16 December 2021
EMA/33031/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Keytruda

International non-proprietary name: pembrolizumab

Procedure No. EMEA/H/C/003820/II/0108

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
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Table of contents

List of abbreviations

ADA	antidrug antibodies
ApaT	all participants as treated
BICR	blinded independent central review
cHL	classic Hodgkin lymphoma
CI	confidence interval
COVID-19	Coronavirus disease caused by severe acute respiratory syndrome
CPS	combined positive score
CSR	clinical study report
CT	computed tomography
DFS	disease-free survival
DRSS	disease recurrence-specific survival
ECOG PS	Eastern Cooperative Oncology Group performance status
EDR	early discrepancy rate
EFS	event-free survival
eDMC	external Data Monitoring Committee
EORTC QLQ-C30	European Organization for the Research and Treatment of Cancer Quality of life Questionnaire Core 30
EQ-5D-5L	EuroQoL 5 Dimensions 5 Levels
E-R	exposure-response
ESMO	European Society of Medical Oncology
FKSI-DRS	Functional Assessment of Cancer Therapy Kidney Symptom index – Disease-related Symptoms
GC	gastric carcinoma
HCC	hepatocellular carcinoma
HR	hazard ratio
HNSCC	head and neck squamous cell carcinoma
IA1	first interim analysis
ITT	intent-to-treat
KM	Kaplan-Meier
LDR	late discrepancy rate
MRI	magnetic resonance imaging
MSI-H	microsatellite instability-high
NCCN	National Comprehensive Cancer Network

NED	no evidence of disease
OS	overall survival
PD-1	programmed cell death 1
PD-L1	programmed cell death ligand 1
PFS2	progression-free survival 2
PK	pharmacokinetic
PMBCL	primary mediastinal large B-cell lymphoma
PRO	patient-reported outcome
Q2W/Q3W/Q6W	every 2/3/6 weeks
QoL	quality of life
RCC	renal cell carcinoma
sSAP	supplemental statistical analysis plan
UC	urothelial carcinoma
US	United States
VEGF	vascular endothelial growth factor
VEGFR	vascular endothelial growth factor receptor

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Merck Sharp & Dohme B.V. submitted to the European Medicines Agency on 25 June 2021 an application for a variation.

The following variation was requested:

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

Update of sections 4.1, 4.2 and 5.1 of the SmPC in order to extend the existing therapeutic indications for Keytruda to include the adjuvant treatment in monotherapy of adults with renal cell carcinoma (RCC) at intermediate-high or high risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions. The Package Leaflet are updated accordingly. The RMP version 35.1 has also been submitted

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

Information on paediatric requirements

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

At the time of submission of the application, the PIP (EMEA-001474-PIP01-13-M01) covering the condition 'Treatment of all conditions included in the category of malignant neoplasms (except nervous system, haematopoietic and lymphoid tissue) was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

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

Derogation(s) of market exclusivity

NA

Scientific advice

The Applicant consulted CHMP on the clinical development program for adjuvant RCC (EMEA/H/SA/2437/16/2016/II).

1.2. Steps taken for the assessment of the product

The Co-Rapporteur appointed by the CHMP was:

Co-Rapporteur: Jan Mueller-Berghaus

Timetable	Actual dates
Submission date	25 June 2021
Start of procedure:	17 July 2021
CHMP Co-Rapporteur Assessment Report	13 September 2021
CHMP Rapporteur Assessment Report (comments)	10 October 2021
PRAC Rapporteur Assessment Report	14 September 2021
PRAC Outcome	30 September 2021
CHMP members comments	04 October 2021
Updated CHMP Rapporteur(s) (Joint) Assessment Report	07 October 2021
Request for supplementary information (RSI)	14 October 2021
CHMP Co-Rapporteur Assessment Report	22 November 2021
PRAC Rapporteur Assessment Report	23 November 2021
PRAC members comments	n/a
Updated PRAC Rapporteur Assessment Report	n/a
PRAC Outcome	02 December 2021
CHMP members comments	06 December 2021
Updated CHMP Rapporteur Assessment Report	09 December 2021
Opinion	16 December 2021

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

This application concerns an extension of indication for pembrolizumab (Keytruda) to include the adjuvant treatment in monotherapy of adults with renal cell carcinoma (RCC) at intermediate-high or high risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions.

Disease or condition, Epidemiology, Biological Feature

Renal cell carcinoma (RCC) represents the sixth most common cancer in men and the eighth most common cancer in women, accounting for 3%-4% of all adult malignancies in the US (Siegel et al. CA A Cancer J Clin. 2019). In 2020, an estimated 138,611 new cases of kidney cancer were expected to be

diagnosed in Europe with approximately 54,054 people expected to die from the disease (GLOBOCAN, 2020).

Well-known risk factors for RCC are cigarette smoking, obesity and hypertension (Chow et al. 2010).

Renal cell carcinoma generally resists both traditional chemotherapy and radiation therapy. Surgical resection can be curative for patients presenting with localized disease. However, one third of patients present with regional or distant metastases and the 5-year survival rate for metastatic disease is approximately 12%. Of patients with localized RCC treated with nephrectomy with curative intent, approximately one quarter relapse at distant sites. The prognosis in these cases is poor (Choueiri and Motzer 2017). Advanced RCC entails both locally advanced disease that is not amenable to local therapy, i.e. curative surgery or radiation therapy, as well as metastatic disease. Advanced RCC thus requires systemic treatment. There are currently no approved adjuvant treatments for RCC and observation remains the standard of care after nephrectomy.

State the claimed therapeutic indication

The proposed new indication for Keytruda in this procedure is:

"KEYTRUDA as monotherapy is indicated for the adjuvant treatment of adults with RCC at intermediate-high or high-risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions."

Management

Patients diagnosed with renal cancer are usually managed with nephron-sparing or total nephrectomy. However, a significant percentage of patients will develop recurrent disease and eventually die of RCC. Most patients with intermediate-high or high-risk lesions will experience recurrence within 2 to 3 years following surgery. These patients have a higher incidence of metastasis at the time of disease recurrence. The estimated 5-year survival of patients with localized low-, intermediate-, and high-risk RCC is approximately 92%, 67%, and 44% (respectively), and decreases to 12% in metastatic RCC patients.

Currently, there is no globally accepted standard of care in adjuvant RCC, including patients with resected metastatic disease (M1 NED). NCCN and ESMO guidelines recommend a clinical trial as an alternative adjuvant option, while post-nephrectomy surveillance (category 2A) and adjuvant sunitinib (category 3) are also recommended in the 2021 NCCN guidelines. The EMA, however, has not approved adjuvant therapy with sunitinib. Therefore, novel treatments in the adjuvant setting are needed to prevent disease recurrence in patients with RCC at intermediate-high or high risk of recurrence.

2.1.2. About the product

Pembrolizumab is a humanized monoclonal antibody (mAb) of the IgG4/kappa isotype designed to inhibit the interaction between PD-1 and its ligands, PD-L1 and PD-L2. This blockade enhances functional activity of the target lymphocytes to facilitate tumor regression and, ultimately, immune rejection.

Currently, Keytruda is approved in the EU (SmPC Keytruda):

- as monotherapy is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults.
- as monotherapy is indicated for the adjuvant treatment of adults with Stage III melanoma and lymph node involvement who have undergone complete resection.
- as monotherapy is indicated for the first line treatment of metastatic non-small cell lung

carcinoma in adults whose tumours express PD L1 with a ⩾ 50% tumour proportion score (TPS) with no EGFR or ALK positive tumour mutations.

- in combination with pemetrexed and platinum chemotherapy, is indicated for the first line treatment of metastatic non squamous non-small cell lung carcinoma in adults whose tumours have no EGFR or ALK positive mutations.
- in combination with carboplatin and either paclitaxel or nab paclitaxel, is indicated for the first line treatment of metastatic squamous non-small cell lung carcinoma in adults.
- as monotherapy is indicated for the treatment of locally advanced or metastatic non-small cell lung carcinoma in adults whose tumours express PD L1 with a ⩾ 1% TPS and who have received at least one prior chemotherapy regimen. Patients with EGFR or ALK positive tumour mutations should also have received targeted therapy before receiving KEYTRUDA.
- as monotherapy is indicated for the treatment of adult and paediatric patients aged 3 years and older with relapsed or refractory classical Hodgkin lymphoma who have failed autologous stem cell transplant (ASCT) or following at least two prior therapies when ASCT is not a treatment option.
- as monotherapy is indicated for the treatment of locally advanced or metastatic urothelial carcinoma
- as monotherapy is indicated for the treatment of locally advanced or metastatic urothelial carcinoma in adults who are not eligible for cisplatin containing chemotherapy and whose tumours express PD L1 with a combined positive score (CPS) ⩾ 10.
- as monotherapy or in combination with platinum and 5 fluorouracil (5 FU) chemotherapy, is indicated for the first line treatment of metastatic or unresectable recurrent head and neck squamous cell carcinoma in adults whose tumours express PD L1 with a CPS ⩾1.
- as monotherapy is indicated for the treatment of recurrent or metastatic head and neck squamous cell carcinoma in adults whose tumours express PD L1 with a ⩾ 50% TPS and progressing on or after platinum containing chemotherapy.
- in combination with axitinib, is indicated for the first line treatment of advanced renal cell carcinoma in adults.
- in combination with lenvatinib first line treatment of adults with advanced renal cell carcinoma (RCC)
- as monotherapy is indicated for the first line treatment of metastatic microsatellite instability high (MSI H) or mismatch repair deficient (dMMR) colorectal cancer in adults.
- in combination with platinum and fluoropyrimidine based chemotherapy, is indicated for the first-line treatment of locally advanced unresectable or metastatic carcinoma of the oesophagus or HER-2 negative gastroesophageal junction adenocarcinoma in adults whose tumours express PD-L1 with a CPS ⩾ 10.
- in combination with chemotherapy, is indicated for the treatment of locally recurrent unresectable or metastatic triple-negative breast cancer in adults whose tumours express PD-L1 with a CPS ⩾ 10 and who have not received prior chemotherapy for metastatic disease
- in combination with lenvatinib, is indicated for the treatment of advanced or recurrent endometrial carcinoma in adults who have disease progression on or following prior treatment with a platinum-containing therapy in any setting and who are not candidates for curative surgery or radiation

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

Scientific Advice was sought from CHMP on the adequacy of the design and statistical analysis of a

phase 3 study to support the proposed indication. The overall design and statistical plan of the pivotal study for the adjuvant treatment of RCC (KEYNOTE-564) were generally agreed to. As part of the discussion, it was noted that the proposed eligibility criteria were considered to result in a heterogeneous patient population with regard to prognosis and risk of relapse due to inclusion of M1 NED patients, and that data to support a filing should be sufficiently mature.

2.1.4. General comments on compliance with GCP

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

2.2. Non-clinical aspects

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

2.2.1. Ecotoxicity/environmental risk assessment

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

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

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

- Tabular overview of clinical studies

Table 1 Overview of the KEYTRUDA RCC Clinical Development Program

Study Number Status NCT Number	**Design**	**Population**	**Dosage Regimen**	**Primary Endpoint(s)**
KEYNOTE-035 (Study A4061079) Completed NCT02133742	Phase 1b, open-label, dose-finding study to evaluate the safety, pharmacokinetics, and pharmacodynamics of axitinib in combination with pembrolizumab	Participants with previously untreated advanced ccRCC	Dose-finding: Axitinib: 5 mg BID[a] + pembrolizumab 2 mg/kg Q3W Dose Expansion Axitinib 5 mg BID[b] + pembrolizumab 2 mg/kg Q3W	Determination of MTD for axitinib Safety

Study Number Status NCT Number	Design	Population	Dosage Regimen	Primary Endpoint(s)
KEYNOTE-146 Ongoing; closed to enrollment NCT02501096	Phase 1b/2, open-label, multicenter study to evaluate pembrolizumab and lenvatinib in selected solid tumors	Phase 1b: Participants with predominantly ccRCC who have progressed after treatment with approved therapies or for which there are no standard therapies available Phase 2: Participants with predominantly ccRCC who have received up to 2 lines of systemic therapy	Cohort 2 (RCC): Phase 1b: Pembrolizumab 200 mg Q3W + lenvatinib 24 mg/day[c] Phase 2: Pembrolizumab 200 mg Q3W + lenvatinib 20 mg/day[d]	Determination of MTD (Phase 1b) ORR using irRECIST at Week 24
KEYNOTE-426 Ongoing; closed for enrollment NCT02853331	Phase 3, open-label, multicenter, global study to evaluate the efficacy and safety of pembrolizumab in combination with axitinib versus sunitinib monotherapy	Treatment-naïve participants with advanced ccRCC	Arm 1: Pembrolizumab 200 mg Q3W + axitinib 5 mg BID Arm 2: Sunitinib 50 mg QD; 4 weeks on and 2 weeks off	PFS, OS
KEYNOTE-427 Ongoing; closed for enrollment NCT02853344	Phase 2, open-label, multicenter, global study to evaluate the efficacy and safety of pembrolizumab in locally advanced/metastatic RCC	Treatment-naïve participants with advanced ccRCC (Cohort A) or nccRCC (Cohort B)	Pembrolizumab 200 mg Q3W	ORR
KEYNOTE-564 Ongoing; closed to enrollment NCT03142334	Phase 3, randomized, double-blind, placebo-controlled, multicenter, global study to evaluate the efficacy and safety of pembrolizumab as adjuvant treatment post nephrectomy	Participants with RCC at intermediate-high risk or high risk of recurrence following nephrectomy or following nephrectomy and resection of metastatic disease	Arm 1: Pembrolizumab 200 mg Q3W Arm 2: Placebo (normal saline) Q3W	DFS
KEYNOTE-581 Ongoing; closed to enrollment NCT02811861	Phase 3, open-label, multicenter, global study to evaluate the efficacy and safety of lenvatinib + pembrolizumab or lenvatinib + everolimus versus sunitinib	Treatment-naïve participants with advanced ccRCC	Arm A: lenvatinib 18 mg QD + everolimus 5 mg QD Arm B: lenvatinib 20 mg QD + pembrolizumab 200 mg Q3W Arm C: Sunitinib 50 mg QD; 4 weeks on and 2 weeks off	PFS
KEYNOTE-679	Phase 3, randomized, open-	Participants with	Group 1: Pembrolizumab	ORR

Study Number Status NCT Number	Design	Population	Dosage Regimen	Primary Endpoint(s)
Ongoing, enrollment terminated NCT03260894	label, parallel-group study to evaluate the efficacy and safety of pembrolizumab plus epacadostat compared with sunitinib or pazopanib	locally advanced/metastatic ccRCC who have not received prior systemic therapy	200 mg Q3W + epacadostat 100 mg BID Group 2: Sunitinib 50 mg QD; 4 weeks on and 2 weeks off or pazopanib 800 mg QD	
MK-3475-U03A Ongoing NCT04626479	Phase 1b/2 parallel, rolling-arm study of immune and targeted combination therapies	Treatment-naïve participants with advanced ccRCC	Arm 1: MK-1308A (coformulation of 25 mg of MK-1308 and 400 mg of pembrolizumab) Q6W and 20 mg of lenvatinib QD Arm 2: MK-4280A (coformulation of 800 mg MK-4280 and 200 mg of pembrolizumab) Q3W and 20 mg of lenvatinib QD Arm 4: 120 mg of belzutifan QD, 400 mg of pembrolizumab Q6W, and 20 mg lenvatinib QD Reference arm: 400 mg of pembrolizumab Q6W and 20 mg lenvatinib QD	DLTs, AEs, discontinuations of treatment due to AEs, ORR
MK-3475-U03B Ongoing NCT04626518	Phase 1b/2 parallel, rolling-arm study of immune and targeted combination therapies	Participants who experienced disease progression on or after receiving systemic treatment for advanced disease with PD-(L)1 checkpoint inhibitors and a VEGF-TKI (2L+ RCC)	Arm 1: MK-1308A (coformulation of 25 mg of MK-1308 and 400 mg of pembrolizumab) Q6W Arm 2: MK-4280A (coformulation of 800 mg MK-4280 and 200 mg of pembrolizumab) Q3W Arm 3: 800 mg of MK-4830 and 200 mg of pembrolizumab Q3W Arm 4: 120 mg of belzutifan QD and 400 mg of pembrolizumab Q6W Arm 5: 120 mg of belzutifan QD and 20 mg of lenvatinib QD Reference arm: 400 mg of pembrolizumab Q6W and 20 mg lenvatinib QD	DLTs, AEs, discontinuations of treatment due to AEs, ORR

Study Number Status NCT Number	Design	Population	Dosage Regimen	Primary Endpoint(s)
2L=second-line; AE=adverse event; BID=twice daily; cc=clear cell; DFS=disease-free survival; DLT=dose-limiting toxicity; irRECIST=immune-related Response Evaluation Criteria for Solid Tumors; MTD=maximum tolerated dose; ncc=nonclear cell; ORR=objective response rate; OS=overall survival; PD-(L)1=programmed cell death (ligand) 1; PFS=progression-free survival; Q3W=every 3 weeks; Q6W=every 6 weeks; QD=once daily; RCC=renal cell carcinoma; TKI=tyrosine kinase inhibitor; VEGF=vascular endothelial growth factor. [a] The starting dose of axitinib was 5 mg but could be reduced based on dose-limiting toxicities. [b] The MTD was determined to be 5 mg BID. [c] Phase 1b was a dose-finding phase to determine the MTD. The starting dose of lenvatinib was 24 mg but could be reduced based on dose-limiting toxicities. [d] The MTD was determined to be 20 mg/day.				

2.3.2. Clinical Pharmacology

No new pharmacology data were submitted in support of this application.

2.3.3. Discussion and Conclusions on clinical pharmacology

No additional data have been provided with this submission which is considered acceptable as the clinical pharmacology properties of pembrolizumab were described in detail in the original marketing application and previous supplemental applications with new clinical data are consistent with results in the original marketing application. Available clinical pharmacology data are considered sufficient to support this application

2.4. Clinical efficacy

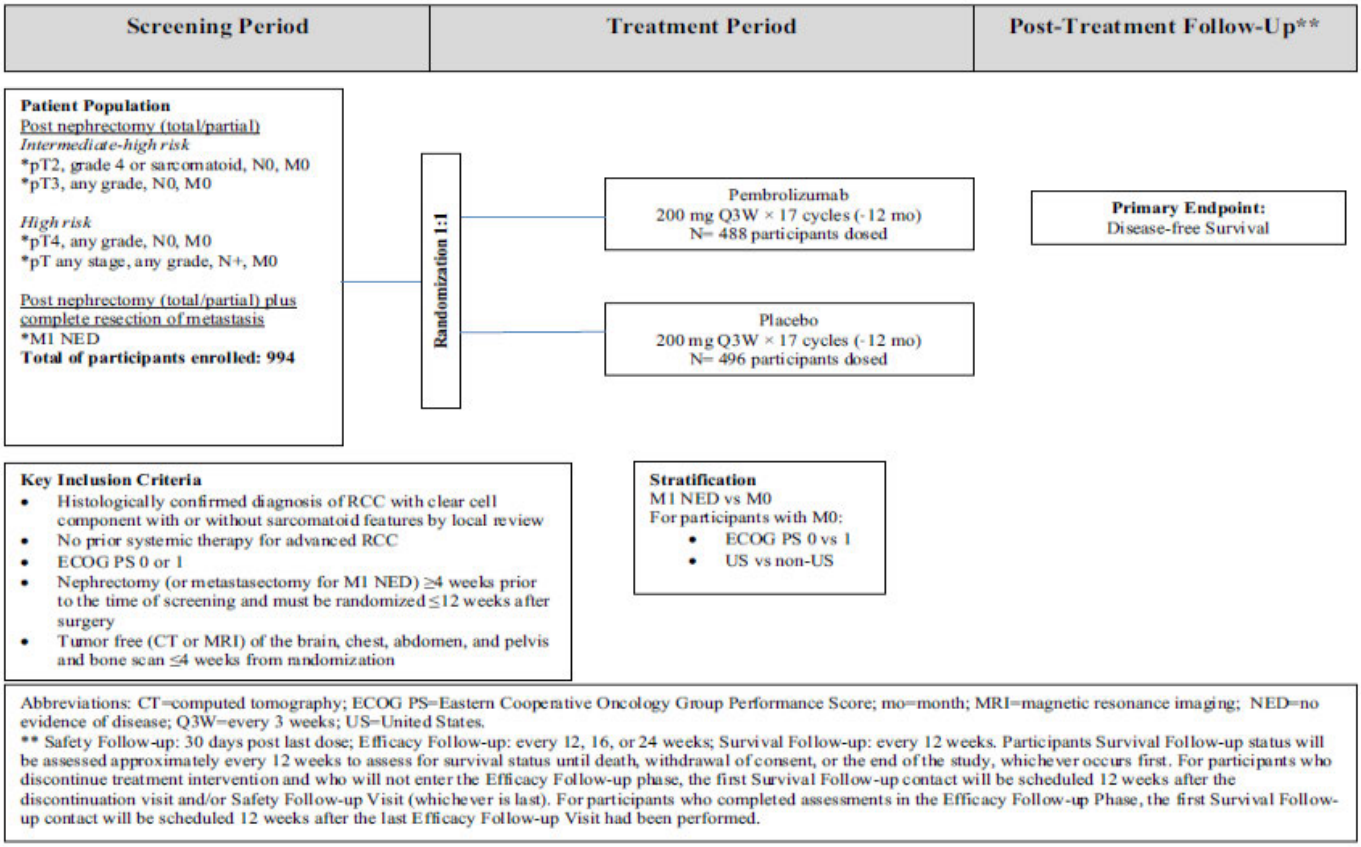
2.4.1. Dose response study(ies)

No formal dose-response studies have been carried out for the adjuvant RCC indication. Pembrolizumab dose and regimen used in the pivotal KEYNOTE-564 study 200 mg Q3W IV is the dosage currently approved in combination with chemotherapy for other indications (NSCLC, HNSCC).

2.4.2. Main study(ies)

A Phase 3, Randomized, Double-Blind, Placebo-Controlled Clinical Trial of Pembrolizumab (MK-3475) as Monotherapy in the Adjuvant Treatment of Renal Cell Carcinoma Post Nephrectomy (KEYNOTE-564)

Study Design



Methods

Study participants

Key inclusion criteria:

- Histologically confirmed diagnosis of RCC with clear cell component with or without sarcomatoid features by local review
- Had intermediate-high risk, high-risk, or M1 NED RCC as defined by the following pathological tumor-node-metastasis and Fuhrman grading status:

- Intermediate-high risk RCC

◦ pT2, Grade 4 or sarcomatoid, N0, M0

◦ pT3, any grade**,** N0, M0

- High-risk RCC

◦ pT4, any grade, N0, M0

◦ pT any stage, any grade, N+, M0

- M1 NED RCC participants who presented not only with the primary kidney tumor, but also solid, isolated, soft tissue metastases that could be completely resected at one of the following:

◦ the time of nephrectomy (synchronous) or,

◦ ≤1 year from nephrectomy (metachronous)

- Have no prior systemic therapy for advanced RCC
- Have ECOG PS 0 or 1
- Underwent a partial nephroprotective or radical complete nephrectomy (and complete resection of solid, isolated, soft tissue metastatic lesion(s) in M1 NED participants) with negative surgical margins ≥4 weeks prior to the time of screening
- Was tumor free (CT or MRI of the brain, chest, abdomen, and pelvis, and a bone scan ≤28 days from randomization) as assessed by the investigator

Exclusion Criteria

Participants were excluded from the study if they had any of the following:

- Major surgery, other than nephrectomy and/or resection of pre-existing metastases for M1 NED participants, within 12 weeks prior to randomization
- Received prior radiotherapy for RCC.
- Have pre-existing brain or bone metastatic lesion.
- Have residual thrombus post nephrectomy in the vena renalis or vena cava.
- Have other medical conditions or history that would interfere with the participant's participation for the full duration of the study, or was not in the best interest of the participant to participate

Treatments

Pembrolizumab 200 mg or matching placebo (saline 200 mg infusion) were administered intravenously Q3W for a total of 17 cycles or 1 year.

Objectives/Endpoints

Study objectives are summarized in the Table 1

Table 2 Study objectives and endpoints

Objective/Hypothesis	Endpoint(s)
Primary	
• Objective: To compare DFS as assessed by the investigator for participants treated with pembrolizumab vs those receiving placebo Hypothesis: Pembrolizumab is superior to placebo with respect to DFS	• DFS as assessed by the investigator: time from randomization to the first documented local recurrence, or occurrence of distant kidney cancer metastasis(es), or death due to any cause, whichever occurs first
Secondary	
Key Secondary	
• Objective: To compare OS for participants treated with pembrolizumab vs those receiving placebo Hypothesis: Pembrolizumab is superior to placebo with respect to OS	• OS: time from randomization to death due to any cause
Other Secondary	
• To compare the safety and tolerability profiles for participants treated with pembrolizumab vs those receiving placebo	• AEs, SAEs, AEs leading to discontinuation, deaths, laboratory values, and vital signs
• To compare measures of DRSS as assessed by the investigator, in participants treated with pembrolizumab vs those receiving placebo	• DRSS1 as assessed by the investigator: time from randomization to the first documented local recurrence of RCC • DRSS2 as assessed by the investigator: time from randomization to the first documented local recurrence with visceral lesion or occurrence of distant kidney cancer metastasis(es) with visceral lesion, whichever occurs first
• To compare EFS as assessed by the blinded independent radiology review for participants treated with pembrolizumab vs those receiving placebo	• EFS is to be assessed by BICR. EFS is defined as time from randomization to the first documented local recurrence or occurrence of distant kidney cancer metastasis(es) among participants, which by BICR were considered M0/M1 NED; or disease progression among participants, which by BICR were considered to have M1, or death due to any cause, whichever occurs first.

Objective/Hypothesis	Endpoint(s)
• To compare DFS and OS according to participants' PD-L1 expression status (positive, negative) for participants treated with pembrolizumab vs those receiving placebo	• DFS as assessed by the investigator: time from randomization to the first documented local recurrence, or occurrence of distant kidney cancer metastasis(es), or death due to any cause, whichever occurs first • OS: time from randomization to death due to any cause
• To evaluate PROs with EORTC-QLQ-C30 and the FKSI-DRS	• Mean change from baseline in EORTC QLQ-C30 global health status/quality of life scores • Mean change from baseline in EORTC QLQ-C30 functional subscales: physical functioning • Mean change from baseline in FKSI-DRS score
Tertiary/Exploratory	
• To evaluate PK parameters and the presence of ADA	• PK parameters (clearance and volume of distribution) • ADA to pembrolizumab
• To identify molecular (genomic, metabolic, and/or proteomic) biomarkers that may be indicative of clinical response/resistance, safety, pharmacodynamic activity, and/or the mechanism of action of pembrolizumab	• Biomarker analyses may include germline genetic variation, genetic (DNA) mutations from tumor, tumor and blood RNA variation, proteomics and immunohistochemistry, and other blood-derived biomarkers.
• To evaluate PROs with the EORTC QLQ-C30 and FKSI-DRS and to characterize utilities with the EQ-5D-5L	• Scales and subscales for select endpoints of the EORTC QLQ-C30, FKSI-DRS, and EQ-5D-5L (refer to Section 3.4.3.2 of the sSAP [16.1.9] for details)

Sample size

Sample size calculation for primary endpoint DFS and key-secondary endpoint OS:

The study was initially planned to randomize 950 subjects in a 1:1 ratio between the pembrolizumab and the placebo group (495:495). To be more in line with the actual final number of randomized subjects, power calculation in Amendment 03 was changed to be based on 994 subjects.

The study was event-driven with minimum follow-up (calendar time) requirement at first interim analysis. For primary DFS and key-secondary OS endpoint, a Lan-DeMets O'Brien-Fleming alpha-spending function was constructed to implement group sequential efficacy boundaries to control the Type I error and a Hwang-Shih-DeCani spending function with gamma = -6 to derive futility boundaries.

The power calculation of the **primary endpoint DFS** was based on the following assumptions: 1) DFS follows a Poisson mixture cure rate model (de Castro, M., et al 2010) with assumed cure rate of 0.3 (Leibovich, B. C., et al 2003) and with a median of 45 months for those not cured in the placebo group; 2) An enrollment period of 27 months; 3) A yearly drop-out rate of 2%; 4) the true HR was 0.67.

With 265 DFS events, there was approximately 84% power at IA1 to detect a hazard ratio of 0.67 (pembrolizumab versus placebo) with one-sided alpha spending of 1.22% under the DFS assumptions (see above). At IA2 of the study (final DFS analysis), with 332 DFS events there was 95% power to detect a hazard ratio of 0.67 at a one-sided alpha bound of 2.14% level. Overall, based on a target total number of 332 DFS events and one IA at approximately 80% of the target number of events (I.e. 265 DFS events), the study has approximately 95% power to detect a hazard ratio of 0.67 at an overall alpha level of 2.5% (1-sided).

For the **key-secondary OS endpoint**, the power was conditional on the null hypothesis of DFS being rejected. The power calculation was based on the following assumptions: 1) OS follows an exponential distribution with a median of 145 months in the placebo group; 2) An enrollment period of 27 months ; 3) A yearly dropout rate of 1%; 4) the true HR is 0.67 for OS.

With 200 OS events at final analysis and three interim analyses at approximately 47%, 66%, and 86% of the target number of events, there was approximately 79% power to detect a HR of 0.67 or approximately 88% power to detect a HR of 0.635 at one-sided 2.5% alpha level. This hypothesis may only be tested if primary endpoint DFS was supported when the hypothesis testing of DFS met statistical significance criterion.

Randomisation

990 subjects were planned to be randomized in a 1:1 ratio into pembrolizumab group or placebo group using the IVRS/IWRS. Treatment allocation/randomization was planned to be stratified according to metastasis status (M0 versus M1 NED) and within M0 group additionally by ECOG PS (0 versus 1) and US participant (YES versus NO).

Table 3 Subjects Characteristics (ITT population)

	Pembrolizumab		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Metastatic Staging						
M0	467	(94.2)	469	(94.2)	936	(94.2)
M1 NED	29	(5.8)	29	(5.8)	58	(5.8)
RCC Risk Category						
M0-Intermediate-High Risk	422	(85.1)	433	(86.9)	855	(86.0)
M0-High Risk	40	(8.1)	36	(7.2)	76	(7.6)
M0-Others	5	(1.0)	0	(0.0)	5	(0.5)
M1 NED	29	(5.8)	29	(5.8)	58	(5.8)
ECOG Performance Scale						
0	421	(84.9)	426	(85.5)	847	(85.2)
1	75	(15.1)	72	(14.5)	147	(14.8)
Geographic Region of Enrolling Site						
North America	133	(26.8)	125	(25.1)	258	(26.0)
European Union	188	(37.9)	187	(37.6)	375	(37.7)
Rest of World	175	(35.3)	186	(37.3)	361	(36.3)
Region						
US	114	(23.0)	117	(23.5)	231	(23.2)
Non-US	382	(77.0)	381	(76.5)	763	(76.8)

Blinding (masking)

The study was planned to be double-blind. Pembrolizumab and placebo were to be prepared and/or administered in a blinded fashion by an unblinded pharmacist or qualified trial site personnel. The participant and the investigator who were involved in the study treatment administration or clinical evaluation of the participants were to remain unaware of the group assignments.

An external Data Monitoring Committee (eDMC) had access to unblinded patient treatment assignment.

Statistical methods

Study populations

The primary and key secondary efficacy analyses were performed on the Intention-to-Treat (ITT) population, which includes all randomized participants. Participants were analyzed in the treatment group to which they were randomized. The safety analysis was performed on the All Participants as Treated population (APaT), including all randomized participants who received at least one dose of study treatment. The Patient reported outcomes (PRO) analyses were performed on the PRO full analysis set (FAS), defined as participants who received at least one study treatment and completed at least one PRO assessment. Efficacy data from participants in ITT population were analyzed in the treatment group to which they were randomized. Safety data from participants in APaT population were analyzed in the treatment group they actually received, which is the same as the treatment group to which they were randomized in this study.

Statistical methods

The primary endpoint was planned to be DFS assessed by investigator, defined as time from randomization to the first documented local recurrence, or occurrence of distant kidney cancer metastasis(es), or death due to any cause, whichever occurs first. The time of recurrence was defined by the first documented recurrence, regardless of discontinuation of study treatment.

Key-secondary endpoint was planned to be OS, defined as time from randomization to death due to any cause.

Treatment differences in the primary and key-secondary endpoint were assessed by the stratified log-rank test. Hazard ratios (HR) and 95% confidence intervals from stratified Cox Model with Efron's tie handling method were reported. The stratification factors used in the randomisation were used as stratification factors in the primary and key-secondary analysis.

Further secondary endpoints were DRSS1 and DRSS2. Curves in each treatment group were estimated by nonparametric cumulative incidence estimator. EFS was analysed by Kaplan-Meier method. The ITT population was used for analysing those secondary endpoints.

Patient reported outcomes (PRO) were assessed by visit. A constrained longitudinal data analysis (cLDA) was performed for the analysis of change from baseline in PROs using the PRO FAS.

Sensitivity analyses for primary endpoint

One sensitivity analysis with different censoring rules for DFS was planned to be performed for the primary analysis, see Table below. The sensitivity analysis was the same as the primary analysis except that events immediately after 2 consecutive missed disease assessments or after new anticancer therapy, if any, should be censored at last disease assessment prior to the earlier date of ≥2 consecutive missed disease assessments and new anticancer therapy.

The censoring rules for primary and sensitivity analysis are summarized as follows:

Table 4 censoring Rules for Primary and Sensitivity Analysis of Disease-Free Survival

Situation	Primary Analysis	Sensitivity Analysis
No recurrence and no death; new anticancer treatment is not initiated	Censored at last disease assessment	Censored at last disease assessment
No recurrence and no death; new anticancer treatment is initiated	Censored at last disease assessment	Censored at last disease assessment before new anticancer treatment
Recurrence or death documented after ≤1 missed disease assessment and before new anticancer treatment, if any	Event at date of documented recurrence or death	Event at date of documented recurrence or death
Recurrence or death documented immediately after ≥2 consecutive missed disease assessments, or after new anticancer treatment, if any	Event at date of documented recurrence or death	Censored at the last disease assessment prior to the earlier date of ≥2 consecutive missed disease assessments and new anticancer treatment, if any

To evaluate the robustness of the results from the primary analysis method after adjusting the potential confounding effect of baseline disease status, the following sensitivity analyses were added resulting from Amendment 03 and 04. DFS by investigator assessment was evaluated using stratification factors for randomization with baseline disease status as assessed by BICR (no evidence of disease [ie, NED] vs. evidence of disease [ie, non-NED]) as an additional stratum. In addition, DFS by BICR were analyzed as a sensitivity analysis in which participants enrolled with baseline disease by BICR will be censored at randomization date.

Interim analyses

Three interim analyses were planned for the study. Results were planned to be reviewed by an external DMC. The timing for the interim analyses and final analysis were defined as follows:

Table 5 Boundary Properties for Planned Interim and Final Analyses for DFS

Analysis	Value	Efficacy	Futility†
IA1: 80% (First Interim for DFS) N: 990 Events: 265 Month: 39	Z p (1-sided) HR at bound P(Cross) if HR=1 P(Cross) if HR=0.67	2.2504 0.0122 0.7584 0.0122 0.8402	-0.5476 0.7080 1.0696 0.2920 0.0001
IA2: (Final Analysis for DFS) N: 990 Events: 332 Month: 50	Z p (1-sided) HR at bound P(Cross) if HR=1 P(Cross) if HR=0.67	2.0249 0.0214 0.8005 0.0250 0.9490	2.0249 0.0214 0.8005 0.9750 0.0510
IA = Interim Analysis. †: Futility boundary is non-binding.			

Table 6 Boundary Properties for Planned Interim and Final Analyses for OS

Analysis	Value	Efficacy	Futility†
IA1: 47% (First Interim for OS) N: 990 Events: 94 Month: 39	Z p (1-sided) HR at bound P(Cross) if HR=1 P(Cross) if HR=0.67	3.0679 0.0011 0.5305 0.0011 0.1280	-1.7717 0.9618 1.4421 0.0382 0.0001
IA2: 66% (Second Interim for OS) N: 990 Events: 132 Month: 50	Z p (1-sided) HR at bound P(Cross) if HR=1 P(Cross) if HR=0.67	2.5455 0.0055 0.6416 0.0058 0.4033	-1.1786 0.8807 1.2281 0.1247 0.0003
IA3: 86% (Third Interim for OS) N: 990 Events: 172 Month: 63	Z p (1-sided) HR at bound P(Cross) if HR=1 P(Cross) if HR=0.67	2.2023 0.0138 0.7143 0.0157 0.6688	-0.2090 0.5828 1.0324 0.4195 0.0025
Final N: 990 Events: 200 Month: 72	Z p (1-sided) HR at bound P(Cross) if HR=1 P(Cross) if HR=0.67	2.0534 0.0200 0.7476 0.0250 0.7930	2.0534 0.0200 0.7476 0.9750 0.2070
IA = Interim Analysis. †: Futility boundary is non-binding.			

One interim analysis of DFS after approximately 265 events (80% information fraction) and a minimum follow-up of at least 12 months and a final analysis of DFS after 332 events were planned to be performed. Four analyses of OS were planned, where the final analysis of OS was planned to be conducted based on 200 events, and interim analyses were planned at the time of interim and final DFS analysis (47%, i.e. 94 OS events, and 66%, i.e. 132 OS events, of information fraction expected) and one year thereafter (86%, i.e. 172 OS events, of information fraction expected). The first IA was always to be driven by the number of DFS events. The second IA was to be driven by DFS events unless DFS was to be rejected in the first IA. In this case, it was to be driven by the number of OS events.

For primary DFS and key-secondary OS endpoint, a Lan-DeMets O'Brien-Fleming alpha-spending function was constructed to implement group sequential efficacy boundaries to control the Type I error and a Hwang-Shih-DeCani spending function with gamma = -6 to derive non-binding futility boundaries. Bounds were planned to be adjusted according to the actual number of events at each analysis.

The alpha-reallocation was pre-specified in advance, see paragraph on Multiplicity below.

As the information fraction is based on sample sizes (number of events) that were estimated, the alphas may change according to the available information (observed data).

Multiplicity

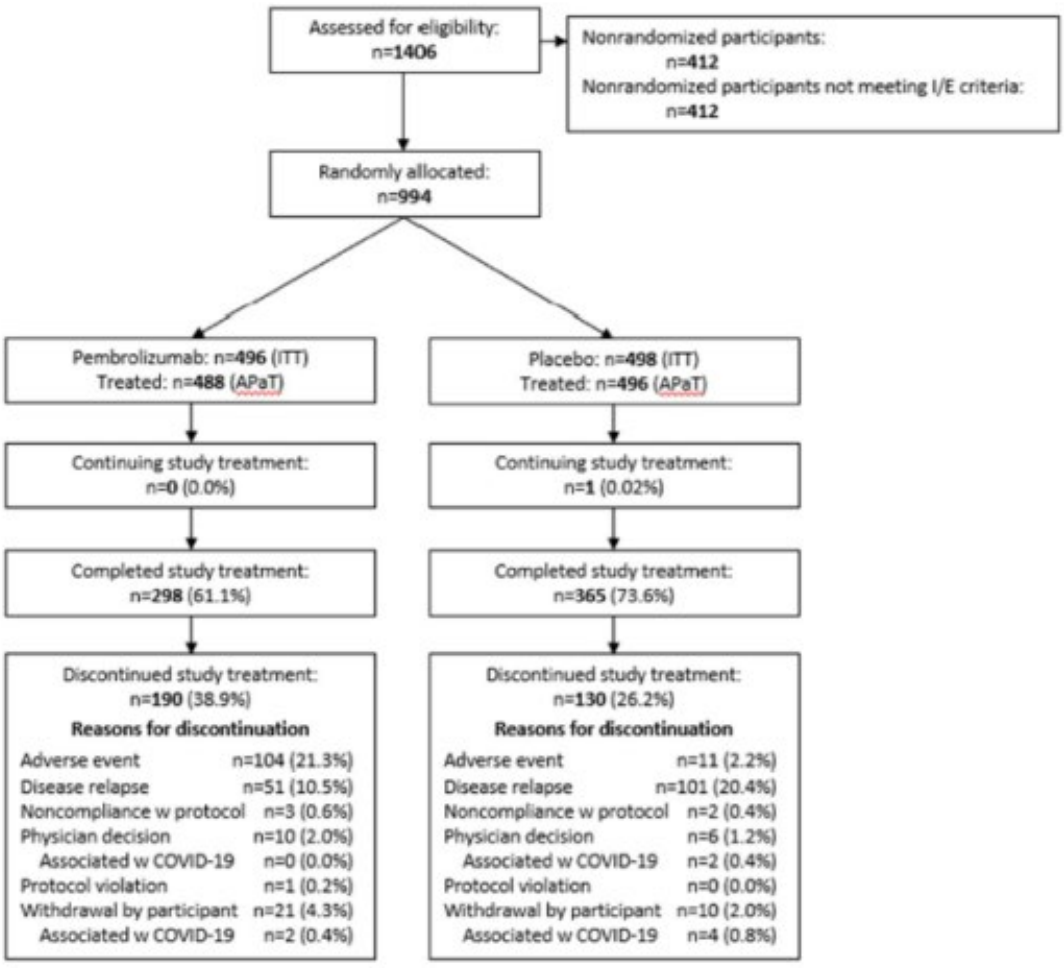
The family-wise type-I error was planned to be controlled on the one-sided 2.5% level, covering the primary and key-secondary hypotheses. If the DFS null hypothesis would be rejected at the 2.5% level, then the OS null hypothesis was planned to be formally evaluated for statistical significance at the 2.5% level. For each endpoint, group sequential methods were planned to be used to adjust for the interim and final analyses planned. If the DFS null hypothesis would be rejected at an interim or final analysis, each OS interim and final analysis test was planned to be compared to its rejection boundary for formal testing. For instance, the OS hypothesis would not be formally evaluated for statistical significance until the DFS null hypothesis would be rejected.

Safety analysis

The analysis of safety results were performed by tiered approach. Summary statistics for baseline, on-treatment, and change from baseline values were provided by treatment group. For Tier 2 endpoints, point estimates and 95% Cis were provided for between-treatment differences; only point estimates by treatment group were provided for Tier 3 safety parameters in percentage of subjects with events using the Miettinen and Nurminen method. Additionally, exploratory analyses were performed for time to first Grade 3-5 AEs by Kaplan-Meier method and Cox proportional hazard model with Efron's method of tie handling.

Results

Participant flow



Note: The participant for whom study treatment was reported as ongoing at the time of the data cutoff date for IA1 had received the last dose of study treatment but had not completed the study treatment discontinuation visit at the time of the data cutoff date.

Table 7 Disposition of Participants (ITT Population)

	Pembrolizumab		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	496		498		994	
Status for Study Treatment						
Started	488		496		984	
Completed	298	(61.1)	365	(73.6)	663	(67.4)
Discontinued	190	(38.9)	130	(26.2)	320	(32.5)
Adverse Event	104	(21.3)	11	(2.2)	115	(11.7)
Disease Relapse	51	(10.5)	101	(20.4)	152	(15.4)
Non-Compliance With Protocol	3	(0.6)	2	(0.4)	5	(0.5)
Physician Decision	10	(2.0)	6	(1.2)	16	(1.6)
Associated With Covid-19	0	(0.0)	2	(0.4)	2	(0.2)
Protocol Violation	1	(0.2)	0	(0.0)	1	(0.1)
Withdrawal By Subject	21	(4.3)	10	(2.0)	31	(3.2)
Associated With Covid-19	2	(0.4)	4	(0.8)	6	(0.6)
Participants Ongoing	0	(0.0)	1	(0.2)	1	(0.1)
Status for Trial						
Discontinued	33	(6.7)	44	(8.8)	77	(7.7)
Death	18	(3.6)	33	(6.6)	51	(5.1)
Withdrawal By Subject	15	(3.0)	11	(2.2)	26	(2.6)
Associated With Covid-19, No Further Information	1	(0.2)	0	(0.0)	1	(0.1)
Association With Covid-19 Unspecified, No Further Information	14	(2.8)	11	(2.2)	25	(2.5)
Participants Ongoing	463	(93.3)	454	(91.2)	917	(92.3)

If the overall count of participants is calculated and displayed within a section in the first row, then it is used as the denominator for the percentage calculation. Otherwise, participants in population is used as the denominator for the percentage calculation.
Database Cutoff Date: 14DEC2020

Recruitment

A total of 1406 participants were screened and 994 were randomly allocated across 212 global study sites in 21 countries.

The first patient, first visit was done on 30-JUN-2017 while the last patient, last visit was done on 14-DEC-2020: data cut-off for IA1. The median follow-up time was 23.9 months (range 2.5 to 41.5 months).

Conduct of the study

Protocol amendments

The key changes introduced by the protocol amendments are summarized below

Protocol Amendment	Most relevant changes

#01 (02 Nov 2017)	-To include metachronous and synchronous M1 NED post-operative nephrectomy ≤1 year. Since study inception, the inclusion of metachronous and synchronous M1 NED patients was intended; however, during protocol finalization metachronous was inadvertently removed. -Collection of PK and ADA revised from "30 days after treatment discontinuation (or until participant starts new anticancer treatment)" to "at Safety Follow up"
#2 (4 Sep 2019)	- Deleted PK/ADA objective The PK/ADA objective is now exploratory, not a secondary objective. - Changed from 4 to 3 interim analyses may be conducted. Removed IA1 due to insufficient duration of minimum follow-up resulting from prolonged enrollment period. - Updated the total number of DFS events expected at 48 months with at least 91.7% power to detect an HR of 0.67 when the study enrollment is extended from 18 months to 25 months. - Updated the censoring rules for DFS. Updated the censoring rules per the most recent oncology standard. - Updated analysis strategy for safety parameters, ie, updated the criterion for Tier 2 safety events and updated the list of additional events to be considered as Tier 2 or Tier 3 safety events. Subjects enrolled in this study usually experience various adverse events of similar types, adverse events reported less frequent than in 10%, or SAE, Grade 3-5 events reported in less than 5% of subjects would obscure the assessment of overall safety profile and add little to meaningful interpretation.
# 3 (11 May 2020)	- Added secondary endpoint to compare event-free survival (EFS) as assessed by the blinded independent radiology review for participants treated with pembrolizumab versus those receiving placebo. - Changed duration of trial required to achieve the primary objective from 48 months to approximately 50 months. Projected duration of trial extended due to increased total targeted number of DFS events at IA2. (1) Changed the timing of interim analyses and final analysis. (2) Changed α-spending function for primary DFS from Hwang-Shih-DeCani (HSD) spending function with γ= -15 to Lan-DeMets O'Brien-Fleming spending approximation α-spending function.
#4 (13 Oct 2020)	- Removed PK/ADA sample collection. - Updated censoring rules for the primary analysis and the sensitivity analysis. The new primary analysis is the old sensitivity analysis 1

	and new sensitivity analysis is the old primary analysis. The old sensitivity analysis 2 is removed. -

Protocol deviations

Table 8 Summary of Important Protocol Deviations Considered to be Clinically Important (All Randomized Subjects)

	Pembrolizumab		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	496		498		994	
with one or more clinically important protocol deviations	2	(0.4)	3	(0.6)	5	(0.5)
with no clinically important protocol deviations	494	(99.6)	495	(99.4)	989	(99.5)
Inclusion/ Exclusion Criteria	**2**	**(0.4)**	**2**	**(0.4)**	**4**	**(0.4)**
Participant was randomized with pre-existing brain or bone metastatic lesion(s).	1	(0.2)	1	(0.2)	2	(0.2)
Participant was randomized with residual thrombus post-nephrectomy in the vena renalis or vena cava.	1	(0.2)	1	(0.2)	2	(0.2)
Safety Reporting	**0**	**(0.0)**	**1**	**(0.2)**	**1**	**(0.1)**
Participant had a reportable Safety Event and/or follow up Safety Event information that was not reported per the timelines outlined in the protocol.	0	(0.0)	1	(0.2)	1	(0.1)
Every participant is counted a single time for each applicable row and column. Database Cutoff Date: 14DEC2020.						

Table 9 Summary of Protocol Deviations Associated With COVID-19 (All Randomized Subjects)

	Pembrolizumab		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	496		498		994	
with one or more protocol deviations associated with COVID-19	127	(25.6)	117	(23.5)	244	(24.5)
with no protocol deviations associated with COVID-19	369	(74.4)	381	(76.5)	750	(75.5)
Informed Consent	**6**	**(1.2)**	**5**	**(1.0)**	**11**	**(1.1)**
Not Important Informed Consent deviation	6	(1.2)	5	(1.0)	11	(1.1)
Safety Reporting	**0**	**(0.0)**	**1**	**(0.2)**	**1**	**(0.1)**
Not Important Safety Reporting deviation	0	(0.0)	1	(0.2)	1	(0.1)
Study Intervention	**3**	**(0.6)**	**3**	**(0.6)**	**6**	**(0.6)**
Not Important Study Intervention deviation	3	(0.6)	3	(0.6)	6	(0.6)
Trial Procedures	**125**	**(25.2)**	**113**	**(22.7)**	**238**	**(23.9)**
Not Important Trial Procedures deviation	125	(25.2)	113	(22.7)	238	(23.9)
Every participant is counted a single time for each applicable row and column. Database Cutoff Date: 14DEC2020.						

Source: [P564V01MK3475: adam-adsl] [P564V01MK3475: sdtm-dv; suppdv]

Baseline data

Table 10 Demographic and Baseline Characteristics

	Pembrolizumab		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	496		498		994	
Sex						
Male	347	(70.0)	359	(72.1)	706	(71.0)
Female	149	(30.0)	139	(27.9)	288	(29.0)
Age (Years)						
<65	338	(68.1)	326	(65.5)	664	(66.8)
>=65	158	(31.9)	172	(34.5)	330	(33.2)
Mean	58.3		58.6		58.4	
SD	10.6		11.0		10.8	
Median	60.0		60.0		60.0	
Range	27 to 81		25 to 84		25 to 84	
Race						
American Indian Or Alaska Native	10	(2.0)	2	(0.4)	12	(1.2)
Asian	63	(12.7)	75	(15.1)	138	(13.9)
Black Or African American	7	(1.4)	5	(1.0)	12	(1.2)

	Pembrolizumab		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Multiple	8	(1.6)	5	(1.0)	13	(1.3)
American Indian Or Alaska Native Black Or African American	2	(0.4)	0	(0.0)	2	(0.2)
American Indian Or Alaska Native White	3	(0.6)	2	(0.4)	5	(0.5)
Black Or African American White	2	(0.4)	3	(0.6)	5	(0.5)
White Asian	1	(0.2)	0	(0.0)	1	(0.1)
White	372	(75.0)	377	(75.7)	749	(75.4)
Missing	36	(7.3)	34	(6.8)	70	(7.0)
Ethnicity						
Hispanic Or Latino	72	(14.5)	62	(12.4)	134	(13.5)
Not Hispanic Or Latino	381	(76.8)	394	(79.1)	775	(78.0)
Not Reported	21	(4.2)	20	(4.0)	41	(4.1)
Unknown	21	(4.2)	21	(4.2)	42	(4.2)
Missing	1	(0.2)	1	(0.2)	2	(0.2)
Geographic Region of Enrolling Site						
North America	133	(26.8)	125	(25.1)	258	(26.0)
European Union	188	(37.9)	187	(37.6)	375	(37.7)
Rest of World	175	(35.3)	186	(37.3)	361	(36.3)

	Pembrolizumab		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Region						
US	114	(23.0)	117	(23.5)	231	(23.2)
Non-US	382	(77.0)	381	(76.5)	763	(76.8)
ECOG Performance Scale						
0	421	(84.9)	426	(85.5)	847	(85.2)
1	75	(15.1)	72	(14.5)	147	(14.8)
Type of nephrectomy						
Partial	37	(7.5)	38	(7.6)	75	(7.5)
Radical	459	(92.5)	460	(92.4)	919	(92.5)
PD-L1 Status						
CPS < 1	124	(25.0)	113	(22.7)	237	(23.8)
CPS >= 1	365	(73.6)	383	(76.9)	748	(75.3)
Missing	7	(1.4)	2	(0.4)	9	(0.9)
Primary Tumor						

	Pembrolizumab		Placebo		Total	
	n	(%)	n	(%)	n	(%)
T1	11	(2.2)	15	(3.0)	26	(2.6)
T2	27	(5.4)	33	(6.6)	60	(6.0)
T3	444	(89.5)	437	(87.8)	881	(88.6)
T4	14	(2.8)	13	(2.6)	27	(2.7)
Tumor Grade						
Grade 1	19	(3.8)	16	(3.2)	35	(3.5)
Grade 2	153	(30.8)	150	(30.1)	303	(30.5)
Grade 3	219	(44.2)	213	(42.8)	432	(43.5)
Grade 4	103	(20.8)	119	(23.9)	222	(22.3)
Missing	2	(0.4)	0	(0.0)	2	(0.2)
Sarcomatoid Feature						
Presence	52	(10.5)	59	(11.8)	111	(11.2)
Absence	417	(84.1)	415	(83.3)	832	(83.7)
Unknown	27	(5.4)	24	(4.8)	51	(5.1)
Lymph Nodes Stage						
N0	465	(93.8)	467	(93.8)	932	(93.8)
N1	31	(6.3)	31	(6.2)	62	(6.2)
Metastatic Staging						
M0	467	(94.2)	469	(94.2)	936	(94.2)
M1 NED	29	(5.8)	29	(5.8)	58	(5.8)
RCC Risk Category						
M0-Intermediate-High Risk	422	(85.1)	433	(86.9)	855	(86.0)
M0-High Risk	40	(8.1)	36	(7.2)	76	(7.6)
M0-Others	5	(1.0)	0	(0.0)	5	(0.5)
M1 NED	29	(5.8)	29	(5.8)	58	(5.8)

Participants in M0-Intermediate-high risk are pT2 (Grade 4 or sarcomatoid), N0, M0 or pT3 (Any Grade), N0, M0. Participants in M0-high risk are pT4 (Any Grade), N0, M0 or pT Any (Any Grade), N1 or greater, M0. Participants in M1 NED are participants who present not only with the primary kidney tumor but also solid, isolated, soft tissue metastases that were completely resected at the time of nephrectomy (synchronous) or <=1 year from nephrectomy (metachronous). Participants in M0-Others are T2 (grade <= 3) N0 M0 or T1 N0 M0.
Database Cutoff Date: 14DEC2020.

Numbers analysed

For IA1, efficacy analyses were conducted using the intention-to-treat (ITT) population, and safety analyses were conducted using the All Participants as Treated (APaT) population, which included all randomized participants who received at least 1 dose of study intervention.

Outcomes and estimation

Disease free survival (DFS)

As of the data cutoff for IA1, a total of 260 DFS events (78% of the total planned events at the final analysis) were observed in the 2 treatment groups (109 in the pembrolizumab group and 151 in the placebo group). At the prespecified 2.5% overall alpha level (one-sided), pembrolizumab demonstrated a statistically significant improvement in DFS compared with placebo (median DFS was not reached in either treatment group; HR: 0.68 [95% CI: 0.53, 0.87]; and log-rank test p-value 0.0010, p-value boundary: 0.0114) **Table 11**. The KM curve separated from the outset in favour of pembrolizumab. The difference in the DFS rates between treatment groups at 12, 18, and 24 months ranged from 9.2% to 9.6%.

Table 11. Analysis of Disease-Free Survival (Primary Censoring Rule) Based on Investigator Assessment (ITT Population) Database Cutoff Date: 14DEC2020

	Pembrolizumab (N=496)	Placebo (N=498)
Number of Events (%)	109 (22.0)	151 (30.3)
Death	6 (1.2)	2 (0.4)
Disease Recurrence	103 (20.8)	149 (29.9)
Number of Censored (%)	387 (78.0)	347 (69.7)
Last Tumor Assessment Showing No Disease Recurrence	375 (75.6)	344 (69.1)
No Post-Baseline Disease Status Assessment	12 (2.4)	3 (0.6)
Kaplan-Meier Estimates (months)[a]		
Median (95% CI)	NR (NR, NR)	NR (NR, NR)
[Q1, Q3]	[25.8, NR]	[13.8, NR]
person-months	9759.0	9241.1
Event Rate / 100 person-months	1.1	1.6
vs Placebo		
Hazard Ratio (95% CI)[b]	0.68 (0.53, 0.87)	
p-value[c]	0.0010	
DFS Rate at month 12 (%) (95% CI)	85.7 (82.2, 88.5)	76.2 (72.2, 79.7)
DFS Rate at month 18 (%) (95% CI)	81.5 (77.7, 84.8)	71.9 (67.7, 75.7)
DFS Rate at month 24 (%) (95% CI)	77.3 (72.8, 81.1)	68.1 (63.5, 72.2)

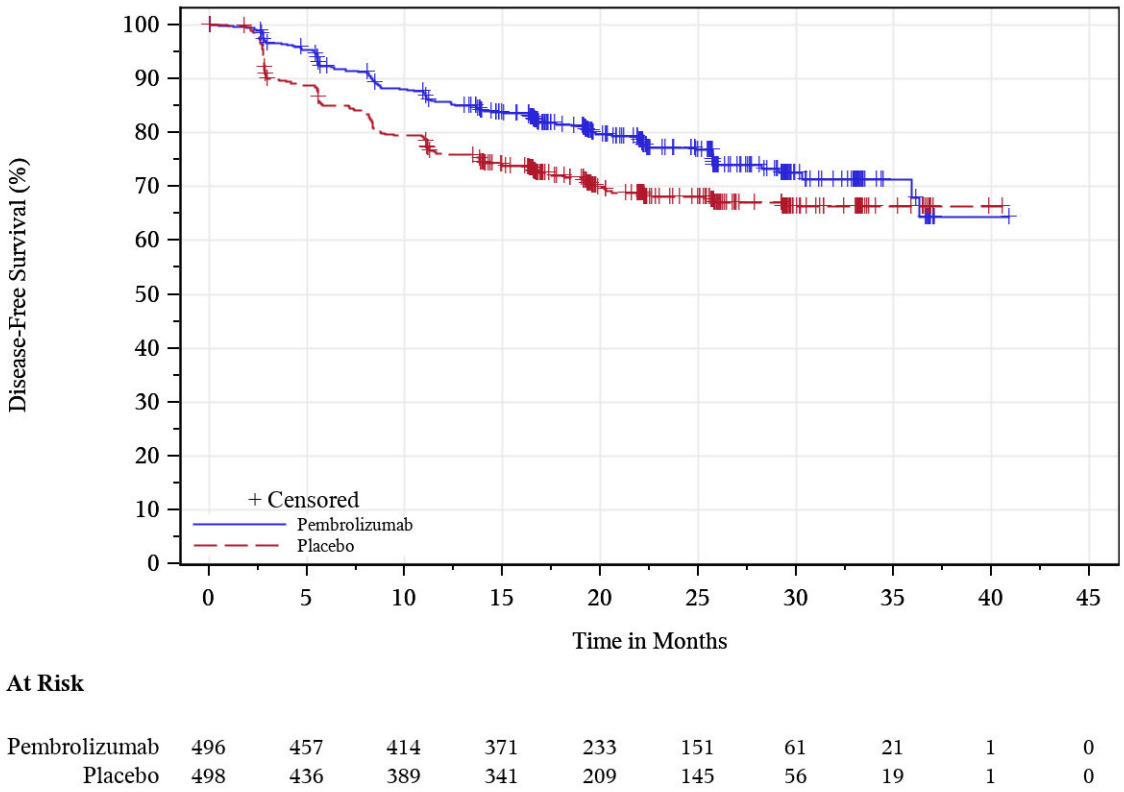
[a] From product-limit (Kaplan-Meier) method for censored data.

[b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by metastasis status (M0 versus M1 NED by investigator) and ECOG PS (0 versus 1),US participant (Yes versus No) within M0 group by investigator.

[c] One-sided p-value based on log-rank test stratified by metastasis status (M0 versus M1 NED by investigator) and ECOG PS (0 versus 1),US participant (Yes versus No) within M0 group by investigator.

NR = Not reached.

Database Cutoff Date: 14DEC2020



At Risk

Pembrolizumab	496	457	414	371	233	151	61	21	1	0
Placebo	498	436	389	341	209	145	56	19	1	0

Figure 1 Kaplan-Meier Plot of Disease-Free Survival (Primary Censoring Rule)

Updated efficacy results (data cut-off date 14JUN2021) with a median follow-up time of 29.7 months are summarised in Table 12 and Figure 2.

Table 12 Efficacy results in KEYNOTE-564 (data cut-off date 14JUN2021)

Endpoint	**Pembrolizumab 200 mg every 3 weeks n=496**	**Placebo n=498**
DFS		
Number (%) of patients with event	114 (23%)	169 (34%)
Median in months (95% CI)	NR (NR, NR)	NR (40.5, NR)
Hazard ratio* (95% CI)	0.63 (0.50, 0.80)	
p-Value†	< 0.0001	

* Based on the stratified Cox proportional hazard model
† Nominal p-Value based on stratified log-rank test
NR = not reached

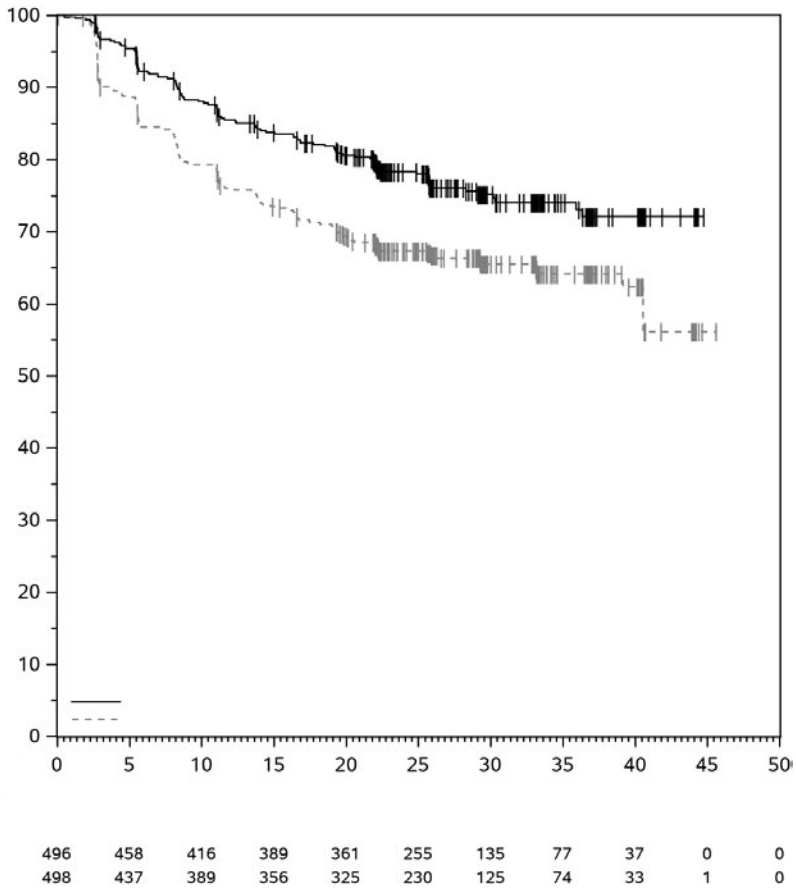


Figure 2 Kaplan-Meier curve for disease-free survival by treatment arm in KEYNOTE-564 (intent to treat population) (Data cut-off date 14JUN2021)

Secondary endpoints

Overall survival (OS)

The OS data were immature at IA1 with 51 deaths (26% of total planned OS events at the final analysis). For OS, the HR was 0.54 (95% CI: 0.30, 0.96) (p=0.0164037) and the median OS was not reached in either group. The p-value did not cross the statistical hypothesis testing p-value boundary of 9.3×10^{-6} at IA1. The upper bound of 95% CI for the OS HR was below 1.0, with nearly twice as many deaths in the placebo group (33) compared with the pembrolizumab group (18).

Table 13 Analysis of Overall Survival (ITT Population)

	Pembrolizumab (N=496)	Placebo (N=498)
Number of Events (%)	18 (3.6)	33 (6.6)
Kaplan-Meier Estimates (months)[a]		
Median (95% CI)	NR (NR, NR)	NR (NR, NR)
[Q1, Q3]	[NR, NR]	[NR, NR]
person-months	12195.5	12096.2

Event Rate / 100 person-months	0.1	0.3
vs Placebo		
Hazard Ratio (95% CI)[b]	0.54 (0.30, 0.96)	
p-value[c]	.0164037	
OS Rate at month 12 (%) (95% CI)	98.6 (97.0, 99.3)	98.0 (96.3, 98.9)
OS Rate at month 18 (%) (95% CI)	97.9 (96.1, 98.9)	96.8 (94.8, 98.0)
OS Rate at month 24 (%) (95% CI)	96.6 (94.3, 98.0)	93.5 (90.5, 95.6)

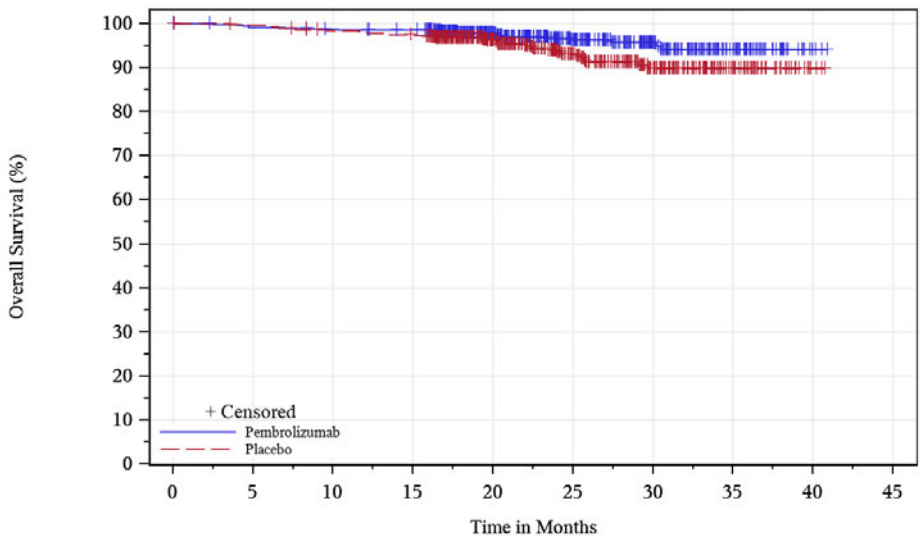
[a] From product-limit (Kaplan-Meier) method for censored data.

[b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by metastasis status (M0 versus M1 NED by investigator) and ECOG PS (0 versus 1),US participant (Yes versus No) within M0 group by investigator.

[c] One-sided p-value based on log-rank test stratified by metastasis status (M0 versus M1 NED by investigator) and ECOG PS (0 versus 1),US participant (Yes versus No) within M0 group by investigator.

NR = Not reached.

Database Cutoff Date: 14DEC2020



At Risk

Pembrolizumab	496	490	486	482	338	215	124	51	3	0
Placebo	498	494	485	480	336	209	117	48	3	0

Figure 3. Kaplan-Meier Plot of Overall Survival (ITT Population***)***

Updated OS results were not yet mature at the updated data cut-off date of 14JUN2021 and are summarised below.

Table 14 Analysis of Overall Survival (ITT Population) (data cut-off date 14JUN2021

	Pembrolizumab (N=496)	Placebo (N=498)
Number of Events (%)	23 (4.6)	43 (8.6)
Kaplan-Meier Estimates (months)[a]		
Median (95% CI)	NR (NR, NR)	NR (NR, NR)
[Q1, Q3]	[NR, NR]	[NR, NR]
person-months	14948.1	14797.1
Event Rate / 100 person-months	0.2	0.3
vs Placebo		
Hazard Ratio (95% CI)[b]	0.52 (0.31, 0.86)	
p-value[c]	.0047677	
OS Rate at month 12 (%) (95% CI)	98.6 (97.0, 99.3)	98.0 (96.3, 98.9)
OS Rate at month 18 (%) (95% CI)	97.8 (96.0, 98.8)	96.8 (94.8, 98.0)
OS Rate at month 24 (%) (95% CI)	96.2 (94.1, 97.6)	93.8 (91.3, 95.6)

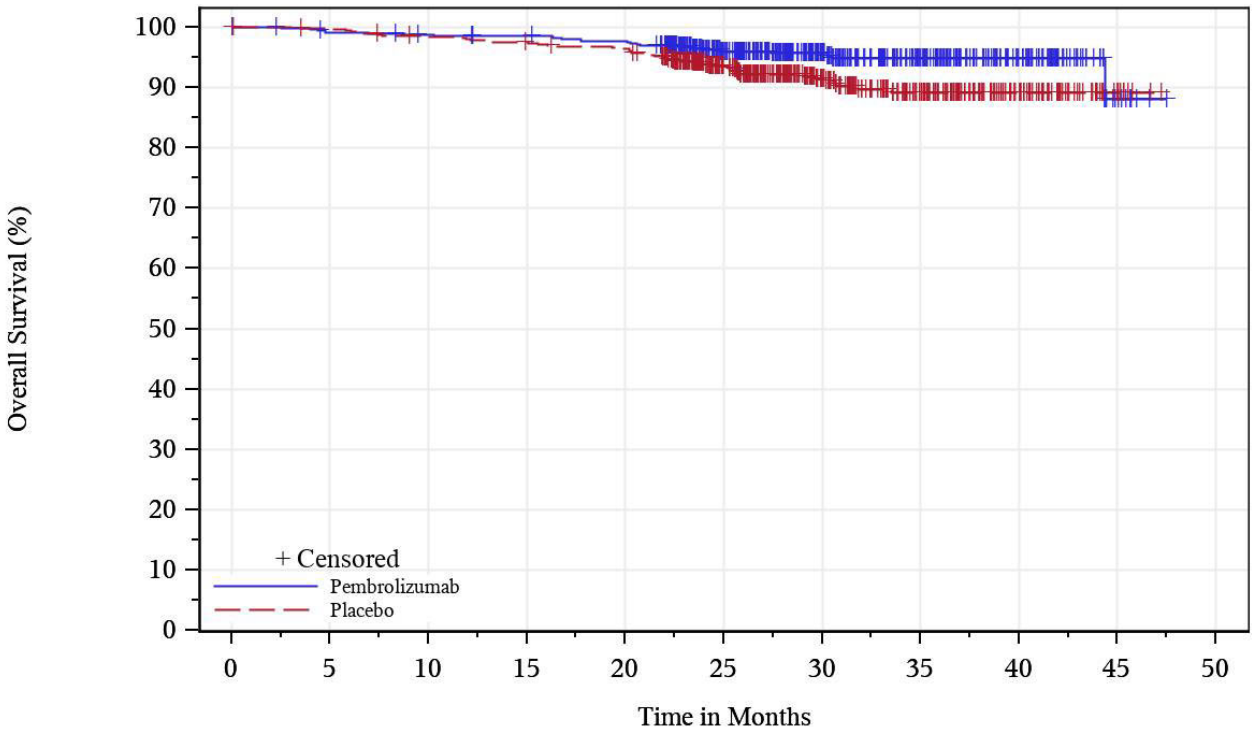
[a] From product-limit (Kaplan-Meier) method for censored data.

[b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by metastasis status (M0 versus M1 NED by investigator) and ECOG PS (0 versus 1),US participant (Yes versus No) within M0 group by investigator.

[c] One-sided p-value based on log-rank test stratified by metastasis status (M0 versus M1 NED by investigator) and ECOG PS (0 versus 1),US participant (Yes versus No) within M0 group by investigator.

NR = Not reached.

Database Cutoff Date: 14JUN2021



At Risk

Pembrolizumab	496	489	485	482	477	360	231	146	63	8	0
Placebo	498	494	486	481	474	352	219	138	61	9	0

Figure 4 Kaplan-Meier Plot of Overall Survival (ITT Population***)***

Other Secondary Efficacy Endpoint:

Disease Recurrence-specific Survival

The cumulative incidences of the event of interest in the pembrolizumab group were consistently lower compared with the placebo group over time for both DRSS1 and DRSS2, showing a favourable numeric trend in DRSS1 and DRSS2 for pembrolizumab compared with placebo.

Table 15 Analysis of Disease Recurrence Specific Survival 1 Based on Investigator Assessment (ITT Population

	Pembrolizumab (N=496)	Placebo (N=498)
Number of Events (%)[a]	17 (3.4)	32 (6.4)
Number of Competing Events (%)[b]	92 (18.5)	119 (23.9)
Number of Censored (%)	387 (78.0)	347 (69.7)

Cumulative Incidence of Event at month 12 (%) (95% CI)	1.9 (0.9, 3.4)	5.5 (3.7, 7.8)
Cumulative Incidence of Event at month 18 (%) (95% CI)	2.8 (1.6, 4.6)	5.9 (4.1, 8.3)
Cumulative Incidence of Event at month 24 (%) (95% CI)	3.4 (2.0, 5.4)	6.6 (4.6, 9.2)

[a] Local recurrence of RCC is counted as event.

[b] Distant kidney cancer metastasis(es) or death are counted as competing event.

Cumulative incidence estimates at specified time points are based on nonparametric estimation of cumulative incidence of the event of interest accounting for competing risk events.

Database Cutoff Date: 14DEC2020

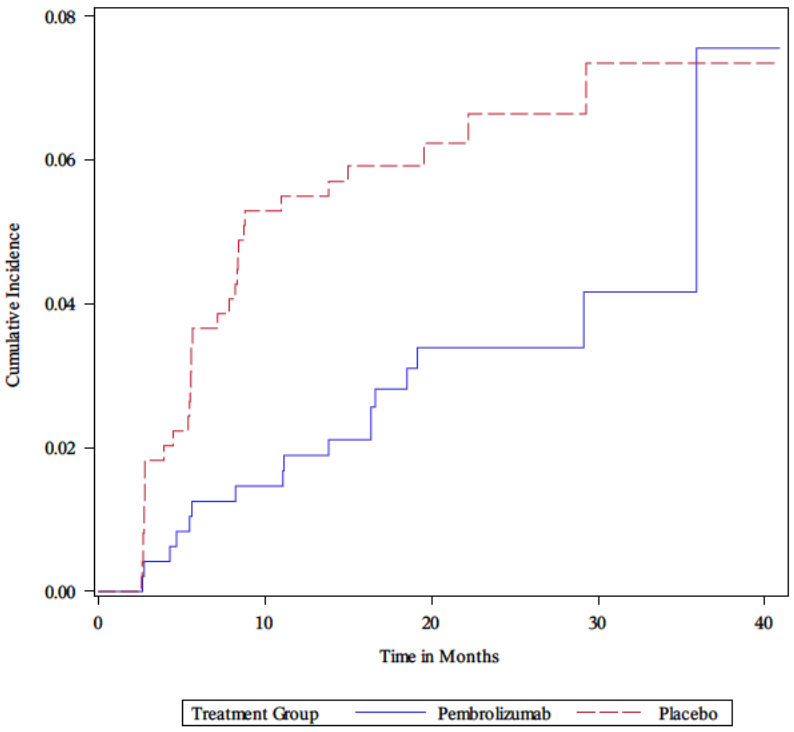


Figure 5 Cumulative Incidence Plot of Disease Recurrence Specific Survival 1

Table 16 Analysis of Disease Recurrence Specific Survival 2 Based on Investigator Assessment (ITT Population)

	Pembrolizumab (N=496)	Placebo (N=498)
Number of Events (%)[a]	94 (19.0)	134 (26.9)

Number of Competing Events (%)[b]	15 (3.0)	17 (3.4)
Number of Censored (%)	387 (78.0)	347 (69.7)
Cumulative Incidence of Event at month 12 (%) (95% CI)	12.8 (10.0, 16.0)	21.2 (17.7, 24.9)
Cumulative Incidence of Event at month 18 (%) (95% CI)	16.3 (13.1, 19.8)	25.0 (21.2, 28.9)
Cumulative Incidence of Event at month 24 (%) (95% CI)	19.8 (16.1, 23.9)	28.2 (24.1, 32.5)

[a] Local recurrence with visceral lesion or distant kidney cancer metastasis(es) with visceral lesion are counted as event.

[b] Death, local recurrence without visceral lesion, distant metastasis without visceral lesion are counted as competing event.

Cumulative incidence estimates at specified time points are based on nonparametric estimation of cumulative incidence of the event of interest accounting for competing risk events.

Database Cutoff Date: 14DEC2020

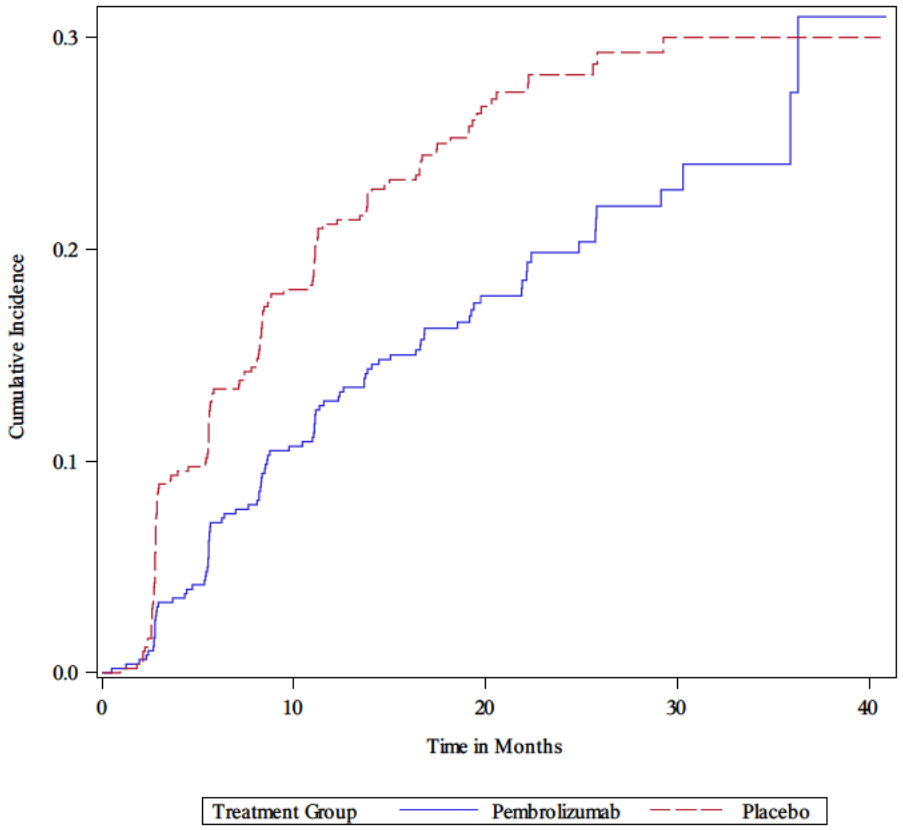


Figure 6 Cumulative Incidence Plot of Disease Recurrence Specific Survival 2 based on Investigator Assessment (ITT population)

Event-Free Survival (EFS) by BICR

EFS was defined as time from randomization to the first disease recurrence by BICR among participants who were assessed by BICR with no evidence of disease (ie, NED) at baseline, or disease progression

among participants who were assessed by BICR with evidence of disease (ie, non-NED) at baseline, or death due to any cause, whichever occurs first. The baseline disease status by BICR determined whether disease recurrence or disease progression was tracked for a participant.

Table 17 Analysis of Event-Free Survival Based on BICR (Baseline Disease Status Based on BICR Review of Baseline Scan Only) (ITT Population)

	Pembrolizumab (N=496)	Placebo (N=498)
Number of Events (%)	116 (23.4)	155 (31.1)
Death	7 (1.4)	2 (0.4)
Disease Progression	14 (2.8)	25 (5.0)
Disease Recurrence	95 (19.2)	128 (25.7)
Number of Censored (%)	380 (76.6)	343 (68.9)
Last Tumor Assessment Showing No Disease Recurrence/Progression	368 (74.2)	340 (68.3)
No Post-Baseline Tumor Status Assessment	12 (2.4)	3 (0.6)
Kaplan-Meier Estimates (months)[a]		
Median (95% CI)	NR (NR, NR)	NR (NR, NR)
[Q1, Q3]	[25.7, NR]	[10.9, NR]
person-months	9216.3	8613.8
Event Rate / 100 person-months	1.3	1.8
vs Placebo		
Hazard Ratio (95% CI)[b]	0.72 (0.56, 0.91)	
p-value[c]	0.0035	
EFS Rate at month 12 (%) (95% CI)	81.6 (77.8, 84.8)	73.0 (68.9, 76.8)
EFS Rate at month 18 (%) (95% CI)	77.7 (73.5, 81.2)	70.9 (66.7, 74.8)
EFS Rate at month 24 (%) (95% CI)	75.6 (71.3, 79.4)	66.5 (61.8, 70.8)

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

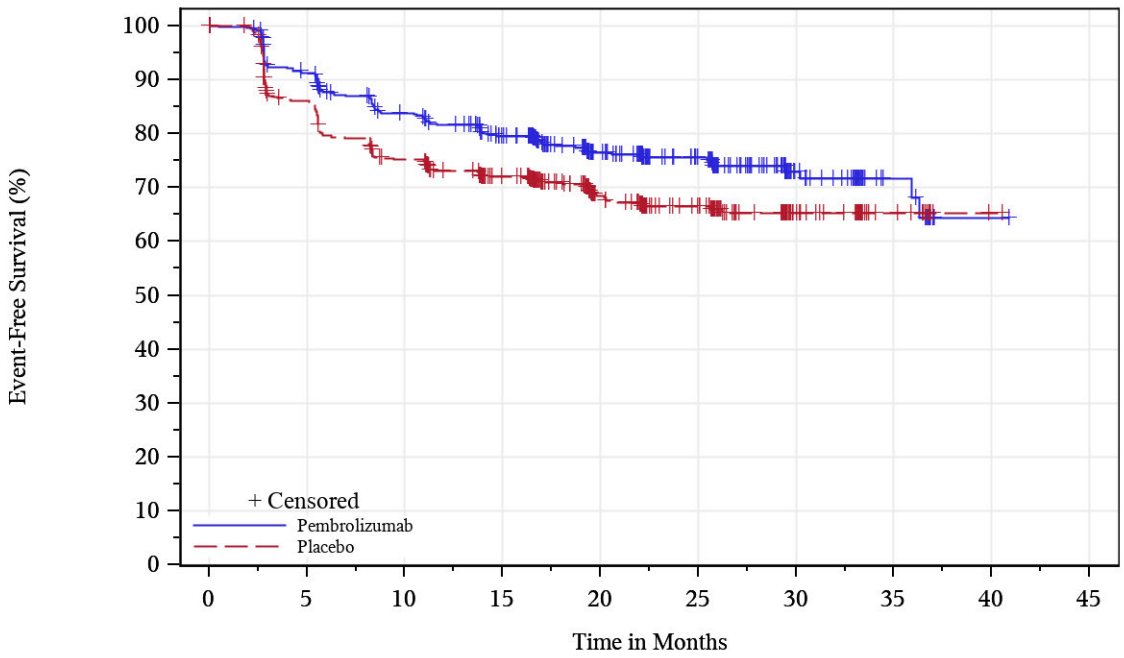
[b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by baseline disease status by BICR (NED by BICR versus Non-NED by BICR), then within NED by BICR further stratified by randomization strata: M0 versus M1 NED by investigator and ECOG PS (0 versus 1),US participant (Yes versus No) within M0 group by investigator..

[c] One-sided p-value based on log-rank test stratified by baseline disease status by BICR (NED by BICR versus Non-NED by BICR), then within NED by BICR further stratified by randomization strata: M0 versus M1 NED by investigator and ECOG PS (0 versus 1),US participant (Yes versus No) within M0 group by investigator..

NR = Not reached.

For participants who were assessed as baseline NED based on BICR review of baseline scan only but had a post-baseline scan that triggered retrospective assessment of the baseline disease, the date of that scan is used as the event date.

Database Cutoff Date: 14DEC2020



At Risk

Pembrolizumab	496	435	386	343	216	142	58	20	1	0
Placebo	498	417	358	312	189	130	52	16	1	0

Figure 7 Kaplan-Meier Plot of Event-Free Survival Based on BICR (Baseline Disease Status Based on BICR Review of Baseline Scan Only) (ITT Population)

Consistent results were obtained based on a sensitivity analysis of EFS by BICR without the additional stratum of baseline disease status by BICR (stratified on randomization strata only) (HR 0.71, 95% CI: 0.55, 0.90).

Disease-Free Survival (DFS) by BICR (Cutoff Date: 14JUN2021)

Table 18 Analysis of Disease-Free Survival Based on BICR (Participants with Baseline Non-NED Based on BICR Review of Baseline Scan Only are Censored at Baseline) (ITT Population)

	Pembrolizumab (N=496)	Placebo (N=498)
Number of Events (%)	117 (23.6)	141 (28.3)
Death	6 (1.2)	2 (0.4)
Disease Recurrence	111 (22.4)	139 (27.9)

Number of Censored (%)	379 (76.4)	357 (71.7)
Censored At Baseline	19 (3.8)	29 (5.8)
Last Tumor Assessment Showing No Disease Recurrence	360 (72.6)	328 (65.9)
Kaplan-Meier Estimates (months)[a]		
Median (95% CI)	NR (NR, NR)	NR (NR, NR)
[Q1, Q3]	[25.9, NR]	[13.8, NR]
person-months	10746.4	10132.4
Event Rate / 100 person-months	1.1	1.4
vs Placebo		
Hazard Ratio (95% CI)[b]	0.78 (0.61, 0.99)	
p-value[c]	0.0212	
DFS Rate at month 12 (%) (95% CI)	82.4 (78.6, 85.6)	75.6 (71.4, 79.3)
DFS Rate at month 18 (%) (95% CI)	78.8 (74.7, 82.3)	73.6 (69.3, 77.4)
DFS Rate at month 24 (%) (95% CI)	76.1 (71.8, 79.8)	70.3 (65.8, 74.3)

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

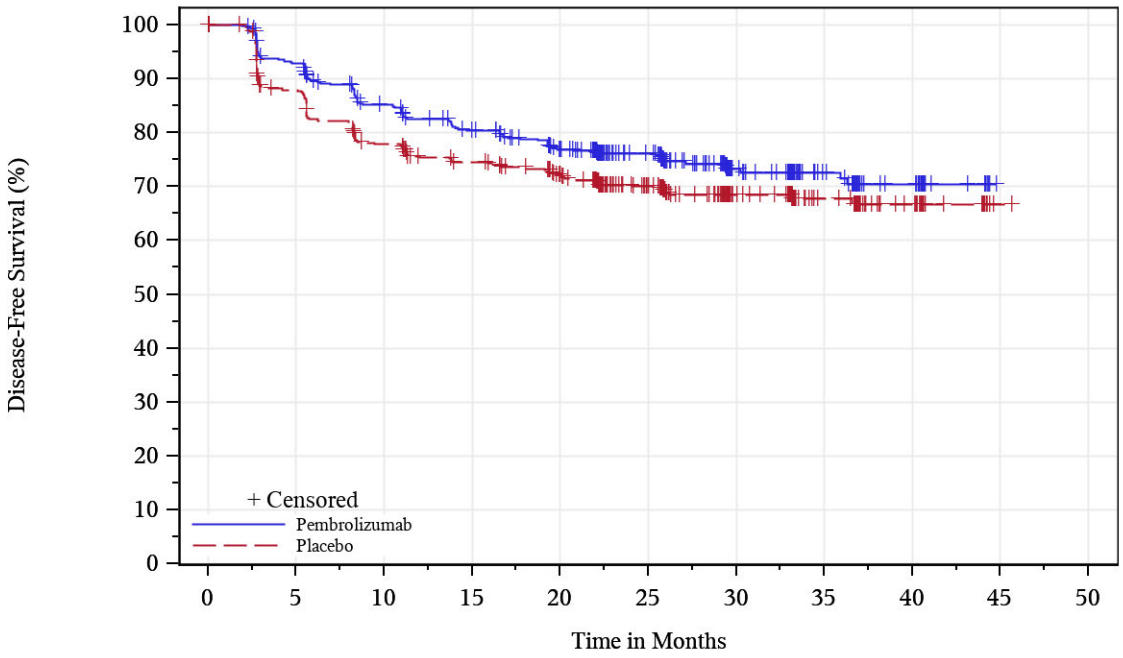
[b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by metastasis status (M0 versus M1 NED by investigator) and ECOG PS (0 versus 1),US participant (Yes versus No) within M0 group by investigator.

[c] One-sided p-value based on log-rank test stratified by metastasis status (M0 versus M1 NED by investigator) and ECOG PS (0 versus 1),US participant (Yes versus No) within M0 group by investigator.

NR = Not reached.

Baseline Non-NED was assessed by BICR review of baseline scan only.

Database Cutoff Date: 14JUN2021



At Risk

Pembrolizumab	496	428	380	350	319	228	123	70	33	0	0
Placebo	498	403	352	324	298	211	114	67	31	1	0

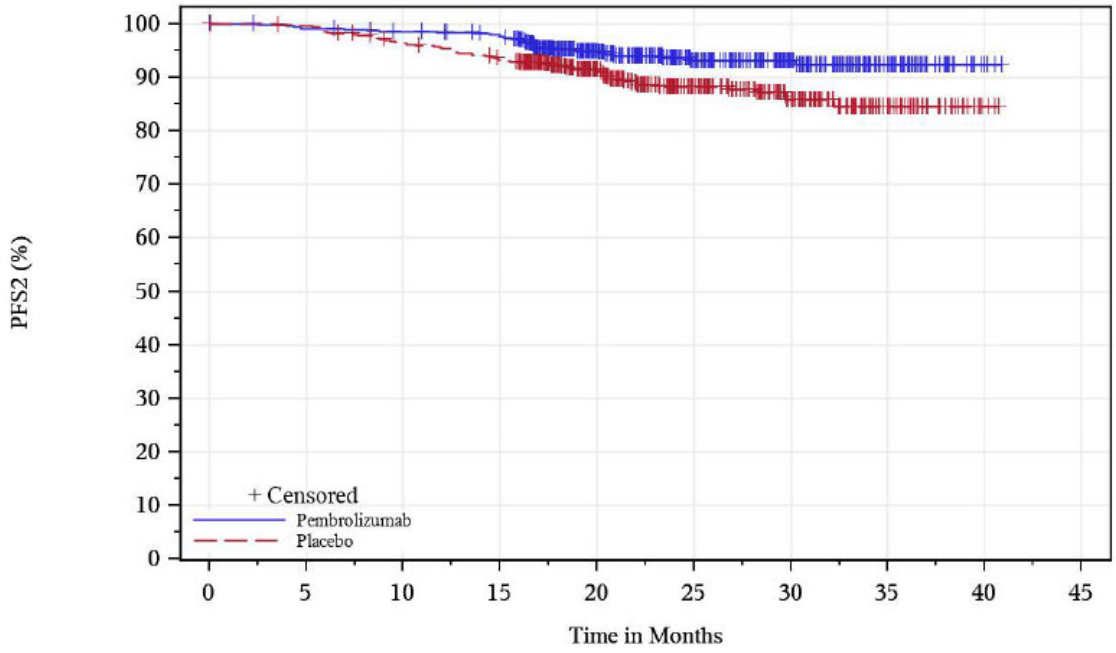
Exploratory Endpoint:

Progression-Free Survival 2

A post hoc exploratory analysis of PFS2 based on investigator assessment was conducted. PFS2 was defined as the time from randomization to disease progression on next-line anticancer drug therapy, or death from any cause, whichever occurred first. A total of 63 participants in the pembrolizumab group and 86 participants in the placebo group received subsequent anticancer drug therapy.

	Pembrolizumab (N=496)	Placebo (N=498)
Number of Events (%)	30 (6.0)	56 (11.2)
Death	11 (2.2)	13 (2.6)
Progression After Next-Line Therapy	19 (3.8)	43 (8.6)
Number of Censored (%)	466 (94.0)	442 (88.8)
Last Known Alive Date	458 (92.3)	439 (88.2)
Second Next-Line Therapy Start Date	8 (1.6)	3 (0.6)
Kaplan-Meier Estimates (months)[a]		
Median (95% CI)	NR (NR, NR)	NR (NR, NR)
[Q1, Q3]	[NR, NR]	[NR, NR]
person-months	11941.6	11683.9
Event Rate / 100 person-months	0.3	0.5
vs Placebo		
Hazard Ratio (95% CI)[b]	0.52 (0.34, 0.81)	
p-value[c]	0.0018	
PFS2 Rate at month 12 (%) (95% CI)	98.4 (96.8, 99.2)	95.3 (93.1, 96.9)
PFS2 Rate at month 18 (%) (95% CI)	95.2 (92.8, 96.8)	92.2 (89.5, 94.3)
PFS2 Rate at month 24 (%) (95% CI)	93.6 (90.7, 95.5)	88.3 (84.7, 91.0)
PFS2 Rate at month 30 (%) (95% CI)	93.1 (90.1, 95.2)	85.7 (81.2, 89.1)

[a] From product-limit (Kaplan-Meier) method for censored data.
[b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate.
[c] One-sided p-value based on log-rank test.
NR = Not reached.
Database Cutoff Date: 14DEC2020



At Risk

Pembrolizumab	496	490	483	474	321	200	117	49	3	0
Placebo	498	494	474	456	315	193	111	44	3	0

Patient-Reported Outcomes

PROs were assessed at Cycles 1, 5, 9, 13, and 17, as well as at discontinuation, 30-day follow-up, and annually during post-treatment follow-up until disease recurrence or new anticancer treatment was initiated.

The 3 prespecified PRO endpoints were mean ***change from baseline in FKSI-DRS score, EORTC-QLQ-C30 global health status/quality of life scores, and EORTC-QLQ-C30 physical functioning scale***. Nominal p-values were computed for between-treatment group comparisons. Results were not adjusted for multiplicity, and therefore should be interpreted with caution.

Completion rates for FKSI-DRS by visit at baseline through Week 52 were generally high (90.4% at baseline, 64.3% at Week 52) as were compliance rates overall (90.4% at baseline, 85.0% at Week 52), and were similar in both treatment groups.

The completion and compliance rates for EORTC QLQC30 and EQ-5D-5L were similar to those for the FKSI-DRS.

Key PRO Endpoints

Change from Baseline in FKSI-DRS and EORTC QLQ-C30 Global Health Status/Quality of Life

A change in FKSI-DRS score of ≥3 and a change in EORTC QLQ-C30 score of ≥10 were considered to be clinically meaningful.

For both FKSI-DRS and EORTC QLQ-C30 global health status/QoL score, no clinically meaningful decreases from baseline to Week 52 were observed in either the pembrolizumab or placebo groups.

Table 20 Analysis of Change from Baseline in EORTC QLQ-C30 Global Health Status/QoL to Week 52 (PRO FAS Population)

Treatment	Baseline		Week 52		Change from Baseline to Week 52	
	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI)[a]
Pembrolizumab	438	79.22 (18.46)	301	74.92 (18.26)	484	-4.25 (-6.32, -2.19)
Placebo	450	77.04 (17.61)	325	76.82 (19.56)	492	-1.68 (-3.69, 0.32)
Pairwise Comparison					Difference in LS Means[a] (95% CI)	p-Value[a]
Pembrolizumab vs. Placebo					-2.57 (-5.22, 0.08)	0.0571

[a] Based on a cLDA model with the PRO scores as the response variable with covariates for treatment by study visit interaction, stratification factors metastasis status (M0 versus M1 NED), and within M0 group further stratified by ECOG PS (0 versus 1) and US participant (Yes versus No) as covariates.
For baseline and Week 52, N is the number of subjects in each treatment group with non-missing assessments at the specific time point; for change from baseline, N is the number of subjects in the analysis population in each treatment group.
Database Cutoff Date: 14DEC2020

Table 21 Analysis of Change from Baseline in FKSI-DRS Score to Week 52 (PRO FAS Population)

Treatment	Baseline		Week 52		Change from Baseline to Week 52	
	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI)[a]
Pembrolizumab	435	32.86 (3.50)	300	31.85 (4.69)	483	-1.12 (-1.53, -0.71)
Placebo	447	32.79 (3.53)	328	32.51 (4.13)	492	-0.45 (-0.84, -0.05)
Pairwise Comparison					Difference in LS Means[a] (95% CI)	p-Value[a]
Pembrolizumab vs. Placebo					-0.67 (-1.23, -0.12)	0.0170

[a] Based on a cLDA model with the PRO scores as the response variable with covariates for treatment by study visit interaction, stratification factors metastasis status (M0 versus M1 NED), and within M0 group further stratified by ECOG PS (0 versus 1) and US participant (Yes versus No) as covariates.
For baseline and Week 52, N is the number of subjects in each treatment group with non-missing assessments at the specific time point; for change from baseline, N is the number of subjects in the analysis population in each treatment group.
Database Cutoff Date: 14DEC2020

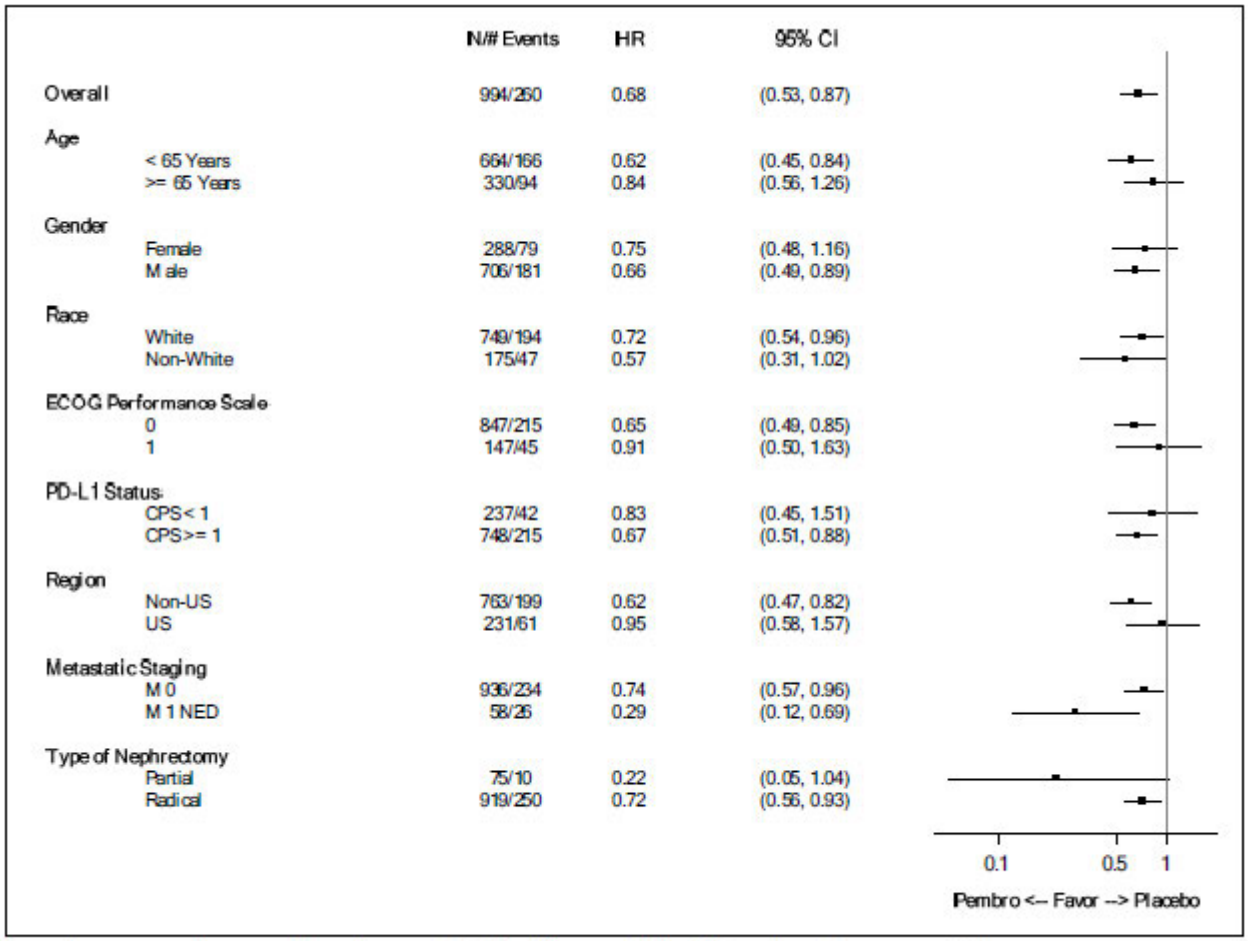
Overall Improvement and Overall Improvement/Stability in FKSI-DRS and EORTC QLQ-C30 Global Health Status/Quality of Life

The percentage of participants with improvement and improvement/stability in FKSI-DRS score was numerically higher in the placebo group (12.2% [95% CI: 9.4, 15.4] and 66.1% [95% CI: 61.8, 70.3], respectively) compared with the pembrolizumab group (7.7% [95% CI: 5.5, 10.4] and 56.9% [95% CI: 52.4, 61.4], respectively). The percentage of participants who experienced deterioration in FKSI-DRS score was 30.6% (95% CI: 26.6, 35.0) in the pembrolizumab group and 23.1% (95% CI: 19.5, 27.1) in the placebo group.

Ancillary analyses

Subgroup analyses

Consistent treatment effects were observed for DFS by investigator assessment across the prespecified subgroups with all CIs overlapping the CI for the primary DFS HR.



The subgroup analyses are based on unstratified Cox model with treatment as a covariate.
Database Cutoff Date: 14DEC2020.

Figure 10 Forest Plot of Disease-Free Survival Hazard Ratio by Subgroup Factors Based on Investigator Assessment (Primary Censoring Rule) (ITT Population)

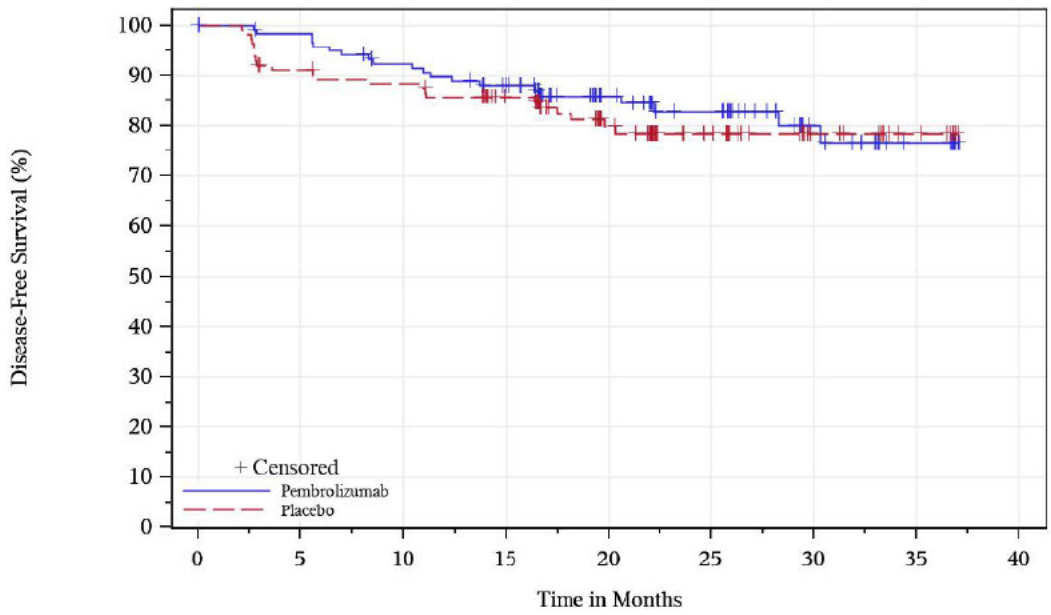
PD-L1 expression subgroups

PD-L1 Expression (CPS<1)

Table 22 Analysis of Disease-Free Survival (Primary Censoring Rule) Based on Investigator Assessment (ITT Population)(CPS<1)

	Pembrolizumab (N=124)	Placebo (N=113)
Number of Events (%)	20 (16.1)	22 (19.5)
Death	2 (1.6)	0 (0)
Disease Recurrence	18 (14.5)	22 (19.5)
Number of Censored (%)	104 (83.9)	91 (80.5)
Last Tumor Assessment Showing No Disease Recurrence	99 (79.8)	91 (80.5)
No Post-Baseline Disease Status Assessment	5 (4.0)	0 (0)
Kaplan-Meier Estimates (months)[a]		
Median (95% CI)	NR (NR, NR)	NR (NR, NR)
[Q1, Q3]	[NR, NR]	[NR, NR]
person-months	2566.6	2282.7
Event Rate / 100 person-months	0.8	1.0
vs Placebo		
Hazard Ratio (95% CI)[b]	0.83 (0.45, 1.51)	
p-value[c]	0.2678	
DFS Rate at month 12 (%) (95% CI)	89.8 (82.7, 94.1)	85.7 (77.7, 91.0)
DFS Rate at month 18 (%) (95% CI)	86.0 (78.1, 91.2)	82.4 (73.7, 88.4)
DFS Rate at month 24 (%) (95% CI)	82.7 (73.5, 89.0)	78.5 (69.0, 85.4)

[a] From product-limit (Kaplan-Meier) method for censored data.
[b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate.
[c] One-sided p-value based on log-rank test.
NR = Not reached.
Database Cutoff Date: 14DEC2020



At Risk

Pembrolizumab	124	116	107	96	57	45	23	12	0
Placebo	113	101	97	84	60	33	17	8	0

Figure 11 Kaplan-Meier Plot of Disease-Free Survival (Primary Censoring Rule) Based on Investigator Assessment (ITT Population)(CPS<1)

Table 23 Analysis of Disease-Free Survival (Primary Censoring Rule)
Based on Investigator Assessment (ITT Population)(CPS<1) (updated Data cutoff 14 Jun 2021)

	Pembrolizumab (N=124)	Placebo (N=113)
Number of Events (%)	19 (15.3)	25 (22.1)
Death	2 (1.6)	1 (0.9)
Disease Recurrence	17 (13.7)	24 (21.2)
Number of Censored (%)	105 (84.7)	88 (77.9)
Last Tumor Assessment Showing No Disease Recurrence	100 (80.6)	88 (77.9)
No Post-Baseline Disease Status Assessment	5 (4.0)	0 (0)
Kaplan-Meier Estimates (months)[a]		
Median (95% CI)	NR (NR, NR)	NR (NR, NR)
[Q1, Q3]	[NR, NR]	[39.2, NR]
person-months	3130.6	2810.7
Event Rate / 100 person-months	0.6	0.9
vs Placebo		
Hazard Ratio (95% CI)[b]	0.68 (0.37, 1.24)	
p-value[c]	0.1018	
DFS Rate at month 12 (%) (95% CI)	89.8 (82.8, 94.1)	85.7 (77.8, 91.0)
DFS Rate at month 18 (%) (95% CI)	87.3 (79.8, 92.1)	83.0 (74.6, 88.8)
DFS Rate at month 24 (%) (95% CI)	85.3 (77.4, 90.6)	78.0 (68.9, 84.7)

[a] From product-limit (Kaplan-Meier) method for censored data.
[b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate.
[c] One-sided p-value based on log-rank test.

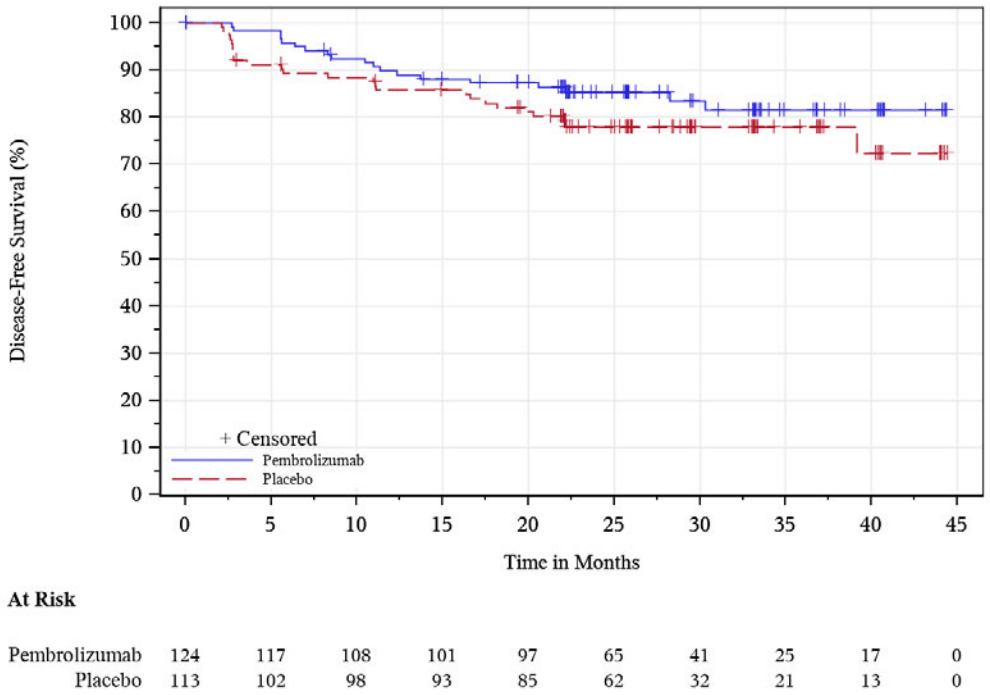


Figure 12 Kaplan-Meier Plot of Disease-Free Survival (Primary Censoring Rule) Based on Investigator Assessment (ITT Population)(CPS<1) (updated Data cutoff date 14 Jun 2021)

PD-L1 Expression(CPS>=1)

Table 24 Analysis of Disease-Free Survival (Primary Censoring Rule) Based on Investigator Assessment (ITT Population)(CPS>=1)

	Pembrolizumab (N=365)	Placebo (N=383)
Number of Events (%)	87 (23.8)	128 (33.4)
Death	4 (1.1)	2 (0.5)
Disease Recurrence	83 (22.7)	126 (32.9)
Number of Censored (%)	278 (76.2)	255 (66.6)
Last Tumor Assessment Showing No Disease Recurrence	272 (74.5)	252 (65.8)
No Post-Baseline Disease Status Assessment	6 (1.6)	3 (0.8)
Kaplan-Meier Estimates (months)[a]		
Median (95% CI)	NR (35.9, NR)	NR (NR, NR)
[Q1, Q3]	[24.9, NR]	[11.1, NR]
person-months	7089.4	6930.7
Event Rate / 100 person-months	1.2	1.8
vs Placebo		
Hazard Ratio (95% CI)[b]	0.67 (0.51, 0.88)	
p-value[c]	0.0019	
DFS Rate at month 12 (%) (95% CI)	84.7 (80.5, 88.0)	73.5 (68.8, 77.7)
DFS Rate at month 18 (%) (95% CI)	80.3 (75.7, 84.1)	69.0 (64.1, 73.5)
DFS Rate at month 24 (%) (95% CI)	75.7 (70.4, 80.2)	65.1 (59.8, 70.0)

[a] From product-limit (Kaplan-Meier) method for censored data.
[b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate.
[c] One-sided p-value based on log-rank test.
NR = Not reached.
Database Cutoff Date: 14DEC2020

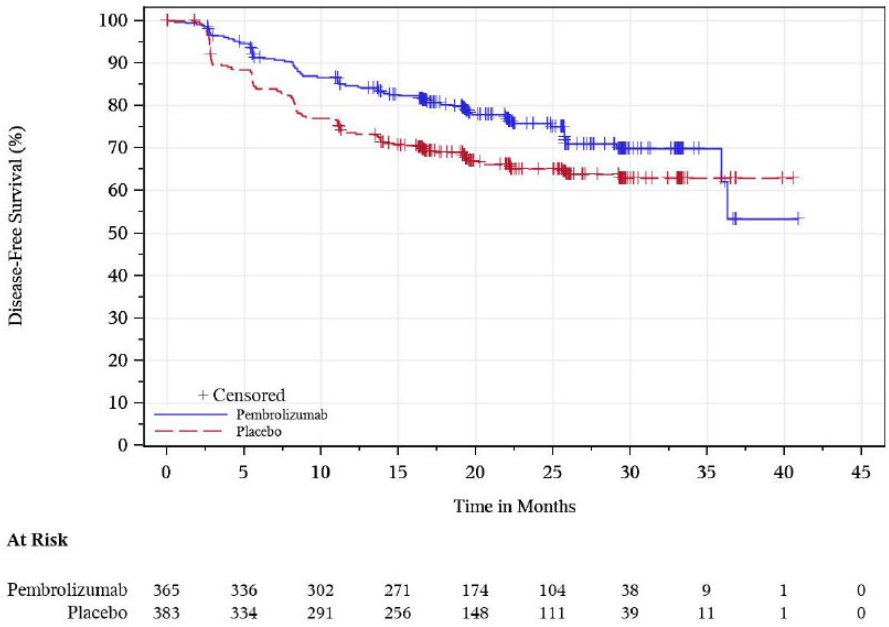


Figure 13 Kaplan-Meier Plot of Disease-Free Survival (Primary Censoring Rule) Based on Investigator Assessment (ITT Population)(CPS>=1)

Subgroups with different prognosis

Summary of DFS Results in Baseline Disease Status Subgroups based on updated dataset (14. Jun 2021).

Baseline Disease Status by Investigator	Hazard Ratio (95% CI)
Baseline Disease Status of M0	0.68 (0.53, 0.88)
Baseline Disease Status of M0-Intermediate-High Risk	0.68 (0.52, 0.89)
Baseline Disease Status of M0-High Risk	0.60 (0.33, 1.10)
Baseline Disease Status of M1 NED	0.28 (0.12, 0.66)

M1 NED

Table 25 Analysis of Disease-Free Survival (Primary Censoring Rule) Based on Investigator Assessment (ITT Population)(Baseline Disease Status of M1 NED by Investigator)(updated data cut-off 14JUN2021)

	Pembrolizumab (N=29)	Placebo (N=29)
Number of Events (%) Death	7 (24.1) 1 (3.4)	19 (65.5) 1 (3.4)

Disease Recurrence	6 (20.7)	18 (62.1)
Number of Censored (%)	22 (75.9)	10 (34.5)
Last Tumor Assessment Showing No Disease Recurrence	21 (72.4)	10 (34.5)
No Post-Baseline Disease Status Assessment	1 (3.4)	0 (0)
Kaplan-Meier Estimates (months)[a]		
Median (95% CI)	NR (25.7, NR)	11.6 (5.6, NR)
[Q1, Q3]	[25.7, NR]	[5.5, NR]
person-months	665.6	479.0
Event Rate / 100 person-months	1.1	4.0
vs Placebo		
Hazard Ratio (95% CI)[b]	0.28 (0.12, 0.66)	
p-value[c]	0.0010	
DFS Rate at month 12 (%) (95% CI)	82.1 (62.3, 92.1)	48.3 (29.5, 64.8)
DFS Rate at month 18 (%) (95% CI)	82.1 (62.3, 92.1)	41.4 (23.7, 58.3)
DFS Rate at month 24 (%) (95% CI)	78.4 (58.1, 89.7)	37.9 (20.9, 54.9)

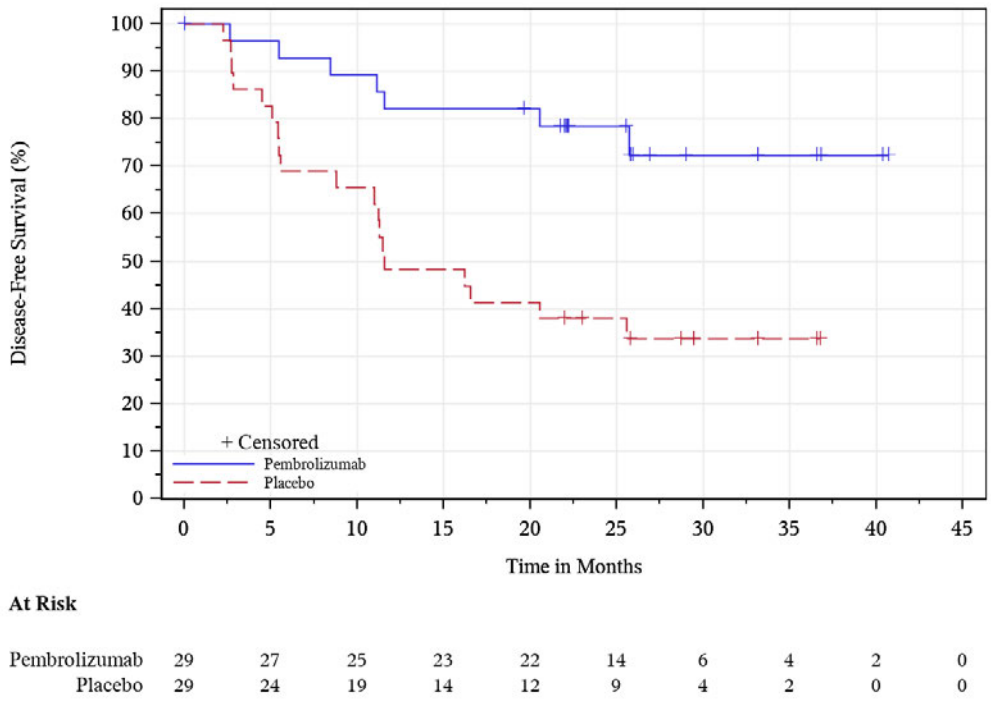
[a] From product-limit (Kaplan-Meier) method for censored data.

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

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

NR = Not reached.

Database Cutoff Date: 14JUN2021



At Risk

Pembrolizumab	29	27	25	23	22	14	6	4	2	0
Placebo	29	24	19	14	12	9	4	2	0	0

Figure 14 Kaplan-Meier Plot of Disease-Free Survival (Primary Censoring Rule) Based on Investigator Assessment
(ITT Population)(Baseline Disease Status of M1 NED by Investigator) 14JUN2021

M0

DFS by Investigator Assessment in M0

	Pembrolizumab (N=467)	Placebo (N=469)
Number of Events (%)	107 (22.9)	150 (32.0)
Death	5 (1.1)	2 (0.4)
Disease Recurrence	102 (21.8)	148 (31.6)
Number of Censored (%)	360 (77.1)	319 (68.0)
Last Tumor Assessment Showing No Disease Recurrence	349 (74.7)	316 (67.4)
No Post-Baseline Disease Status Assessment	11 (2.4)	3 (0.6)
Kaplan-Meier Estimates (months)[a]		
Median (95% CI)	NR (NR, NR)	NR (40.5, NR)
[Q1, Q3]	[30.2, NR]	[15.0, NR]
person-months	11095.7	10594.8
Event Rate / 100 person-months	1.0	1.4
vs Placebo		
Hazard Ratio (95% CI)[b]	0.68 (0.53, 0.88)	
p-value[c]	0.0012	
DFS Rate at month 12 (%) (95% CI)	85.7 (82.2, 88.7)	77.8 (73.7, 81.3)
DFS Rate at month 18 (%) (95% CI)	82.1 (78.2, 85.3)	73.2 (68.9, 77.0)
DFS Rate at month 24 (%) (95% CI)	78.3 (74.1, 81.9)	69.2 (64.7, 73.2)

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

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

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

NR = Not reached.

Database Cutoff Date: 14JUN2021

Figure 15 Analysis of Disease-Free Survival (Primary Censoring Rule)
Based on Investigator Assessment (ITT Population)(Baseline Disease Status of M0 by Investigator)
updated data cut-off 14JUN2021

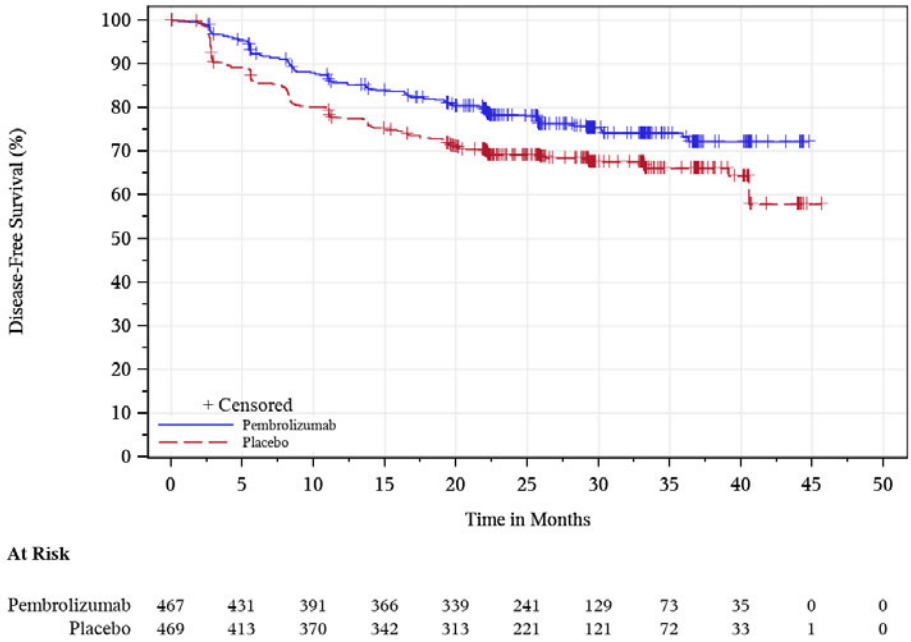


Figure 16 Kaplan-Meier Plot of Disease-Free Survival (Primary Censoring Rule Based on Investigator Assessment (ITT Population)(Baseline Disease Status of M0 by Investigator)

DFS by Investigator Assessment in Intermediate-High and High-Risk Subgroups

A post hoc analysis was conducted to evaluate DFS by investigator assessment in subgroups of participants with RCC at M0-intermediate-high risk versus M0-high risk of recurrence.

Table 26 Analysis of Disease-Free Survival (Primary Censoring Rule)
Based on Investigator Assessment (ITT Population) (M0-Intermediate-High Risk by Investigator)
Database Cutoff Date: 14DEC2020

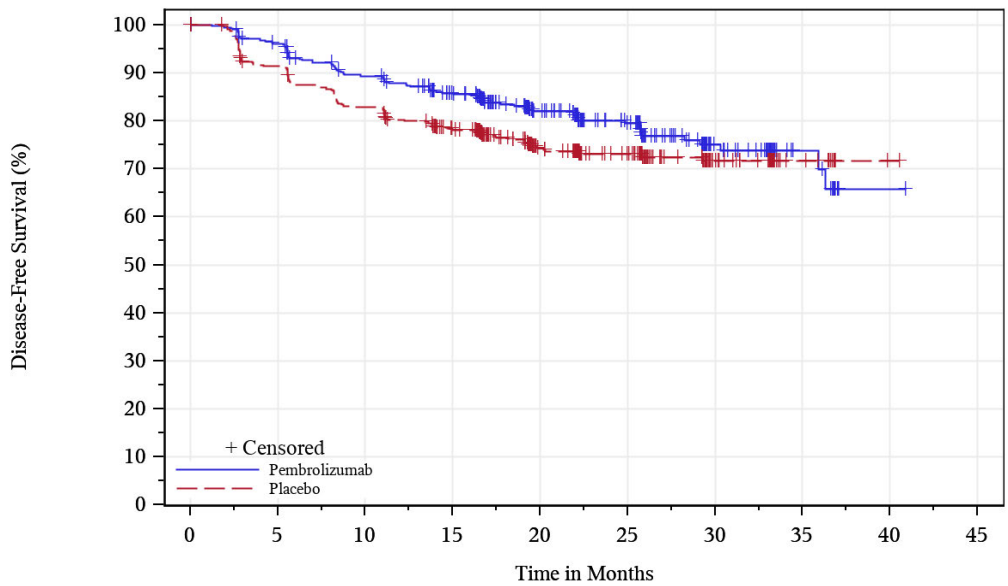
	Pembrolizumab (N=422)	Placebo (N=433)
Number of Events (%)	83 (19.7)	110 (25.4)
Death	5 (1.2)	1 (0.2)
Disease Recurrence	78 (18.5)	109 (25.2)
Number of Censored (%)	339 (80.3)	323 (74.6)
Last Tumor Assessment Showing No Disease Recurrence	328 (77.7)	320 (73.9)
No Post-Baseline Disease Status Assessment	11 (2.6)	3 (0.7)
Kaplan-Meier Estimates (months)[a]		
Median (95% CI)	NR (NR, NR)	NR (NR, NR)
[Q1, Q3]	[30.3, NR]	[19.5, NR]

person-months	8425.6	8345.5
Event Rate / 100 person-months	1.0	1.3
vs Placebo		
Hazard Ratio (95% CI)[b]	0.75 (0.57, 1.00)	
p-value[c]	0.0244	
DFS Rate at month 12 (%) (95% CI)	87.9 (84.3, 90.7)	80.3 (76.2, 83.8)
DFS Rate at month 18 (%) (95% CI)	83.4 (79.4, 86.8)	76.4 (72.0, 80.2)
DFS Rate at month 24 (%) (95% CI)	80.1 (75.5, 84.0)	73.1 (68.3, 77.3)

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

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

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



At Risk

Pembrolizumab	422	391	356	321	202	132	56	19	1	0
Placebo	433	389	352	311	191	132	55	18	1	0

Figure 17 Kaplan-Meier Plot of Disease-Free Survival (Primary Censoring Rule)Based on Investigator Assessment (ITT Population) (M0-Intermediate-High Risk by Investigator) Database Cutoff Date: 14DEC2020

Table 27 Analysis of Disease-Free Survival (Primary Censoring Rule) Based on Investigator Assessment (ITT Population)(M0-Intermediate-High Risk by Investigator) (updated data cut-off 14JUN2021)

	Pembrolizumab	Placebo

	(N=422)	(N=433)
Number of Events (%)	87 (20.6)	127 (29.3)
Death	5 (1.2)	2 (0.5)
Disease Recurrence	82 (19.4)	125 (28.9)
Number of Censored (%)	335 (79.4)	306 (70.7)
Last Tumor Assessment Showing No Disease Recurrence	324 (76.8)	303 (70.0)
No Post-Baseline Disease Status Assessment	11 (2.6)	3 (0.7)
Kaplan-Meier Estimates (months)[a]		
Median (95% CI)	NR (NR, NR)	NR (40.5, NR)
[Q1, Q3]	[36.3, NR]	[19.1, NR]
person-months	10191.2	10065.0
Event Rate / 100 person-months	0.9	1.3
vs Placebo		
Hazard Ratio (95% CI)[b]	0.68 (0.52, 0.89)	
p-value[c]	0.0025	
DFS Rate at month 12 (%) (95% CI)	87.6 (84.0, 90.5)	80.1 (76.0, 83.6)
DFS Rate at month 18 (%) (95% CI)	84.1 (80.1, 87.3)	75.8 (71.5, 79.6)
DFS Rate at month 24 (%) (95% CI)	81.1 (76.8, 84.6)	72.0 (67.5, 76.1)

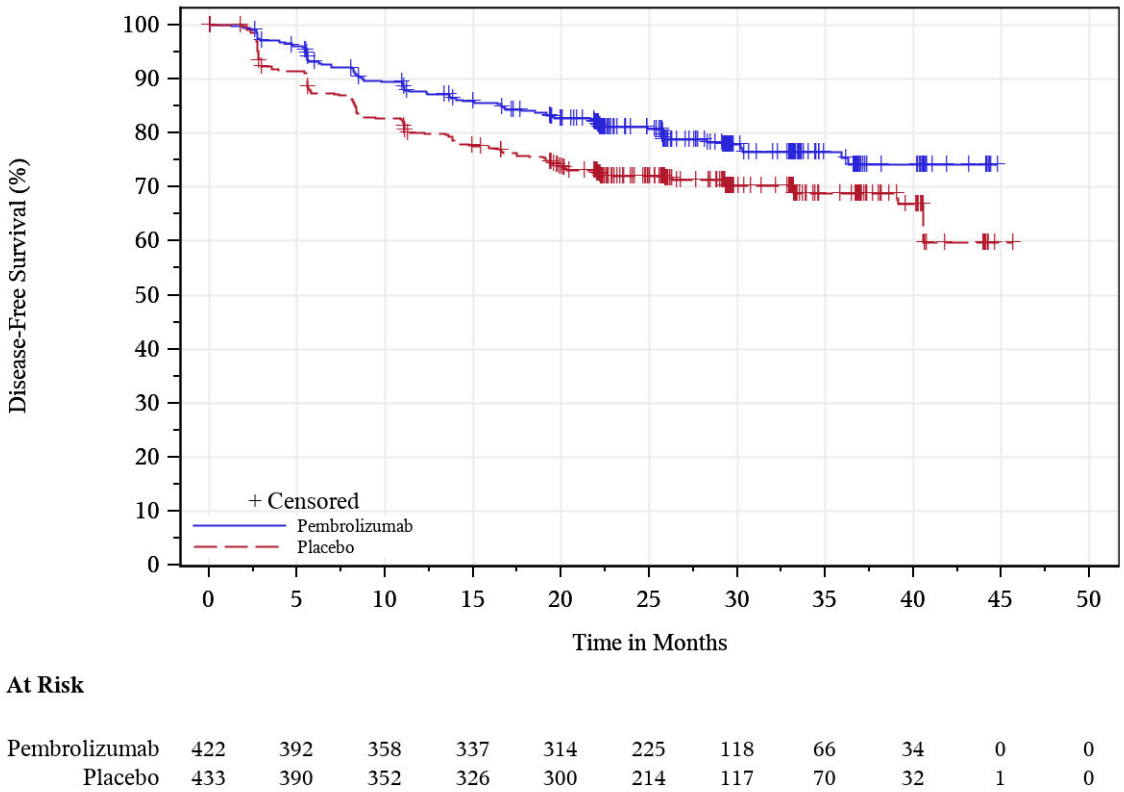
[a] From product-limit (Kaplan-Meier) method for censored data.

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

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

NR = Not reached.

Database Cutoff Date: 14JUN2021



At Risk

Pembrolizumab	422	392	358	337	314	225	118	66	34	0	0
Placebo	433	390	352	326	300	214	117	70	32	1	0

Figure 18 Kaplan-Meier Plot of Disease-Free Survival (Primary Censoring Rule)

Based on Investigator Assessment (ITT Population)(M0-Intermediate-High Risk by Investigator) **(14JUN2021)**

Table 28 Analysis of Disease-Free Survival (Primary Censoring Rule)
Based on Investigator Assessment (ITT Population) (M0-High Risk by Investigator) Database Cutoff Date: 14DEC2020

	Pembrolizumab	Placebo
	(N=40)	(N=36)
Number of Events (%)	19 (47.5)	22 (61.1)
Disease Recurrence	19 (47.5)	22 (61.1)
Number of Censored (%)	21 (52.5)	14 (38.9)
Last Tumor Assessment Showing No Disease Recurrence	21 (52.5)	14 (38.9)
Kaplan-Meier Estimates (months)[a]		
Median (95% CI)	22.4 (11.1, NR)	11.4 (2.9, NR)
[Q1, Q3]	[8.6, NR]	[2.9, NR]

person-months	676.2	469.6
Event Rate / 100 person-months	2.8	4.7
vs Placebo		
Hazard Ratio (95% CI)[b]	0.60 (0.33, 1.11)	
p-value[c]	0.0523	
DFS Rate at month 12 (%) (95% CI)	65.0 (48.2, 77.6)	50.0 (32.9, 64.9)
DFS Rate at month 18 (%) (95% CI)	59.8 (42.9, 73.1)	44.4 (28.0, 59.6)
DFS Rate at month 24 (%) (95% CI)	48.4 (30.7, 63.9)	35.6 (19.3, 52.3)

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

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

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

NR = Not reached.

Database Cutoff Date: 14DEC2020

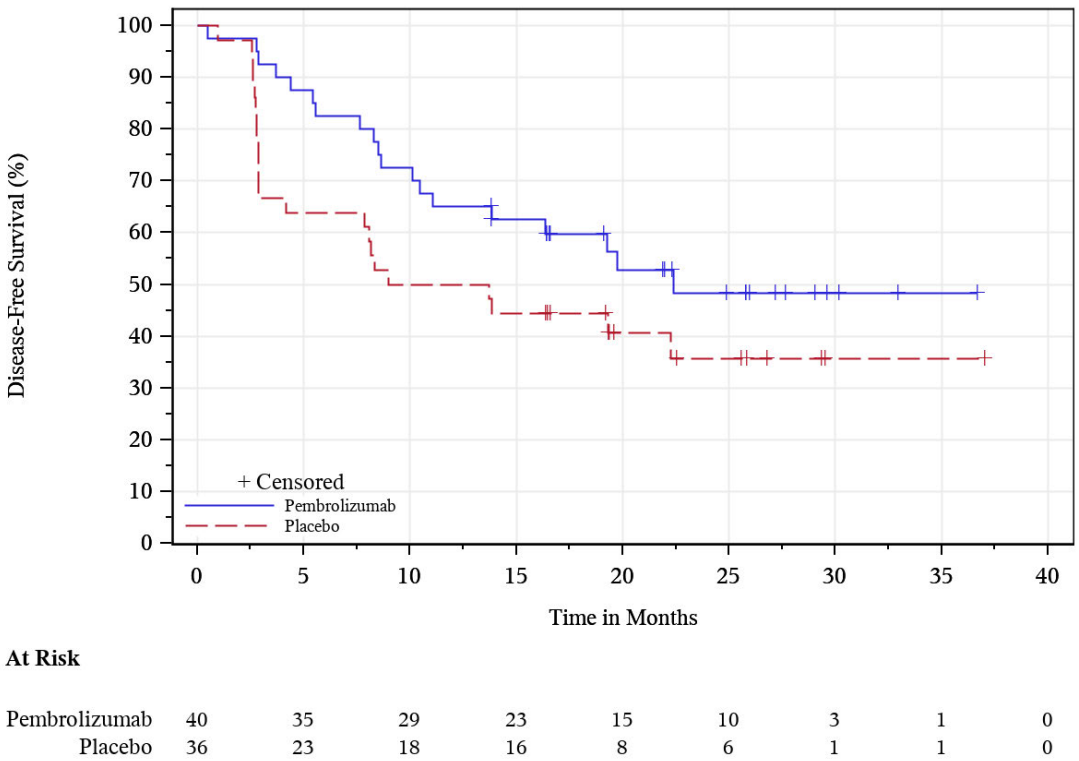


Figure 19 Kaplan-Meier Plot of Disease-Free Survival (Primary Censoring Rule)Based on Investigator Assessment (ITT Population) (M0-High Risk by Investigator) Database Cutoff Date:14DEC2020

Table 29 Analysis of Disease-Free Survival (Primary Censoring Rule) Based on Investigator Assessment (ITT Population) (pT3, N0, M0, Grade 2-4) (Database Cutoff Date: 14DEC2020)

	Pembrolizumab (N=385)	Placebo (N=398)
Number of Events (%)	73 (19.0)	99 (24.9)
Death	4 (1.0)	1 (0.3)
Disease Recurrence	69 (17.9)	98 (24.6)
Number of Censored (%)	312 (81.0)	299 (75.1)
Last Tumor Assessment Showing No Disease Recurrence	301 (78.2)	296 (74.4)
No Post-Baseline Disease Status Assessment	11 (2.9)	3 (0.8)
Kaplan-Meier Estimates (months)[a]		
Median (95% CI)	NR (NR, NR)	NR (NR, NR)
[Q1, Q3]	[30.3, NR]	[19.8, NR]
person-months	7691.6	7696.3
Event Rate / 100 person-months	0.9	1.3
vs Placebo		
Hazard Ratio (95% CI)[b]	0.74 (0.55, 1.00)	
p-value[c]	0.0264	
DFS Rate at month 12 (%) (95% CI)	88.6 (84.8, 91.4)	80.6 (76.3, 84.2)
DFS Rate at month 18 (%) (95% CI)	84.2 (80.0, 87.7)	76.9 (72.3, 80.8)
DFS Rate at month 24 (%) (95% CI)	80.9 (76.0, 84.9)	73.7 (68.7, 78.0)

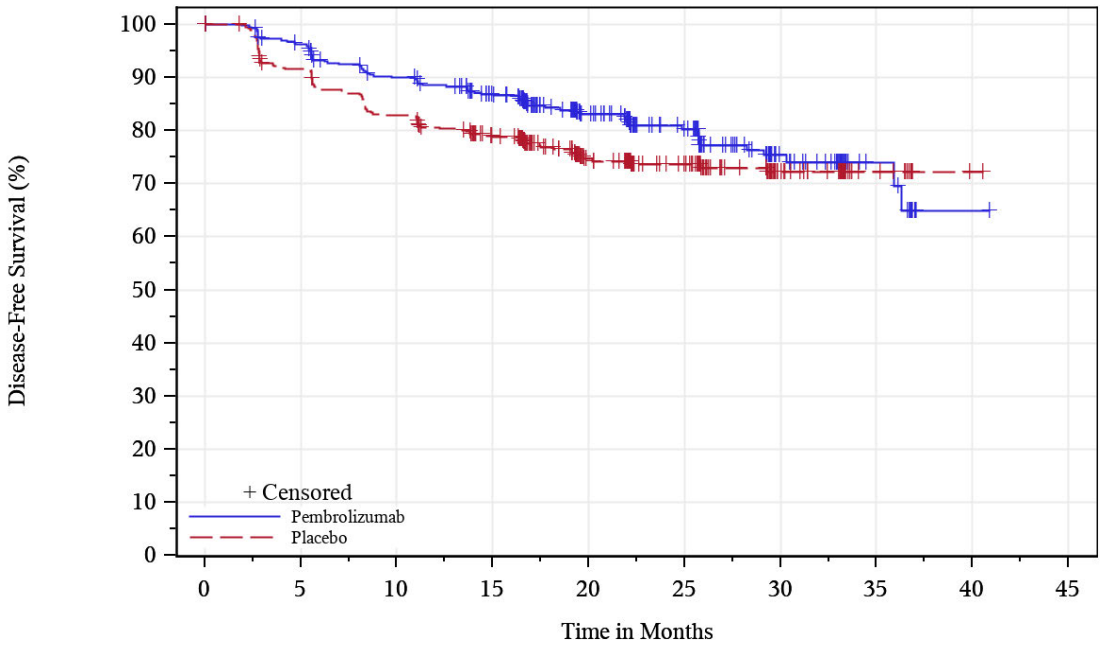
[a] From product-limit (Kaplan-Meier) method for censored data.

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

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

NR = Not reached.

Database Cutoff Date: 14DEC2020



At Risk

Pembrolizumab	385	356	325	295	184	121	53	17	1	0
Placebo	398	358	323	287	175	122	53	16	1	0

Figure 20 Kaplan-Meier Plot of Disease-Free Survival (Primary Censoring Rule) Based on Investigator Assessment (ITT Population) (pT3, N0, M0, Grade 2-4) (Database Cutoff Date: 14DEC2020)

Table 30 Analysis of Disease-Free Survival (Primary Censoring Rule) Based on Investigator Assessment (ITT Population) (pT3, N0, M0, Grade 2-4) (Database Cutoff Date: 14JUN2021)

	Pembrolizumab (N=385)	Placebo (N=398)
Number of Events (%)	76 (19.7)	115 (28.9)
Death	4 (1.0)	2 (0.5)
Disease Recurrence	72 (18.7)	113 (28.4)
Number of Censored (%)	309 (80.3)	283 (71.1)
Last Tumor Assessment Showing No Disease Recurrence	298 (77.4)	280 (70.4)
No Post-Baseline Disease Status Assessment	11 (2.9)	3 (0.8)
Kaplan-Meier Estimates (months)[a]		

Median (95% CI)	NR (NR, NR)	NR (40.5, NR)
[Q1, Q3]	[36.3, NR]	[19.3, NR]
person-months	9301.3	9282.1
Event Rate / 100 person-months	0.8	1.2
vs Placebo		
Hazard Ratio (95% CI)[b]	0.66 (0.49, 0.88)	
p-value[c]	0.0024	
DFS Rate at month 12 (%) (95% CI)	88.3 (84.6, 91.2)	80.4 (76.1, 84.0)
DFS Rate at month 18 (%) (95% CI)	84.9 (80.9, 88.2)	76.2 (71.7, 80.1)
DFS Rate at month 24 (%) (95% CI)	82.2 (77.8, 85.8)	72.6 (67.9, 76.8)

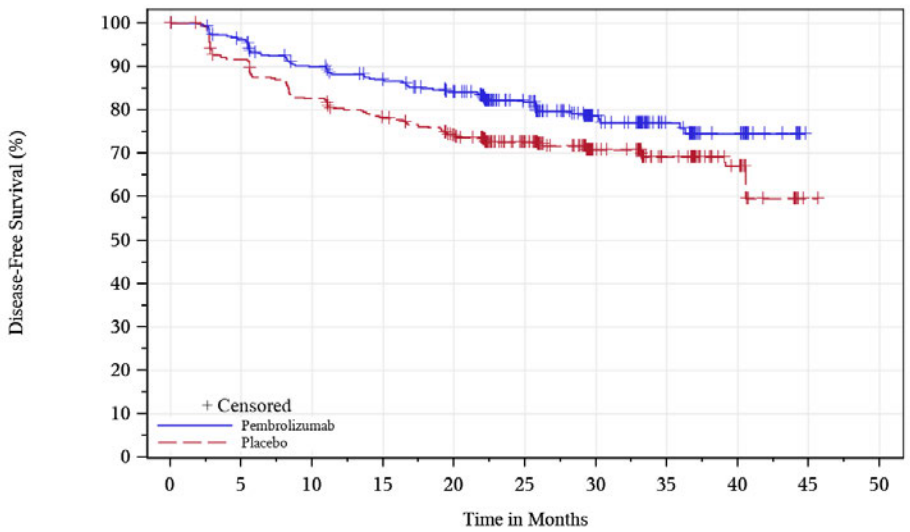
[a] From product-limit (Kaplan-Meier) method for censored data.

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

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

NR = Not reached.

Database Cutoff Date: 14JUN2021



At Risk

Pembrolizumab	385	357	327	310	289	204	106	60	31	0	0
Placebo	398	359	323	301	276	197	108	67	30	1	0

Table 31 Analysis of Disease-Free Survival (Primary Censoring Rule) Based on Investigator Assessment (ITT Population) (pT3, N0, M0, Grade 1 or pT2 (Grade 4 or sarcomatoid), N0, M0) (Database Cutoff Date: 14DEC2020***)***

	Pembrolizumab (N=37)	Placebo (N=35)
Number of Events (%)	10 (27.0)	11 (31.4)
Death	1 (2.7)	0 (0)
Disease Recurrence	9 (24.3)	11 (31.4)
Number of Censored (%)	27 (73.0)	24 (68.6)
Last Tumor Assessment Showing No Disease Recurrence	27 (73.0)	24 (68.6)
Kaplan-Meier Estimates (months)[a]		
Median (95% CI)	NR (NR, NR)	NR (20.3, NR)
[Q1, Q3]	[19.2, NR]	[13.8, NR]
person-months	734.0	649.2
Event Rate / 100 person-months	1.4	1.7
vs Placebo		
Hazard Ratio (95% CI)[b]	0.83 (0.35, 1.95)	
p-value[c]	0.3360	
DFS Rate at month 12 (%) (95% CI)	81.1 (64.4, 90.5)	77.1 (59.5, 87.9)
DFS Rate at month 18 (%) (95% CI)	75.7 (58.5, 86.5)	71.4 (53.4, 83.5)
DFS Rate at month 24 (%) (95% CI)	72.4 (54.6, 84.1)	67.0 (47.8, 80.4)

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

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

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

NR = Not reached.

Database Cutoff Date: 14DEC2020

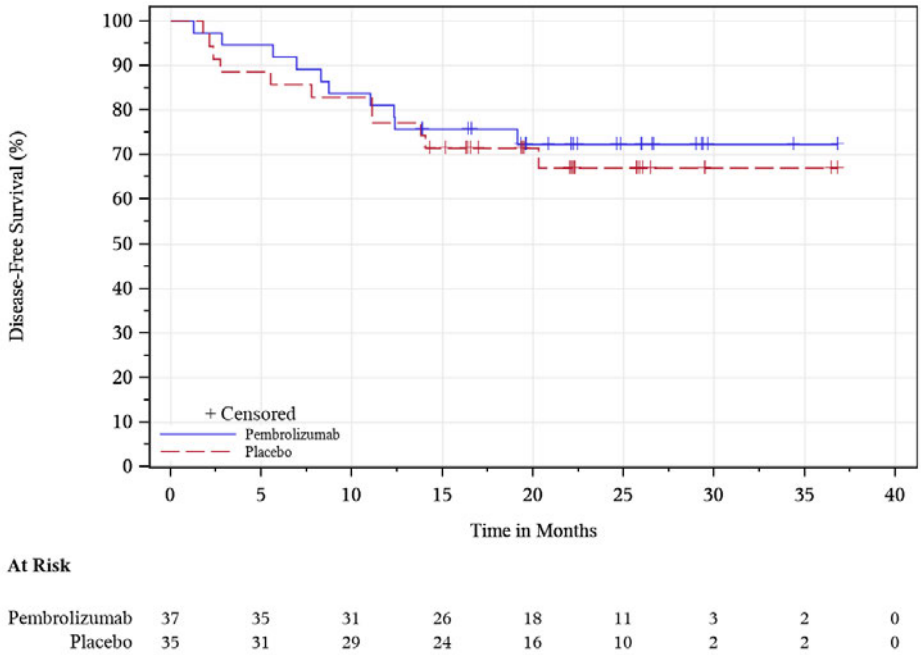


Figure 22 Kaplan-Meier Plot of Disease-Free Survival (Primary Censoring Rule) Based on Investigator Assessment (ITT Population) (pT3, N0, M0, Grade 1 or pT2 (Grade 4 or sarcomatoid), N0, M0) (Database Cutoff Date: 14DEC2020)

Table 32 Analysis of Disease-Free Survival (Primary Censoring Rule) Based on Investigator Assessment (ITT Population)(pT3, N0, M0, Grade 1 or pT2 (Grade 4 or sarcomatoid), N0, M0) (Database Cutoff Date: 14JUN2021***)***

	Pembrolizumab (N=37)	Placebo (N=35)
Number of Events (%)	11 (29.7)	12 (34.3)
Death	1 (2.7)	0 (0)
Disease Recurrence	10 (27.0)	12 (34.3)
Number of Censored (%)	26 (70.3)	23 (65.7)
Last Tumor Assessment Showing No Disease Recurrence	26 (70.3)	23 (65.7)
Kaplan-Meier Estimates (months)[a]		
Median (95% CI)	NR (NR, NR)	NR (22.0, NR)
[Q1, Q3]	[19.2, NR]	[13.8, NR]

person-months	889.9	782.8
Event Rate / 100 person-months	1.2	1.5
vs Placebo		
Hazard Ratio (95% CI)[b]	0.84 (0.37, 1.91)	
p-value[c]	0.3424	
DFS Rate at month 12 (%) (95% CI)	81.1 (64.4, 90.5)	77.1 (59.5, 87.9)
DFS Rate at month 18 (%) (95% CI)	75.7 (58.5, 86.5)	71.4 (53.4, 83.5)
DFS Rate at month 24 (%) (95% CI)	70.1 (52.5, 82.2)	65.3 (47.1, 78.6)

[a] From product-limit (Kaplan-Meier) method for censored data. [b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate. [c] One-sided p-value based on log-rank test. NR = Not reached. Database Cutoff Date: 14JUN2021

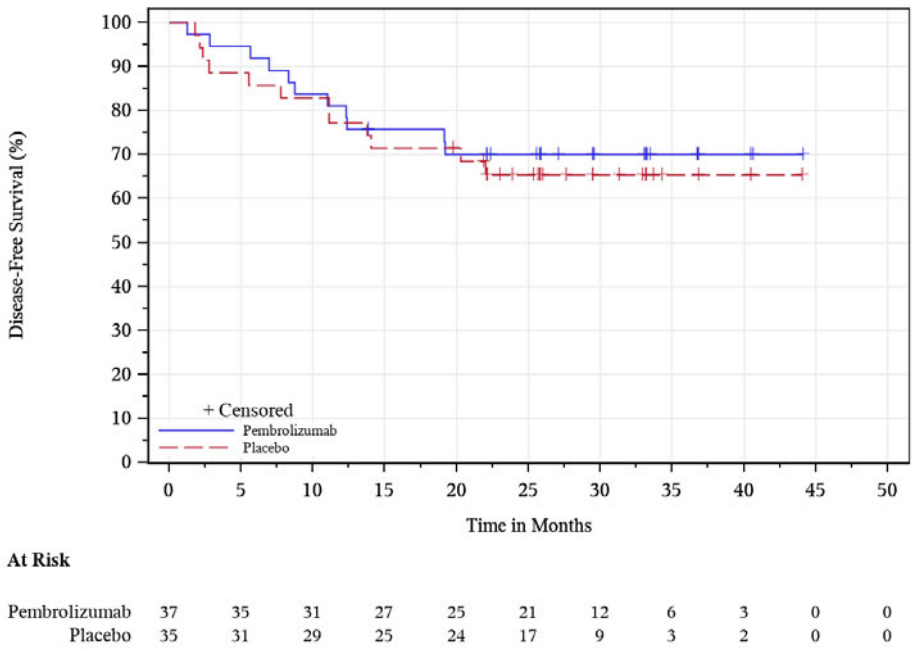


Figure 23 Figure 9 Kaplan-Meier Plot of Disease-Free Survival (Primary Censoring Rule) Based on Investigator Assessment (ITT Population) (pT3, N0, M0, Grade 1 or pT2 (Grade 4 or sarcomatoid), N0, M0) (Database Cutoff Date: 14JUN2021)

ECOG-Status

Table 33 Analysis of Disease-Free Survival (Primary Censoring Rule) Based on Investigator Assessment (ITT Population)(ECOG 1)

	Pembrolizumab (N=75)	Placebo (N=72)
Number of Events (%)	22 (29.3)	23 (31.9)
Death	3 (4.0)	0 (0)
Disease Recurrence	19 (25.3)	23 (31.9)
Number of Censored (%)	53 (70.7)	49 (68.1)
Last Tumor Assessment Showing No Disease Recurrence	48 (64.0)	49 (68.1)
No Post-Baseline Disease Status Assessment	5 (6.7)	0 (0)
Kaplan-Meier Estimates (months)[a]		
Median (95% CI)	36.3 (25.7, NR)	NR (22.2, NR)
[Q1, Q3]	[16.8, NR]	[11.1, NR]
person-months	1309.9	1233.2
Event Rate / 100 person-months	1.7	1.9
vs Placebo		
Hazard Ratio (95% CI)[b]	0.91 (0.50, 1.63)	
p-value[c]	0.3699	
DFS Rate at month 12 (%) (95% CI)	79.6 (68.0, 87.4)	74.3 (62.3, 82.9)
DFS Rate at month 18 (%) (95% CI)	74.3 (61.8, 83.3)	69.0 (56.3, 78.7)
DFS Rate at month 24 (%) (95% CI)	71.7 (58.4, 81.4)	61.7 (46.4, 73.8)

[a] From product-limit (Kaplan-Meier) method for censored data.
[b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate.
[c] One-sided p-value based on log-rank test.
NR = Not reached.
Database Cutoff Date: 14DEC2020

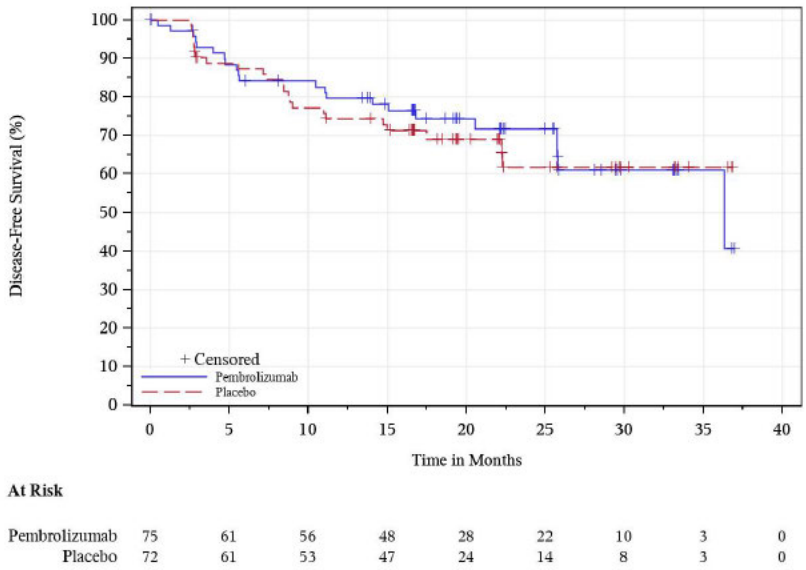


Figure 24 *Kaplan-Meier Plot of Disease-Free Survival (Primary Censoring Rule) Based on Investigator Assessment (ITT Population)(ECOG 1)*

Sarcomatoid (absent/present)

In a post hoc analysis, DFS by investigator assessment was evaluated in subgroups with and without sarcomatoid features since the presence of sarcomatoid features is considered to be associated with high risk of disease recurrence. Consistent DFS results with pembrolizumab compared with placebo were observed regardless of the presence or absence of sarcomatoid features. The DFS rate at 12 months was 78.2% in the pembrolizumab group and 62.7% in the placebo group in the presence of sarcomatoid features (HR 0.56, 95% CI: 0.29, 1.06) and 86.3% and 78.0%, respectively, in the absence of sarcomatoid features (HR 0.70, 95% CI: 0.53, 0.92).

Table 34 Analysis of Disease-Free Survival (Primary Censoring Rule) Based on Investigator Assessment (ITT Population)(Sarcomatoid Absent at Baseline)

	Pembrolizumab (N=417)	Placebo (N=415)
Number of Events (%)	87 (20.9)	118 (28.4)
Death	5 (1.2)	1 (0.2)
Disease Recurrence	82 (19.7)	117 (28.2)
Number of Censored (%)	330 (79.1)	297 (71.6)
Last Tumor Assessment Showing No Disease Recurrence	321 (77.0)	294 (70.8)
No Post-Baseline Disease Status Assessment	9 (2.2)	3 (0.7)
Kaplan-Meier Estimates (months)[a]		
Median (95% CI)	NR (NR, NR)	NR (NR, NR)
[Q1, Q3]	[29.1, NR]	[16.6, NR]
person-months	8325.5	7882.0
Event Rate / 100 person-months	1.0	1.5
vs Placebo		
Hazard Ratio (95% CI)[b]	0.70 (0.53, 0.92)	
p-value[c]	0.0055	
DFS Rate at month 12 (%) (95% CI)	86.3 (82.5, 89.3)	78.0 (73.7, 81.7)
DFS Rate at month 18 (%) (95% CI)	82.6 (78.4, 86.0)	74.0 (69.4, 78.0)
DFS Rate at month 24 (%) (95% CI)	78.5 (73.8, 82.5)	70.3 (65.3, 74.6)

[a] From product-limit (Kaplan-Meier) method for censored data.
[b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate.
[c] One-sided p-value based on log-rank test.
NR = Not reached.
Database Cutoff Date: 14DEC2020

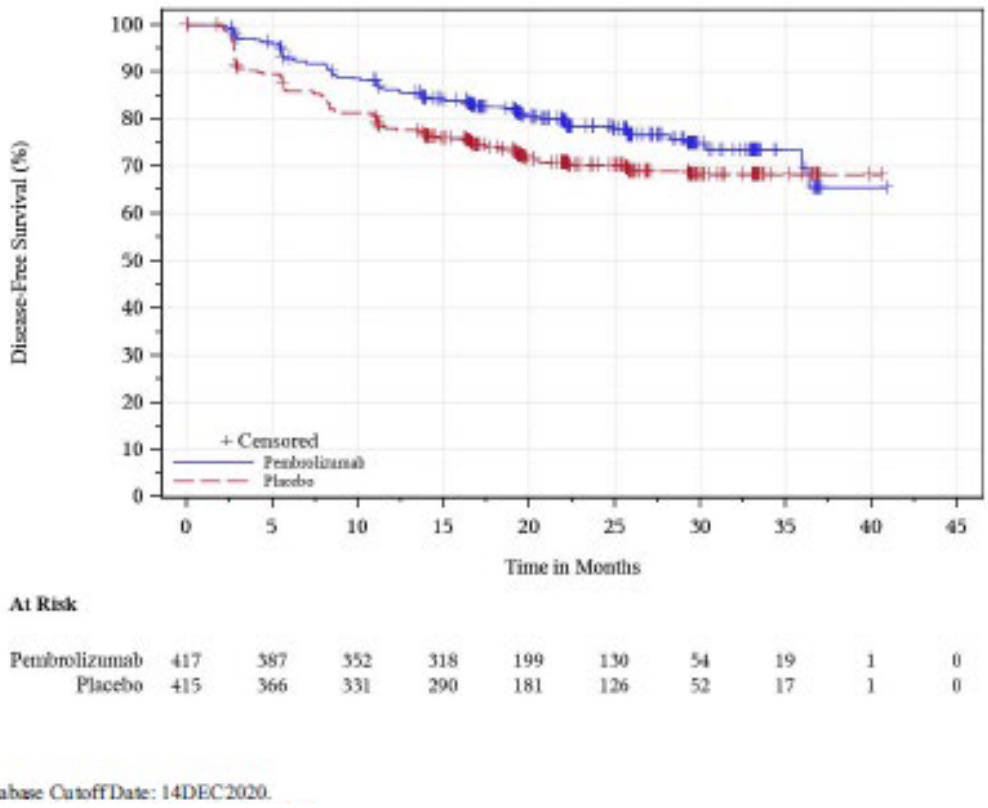


Figure 25 Kaplan-Meier Plot of Disease-Free Survival (Primary Censoring Rule) Based on Investigator Assessment (ITT Population)(Sarcomatoid Absent at Baseline)

Table 35 Analysis of Disease-Free Survival (Primary Censoring Rule) Based on Investigator Assessment (ITT Population)(Sarcomatoid Presented at Baseline)

	Pembrolizumab (N=52)	Placebo (N=59)
Number of Events (%)	14 (26.9)	26 (44.1)
Death	0 (0)	1 (1.7)
Disease Recurrence	14 (26.9)	25 (42.4)
Number of Censored (%)	38 (73.1)	33 (55.9)
Last Tumor Assessment Showing No Disease Recurrence	38 (73.1)	33 (55.9)
Kaplan-Meier Estimates (months)[a]		
Median (95% CI)	NR (25.7, NR)	NR (11.3, NR)
[Q1, Q3]	[22.4, NR]	[7.2, NR]
person-months	938.1	952.1
Event Rate / 100 person-months	1.5	2.7
vs Placebo		
Hazard Ratio (95% CI)[b]	0.56 (0.29, 1.06)	
p-value[c]	0.0360	
DFS Rate at month 12 (%) (95% CI)	78.2 (64.0, 87.3)	62.7 (49.1, 73.6)
DFS Rate at month 18 (%) (95% CI)	75.9 (61.5, 85.6)	59.3 (45.7, 70.6)
DFS Rate at month 24 (%) (95% CI)	71.5 (54.7, 83.0)	53.4 (38.8, 65.9)

[a] From product-limit (Kaplan-Meier) method for censored data.
[b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate.
[c] One-sided p-value based on log-rank test.
NR = Not reached.
Database Cutoff Date: 14DEC2020

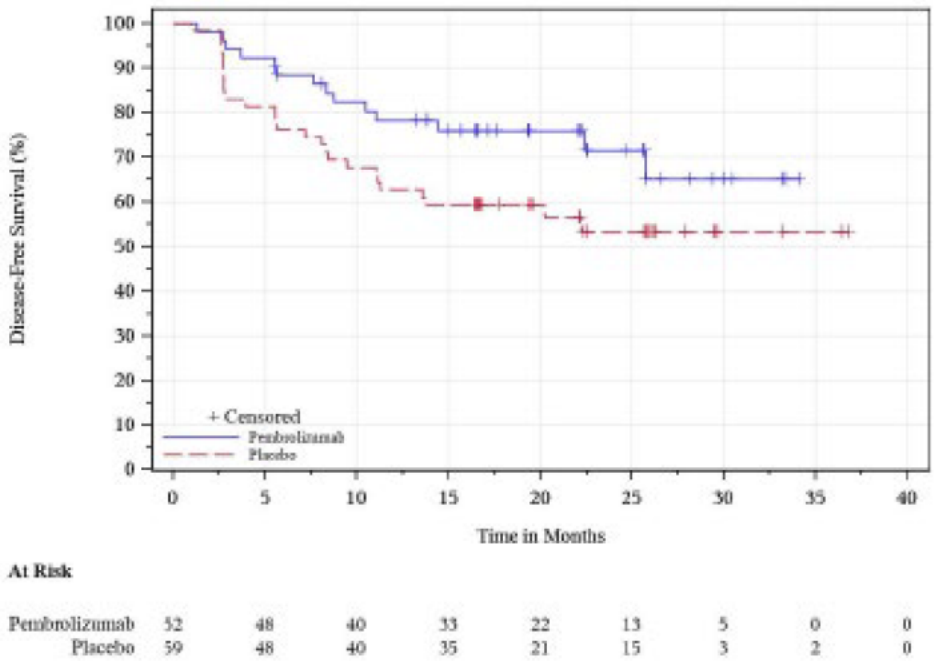


Figure 26 Kaplan-Meier Plot of Disease-Free Survival (Primary Censoring Rule) Based on Investigator Assessment (ITT Population)(Sarcomatoid Presented at baseline.

Concordance of Disease Recurrence Assessments

Concordance of Disease Recurrence Assessments pf Investigator vs. BICR in the ITT Population is presented in the Table 36.

Table 36 Concordance of Disease Recurrence Assessments (Investigator vs. BICR) (ITT Population)

	Pembrolizumab		Placebo	
	n	(%)	n	(%)
Participants in population	496		498	
Assessment				
Investigator Assessment – Disease Recurred	103		149	
Bicr Agreed	84	(81.6)	129	(86.6)
Bicr And Investigator Agreed On Time	52	(50.5)	86	(57.7)
Bicr Declared At Earlier Time	32	(31.1)	43	(28.9)
Bicr Disagreed	19	(18.4)	20	(13.4)
Investigator Assessment – No Disease Recurred	379		346	
Bicr Agreed	351	(92.6)	319	(92.2)
Bicr Disagreed	28	(7.4)	27	(7.8)
No Post-Baseline Assessment By Investigator	14		3	
No Bicr Assessment	14	(100.0)	3	(100.0)

Number of participants with disease recurred, not recurred and no post-baseline assessments by investigator are used as the denominators for the percentage calculation for the corresponding block of rows.

BICR: Blinded independent central review.

Discrepancy on disease recurrence time is counted when more than 1 imaging assessment timepoint difference is observed.

Database Cutoff Date: 14DEC2020

Differential discordance of disease recurrence based on investigator review versus BICR was estimated and are presented in the table below. The early discrepancy rate was calculated to quantify the frequency with which the investigator review declared disease recurrence early relative to BICR within each treatment group; the late discrepancy rate was calculated to quantify the frequency with which the investigator review declared disease recurrence later than BICR within each treatment group. Based on the criteria in Mannino et al , the estimated difference of early discrepancy rate (0.050) did not cross its threshold value of ≤-0.05 and the estimated difference of late discrepancy rate (-0.056) also did not cross its threshold value of ≥0.075.

Table 37 Differential Discordance of Disease Recurrence Assessments (Investigator vs. BICR) (ITT Population)

	Pembrolizumab		Placebo	
	n	(%)	n	(%)
Participants in population	496		498	
Assessment				
Investigator Assessment – Disease Recurred	103		149	
BICR Agreed	84	(81.6)	129	(86.6)
BICR And Investigator Agreed On Time	52	(50.5)	86	(57.7)
BICR Declared At Earlier Time	32	(31.1)	43	(28.9)
BICR Disagreed	19	(18.4)	20	(13.4)

EDR	0.184	0.134
LDR	0.627	0.683
Difference in EDR (Pembro – Placebo)	0.050	
Difference in LDR (Pembro – Placebo)	-0.056	

Number of participants with disease recurred is used as the denominators for the percentage calculation. BICR: Blinded independent central review. Discrepancy on disease recurrence time is counted when more than 1 imaging assessment timepoint difference is observed. EDR= Early discrepancy rate, calculated as BICR disagreed / (BICR agreed + BICR disagreed). LDR= Late discrepancy rate, calculated as BICR declared at earlier time / (BICR declared at earlier time + BICR disagreed). A difference in EDR <=-0.05 or a difference in LDR>=0.075 are suggestive of a systematic bias in the investigator assessment favoring the pembrolizumab arm. Database Cutoff Date: 14DEC2020

In this study, the protocol required radiographic evidence for disease recurrence, while the confirmation by pathological assessments (eg, biopsy) was strongly encouraged. Concordance and discordance of radiographic disease recurrence and local pathological assessment of disease recurrence was analyzed post hoc. Of the 39 participants with disease recurrence determined by investigator review but not by BICR, 17.9% (7 participants, 3 in the pembrolizumab group and 4 in the placebo group) were declared with disease recurrence by investigator review based on both radiographic and pathological evidence, while no disease recurrence was declared by BICR based on imaging only. In addition, of the 55 participants with disease recurrence determined by BICR but not by investigator review, 9.1% (5 participants, 4 in the pembrolizumab group and 1 in the placebo group) were declared with disease recurrence by BICR of imaging, while no disease recurrence was declared by investigator's assessment of imaging plus negative local pathological assessment results. As a result, in the total of 94 participants with discordance of disease recurrence assessments between investigator review and BICR, discordance was generally similar in both groups and 12 (13%) could be explained by the additional local pathological results that were only available for investigator review.

Table 38 Summary of Pathological Assessments for Disease Recurrence (ITT Population)

	Pembrolizumab		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	496		498		994	
Disease recurrence by INV, with BICR agreed	84		129		213	
Determined by imaging without pathological confirmation	68	(81.0)	105	(81.4)	173	(81.2)
Determined by imaging first with subsequent pathological confirmation	16	(19.0)	20	(15.5)	36	(16.9)
Determined by pathological assessment first with subsequent imaging confirmation			4	(3.1)	4	(1.9)
Disease recurrence by INV, with BICR disagreed	19		20		39	
Determined by imaging without pathological confirmation	16	(84.2)	15	(75.0)	31	(79.5)
Determined by imaging first with subsequent pathological confirmation	3	(15.8)	4	(20.0)	7	(17.9)
Determined by pathological assessment without imaging confirmation			1	(5.0)	1	(2.6)
No disease recurrence by INV, with BICR disagreed	28		27		55	
Pathological assessment was taken with negative results by INV	4	(14.3)	1	(3.7)	5	(9.1)

BICR: Blinded independent central review. INV: Investigator assessment.
Pathological assessment of radiographic disease recurrence by investigator's review is optional. Disease recurrence by BICR is determined by BICR of imaging alone, regardless of pathological assessment results.
Database Cutoff Date: 14DEC2020

Source: [P564V01MK3475: adam-adsl] [P564V01MK3475: analysis- biopsy]

Summary of main study(ies)

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

Table 39 Summary of Efficacy for Trial KEYNOTE-564

Title: A Phase 3, Randomized, Double-Blind, Placebo-Controlled Clinical Trial of Pembrolizumab (MK-3475) as Monotherapy in the Adjuvant Treatment of Renal Cell Carcinoma Post Nephrectomy (KEYNOTE-564)			
Study identifier	KEYNOTE-564; P564V01MK3475 EudraCT: 2016-004351-75 NCT: NCT03142334		
Design	Phase 3, multicenter, efficacy, safety, randomized, double-blind, placebo-controlled, intervention study		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		Approximately 1 year Not applicable Post-treatment follow-up 5 years and beyond
Hypotheses	Pembrolizumab is superior to placebo with respect to the primary endpoint of disease-free survival (DFS). Pembrolizumab is superior to placebo with respect to the key secondary endpoint of overall survival (OS).		
Treatment groups	Pembrolizumab		Pembrolizumab 200 mg infusion every 3 weeks (Q3W) for up to 17 cycles (approximately 1 year) 496 participants randomized (Intent-to-Treat [ITT] population) 488 participants treated Discontinued study treatment: 190 participants Most common reason: Adverse event (AE): 104 (21.3%)
	Placebo		Placebo (saline) infusion Q3W for up to 17 cycles (approximately 1 year) 498 participants randomized (ITT population) 496 participants treated Discontinued study treatment: 130 participants Most common reason: Disease relapse: 101 (20.4%)
Endpoints and definitions	Primary endpoint	DFS by Investigator Assessment	DFS as assessed by the investigator: time from randomization to the first documented local recurrence, or occurrence of distant kidney cancer metastasis(es), or death due to any cause, whichever occurs first
	Key secondary endpoint	OS	OS: time from randomization to death due to any cause
Database lock	26-JAN-2021; data cutoff date for interim analysis 1 (IA1) was 14-DEC-2020.		
Results and Analysis			
Analysis description	**Primary analysis: DFS by Investigator Assessment**		
Analysis population and time point description	ITT (all randomized participants, analyzed in the treatment group to which they were randomized) Event-driven by prespecified number of DFS events		

Descriptive statistics and estimate variability	Treatment group	Pembrolizumab	Placebo
	Number of subjects	496	498
	Death: Disease Recurrence: Kaplan-Meier Estimates: Median, months (95% CI): Q1, Q3:	6 (1.2%) 103 (20.8%) Not reached (NR, NR) 25.8, NR	2 (0,4%) 149 (29.9%) Not reached (NR, NR) 13.8, NR
		From product-limit (Kaplan-Meier) method for censored data. Primary censoring rule.	
Effect estimate per comparison	Primary endpoint: DFS by Investigator Assessment	Comparison groups	Pembrolizumab vs. Placebo
		Hazard ratio:	0.68
		95% CI	0.53, 0.87
		Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by metastasis status (M0 versus M1 NED by investigator) and Eastern Oncology Cooperative Group (ECOG) performance score (PS) (0 versus 1), US participant (Yes vs. No) within M0 group by investigator.	
		P-value	0.0010
		One-sided p-value based on log-rank test stratified by metastasis status (M0 versus M1 NED by investigator) and ECOG PS (0 versus 1), US participant (Yes vs. No) within M0 group by investigator.	
Notes	A total of 260 DFS events (78% of the total planned events at final analysis) were observed in the 2 treatment groups (109 in the pembrolizumab group and 151 in the placebo group). At the prespecified 2.5% overall alpha level (one-sided), pembrolizumab demonstrated a statistically significant and clinically meaningful improvement in DFS compared with placebo (median DFS was not reached in either treatment group).		

Analysis description	**Key secondary endpoint: OS**		
Analysis population and time point description	ITT (all randomized participants, analyzed in the treatment group to which they were randomized) Event-driven by prespecified number of DFS events		
Descriptive statistics and estimate variability	Treatment group	Pembrolizumab	Placebo
	Number of subjects	496	498
	Number of events	18 (3.6%)	33 (6.6%)
	Kaplan-Meier Estimates: Median, months (95% CI): Q1, Q3:	NR (NR, NR) NR, NR	NR (NR, NR) NR, NR
		From product-limit (Kaplan-Meier) method for censored data	
Effect estimate per comparison	Primary endpoint: DFS by Investigator Assessment	Comparison groups	Pembrolizumab vs. Placebo
		Hazard ratio:	0.54
		95% CI	0.30, 0.96
		Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by metastasis status (M0 versus M1 NED by investigator) and ECOG PS (0 versus 1), US participant (Yes vs. No) within M0 group by investigator.	
		P-value	0.0164037
		One-sided p-value based on log-rank test stratified by metastasis status (M0 versus M1 NED by investigator) and ECOG PS (0 versus 1), US participant (Yes vs. No) within M0 group by investigator.	
Notes	The OS data were immature at IA1 with 51 deaths (26% of total planned OS events at the final analysis). The p-value did not cross the statistical hypothesis testing p-value boundary of 9.3×10^{-6} at IA1. The upper bound of 95% CI for the OS hazard ratio was below 1.0, with nearly twice as many deaths in the placebo group (33) compared with the pembrolizumab group (18).		
Results and Analysis			
Analysis description	**Updated analysis (data cut-off 14. Jun 2021): DFS by Investigator Assessment**		
Analysis population and time point description	ITT (all randomized participants, analyzed in the treatment group to which they were randomized)		
Descriptive statistics and estimate variability	Treatment group	Pembrolizumab	Placebo
	Number of subjects	496	498
	Deaths: Disease recurrence: Kaplan-Meier Estimates:	6 (1.2%) 108 (21.8%)	3 (0.6) 166 (33.3)

		From product-limit (Kaplan-Meier) method for censored data. Primary censoring rule.	
Effect estimate per comparison	Primary endpoint: DFS by Investigator Assessment	Comparison groups	Pembrolizumab vs. Placebo
		Hazard ratio:	0.63
		95% CI	0.50, 0.80
		P-value	< 0.0001
Analysis description	**Updated analysis (14 Jun 2021): Key secondary endpoint: OS**		
Analysis population and time point description	ITT (all randomized participants, analyzed in the treatment group to which they were randomized)		
Descriptive statistics and estimate variability	Treatment group	Pembrolizumab	Placebo
	Number of subjects	496	498
	Number of events	23 (4.6%)	43(8.6%)
	Kaplan-Meier Estimates: Median, months (95% CI): Q1, Q3:	 NR (NR, NR) [NR, NR]	 NR (NR, NR) [NR, NR]
		From product-limit (Kaplan-Meier) method for censored	
Effect estimate per comparison	Primary endpoint: DFS by Investigator Assessment	Comparison groups	Pembrolizumab vs. Placebo
		Hazard ratio:	0.52
		95% CI	0.31, 0.86
		P-value	0. 0047677
Notes	The OS data were immature at the updated analysis with 66 deaths (33% of total planned OS events at the final analysis).		

Clinical studies in special populations

No data in special populations have been provided.

2.4.3. Discussion on clinical efficacy

This is an extension of indication for pembrolizumab in the adjuvant treatment of patients at immediate/high and high risk of recurrent renal carcinoma (RCC) post nephrectomy supported by the results from the pivotal phase III study KEYNOTE-564 of pembrolizumab vs. placebo.

Design and conduct of clinical studies

KEYNOTE-564 is an international, multicenter, randomized, double-blind, Phase III study of adjuvant pembrolizumab 200 mg Q3W for 17 cycles or 1 year vs. placebo in patients with RCC at intermediate-high or high risk of recurrence following nephrectomy.

Overall, the population recruited is a so-called "intermediate–high" and "high" risk subset. In the literature, there is no clear consensus about the definition for high risk. The MAH definition seems to replicate partially the UCLA Integrated Staging System (UISS) that incorporates the TNM classification, ECOG PS score, and Fuhrman grade. To define the "intermediate-high" risk group, the MAH included a subset of the UISS intermediate risk criteria and a subset of UISS high risk criteria to select patients with higher risk of recurrence. Considering the outcome in the control arm, the chosen criteria appear to be relevant to determine a more dismal prognosis. Therefore, criteria used to define the proposed target population "adults with RCC at intermediate-high or high risk of recurrence " can be considered acceptable.

Indication wording

KEYTRUDA as monotherapy is indicated for the adjuvant treatment of adults with RCC at increased risk of recurrence following nephrectomy or following nephrectomy and resection of metastatic lesions (for selection of criteria, please see section 5.1)

Only patients with ECOG PS 0-1 were enrolled. Median age was 60 years, which is younger than the usual age at diagnosis of RCC (64 years (NCI).

Since there are currently no approved adjuvant treatments for RCC, the placebo-controlled design appears appropriate.

DFS according to investigator review could be an acceptable primary endpoint considering the adjuvant treatment setting, the inclusion of OS as secondary endpoint and the double-blind placebo controlled trial. However, in the Scientific Advice (EMEA/H/SA/2437/16/2016/II) the MAH stated that DFS by Blinded independent central review (BICR) was planned to be the primary endpoint of KN564. In the light of the typical safety profile of pembrolizumab, it could be anticipated that the blinding of the investigator could be corrupted and therefore the assessment of the investigator could be biased.

The statistical analysis plan is overall acceptable. The definition of time-to-event variables DFS and OS as time from randomization to the event is supported. The approach to DFS as a composite of objective disease recurrence or death from any cause (whichever occurs first), and an additional analysis of OS as key-secondary endpoint is in line with current guidance (Guideline on multiplicity issues in clinical trials, EMA/CHMP/44762/201). Censoring rules for the primary endpoint DFS are generally supported. The approach to interim analyses is in principle acceptable.

Efficacy data and additional analyses

The data cut-off for the submitted IA1 was 14th Dec 2020 with a median follow-up of 23.9 months (range 2.5 to 41.5 months). Efficacy analyses were performed on the **ITT** population. Baseline patients and disease characteristics appeared overall balanced between the two arms. Patients were classified in "intermediate-high" (pT2, Grade 4 or sarcomatoid, N0, M0 / pT3, any grade, N0, M0) with n=86% of the study population, "high" (pT4, any grade, N0, M0/ pT any stage, any grade, N+, M0) with n=7.6% and "M1 NED" RCC participants with n=5.8%. Overall, the population is dominated by a so called "intermediate – high" risk subset.

In the ITT population pembrolizumab showed a statistically significant advantage over placebo in DFS according to investigator assessment [median DFS not reached; HR 0.68 (95%CI: 0.53, 0.87), p =

0.001]. The probability of being event free at year 1 and year 2 was 85.7% vs. 76.2% and 77.3% vs. 68.1% for pembrolizumab and placebo, respectively. Data were based on 260 events (78% of final analyses). A high number of censoring after 1 year was noted.

The OS data were immature at IA1 with 51 deaths (26% of total planned OS events at the final analysis). For OS, the HR was 0.54 (95% CI: 0.30, 0.96) and the median OS was not reached in either group. As OS data were too immature, the MAH provided DRSS1 and DRSS2 data (Disease Recurrence-specific Survival as assessed by the investigator) which could support the assumption that DFS results will translate into OS benefit. In addition, a post hoc exploratory analysis of PFS2 based on investigator assessment (HR: 0.52; 95% CI: 0.34, 0.81) indicated a reduced risk of disease progression or death on next-line drug therapy in the pembrolizumab group compared with the placebo group based on still limited event rates.

PRO assessments, including FKSI-DRS scale, EORTC QLQ-C30 global health status/QoL scale, EORTC QLQ-C30 functional scales, and EORTC QLQ-C30 symptom scales, generally showed limited differences between treatment groups.

During the procedure the MAH Applicant provided updated efficacy results with additional 6 months of follow up (median duration of follow-up 29.7 months based on a data cutoff date of 14-JUN-2021).

In the ITT population 23 additional DFS events had occurred with 5 additional DFS events in the pembrolizumab arm and 18 additional events in the placebo arm; the higher number of additional events in the placebo arm is considered reassuring. The HR for DFS at the updated analysis was 0.63 (95% CI: 0.50, 0.80) in the ITT population, compared with an HR of 0.68 [95% CI: 0.53, 0.87] at IA1. At the updated data cut-off the DFS event rates were 23% and 33.9% in the pembrolizumab arm vs the placebo arm, respectively, thus representing 85% of the planned events at the final DFS analysis. DFS KM curves do not converge anymore at the updated data cut-off and the curves could suggest a trend towards reaching a plateau. In conclusion, the updated results support the DFS benefit that demonstrated statistical significance in the first IA. Overall survival data in the ITT population are still too immature to draw any reliable conclusions; at the updated analyses only 66 events had occurred (33% of the targeted 200 OS events at the final analysis). However, despite the low absolute event rates, nearly twice as many OS events were reported in the placebo arm compared with the pembrolizumab treatment arm (with 5 vs 10 additional OS events in the pembrolizumab vs the placebo arm at the updated DCO date). Nevertheless, the OS data is still immature and the MAH is recommended to provide updated OS data from study KEYNOTE-564 (REC).

Exploratory results of DFS by independent assessment were provided. The HR for DFS by BICR was 0.78 (95% CI: 0.61, 0.99) as compared to 0.63 (95% CI 0.50, 0.80) for the HR of DFS by investigators, based on the most recent data cut-off of June 2021. In line with the inferior point estimate of the HR by BICR the difference of 24 months DFS rates between both treatment arms was smaller for the independent assessment compared to the investigator assessment (5.8% vs 11% for BICR vs. INV, respectively). The disease recurrence assessments by BICR and investigators cannot be considered highly concordant (rates of 80.6% in the pembrolizumab arm and 86.7% in the placebo arm).

Nonetheless, it should be taken into account that the DFS analysis by investigators is rather reflecting the real practice use in the clinical setting. In addition, since the assessment of EFS is a more comprehensive measure of the treatment effect of pembrolizumab in all study participants (also reflecting a delay of disease progression for patients with baseline disease), the results of the EFS analysis by BICR based on the December 2020 data cutoff can be considered supportive: EFS HR 0.72 (95% CI 0.56, 0.91).

As already outlined above, the proposed eligibility criteria (**intermediate-high**/high/M1) resulted in a heterogeneous population with regard to prognosis and risk of relapse. While it could be reasonably

assumed that the absolute anti-tumour activity of pembrolizumab was not so much influenced by the stage of disease, the relative magnitude of the effect, and consequently the B/R, might change depending on the baseline risk of relapse. While a clear DFS benefit was detected in the small groups with high risk (HR of 0.60; 95% CI 0.33, 1.11) and M1NED (HR of 0.29; 95% CI 0.12, 0.69), the benefit/risk in the large group of the intermediate-high risk patients (HR of 0.75; 95% CI 0.57, 1.00) could not be adequately determined with the initial submission given the considerable heterogeneity of this subgroup and the immaturity of OS provided, but reassurance was provided with the updated data where the HR for DFS decreased to 0.68 (95% CI: 0.37, 1.24). Attempts to divide the large heterogeneous "intermediate-high" risk subgroup further into T3 N0 M0 G2-4 (as classified as high risk by UISS) and the complementary group of intermediate-high group risk did not identify a subgroup that would certainly not benefit from the treatment. Although the results in the complementary subgroup (pT3, N0, M0, Grade 1 or pT2 [Grade 4 or sarcomatoid], N0, M0) appeared inferior compared to the T3 N0 M0 G2-4 subgroup, the patient numbers were too small to draw reliable conclusions and given the observed similar dismal prognosis, there is no rationale to assume a lower treatment effect in one of these subgroups.

With the initial data cutoff, the DFS HR was 0.83 (95% CI: 0.45, 1.51) in participants whose tumours express **PD-L1 CPS <1**, for the comparison of pembrolizumab compared to placebo. KM curves indicated no clinically meaningful treatment effect in this subgroup. Cumulative data from both arms suggested that PD-L1 expression could be a negative prognostic marker (also based on published literature), resulting in a better prognosis for PD-L1 negative patients as seen in several other indications, which could influence the relative magnitude of the effect. In addition, there is a strong biological plausibility for PD-L1 being predictive. Considering the association of biomarker status and efficacy outcomes, the treatment benefit of pembrolizumab in the overall study population appeared to be driven by the subgroup of patients with high PD-L1 expression status.

With the updated DFS data (DCO 14-Jun-2021) the point estimate of the HR decreased from 0.83 (95% CI 0.45, 1.51) to 0.68 (0.37, 1.24) in the PD-L1 negative subgroup. Thus, the point estimates of the DFS HRs became very similar between the PD-L1 negative and positive subgroups. Considering the point estimates the concern regarding a smaller (and not clinically relevant) benefit in the PD-L1 negative population appears not valid anymore. Updated DFS KM curve for the CPS<1 subgroup showed a separation (Figure 11).

2.4.1. Conclusions on the clinical efficacy

Interim data of Study KEYNOTE-564 showed a statistically significant DFS advantage of pembrolizumab over placebo in the adjuvant treatment of RCC. Updated results with additional 6 months of follow-up supported a clinically meaningful DFS benefit in the overall study population. Although survival data were still immature, OS results indicated a trend in favour of pembrolizumab. Further OS data are expected to be submitted as soon as available (REC). Taking the supportive Disease Recurrence-specific Survival and PFS2 results into consideration, a favourable B/R balance is concluded on for patients with RCC at increased risk of recurrence following nephrectomy.

2.5. Clinical safety

Introduction

The safety data set in support of the new indication of pembrolizumab monotherapy in the adjuvant treatment of RCC post nephrectomy derived from 488 participants in Study KEYNOTE-564 (KN564)

received pembrolizumab (Indication Dataset) and n=496 received placebo. In addition, safety data from the Pembrolizumab Monotherapy Reference Safety Dataset (RSD, n=5884) were included for comparison.

Table 40 Safety Datasets

KEYNOTE-564 Pembrolizumab (Indication Dataset) N=488	KEYNOTE-564 Placebo N=496	Pembrolizumab Monotherapy RSD N=5884	Cumulative Running Safety Dataset for Pembrolizumab Monotherapy N=9218
All participants with target indication in KEYNOTE-564 who received pembrolizumab monotherapy	All participants with target indication in KEYNOTE-564 who received placebo	Represents the established safety profile of pembrolizumab	Provided to demonstrate that no clinically significant changes from the RSD have occurred, supporting the consistency of the safety data of pembrolizumab across indications; this dataset is not used as a comparison with KEYNOTE-564 safety data

The Pembrolizumab Monotherapy Reference Safety Dataset (RSD) RDS comprises pooled safety data from approved indications in the EU from following studies: KN001, KN002, KN006, KN010, KN012 (HNSCC), KN013 Cohort 3 (Hodgkin Lymphoma), KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055, and KN087.

Patient exposure

The median duration of exposure to pembrolizumab was >2-fold longer for participants in the Indication Dataset compared with the RSD (11.1 months vs 4.9 months, respectively), which is expected for pembrolizumab monotherapy when used as an adjuvant treatment.

Table 41 Summary of Drug Exposure

	Pembrolizumab (N=488)	Placebo (N=496)
Duration on therapy (months)		
Mean	9.0	9.8
Median	11.1	11.1
SD	3.7	3.1
Range	0.0 to 14.3	0.0 to 15.4
Number of Administrations		
Mean	13.5	14.7
Median	17.0	17.0
SD	5.2	4.4
Range	1.0 to 17.0	1.0 to 17.0
Duration on therapy (months) is calculated as (last dose date - first dose date + 1)/30.4367. Database Cutoff Date: 14DEC2020		

	Pembrolizumab (N=488)			Placebo (N=496)		
	n	(%)	Person-time	n	(%)	Person-time
Duration of Exposure						
> 0 m	488	(100.0)	4,371.1	496	(100.0)	4,842.7
>=1 m	463	(94.9)	4,357.8	493	(99.4)	4,841.3
>=3 m	428	(87.7)	4,284.2	447	(90.1)	4,732.1
>=6 m	370	(75.8)	4,012.8	413	(83.3)	4,571.2
>=9 m	325	(66.6)	3,680.6	386	(77.8)	4,363.3
>=12 m	32	(6.6)	414.9	27	(5.4)	353.3

Each subject is counted once on each applicable duration category row.
Duration of exposure is the time from the first dose date to the last dose date.
Person-time is calculated as person time in months.
Database Cutoff Date: 14DEC2020.

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

Duration of Exposure (months) is calculated as (last dose date - first dose date + 1)/30.4367.

[a]Includes all participants who received at least one dose of pembrolizumab in KN564.

[b]Includes all participants who received at least one dose of placebo in KN564.

[c]Includes all participants who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 (HNSCC), KN013 Cohort 3 (Hodgkin Lymphoma), KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055 and KN087.

[d]Includes all subjects who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3; KN002 (original phase); KN006; KN010; KN012 Cohorts B and B2 (HNSCC), Cohort C (Urothelial Tract Cancer) and Cohort D (Gastric Cancer); KN013 Cohort 3 (cHL) and Cohort 4A (PMBCL); KN024; KN028 Cohort A4 (Esophageal), Cohort B4 (Cervical) and Cohort C1 (SCLC); KN040; KN042; KN045; KN048; KN052; KN054; KN055; KN057; KN059 Cohort 1 and Cohort 3; KN061; KN062; KN087; KN158 Cohort E (Cervical), Cohort G (SCLC) and TMB-H; KN164 Cohort A; KN170; KN177; KN180; KN181; KN204; KN224; KN427 Cohort A ; KN564; KN629; P017.

Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 02OCT2017)

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

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

Database cutoff date for Gastric (KN012-Gastric: 26APR2016, KN059-Cohort 1 and Cohort 3: 08AUG2018, KN061: 26OCT2017, KN062: 26MAR2019)

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

Database cutoff date for Bladder (KN012-Urothelial: 01SEP2015, KN045: 26OCT2017, KN052: 26SEP2018)

Database cutoff date for Colorectal (KN164-Cohort A: 03AUG2016, KN177: 19FEB2020)

Database cutoff date for PMBCL (KN013-Cohort 4A: 04AUG2017. KN170: 07MAY2020)

Database cutoff date for Cervical (KN028-Cohort B4: 20FEB2017, KN158-Cohort E: 27JUN2019)

Database cutoff date for HCC (KN224: 15MAY2018)

Database cutoff date for Merkel Cell (P017: 06FEB2018)

Database cutoff date for Esophageal (KN028-Cohort A4: 31JAN2018, KN180: 30JUL2018, KN181: 15OCT2018)

Database cutoff date for RCC (KN427-Cohort A : 07SEP2018, KN564: 14DEC2020)

Database cutoff date for TMB-H (KN158: 27JUN2019)

Database cutoff date for SCLC (KN028-Cohort C1: 31JUL2018, KN158-Cohort G: 27JUN2019)

Database cutoff date for NMIBC (KN057: 24MAY2019)

Database cutoff date for cSCC (KN629: 29JUL2020)

Demographic and Other Characteristics of Study Population

The demographics and baseline characteristics were generally similar between the Indication Dataset and the RSD apart from ECOG PS and age (lower rate of ECOG PS 1 and more participants ≤65 years of age in the Indication Dataset versus the RSD; see Table 5.5.4). The characteristics of participants were well balanced for the Indication Dataset and the placebo group.

Table 42 Participant Characteristics (APaT Population)

	KN564 Data for Pembrolizumab		KN564 Data for Placebo		Reference Safety Dataset for Pembrolizumab		Cumulative Running Safety Dataset for Pembrolizumab	
	n	(%)	n	(%)	n	(%)	n	(%)
Age Class (Years)								
<65	333	(68.2)	324	(65.3)	3,385	(57.5)	5,283	(57.3)
65-74	137	(28.1)	147	(29.6)	1,737	(29.5)	2,742	(29.7)
75-84	18	(3.7)	25	(5.0)	663	(11.3)	1,029	(11.2)
>=85	0	(0.0)	0	(0.0)	99	(1.7)	164	(1.8)
ECOG Performance Scale								
[0] Normal Activity	416	(85.2)	424	(85.5)	2,761	(46.9)	4,413	(47.9)
[1] Symptoms, but ambulatory	72	(14.8)	72	(14.5)	2,931	(49.8)	4,494	(48.8)
Other/Missing	0	(0.0)	0	(0.0)	192	(3.3)	311	(3.4)

Adverse events

Adverse event summary

AEs were coded using MedDRA (Version 23.1). AEs were monitored throughout the study and graded in severity according to the guidelines outlined in the NCI CTCAE Version 4.0.

Table 43 Adverse Event Summary (APaT Population)

	KN564 Data for Pembrolizumab		KN564 Data for Placebo		Reference Safety Dataset for Pembrolizumab		Cumulative Running Safety Dataset for Pembrolizumab	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	488		496		5,884		9,218	
with one or more adverse events	470	(96.3)	452	(91.1)	5,690	(96.7)	8,890	(96.4)
with no adverse event	18	(3.7)	44	(8.9)	194	(3.3)	328	(3.6)
with drug-relateda adverse events	386	(79.1)	265	(53.4)	4,132	(70.2)	6,375	(69.2)
with toxicity grade 3-5 adverse events	158	(32.4)	88	(17.7)	2,829	(48.1)	4,444	(48.2)
with toxicity grade 3-5 drug-related adverse events	92	(18.9)	6	(1.2)	913	(15.5)	1,490	(16.2)
with serious adverse events	100	(20.5)	56	(11.3)	2,266	(38.5)	3,449	(37.4)
with serious drug-related adverse events	59	(12.1)	1	(0.2)	656	(11.1)	1,049	(11.4)
who died	2	(0.4)	1	(0.2)	312	(5.3)	484	(5.3)
who died due to a drug-related adverse event	0	(0.0)	0	(0.0)	39	(0.7)	66	(0.7)
discontinued drug due to an adverse event	101	(20.7)	10	(2.0)	790	(13.4)	1,215	(13.2)
discontinued drug due to a drug-related adverse event	86	(17.6)	3	(0.6)	410	(7.0)	676	(7.3)
discontinued drug due to a serious adverse event	49	(10.0)	5	(1.0)	572	(9.7)	855	(9.3)
discontinued drug due to a serious drug-related adverse event	37	(7.6)	0	(0.0)	245	(4.2)	392	(4.3)

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

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

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

Table 44 Exposure-Adjusted Adverse Event Summary (Including Multiple Occurrences of Events)

	Event Count and Rate (Events/100 person-months)[a]			
	KN564 Data for Pembrolizumab	KN564 Data for Placebo	Reference Safety Dataset for Pembrolizumab	Cumulative Running Safety Dataset for Pembrolizumab
Number of participants exposed	488	496	5884	9218
Total exposure[b] in person-months	4852.07	5331.33	47883.80	74360.62
Total events (rate)				
adverse events	4345 (89.55)	3111 (58.35)	61600 (128.64)	91873 (123.55)
drug-related adverse events	1760 (36.27)	854 (16.02)	19283 (40.27)	27860 (37.47)
toxicity grade 3-5 adverse events	286 (5.89)	121 (2.27)	6162 (12.87)	9827 (13.22)
toxicity grade 3-5 drug-related adverse events	139 (2.86)	6 (0.11)	1374 (2.87)	2250 (3.03)
serious adverse events	137 (2.82)	75 (1.41)	4094 (8.55)	6089 (8.19)
serious drug-related adverse events	68 (1.40)	1 (0.02)	916 (1.91)	1426 (1.92)
adverse events leading to death	2 (0.04)	1 (0.02)	319 (0.67)	493 (0.66)
drug-related adverse events leading to death	0 (0.00)	0 (0.00)	39 (0.08)	66 (0.09)
adverse events resulting in drug discontinuation	118 (2.43)	10 (0.19)	863 (1.80)	1316 (1.77)
drug-related adverse events resulting in drug discontinuation	101 (2.08)	3 (0.06)	448 (0.94)	734 (0.99)
serious drug-related adverse events resulting in drug discontinuation	38 (0.78)	0 (0.00)	259 (0.54)	410 (0.55)

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

[b] Drug exposure (months) is defined as the duration between the first dose date and the earlier of the last dose date + 30 or the database cutoff date, which is calculated by (min(last dose date+30, Cutoff date) – first dose date + 1)/30.4367.

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

Most common Adverse Events

Table 45 Participants With Adverse Events (Incidence ≥10% in One or More Treatment Groups) By Decreasing Frequency of Preferred Term (APaT Population)

	KN564 Data for Pembrolizumab[a]		KN564 Data for Placebo[b]		Reference Safety Dataset for Pembrolizumab[c]		Cumulative Running Safety Dataset for Pembrolizumab[d]	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	488		496		5,884		9,218	
with one or more adverse events	470	(96.3)	452	(91.1)	5,690	(96.7)	8,890	(96.4)
with no adverse events	18	(3.7)	44	(8.9)	194	(3.3)	328	(3.6)
Fatigue	145	(29.7)	120	(24.2)	1,884	(32.0)	2,789	(30.3)
Diarrhoea	124	(25.4)	111	(22.4)	1,200	(20.4)	1,870	(20.3)
Pruritus	111	(22.7)	65	(13.1)	1,060	(18.0)	1,591	(17.3)
Arthralgia	108	(22.1)	93	(18.8)	1,104	(18.8)	1,593	(17.3)
Hypothyroidism	103	(21.1)	18	(3.6)	651	(11.1)	1,034	(11.2)

Rash	98	(20.1)	53	(10.7)	904	(15.4)	1,291	(14.0)
Nausea	80	(16.4)	48	(9.7)	1,213	(20.6)	1,861	(20.2)
Cough	76	(15.6)	50	(10.1)	1,148	(19.5)	1,639	(17.8)
Headache	69	(14.1)	62	(12.5)	711	(12.1)	989	(10.7)
Hyperthyroidism	58	(11.9)	1	(0.2)	247	(4.2)	435	(4.7)
Asthenia	50	(10.2)	36	(7.3)	666	(11.3)	1,051	(11.4)
Blood creatinine increased	50	(10.2)	42	(8.5)	256	(4.4)	455	(4.9)
Back pain	49	(10.0)	64	(12.9)	662	(11.3)	1,023	(11.1)
Vomiting	41	(8.4)	28	(5.6)	732	(12.4)	1,173	(12.7)
Constipation	35	(7.2)	40	(8.1)	995	(16.9)	1,530	(16.6)
Decreased appetite	35	(7.2)	10	(2.0)	1,136	(19.3)	1,749	(19.0)
Dyspnoea	31	(6.4)	27	(5.4)	989	(16.8)	1,323	(14.4)
Pyrexia	31	(6.4)	23	(4.6)	746	(12.7)	1,135	(12.3)
Anaemia	20	(4.1)	18	(3.6)	836	(14.2)	1,340	(14.5)

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

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

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

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

The most frequently reported AEs (incidence ≥20%) in the pembrolizumab arm of study KN564 were fatigue, diarrhoea, pruritus, arthralgia, hypothyroidism, and rash. The AEs with greatest percentage difference (risk difference of approximately ≥10%) between the pembrolizumab and placebo groups were hypothyroidism, hyperthyroidism, pruritus, and rash (see Figure 28).

The observed incidences of hypothyroidism (21.1% vs 11.1%) and hyperthyroidism (11.9% vs 4.2%) were higher in the Indication Dataset than in the RSD; all hypothyroidism and hyperthyroidism events in the Indication Dataset were Grade 1 and Grade 2 except for 1 participant each with Grade 3 hypothyroidism and Grade 3 hyperthyroidism. Blood creatinine increased (10.2% vs 4.4%) were also higher in the Indication Dataset than in the RSD; however, participants in study KN564 had prior nephrectomy (rate of blood creatinine increase was 8.5% in the placebo arm).

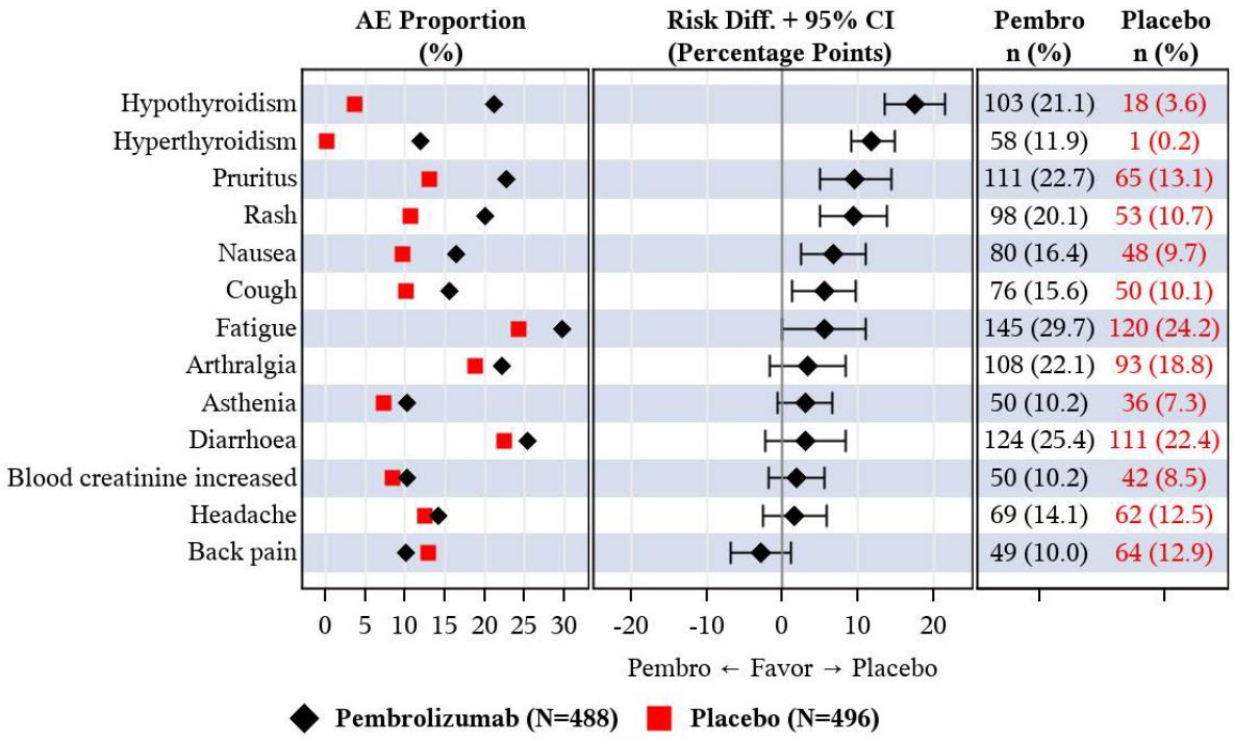


Figure 27 Between-treatment Comparisons in AEs; Selected AEs (≥ 10% Incidence) and Sorted by Risk Difference

Table 46 Exposure-Adjusted Adverse Events by Observation Period (Including Multiple Occurrences of Events) (Excerpt from Table 14.3-6)

	Event Count and Rate (Events/100 person-months)[a]							
	Pembrolizumab				Placebo			
Observation period of drug exposure	0-3 months	3-6 months	6-12 months	Beyond 12 months	0-3 months	3-6 months	6-12 months	Beyond 12 months
Number of subjects exposed[b]	488	453	390	278	496	488	425	347
Total exposure[c] in person-months	1422.11	1262.21	2041.25	126.50	1480.43	1344.14	2378.21	128.55

The highest AE rates in occurred in the first 3 months of treatment, and AE rates decreased at 3 to 6 months in most cases and continued to decrease through >12 months.

Treatment-related Adverse Events

Table 47 Participants With Drug-Related Adverse Events (Incidence ≥ 5% in One or More Treatment Groups) By Decreasing Frequency of Preferred Term

	KN564 Data for Pembrolizumab [a]		KN564 Data for Placebo[b]		Reference Safety Dataset for Pembrolizumab[c]		Cumulative Running Safety Dataset for Pembrolizumab [d]	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	488		496		5,884		9,218	
with one or more adverse events	386	(79.1)	265	(53.4)	4,132	(70.2)	6,375	(69.2)

with no adverse events	102	(20.9)	231	(46.6)	1,752	(29.8)	2,843	(30.8)
Fatigue	99	(20.3)	71	(14.3)	1,170	(19.9)	1,686	(18.3)
Pruritus	91	(18.6)	57	(11.5)	836	(14.2)	1,230	(13.3)
Hypothyroidism	86	(17.6)	13	(2.6)	565	(9.6)	895	(9.7)
Diarrhoea	77	(15.8)	51	(10.3)	630	(10.7)	956	(10.4)
Rash	73	(15.0)	36	(7.3)	676	(11.5)	957	(10.4)
Hyperthyroidism	50	(10.2)	0	(0.0)	219	(3.7)	384	(4.2)
Arthralgia	46	(9.4)	43	(8.7)	464	(7.9)	673	(7.3)
Nausea	39	(8.0)	23	(4.6)	535	(9.1)	748	(8.1)
Myalgia	30	(6.1)	20	(4.0)	232	(3.9)	341	(3.7)
Asthenia	28	(5.7)	23	(4.6)	363	(6.2)	545	(5.9)
Decreased appetite	15	(3.1)	2	(0.4)	461	(7.8)	657	(7.1)

Grade ≥3 Adverse Events

Table 48 Participants With Grade 3-5 Adverse Events (Incidence ≥ 1% in One or More Treatment Groups) By Decreasing Frequency of Preferred Term

	KN564 Data for Pembrolizumab		KN564 Data for Placebo		Reference Safety Dataset for Pembrolizumab		Cumulative Running Safety Dataset for Pembrolizumab	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	488		496		5,884		9,218	
with one or more adverse events	158	(32.4)	88	(17.7)	2,829	(48.1)	4,444	(48.2)
with no adverse events	330	(67.6)	408	(82.3)	3,055	(51.9)	4,774	(51.8)
Hypertension	14	(2.9)	13	(2.6)	102	(1.7)	152	(1.6)
Alanine aminotransferase increased	11	(2.3)	1	(0.2)	61	(1.0)	120	(1.3)
Aspartate aminotransferase increased	8	(1.6)	1	(0.2)	65	(1.1)	141	(1.5)
Diarrhoea	8	(1.6)	1	(0.2)	79	(1.3)	129	(1.4)
Hyperglycaemia	7	(1.4)	3	(0.6)	64	(1.1)	111	(1.2)
Pneumonia	7	(1.4)	1	(0.2)	242	(4.1)	351	(3.8)
Adrenal insufficiency	6	(1.2)	1	(0.2)	18	(0.3)	32	(0.3)
Lipase increased	6	(1.2)	0	(0.0)	16	(0.3)	27	(0.3)
Acute kidney injury	5	(1.0)	0	(0.0)	51	(0.9)	86	(0.9)
Diabetic ketoacidosis	5	(1.0)	0	(0.0)	9	(0.2)	17	(0.2)
Fatigue	5	(1.0)	0	(0.0)	144	(2.4)	224	(2.4)
Colitis	4	(0.8)	0	(0.0)	60	(1.0)	93	(1.0)
Pulmonary embolism	3	(0.6)	3	(0.6)	91	(1.5)	133	(1.4)
Vomiting	3	(0.6)	0	(0.0)	42	(0.7)	89	(1.0)
Abdominal pain	2	(0.4)	1	(0.2)	42	(0.7)	106	(1.1)
Arthralgia	2	(0.4)	2	(0.4)	58	(1.0)	75	(0.8)
Hypokalaemia	2	(0.4)	1	(0.2)	58	(1.0)	89	(1.0)
Hyponatraemia	2	(0.4)	6	(1.2)	153	(2.6)	231	(2.5)
Pneumonitis	2	(0.4)	0	(0.0)	83	(1.4)	109	(1.2)
Urinary tract infection	2	(0.4)	3	(0.6)	73	(1.2)	104	(1.1)
Anaemia	1	(0.2)	0	(0.0)	233	(4.0)	427	(4.6)
Asthenia	1	(0.2)	1	(0.2)	58	(1.0)	108	(1.2)
Back pain	1	(0.2)	1	(0.2)	64	(1.1)	97	(1.1)
Blood alkaline phosphatase increased	1	(0.2)	0	(0.0)	48	(0.8)	95	(1.0)
Decreased appetite	1	(0.2)	0	(0.0)	74	(1.3)	120	(1.3)
Dehydration	1	(0.2)	0	(0.0)	62	(1.1)	102	(1.1)

Dyspnoea	1	(0.2)	0	(0.0)	131	(2.2)	177	(1.9)
Pleural effusion	1	(0.2)	1	(0.2)	68	(1.2)	100	(1.1)

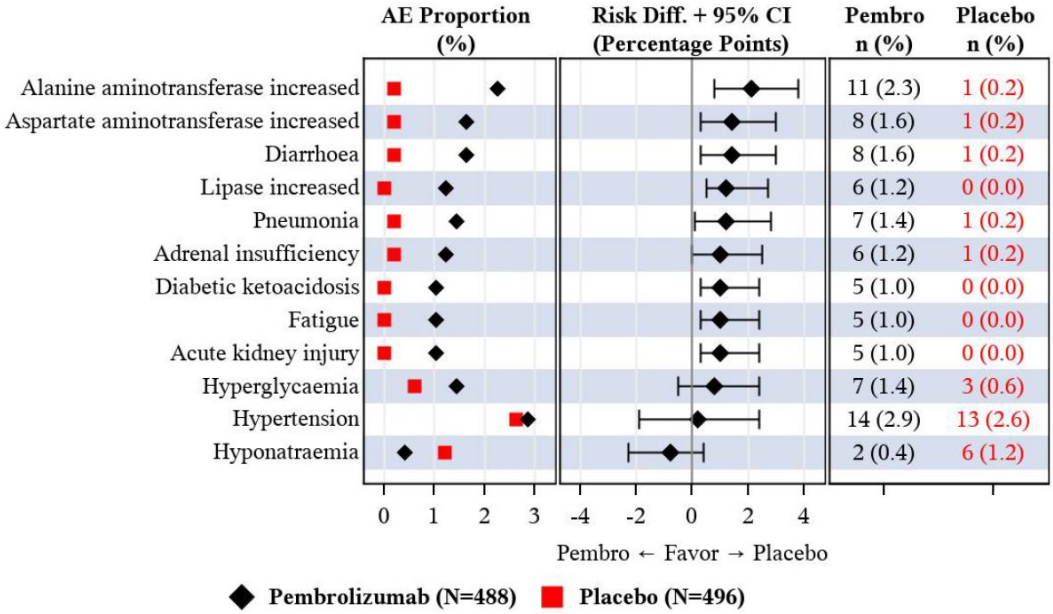


Figure 28 Between-treatment Comparisons in Grade 3-5 Adverse Events Selected Adverse Events (≥ 1% Incidence) and Sorted by Risk Difference

Treatment-related Grade ≥3 Adverse Events

Table 49 Participants With Grade 3-5 Drug-Related Adverse Events (Incidence ≥ 1% in One or More Treatment Groups) By Decreasing Frequency of Preferred Term

	KN564 Data for Pembrolizumab		KN564 Data for Placebo		Reference Safety Dataset for Pembrolizumab		Cumulative Running Safety Dataset for Pembrolizumab	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	488		496		5,884		9,218	
with one or more adverse events	92	(18.9)	6	(1.2)	913	(15.5)	1,490	(16.2)
with no adverse events	396	(81.1)	490	(98.8)	4,971	(84.5)	7,728	(83.8)
Alanine aminotransferase increased	9	(1.8)	1	(0.2)	35	(0.6)	68	(0.7)
Diarrhoea	8	(1.6)	0	(0.0)	55	(0.9)	86	(0.9)
Adrenal insufficiency	6	(1.2)	0	(0.0)	13	(0.2)	25	(0.3)
Aspartate aminotransferase increased	6	(1.2)	0	(0.0)	35	(0.6)	69	(0.7)
Diabetic ketoacidosis	5	(1.0)	0	(0.0)	8	(0.1)	16	(0.2)
Fatigue	4	(0.8)	0	(0.0)	63	(1.1)	100	(1.1)
Pneumonitis	2	(0.4)	0	(0.0)	78	(1.3)	103	(1.1)

Serious adverse event/deaths/other significant events

Serious Adverse Events (SAEs)

Table 50 Participants With Serious Adverse Events Up to 90 Days of Last Dose (Incidence ≥1% in One or More Treatment Groups) By Decreasing Frequency of Preferred Term

	KN564 Data for Pembrolizumab [a]		KN564 Data for Placebo [b]		Reference Safety Dataset for Pembrolizumab [c]		Cumulative Running Safety Dataset for Pembrolizumab [d]	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	488		496		5,884		9,218	
with one or more adverse events	100	(20.5)	56	(11.3)	2,266	(38.5)	3,449	(37.4)
with no adverse events	388	(79.5)	440	(88.7)	3,618	(61.5)	5,769	(62.6)
Acute kidney injury	6	(1.2)	0	(0.0)	50	(0.8)	95	(1.0)
Adrenal insufficiency	6	(1.2)	0	(0.0)	18	(0.3)	32	(0.3)
Pneumonia	6	(1.2)	1	(0.2)	246	(4.2)	348	(3.8)
Colitis	5	(1.0)	1	(0.2)	59	(1.0)	88	(1.0)
Diabetic ketoacidosis	5	(1.0)	0	(0.0)	9	(0.2)	17	(0.2)
Pneumonitis	3	(0.6)	0	(0.0)	117	(2.0)	157	(1.7)
Diarrhoea	1	(0.2)	0	(0.0)	59	(1.0)	84	(0.9)
Dyspnoea	1	(0.2)	0	(0.0)	81	(1.4)	97	(1.1)
Pleural effusion	1	(0.2)	1	(0.2)	83	(1.4)	113	(1.2)
Pulmonary embolism	1	(0.2)	3	(0.6)	71	(1.2)	99	(1.1)
Urinary tract infection	1	(0.2)	2	(0.4)	59	(1.0)	83	(0.9)
Anaemia	0	(0.0)	0	(0.0)	59	(1.0)	101	(1.1)
Pyrexia	0	(0.0)	1	(0.2)	67	(1.1)	102	(1.1)

Drug-related Serious Adverse Events (SAEs)

Table 51 Participants With Drug-related SAEs Up to 90 Days of Last Dose (Incidence ≥ 1% in One or More Treatment Groups) By Decreasing Frequency of Preferred Term

	KN564 Data for Pembrolizumab [a]		KN564 Data for Placebo [b]		Reference Safety Dataset for Pembrolizumab [c]		Cumulative Running Safety Dataset for Pembrolizumab [d]	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	488		496		5,884		9,218	
with one or more adverse events	59	(12.1)	1	(0.2)	656	(11.1)	1,049	(11.4)
with no adverse events	429	(87.9)	495	(99.8)	5,228	(88.9)	8,169	(88.6)
Adrenal insufficiency	6	(1.2)	0	(0.0)	14	(0.2)	26	(0.3)
Colitis	5	(1.0)	1	(0.2)	51	(0.9)	78	(0.8)
Diabetic ketoacidosis	5	(1.0)	0	(0.0)	8	(0.1)	16	(0.2)
Pneumonitis	3	(0.6)	0	(0.0)	111	(1.9)	150	(1.6)

Deaths

The incidence of deaths (up to 90 days after the last dose of study intervention) due to AEs was 0.4% (n=2) in the Indication Dataset compared with 5.3% in the RSD.

The two deaths in the Indication Dataset were reported due to AEs with PTs of pneumonia and multiple organ dysfunction syndrome; and 1 death due to AEs was reported in the placebo group (PT: hemorrhage intracranial). None of the deaths were considered treatment related by the investigator.

Other significant events - Adverse Events of Special Interest (AEOSI)

AEOSI are immune-related events and infusion-related reactions associated with pembrolizumab.

Table 52 Adverse Event Summary AEOSI (APaT Population)

	KN564 Data for Pembrolizumab		KN564 Data for Placebo		Reference Safety Dataset for Pembrolizumab		Cumulative Running Safety Dataset for Pembrolizumab	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	488		496		5,884		9,218	
with one or more adverse events	173	(35.5)	34	(6.9)	1,475	(25.1)	2,295	(24.9)
with no adverse event	315	(64.5)	462	(93.1)	4,409	(74.9)	6,923	(75.1)
with drug-related adverse events	155	(31.8)	22	(4.4)	1,282	(21.8)	2,005	(21.8)
with toxicity grade 3-5 adverse events	44	(9.0)	3	(0.6)	381	(6.5)	603	(6.5)
with toxicity grade 3-5 drug-related adverse events	43	(8.8)	0	(0.0)	331	(5.6)	532	(5.8)
with serious adverse events	41	(8.4)	1	(0.2)	381	(6.5)	583	(6.3)
with serious drug-related adverse events	39	(8.0)	1	(0.2)	337	(5.7)	522	(5.7)
who died	0	(0.0)	0	(0.0)	11	(0.2)	20	(0.2)
who died due to a drug-related adverse event	0	(0.0)	0	(0.0)	11	(0.2)	20	(0.2)
discontinued drug due to an adverse event	39	(8.0)	0	(0.0)	232	(3.9)	372	(4.0)
discontinued drug due to a drug-related adverse event	38	(7.8)	0	(0.0)	228	(3.9)	367	(4.0)
discontinued drug due to a serious adverse event	21	(4.3)	0	(0.0)	156	(2.7)	238	(2.6)
discontinued drug due to a serious drug-related adverse event	21	(4.3)	0	(0.0)	154	(2.6)	236	(2.6)

Table 53 Exposure-Adjusted Adverse Event Summary (Including Multiple Occurrences of Events) AEOSI (APaT Population)

	Event Count and Rate (Events/100 person-months)[a]			
	KN564 Data for Pembrolizumab[d]	KN564 Data for Placebo[e]	Reference Safety Dataset for Pembrolizumab[f]	Cumulative Running Safety Dataset for Pembrolizumab[g]
Number of participants exposed	488	496	5884	9218
Total exposure[b] in person-months	4852.07	5331.33	47883.80	74360.62
Total events (rate)				
adverse events	292 (6.02)	39 (0.73)	2155 (4.50)	3347 (4.50)
drug-related[c] adverse events	259 (5.34)	27 (0.51)	1860 (3.88)	2888 (3.88)
toxicity grade 3-5 adverse events	53 (1.09)	3 (0.06)	452 (0.94)	705 (0.95)
toxicity grade 3-5 drug-related adverse events	51 (1.05)	0 (0.00)	395 (0.82)	621 (0.84)
serious adverse events	44 (0.91)	1 (0.02)	448 (0.94)	676 (0.91)
serious drug-related adverse events	42 (0.87)	1 (0.02)	400 (0.84)	606 (0.81)
adverse events leading to death	0 (0.00)	0 (0.00)	11 (0.02)	20 (0.03)
drug-related adverse events leading to death	0 (0.00)	0 (0.00)	11 (0.02)	20 (0.03)
adverse events resulting in drug discontinuation	40 (0.82)	0 (0.00)	238 (0.50)	381 (0.51)
drug-related adverse events resulting in drug discontinuation	39 (0.80)	0 (0.00)	234 (0.49)	376 (0.51)
serious adverse events resulting in drug discontinuation	22 (0.45)	0 (0.00)	161 (0.34)	245 (0.33)
serious drug-related adverse events resulting in drug discontinuation	22 (0.45)	0 (0.00)	159 (0.33)	243 (0.33)

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

[b] Drug exposure (months) is defined as the duration between the first dose date and the earlier of the last dose date + 30 or the database cutoff date, which is calculated by (min(last dose date+30, Cutoff date) – first dose date + 1)/30.4367.

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

Table 54 Participants With AEOSI (Incidence > 0% in One or More Treatment Groups) By AEOSI Category (APaT Population)

	KN564 Data for Pembrolizumab		KN564 Data for Placebo		Reference Safety Dataset for Pembrolizumab ¶	
	n	(%)	n	(%)	n	(%)
Participants in population	488		496		5,884	
with one or more adverse events	173	(35.5)	34	(6.9)	1,475	(25.1)
with no adverse events	315	(64.5)	462	(93.1)	4,409	(74.9)
Adrenal Insufficiency	10	(2.0)	1	(0.2)	47	(0.8)
Colitis	8	(1.6)	1	(0.2)	110	(1.9)
Encephalitis	1	(0.2)	0	(0.0)	3	(0.1)
Guillain-Barre Syndrome	0	(0.0)	0	(0.0)	4	(0.1)
Hepatitis	5	(1.0)	0	(0.0)	56	(1.0)
Hyperthyroidism	58	(11.9)	1	(0.2)	247	(4.2)
Hypophysitis	2	(0.4)	0	(0.0)	36	(0.6)
Hypothyroidism	103	(21.1)	18	(3.6)	652	(11.1)
Infusion Reactions	7	(1.4)	5	(1.0)	138	(2.3)
Myasthenic Syndrome	3	(0.6)	0	(0.0)	3	(0.1)
Myocarditis	1	(0.2)	0	(0.0)	5	(0.1)
Myositis	2	(0.4)	1	(0.2)	19	(0.3)

Nephritis	3	(0.6)	0	(0.0)	23	(0.4)
Pancreatitis	0	(0.0)	0	(0.0)	18	(0.3)
Pneumonitis	11	(2.3)	5	(1.0)	264	(4.5)
Sarcoidosis	4	(0.8)	0	(0.0)	10	(0.2)
Severe Skin Reactions	8	(1.6)	2	(0.4)	97	(1.6)
Thyroiditis	6	(1.2)	1	(0.2)	58	(1.0)
Type 1 Diabetes Mellitus	9	(1.8)	0	(0.0)	20	(0.3)
Uveitis	0	(0.0)	1	(0.2)	21	(0.4)
Vasculitis	2	(0.4)	0	(0.0)	2	(0.0)

Table 55 Exposure-Adjusted AEOSI (Including Multiple Occurrences of Events) By AEOSI Category

	Event Count and Rate (Events/100 person-months)[a]			
	KN564 Data for Pembrolizumab[c]	KN564 Data for Placebo[d]	Reference Safety Dataset for Pembrolizumab[e]	Cumulative Running Safety Dataset for Pembrolizumab[f]
Number of participants exposed	488	496	5884	9218
Total exposure[b] person-months	4852.07	5331.33	47883.80	74360.62
Total events (rate)	292 (6.02)	39 (0.73)	2155 (4.50)	3347 (4.50)
AEOSI Category				
Adrenal Insufficiency	10(0.2)	1(0.0)	54 (0.1)	92 (0.1)
Hyperthyroidism	60 (1.2)	1(0.0)	271 (0.6)	463 (0.6)
Hypothyroidism	111 (2.3)	20(0.4)	730 (1.5)	1149 (1.5)
Sarcoidosis	4 (0.1)	0 (0.0)	13 (0.0)	18 (0.0)
Type 1 Diabetes Mellitus	11 (0.2)	0 (0.0)	30 (0.1)	58(0.1)

Table 56 Participants With AEOSI by Maximum Toxicity Grade

	KN564 Data for Pembrolizumab[a]		KN564 Data for Placebo[b]		Reference Safety Dataset for Pembrolizumab[c]		Cumulative Running Safety Dataset for Pembrolizumab[d]	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	488		496		5,884		9,218	
with one or more adverse events	173	(35.5)	34	(6.9)	1,475	(25.1)	2,295	(24.9)
Grade 1	26	(5.3)	18	(3.6)	368	(6.3)	542	(5.9)
Grade 2	103	(21.1)	13	(2.6)	726	(12.3)	1,150	(12.5)
Grade 3	39	(8.0)	3	(0.6)	325	(5.5)	514	(5.6)
Grade 4	5	(1.0)	0	(0.0)	45	(0.8)	69	(0.7)
Grade 5	0	(0.0)	0	(0.0)	11	(0.2)	20	(0.2)
with no adverse events	315	(64.5)	462	(93.1)	4,409	(74.9)	6,923	(75.1)

Table 57 Participants With grade 3-4 AEOSI (Incidence >0% in Indication Dataset)

	KN564 Data for Pembrolizumab		KN564 Data for Placebo		Reference Safety Dataset for Pembrolizumab¶	
	n	(%)	n	(%)	n	(%)
Participants in population	488		496		5,884	
with one or more Grade 3-4 adverse events	44	(9.0)	3	(0.6)	370	(6.3)
Adrenal Insufficiency	6	(1.2)	1	(0.2)	23	(0.4)
Colitis	5	(1.0)	0	(0.0)	67	(1.1)
Encephalitis	1	(0.2)	0	(0.0)	2	(0.0)
Hepatitis	4	(0.8)	0	(0.0)	44	(0.7)
Hyperthyroidism	1	(0.2)	0	(0.0)	7	(0.1)
Hypophysitis	2	(0.4)	0	(0.0)	20	(0.3)
Hypothyroidism	1	(0.2)	0	(0.0)	7	(0.1)
Infusion Reactions	2	(0.4)	0	(0.0)	14	(0.2)
Myocarditis	1	(0.2)	0	(0.0)	5	(0.1)
Nephritis	1	(0.2)	0	(0.0)	16	(0.3)
Pneumonitis	4	(0.8)	0	(0.0)	82	(1.4)
Severe Skin Reactions	8	(1.6)	2	(0.4)	74	(1.3)
Thyroiditis	2	(0.4)	0	(0.0)	1	(0.0)
Type 1 Diabetes Mellitus	9	(1.8)	0	(0.0)	19	(0.3)
Vasculitis	1	(0.2)	0	(0.0)	1	(0.0)

Table 58 Time to Onset and Duration of AEOSI

	KN564 Data for Pembrolizumab[c]		KN564 Data for Placebo[d]		Reference Safety Dataset for Pembrolizumab[e]		Cumulative Running Safety Dataset for Pembrolizumab[f]	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	488		496		5884		9218	
Participants with AEOSI	173	(35.5)	34	(6.9)	1475	(25.1)	2295	(24.9)
Time to Onset of First AEOSI (days)[a]								
Mean (Std)	100.9 (94.8)		146.4 (89.1)		117.9 (121.0)		116.5 (123.1)	
Median	64.0		147.5		79.0		71.0	
Range	1 to 426		1 to 364		1 to 787		1 to 787	
Total episodes of AEOSI	292		39		2105		3297	
Average Episodes per participant	1.69		1.15		1.43		1.44	
Episode duration (days)[b]								
Median	101.0		42.0		86.0		88.0	
Range	1 to 1148+		1 to 1022+		1 to 1640+		1 to 1640+	

(%) = Number of participants with AEOSI / Number of participants in population.

[a] Time to onset statistics are based on number of participants with AEOSI.

[b] From product-limit (Kaplan-Meier) method for censored data. If an adverse event is not resolved at the time of analysis or the participant died without adverse event resolved, the duration is censored at either data cutoff date or date of death, whichever occurred first.

+ indicates the AE episode is not recovered/resolved by the time of the cutoff date or date of death.

Std = Standard Deviation.

Table 59 Summary of Outcome for Participants With AEOSI

	Outcome	KN564 Data for Pembrolizumab[a]		KN564 Data for Placebo[b]		Reference Safety Dataset for Pembrolizumab[c]		Cumulative Running Safety Dataset for Pembrolizumab[d]	
		n	(%)	n	(%)	n	(%)	n	(%)
Participants in population		488		496		5884		9218	
With one or more AEOSI	**Overall**	**173**	**(35.5)**	**34**	**(6.9)**	**1475**	**(25.1)**	**2295**	**(24.9)**
	Fatal	0	(0.0)	0	(0.0)	11	(0.7)	20	(0.9)
	Not Resolved	73	(42.2)	9	(26.5)	692	(46.9)	1051	(45.8)
	Resolving	32	(18.5)	4	(11.8)	97	(6.6)	195	(8.5)
	Unknown	0	(0.0)	0	(0.0)	27	(1.8)	30	(1.3)
	Sequelae	15	(8.7)	0	(0.0)	34	(2.3)	64	(2.8)
	Resolved	53	(30.6)	21	(61.8)	614	(41.6)	935	(40.7)

Table 60 Summary of Outcome for Participants of AEOSI in the Indication Dataset

AEOSI	Not resolved or resolved with sequelae (%)	Resolving (%)	Resolved (%)
Adrenal Insufficiency	70	20	10
Colitis	25	0	75
Encephalitis	0	0	100
Hepatitis	0	0	100
Hyperthyroidism	13.8	5.2	81
Hypophysitis	0	0	100
Hypothyroidism	60.2	25.2	14.6
Infusion Reactions	0	0	100
Myasthenic Syndrome	33.3	0	66.7
Myocarditis	0	100	0
Myositis	100	0	0
Nephritis	33.3	33.3	33.3
Pneumonitis	9.1	0	90.9
Sarcoidosis	75	0	25
Severe Skin Reactions	25	0	75
Thyroiditis	50	0	50
Type 1 Diabetes Mellitus	88.9	11.1	0
Vasculitis	0	0	100

Table 61 Summary of Concomitant Corticosteroid Use for AEOSI

	KN564 Data for Pembrolizumab[a] (N=488)		KN564 Data for Placebo[b] (N=496)		Reference Safety Dataset for Pembrolizumab[c] (N=5884)		Cumulative Running Safety Dataset for Pembrolizumab[d] (N=9218)	
	n	%	n	%	n	%	n	%
Participants with one or more AEOSI	173		34		1475		2295	
Treated with systemic corticosteroid	52	30.1	6	17.6	460	31.2	766	33.4
Not treated with systemic corticosteroid	121	69.9	28	82.4	1015	68.8	1529	66.6
The number of participants with one or more AEOSI is used as the denominator for the percentage calculation.								

Safety data in pooled adjuvant studies

During the procedure the MAH provided safety data for the pembrolizumab adjuvant studies in RCC and melanoma (KEYNOTE-564, KEYNOTE-054, and KEYNOTE-716, n=1480; Adjuvant Dataset) and for the pembrolizumab studies in the advanced/metastatic setting (ie, the pembrolizumab monotherapy dataset without adjuvant study KEYNOTE-054, n=5375; Advanced/Metastatic Dataset).

Table 62 Adverse Event Summary (APaT population)

	KN564 Data for Pembrolizumab[b]		KN564 Data for Placebo[c]		Reference Safety Dataset for Pembrolizumab[d]		Cumulative Running Safety Dataset for Pembrolizumab[e]	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	488		496		5,884		9,218	
with one or more adverse events	470	(96.3)	452	(91.1)	5,690	(96.7)	8,890	(96.4)
with no adverse event	18	(3.7)	44	(8.9)	194	(3.3)	328	(3.6)
with drug-related[a] adverse events	386	(79.1)	265	(53.4)	4,132	(70.2)	6,375	(69.2)
with toxicity grade 3-5 adverse events	158	(32.4)	88	(17.7)	2,829	(48.1)	4,444	(48.2)
with toxicity grade 3-5 drug-related adverse events	92	(18.9)	6	(1.2)	913	(15.5)	1,490	(16.2)
with serious adverse events	100	(20.5)	56	(11.3)	2,266	(38.5)	3,449	(37.4)
with serious drug-related adverse events	59	(12.1)	1	(0.2)	656	(11.1)	1,049	(11.4)
who died	2	(0.4)	1	(0.2)	312	(5.3)	484	(5.3)
who died due to a drug-related adverse event	0	(0.0)	0	(0.0)	39	(0.7)	66	(0.7)
discontinued drug due to an adverse event	101	(20.7)	10	(2.0)	790	(13.4)	1,215	(13.2)
discontinued drug due to a drug-related adverse event	86	(17.6)	3	(0.6)	410	(7.0)	676	(7.3)
discontinued drug due to a serious adverse event	49	(10.0)	5	(1.0)	572	(9.7)	855	(9.3)
discontinued drug due to a serious drug-related adverse event	37	(7.6)	0	(0.0)	91	(6.1)	223	(4.1)	245	(4.2)

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

[b]Includes all participants who received at least one dose of pembrolizumab in KN564.

[c]Includes all participants who received at least one dose of placebo in KN564.

[d]Includes all participants who received at least one dose of pembrolizumab in KN564, KN054 and KN716.

[e]Includes all participants who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 (HNSCC), KN013 Cohort 3 (Hodgkin Lymphoma), KN024, KN040, KN042, KN045, KN048, KN052, KN055 and KN087.

[f]Includes all participants who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 (HNSCC), KN013 Cohort 3 (Hodgkin Lymphoma), KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055 and KN087.

Database Cutoff Date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 03APR2020/02OCT2017 in EU RSD, KN716: 21JUN2021)

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

Database Cutoff Date for Hodgkin Lymphoma (KN013-Cohort 3: 28SEP2018, KN087: 21MAR2019)

Database Cutoff Date for HNSCC (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)

Database Cutoff Date for Bladder (KN045: 26OCT2017, KN052: 26SEP2018)

Database cutoff date for RCC (KN564: 14DEC2020)

Table 63 Adverse Event Summary AEOSI

	KN564 Data for Pembrolizumab[b]		KN564 Data for Placebo[c]		KN564 + KN054 + KN716 Safety Dataset for Pembrolizumab[d]		Safety Dataset for Pembrolizumab in Advanced/Metastatic Setting[e]		Reference Safety Dataset for Pembrolizumab[f]	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	488		496		1,480		5,375		5,884	
with one or more adverse events	173	(35.5)	34	(6.9)	534	(36.1)	1,300	(24.2)	1,474	(25.1)
with no adverse event	315	(64.5)	462	(93.1)	946	(63.9)	4,075	(75.8)	4,410	(74.9)
with drug-related[a] adverse events	155	(31.8)	22	(4.4)	495	(33.4)	1,118	(20.8)	1,281	(21.8)
with toxicity grade 3-5 adverse events	44	(9.0)	3	(0.6)	132	(8.9)	342	(6.4)	380	(6.5)
with toxicity grade 3-5 drug-related adverse events	43	(8.8)	0	(0.0)	125	(8.4)	296	(5.5)	330	(5.6)
with serious adverse events	41	(8.4)	1	(0.2)	115	(7.8)	337	(6.3)	380	(6.5)
with serious drug-related adverse events	39	(8.0)	1	(0.2)	108	(7.3)	297	(5.5)	336	(5.7)
who died	0	(0.0)	0	(0.0)	0	(0.0)	11	(0.2)	11	(0.2)
who died due to a drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	11	(0.2)	11	(0.2)
discontinued drug due to an adverse event	39	(8.0)	0	(0.0)	117	(7.9)	199	(3.7)	232	(3.9)
discontinued drug due to a drug-related adverse event	38	(7.8)	0	(0.0)	116	(7.8)	195	(3.6)	228	(3.9)
discontinued drug due to a serious adverse event	21	(4.3)	0	(0.0)	58	(3.9)	144	(2.7)	156	(2.7)
discontinued drug due to a serious drug-related adverse event	21	(4.3)	0	(0.0)	58	(3.9)	142	(2.6)	154	(2.6)

Table 64 Exposure-Adjusted AE Summary (Including Multiple Occurrences of Events) AEOSI

	Event Count and Rate (Events/100 person-months)[a]				
	KN564 Data for Pembrolizumab[d]	KN564 Data for Placebo[e]	KN564 + KN054 + KN716 Safety Dataset for Pembrolizumab[f]	Safety Dataset for Pembrolizumab in Advanced/Metastatic Setting[g]	Reference Safety Dataset for Pembrolizumab[h]
Number of participants exposed	488	496	1480	5375	5884
Total exposure[b] in person-months	4852.07	5331.33	14990.36	42682.29	47883.80
Total events (rate)					
adverse events	292 (6.02)	39 (0.73)	926 (6.18)	1801 (4.22)	2154 (4.50)
drug-related[c] adverse events	259 (5.34)	27 (0.51)	850 (5.67)	1530 (3.58)	1859 (3.88)
toxicity grade 3-5 adverse events	53 (1.09)	3 (0.06)	175 (1.17)	387 (0.91)	451 (0.94)
toxicity grade 3-5 drug-related adverse events	51 (1.05)	0 (0.00)	164 (1.09)	336 (0.79)	394 (0.82)
serious adverse events	44 (0.91)	1 (0.02)	145 (0.97)	382 (0.89)	447 (0.93)
serious drug-related adverse events	42 (0.87)	1 (0.02)	137 (0.91)	339 (0.79)	399 (0.83)
adverse events leading to death	0 (0.00)	0 (0.00)	0 (0.00)	11 (0.03)	11 (0.02)
drug-related adverse events leading to death	0 (0.00)	0 (0.00)	0 (0.00)	11 (0.03)	11 (0.02)
adverse events resulting in drug discontinuation	40 (0.82)	0 (0.00)	119 (0.79)	205 (0.48)	238 (0.50)
drug-related adverse events resulting in drug discontinuation	39 (0.80)	0 (0.00)	118 (0.79)	201 (0.47)	234 (0.49)
serious adverse events resulting in drug discontinuation	22 (0.45)	0 (0.00)	59 (0.39)	149 (0.35)	161 (0.34)
serious drug-related adverse events resulting in drug discontinuation	22 (0.45)	0 (0.00)	59 (0.39)	147 (0.34)	159 (0.33)

Table 65 Participants With AEOSI by Maximum Toxicity Grade

	KN564 Data for Pembrolizumab[a]		KN564 Data for Placebo[b]		KN564 + KN054 + KN716 Safety Dataset for Pembrolizumab[c]		Safety Dataset for Pembrolizumab in Advanced/Metastatic Setting[d]		Reference Safety Dataset for Pembrolizumab[e]	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	488		496		1,480		5,375		5,884	
with one or more adverse events	173	(35.5)	34	(6.9)	534	(36.1)	1,300	(24.2)	1,474	(25.1)
Grade 1	26	(5.3)	18	(3.6)	106	(7.2)	327	(6.1)	368	(6.3)
Grade 2	103	(21.1)	13	(2.6)	296	(20.0)	631	(11.7)	726	(12.3)
Grade 3	39	(8.0)	3	(0.6)	119	(8.0)	290	(5.4)	324	(5.5)
Grade 4	5	(1.0)	0	(0.0)	13	(0.9)	41	(0.8)	45	(0.8)
Grade 5	0	(0.0)	0	(0.0)	0	(0.0)	11	(0.2)	11	(0.2)
with no adverse events	315	(64.5)	462	(93.1)	946	(63.9)	4,075	(75.8)	4,410	(74.9)

Table 66 Participants With AEOSI By Category and Grade 3-4 (Incidence > 0% in KN564)

	KN564 Data for Pembrolizumab		KN564 Data for Placebo		KN564 + KN054 + KN716 Safety Dataset for Pembrolizumab	Safety Dataset for Pembrolizumab In Advanced/Metastatic Setting	Reference Safety Dataset for Pembrolizumab¶	
	n	(%)	n	(%)	n (%)	n (%)	n	(%)
Participants in population	488		496		1,480	5,375	5,884	
with one or more adverse events	173	(35.5)	34	(6.9)	534 (36.1)	1,300 (24.2)	1,475	(25.1)
with no adverse events	315	(64.5)	462	(93.1)	946 (63.9)	4.075 (75.8)	4,409	(74.9)
Adrenal Insufficiency	**10**	**(2.0)**	**1**	**(0.2)**	**27 (1.8)**	**42 (0.8)**	**47**	**(0.8)**
Grade 3-4		6 (1.2)		1 (0.2)	11(0.7)	22 (0.4)		23 (0.4)
Colitis	**8**	**(1.6)**	**1**	**(0.2)**	**46 (3.1)**	**91 (1.7)**	**110**	**(1.9)**
Grade 3-4		5 (1.0)		0 (0.0)	24 (1.6)	57 (1.1)		67 (1.1)
Encephalitis	**1**	**(0.2)**	**0**	**(0.0)**	**1 (0.1)**	**3 (0.1)**	**3**	**(0.1)**
Grade 3-4		1(0.2)		0 (0.0)	1 (0.1)	2 (0.0)		2 (0.0)
Hepatitis	**5**	**(1.0)**	**0**	**(0.0)**	**25 (1.7)**	**46 (0.9)**	**55**	**(0.9)**
Grade 3-4		4 (0.8)		0 (0.0)	20 (1.4)	36 (0.7)		43 (0.7)
Hyperthyroidism	**58**	**(11.9)**	**1**	**(0.2)**	**161 (10.9)**	**194 (3.6)**	**247**	**(4.2)**
Grade 3-4		1 (0.2)		0 (0.0)	2 (0.1)	6 (0.1)		7 (0.1)
Hypophysitis	**2**	**(0.4)**	**0**	**(0.0)**	**25 (1.7)**	**25 (0.5)**	**36**	**(0.6)**
Grade 3-4		2 (0.4)		0 (0.0)	8 (0.5)	17 (0.3)		20 (0.3)
Hypothyroidism	**103**	**(21.1)**	**18**	**(3.6)**	**262 (17.7)**	**577 (10.7)**	**652**	**(11.1)**
Grade 3-4		1 (0.2)		0 (0.0)	1 (0.1)	7 (0.1)		7 (0.1)
Infusion Reactions	**7**	**(1.4)**	**5**	**(1.0)**	**21 (1.4)**	**130 (2.4)**	**138**	**(2.3)**
Grade 3-4		2 (0.4)		0 (0.0)	4 (0.3)	13 (0.2)		14 (0.2)
Myasthenic Syndrome	**3**	**(0.6)**	**0**	**(0.0)**	**6 (0.4)**	**2 (0.0)**	**3**	**(0.1)**
Grade 3-4		0 (0.0)		0 (0.0)	2 (0.1)	1 (0.0)		1 (0.0)
Myocarditis	**1**	**(0.2)**	**0**	**(0.0)**	**2 (0.1)**	**4 (0.1)**	**5**	**(0.1)**
Grade 3-4		1 (0.2)		0 (0.0)	2 (0.1)	4 (0.1)		5 (0.1)
Myositis	**2**	**(0.4)**	**1**	**(0.2)**	**9 (0.6)**	**18 (0.3)**	**19**	**(0.3)**

Grade 3-4		0 (0.0)		0 (0.0)		4 (0.3)		2 (0.0)		3 (0.1)
Nephritis	**3**	**(0.6)**	**0**	**(0.0)**		**12 (0.8)**		**21 (0.4)**	**23**	**(0.4)**
Grade 3-4		1 (0.2)		0 (0.0)		6 (0.4)		14 (0.2)		16 (0.3)
Pneumonitis	**11**	**(2.3)**	**5**	**(1.0)**		**40 (2.7)**		**247 (4.6)**	**264**	**(4.5)**
Grade 3-4		4 (0.8)		0 (0.0)		9 (0.6)		78 (1.5)		82 (1.4)
Sarcoidosis	**4**	**(0.8)**	**0**	**(0.0)**		**16 (1.1)**		**3 (0.1)**	**10**	**(0.2)**
Grade 3-4		0 (0.0)		0 (0.0)		0 (0.0)		0 (0.0)		0 (0.0)
Severe Skin Reactions	**8**	**(1.6)**	**2**	**(0.4)**		**27 (1.8)**		**92 (1.7)**	**97**	**(1.6)**
Grade 3-4		8 (1.6)		2 (0.4)		26 (1.8)		69 (1.3)		74 (1.3)
Thyroiditis	**6**	**(1.2)**	**1**	**(0.2)**		**28 (1.9)**		**42 (0.8)**	**58**	**(1.0)**
Grade 3-4		2 (0.4)		0 (0.0)		2 (0.1)		1 (0.0)		1 (0.0)
Type 1 Diabetes Mellitus	**9**	**(1.8)**	**0**	**(0.0)**		**16 (1.1)**		**15 (0.3)**	**20**	**(0.3)**
Grade 3-4		9 (1.8)		0 (0.0)		16 (1.1)		14 (0.3)		19 (0.3)
Uveitis	**0**	**(0.0)**	**1**	**(0.2)**		**3 (0.2)**		**19 (0.4)**	**21**	**(0.4)**
Grade 3-4		0 (0.0)		0 (0.0)		0 (0.0)		2 (0.0)		2 (0.0)
Vasculitis	**2**	**(0.4)**	**0**	**(0.0)**		**2 (0.1)**		**2 (0.0)**	**2**	**(0.0)**
Grade 3-4		1 (0.2)		0 (0.0)		1 (0.1)		0 (0.0)		1 (0.0)

	KN564 Data for Pembrolizumab[a] n (%)	KN564 Data for Placebo[b] n (%)	KN564 + KN054 + KN716 Safety Dataset for Pembrolizumab[c] n (%)	Safety Dataset for Pembrolizumab in Advanced/ Metastatic Setting[d] n (%)	Reference Safety Dataset for Pembrolizumab[e] n (%)
Participants in population	488	496	1480	5375	5884
Participants with AEOSI	173 (35.5)	34 (6.9)	534 (36.1)	1300 (24.2)	1474 (25.1)
Time to Onset of First AEOSI (days)[a]					
Mean (Std)	100.9 (94.8)	146.4 (89.1)	109.6 (95.8)	117.4 (123.6)	118.0 (121.0)
Median	64.0	147.5	78.0	75.0	79.5
Range	1 to 426	1 to 364	1 to 441	1 to 787	1 to 787
Total episodes of AEOSI	292	39	926	1751	2104
Average Episodes per participant	1.69	1.15	1.73	1.35	1.43
Episode duration (days)[b]					
Median	101.0	42.0	68.0	111.0	86.0
Range	1 to 1148+	1 to 1022+	1 to 1548+	1 to 1640+	1 to 1640+

Table 68 Summary of Outcome for Participants With AEOSI (Incidence > 0% in One or More Treatment Groups)

	Outcome	KN564 Data for Pembrolizumab n	(%)	KN564 Data for Placebo n	(%)	KN564 + KN054 + KN716 Safety Dataset for Pembrolizumab n	(%)	Safety Dataset for Pembrolizumab in Advanced/Meta-static Setting n	(%)	Reference Safety Dataset for Pembrolizumab n	(%)
Participants in population		488		496		1480		5375		5884	
With one or more AEOSI	**Overall**	**173**	**(35.5)**	**34**	**(6.9)**	**534**	**(36.1)**	**1300**	**(24.2)**	**1474**	**(25.1)**
	Fatal	0	(0.0)	0	(0.0)	0	(0.0)	11	(0.8)	11	(0.7)
	Not Resolved	73	(42.2)	9	(26.5)	254	(47.6)	581	(44.7)	692	(46.9)
	Resolving	32	(18.5)	4	(11.8)	62	(11.6)	97	(7.5)	97	(6.6)
	Unknown	0	(0.0)	0	(0.0)	1	(0.2)	27	(2.1)	27	(1.8)
	Sequelae	15	(8.7)	0	(0.0)	25	(4.7)	27	(2.1)	34	(2.3)
	Resolved	53	(30.6)	21	(61.8)	192	(36.0)	557	(42.8)	613	(41.6)

Table 69 Summary of Concomitant Corticosteroid Use for AEOSI

	KN564 Data for Pembrolizumab[a] (N=488)		KN564 Data for Placebo[b] (N=496)		KN564 + KN054 + KN716 Safety Dataset for Pembrolizumab[c] (N=1480)		Safety Dataset for Pembrolizumab in Advanced/Metastatic Setting[d] (N=5375)		Reference Safety Dataset for Pembrolizumab[c] (N=5884)	
	n	%	n	%	n	%	n	%	n	%
Participants with one or more AEOSI	173		34		534		1300		1474	
Treated with systemic corticosteroid	52	30.1	6	17.6	106	19.9	459	35.3	515	34.9
Not treated with systemic corticosteroid	121	69.9	28	82.4	428	80.1	841	64.7	959	65.1

Table 70 Summary of Hormone Replacement Therapy Use for AEOSI (

	Pembrolizumab n	(%)	Placebo n	(%)
Subjects in population	488		496	
Subjects with one or more events	119		20	
Treated with systemic hormone replacement	109	(91.6)	12	(60.0)
Not treated with systemic hormone replacement	10	(8.4)	8	(40.0)

Laboratory findings

The percentage of participants with laboratory abnormalities during the study were higher in the pembrolizumab group compared with the placebo group. The most frequently reported laboratory abnormalities (incidence ≥20%) in the Indication Dataset were generally consistent with the RSD, and the majority had a CTCAE toxicity Grade of 1 to 2.

Grade 3 to 4 laboratory abnormalities with an incidence of ≥2% in the pembrolizumab group were the following: ALT increased (3.8%), AST increased (2.7%), glucose increased (8.0%), lymphocyte decreased (2.5%), phosphate decreased (2.2%), and sodium decreased (3.3%).

Table 71 Summary of Participants with Increases from Baseline in Laboratory Test Toxicity Grade Based on Highest Post-baseline Toxicity Grade

Laboratory Test	KN564 Data for Pembrolizumab[a] (N=488) n	(%)	KN564 Data for Placebo[b] (N=496) n	(%)	Reference Safety Dataset for Pembrolizumab[c] (N=5884) n	(%)	Cumulative Running Safety Dataset for Pembrolizumab[d] (N=9218) n	(%)
Alanine Aminotransferase Increased (Alanine aminotransferase increased)								
Participants with Baseline and Post-baseline Measurements	449		469		4984		8089	
Grade 3-4	17	(3.8)	1	(0.2)	139	(2.8)	285	(3.5)
All Grades	90	(20.0)	52	(11.1)	1261	(25.3)	2043	(25.3)
Aspartate Aminotransferase Increased (Aspartate aminotransferase increased)								
Participants with Baseline and Post-baseline Measurements	448		468		4981		8079	
Grade 3-4	12	(2.7)	2	(0.4)	146	(2.9)	322	(4.0)
All Grades	70	(15.6)	33	(7.1)	1421	(28.5)	2325	(28.8)
Creatinine Increased (Creatinine increased)								
Participants with Baseline and Post-baseline Measurements	448		469		4991		8100	
Grade 3-4	5	(1.1)	1	(0.2)	70	(1.4)	127	(1.6)
All Grades	178	(39.7)	130	(27.7)	951	(19.1)	1701	(21.0)
Glucose Increased (Hyperglycemia)								
Participants with Baseline and Post-baseline Measurements	449		469		4906		7949	
Grade 3-4	36	(8.0)	21	(4.5)	247	(5.0)	431	(5.4)
All Grades	217	(48.3)	212	(45.2)	2493	(50.8)	3919	(49.3)
Lymphocytes Decreased (Lymphocyte count decreased)								
Participants with Baseline and Post-baseline Measurements	437		456		4673		7739	
Grade 3-4	11	(2.5)	3	(0.7)	524	(11.2)	801	(10.4)
All Grades	74	(16.9)	49	(10.7)	1791	(38.3)	2846	(36.8)
Phosphate Decreased (Hypophosphatemia)								
Participants with Baseline and Post-baseline Measurements	449		470		4721		7198	
Grade 3-4	10	(2.2)	8	(1.7)	260	(5.5)	380	(5.3)
All Grades	71	(15.8)	74	(15.7)	1043	(22.1)	1501	(20.9)
Sodium Decreased (Hyponatremia)								
Participants with Baseline and Post-baseline Measurements	449		469		5332		8438	
Grade 3-4	15	(3.3)	9	(1.9)	452	(8.5)	714	(8.5)
All Grades	94	(20.9)	60	(12.8)	1932	(36.2)	2874	(34.1)

Abnormal liver enzyme and function tests

A total of 3 participants (0.6%) in the pembrolizumab group and no participant in the placebo group had concurrent increases in aminotransferase to ≥3 x ULN plus bilirubin to ≥2 x ULN plus ALP to <2 x ULN. In the three cases meeting potential DILI screening laboratory criteria the participants were taking multiple concomitant medications associated with liver toxicity and the MAH concluded that the DILI screening laboratory test results were most likely related to the concomitant application of medications and not related to pembrolizumab.

Safety in special populations

Age

The AE profile in the Indication Dataset was generally similar across age groups of <65, 65 to 74, and 75 to 84, although there was a small number of participants in the 75 to 84 years category (n=18; no participant was ≥85 years) and generally similar between participants who were <65 years and those ≥65 years.

The AE profile for categories of interest (central nervous system confusion/extrapyramidal, AE related to falling, cardiovascular events, cerebrovascular events, and infections) in the Indication Dataset was also generally similar across age groups of <65, 65 to 74, and 75 to 84.

Table 72 Summary by Age Category (<65, ≥65 Years)

	KN564 Data for Pembrolizumab[b]				KN564 Data for Placebo[c]				Reference Safety Dataset for Pembrolizumab[d]			
	<65		>=65		<65		>=65		<65		>=65	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	333		155		324		172		3,385		2,499	
with one or more adverse events	322	(96.7)	148	(95.5)	294	(90.7)	158	(91.9)	3,268	(96.5)	2,422	(96.9)
with no adverse event	11	(3.3)	7	(4.5)	30	(9.3)	14	(8.1)	117	(3.5)	77	(3.1)
with drug-related[a] adverse events	270	(81.1)	116	(74.8)	182	(56.2)	83	(48.3)	2,366	(69.9)	1,766	(70.7)
with toxicity grade 3-5 adverse events	104	(31.2)	54	(34.8)	45	(13.9)	43	(25.0)	1,505	(44.5)	1,324	(53.0)
with toxicity grade 3-5 drug-related adverse events	60	(18.0)	32	(20.6)	4	(1.2)	2	(1.2)	456	(13.5)	457	(18.3)
with serious adverse events	62	(18.6)	38	(24.5)	29	(9.0)	27	(15.7)	1,182	(34.9)	1,084	(43.4)
with serious drug-related adverse events	36	(10.8)	23	(14.8)	1	(0.3)	0	(0.0)	346	(10.2)	310	(12.4)
who died	1	(0.3)	1	(0.6)	1	(0.3)	0	(0.0)	144	(4.3)	168	(6.7)
who died due to a drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	21	(0.6)	18	(0.7)
discontinued drug due to an adverse event	59	(17.7)	42	(27.1)	5	(1.5)	5	(2.9)	399	(11.8)	391	(15.6)
discontinued drug due to a drug-related adverse event	49	(14.7)	37	(23.9)	2	(0.6)	1	(0.6)	207	(6.1)	203	(8.1)
discontinued drug due to a serious adverse event	29	(8.7)	20	(12.9)	2	(0.6)	3	(1.7)	287	(8.5)	285	(11.4)
discontinued drug due to a serious drug-related adverse event	21	(6.3)	16	(10.3)	0	(0.0)	0	(0.0)	123	(3.6)	122	(4.9)

	KN564 Data for Pembrolizumab[b]								KN564 Data for Placebo[c]							
	<65		65-74		75-84		>=85		<65		65-74		75-84		>=85	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	333		137		18		0		324		147		25		0	
with one or more adverse events	322	(96.7)	131	(95.6)	17	(94.4)	0	(0.0)	294	(90.7)	133	(90.5)	25	(100.0)	0	(0.0)
with no adverse event	11	(3.3)	6	(4.4)	1	(5.6)	0	(0.0)	30	(9.3)	14	(9.5)	0	(0.0)	0	(0.0)
with drug-related[a] adverse events	270	(81.1)	102	(74.5)	14	(77.8)	0	(0.0)	182	(56.2)	72	(49.0)	11	(44.0)	0	(0.0)
with toxicity grade 3-5 adverse events	104	(31.2)	44	(32.1)	10	(55.6)	0	(0.0)	45	(13.9)	35	(23.8)	8	(32.0)	0	(0.0)
with toxicity grade 3-5 drug-related adverse events	60	(18.0)	27	(19.7)	5	(27.8)	0	(0.0)	4	(1.2)	2	(1.4)	0	(0.0)	0	(0.0)
with serious adverse events	62	(18.6)	30	(21.9)	8	(44.4)	0	(0.0)	29	(9.0)	20	(13.6)	7	(28.0)	0	(0.0)
with serious drug-related adverse events	36	(10.8)	18	(13.1)	5	(27.8)	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
who died	1	(0.3)	1	(0.7)	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
who died due to a drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued drug due to an adverse event	59	(17.7)	34	(24.8)	8	(44.4)	0	(0.0)	5	(1.5)	5	(3.4)	0	(0.0)	0	(0.0)
discontinued drug due to a drug-related adverse event	49	(14.7)	30	(21.9)	7	(38.9)	0	(0.0)	2	(0.6)	1	(0.7)	0	(0.0)	0	(0.0)
discontinued drug due to a serious adverse event	29	(8.7)	15	(10.9)	5	(27.8)	0	(0.0)	2	(0.6)	3	(2.0)	0	(0.0)	0	(0.0)

discontinued drug due to a serious drug-related adverse event	21	(6.3)	12	(8.8)	4	(22.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

	Reference Safety Dataset for Pembrolizumab[d]								Cumulative Running Safety Dataset for Pembrolizumab[e]					
	<65		65-74		75-84		>=85		<65		65-74		75-84		>=85	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	3,385		1,737		663		99		5,283		2,742		1,029		164	
with one or more adverse events	3,268	(96.5)	1,678	(96.6)	646	(97.4)	98	(99.0)	5,096	(96.5)	2,635	(96.1)	998	(97.0)	161	(98.2)
with no adverse event	117	(3.5)	59	(3.4)	17	(2.6)	1	(1.0)	187	(3.5)	107	(3.9)	31	(3.0)	3	(1.8)
with drug-related[a] adverse events	2,366	(69.9)	1,224	(70.5)	467	(70.4)	75	(75.8)	3,622	(68.6)	1,921	(70.1)	714	(69.4)	118	(72.0)
with toxicity grade 3-5 adverse events	1,505	(44.5)	891	(51.3)	373	(56.3)	60	(60.6)	2,413	(45.7)	1,366	(49.8)	571	(55.5)	94	(57.3)
with toxicity grade 3-5 drug-related adverse events	456	(13.5)	311	(17.9)	128	(19.3)	18	(18.2)	764	(14.5)	493	(18.0)	200	(19.4)	33	(20.1)
with serious adverse events	1,182	(34.9)	719	(41.4)	315	(47.5)	50	(50.5)	1,815	(34.4)	1,081	(39.4)	476	(46.3)	77	(47.0)
with serious drug-related adverse events	346	(10.2)	213	(12.3)	85	(12.8)	12	(12.1)	547	(10.4)	346	(12.6)	135	(13.1)	21	(12.8)
who died	144	(4.3)	103	(5.9)	54	(8.1)	11	(11.1)	214	(4.1)	164	(6.0)	86	(8.4)	20	(12.2)
who died due to a drug-related adverse event	21	(0.6)	12	(0.7)	5	(0.8)	1	(1.0)	29	(0.5)	24	(0.9)	11	(1.1)	2	(1.2)
discontinued drug due to an adverse event	399	(11.8)	246	(14.2)	131	(19.8)	14	(14.1)	605	(11.5)	385	(14.0)	196	(19.0)	29	(17.7)
discontinued drug due to a drug-related adverse event	207	(6.1)	135	(7.8)	62	(9.4)	6	(6.1)	336	(6.4)	225	(8.2)	102	(9.9)	13	(7.9)
discontinued drug due to a serious adverse event	287	(8.5)	174	(10.0)	100	(15.1)	11	(11.1)	425	(8.0)	263	(9.6)	145	(14.1)	22	(13.4)
discontinued drug due to a serious drug-related adverse event	123	(3.6)	81	(4.7)	38	(5.7)	3	(3.0)	194	(3.7)	130	(4.7)	62	(6.0)	6	(3.7)

Table 74 Adverse Event Summary "for Categories of Interest" in Elderly Subjects by Age

	Age (Years)											
	Pembrolizumab						Placebo					
	<65		65-74		75-84		<65		65-74		75-84	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in Population	333		137		18		324		147		25	
with one or more adverse events	322	(96.7)	131	(95.6)	17	(94.4)	294	(90.7)	133	(90.5)	25	(100.0)
who died	1	(0.3)	1	(0.7)	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0)
with serious adverse events	62	(18.6)	30	(21.9)	8	(44.4)	29	(9.0)	20	(13.6)	7	(28.0)
discontinued due to an adverse event	59	(17.7)	34	(24.8)	8	(44.4)	5	(1.5)	5	(3.4)	0	(0.0)
CNS (confusion/extrapyramidal)	25	(7.5)	6	(4.4)	2	(11.1)	18	(5.6)	10	(6.8)	1	(4.0)
AE related to falling	21	(6.3)	8	(5.8)	0	(0.0)	24	(7.4)	13	(8.8)	5	(20.0)
CV events	59	(17.7)	17	(12.4)	5	(27.8)	45	(13.9)	22	(15.0)	3	(12.0)
Cerebrovascular events	3	(0.9)	0	(0.0)	0	(0.0)	3	(0.9)	1	(0.7)	1	(4.0)
Infections	154	(46.2)	52	(38.0)	9	(50.0)	117	(36.1)	55	(37.4)	10	(40.0)

ECOG Performance Status

The AE profile was generally similar between participants with an ECOG PS of 0 and ECOG PS of 1 in the Indication Dataset, although there was a small number of participants with ECOG PS of 1 (n=72).

Table 75 Adverse Event Summary by ECOG Status Category (0, 1)

discontinued drug due to a serious drug-related adverse event	32	(7.7)	5	(6.9)	0	(0.0)	0	(0.0)	106	(3.8)	130	(4.4)

Gender

Table 76 AE Summary by Gender (Male, Female)

	KN564 Data for Pembrolizumab[b]				KN564 Data for Placebo[c]				Reference Safety Dataset for Pembrolizumab[d]			
	M		F		M		F		M		F	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	340		148		357		139		3,887		1,997	
with one or more adverse events	322	(94.7)	148	(100.0)	323	(90.5)	129	(92.8)	3,756	(96.6)	1,934	(96.8)
with no adverse event	18	(5.3)	0	(0.0)	34	(9.5)	10	(7.2)	131	(3.4)	63	(3.2)
with drug-related[a] adverse events	265	(77.9)	121	(81.8)	196	(54.9)	69	(49.6)	2,710	(69.7)	1,422	(71.2)
with toxicity grade 3-5 adverse events	106	(31.2)	52	(35.1)	67	(18.8)	21	(15.1)	1,894	(48.7)	935	(46.8)
with toxicity grade 3-5 drug-related adverse events	67	(19.7)	25	(16.9)	5	(1.4)	1	(0.7)	630	(16.2)	283	(14.2)
with serious adverse events	69	(20.3)	31	(20.9)	46	(12.9)	10	(7.2)	1,534	(39.5)	732	(36.7)
with serious drug-related adverse events	46	(13.5)	13	(8.8)	1	(0.3)	0	(0.0)	448	(11.5)	208	(10.4)
who died	1	(0.3)	1	(0.7)	1	(0.3)	0	(0.0)	221	(5.7)	91	(4.6)
who died due to a drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	25	(0.6)	14	(0.7)
discontinued drug due to an adverse event	69	(20.3)	32	(21.6)	6	(1.7)	4	(2.9)	529	(13.6)	261	(13.1)
discontinued drug due to a drug-related adverse event	61	(17.9)	25	(16.9)	1	(0.3)	2	(1.4)	278	(7.2)	132	(6.6)
discontinued drug due to a serious adverse event	33	(9.7)	16	(10.8)	5	(1.4)	0	(0.0)	386	(9.9)	186	(9.3)
discontinued drug due to a serious drug-related adverse event	28	(8.2)	9	(6.1)	0	(0.0)	0	(0.0)	167	(4.3)	78	(3.9)

The AE profile was generally similar between male and female participants in the Indication Dataset.

Geographic Region

Table 77 Adverse Event Summary by Region (EU, Ex-EU)

	KN564 Data for Pembrolizumab				KN564 Data for Placebo				Reference Safety Dataset for Pembrolizumab			
	EU		Ex-EU		EU		Ex-EU		EU		Ex-EU	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	184		304		187		309		2,092		3,792	
with one or more adverse events	174	(94.6)	296	(97.4)	172	(92.0)	280	(90.6)	2,014	(96.3)	3,676	(96.9)
with no adverse event	10	(5.4)	8	(2.6)	15	(8.0)	29	(9.4)	78	(3.7)	116	(3.1)
with drug-related[a] adverse events	147	(79.9)	239	(78.6)	111	(59.4)	154	(49.8)	1,430	(68.4)	2,702	(71.3)
with toxicity grade 3-5 adverse events	62	(33.7)	96	(31.6)	36	(19.3)	52	(16.8)	960	(45.9)	1,869	(49.3)
with toxicity grade 3-5 drug-related adverse events	36	(19.6)	56	(18.4)	2	(1.1)	4	(1.3)	317	(15.2)	596	(15.7)
with serious adverse events	45	(24.5)	55	(18.1)	25	(13.4)	31	(10.0)	796	(38.0)	1,470	(38.8)
with serious drug-related adverse events	26	(14.1)	33	(10.9)	0	(0.0)	1	(0.3)	241	(11.5)	415	(10.9)
who died	1	(0.5)	1	(0.3)	0	(0.0)	1	(0.3)	109	(5.2)	203	(5.4)
who died due to a drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	12	(0.6)	27	(0.7)
discontinued drug due to an adverse event	46	(25.0)	55	(18.1)	6	(3.2)	4	(1.3)	267	(12.8)	523	(13.8)
discontinued drug due to a drug-related adverse event	39	(21.2)	47	(15.5)	1	(0.5)	2	(0.6)	151	(7.2)	259	(6.8)
discontinued drug due to a serious adverse event	23	(12.5)	26	(8.6)	4	(2.1)	1	(0.3)	193	(9.2)	379	(10.0)
discontinued drug due to a serious drug-related adverse event	16	(8.7)	21	(6.9)	0	(0.0)	0	(0.0)	89	(4.3)	156	(4.1)

Safety related to drug-drug interactions and other interactions

As pembrolizumab is an IgG antibody that is administered parenterally and cleared by catabolism, food and DDI are not anticipated to influence exposure. Drugs that affect the cytochrome P450 enzymes, and other metabolizing enzymes, are not expected to interfere with the metabolism of an IgG antibody. The IgG antibodies, in general, do not directly regulate the expression of cytochrome P450 enzymes, other

enzymes, or transporters involved in drug elimination. Therefore, no dedicated DDI studies have been performed which is considered acceptable.

Discontinuation due to adverse events

Table 78 Participants With AEs Resulting in Treatment Discontinuation – Excerpt: (AE in ≥ 2 participants in the Indication Dataset) By Decreasing Frequency of Preferred Term (APaT Population)

	KN564 Data for Pembrolizumab[a]		KN564 Data for Placebo[b]		Reference Safety Dataset for Pembrolizumab[c]		Cumulative Running Safety Dataset for Pembrolizumab[d]	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	488		496		5,884		9,218	
with one or more adverse events	101	(20.7)	10	(2.0)	790	(13.4)	1,215	(13.2)
with no adverse events	387	(79.3)	486	(98.0)	5,094	(86.6)	8,003	(86.8)
Alanine aminotransferase increased	8	(1.6)	0	(0.0)	19	(0.3)	35	(0.4)
Adrenal insufficiency	5	(1.0)	0	(0.0)	4	(0.1)	12	(0.1)
Colitis	5	(1.0)	0	(0.0)	27	(0.5)	44	(0.5)
Acute kidney injury	4	(0.8)	0	(0.0)	6	(0.1)	15	(0.2)
Aspartate aminotransferase increased	4	(0.8)	0	(0.0)	19	(0.3)	29	(0.3)
Blood creatinine increased	4	(0.8)	1	(0.2)	1	(0.0)	10	(0.1)
Arthritis	3	(0.6)	0	(0.0)	2	(0.0)	6	(0.1)
Diarrhoea	3	(0.6)	0	(0.0)	13	(0.2)	22	(0.2)
Pneumonia	3	(0.6)	0	(0.0)	31	(0.5)	46	(0.5)
Pneumonitis	3	(0.6)	0	(0.0)	96	(1.6)	130	(1.4)
Rash	3	(0.6)	0	(0.0)	6	(0.1)	9	(0.1)
Sarcoidosis	3	(0.6)	0	(0.0)	3	(0.1)	6	(0.1)
Type 1 diabetes mellitus	3	(0.6)	0	(0.0)	4	(0.1)	9	(0.1)
Arthralgia	2	(0.4)	1	(0.2)	10	(0.2)	12	(0.1)
Diabetes mellitus	2	(0.4)	0	(0.0)	1	(0.0)	3	(0.0)
Diabetic ketoacidosis	2	(0.4)	0	(0.0)	2	(0.0)	4	(0.0)
Hypothyroidism	2	(0.4)	0	(0.0)	2	(0.0)	5	(0.1)
Immune-mediated pneumonitis	2	(0.4)	0	(0.0)	0	(0.0)	2	(0.0)
Myocardial infarction	2	(0.4)	0	(0.0)	6	(0.1)	10	(0.1)
Nephritis	2	(0.4)	0	(0.0)	1	(0.0)	4	(0.0)
Pulmonary embolism	2	(0.4)	0	(0.0)	12	(0.2)	15	(0.2)
Sjogren's syndrome	2	(0.4)	0	(0.0)	1	(0.0)	3	(0.0)
Thrombocytopenia	2	(0.4)	0	(0.0)	3	(0.1)	7	(0.1)
Thyroiditis	2	(0.4)	0	(0.0)	0	(0.0)	2	(0.0)

Table 79 Participants With AEs Resulting in Treatment Discontinuation By SOC and PTs

	KN564 Data for Pembrolizumab[a]		KN564 Data for Placebo[b]		Reference Safety Dataset for Pembrolizumab[c]		Cumulative Running Safety Dataset for Pembrolizumab[d]	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	488		496		5,884		9,218	
with one or more adverse events	101	(20.7)	10	(2.0)	790	(13.4)	1,215	(13.2)
with no adverse events	387	(79.3)	486	(98.0)	5,094	(86.6)	8,003	(86.8)
Blood and lymphatic system disorders	**2**	**(0.4)**	**0**	**(0.0)**	**12**	**(0.2)**	**18**	**(0.2)**
Cardiac disorders	**5**	**(1.0)**	**0**	**(0.0)**	**37**	**(0.6)**	**56**	**(0.6)**
Endocrine disorders	**11**	**(2.3)**	**0**	**(0.0)**	**17**	**(0.3)**	**34**	**(0.4)**
Eye disorders	**2**	**(0.4)**	**1**	**(0.2)**	**3**	**(0.1)**	**5**	**(0.1)**
Gastrointestinal disorders	**12**	**(2.5)**	**0**	**(0.0)**	**83**	**(1.4)**	**149**	**(1.6)**
General disorders and administration site conditions	**3**	**(0.6)**	**1**	**(0.2)**	**86**	**(1.5)**	**109**	**(1.2)**
Hepatobiliary disorders	**4**	**(0.8)**	**2**	**(0.4)**	**30**	**(0.5)**	**71**	**(0.8)**
Immune system disorders	**4**	**(0.8)**	**0**	**(0.0)**	**9**	**(0.2)**	**13**	**(0.1)**
Infections and infestations	**4**	**(0.8)**	**0**	**(0.0)**	**81**	**(1.4)**	**113**	**(1.2)**
Investigations	**16**	**(3.3)**	**1**	**(0.2)**	**45**	**(0.8)**	**89**	**(1.0)**
Metabolism and nutrition disorders	**7**	**(1.4)**	**0**	**(0.0)**	**25**	**(0.4)**	**42**	**(0.5)**
Musculoskeletal and connective tissue disorders	**8**	**(1.6)**	**1**	**(0.2)**	**38**	**(0.6)**	**54**	**(0.6)**
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**3**	**(0.6)**	**2**	**(0.4)**	**45**	**(0.8)**	**60**	**(0.7)**
Nervous system disorders	**6**	**(1.2)**	**1**	**(0.2)**	**50**	**(0.8)**	**74**	**(0.8)**
Renal and urinary disorders	**9**	**(1.8)**	**0**	**(0.0)**	**24**	**(0.4)**	**46**	**(0.5)**
Respiratory, thoracic and mediastinal disorders	**8**	**(1.6)**	**0**	**(0.0)**	**188**	**(3.2)**	**255**	**(2.8)**
Skin and subcutaneous tissue disorders	**5**	**(1.0)**	**0**	**(0.0)**	**28**	**(0.5)**	**38**	**(0.4)**
Vascular disorders	**1**	**(0.2)**	**0**	**(0.0)**	**11**	**(0.2)**	**13**	**(0.1)**

Table 80 Participants With Adverse Events Resulting in Treatment Discontinuation by Maximum Toxicity Grade

	KN564 Data for Pembrolizumab[a]		KN564 Data for Placebo[b]		Reference Safety Dataset for Pembrolizumab[c]		Cumulative Running Safety Dataset for Pembrolizumab[d]	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	488		496		5,884		9,218	
with one or more adverse events	101	(20.7)	10	(2.0)	790	(13.4)	1,215	(13.2)
Grade 1	5	(1.0)	0	(0.0)	33	(0.6)	43	(0.5)
Grade 2	28	(5.7)	3	(0.6)	152	(2.6)	239	(2.6)
Grade 3	55	(11.3)	6	(1.2)	309	(5.3)	484	(5.3)
Grade 4	11	(2.3)	1	(0.2)	83	(1.4)	127	(1.4)
Grade 5	2	(0.4)	0	(0.0)	213	(3.6)	322	(3.5)
with no adverse events	387	(79.3)	486	(98.0)	5,094	(86.6)	8,003	(86.8)

Post marketing experience

The safety profile of pembrolizumab was summarized in the Periodic Safety Update Report covering the period 04-SEP-2019 through 03-SEP-2020. There are no records of any pembrolizumab registration being revoked or withdrawn for safety reasons in any country.

2.5.1. Discussion on clinical safety

The safety data set in support of the new indication of pembrolizumab monotherapy in the adjuvant treatment of RCC post nephrectomy derived from 488 participants in Study KEYNOTE-564 (KN564) received pembrolizumab (Indication Dataset) and n=496 received placebo. In addition, safety data from the Pembrolizumab Monotherapy Reference Safety Dataset (RSD, n=5884) were included for comparison.

The median duration of **exposure** to pembrolizumab was >2-fold longer for participants in the Indication Dataset compared with the RSD (11.1 months vs 4.9 months, respectively), which is expected for pembrolizumab monotherapy when used as an adjuvant treatment. Although the median duration on therapy was the same for both treatment arms of study KN564, drug exposure by duration was lower in the pembrolizumab arm reflecting the higher discontinuation rates of pembrolizumab.

The **adverse event summary** showed higher incidences across all AE categories for the Indication Dataset versus the placebo group, as expected for the comparison of an active treatment versus placebo. Regarding the comparison of the Indication Dataset versus the RSD, participants in the KN564 pembrolizumab group had fewer overall SAEs and Grade 3 to 5 AEs compared with the RSD (20.5% vs 38.5% and 32.4% vs 48.1%), which is likely attributed to participants in the KN564 Safety Dataset being generally younger, without evidence of metastatic disease, but with better ECOG performance status at study entry. Incidences of drug-related AEs (79.1% vs 70.2%), related Grade 3 to 5 AEs (18.9% vs. 15.5%) and related SAEs (12.1% vs 11.1%) were numerically higher or similar in the Indication Dataset compared to the RSD.

Incidences of treatment discontinuations due to AEs were higher in the Indication Dataset compared with the RSD (AEs: 20.7% vs 13.4%; drug-related AEs: 17.6% vs 7.0%) and remained numerically higher also after adjustment for duration of exposure (all-cause AEs: 2.43 vs 1.80; drug-related AEs: 2.08 vs 0.94 events/100 person-months in the Indication Dataset vs RSD).

The same pattern was observed when pooled safety data from adjuvant pembrolizumab studies were compared with study data from the advanced/metastatic setting.

The **most common**ly reported AEs (incidence ≥20%) in the pembrolizumab arm of study KN564 were fatigue, diarrhea, pruritus, arthralgia, hypothyroidism, and rash. Most common adverse events of pembrolizumab in study KN564 were generally consistent with the RSD apart from notably higher incidences of hypothyroidism (21.1% vs 11.1%) and hyperthyroidism (11.9% vs 4.2%). The higher rate of blood creatinine observed in the Indication Dataset compared to the RSD (10.2% vs 4.4%) is likely partly associated with the prior nephrectomy (rate of blood creatinine increased 8.5% in the placebo arm). In addition, diarrhoea, pruritus, arthralgia and rash were reported with numerically slightly higher frequencies in the Indication Dataset compared with the RSD (Table 43).

Most frequently reported **Grade 3 to 5 AEs** (incidence ≥1.6%) were hypertension, alanine aminotransferase increased, aspartate aminotransferase increased and diarrhoea. Higher incidences for related Grade 3 to 5 AEs in the Indication Dataset compared to the RSD were reported for ALT and AST

increased (1.8% vs 0.6% and 1.2% vs 0.6%), diarrhoea (1.6% vs. 0.9%), adrenal insufficiency (1.2% vs. 0.2%) and diabetic ketoacidosis (1.0% vs. 0.1%).

The most frequently reported **SAEs** (incidence ≥1%) in the Indication Dataset were acute kidney injury, adrenal insufficiency, pneumonia, colitis, and diabetic ketoacidosis. Though the incidences of these SAEs were low (≤1.2%), higher rates for adrenal insufficiency and diabetic ketoacidosis (both drug-related) were observed in the Indication Dataset compared to the RSD (1.2% vs 0.3% and 1.0% vs 0.2%). Some clinically relevant SAEs with frequency <1% are notable: meningitis aseptic (0.4% [2 events] in the Indication Dataset vs. 0% [no event] in the RSD; both AEs drug-related); Stevens-Johnson syndrome (0.2% vs. 0% [2 events overall in the RSD]); vasculitis (0.2% vs. 0% in the RSD; AE drug-related); type 1 diabetes (0.8% vs. 0.2%), and myocardial infarction (0.6% vs 0.3%; 2 events [0.4%] drug-related).

Two **deaths due to AEs** (0.4%) were observed in the Indication Dataset (multiple organ dysfunction after accident and pneumonia) compared to 0.2% in the placebo group and 5.3% in the RSD.

The incidence of **AEOSI** was higher in the Indication Dataset compared with the RSD (any 35.5% vs 25.1%; drug-related 31.8% vs 21.8%); higher incidences were also reported for any and drug-related grade 3-5 AEOSI, serious AEOSI and AEOSI leading to discontinuations (see Table 52). After adjustment for different exposure higher rates of all-cause and drug-related AEs and AEs resulting in drug discontinuations remained, whereas grade 3-5 and serious AEs were comparable between both datasets.

The higher incidence of any AEOSI in the Indication Dataset compared with the RSD was primarily driven by the increased incidences of hypothyroidism (21.1% vs 11.1%) and hyperthyroidism (11.9% vs 4.2%). However, numerically higher frequencies in the Indication Dataset versus the RSD were also observed for adrenal insufficiency (2% vs 0.8%), type 1 diabetes mellitus (1.8% vs. 0.3%) and sarcoidosis (0.8% vs 0.2%), which also remained higher after adjustment by exposure.

Regarding severity of AEOSI, Grade 2 events were observed in 21.1% vs 12.3% in the Indication Dataset vs the RSD while Grade ≥3 of were observed in 9.0% in the Indication Dataset versus 6.5% in RSD. Of note were e.g. higher rates of Grade 3-4 type 1 diabetes mellitus (1.8% vs. 0.3%) or adrenal insufficiency (1.2% vs. 0.4), although slightly higher rates were observed across most categories.

Summary of outcome of AEOSI at a cutoff at June 2021 (with 6 months of longer follow-up) showed that in both, the Indication Dataset and the RSD, approximately half of the patients had AEOSI reported as not resolved or with sequelae. The proportion of resolving AEOSI was higher in study KN564 (17.8% vs 6.6% in the RSD); according to the MAH the resolving AEOSI in KN564 were primarily low grade hypothyroidism AEs which are likely to require ongoing long-term hormone replacement therapy. Therefore overall, the proportion of resolved AEOSI is slightly lower in study KN564 compared to the RSD (33.9% vs. 41.6%).

To better characterize the safety profile in the adjuvant setting and identify possible differences compared to the established toxicity profile of pembrolizumab in the metastatic setting pooled safety analyses for the adjuvant studies were submitted.

Side-by-side presentation showed that the safety profile of pembrolizumab in KEYNOTE-564 was overall consistent with that of the pooled pembrolizumab adjuvant monotherapy dataset and the observed differences compared to the RSD were mainly confirmed.

The incidence of AEOSI was higher in the Adjuvant Dataset compared with the Advanced/Metastatic Dataset (all 36.1% vs 24.2%, drug-related AEOSI 33.4% vs 20.8%, respectively). Although these differences were again primarily driven by the increased incidences of low-grade hypothyroidism and hyperthyroidism, also Grade 3-5 and serious AEOSI were reported with numerically slightly higher incidences in the adjuvant compared to the metastatic setting (exposure adjusted events/100 person

months: drug-related Grade 3-5 AEs 1.09 vs. 0.79; drug-related SAEs 0.91 vs 0.79 in adjuvant vs metastatic studies, respectively); besides colitis and hepatitis, numerically higher rates were also observed for endocrine AEOSI of adrenal insufficiency, hypophysitis, thyroiditis and type 1 diabetes mellitus. Discontinuations due to AEOSI were 7.9% vs 3.7%, respectively. The higher incidences of AEOSI in the adjuvant vs the metastatic setting is reflected in the SmPC

Incidences of treatment **discontinuations due to AEs** were higher in the Indication Dataset compared with the RSD. The most frequent (incidence ≥1%) AEs resulting in treatment discontinuation (any and drug-related) in the Indication Dataset were ALT increased, adrenal insufficiency, and colitis; all occurred at higher frequencies than in the RSD. AEs with incidences ≥0.6% with higher incidences in the Indication Dataset compared to the RSD were aspartate aminotransferase increased, acute kidney injury, blood creatinine increased, arthritis, diarrhoea, rash, sarcoidosis and type 1 diabetes mellitus. 5 participants (1%) discontinued due to cardiac disorders which were all considered drug-related (2 participants due to myocardial infarction and 1 each for atrial fibrillation, cardiac failure and pleuropericarditis).

The severity and time to onset of AE resulting in treatment discontinuation in the Indication Dataset did not show relevant differences compared to the dataset in the metastatic setting. The higher frequency of drug discontinuation due to AEs reported in KEYNOTE-564 as compared with the RSD is likely attributed to the lower rate of treatment discontinuation due to disease progression in KEYNOTE-564 (10.5% in KEYNOTE-564 vs >=34% in the RSD) that resulted in a longer duration of exposure, which contributes to a higher likelihood for treatment discontinuation due to AEs.

Safety in special populations

The AE profiles showed a general trend towards higher rates of toxicities with increasing **age**. Comparing the age groups below and above 65 years, the largest difference was notable for discontinuations due to AEs in the Indication Dataset (17.7% vs 27.1%). This was even more emphasized in the age group of 75-84 years with discontinuation rates of 44.4% (for comparison discontinuation rates of 19.8% for the same age group in the RSD).

In addition, large increases of grade 3-5 AEs and SAEs were notable for patients with 75-84 years compared to younger age groups in the Indication Dataset (see Table 5.4.26). These data suggest a worse tolerability of pembrolizumab in the adjuvant setting for elderly patients beyond 75 years (even though conclusions are limited by the small sample size of the age group 75-84 years, n=43).

For patients with **ECOG PS** 1, higher incidences of grade 3-4 and SAEs were generally observed in study KN564 and the RSD. Of note, high rates of discontinuation due to AEs were reported for patients with ECOG PS of 1 in the Indication Dataset (27.8% compared to 19.5% for patients with good PS in the Indication Dataset and 15.4% for patients with PS 1 in the RSD).

2.5.2. Conclusions on clinical safety

The safety data of pembrolizumab in Study KEYNOTE-564 were generally consistent with the established safety profile of pembrolizumab; however, higher rates of discontinuations due to AEs and higher incidences of AEOSI were observed in the Indication Dataset compared with the RSD. The differences were driven by increased low-grade incidences of hypothyroidism and hyperthyroidism but included also

higher rates of grade 3-4 and serious AEs such as type 1 diabetes mellitus. The higher rates of AEOSI were confirmed in the pooled safety data for the pembrolizumab adjuvant studies in comparison to the dataset in the advanced/metastatic setting. For half of the participants AEOSI were not resolved or resolved with sequelae. The proportion of resolving AEOSI which likely requires ongoing long-term hormone replacement therapy was higher in the adjuvant than the metastatic studies. Since long-term toxicities are of special clinical relevance in the adjuvant setting, these differences in the rate of AEOSI are reflected in the SmPC.

2.5.3. PSUR cycle

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

2.6. Risk management plan

The MAH submitted/was requested to submit an updated RMP version with this application.

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

The PRAC considered that the risk management plan version 34 is acceptable.

The CHMP endorsed the Risk Management Plan version 34 with the following content:

Safety concerns

Table SVIII.1: Summary of Safety Concerns

Summary of safety concerns	
Important identified risks	Immune-related adverse reactions (including immune related pneumonitis, colitis, hepatitis, nephritis, and endocrinopathies)
Important potential risks	For hematologic malignancies: increased risk of severe complications of allogeneic stem cell transplantation (SCT) in patients who have previously received pembrolizumab Graft versus host disease (GVHD) after pembrolizumab administration in patients with a history of allogeneic stem cell transplant (SCT)
Missing information	None

Pharmacovigilance plan

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

Risk minimisation measures

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

Safety Concern	Risk minimisation Measures	Pharmacovigilance Activities
Important Identified Risks: Immune-Related Adverse Reactions		
Immune-related adverse reactions (including immune-related pneumonitis, colitis, hepatitis, nephritis and endocrinopathies)	Routine risk minimisation measures: ▪ The risk of the immune-related adverse reactions (including immune-related pneumonitis colitis, hepatitis, nephritis, and endocrinopathies) associated with the use of pembrolizumab is described in the SmPC, Section 4.2, 4.4, 4.8 and appropriate advice is provided to the prescriber to minimize the risk.	Routine pharmacovigilance activities Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted questionnaire for spontaneous postmarketing reports of all adverse events
	Additional risk minimisation measures: Patient educational materials	Additional pharmacovigilance including: • Safety monitoring in all ongoing MAH-sponsored clinical trials for pembrolizumab in various tumor types

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

Safety Concern	Risk minimisation Measures	Pharmacovigilance Activities
Important Potential Risks		
For hematologic malignancies: increased risk of severe complications of allogeneic SCT in patients who have previously received pembrolizumab	Routine risk minimisation measures: ▪ For Hematologic malignancies: the increased risk of severe complications of allogeneic SCT in patients who have previously received pembrolizumab is described in the SmPC, Section 4.4, 4.8 and appropriate advice is provided to the prescriber to minimize the risk. No additional risk minimisation measures warranted	Routine pharmacovigilance activities Additional pharmacovigilance including: ▪ Safety monitoring in the ongoing HL trials (KN087, KN204).
GVHD after pembrolizumab administration in patients with a history of allogeneic SCT	Routine risk minimisation measures: ▪ GVHD after pembrolizumab administration in patients with a history of allogeneic SCT is described in the SmPC, Section 4.4 and appropriate advice is provided to the prescriber to minimize the risk. No additional risk minimisation measures warranted	Routine pharmacovigilance activities Additional pharmacovigilance including: • Safety monitoring in all ongoing MAH-sponsored clinical trials for pembrolizumab in various tumor types

2.7. Update of the Product information

As a result of this variation, sections 4.1, 4.2 and 5.1 of the SmPC are being updated. The Package Leaflet (PL) is updated accordingly.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons: The proposed changes in the context of this extension of indication do not involve a relevant impact on the PIL.

The design, layout and format of the package leaflet will not be affected.

2.7.2. Additional monitoring

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

3. Benefit-Risk Balance

3.1. Therapeutic Context

The claimed indication is for pembrolizumab (Keytruda) as monotherapy for the adjuvant treatment of adults with renal cell carcinoma (RCC) at intermediate-high or high risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions.

During the procedure, the indication was updated as follows:

Keytruda as monotherapy is indicated for the adjuvant treatment of adults with renal cell carcinoma at ~~intermediate-high or high~~ **increased** risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions (for selection criteria, please see section 5.1).

3.1.1. Disease or condition

Renal cell carcinoma (RCC) represents the sixth most common cancer in men and the eighth most common cancer in women, accounting for 3%-4% of all adult malignancies in the US (Siegel et al. CA A Cancer J Clin. 2019). In 2020, an estimated 138,611 new cases of kidney cancer were expected to be diagnosed in Europe with approximately 54,054 people expected to die from the disease (GLOBOCAN, 2020).

Well-known risk factors for RCC are cigarette smoking, obesity and hypertension (Chow et al. 2010).

Renal cell carcinoma generally resists both traditional chemotherapy and radiation therapy. Surgical resection can be curative for patients presenting with localized disease. However, one third of patients present with regional or distant metastases and the 5-year survival rate for metastatic disease is approximately 12%. Of patients with localized RCC treated with nephrectomy with curative intent, approximately one quarter relapse at distant sites. The prognosis in these cases is poor (Choueiri and Motzer 2017). Advanced RCC entails both locally advanced disease that is not amenable to local therapy, i.e. curative surgery or radiation therapy, as well as metastatic disease. Advanced RCC thus requires systemic treatment. There are currently no approved adjuvant treatments for RCC and observation remains the standard of care after nephrectomy.

3.1.2. Available therapies and unmet medical need

The treatment of choice for localized RCC (Stage I-III) is surgical resection, which is the only curative therapy. After nephrectomy, observation remains the standard of care, and no treatment is currently approved in the adjuvant setting in the EU.

3.1.3. Main clinical studies

The main evidence for efficacy and safety to support the present extension of indication is the Phase III study KEYNOTE-564, an international, multicenter, randomized, double-blind trial of adjuvant pembrolizumab vs. placebo. The ITT population includes 994 patients (496 in pembrolizumab arm and 498 in the placebo arm).

3.2. Favourable effects

The primary efficacy outcome measure was investigator-assessed disease-free-survival (DFS) in the ITT population. At the pre-specified interim analysis with a median follow-up time of 23.9 months, the study showed a statistically significant improvement in DFS (HR 0.68; 95% CI 0.53, 0.87; p-Value = 0.0010) for patients randomised to the pembrolizumab arm compared with placebo. Median DFS was not reached in both arms. The probability of being event free at year 1 and year 2 was 85.7% and 77.3% for pembrolizumab vs. 76.2% and 68.1% for placebo. Data were based on 260 events (78% of final analyses). With an additional 6 months of follow up (median duration of follow-up 29.7 months based on a data cutoff date of 14-JUN-2021) the HR for DFS was 0.63 (95% CI: 0.50, 0.80) in the ITT population.

A clear DFS benefit was observed in patients with high risk of recurrence (MO high) (HR 0.60; 95% CI 0.33, 1.11) and M1 NED (HR 0.29; 95% CI 0.12, 0.69).

Regarding OS, in the pre-specified interim analysis the HR was 0.54 (95% CI: 0.30, 0.96) (p=0.016) and the median OS was not reached in either group. With an additional 6 months of follow up (cut-off date 14-JUN-2021) the HR for OS was 0.52 (95% CI: 0.31, 0.86) in the ITT population.

For Disease Recurrence-specific Survival the cumulative incidences of the event of interest (local and distant recurrence) were lower over time in the pembrolizumab group compared with the placebo group.

Thirty participants in the pembrolizumab group and 56 participants in placebo group experienced a PFS2 event (HR: 0.52; 95% CI: 0.34, 0.81; nominal p-value 0.0018 at IA1), indicating a reduced risk of disease progression or death on next-line drug therapy in the pembrolizumab group compared with the placebo group.

3.3. Uncertainties and limitations about favourable effects

At the pre-defined data cut-off date 14 DEC 2020 the OS was events were largely immature with approximately 26% of the total events. With the updated analyses the OS events passed from 51 to 66 which is still considered immature but showed a trend in favour of pembrolizumab. Further OS data are expected to be submitted as soon as available (REC).

3.4. Unfavourable effects

The incidence of AEOSI was higher in the Indication Dataset compared with the RSD with any AEOSI been 35.5% vs 25.1% and the drug-related AEOSI been 31.8% vs 21.8%, including higher grade 3-5 AEOSI, serious AEOSI and AEOSI leading to discontinuation. For half of the participants the AEOSI were not resolved or resolved with sequelae at the time of data cutoff.

The higher rates of AEOSI were confirmed in the pooled safety data for the pembrolizumab adjuvant studies in comparison to the dataset in the advanced/metastatic setting (all 36.1% vs 24.2%, drug-related AEOSI 33.4% vs 20.8%, respectively).

The incidences of treatment discontinuations due to AEs were higher in the Indication Dataset compared with the RSD (AEs: 20.7% vs 13.4%; drug-related AEs: 17.6% vs 7.0%) and remained numerically higher also after adjustment for duration of exposure (all-cause AEs: 2.43 vs 1.80; drug-related AEs: 2.08 vs 0.94 events/100 person-months in the Indication Dataset vs RSD).

3.5. Uncertainties and limitations about unfavourable effects

There were no uncertainties that are key to the description of the harms of the product.

3.6. Effects Table

Table 81 Effects Table for Keytruda in KN564 for the adjuvant treatment of RCC

Effect	Short description	Unit	Pembro	Placebo	Uncertainties / Strength of evidence
Favourable Effects Data cut-off 14 DEC 2020)					
DFS by investigator	Median (95% CI)	years	NR	NR	no independent radiologic assessment Effect in subgroups difficult to interpret in view of the large heterogeneity with regard to prognosis and risk of relapse.
	HR (95% CI)		0.68 (0.53, 0.87) P=0.0010		
OS	Median (95% CI)	years	NR	NR	Secondary endpoint; immature data
	HR (95% CI)		0.54 (0.30, 0.96) P=0.0164037		
Favourable Effects Data cut-off 14 JUNE 2021)					
DFS by investigator	Median (95% CI)	years	NR	NR	no independent radiologic assessment Effect in subgroups difficult to interpret in view of the large heterogeneity with regard to prognosis and risk of relapse.
	HR (95% CI)		0.63 (0.5, 0.8) P<0.0001		
Unfavourable Effects (Data cut-off 14 DEC 2020)					
			Indication data set	**RSD***	
Safety	Drug-related AEs	%	79.1	70.2	Higher rates of AEOSI and discontinuations due to AEs for Indication Dataset vs RSD* Data suggest worse tolerability for elderly beyond 75 years.
	Drug-related G 3-5 AEs	%	18.9	15.5	
	Drug-related SAEs	%	12.1	11.1	
	Discontinuation due to drug-related AEs	%	17.6	7.0	
	All-cause AEOSI	%	35.5	25.1	
	Drug-related AEOSI	%	31.8	21.8	

* Pembrolizumab Monotherapy Reference Safety Dataset

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Pembrolizumab showed a statistically significant advantage over placebo in DFS according to investigator assessment in the ITT population. Secondary and explorative analyses for OS, DRSS1 and PFS2 are overall supportive; but data are still immature with a median follow-up duration of 29.7 months (updated analysis). The MAH is recommended to provide updated OS data from study KEYNOTE-564.

Although the safety profile of pembrolizumab is well established in the metastatic setting, higher incidences of AEOSI (including grade 3-4 AEs, SAEs) and higher rates of discontinuations due to AEs were observed in the adjuvant treatment compared to the established safety dataset. Long-term toxicities are of special clinical relevance in the adjuvant setting and are reflected in the SmPC.

3.7.2. Balance of benefits and risks

Updated results provided support for a beneficial treatment effect of pembrolizumab over placebo in the adjuvant setting of adults with renal cell carcinoma at increased risk of recurrence.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable

3.8. Conclusions

The overall benefit/risk balance of Keytruda is considered positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

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

Extension of indication to include the adjuvant treatment in monotherapy of adults with renal cell carcinoma at increased risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions. As a consequence, sections 4.1, 4.2, and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 34.0 of the RMP has also been submitted.

Amendments to the marketing authorisation

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