labeling documents. The current language in the pembrolizumab label states that pembrolizumab is "not recommended during pregnancy unless the clinical benefit outweighs the potential risk to the fetus." In addition, female patients who are of childbearing age are recommended to use "effective contraception during treatment with pembrolizumab and for at least 4 months after the last dose of pembrolizumab." As of 03-Mar-2024 there was a total of 70,323 patients treated with pembrolizumab in the Company sponsored clinical trial program and approximately 1,324,801 patient years of exposure to pembrolizumab in the post marketing setting. The very low number of cases of infants with in-utero exposure shows that the current risk minimization measures (labeling information) are sufficient to manage the risk.

Table 16.2.16.1 Signal evaluation for immune-mediated adverse events in infants following in utero exposure to pembrolizumab to check the appropriateness of current labeling/risk minimization measures

	Please refer to Appendix 21.10.2.14 for further details.
Conclusion	Signal refuted Based on the totality of data, the possibility of irAEs in infants following in-utero exposure cannot be ruled out. Based on available data reviewed in this assessment, the Company considers the current risk minimization measures (labeling) to be sufficient. No update to the pembrolizumab label is currently required. The Company will continue to monitor irAEs in infants following in-utero exposure through routine pharmacovigilance activities

16.3 Evaluation of Risks and New Information

NEW INFORMATION ON KNOWN RISKS AND MISSING INFORMATION

The MAH has an established process for continuous monitoring of new safety information for our Company's products. Clinically relevant new information relating to previously recognized identified risks/potential risks and missing information is detailed in section 16.2 (if the new information constituted a "signal" and that "signal" was closed during the reporting interval) and in this section, below (other new information).

During the reporting period of this PSUR, the signals of autoimmune haemolytic anemia, pancreatic failure/exocrine pancreatic insufficiency and pericarditis were confirmed and added to the known identified risks of pembrolizumab under "other immune mediated adverse events" to further characterize the risk profile of pembrolizumab and are detailed in Section 16.2

Hemolytic anemia, exocrine pancreatic insufficiency and pericarditis were added to the Warnings and Precautions section of the CCDS of pembrolizumab under "other immune-mediated adverse reactions".

16.4 Characterization of Risks

During the reporting period of this PSUR, exocrine pancreatic insufficiency, hemolytic anemia, and pericarditis were added to the known identified risks of pembrolizumab under "other immune-mediated adverse effects" to further characterize the risk profile of pembrolizumab.

During the reporting period of this PSUR, safety related updates were added to the CCSI for pembrolizumab to further characterize the known (identified/potential) risks (refer to CCSI update table in section 4). Evaluation of information received during the PSUR reporting interval relating to the known important (identified/potential) risks and missing information of pembrolizumab has identified clinically relevant new safety information for the important identified risks. The characterization of the safety concerns has been updated accordingly.

The product-specific safety concerns (important identified and potential risks, and missing information) at the end of the PSUR reporting interval are tabulated in Table 16.4.1.

Table 16.4.1 Summary of Safety Concerns (End of the Reporting Interval)

Important identified risks	• Immune-Mediated Adverse Reactions
	  • Immune-Mediated pneumonitis*
	  • Immune-Mediated colitis
	  • Immune-Mediated hepatitis
	  • Immune-Mediated nephritis
	  • Immune-Mediated endocrinopathies
	  ▪ Hypophysitis (including hypopituitarism))
	  ▪ Thyroid Disorder (hypothyroidism, hyperthyroidism, thyroiditis)
	  ▪ Type 1 diabetes mellitus
	  ▪ Adrenal insufficiency (primary and secondary)
	  • Severe skin reactions, including Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN)
	  • Other Immune-Mediated Adverse Reactions
	  ▪ Uveitis
	  ▪ Myositis
	  ▪ Guillain-Barre Syndrome
	  ▪ Pancreatitis
	  ▪ Myocarditis
	  ▪ Solid organ transplant rejection following pembrolizumab treatment in donor organ recipients
	  ▪ Encephalitis
	  ▪ Sarcoidosis
	  ▪ Myasthenic Syndrome
	  ▪ Myelitis
	  ▪ Vasculitis
	  ▪ Sclerosing cholangitis
	  ▪ Hypoparathyroidism
	  ▪ Gastritis
	  ▪ Exocrine pancreatic insufficiency
	  ▪ Hemolytic Anemia
	  ▪ Pericarditis
	  • Infusion-Related Reactions

Important potential risks	• Immune-Mediated Adverse Events
	  • 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	• Safety in patients with severe hepatic impairment • Safety in patients with severe renal impairment • Safety in patients with active systemic autoimmune disease • Safety in patients with HIV • Reproductive and lactation data • Potential pharmacodynamic interaction with systemic immunosuppressants
*Safety concern is also included in the Core RMP	

Detailed information characterizing the Important Identified and Potential Risks and Missing Information is provided in Appendix 21.10.1.

The characterization of the risk profile of pembrolizumab is presented based on four data sets (n=2799), the melanoma and NSCLC patient populations in KN00l, 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 (RSD) for pembrolizumab. The RSD serves as the locked dataset for the characterization of each risk associated with pembrolizumab and is presented in tabular format.

16.5 Effectiveness of Risk Minimization (if applicable)

No new information regarding the effectiveness of risk minimization activities relevant to the benefit-risk assessment were received during the PSUR reporting interval.