14 September 2023
EMA/451876/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Keytruda

International non-proprietary name: pembrolizumab

Procedure No. EMEA/H/C/003820/II/0121

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
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of contents

List of abbreviations

Abbreviation	Definition
ADA	antidrug antibodies
AE	adverse event
AEOSI	adverse event of special interest
AJCC	American Joint Committee on Cancer
APaT	All Participants as Treated
cHL	classical Hodgkin lymphoma
CHMP	Committee for Medicinal Products
CI	confidence interval
COVID-19	coronavirus disease caused by severe acute respiratory syndrome coronavirus 2
CRC	colorectal carcinoma
CSCC	cutaneous squamous cell carcinoma
DFS	Disease-free survival
DILI	drug-induced liver injury
ECOG	Eastern Cooperative Oncology Group
EFS	event-free survival
EGFR	epidermal growth factor receptor
EMA	European Medicines Agency
E-R	exposure-response
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HCC	hepatocellular carcinoma
HNSCC	head and neck squamous cell carcinoma
HR	hazard ratio
IA	interim analysis
IASLC	International Association for the Study of Lung Cancer
IB	Investigator Brochure
IFNγ	interferon gamma
IL-2	interleukin 2
ITT	Intention-to-treat

Abbreviation	Definition
KM	Kaplan-Meier
mAb	monoclonal antibody
MAH	marketing authorization holder
MCC	Merkel cell carcinoma
MSI-H	microsatellite instability-high
NSCLC	non-small-cell lung cancer
OS	overall survival
PD-1	programmed cell death 1
PD-L1/2	programmed cell death ligand 1 or 2
PK	pharmacokinetics
PMBCL	primary mediastinal large B-cell lymphoma
Q3W	every 3 weeks
Q6W	every 6 weeks
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RSD	Reference Safety Dataset
SAE	serious adverse event
SAP	Statistical Analysis Plan
sBLA	supplemental Biologics License Application
SCLC	small-cell lung cancer
SmPC	Summary of Products Characteristics
TC	tumor cells
TMB-H	tumor mutational burden-high
TNFα	tumor necrosis factor alpha
TNM	tumor-node-metastases
TPS	tumor proportion score
UICC	Union for International Cancer Control
UK	United Kingdom
US	United States
USPI	US Prescribing Information
Vs	versus

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 6 April 2022 an application for a variation.

The following variation was requested:

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

Extension of indication to include Keytruda as monotherapy for the adjuvant treatment of adults with Stage IB (T2a ≥ 4 cm), II or IIIA non-small cell lung carcinoma (NSCLC) who have undergone complete resection, based on study KEYNOTE-091; an ongoing Phase 3, randomized, triple-blinded, placebo-controlled, multicentre study of pembrolizumab versus placebo in patients with early-stage NSCLC after resection and completion of standard adjuvant therapy. As a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are being updated and the Package Leaflet is updated in accordance. An updated RMP version 39.1 was also submitted.

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

Information on paediatric requirements

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

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

Information relating to orphan market exclusivity

Similarity

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

Scientific advice

The MAH received Scientific Advice from the CHMP on 22 January 2015 (EMA/H/SA/2437/7/2014/II). The Scientific Advice pertained to clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Paolo Gasparini Co-Rapporteur: N/A

Timetable	Actual dates
Submission date	6 April 2022
Start of procedure	23 April 2022
CHMP Rapporteur's preliminary assessment report circulated on	24 June 2022
PRAC Rapporteur's preliminary assessment report circulated on	29 June 2022
PRAC RMP advice and assessment overview adopted by PRAC on	7 July 2022
CHMP Rapporteur's updated assessment report circulated on	15 July 2022
Request for supplementary information adopted by the CHMP on	21 July 2022
MAH's responses submitted to the CHMP on	11 August 2022
Re-start of procedure	15 August 2022
CHMP Rapporteur's preliminary assessment report on the MAH's responses circulated on	15 September 2022
PRAC Rapporteur's preliminary assessment report on the MAH's responses circulated on	14 September 2022
PRAC RMP advice and assessment overview adopted by PRAC on	29 September 2022
CHMP Rapporteur's updated assessment report on the MAH's responses circulated on	7 October 2022
2nd Request for supplementary information adopted by the CHMP on	13 October 2022
MAH's responses submitted to the CHMP on	6 July 2023
Re-start of procedure	17 July 2023
PRAC Rapporteur's preliminary assessment report on the MAH's responses circulated on	3 August 2023
CHMP Rapporteur's preliminary assessment report on the MAH's responses circulated on	11 August 2023
PRAC RMP advice and assessment overview adopted by PRAC on	31 August 2023
CHMP Rapporteur's updated assessment report on the MAH's responses circulated on	9 September 2023
CHMP opinion adopted on	14 September 2023

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Lung cancer is one of the most common malignancies in the world, with an estimated global incidence of 2.2 million in 2020 and an associated 1.8 million deaths. In Europe, age standardized incidence rates (per 100.000) vary between 33.3 - 49 in male, and between 11.6 - 26.8 in female, while age standardized mortality rates vary between 26.9 – 32.7 in male, and between 20.1 - 23.8 in female.[1] NSCLC accounts for approximately 85% of all lung cancers, the most common histological subtypes being adenocarcinoma, squamous cell carcinoma, and large-cell carcinoma[2].

At the time of diagnosis, approximately 19% of patients with NSCLC have localized disease (Stage I), 22% have locally advanced or regional disease (Stages II and III), and 55% have metastatic disease (Stage IV). Stage is a main prognostic factor. According to stage, 5-years relative survival ranges between 61.2% in localized, 33.5% in regional, and 7% in distant disease[3].

State the claimed the therapeutic indication

The MAH's sought indication is: "KEYTRUDA as monotherapy is indicated for the adjuvant treatment of adults with Stage IB (T2a ≥ 4 cm), II or IIIA non-small cell lung carcinoma who have undergone complete resection."

Risk factors, screening tools/prevention

Global statistics estimate that 15% of lung cancers in men and 53% in women are not attributable to smoking. To date, there are no specific recommendation for screening for lung cancer.[4]

Biologic features

Molecular characteristics

Histological diagnosis of NSCLC is crucial to many treatment decisions and should be as exact and detailed as the samples and available technology allow. After morphological diagnosis, the next consideration is therapy-predictive biomarker testing. Several molecular drivers for oncogene addiction represent strong predictive biomarkers and excellent therapeutic targets. They are generally mutually exclusive of each other. The vast majority of oncogene-addicted lung cancers are adenocarcinomas.

[1] International Agency for Research on Cancer. Lung. Lyon (France): International Agency for Research on Cancer (IARC); 2020. 2p. Available from: https://gco.iarc.fr/today/fact-sheets-cancers.
[2] National Cancer Institute. SEER Cancer Statistics Review 1975-2017: cancer of the lung and bronchus (invasive). Bethesda (MD): National Cancer Institute (NCI); 2020.
[3] Surveillance, Epidemiology, and End Results Program [Internet]. Bethesda (MD): National Cancer Institute (NCI). Cancer stat facts: lung and bronchus cancer; [cited 2021 Sep 20]; [about 18 screens]. Available from: https://seer.cancer.gov/statfacts/html/lungb.html
[4] Postmus PE, Kerr KM, Oudkerk M, Senan S, Waller DA, Vansteenkiste J, Escriu C, Peters S; ESMO Guidelines Committee. Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2017 Jul 1;28(suppl_4):iv1-iv21.

Patients, in general, tend to be younger, female gender and East Asian ethnicity. To date, relevant biomarkers for NSCLC are EGFR mutations, rearrangements involving the ALK and ROS1 genes, BRAF V600E mutations, NTRK1 fusion, HER2 and MET exon 14 mutations and fusion genes involving RET[5]. To date, the only approved targeted treatment in the EU in the adjuvant setting is osimertinib (see section "management" below).

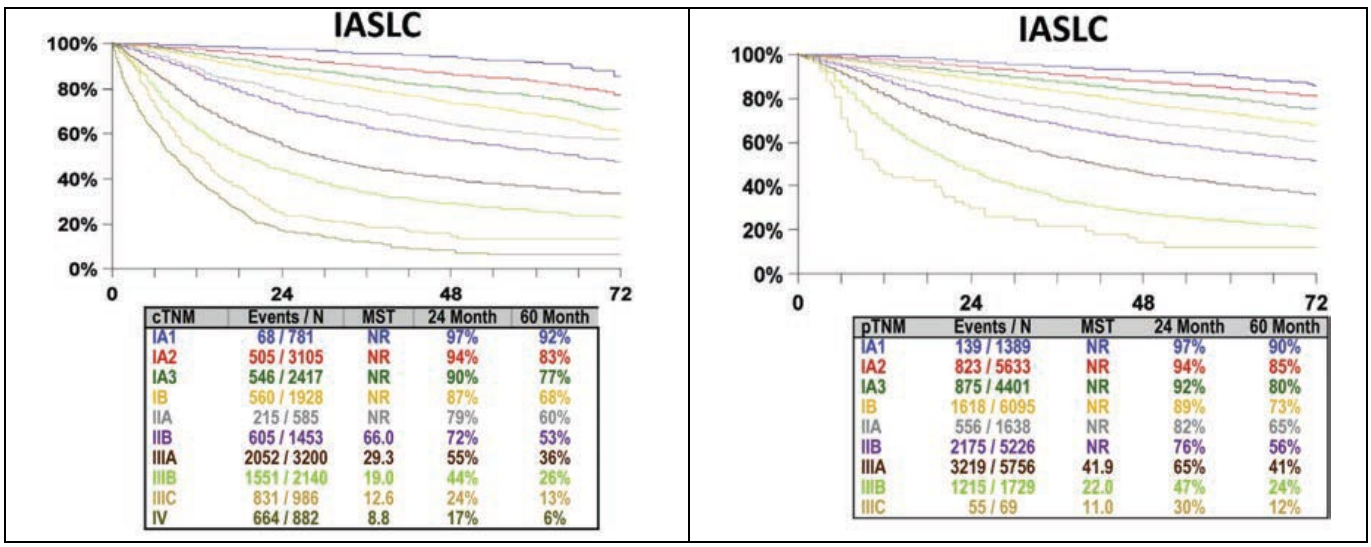
Clinical presentation, diagnosis and stage/prognosis

Update to AJCC Staging Guidelines

Study KEYNOTE-091 was initiated in 2015. The study enrolled participants who had Stages IB (T2a≥4 cm), II, or IIIA NSCLC under the AJCC 7th edition. The tumour stage was also used as a stratification factor. During the conduct of the study in January 2017, a major update to staging guidelines was provided with the release of the 8th edition of the UICC/IASLC and was implemented clinically in January 2018. In order to maintain consistency in participant eligibility and stratification, use of the AJCC 7th edition staging system was continued throughout the study.

The key feature of this update was changes in determination of the T (primary tumour) component of the staging system, which led to migration in certain overall stages[6]. For example, some participants enrolled in KEYNOTE-091 with Stage IB (T2a>4 cm) in the 7th edition would be considered to have Stage IIA (T2b) in 8th edition. Participants with Stage IB (T2a =4 cm) in the 7th edition would remain Stage IB (T2a) in the 8th edition. Additionally, some participants with Stage IIIA [T (2–3) N2] under the 7th edition would become Stage IIIB [T (3-4) N2] under the 8th edition.

In summary, KEYNOTE-091 enrolled participants with Stages IB (T2a ≥ 4 cm), II, or IIIA NSCLC under the AJCC 7th edition. This is equivalent to Stage IB (T2a = 4 cm) through IIIB [(T3-4 (>7cm), N2] under the AJCC 8th edition.



Stage groups for NSCLC. Overall survival in patients with NSCLC according to the eighth edition stage groups in the International Association for the Study of Lung Cancer (IASLC) data sets. (A) Clinically staged (cTNM) tumors. (B) Pathologically staged (pTNM) tumors. MST, median survival time (months). From Chansky K, 2017.

[5] Planchard D, et al, on behalf of the ESMO Guidelines Committee. Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2018;29(Suppl 4): iv192–iv237 - Updated version published 15 September 2020 by the ESMO Guidelines Committee.
[6] Chansky K, Detterbeck FC, Nicholson AG, Rusch VW, Vallieres E, Groome P, et al. The IASLC Lung Cancer Staging Project: external validation of the revision of the TNM stage groupings in the eighth edition of the TNM classification of lung cancer. J Thorac Oncol. 2017 Jul;12(7):1109-21.

Management

In early-stage NSCLC, both prognosis and the treatment strategy, particularly with regards to surgical intervention and the use of adjuvant chemotherapy, are dependent on disease stage[7]. The cornerstone of treatment of potentially resectable lung cancer is surgical removal of the tumour, which includes lobectomy, pneumonectomy, and mediastinal lymph node dissection/sampling depending on the extent of the disease and the cardiopulmonary reserve of the patient[6, 8]. The management of lymph nodes during surgery is mainly dictated by the staging requirements for guaranteed "R0 resection" status[6]. For those who are not willing to accept the risks, or are at very high risk, curative RT should be offered, either SABR or hypofractionated high-dose RT[6].

Adjuvant chemotherapy with up to 4 cycles of a platinum-based doublet has been utilized to reduce the risk of disease recurrence. The most frequently studied regimen is cisplatin–vinorelbine. According to ESMO guidelines, adjuvant ChT should be offered to patients with resected stage II and III NSCLC and can be considered in patients with resected stage IB disease and a primary tumour > 4 cm. Pre-existing comorbidity, time from surgery and postoperative recovery need to be taken into account in this decision taken in a multidisciplinary tumour board[6]. Meta-analyses have shown an absolute OS and DFS benefit at 5 years of approximately 5% with adjuvant chemotherapy in early-stage NSCLC [9]. ESMO guidelines underline that in view of the equivalence of neoadjuvant and adjuvant chemotherapy for OS, the consistent results and broad evidence base support adjuvant chemotherapy as the timing of choice[6].

For patients with actionable EGFR tumour mutations, results from the Phase 3 ADAURA study showed that osimertinib improved DFS in patients with Stage IB-IIIA (AJCC 7th ed) NSCLC as compared to placebo[10]. In the EU, Tagrisso was approved in May 2021 for the adjuvant treatment after complete tumour resection in adult patients with stage IB-IIIA NSCLC whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations[13]. The subsequent final analysis of ADAURA study, at median follow-up of about 60 months, demonstrated also statistical significant improvement in OS: in patients with stage II to IIIA disease, the 5-year OS was 85% (95% CI, 79 to 89) in the osimertinib group and 73% (95% CI, 66 to 78) in the placebo group (overall HR 0.49; 95.03% CI, 0.33 to 0.73; P<0.001). In the overall population (stage IB to IIIA disease) the 5-year OS was 88% (95% CI, 83 to 91) in the osimertinib group and 78% (95% CI, 73 to 82) in the placebo group (overall HR for death, 0.49; 95.03% CI, 0.34 to 0.70; P<0.001)[11].

Checkpoint inhibitors have proven clinical benefits in advanced lung cancer. A recent study IMpower010 evaluating the anti-PD-L1 antibody atezolizumab (every 3 weeks for 16 cycles) demonstrated improvement in DFS compared with best supportive care when given as adjuvant therapy following surgery and chemotherapy in participants with Stage II-IIIA (AJCC 7th ed) NSCLC[12]. At data cutoff of 21 January 2021, median follow-up was 32.2 months in the ITT population. In hierarchical testing, atezolizumab showed statistically significant DFS benefit vs BSC in the PD-L1 TC ≥1% (SP263 assay) Stage II-IIIA (median DFS not reached versus 35.3 months, HR 0.66, 95% CI 0.50-0.88, p=0.0039) and in all randomized Stage II-IIIA populations (median DFS 42.3 versus 35.3

[7] Heineman DJ, Daniels JM, Schreurs WH. Clinical staging of NSCLC: current evidence and implications for adjuvant chemotherapy. Ther Adv Med Oncol. 2017;9(9):599-609.
[8] National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: non-small cell lung cancer; version 8.2020. Plymouth Meeting (PA): National Comprehensive Cancer Network (NCCN); 2020. 254 p.
[9] Pignon JP, Tribodet H, Scagliotti GV, Douillard JY, Shepherd FA, Stephens RJ, et al. Lung adjuvant cisplatin evaluation: a pooled analysis by the LACE Collaborative Group. J Clin Oncol. 2008 Jul 20;26(21):3552-9.
[10] Wu YL, Tsuboi M, He J, John T, et al; ADAURA Investigators. Osimertinib in Resected EGFR-Mutated Non-Small-Cell Lung Cancer. N Engl J Med. 2020 Oct 29;383(18):1711-1723.
[11] Tsuboi M, Herbst RS, John T, et al; ADAURA Investigators. Overall Survival with Osimertinib in Resected EGFR-Mutated NSCLC. N Engl J Med. 2023 Jul 13;389(2):137-147.
[12] Felip E, Altorki N, Zhou C, Csoszi T, Vynnychenko I, Goloborodko O, et al. Adjuvant atezolizumab after adjuvant chemotherapy in resected stage IB-IIIA non-small-cell lung cancer (IMpower010): a randomised, multicentre, open-label, phase 3 trial. Lancet. 2021 Oct 9;398:1344-57.

months, (HR 0.79, 95% CI 0.64-0.96, p=0.0205); on the contrary the significance boundary was not crossed for DFS in the ITT population that included stage IB (≥4 cm) disease (HR 0.81, 95% CI 0.67-0.99, p=0.04)[14, 13]. OS data were immature and not formally tested. IMpower010 study did not show a consistent benefit in DFS by PD-L1 subgroups: PD-L1 TC <1% (HR 0.97; 95% CI: 0.72, 1.31) (about 45% of the population), 1-49% (HR 0.87; 95% CI: 0.60, 1.26), PD-L1 TC≥50% (HR 0.43; 95%CI: 0·27–0·68)[14]. In the EU, Tecentriq was approved in June 2022 for patients whose tumours express PD-L1 TC ≥50%, with the following indication: "Tecentriq as monotherapy is indicated as adjuvant treatment following complete resection and platinum-based chemotherapy for adult patients with NSCLC with a high risk of recurrence whose tumours have PD-L1 expression on ≥ 50% of tumour cells (TC) and who do not have EGFR mutant or ALK-positive NSCLC (see section 5.1 for selection criteria)" [14]. Recent updated data from IMpower010 showed improved OS for adjuvant atezolizumab with HR of 0.43 in the PD-L1 TC ≥50%[15]

The immune-checkpoint inhibitors were also explored in the neoadjuvant NSCLC setting. In the open-label, phase 3 CheckMate 816 trial, patients with stage IB (≥4cm) to IIIA (AJCC 7th ed) resectable NSCLC were randomized to receive nivolumab plus platinum-based chemotherapy or platinum-based chemotherapy alone, followed by resection. The primary end points were event-free survival and pathological complete response by blinded independent review. At the prespecified interim analysis 1 of (minimum follow-up, 21 months; median follow-up, 29.5 months) the median EFS was 31.6 months (95%CI, 30.2 to NR) with nivolumab plus chemotherapy and 20.8 months (95% CI, 14.0 to 26.7) with chemotherapy alone (HR 0.63; 97.38% CI, 0.43 to 0.91; P=0.005). The percentage of patients with a pathological complete response at the final analysis for pCR was 24% (95% CI, 18 to 31) and 2.2% (95% CI, 0.6 to 5.6), respectively. [16] Based on this study, Opdivo in combination with platinum-based chemotherapy was approved in the EU in June 2023 for the neoadjuvant treatment of resectable NSCLC at high risk of recurrence in adult patients whose tumours have PD-L1 expression ≥1%[17].

In addition, the strategy including both **neoadjuvant and adjuvant** treatment (i.e. perioperative) regimens for early-stage NSCLC with anti-PD(L)1 drugs is currently under investigation, although none is approved to date. KEYNOTE-671 study evaluated, in 786 participants with resectable stage II, IIIA, or IIIB (N2 stage) NSCLC, neoadjuvant pembrolizumab or placebo plus 4 cycles of cisplatin-based chemotherapy followed by surgery and adjuvant pembrolizumab or placebo for up to 13 cycles. The first IA, with a median follow-up of 25.2 months, showed statistically significant improvement in EFS (HR for progression, recurrence, or death, 0.58; 95% CI, 0.46 to 0.72; P<0.001; EFS at 24 months 62.4% vs 40.6%). A major pathological response occurred in 30.2% vs 11% and a pathological complete response occurred in 18.1% and 4% of patients in the experimental vs control arm, respectively[18]. The double-blind phase III study AEGEAN assessing neoadjuvant durvalumab + chemotherapy followed by surgery and adjuvant durvalumab in patients with resectable NSCLC (stage II-IIIB[N2]; AJCC 8th ed) was reported to have met its primary endpoints of pCR (17.2% vs 4.3%) and EFS (HR 0.68, 95%CI 0.53-0.88, median EFS NR vs 25.9 months) at the first interim analysis of

[13] Wakelee HA, Altorki NK, Zhou C, Csoszi T, Vynnychenko IO, Goloborodko O, et al. IMpower010: primary results of a phase III global study of atezolizumab versus best supportive care after adjuvant chemotherapy in resected stage IB-IIIA non-small cell lung cancer (NSCLC) [abstract]. Presented at: 2021 American Society of Clinical Oncology (ASCO) Annual Meeting; 2021 Jun 4-8; [online meeting]. J Clin Oncol. 2021;39(15 suppl).
[14] EMA/CHMP/219365/2022 CHMP Summary of Opinion Tecentriq
[15] Wakelee H, et al: IMpower010: Overall survival interim analysis of a phase III study of atezolizumab vs best supportive care in resected NSCLC. 2022 World Conference on Lung Cancer. Abstract PL03.09. Presented August 8, 2022.
[16] Forde PM, Spicer J, Lu S, et al; CheckMate 816 Investigators. Neoadjuvant Nivolumab plus Chemotherapy in Resectable Lung Cancer. N Engl J Med. 2022 May 26;386(21):1973-1985.
[17] EMA/287093/2023 EPAR CHMP Assessment Report Opdivo EMEA/H/C/003985/II/0117
[18] Wakelee H, Liberman M, Kato T, et al; KEYNOTE-671 Investigators. Perioperative Pembrolizumab for Early-Stage Non-Small-Cell Lung Cancer. N Engl J Med. 2023 Jun 3.

after a median EFS follow-up of 11.7 months[19].

An unmet need for introducing tolerable treatments in earlier stages of disease in order to provide the best chance of survival by decreasing the risk of recurrence is recognised.

2.1.2. About the product

Pembrolizumab is humanized mAb of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. This blockade enhances functional activity of the target lymphocytes to facilitate tumor regression and, ultimately, immune rejection. The antibody potentiates existing immune responses in the presence of antigen only; it does not nonspecifically activate T cells.

Keytruda was granted first approval by the European Commission on 17-JUL-2015 for patients with advanced melanoma. At the time of submission, in the EU, Keytruda is currently approved as monotherapy and in combination with other agents in adults in several tumor types: melanoma, NSCLC, HNSCC, TNBC, RCC, cHL, urothelial carcinoma, esophageal cancer, gastric or gastro-oesophageal junction adnocarcinoma, endometrial carcinoma, MSI-H selected tumor types (colorectal cancer, gastric, biliary and small intestine cancer). In the pediatric setting, it is approved in 3 years and older cHL and in 12 years and older melanoma.

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

EU CHMP scientific advice was obtained on the clinical development program for adjuvant NSCLC (EMEA/H/SA/2437/7/2014/II). The CHMP generally agreed to the overall study design for study KEYNOTE-091, patient population, DFS as primary endpoint, and the choice of placebo as a comparator.

The patient population was considered rather heterogeneous, and subgroup analyses according to stratification/minimisation factors are expected. The impact on the final indication of any potential contrasting results will be a matter of assessment at time of evaluation. This is true not only for PD-L1 expression levels (a factor already taken into account for the main statistical analysis), but for other important factors (e.g. stage, histology, nature of background adjuvant treatment).

The CHMP suggested a minimum enrolment for each subgroup to at least allow meaningful analysis of trends. In this respect, a larger study with more stringent hypotheses should be considered. The CHMP also noted that study maturity will progress differently across prognostic subgroups. Further, the Applicant was advised to consider limiting the number of patients with stage IB disease (*A cap of 35% to stage IB subgroup was implemented).*

According to the CHMP, taking into account the size of the planned study and the significant number of patients harbouring EGFR mutations or ALK rearrangements expected, the Applicant should consider genotyping the tumours of all patients to enable future exploratory analysis in different specific subgroups of patients defined by these aberrations *(this was not implemented).*

The CHMP commented that the second interim analysis (for efficacy) may limit the feasibility of a final powerful analysis if enrolment is not achieved, which conditions the acceptability of this interim analysis. Study maturity will progress differently across prognostic subgroups. This is true for the

[19] Heymach JV, et al. AEGEAN: A phase 3 trial of neoadjuvant durvalumab + chemotherapy followed by adjuvant durvalumab in patients with resectable NSCLC. In: Proceedings of the 114th Annual Meeting of the American Association for Cancer Research; 2023 April 14-19; Orlando, FL. Philadelphia (PA): AACR; 2023. Abstract nr CT005.

interim efficacy analysis with an overrepresentation of patients with early progressive disease and limited relevance in patients with relatively late progression and good prognosis. For the final analysis, any conclusion on cure rates that could be obtained by discussion on the terminal plateau should incorporate all subgroups, including those with less mature observation.

2.1.4. General comments on compliance with GCP

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

Keytruda is a protein and is therefore exempt from the ERA requirements. This is compliant with the current Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00).

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

Study ID	Phase	Country/ Region	Study Title	Study design	Dosing regimen	Study population	Participant exposure
KEYNOTE-091 [Ref. 5.3.5.1: P091V01MK3475]	3	Australia Asia (Japan, South Korea) Europe (Austria, Belgium, Czech Republic, Denmark, Estonia, France, Germany, Greece, Hungary, Ireland, Israel, Italy, Latvia, Netherlands, Poland, Portugal, Slovenia, Spain, Switzerland, Turkey, United Kingdom) North America (Canada) Russia Federation South America (Brazil, Chile, Peru)	A randomized, phase 3 trial with anti-PD-1 monoclonal antibody pembrolizumab (MK-3475) versus placebo for patients with early stage NSCLC after resection and completion of standard adjuvant therapy (PEARLS) KEYNOTE-091	A phase 3, randomized, triple-blinded, placebo-controlled, multicenter study to evaluate the efficacy and safety of pembrolizumab vs placebo in participants with early stage NSCLC who have undergone complete resection with or without standard adjuvant chemotherapy.	Pembrolizumab: 200 mg by intravenous infusion every 3 weeks for approximately 1 year (18 infusions) Placebo: 0 mg by intravenous infusion every 3 weeks for approximately 1 year (18 infusions)	Males and females Age: 31 to 87 Participants with Stage IB (T2a ≥4 cm), II, or IIIA NSCLC, who have undergone complete resection with or without standard adjuvant chemotherapy.	Pembrolizumab: 590 Placebo: 587

2.3.2. Pharmacokinetics

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

Within this Application, the MAH proposes an extension of indication for "*KEYTRUDA as monotherapy for the adjuvant treatment of patients with Stage IB (T2a ≥4 cm), II, or IIIA non-small cell lung carcinoma (NSCLC) who have undergone complete resection.*"
The focus of the clinical pharmacology data submitted with this application is on the integrated immunogenicity assessment from studies KEYNOTE-054 and KEYNOTE-091, to characterize the immunogenicity profile of pembrolizumab in the adjuvant setting in patients with completely resected lymph node-positive stage III melanoma or completely resected stages IB, II, or IIIA NSCLC, respectively.

Absorption

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

Distribution

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

Elimination

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

Pharmacokinetic data submitted within this EoI

The existing immunogenicity assessment for pembrolizumab for the monotherapy in the non-adjuvant setting is based on a sufficiently large dataset of patients across several indications, with very low observed rates of total treatment ADA across different pembrolizumab regimens (1.4 – 3.8%) as well as of neutralizing antibodies (0.4 – 1.6%). This analysis has not demonstrated impact on efficacy or safety. The low rate of immunogenicity has been shown to be consistent across tumour type and no clinically meaningful consequences have been observed in the subjects with a positive immunogenicity reading.

The incidence of ADA has not been impacted by the presence of another small molecule or chemotherapy in combination with pembrolizumab.

However, as immunogenicity has not been characterized in the adjuvant setting, it was agreed to assess the immunogenicity of pembrolizumab in this setting in studies KEYNOTE-054 (most recent ADA sample of 2 October 2017) and KEYNOTE-091 (most recent ADA sample of 2 June 2021).

KEYNOTE-054 / EORTC-1325-MG is a phase 3 trial with pembrolizumab monotherapy administration (MK-3475, 200 mg Q3W) as adjuvant treatment in participants with completely resected lymph node-positive stage III melanoma. KEYNOTE-091/EORTC-1416-LCG is a phase 3 trial with pembrolizumab monotherapy administration (MK-3475, 200 mg Q3W) as adjuvant treatment in participants with completely resected stages IB, II, or IIIA NSCLC.

IMMUNOGENICITY DATA and EVALUATION

ADA samples were available from 1067 participants. A subset of the participants was not assessable for drug induced immunogenicity analysis, because only a pre-treatment ADA sample was available (N=10). The remaining 1057 participants were assessable for drug-induced immunogenicity analysis.

An overview of the participants included in the analysis is summarized in Table 1.

Table 1: Overview of participants included in the immunogenicity analysis after pembrolizumab adjuvant treatment (200 mg pembrolizumab Q3W) in participants with completely resected lymph node-positive stage III melanoma (KEYNOTE-054/ EORTC-1325-MG) or completely resected early stage NSCLC (KEYNOTE-091/EORTC-1416-LCG)

Study	Participants		
	Participants Providing ADA Samples	Participants Dosed with Pembrolizumab	Assessable Participants Participants Dosed with Pembrolizumab and Post Treatment Samples
Pembrolizumab Therapy			
Keynote 054 EORTC-1325-MG	500	500	496
Keynote 091 EORTC-1416-LCG	567	566	561
Total	1067	1066	1057

Data source – 07Z6N3: analysis-p054pkada03 and analysis-adada

The overall immunogenicity was defined as the proportion of treatment emergent positive participants to the total number of evaluable participants (treatment emergent positive, non-treatment emergent positive and negative immunogenicity status).

Table 2 presents an overview of the immunogenicity status of all assessable participants:

Table 2: Summary of subject immunogenicity results after pembrolizumab adjuvant treatment (200 mg pembrolizumab Q3W) in participants with completely resected lymph node-positive stage III melanoma (KEYNOTE-054/ EORTC-1325-MG) or completely resected early stage NSCLC (KEYNOTE-091/EORTC-1416-LCG)

Pembrolizumab Therapy			
Immunogenicity status	**Total**	**Melanoma** KEYNOTE-054 / EORTC-1325-MG	**NSCLC** KEYNOTE-091 / EORTC-1416-LCG
Assessable participants[a]	1057	496	561
Inconclusive participants[b]	4	1	3
Evaluable participants[c]	**1053**	**495**	**558**
Negative[d]	1011 (96.0%)	473 (95.6%)	538 (96.4%)
Non-Treatment emergent positive[d]	12 (1.1%)	5 (1.0%)	7 (1.3%)
Neutralizing negative	9 (0.8%)	5 (1.0%)	4 (0.7%)
Neutralizing positive	3 (0.3%)	0	3 (0.5%)
Treatment emergent positive[d]	30 (2.8%)	17 (3.4%)	13 (2.3%)
Neutralizing negative	30 (2.8%)	17 (3.4%)	13 (2.3%)
Neutralizing positive	0	0	0

a: Included are participants with at least one ADA sample available after treatment with pembrolizumab
b: Inconclusive participants are the number of participants with no positive ADA samples present and the drug concentration in the last sample above the drug tolerance level.
c: Evaluable participants are the total number of negative and positive participants (non-treatment emergent and treatment emergent.
d: Denominator was total number of evaluable participants.

Data source – 07Z6N3: analysis-p054pkada03 and analysis-adada

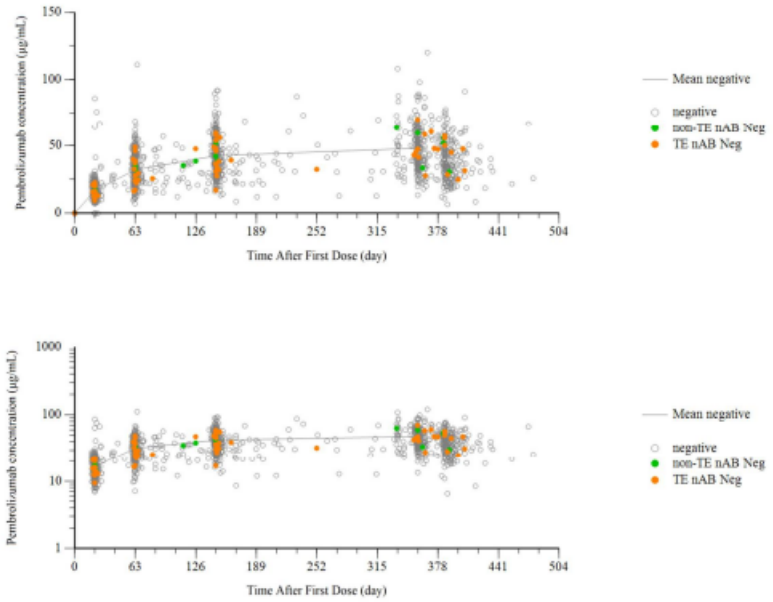
Out of the 1057 participants included in the immunogenicity assessment, 4 participants were inconclusive, resulting in 1053 evaluable participants. The observed incidence of treatment emergent ADA in evaluable participants with completely resected lymph-node positive stage III melanoma or completely resected early-stage NSCLC and completion of standard adjuvant therapy is 2.8% (30 out of 1053), based on 30 participants with treatment emergent positive status, 12 participants with non-treatment emergent positive status and 1011 with negative immunogenicity status.

None of the 30 treatment-emergent positive participants had antibodies with neutralizing capacity.

IMPACT OF ANTI-DRUG ANTIBODIES ON EXPOSURE

The effect of ADA on pembrolizumab levels, for the participants with ADA positive samples, is compared with the participants treated with the same regimen that only have ADA negative samples. For the ADA positive participants, the pembrolizumab exposure was comparable with the exposures observed for the negative participants treated with the same regimen [Figure 1] and [Figure 2].

Figure 1: Effect of ADA on pembrolizumab exposure after pembrolizumab adjuvant treatment (200 mg pembrolizumab Q3W) in participants with completely resected lymph node-positive stage III melanoma (KEYNOTE-054/ EORTC-1325-MG) Linear scale (top) and Log scale (bottom)



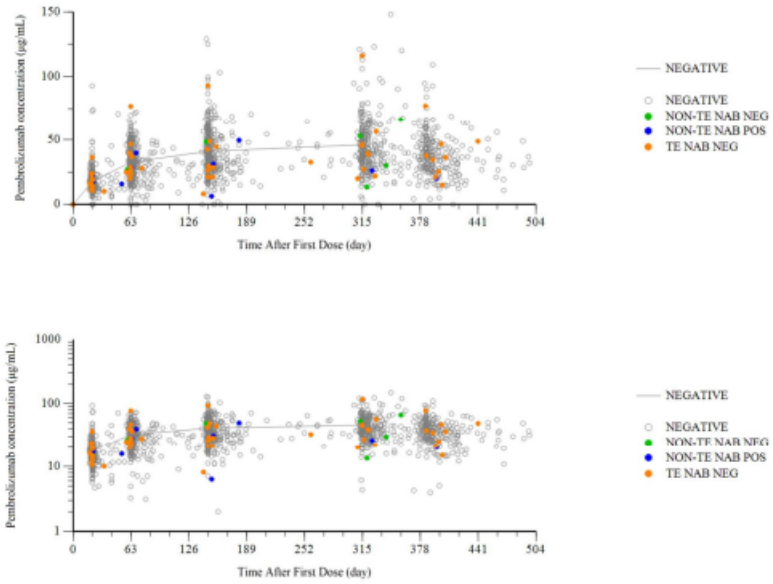
Footnote: Figure includes ADA samples with corresponding PK concentrations. Samples taken > 42 days after last dose (> 2 times the scheduled time) are excluded.

Individual pembrolizumab concentrations for the ADA negative participants (grey circles), mean value of the negative participants (grey line), non-treatment emergent neutralizing negative participants (green dot), treatment emergent neutralizing negative participants (orange dot).

Mean pembrolizumab concentration is calculated based on nominal time after first dose. Given EOT is not related to any nominal timepoint (actual time after first dose > 365 days), the mean pembrolizumab concentration was not included in the figure.

If a subject is determined to be ADA positive (non-TE or TE, based on one or more positive samples), all data-points belonging to that subject are shown in the color of the corresponding ADA status group.

Figure 2: Effect of ADA on pembrolizumab exposure after pembrolizumab adjuvant treatment (200 mg pembrolizumab Q3W) in participants with completely resected early stage NSCLC (KEYNOTE-091/EORTC-1416-LCG) Linear scale (top) and Log scale (bottom)



Footnote: Figure includes ADA samples with corresponding PK concentrations. Samples taken > 42 days after last dose (> 2 times the scheduled time) are excluded. Pembrolizumab concentrations for samples with Cycle 1 predose PK concentrations >0 were set to missing as their results are unreliable.

Individual pembrolizumab concentrations for the ADA negative participants (grey circles), mean value of the negative participants (grey line), non-treatment emergent neutralizing negative participants (green dot), non-treatment emergent neutralizing positive participants (blue dot), treatment emergent neutralizing negative participants (orange dot).

Mean pembrolizumab concentration is calculated based on nominal time after first dose. Given EOT is not related to any nominal timepoint (actual time after first dose > 336 days), the mean pembrolizumab concentration was not included in the figure.

If a subject is determined to be ADA positive (non-TE or TE, based on one or more positive samples), all data-points belonging to that subject are shown in the color of the corresponding ADA status group.

non-TE nAB Neg: non-treatment emergent positive neutralizing antibody negative subject.
non-TE nAB Pos: non-treatment emergent positive neutralizing antibody positive subject.
TE nAB Neg: treatment emergent positive neutralizing antibody negative subject.

Bioanalytical methods

KEYNOTE-091 bioanalytical report for ADA and nAB

The samples were assayed for anti-pembrolizumab antibodies presence using a validated electrochemiluminescence (ECL) immunoassay on the Meso-Scale Discovery (MSD) platform. Bioanalysis of pembrolizumab ADA was carried out using the standard 3-tiered assay approach that consisted of screening (Tier 1), confirmation (Tier 2) and antibody titer assessment (Tier 3). Only Tier 2 confirmed ADA positive samples were moved to Tier 3 and reported with a titer value and a neutralizing antibody (nAB) result.

The DTL for the ADA assay, executed at the vendor PPD, is 124 µg/mL.

ADA: Human serum samples were analysed for the presence of MK-3475 antibodies in support of Protocol Number MK-3475-091. This interim report covers the analysis of samples received through 22 September 2021 and analysed in runs 1RFWC through 142RFWC.

Five thousand eight hundred seventy-four (5874) original and six thousand thirty-six (6036) replicate human serum samples were received frozen and in good condition. Project samples were analysed according to the bioanalytical plan and Method ICDIM 201 V 1.01, entitled "An

Electrochemiluminescent (ECL) Method for the Detection of Anti MK 3475 Antibodies in Human Serum," which was validated under Project Code "RCZO2."

Analysis of human serum samples began on 27 September 2016 and was completed on 22 December 2021. Sample results for 2821 samples were provided. Forty-eight samples screened potentially positive for anti-MK-3475 antibodies. Twenty-four out of the 48 samples that screened potentially positive for anti-MK-3475 antibodies were confirmed positive.

Reassayed samples for this project were provided and listed with reasons for reanalysis. All sample analysis runs conducted for this study were showed. Data for the positive and negative controls used for run acceptance and data for the confirmatory positive controls used for run acceptance were also provided.

nAB: Human serum samples were analysed to detect anti-MK-3475 neutralizing antibodies (NAb) in support of Protocol Number MK-3475-091. This interim report covers sample analysis through 06 January 2022. The samples were analysed in runs 1RFWD through 10RFWD.

Five thousand eight hundred seventy-four (5874) original and six thousand thirty-six (6036) replicate human serum samples were received frozen and in good condition between 17 February 2016 and 22 September 2021. These samples were first tested in the electrochemiluminescent immunoassay for the detection of anti-MK-3475 antibodies. All samples from project RFWC which confirmed positive in the ADA immunoassay were analysed for the presence of neutralizing antibodies. Sample analysis was conducted under Project Code "RFWD" using Method ICDIM 202 V 2.01, entitled "An ECL Method for the Detection of Anti-MK-3475 Neutralizing Antibodies in Human Serum," which was validated under Project Code "RFRI2." During the course of analysis, the method was manually modified to give the ability to use the Avidien for reagent transfers, effective 09 December 2021.

Analysis of human serum samples took place in ten runs beginning on 18 December 2018 and ending on 06 January 2022. The submitted report contains NAb results from a total of 24 ADA-positive samples. Four samples were positive for the presence of anti-MK-3475 neutralizing antibodies. Sample analysis runs sample results and data for positive and negative controls used for run acceptance were provided.

2.3.3. Discussion on clinical pharmacology

The immunogenicity profile of pembrolizumab was previously not well characterized in the adjuvant setting. The MAH has provided a comprehensive immunogenicity assessment including data of pembrolizumab at 200 mg Q3W as adjuvant treatment from KEYNOTE-091 and KEYNOTE-054.

All the ADA samples, and the actual time after first dose and time after last dose, from ADA positive participants were provided for both studies.

The integrated immunogenicity incidence rate for pembrolizumab monotherapy as adjuvant treatment in participants with completely resected stages IB (T2a≥4 cm), II, or IIIA NSCLC in KEYNOTE-091 and in participants with completely resected, lymph node-positive, stage III melanoma in KEYNOTE-054 is 2.8% (30 out of 1053 evaluable subjects). In particular, the immunogenicity rate observed in each study population was 3.4% (17 out of 495) for KEYNOTE-054 and 2.3% (13 out of 558) for KEYNOTE-091. This is similar to the historical incidence rate of treatment emergent positive subjects reported for monotherapy at 2.1% (27 out of 1289 evaluable subjects; range 1.4 to 3.8%).

Overall, this immunogenicity analysis shows that the ADA incidence rates for pembrolizumab in the adjuvant setting are similar to ADA incidence rates for pembrolizumab in the metastatic and locally advanced settings.

The impact of ADA on pembrolizumab PK profiles indicate that pembrolizumab exposures in ADA positive participants do not differ from pembrolizumab exposures in ADA negative participants.

2.3.4. Conclusions on clinical pharmacology

The ADA incidence rates for pembrolizumab in the adjuvant setting are similar to ADA incidence rates for pembrolizumab in the metastatic and locally advanced settings.

Treatment-emergent ADA status in KEYNOTE-091 and KEYNOTE-054 is not found to affect pembrolizumab exposures, excluding a possible effect on safety and efficacy.

2.4. Clinical efficacy

The efficacy data in this submission is based on **Interim analysis 2** (IA2, data cutoff of 20-SEP-2021) of **KEYNOTE-091**, a phase 3 randomized triple blind clinical trial which evaluated the efficacy and safety of pembrolizumab versus placebo as **adjuvant** therapy in participants with **Stage IB (T2a ≥4 cm), II, or IIIA NSCLC**, as defined by the AJCC 7th edition, who have undergone complete resection with or without standard adjuvant chemotherapy. The results of the **Interim analysis 3** (IA3, data cutoff of 24-JAN-2023) were also submitted during the procedure per CHMP's request.

KEYNOTE-091 is an Intergroup Trial, jointly conducted with ETOP in different countries of EU and third countries. Merck was the Sponsor in all participating countries. The EORTC was the coordinating group in this trial and centrally managed trial design and activation, data collection and quality control of data, statistical analysis and publication.

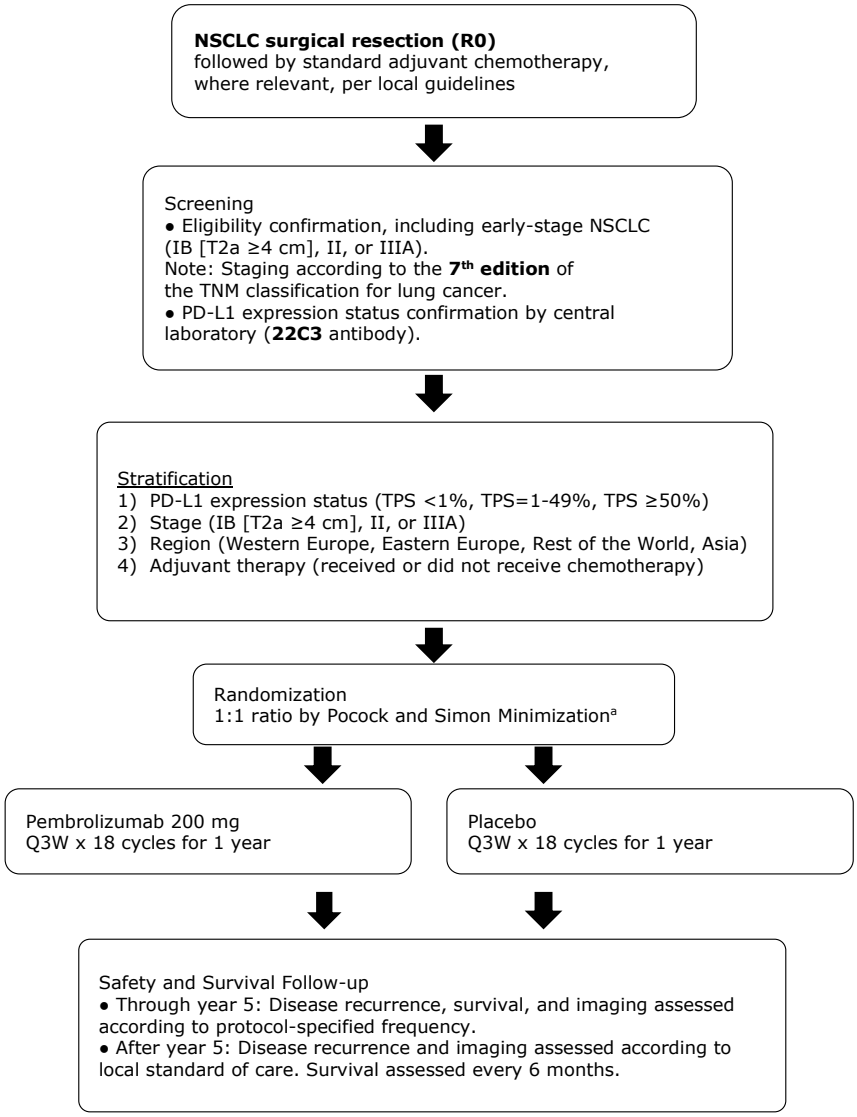
2.4.1. Dose response study(ies)

No dose-response studies were submitted as part of this application.

2.4.2. Main study

KEYNOTE-091: A randomized Phase 3 trial with pembrolizumab versus placebo for patients with early-stage non-small cell lung cancer (NSCLC) after resection and completion of standard adjuvant therapy - PEARLS study (EORTC-1416/ETOP-8-15)

Figure 3: study design



NSCLC=non-small cell lung cancer; PD-L1=programmed death-ligand 1; Q3W=every 3 weeks; R0=no residual tumour; TNM=tumour node metastasis; TPS=tumour proportion score

Methods

Study participants

Key inclusion/exclusion criteria

- At least 18 years; ECOG Performance status 0-1
- Pathological diagnosis of NSCLC confirmed at surgery, **any histology** is eligible;
- Confirmed **UICC v7 stage IB with T ≥ 4 cm, II-IIIA** NSCLC after complete surgical resection (lobectomy, sleeve lobectomy, bi-lobectomy or pneumonectomy) as documented in the pathology report;
- Resection margins proved microscopically free (R0)

- A systematic complete mediastinal lymph node dissection or a lobe-specific mediastinal lymph node dissection is recommended. At a minimum, the pathology and/or operative report must include the examination of at least two different mediastinal lymph node (N2) levels, one of which is the subcarinal (level 7) and the second of which is lobe-specific.
- No extracapsular extension of tumor in resected mediastinal (N2) lymph nodes. Extracapsular tumor extension is permitted in resected N1 lymph nodes
- Availability of tumor sample obtained at surgical resection for PD-L1. Patients must submit the tumor sample during screening for PDL1 IHC expression testing at a **central pathology** laboratory. Patients were eligible to participate regardless of the level of PD-L1 status, however tissue must be considered satisfactory for characterization of PD-L1 status. Patients whose samples are inadequate for PD-L1 determination were not randomized;
- No evidence of disease (NED) at clinical examination and baseline radiological assessment as documented by contrast enhanced chest/upper abdomen CT scan, brain CT/MRI and clinical examination within 12 weeks prior to the randomization date.
- Adequate organ function performed within 10 days of treatment initiation.
- **Adjuvant chemotherapy** is not mandatory but considered for patients with stage IB (T ≥ 4 cm) and strongly recommended for stage II and IIIA, and was administered according to national and local guidelines. Patients who received more than 4 cycles of adjuvant therapy are not eligible.
    - Patients not receiving adjuvant chemotherapy must be randomized and dosed with pembrolizumab/placebo within 12 weeks of their surgery date.
    - Participants who receive adjuvant chemotherapy must begin adjuvant chemotherapy within 12 weeks of their surgery date. Patients receiving adjuvant chemotherapy must be randomized and dosed with pembrolizumab/placebo at least 3 weeks but no more than 12 weeks from the last dose of chemotherapy (Day 1 of last cycle).
- No prior or planned neoadjuvant or adjuvant radiotherapy and/or neoadjuvant chemotherapy for the current malignancy is allowed;
- No prior treatment with anti-PD-1, anti-PD-L1/2, anti-CD137, CTLA-4 modulators or any other immune-modulating agents.
- If of childbearing potential, female patients must be willing to use two adequate barrier methods throughout the study, starting with the screening visit through 120 days after the last infusion of study treatment. Male patients with a female partner(s) of child-bearing potential must agree to use two adequate barrier methods throughout the trial starting with the screening visit through 120 days after the last infusion of study treatment is received.
- Female patients who are breast feeding must discontinue nursing prior to the first infusion of study medication and until 120 days after the last study treatment.
- No known history of HIV, active Hepatitis B or C.
- No chronic use of immunosuppressive agents and/or systemic corticosteroids or any use in the last 3 days prior to the first infusion of trial treatment (corticosteroid use on study for management of pembrolizumab event of clinical interest (ECIs) as premedication for the administration of chemotherapies, and/or a premedication for IV contrast allergies/reactions is allowed). Daily prednisone at doses of 5-7.5 mg is allowed as an example of replacement therapy. Equivalent hydrocortisone doses are also permitted if administered as a replacement therapy;

- No history of interstitial lung disease (ILD) OR a history of (non-infectious) pneumonitis that required oral or IV steroids (other than COPD exacerbation) or current pneumonitis;
- No active autoimmune disease that has required systemic treatment in the past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Any replacement therapy (i.e., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment and is allowed. Patients with hyperthyroidism or hypothyroidism but that are stable on hormone replacement are also allowed;
- No history of a hematologic or primary solid tumor malignancy, unless in remission for at least 5 years. A pT1-2 prostatic cancer Gleason < 6, superficial bladder cancer, non melanomatous skin cancer or carcinoma in situ of the cervix is eligible; Note: prior radiotherapy and prior anti-cancer systemic chemotherapy for another malignancy is not exclusion criteria;
- No previous allogeneic tissue/solid organ transplant;
- No active infection requiring therapy;
- No surgery or chemotherapy related toxicity (nonhematological, toxicity resolved to grade 1 with the exception of alopecia, fatigue, neuropathy and lack of appetite /nausea);
- Absence of severe comorbidities that in the opinion of the Investigator might hamper the participation to the study and/or the treatment administration.

PD-L1 assay testing

PD-L1 22C3 testing for KEYNOTE-091 was conducted at a central laboratory (Q2 Solutions). The PD-L1 22C3 pharmDx kit (investigational use only, IUO) was used. The IUO version and the CE-marked in-vitro diagnostic (IVD) version of the PD-L1 22C3 pharmDx kit are identical from a reagent perspective and protocol perspective, and IFU closely worded. Training and testing of the pathologists were conducted by Agilent to ensure accuracy of these stained slides scored at both the TPS ≥1% and the TPS ≥50% cut-offs. An assay validation including sensitivity and precision was then successfully conducted at Q2 Solutions, specificity was not repeated.

Treatments

Study intervention	Dose	Route of administration
Pembrolizumab	200 mg, Q3W, 18 infusions	IV
Placebo **	Q3W, 18 infusions	IV

** normal saline solution prepared by the local pharmacist, treatment allocation is unblinded to the pharmacist.

Discontinuation criteria: Treatment is discontinued for the completion of the treatment plan, for patient's decision and based on other key criteria for discontinuation: unacceptable adverse events; progression or recurrence of any malignancy that require active treatment; inter-current illness that warrants patient's withdrawal, as per investigator's opinion; treatment-related toxicity prompting drug discontinuation, as per study protocol; positivity of pregnancy test; non-compliance with study requirements.

Tumour assessment: Disease evaluation by imaging (Contrast-enhanced chest and upper abdomen CT scan, and brain CT scan or MRI) was performed at baseline at screening. Patients were monitored with scans every 12 weeks until disease recurrence. Imaging work up (to be based on calendar) included

contrast-enhanced chest and upper abdomen CT scan; contrast-enhanced brain CT scan or MRI only if clinically indicated (new evidence of headache or neurologic symptoms). Patients who receive treatment beyond 1 year from randomization (to compensate for missed or delayed doses), should have imaging performed every 12 weeks until discontinuation of treatment and then will follow the ESMO guidelines.

Objectives

Primary objectives (dual primary)

- To prospectively investigate whether adjuvant treatment with pembrolizumab after completion of radical surgery (lobectomy/pneumonectomy) with or without standard adjuvant chemotherapy for stage IB (T≥4 cm), II-IIIA (7th ed) NSCLC patients improves Disease-Free Survival (DFS), as assessed locally by the investigator, compared to placebo in the PD-L1 strong positive subgroup (i.e., PD-L1 ≥ 50%) or overall population.

Secondary objectives

- To prospectively compare DFS as assessed by the investigator in the PD-L1 positive population (TPS≥1%);
- To prospectively determine and compare OS in the PD-L1 strong positive and overall population;
- To prospectively determine and compare OS in the PD-L1 positive population;
- To prospectively determine and compare the Lung Cancer Specific Survival (LCSS) in the whole population irrespective of PD-L1 status;
- To prospectively assess the safety of pembrolizumab after radical surgery followed by standard adjuvant chemotherapy.

Exploratory Objectives

- To assess outcome according to stratification factors and other prognostic and predictive markers for NSCLC;
- To evaluate these treatments in the elderly (age ≥70 years old);
- To prospectively study the influence of dose and duration of adjuvant chemotherapy on outcome;
- To prospectively assess genetic alterations and biomarkers of immunological pathways with outcome;
- To prospectively assess DNA mutational burden and nanostring RNA analysis with outcome;
- To prospectively assess EQ-5D health state profiles at pre-specified time points;
- To prospectively assess Health-Related Quality of Life (HRQOL);
- To evaluate the pharmacokinetics (PK) of pembrolizumab in this patient population to determine the pembrolizumab exposure-response relationships for measures of effectiveness, toxicity, and pharmacodynamic biomarkers in the study population;
- To evaluate the development of anti-drug antibodies (ADA) against pembrolizumab (immunogenicity evaluation);

- To assess and describe the quality assurance for surgery.

Outcomes/endpoints

Primary endpoints (dual primary)

- DFS in the PD-L1 ≥50% subgroup
- DFS in the overall population.

Secondary endpoints

- DFS in the PD-L1 positive population (TPS≥1%);
- OS in the overall population;
- OS in the PD-L1 strong positive subgroup (TPS≥50%);
- OS in the PD-L1 positive population (TPS≥1%);
- Lung cancer specific survival (LCSS) in the overall population;
- Toxicity according to CTCAE version 4.03.

Exploratory endpoints

- Health-Related Quality of Life (HRQOL);
- Pharmacokinetics (PK) of pembrolizumab in this patient population;
- Anti-drug antibodies (ADA) against pembrolizumab (immunogenicity evaluation);
- Quality assurance for surgery;
- Exploratory assessment of predictive biomarkers and immune dynamics (Translational research).

Endpoint definitions:

DFS: DFS is calculated as the time from randomization to either the date of disease recurrence or the date of death (whatever the cause). The date of first documented disease recurrence (if applicable) will be used as the date of event. Patients alive with no evidence of disease recurrence at the time of their last visit are censored at the time of the last examination. Recurrence of disease can be a loco-regional recurrence, a distant (metastatic) recurrence or a second primary. NSCLC and secondary malignancies were considered to be events.

Recurrence is defined as the first day when the RECIST version 1.1 criteria for disease recurrence are met. The first date when recurrence was observed is taken into account regardless of the method of assessment (imaging and/or pathology).

OS: OS is defined as the time from the date of randomization to the date of death, whatever the cause. The follow-up of patients still alive will be censored at the moment of last visit/contact.

LCSS: LCSS is defined as the time from randomization to the date of death (due to lung cancer specifically). (LCSS was not analyzed at IA2 according to the SAP).

Sample size

The study was designed with dual-primary endpoints (DFS in the whole population and DFS in the PD-L1 strong positive sub-population). Based on the data from ECOG 1505 study, median DFS in the placebo arm was assumed to be equal to 42 months and median OS approximately 86 months. Assumptions and the testing strategy were:

- Overall, an improvement of 14 months in median DFS (from 42 months to 56 months) or equivalent to HR = 0.75 was aimed for the whole population. Improvements of 34.4 and 18 months in median DFS (from 42 months to 76.4 and 60 months) or equivalent to HR=0.55 and 0.7 are the effects targeted in PD-L1 strong positive and PD-L1 positive subgroups, respectively.
- The HRs for OS between the experimental and control arms are 0.6, 0.7 and 0.765, for PD-L1 strong positive, PD-L1 positive and the whole population, respectively.
- It is assumed that approximately 28% of participants are PD-L1 strong positive and approximately 61% are PD-L1 positive. The enrolment duration was expected to be 52 months, with a yearly drop-out rate of 2.5% and 1% for DFS and OS, respectively.

Two interim analyses (IAs) and one final analysis (FA) for DFS were planned. At the time of each DFS analysis, OS analysis was to be performed as well. There are three additional analyses for OS alone after DFS FA.

Approximately **1180** participants were to be randomized in a 1:1 ratio into the experimental arm and the control arm. For DFS, based on a target number of ~551 events at FA, the study has ~86% power at alpha=1.25% (one-sided) and ~92% power at alpha=2.5% (one-sided) for the whole population.

Amendment on Sample Size Calculation

In the initial protocol, sample size was based on the data from Radiant study, where median DFS was approximately 48 months in the placebo arm. The study is designed with primary/co-primary endpoints: DFS in the whole population and DFS in the PD-L1 strong positive subgroup. It was expected:

- an improvement of 13.5 months in median DFS (from 48 months to 61.5 months) or equivalent to HR = 0.78 in the whole population
- An improvement of 39.3 months in median DFS (from 48 months to 87.3 months) or equivalent to HR=0.55 in the PD-L1 strong positive population

It was assumed that around 15% of DFS events at the final analysis were to be in the PD-L1 strong positive population (based on the available limited epidemiology data). Taking into account a dropout rate of 2.5% per year due to loss to follow up, enrollment and total study durations are assumed to be 87 and 100 months based on a total of 640 disease free survival events and a sample size of **1380** randomized patients were required.

In the second amendment, assumption for sample size calculation has been changed. Based on the data from ECOG 1505 study, median DFS was approximately 42 months in the placebo arm. Moreover, it was expected:

- an improvement of 14 months in median DFS (from 42 months to 56 months) or equivalent to HR = 0.75 is aimed for the whole population;
- an improvement of 34.4 and 18 months in median DFS (from 42 months to 76.4 and 60 months) in PD-L1 strong positive and positive patients.

It was assumed that around 30% of patients were PD-L1 strongly positive and 60% PD-L1 positive. With this design, a sample size of **1080** patients was required for the whole population to achieve 83% power for DFS under the assigned alpha at final analysis.

Randomisation

All participants entered have been centrally registered at the EORTC Headquarters. Patient randomization in a 1:1 ratio has been performed automatically in the Interactive Voice Response System (IVRS). IVRS assign to each patient a treatment dynamically, based on the other patients randomized in the study and the stratification factors.

The Pocock and Simon Minimization with Biased-coin Assignment methodology has been utilized to perform participant randomization for this study. Per suggestion of the ICH E9 statistical guidelines, the algorithm has been modified to incorporate a random allocation component in order to ensure 15% of completely random assignments.

Stratification factors were:

- stage (IB vs II vs IIIA),
- adjuvant chemotherapy (no adjuvant chemotherapy versus adjuvant chemotherapy)
- PD-L1 status: negative (TPS=0%) versus weak positive (TPS = 1- 49%) versus strong positive (TPS≥50%)
- region (Western Europe versus Eastern Europe versus Rest of the world versus Asia).

Minimization algorithm was separately applied for each PD-L1 status, to ensure an optimal balance of treatment arms within each PD-L1 level. Treatment allocation was blinded.

The proportion of patients with stage IB has been closely monitored by the study steering committee to ensure that this proportion does not exceed 35% of the study population.

Blinding (masking)

This is a triple blind study. The patient, the investigator and study team at site, the EORTC Headquarters study team, the Sponsor and CRO remained blinded to treatment allocation up to the database lock for the final analysis of the primary/dual-primary endpoints. Only an on-site pharmacist and limited CRO personnel remained unblinded to treatment assignment.

The unblinded Statistician, an independent Statistician at the EORTC Headquarters not involved in the conduct of the trial and the Pharmacovigilance Physician wrote the unblinded interim/safety report for the IDMC.

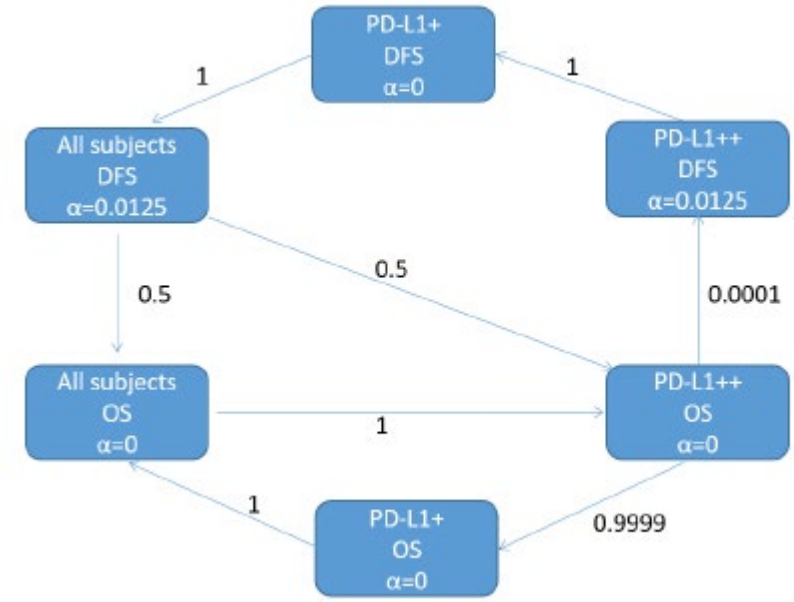
Statistical methods

Multiplicity

The family-wise error rate for DFS and OS hypotheses was strongly controlled at the overall one-sided $\alpha = 0.0125$. The alpha was initially equally split to test DFS in the overall study population and in the TPS ≥50% subgroup. If the null hypothesis for DFS was rejected in the TPS ≥50% subgroup, its alpha would be fully reallocated to DFS testing in the TPS ≥1% subgroup. Hypotheses for OS in the overall study population and in the TPS ≥50% subgroup were to be tested once DFS in the overall study

population was rejected. The Hwang-Shih-DeCani spending function with gamma = -4 was used to control the type I error in the interim/final analysis for each DFS and OS endpoint.

Figure 4: Multiplicity Graph for Alpha Re-allocation Strategy



Interim analysis

Two interim analyses (IAs) and one final analysis (FA) for DFS were planned in the study. At the time of each DFS analysis, OS analysis was to be performed as well. There were three additional analyses for OS alone after DFS FA.

Table 3: Interim and final analyses for DFS: number of events, p-values boundaries and power

		PD-L1++ patients (DFS HR=0.55)		PD-L1+ patients (DFS HR=0.7)		All patients (DFS HR=0.75)	
	DFS	Alpha=0.0125	Alpha=0.025	Alpha=0.0125	Alpha=0.025	Alpha=0.0125	Alpha=0.025
IA1 (~57 months)	Events	90	90	210	210	355	355
	Nominal p	0.0028	0.0055	0.0028	0.0057	0.0028	0.0057
	HR bound	0.5571	0.5852	0.6824	0.7048	0.7454	0.7641
	Power	0.5211	0.6099	0.4269	0.5188	0.4769	0.5691
IA2 (~68 months)	Events	118	118	274	274	463	463
	Nominal p	0.0052	0.0108	0.0053	0.0109	0.0053	0.0109
	HR bound	0.6243	0.6550	0.7343	0.7578	0.7886	0.8079
	Power	0.7612	0.8319	0.6660	0.7537	0.7161	0.7965
DFS FA (~78 months)	Events	141	141	326	326	551	551
	Nominal p	0.0103	0.0212	0.0103	0.0212	0.0103	0.0212
	HR bound	0.6770	0.7105	0.7734	0.7985	0.8208	0.8411
	Power	0.8956	0.9374	0.8255	0.8885	0.8627	0.9155

PD-L1+: PD-L1 positive (TPS≥1%); PD-L1++: PD-L1 strong positive (TPS≥50%)

This table is for illustration purpose. If the actual number of events at the analyses differ from those specified in the table, the efficacy boundaries will be adjusted using the spending function accordingly.

All DFS analyses are DFS event-driven. Beyond the final analysis of DFS, all OS analyses are OS event-driven.

Statistical Analysis

The primary analyses of the primary and secondary efficacy endpoints (DFS, OS and LCSS) were to be performed on all randomized patients according to the intention to treat (ITT) principle.

Estimates of the median DFS, OS and LCSS were obtained by the Kaplan Meier technique. The 95% confidence interval (CI) for the median were calculated using the reflected CI method. Estimates of hazard ratios and their 95% CI were obtained by Cox regression.

For the primary DFS analysis, the date of first documented disease recurrence (if applicable) was used as the date of event. If a randomized participant is not disease free at baseline, the date of randomization was used as the date of event. Participants alive with no evidence of disease recurrence at the time of their last visit are censored at the time of the last disease assessment.

Table 4: Censoring rules for primary and sensitivity analyses of DFS

Situation	Primary Analysis	Sensitivity Analysis 1
Recurrence or death documented after ⩽ 1 missed disease assessment, and before new anti-cancer therapy, if any	Event at earlier date of documented recurrence and death	Event at earlier date of documented recurrence and death
Recurrence or death documented immediately after ⩾ 2 consecutive missed disease assessments or after new anti-cancer therapy, if any	Event at earlier date of documented recurrence and death	Censored at last disease assessment prior to the earlier date of ⩾ 2 consecutive missed disease assessment and new anti-cancer therapy, if any
No recurrence and no death; and 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

Abbreviations: DFS=disease-free survival.

Table 5: Analysis strategy for key efficacy endpoints

Endpoint/Variable	Statistical Method‡	Analysis Population	Missing Data Approach
Primary/dual-primary Endpoints			
DFS	Test: Permutation test with multivariate Cox regression model§ with Efron's tie handling method Estimation: multivariate Cox regression model§ with Efron's tie handling method to assess the magnitude of treatment difference	ITT ♦ all participants, ♦ PD-L1 strong positive ♦ PD-L1 positive	Censored according to rules in [Table 4]
Secondary Endpoints			
OS	Test: Wald test with multivariate Cox regression model§ with Efron's tie handling method Estimation: multivariate Cox regression model§ with Efron's tie handling method to assess the magnitude of treatment difference	ITT ♦ all participants, ♦ PD-L1 strong positive ♦ PD-L1 positive	Censored at the date participant last known to be alive
LCSS	Test: Non-adjusted log-rank test Estimation: multivariate Cox regression model§ with Efron's tie handling method to assess the magnitude of treatment difference	ITT ♦ all participants,	♦ Participants are still alive: censored at the date last known to be alive ♦ Participants die from other causes: censored at the time of death
‡ Statistical models are described in further detail below: § Adjusted by Stage (IB versus II versus IIIA), PD-L1 IHC expression (0 versus 1-49% versus ≥ 50%), Adjuvant Chemo (No chemotherapy vs. adjuvant platinum-based chemotherapy), Histology (squamous vs. non-squamous), smoking status (smokers vs. non-smokers), and regions (Western Europe versus Eastern Europe versus Rest of the world versus Asia).			

Table 6: Analysis strategy for key efficacy variables

Endpoint/Variable (Description, Time Point)	Primary vs. Supportive Approach†	Statistical Method‡	Analysis Population	Missing Data Approach
Primary/dual-primary Endpoints				
DFS	P	Permutation test with multivariate Cox regression model§	ITT ♦ all patients, ♦ PD-L1 strong positive ♦ PD-L1 positive	Model-based
	S	Wald test in multivariate Cox regression model Non-adjusted logrank test	ITT ♦ all patients, ♦ PD-L1 strong positive ♦ PD-L1 positive	Model-based
Secondary Endpoints				
OS	P	Wald test in Multivariate Cox regression model	ITT ♦ all patients, ♦ PD-L1 strong positive ♦ PD-L1 positive	Model-based
LCSS	P	Non-adjusted logrank test	ITT ♦ all patients,	Model-based

† P=Primary approach; S=Secondary approach.

‡ Statistical models are described in further detail below:

§ Adjusted by Stage (IB versus II versus IIIA), PD-L1 IHC expression (0 versus 1-49% versus ≥ 50%), Adjuvant Chemo (No chemotherapy vs. adjuvant platinum-based chemotherapy), Histology (squamous vs. non-squamous), smoking status (smokers vs. non-smokers), and regions (Western Europe versus Eastern Europe versus Rest of the world versus Asia).

Subgroup analyses

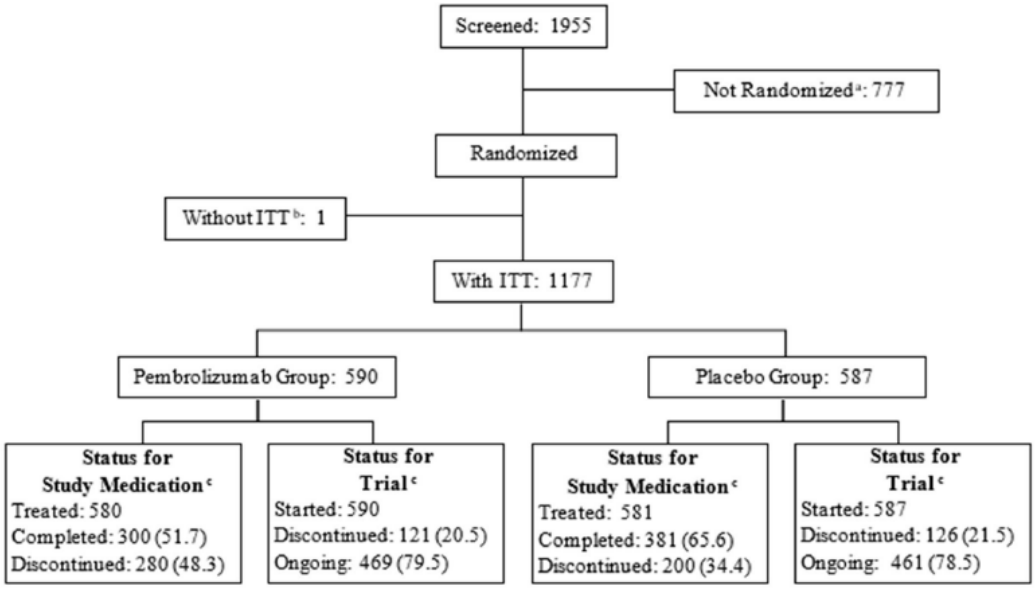
Subgroup analyses are planned to compare DFS and OS by treatment arm in the stratification factors. In addition, subgroup analyses by histology, smoking status, sex, age, baseline ECOG performance status, race, geographic region, and EGFR mutation status were also planned.

Exploratory analyses

The key exploratory endpoint is Health-Related Quality of Life (HRQoL). The global health/QoL scale was be used as primary outcome of interest for this study. A difference of 10 points on the 100-point QLQ-C30 scale either within a patient or between the two arms was considered as clinically relevant. The standard deviation of this scale is approximately 20 points. With the 2-sided alpha set at 5% and a power of 80% to detect a difference of 10 points (effect size of 0.5), a minimum of 128 patients (64 per treatment arm) is required. For an effect size of 0.75 (difference of 15 points), 56 patients (28 per treatment arm) are required.

Results

Participant flow



CONSORT diagram *(Database Cut-off Date: 20SEP2021). Please note that consort diagram is related to IA2. IA3 diagram should be added.*

Abbreviations: ITT=intention-to-treat.

a Reasons for not randomized (ie, screen failure)

b One participant who did not consent to the main study was randomized due to an administrative error; this participant was not included in the ITT population

Table 7: Disposition of participants not randomized

	n (%)
Not Randomized	777
Central Confirmation Of Pd-L1 Expression Was Non-Eligible	7 (0.9)
Patient Could Not Be Randomized Within The Protocol Timelines	74 (9.5)
Patient Does Not Meet Criteria For - No Evidence Of Disease	137 (17.6)
Patient Does Not Meet Ecog Performance Criteria	11 (1.4)
Patient Does Not Meet The Protocol Defined Surgical Criteria	97 (12.5)
Patient Was Ineligible For Another Reason	131 (16.9)
Patient's Refusal	320 (41.2)
Database Cutoff Date: 20SEP2021	

Details of the exact reason for "patient's refusal" and "other reasons" were not collected for most participants. Most common reasons collected for "patient's refusal" were logistic/travel, did not want to receive placebo or AE's following adjuvant chemotherapy, while for "other reasons" were AEs following surgery, lab values and treatment with exclusionary concomitant medications. Overall, no concern is raised over the representativeness of the randomized population.

Table 8: dispositions of participants (IA3)

	Pembrolizumab		Placebo	
	n	(%)	n	(%)
Participants in population	590		587	
Status for Study Medication of Treatment Phase				
Started	580		581	
Completed	300	(51.7)	381	(65.6)
Discontinued	280	(48.3)	200	(34.4)
Administrative Reasons	1	(0.2)	1	(0.2)
Associated with COVID-19	0	(0.0)	1	(0.2)
Adverse Event Not Related To Study Medication	16	(2.8)	6	(1.0)
Ineligible	1	(0.2)	0	(0.0)
Investigator's Decision	19	(3.3)	13	(2.2)
Associated with COVID-19	1	(0.2)	1	(0.2)
Lost To Follow-Up	3	(0.5)	0	(0.0)
Other Malignancy	5	(0.9)	8	(1.4)
Patient's Decision Not Related To Toxicity	46	(7.9)	21	(3.6)
Associated with COVID-19	6	(1.0)	6	(1.0)
Recurrence/Relapse/Death Due To Pd	72	(12.4)	127	(21.9)
Toxicity Due To Study Medication	114	(19.7)	22	(3.8)
Other	3	(0.5)	2	(0.3)
Status for Trial				
Started	590		587	
Discontinued	161	(27.3)	172	(29.3)
Death	136	(23.1)	154	(26.2)
Associated with COVID-19	6	(1.0)	1	(0.2)
Lost to follow-up	0	(0.0)	2	(0.3)
Withdrawal of Consent	25	(4.2)	16	(2.7)
Associated with COVID-19, No further survival info	2	(0.3)	0	(0.0)
Participants Ongoing	429	(72.7)	415	(70.7)

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: 24JAN2023

Recruitment

First participant first visit was on 10-NOV-2015, last patient was randomized on 06-MAY-2020. Study is ongoing. Patients were screened and enrolled across 206 study sites in 29 countries.

At the data cut-off date of IA2 (20-SEP-2021), all patients had had either completed or discontinued treatment. The minimum follow-up time from the last patient randomized to the data cutoff date of IA2 was 16.5 months. The follow-up time off-treatment (i.e., time from the date of last dose of treatment to the data cutoff date) across the arms had a median of 26.0 months (26.8 vs 25.5 months in the pembrolizumab arm and in the placebo arm, respectively. The median follow-up time was 32.4 months (range: 0.6 – 68).

At the data cut-off date of IA3 (24-JAN-2023), the median follow-up was 46.7 months (range: 0.6 - 84.2).

Conduct of the study

Protocol amendments

Protocol version	Date of PRC approval/notification	Amendment reference	
		N°	Classification
Outline Amended	December 02, 2014 April 10, 2015	----	----
1.0	April 23, 2015	----	----
2.0	December 2, 2016	3	Scientific
3.0	August 14, 2018	8	Scientific
4.0	June 15, 2020	13	Scientific

Merck Amendment No.	Date of Issue	Overall Rationale
MK-3475-091-03	15-JUN-2020	Updated the guidelines for management of toxicity due to irAEs. Updated the SAP including addition of OS analysis at each interim analysis for DFS, clarification of text describing the relaxed alpha level for the all comer population, clarification of multiplicity strategy language, and adjustments to the triggers for the first interim analysis.
MK-3475-091-02	14-AUG-2018	Updated the sample size of the study based on the updates of the prevalence of PD-L1 TPS ≥50% NSCLC.
MK-3475-091-01	02-DEC-2016	Updated surgical inclusion criteria to be more inclusive. Modified the mediastinal lymph node dissection requirements.
MK-3475-091-00	23-APR-2015	Original protocol.

Table 9: Summary of Key Changes in KEYNOTE-091 Protocol Amendments

KEYNOTE-091 Amendment 1 / 02-DEC-2016 Overall rationale: Updated surgical inclusion criteria to be more inclusive. Modified the mediastinal lymph node dissection requirements.	
Key Changes	Rationale
Text describing surgical inclusion criteria was added: • Resection margins proved microscopically free (R0); Resection margins should be considered to be the bronchial, venous and arterial stumps, peribronchial soft tissue, any peripheral margin near the tumor or of additionally resected tissue. • A systematic nodal dissection is recommended or at least a lobe-specific systematic nodal dissection. However, the intraoperative lymph node evaluation can be accepted if no lymph nodes are found in those area and there is clear documentation in the operative report by the surgeon of exploration of the required lymph node areas. At minimum, the pathology and/or operative report should include the examination of at least two different mediastinal nodal (N2) station with one being subcarinal (level 7). • No extracapsular nodal extension of the tumor. • The highest mediastinal node removed can be positive. The term "uncertain resection" was proposed for operations in which the highest (furthest from the tumor) mediastinal lymph node was not demonstrated free of metastatic cancer. The concept was never embraced by any of the cancer organization or societies and was removed. Carcinoma in situ can be present at bronchial margin. This does not represent a positive resection margin. Only invasive cancer is considered as a positive margin.	• Many of the early participants were technically ineligible because they did not have the extensive lymph node dissection required by the initial protocol. The eligibility criteria concerning surgery were modified to better reflect clinical practice. • The purpose of the lymph node dissection was to ensure accurate staging.

KEYNOTE-091 Amendment 2 / 14-AUG-2018 Overall rationale: Updated the study design based on new external data from studies in the adjuvant setting in NSCLC and the updated prevalence of PD-L1 TPS ≥50% in KEYNOTE-091.	
Key Changes	Rationale
• Study design was revisited with SAP updated, including - Used a new assumption for median DFS of 42 months in control arm (as opposed to previous 48 months). - The target HR in the overall population was assumed stronger (reduced from 0.78 to 0.75). - Updated the multiplicity strategy to equally split the initial alpha to the dual primary endpoints. - Updated the DFS interim/final analyses timing - Reduced the sample size to 1080. - Dropped the futility interim analysis for PD-L1 negative subgroup. - Made secondary OS endpoints under alpha control. - Introduced OS interim analyses along with DFS analyses. Add 3 additional OS analyses after DFS FA. • The notation of primary/co-primary endpoints was replaced by primary/dual primary endpoints	• ECOG Study (E1505 - adjuvant chemo with Beva in NSCLC) median DFS 42 months [Ref. 5.4: 05P7M4] • Stronger confidence of the role in immune checkpoint inhibitors in early-stage disease based on external data: - PACIFIC study (durvalumab in locally advanced stage III): greater than anticipated intervention benefit (HR = 0.52, median PFS 5.6 to 16.8 months regardless of the PD-L1 status) [Ref. 5.4: 059GPT] - EORTC 1325-MG/KEYNOTE-054 adjuvant study in Melanoma: Pembro is positive regardless of PD-L1 status (HR = 0.57) [Ref. 5.4: 04WXLF] • Percentage of TPS ≥50% was increased to ~30% (compared to previous assumed 15%) based on the pre-planned standard review of blinded study data • Based on rationale stated above • Futility analysis timing close to enrolment completion due to shortened enrolment duration based on reduced sample size. Deemed unnecessary. Details in [Company Response 5]. • Strengthens conclusions regarding OS. • Offered chance to win OS early if treatment effect is pronounced. • Clarify the study will be positive if either of the endpoint is positive – as opposed to co-primary endpoints which suggest both primary objectives need to be reached to conclude that the study is positive

KEYNOTE-091 Amendment 03 / 15-JUN-2020 Overall rationale: Updated the guidelines for management of toxicity due to irAEs.. Clarified text describing the relaxed alpha level for the all-comer population and multiplicity strategy language. Clarified the OS analysis timing. Made adjustments to the triggers for the first interim analysis.	
Key Changes	Rationale
• Update of the approximate number of randomized patients (i.e., 1180 patients instead of 1080 patients) throughout the document. • Section 5.6 updates on withdrawal criteria and follow-up after withdrawal of study treatment, • Section 6.4 / 6.8.2: DFS replaced by disease recurrence • Protocol language regarding multiplicity strategy was modified to use the standard graphical approach without considering the correlation between the populations. • Clarified OS analysis timing.	• The increase in the number of participants was intended to reflect the study over enrolment. Though every effort is made to approximate the target enrolment, the pace of KEYNOTE-091 screening and enrolment was unexpectedly rapid during the final months of the trial. Though the MAH set an end to screening well before reaching the accrual goal, the increase in sample size allowed for participants who had entered screening to enter the trial if eligibility requirements were met (sample size: 1180). • To better clarify reason for discontinuation and avoid discrepancy with Protocol Appendix G and Protocol Section 6 • To correct a misused acronym. • An unpublished novel approach that extended the method of Spiessens and Debois (2010) to the group sequential design was employed in amendment 2 to relax the efficacy boundary of the overall study population, by considering the correlation between the TPS≥1% subgroup and the overall population. This novel multiplicity adjustment approach, however, remained unpublished and was therefore removed and replaced with the standard group sequential testing method based on the graphical approach of Maurer and Bretz (2013). • Clarified OS IAs after DFS FA are event driven. Clarified the OS FA timing if the targeted OS event numbers cannot be reached.

Protocol deviations

Protocol deviations were classified as per the ICH E3 classification of protocol deviations as important (those that may significantly impact the quality or integrity of key study data or that may significantly affect a participant's rights, safety, or well-being) or not important. Important protocol deviations were further classified as either clinically important (deviations that may compromise critical data analyses pertaining to primary efficacy and/or safety endpoints or the participant's safety) or not clinically important.

Important protocol deviations were reported for 175 participants overall (see table below):

Table 10: Summary of important protocol deviation (in the ITT population)

	Pembrolizumab		Placebo	
	n	(%)	n	(%)
Participants in population	590		587	
with one or more important protocol deviations	122	(20.7)	53	(9.0)
with no important protocol deviations	468	(79.3)	534	(91.0)
Discontinuation criteria	**1**	**(0.2)**	**1**	**(0.2)**
Inadherence to Appendix G	1	(0.2)	0	(0.0)
Participants who develop trial specific discontinuation criteria as per Appendix G but were not discontinued from the trial.	0	(0.0)	1	(0.2)
Inclusion/Exclusion criteria	**1**	**(0.2)**	**0**	**(0.0)**
History of a hematologic or primary solid tumor malignancy, unless in remission for at least 5 years	1	(0.2)	0	(0.0)
Prohibited medications	**1**	**(0.2)**	**2**	**(0.3)**
Participant received study prohibited concomitant medications as per Section 5.8.1	1	(0.2)	2	(0.3)
Safety reporting	**117**	**(19.8)**	**47**	**(8.0)**
Participants with reportable Safety Events and/or follow up Safety Event information that were not reported per the timelines outlined in the protocol	117	(19.8)	47	(8.0)
Study Intervention	**4**	**(0.7)**	**3**	**(0.5)**
Participant was administered improperly stored study intervention that was deemed unacceptable for use.	4	(0.7)	1	(0.2)
Participant was dispensed study intervention other than what was assigned in the allocation schedule, cross-treatment	0	(0.0)	1	(0.2)

Part of this study was conducted during the COVID-19 pandemic. Important and not important protocol deviations associated with the pandemic were reported for 225 participants overall, similarly in both treatment arms (18.8% vs 19.4% of patients in the pembrolizumab and placebo arm, respectively). None of the important protocol deviations associated with the pandemic were considered to be clinically important.

No participant's data were excluded from analyses due to an important protocol deviation. No important protocol deviations were classified as a serious GCP compliance issue.

Baseline data

Table 11: Participant Characteristics (ITT Population)

	Pembrolizumab		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	590		587		1,177	
Sex						
Male	401	(68.0)	403	(68.7)	804	(68.3)
Female	189	(32.0)	184	(31.3)	373	(31.7)
Age (Years)						
< 65	285	(48.3)	273	(46.5)	558	(47.4)
>= 65	305	(51.7)	314	(53.5)	619	(52.6)
Mean	64.1		64.5		64.3	
SD	8.5		8.4		8.4	
Median	65.0		65.0		65.0	
Range	31 to 87		37 to 85		31 to 87	
Race						
American Indian Or Alaska Native	1	(0.2)	0	(0.0)	1	(0.1)

Asian	107	(18.1)	107	(18.2)	214	(18.2)
Black Or African American	0	(0.0)	3	(0.5)	3	(0.3)
Multiple	4	(0.7)	1	(0.2)	5	(0.4)
American Indian Or Alaska Native White	1	(0.2)	0	(0.0)	1	(0.1)
Mestiza	1	(0.2)	0	(0.0)	1	(0.1)
Mixed Race	1	(0.2)	0	(0.0)	1	(0.1)
White Black Or African American	1	(0.2)	1	(0.2)	2	(0.2)
Other	6	(1.0)	2	(0.3)	8	(0.7)
White	450	(76.3)	455	(77.5)	905	(76.9)
Missing	22	(3.7)	19	(3.2)	41	(3.5)
Age (Years)						
< 70	420	(71.2)	416	(70.9)	836	(71.0)
>= 70	170	(28.8)	171	(29.1)	341	(29.0)
Age (Years)						
< 65	285	(48.3)	273	(46.5)	558	(47.4)
65 - 74	250	(42.4)	248	(42.2)	498	(42.3)
75 - 84	52	(8.8)	64	(10.9)	116	(9.9)
85+	3	(0.5)	2	(0.3)	5	(0.4)
Geographic Region						
Western Europe	303	(51.4)	301	(51.3)	604	(51.3)
Eastern Europe	116	(19.7)	113	(19.3)	229	(19.5)
Rest of World	65	(11.0)	68	(11.6)	133	(11.3)
Asia	106	(18.0)	105	(17.9)	211	(17.9)
Region						
EU	396	(67.1)	392	(66.8)	788	(66.9)
Non-EU	194	(32.9)	195	(33.2)	389	(33.1)
Region						
East Asia	106	(18.0)	105	(17.9)	211	(17.9)
Non-East Asia	484	(82.0)	482	(82.1)	966	(82.1)
Stage at Baseline per AJCC V7						
IB	84	(14.2)	85	(14.5)	169	(14.4)
II	329	(55.8)	338	(57.6)	667	(56.7)
IIIA	177	(30.0)	162	(27.6)	339	(28.8)
IV	0	(0.0)	2	(0.3)	2	(0.2)
Adjuvant Chemotherapy						
No	84	(14.2)	83	(14.1)	167	(14.2)
Yes	506	(85.8)	504	(85.9)	1,010	(85.8)
PD-L1 Status (Stratification)						
<1%	233	(39.5)	232	(39.5)	465	(39.5)
1-49%	189	(32.0)	190	(32.4)	379	(32.2)
>=50%	168	(28.5)	165	(28.1)	333	(28.3)
Smoking Status						
Never Smoker	87	(14.7)	66	(11.2)	153	(13.0)
Former Smoker	428	(72.5)	431	(73.4)	859	(73.0)
Current Smoker	75	(12.7)	90	(15.3)	165	(14.0)
Baseline ECOG						
0	380	(64.4)	343	(58.4)	723	(61.4)
1	210	(35.6)	244	(41.6)	454	(38.6)
Histology						
Squamous	192	(32.5)	224	(38.2)	416	(35.3)
Non-squamous	398	(67.5)	363	(61.8)	761	(64.7)
EGFR Mutation Status						

N	218	(36.9)	216	(36.8)	434	(36.9)
Y	39	(6.6)	34	(5.8)	73	(6.2)
Unknown	333	(56.4)	337	(57.4)	670	(56.9)
ALK Mutation Status						
N	226	(38.3)	190	(32.4)	416	(35.3)
Y	7	(1.2)	7	(1.2)	14	(1.2)
Unknown	357	(60.5)	390	(66.4)	747	(63.5)
Database Cutoff Date: 20SEP2021						

Table 12: Participant Characteristics (PD-L1 >= 50%)

	Pembrolizumab		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	168		165		333	
Sex						
Male	121	(72.0)	116	(70.3)	237	(71.2)
Female	47	(28.0)	49	(29.7)	96	(28.8)
Age (Years)						
< 65	84	(50.0)	82	(49.7)	166	(49.8)
>= 65	84	(50.0)	83	(50.3)	167	(50.2)
Mean	64.0		64.3		64.2	
SD	7.9		8.8		8.4	
Median	64.5		65.0		65.0	
Range	38 to 82		37 to 85		37 to 85	
Race						
American Indian Or Alaska Native	1	(0.6)	0	(0.0)	1	(0.3)
Asian	29	(17.3)	29	(17.6)	58	(17.4)
Multiple	0	(0.0)	1	(0.6)	1	(0.3)
White Black Or African American	0	(0.0)	1	(0.6)	1	(0.3)
Other	3	(1.8)	1	(0.6)	4	(1.2)
White	128	(76.2)	127	(77.0)	255	(76.6)
Missing	7	(4.2)	7	(4.2)	14	(4.2)
Age (Years)						
< 70	126	(75.0)	114	(69.1)	240	(72.1)
>= 70	42	(25.0)	51	(30.9)	93	(27.9)
Age (Years)						
< 65	84	(50.0)	82	(49.7)	166	(49.8)
65 - 74	72	(42.9)	64	(38.8)	136	(40.8)
75 - 84	12	(7.1)	17	(10.3)	29	(8.7)
85+	0	(0.0)	2	(1.2)	2	(0.6)
Geographic Region						
Western Europe	90	(53.6)	89	(53.9)	179	(53.8)
Eastern Europe	31	(18.5)	30	(18.2)	61	(18.3)
Rest of World	18	(10.7)	17	(10.3)	35	(10.5)

Asia	29	(17.3)	29	(17.6)	58	(17.4)
Region						
EU	115	(68.5)	112	(67.9)	227	(68.2)
Non-EU	53	(31.5)	53	(32.1)	106	(31.8)
Region						
East Asia	29	(17.3)	29	(17.6)	58	(17.4)
Non-East Asia	139	(82.7)	136	(82.4)	275	(82.6)
Stage at Baseline per AJCC V7						
IB	21	(12.5)	22	(13.3)	43	(12.9)
II	95	(56.5)	93	(56.4)	188	(56.5)
IIIA	52	(31.0)	50	(30.3)	102	(30.6)
Adjuvant Chemotherapy						
No	25	(14.9)	24	(14.5)	49	(14.7)
Yes	143	(85.1)	141	(85.5)	284	(85.3)
Smoking Status						
Never Smoker	14	(8.3)	13	(7.9)	27	(8.1)
Former Smoker	130	(77.4)	123	(74.5)	253	(76.0)
Current Smoker	24	(14.3)	29	(17.6)	53	(15.9)
Baseline ECOG						
0	116	(69.0)	101	(61.2)	217	(65.2)
1	52	(31.0)	64	(38.8)	116	(34.8)
Histology						
Squamous	65	(38.7)	60	(36.4)	125	(37.5)
Non-squamous	103	(61.3)	105	(63.6)	208	(62.5)
EGFR Mutation Status						
N	57	(33.9)	67	(40.6)	124	(37.2)
Y	6	(3.6)	5	(3.0)	11	(3.3)
Unknown	105	(62.5)	93	(56.4)	198	(59.5)
ALK Mutation Status						
N	55	(32.7)	58	(35.2)	113	(33.9)
Y	3	(1.8)	0	(0.0)	3	(0.9)
Unknown	110	(65.5)	107	(64.8)	217	(65.2)

Table 13: EGFR Status by Histology (ITT Population)

	Squamous			Non-squamous		
	Pembrolizumab (n=192)	Placebo (n=224)	Total (n=416)	Pembrolizumab (n=398)	Placebo (n=363)	Total (n=761)
EGFR Mutation Status						
N	39 (20.3%)	56 (25.0%)	95 (22.8%)	179 (45.0%)	160 (44.1%)	339 (44.5%)
Y	2 (1.0%)	5 (2.2%)	7 (1.7%)	37 (9.3%)	29 (8.0%)	66 (8.7%)
Unknown	151 (78.6%)	163 (72.8%)	314 (75.5%)	182 (45.7%)	174 (47.9%)	356 (46.8%)

Table 14: EGFR positivity by PD-L1 expression

EGFR (known) positive TOTAL	**39**	**34**
EGFR positive PD-L1<1%	18	15
EGFR positive PD-L1 1-49%	15	14
EGFR positive PD-L1 ≥50%	6	5

No additional assessment of EGFR status was planned in KEYNOTE-091 study.

Prior adjuvant chemotherapy

Approximately 86% of participants in both arms received adjuvant chemotherapy. Of the 14% who did not receive adjuvant chemotherapy 32.3% were Stage IB, 54.5% were Stage II, and 13.2% were Stage IIIA. A higher proportion of participants who did not receive adjuvant chemotherapy were ≥65 years old (74.9% vs. 48.9%; median age 64 vs 71 without and with chemo, respectively), had Stage IB disease (32.3% vs. 11.4%), and had squamous cell histology (44.9% vs. 33.8%) compared with those who received adjuvant chemotherapy.

Table 15: Exposure to prior adjuvant chemotherapy

	Pembrolizumab (N=506)	Placebo (N=504)
Duration on Therapy (days)		
Mean	71.2	72.5
Median	71.0	72.0
SD	19.67	19.47
Range	1.0 to 124.0	1.0 to 133.0
Number of Cycles		
Mean	3.7	3.7
Median	4.0	4.0
SD	0.68	0.62
Range	1.0 to 5.0	1.0 to 4.0
Database Cutoff Date: 20SEP2021		

Table 16: Type of prior adjuvant chemotherapy

	Pembrolizumab		Placebo	
	n	(%)	n	(%)
Participants in population	590		587	
with one or more prior adjuvant chemotherapy	506	(85.8)	504	(85.9)
with no prior adjuvant chemotherapy	84	(14.2)	83	(14.1)
ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS				
ANTINEOPLASTIC AGENTS	**506**	**(85.8)**	**504**	**(85.9)**
ANTINEOPLASTIC AGENTS	24	(4.1)	30	(5.1)
CARBOPLATIN;DOCETAXEL	2	(0.3)	0	(0.0)
CARBOPLATIN;ETOPOSIDE	5	(0.8)	3	(0.5)
CARBOPLATIN;GEMCITABINE	17	(2.9)	14	(2.4)
CARBOPLATIN;PACLITAXEL	60	(10.2)	75	(12.8)
CARBOPLATIN;PEMETREXED	18	(3.1)	9	(1.5)
CARBOPLATIN;VINORELBINE	81	(13.7)	70	(11.9)
CISPLATIN;DOCETAXEL	1	(0.2)	3	(0.5)
CISPLATIN;ETOPOSIDE	0	(0.0)	3	(0.5)
CISPLATIN;GEMCITABINE	27	(4.6)	30	(5.1)
CISPLATIN;IRINOTECAN	0	(0.0)	1	(0.2)
CISPLATIN;PACLITAXEL	2	(0.3)	1	(0.2)
CISPLATIN;PEMETREXED	28	(4.7)	15	(2.6)
CISPLATIN;VINORELBINE	241	(40.8)	250	(42.6)

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

A medication class or specific medication 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.

Database Cutoff Date: 20SEP2021

Table 17: Summary of duration between surgery and adjuvant chemotherapy, adjuvant chemotherapy and study treatment, and between surgery and study treatment

Event	Days	Pembrolizumab	Placebo
Surgery to 1st dose [a] of adjuvant chemotherapy (ITT- participants with adjuvant chemotherapy)		N=504	N=502
	median (range)	46 (16-91)	44 (17-121)
	IQR	18	20
Last dose of adjuvant chemotherapy to 1st dose of study treatment (APaT-participants with adjuvant chemotherapy)		N=496	N=499
	median (range)	43 (16-98)	43 (9-87)
	IQR	19	19
Surgery to 1st dose of study treatment (APaT-participants with adjuvant chemotherapy)		N=496	N=499
	median (range)	161 (71-244)	158 (80-254)
	IQR	36	36
Surgery to 1st dose of study treatment (APaT-participants without adjuvant chemotherapy)		N=84	N=82
	median (range)	57 (28 – 87)	57 (40 – 85)
	IQR	16.5	20
Surgery to 1st dose of study treatment (APaT population)		N=580	N=581
	median (range)	156 (28-244)	154 (40-254)
	IQR	44.5	47
[a] 2 participants in pembrolizumab arm and 2 participants in placebo arm received adjuvant chemotherapy without the 1st dose date of adjuvant chemotherapy reported in the database. These 4 participants are not included in the analysis.			

Table 18: Characteristics of Participants with Adjuvant Chemotherapy (ITT Population)

	Pembrolizumab		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	506		504		1,010	
Sex						
Male	339	(67.0)	347	(68.8)	686	(67.9)
Female	167	(33.0)	157	(31.2)	324	(32.1)
Age (Years)						
< 65	264	(52.2)	252	(50.0)	516	(51.1)
>= 65	242	(47.8)	252	(50.0)	494	(48.9)
Mean	63.3		63.6		63.4	
SD	8.1		7.9		8.0	
Median	64.0		64.5		64.0	
Range	35 to 80		37 to 84		35 to 84	
Race						
Asian	88	(17.4)	89	(17.7)	177	(17.5)
Black Or African American	0	(0.0)	3	(0.6)	3	(0.3)
Multiple	4	(0.8)	1	(0.2)	5	(0.5)
American Indian Or Alaska Native White	1	(0.2)	0	(0.0)	1	(0.1)
Mestiza	1	(0.2)	0	(0.0)	1	(0.1)
Mixed Race	1	(0.2)	0	(0.0)	1	(0.1)
White Black Or African American	1	(0.2)	1	(0.2)	2	(0.2)
Other	6	(1.2)	1	(0.2)	7	(0.7)
White	387	(76.5)	392	(77.8)	779	(77.1)
Missing	21	(4.2)	18	(3.6)	39	(3.9)
Age (Years)						
< 70	384	(75.9)	382	(75.8)	766	(75.8)
>= 70	122	(24.1)	122	(24.2)	244	(24.2)
Age (Years)						
< 65	264	(52.2)	252	(50.0)	516	(51.1)
65 - 74	211	(41.7)	222	(44.0)	433	(42.9)
75 - 84	31	(6.1)	30	(6.0)	61	(6.0)
Geographic Region						

Western Europe	261	(51.6)	266	(52.8)	527	(52.2)
Eastern Europe	105	(20.8)	96	(19.0)	201	(19.9)
Rest of World	53	(10.5)	55	(10.9)	108	(10.7)
Asia	87	(17.2)	87	(17.3)	174	(17.2)
Region						
EU	343	(67.8)	342	(67.9)	685	(67.8)
Non-EU	163	(32.2)	162	(32.1)	325	(32.2)
Region						
East Asia	87	(17.2)	87	(17.3)	174	(17.2)
Non-East Asia	419	(82.8)	417	(82.7)	836	(82.8)
Stage at Baseline per AJCC V7						
IB	60	(11.9)	55	(10.9)	115	(11.4)
II	281	(55.5)	295	(58.5)	576	(57.0)
IIIA	165	(32.6)	152	(30.2)	317	(31.4)
IV	0	(0.0)	2	(0.4)	2	(0.2)
PD-L1 Status (Stratification)						
<1%	198	(39.1)	198	(39.3)	396	(39.2)
1-49%	165	(32.6)	165	(32.7)	330	(32.7)
>=50%	143	(28.3)	141	(28.0)	284	(28.1)
Smoking Status						
Never Smoker	80	(15.8)	57	(11.3)	137	(13.6)
Former Smoker	362	(71.5)	375	(74.4)	737	(73.0)
Current Smoker	64	(12.6)	72	(14.3)	136	(13.5)
Baseline ECOG						
0	326	(64.4)	292	(57.9)	618	(61.2)
1	180	(35.6)	212	(42.1)	392	(38.8)
Histology						
Squamous	157	(31.0)	184	(36.5)	341	(33.8)
Non-squamous	349	(69.0)	320	(63.5)	669	(66.2)
EGFR Mutation Status						
N	190	(37.5)	192	(38.1)	382	(37.8)
Y	36	(7.1)	30	(6.0)	66	(6.5)
Unknown	280	(55.3)	282	(56.0)	562	(55.6)
ALK Mutation Status						
N	196	(38.7)	166	(32.9)	362	(35.8)
Y	6	(1.2)	6	(1.2)	12	(1.2)
Unknown	304	(60.1)	332	(65.9)	636	(63.0)
Database Cutoff Date: 20SEP2021						

Subsequent antineoplastic therapies

Fewer participants initiated subsequent antineoplastic therapies in the pembrolizumab group than the placebo group (14.6% vs 21.0%). Similarly, fewer participants initiated subsequent immunotherapies in the pembrolizumab group than the placebo group (2.5% vs 10.4%). The most commonly prescribed (>2%) subsequent antineoplastic agents in pembrolizumab arm were carboplatin/pemetrexed (3.2%) and carboplatin/paclitaxel (2.4%). In placebo-treated participants, the most commonly prescribed subsequent antineoplastic agents were pembrolizumab (5.3%), pemetrexed (2.6%), and atezolizumab (2.6%) (data related to IA2).

Table 19: participants with subsequent antineoplastic therapy

	Pembrolizumab		Placebo	
	n	(%)	n	(%)
Participants in population	590		587	
with one or more subsequent antineoplastic therapies	86	(14.6)	123	(21.0)
with no subsequent antineoplastic therapies	504	(85.4)	464	(79.0)

Table 20: participants with subsequent immunotherapies

	Pembrolizumab		Placebo	
	n	(%)	n	(%)
Participants in population	590		587	
with one or more subsequent immunotherapies	15	(2.5)	61	(10.4)
with no subsequent immunotherapies	575	(97.5)	526	(89.6)
ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS				
ANTINEOPLASTIC AGENTS	**15**	**(2.5)**	**61**	**(10.4)**
ATEZOLIZUMAB	2	(0.3)	15	(2.6)
CARBOPLATIN;PACLITAXEL;PEMBROLIZUMAB	1	(0.2)	1	(0.2)
CARBOPLATIN;PEMBROLIZUMAB;PEMETREXED	0	(0.0)	1	(0.2)
DURVALUMAB	4	(0.7)	5	(0.9)
IPILIMUMAB;NIVOLUMAB	1	(0.2)	0	(0.0)
NIVOLUMAB	1	(0.2)	10	(1.7)
PEMBROLIZUMAB	8	(1.4)	31	(5.3)
IMMUNOSTIMULANTS	**0**	**(0.0)**	**2**	**(0.3)**
EFTILAGIMOD ALFA	0	(0.0)	1	(0.2)
INTERLEUKIN-2	0	(0.0)	1	(0.2)

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

A medication class or specific medication 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.

Database Cutoff Date: 20SEP2021

Numbers analysed

1955 patients were screened, and a total of 1177 participants were randomized in KEYNOTE-091 and included in the ITT population (590 in the pembrolizumab group, 587 in the placebo group). 333 patients presented with PD-L1 expression ≥50%, of which 168 randomized to pembrolizumab and 165 to placebo. 712 patients had PD-L1≥1%, 357 in pembrolizumab and 355 in placebo arm. 1161 patients were included in the PRO FAS population.

Outcomes and estimation

Efficacy results from prespecified IA2 of KEYNOTE-091 are presented below, followed by efficacy results from the IA3 (data cut-off 24-JAN-2023).

Table 21: Summary of Outcomes for Primary and Key Secondary Endpoints at IA2

Endpoints		Outcome
Primary	DFS in the overall study population	Positive
	DFS in TPS≥50% subgroup	Not positive; To be tested again at next IA
Key Secondary	DFS in TPS≥1% subgroup	Not tested; To be tested once positive DFS in TPS≥50%
	OS in TPS≥50% subgroup	Not positive; To be tested again at next IA
	OS in the overall study population	Not positive; To be tested again at next IA
	OS in TPS≥1% subgroup	Not tested; To be tested once positive OS in TPS≥50%

Table 22: Summary of efficacy at IA2

Endpoint	Overall Study Population		TPS ≥50%		TPS>=1%	
	Pembro N=590	Placebo N=587	Pembro N=168	Placebo N=165	Pembro N=357	Placebo N=355
DFS						
Median in months (95% CI)[a]	53.6 (39.2, NR)	42.0 (31.3, NR)	NR (44.3, NR)	NR (35.8, NR)	53.6 (44.2, NR)	42.0 (31.3, NR)
Hazard ratio (95% CI)[b]	0.76 (0.63, 0.91)		0.82 (0.57, 1.18)		0.73 (0.57, 0.92)	
p-Value[c]	0.00143		0.13639		Not Tested	
OS[d]						
Hazard ratio (95% CI)[b]	0.87 (0.67, 1.15)		0.92 (0.52, 1.62)		0.76 (0.52, 1.09)	
p-Value[e]	0.16811		0.38517		Not Tested	

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

[b] Based on the multivariate Cox regression model with treatment adjusted by the following covariates: stage (IB vs. II vs. IIIA), PD-L1 status (≥50% vs. 1-49% vs. <1%), adjuvant chemotherapy (yes vs. no), region (Western Europe vs. Eastern Europe vs. Rest of World vs. Asia), histology (squamous vs. non-squamous), and smoking status (never vs. former/current).

[c] One-sided p-value based on the permutation test with multivariate Cox regression model.

[d] Median OS (95% CI) was not reached in any of the groups.

[e] One-sided p-value based on the Wald test with multivariate Cox regression model.

Abbreviations: CI=confidence interval; DFS=disease-free survival; IA2=interim analysis 2; NR = not reached; OS=overall survival; Pembro = pembrolizumab; TPS=tumor proportion score

- **DFS in ITT population (primary endpoint)**

Table 23: Analysis of Disease-Free Survival (Primary Censoring Rule) Primary Analysis with Permutation Test (ITT Population)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months	Median DFS[a] (Months) (95% CI)	DFS Rate at Month 12 in %[a] (95% CI)	vs. Placebo	
							Hazard Ratio[b] (95% CI)[b]	p-Value[c]
Pembrolizumab	590	212 (35.9)	13872.6	1.5	53.6 (39.2, .)	78.7 (75.1, 81.9)	0.76 (0.63, 0.91)	0.00143
Placebo	587	260 (44.3)	13089.8	2.0	42.0 (31.3, .)	71.6 (67.7, 75.1)	---	---

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

[b] Based on the multivariate Cox regression model with treatment adjusted by the following covariates: stage (IB vs. II vs. IIIA), PD-L1 status (≥50% vs. 1-49% vs. <1%), adjuvant chemotherapy (yes vs. no), region (Western Europe vs. Eastern Europe vs. Rest of World vs. Asia), histology (squamous vs. non-squamous), and smoking status (never vs. former/current).

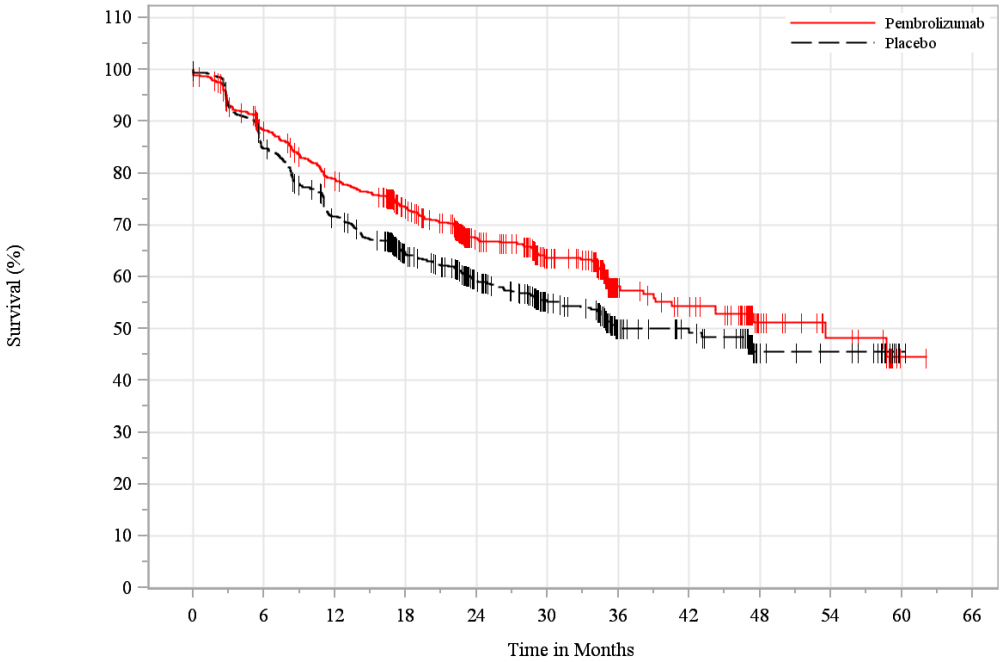
[c] One-sided p-value based on the permutation test with multivariate Cox regression model.

Database Cutoff Date: 20SEP2021

	Pembrolizumab (N=590)	Placebo (N=587)
DFS rate at 12 Months in (95% CI)[a]	78.7 (75.1, 81.9)	71.6 (67.7, 75.1)
DFS rate at 18 Months in (95% CI)[a]	73.4 (69.6, 76.9)	64.3 (60.3, 68.1)
DFS rate at 24 Months in (95% CI)[a]	67.4 (63.2, 71.2)	59.5 (55.2, 63.4)
DFS rate at 30 Months in (95% CI)[a]	63.7 (59.3, 67.8)	55.1 (50.7, 59.3)
DFS rate at 36 Months in (95% CI)[a]	58.1 (53.1, 62.8)	50.1 (45.1, 54.8)
DFS rate at 42 Months in (95% CI)[a]	54.4 (48.7, 59.8)	49.2 (44.1, 54.1)

[a] From the product-limit (Kaplan-Meier) method for censored data.
Database Cutoff Date: 20SEP2021

Figure 5: Kaplan-Meier Estimates of Disease-Free Survival (Primary Censoring Rule) (ITT Population)



Database Cutoff Date: 20SEP2021

Table 24: Disease status – DFS events (ITT population)

	Pembrolizumab n	(%)	Placebo n	(%)
Participants in population	590		587	
Type of First Event in DFS Analysis				
No event	378	(64.1)	327	(55.7)
Event	212	(35.9)	260	(44.3)
Not disease-free at baseline	7	(1.2)	4	(0.7)
Recurrence	157	(26.6)	212	(36.1)
Local and/or regional recurrence	56	(9.5)	70	(11.9)
Distant metastasis	68	(11.5)	101	(17.2)
Both	33	(5.6)	41	(7.0)
New malignancy	21	(3.6)	32	(5.5)
Death	27	(4.6)	12	(2.0)
New malignancy includes the second primary and second malignancies. Database Cutoff Date: 20SEP2021				

- **DFS in PD-L1 TPS≥50% population (primary endpoint)**

Table 25: Analysis of Disease-Free Survival (Primary Censoring Rule) Primary Analysis with Permutation Test with TPS ≥ 50% (ITT Population)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months	Median DFS[a] (Months) (95% CI)	DFS Rate at Month 12 in %[a] (95% CI)	vs. Placebo	
							Hazard Ratio[b] (95% CI)[b]	p-Value[c]
Pembrolizumab	168	54 (32.1)	3948.7	1.4	Not Reached (44.3,)	79.5 (72.4, 85.0)	0.82 (0.57, 1.18)	0.13639
Placebo	165	63 (38.2)	3976.8	1.6	Not Reached (35.8,)	74.5 (67.1, 80.5)	---	---

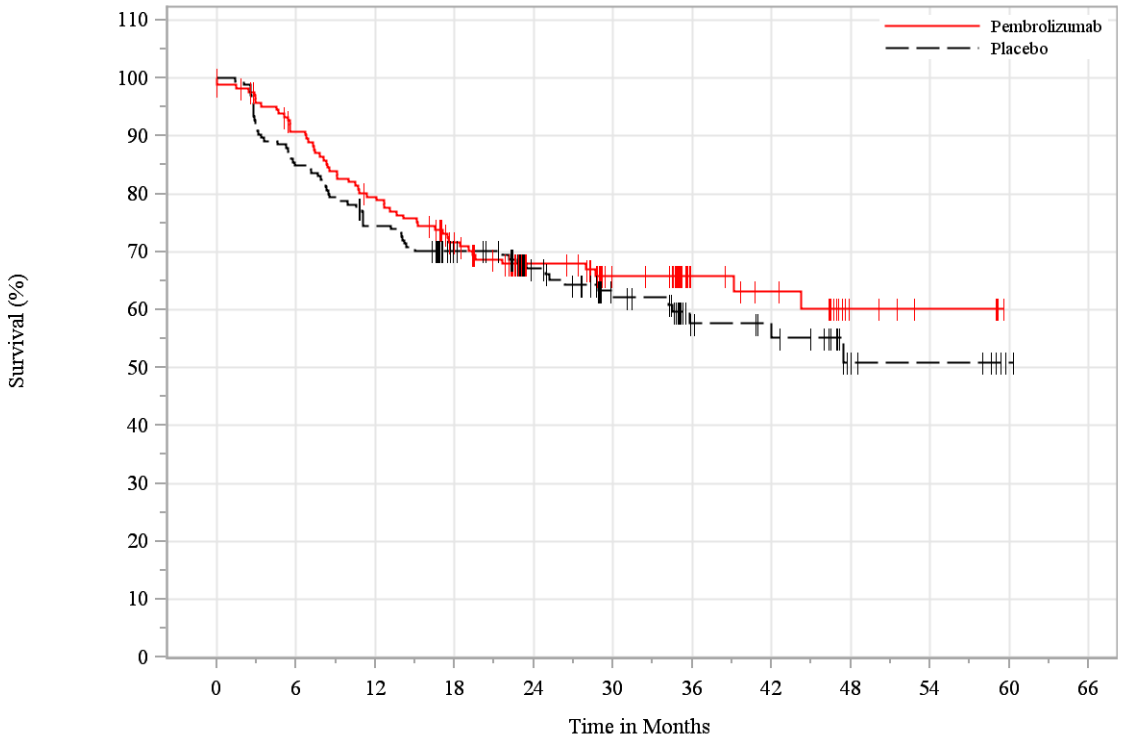
[a] From product-limit (Kaplan-Meier) method for censored data.

[b] Based on the multivariate Cox regression model with treatment adjusted by the following covariates: stage (IB vs. II vs. IIIA), PD-L1 status (≥50% vs. 1-49% vs. <1%), adjuvant chemotherapy (yes vs. no), region (Western Europe vs. Eastern Europe vs. Rest of World vs. Asia), histology (squamous vs. non-squamous), and smoking status (never vs. former/current).

[c] One-sided p-value based on the permutation test with multivariate Cox regression model.

Database Cutoff Date: 20SEP2021

Figure 6: Kaplan-Meier Estimates of Disease-Free Survival (Primary Censoring Rule) with TPS >= 50% (ITT Population)



Number of participants at risk

Pembrolizumab	168	145	126	99	69	50	26	22	7	4	0	0
Placebo	165	140	121	100	75	54	28	22	8	6	1	0

Database Cutoff Date: 20SEP2021

- **OS in the ITT (secondary endpoint)**

  - **OS in the ITT**

For OS in the ITT population, the observed p-value did not cross the multiplicity-adjusted, one-sided p-value boundary at IA2.

Table 26: Analysis of Overall Survival (Primary Analysis) (ITT Population)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months	Median OS[a] (Months) (95% CI)	OS Rate at Month 12 in %[a] (95% CI)	vs. Placebo	
							Hazard Ratio[b] (95% CI)[b]	p-Value[c]
Pembrolizumab	590	98 (16.6)	19215.5	0.5	Not Reached (.,)	95.2 (93.1, 96.7)	0.87 (0.67, 1.15)	0.16811
Placebo	587	111 (18.9)	19071.7	0.6	Not Reached (., .)	95.2 (93.1, 96.7)	---	---

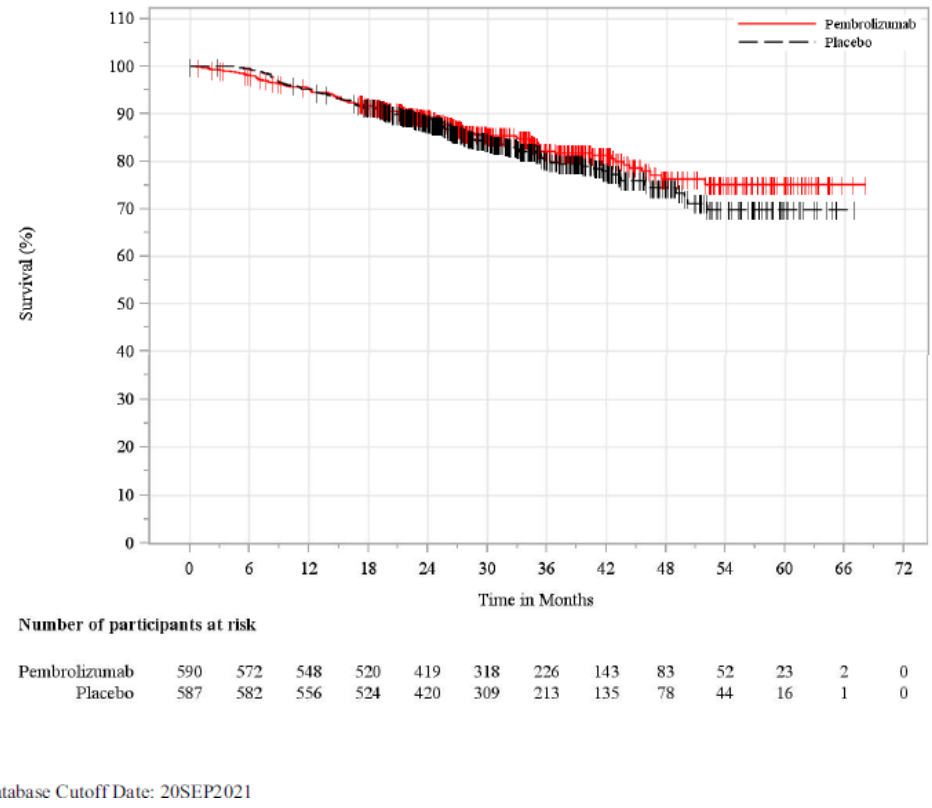
[a] From product-limit (Kaplan-Meier) method for censored data.

[b] Based on the multivariate Cox regression model with treatment adjusted by the following covariates: stage (IB vs. II vs. IIIA), PD-L1 status (≥50% vs. 1-49% vs. <1%), adjuvant chemotherapy (yes vs. no), region (Western Europe vs. Eastern Europe vs. Rest of World vs. Asia), histology (squamous vs. non-squamous), and smoking status (never vs. former/current).

[c] One-sided p-value based on the Wald Test in the multivariate Cox regression model.

Database Cutoff Date: 20SEP2021

Figure 7: Kaplan-Meier Estimates of Overall Survival (Primary analysis) (ITT Population)

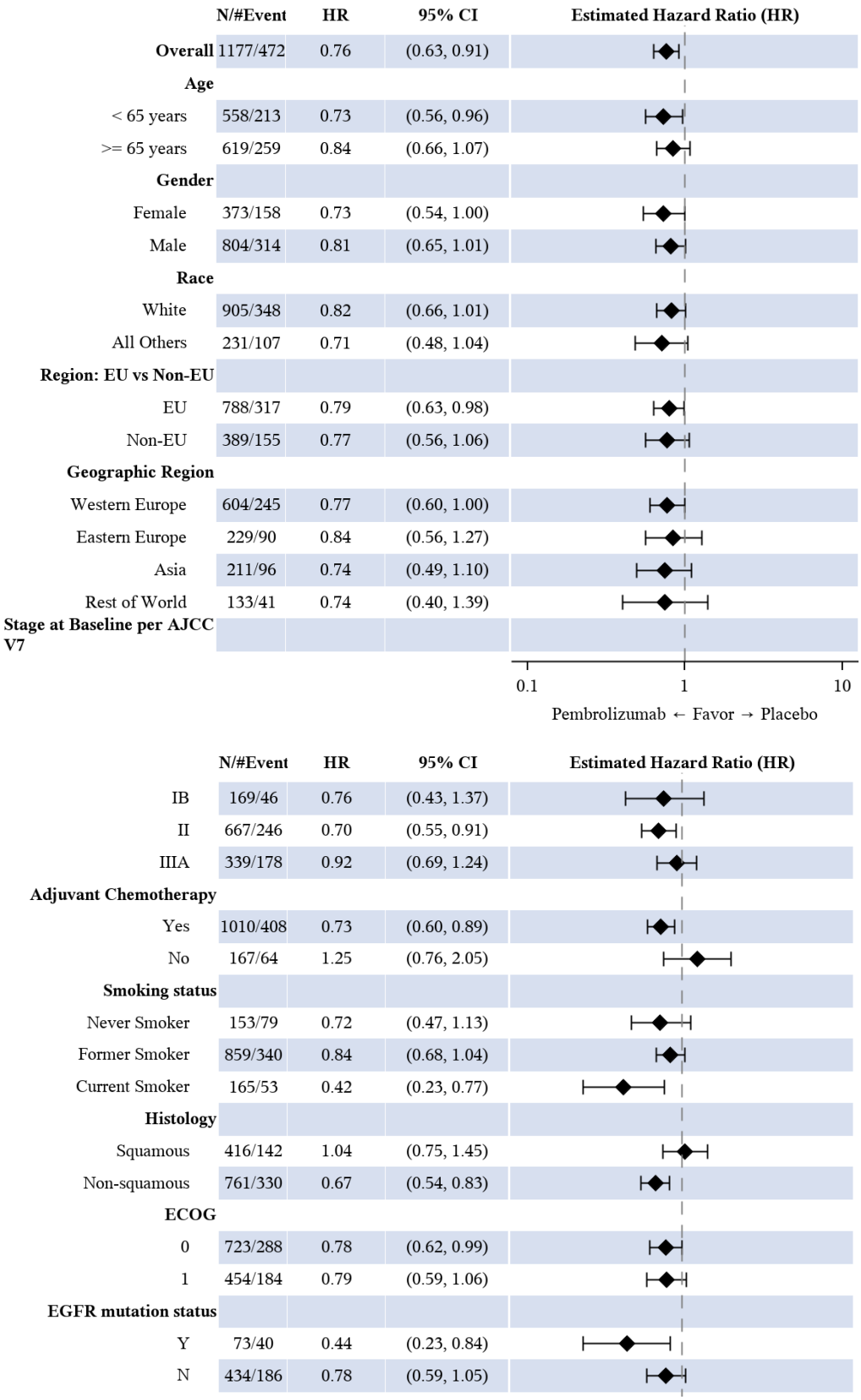


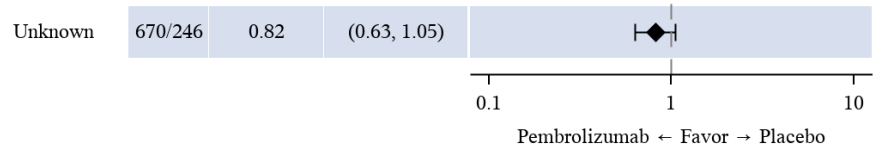
Database Cutoff Date: 20SEP2021

Ancillary analyses

Subgroup analyses

Figure 8: Forest Plot of DFS Hazard Ratio by Subgroup Factors (ITT Population)

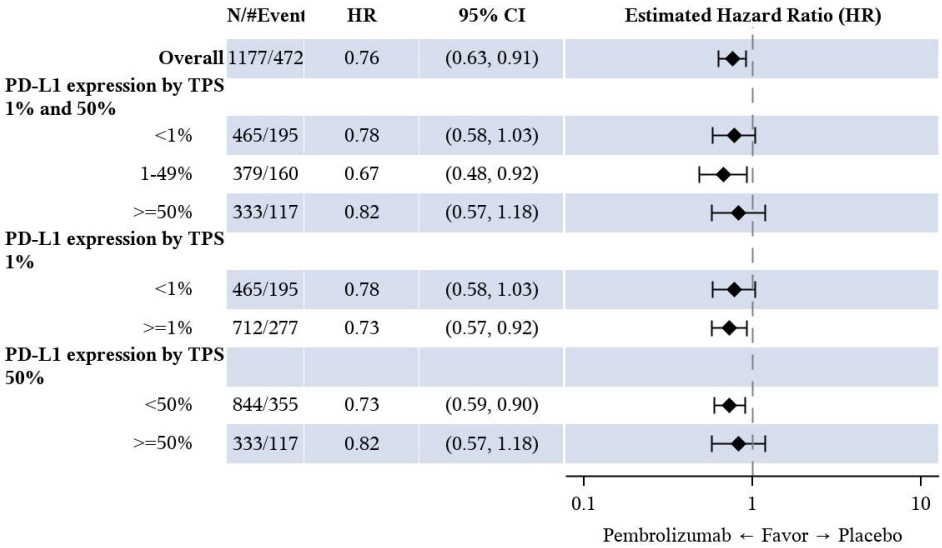




1. For overall population, analysis is based on multivariate Cox regression model with treatment adjusted by the following covariates: stage (IB vs. II vs. IIIA), PD-L1 status (>=50% vs. 1-49% vs. <1%), adjuvant chemotherapy (yes vs. no), region (Western Europe vs. Eastern Europe vs. Rest of World vs. Asia), histology (squamous vs. non-squamous), and smoking status (never vs. former/current). For subgroups, analysis is based on Cox regression model with treatment as a covariate. 2. If a subgroup variable has two levels and one level of the subgroup meets any criteria below, then this subgroup variable will not be displayed: (1) if the number of participants in a category of a subgroup variable is less than 50, (2) the number of events in a category of a subgroup variable is zero in one treatment arm, (3) the number of events in a category of a subgroup variable is less than 5 in the pooled arms. Database Cutoff Date: 20SEP2021

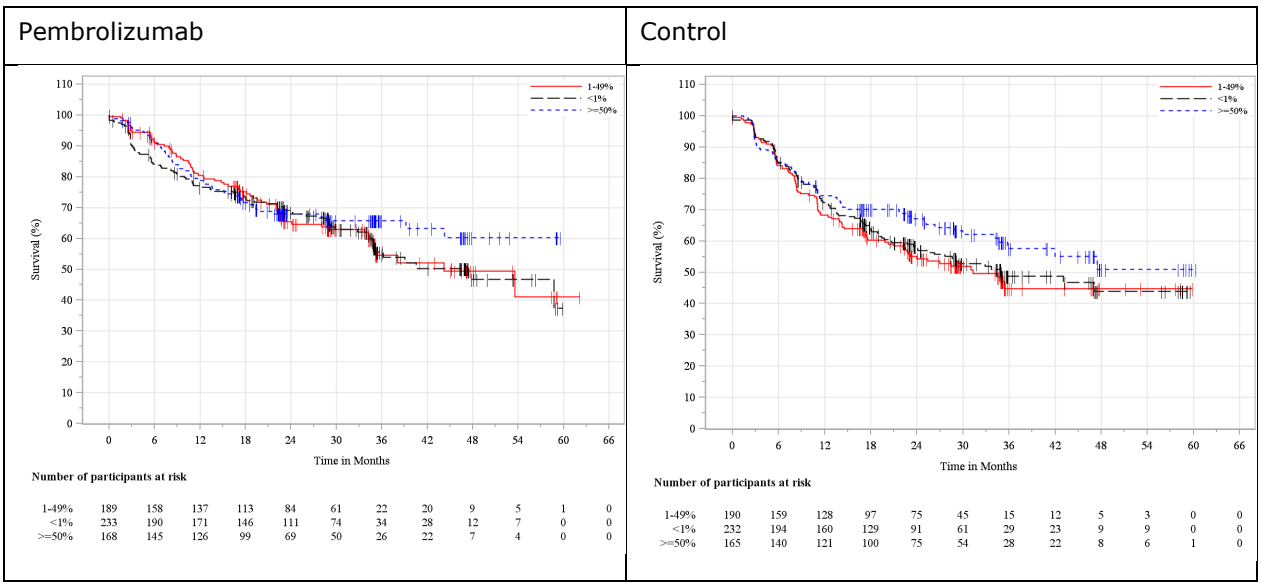
Results by PD-L1 status:

Figure 9: Forest Plot of DFS Hazard Ratio by PD-L1 Expression (ITT Population)



For overall population and the PD-L1 subgroup, analysis is based on multivariate Cox regression model with treatment adjusted by the following covariates: stage (IB vs. II vs. IIIA), PD-L1 status (>=50% vs. 1-49% vs. <1%), adjuvant chemotherapy (yes vs. no), region (Western Europe vs. Eastern Europe vs. Rest of World vs. Asia), histology (squamous vs. non-squamous), and smoking status (never vs. former/current). Database Cutoff Date: 20SEP2021

Figure 10: Kaplan-Meier Estimates of Disease-Free Survival (Primary Censoring Rule) by PD-L1 Expression (ITT population)



Sensitivity analyses

Several prespecified sensitivity analyses for DFS were conducted in the overall study population and in the PD L1 TPS ≥50% and TPS ≥1% subgroups. Results in each sensitivity analysis were consistent with the primary analysis.

Restricted Mean Survival Times (RMST) of DFS

Table 27: Analysis of restricted mean survival times (RMST) of disease-free survival (ITT population)

	Pembrolizumab (N=590)		Placebo (N=587)		Difference (95% CI) Pembrolizumab vs Placebo
	Number of Events	RMST	Number of Events	RMST	
RMST based on 6 months of follow up	67	5.67	89	5.66	0.02 (-0.10 , 0.14)
RMST based on 12 months of follow up	120	10.70	165	10.39	0.31 (-0.04 , 0.66)
RMST based on 18 months of follow up	148	15.27	205	14.47	0.80 (0.18 , 1.42)
RMST based on 24 months of follow up	176	19.49	228	18.20	1.29 (0.38 , 2.20)
RMST based on 30 months of follow up	189	23.46	244	21.64	1.81 (0.61 , 3.02)
RMST:Restricted mean survival time. Database Cutoff Date: 20SEP2021					

Patient-Reported Outcomes (exploratory endpoint)

Based on the early results, global health status/quality of life scores were stable over time in both the pembrolizumab and placebo groups.

Table 28: Summary and Analysis of Overall Improvement / Stability Rate for EORTC QLQ-C30 Global Health Status/QoL (PRO FAS Population)

	Pembrolizumab (N=580)			Placebo (N=581)		
Summary	n	%	95% CI[a]	n	%	95% CI[a]
Improved	**145**	**25.0**	**(21.5, 28.7)**	**200**	**34.4**	**(30.6, 38.4)**
Stable	268	46.2	(42.1, 50.4)	271	46.6	(42.5, 50.8)
Improved + Stable	**413**	**71.2**	**(67.3, 74.9)**	**471**	**81.1**	**(77.6, 84.2)**
Deteriorated	110	19.0	(15.9, 22.4)	83	14.3	(11.5, 17.4)
Unconfirmed	23	4.0	(2.5, 5.9)	20	3.4	(2.1, 5.3)
No Assessment	34	5.9	(4.1, 8.1)	7	1.2	(0.5, 2.5)

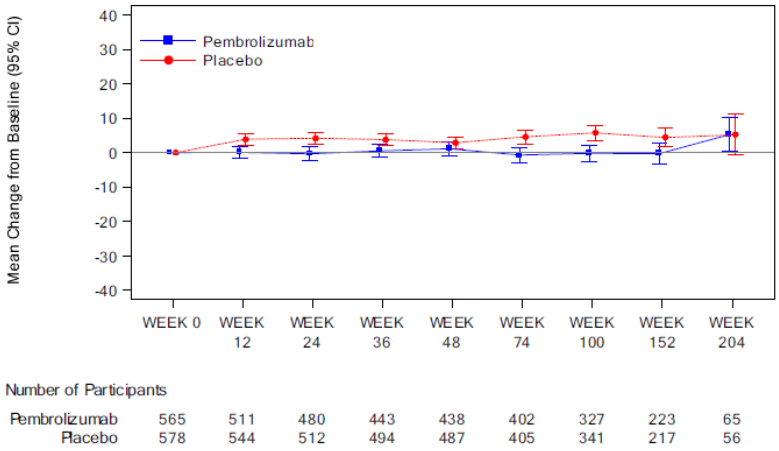
	Difference in % Improved	
Analysis	Estimate (95% CI)[b]	p-Value[b]
Pembrolizumab vs. Placebo	-9.4 (-14.6, -4.2)	0.0004[c]

	Difference in % Improved + Stable	
Analysis	Estimate (95% CI)[b]	p-Value[b]
Pembrolizumab vs. Placebo	-9.9 (-14.7, -5.0)	<.0001[c]

a Based on binomial exact confidence interval method.
b Based on unstratified Miettinen & Nurminen method.
c Two-sided p-value for testing. H0: difference in % = 0 versus H1: difference in % ≠ 0.
Improved is defined as a 10-point or more increase in score (in the positive direction) at any time during the trial and confirmed by a 10-point or more increase in score at the next consecutive visit.
Stable is defined as a 10-point or more increase (in the positive direction) or less than 10-point change in score (in the positive or negative direction) from baseline and confirmed by a less than 10-point change in score at the next consecutive visit; OR a less than 10-point change in score and a 10-point or more increase in score at the next consecutive visit.
Improved + stable is defined as the composite of the improved and stable.
Deteriorated is defined as a ≥10-point deterioration in score from baseline at any time during the trial when the criteria for improved or stable is not met.
Unconfirmed is defined as when the criteria for improved or stable with confirmation or deterioration is not met.
No assessment is defined as participants who do not have baseline or post-baseline assessments available.

Database Cutoff Date: 20SEP2021

Figure 11: Empirical Mean Change from Baseline and 95% CI for the EORTC QLQ-C30 Global Health Status/QoL Over Time by Treatment Group (Observed Data Only) (PRO FAS Population)



RESULTS AT INTERIM ANALYSIS 3

Results from the 3rd efficacy interim analysis with a data cutoff date of 24-Jan-2023, which is the final DFS analysis per protocol, are presented below. DFS in the overall study population was not tested since the study already met the success criterion at IA2. At IA3, neither DFS in participants with TPS ≥50% nor OS were statistically significant. OS will continue to be tested at the next analysis (IA4).

Table 29: IA3 (Final DFS Analysis) Topline Summary of Results for Primary and Key Secondary Endpoints

Endpoints (pembrolizumab vs. placebo)		No. events (IF[e])	HR (95% CI)	Median (Months)	P-value[a] boundary	Observed P-value[a]	Outcome
Primary	[b] DFS in the overall population	561 (102%)	0.81 (0.68, 0.96)	53.8 vs. 43.0	-	0.00812	Not tested (success criterion met at IA2)
	[b] DFS in TPS≥50%	140 (99%)	0.83 (0.59, 1.16)	67.0 vs. 47.6	0.01038	0.13499	Not positive[d]
Key Secondary	[b] DFS in TPS≥1%	331 (102%)	0.78 (0.62, 0.97)	58.7 vs. 42.8	-	0.01327	Not tested[d]
	[c] OS in the overall population	290	0.87 (0.69, 1.10)	NR vs NR		0.11792	Not positive; To be tested again at next IA
	[c] OS in TPS≥50%	67	0.93 (0.57, 1.50)	NR vs NR		0.37780	Not positive; To be tested again at next IA
	[c] OS in TPS≥1%	165	0.83 (0.61, 1.13)	NR vs NR	-	0.12390	Not tested; To be tested once OS positive in TPS≥50%

NR= Not Reached

[a] One-sided P-value

[b] P-values for DFS endpoints are based on the permutation test with the multivariate Cox regression model

[c] P-values for OS endpoints are based on the Wald test in the multivariate Cox regression model

[d] Although the DFS hypothesis in TPS ≥50% can be re-tested at the full alpha level (0.025) after all the OS hypotheses are all rejected, the observed p-value is already above the largest possible p-value boundary and therefore not possible to be statistically significant. As a result, DFS in TPS ≥1% cannot be tested at future analyses given DFS in TPS ≥50% is not positive regardless of OS outcomes.

[e] IF: Information Fraction, the percentage of observed events at the time of analysis divided by protocol specified targeted events at Final Analysis

Table 30: Summary of Efficacy Results From KEYNOTE-091 - IA2 and IA3

Endpoint	**DFS**		**OS**	
Analysis	**IA2**	**IA3 (Final DFS)**	**IA2**	**IA3**
Overall Study Population				
Events ([a]IF)	472 (86%)	561 (102%)	209	290
Number of events (%)	35.9% vs 44.3%	44.7% vs 50.6%	16.6% vs 18.9%	23.1% vs 26.6%
[b] Median (Months)	53.6 vs. 42.0	53.8 vs. 43.0	NR vs. NR	NR vs. NR
[c] HR (95% CI)	0.76 (0.63-0.91)	0.81 (0.68-0.96)	0.87 (0.67-1.15)	0.87 (0.69-1.10)
[d] P-value	0.00143 (stat sign)	0.00812	0.16811	0.11792
TPS ≥50%				
Events ([a]IF)	117 (83%)	140 (99%)	49	67
Number of events (%)	32.1% vs 38.2%	38.7% vs 45.5%	14.3% vs 15.2%	19.6% vs 20.6%
[b] Median (Months)	NR vs. NR	67.0 vs 47.6	NR vs. NR	NR vs. NR
[c] HR (95% CI)	0.82 (0.57-1.18)	0.83 (0.59-1.16)	0.92 (0.52-1.62)	0.93 (0.57-1.50)
[d] P-value	0.13639	0.13499	0.38517	0.3778
TPS ≥1%				
Events ([a]IF)	277 (85%)	331 (102%)	119	165
Number of events (%)	34.5% vs 43.4%	42.6% vs 50.4%	14.6% vs 18.9%	21.3% vs 25.1%
[b] Median (Months)	53.6 vs. 42.0	58.7 vs. 42.8	NR vs. NR.	NR vs. NR
[c] HR (95% CI)	0.73 (0.57-0.92)	0.78 (0.62-0.97)	0.76 (0.52-1.09)	0.83 (0.61-1.13)
[d] P-value	Not Tested	Not Tested	Not Tested	Not Tested

[a] Information Fraction, the percentage of observed events at the time of analysis divided by protocol specified targeted events at Final Analysis

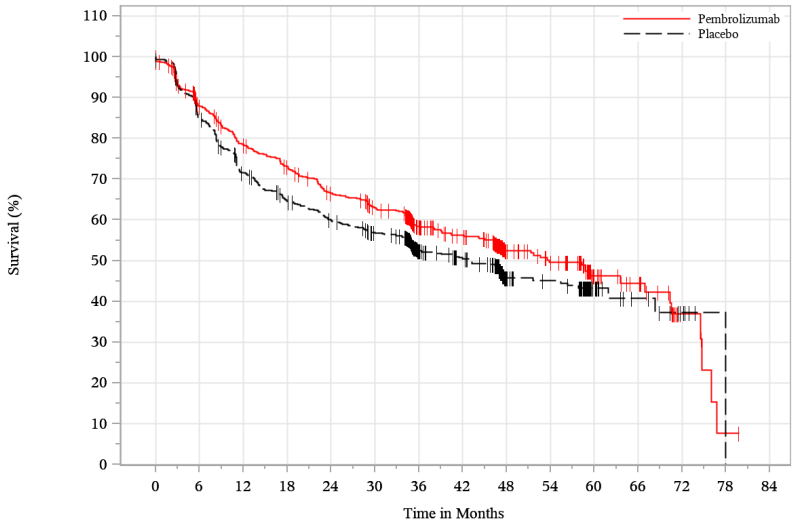
[b] From product-limit (Kaplan-Meier) method for censored data (pembrolizumab vs. placebo).

[c] Based on the multivariate Cox regression model with treatment adjusted by the following covariates: stage (IB vs. II vs. IIIA), PD-L1 status (≥50% vs. 1-49% vs. <1%), adjuvant chemotherapy (yes vs. no), region (Western Europe vs. Eastern Europe vs. Rest of World vs. Asia), histology (squamous vs. non-squamous), and smoking status (never vs. former/current).

[d] One-sided p-value. For DFS, this is based on the permutation test with multivariate Cox regression model; for OS, this is based on the Wald test with multivariate Cox regression model.

Figure 12: Kaplan-Meier Estimates of Disease-Free Survival (Primary Censoring Rule) (ITT Population) - IA3

Overall population

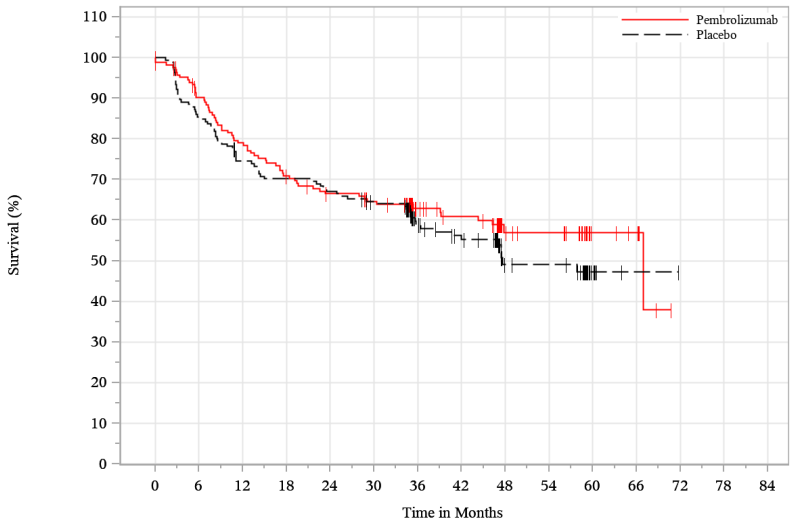


Number of participants at risk

Pembrolizumab	590	493	435	402	361	330	222	194	100	85	34	23	6	1	0
Placebo	587	493	411	366	337	309	202	180	82	73	23	13	5	0	0

Database Cutoff Date: 24JAN2023

TPS >= 50%

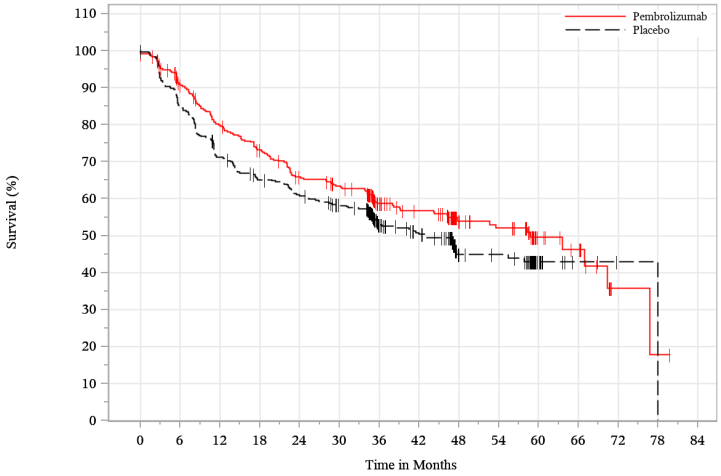


Number of participants at risk

Pembrolizumab	168	145	127	114	104	97	66	59	30	27	8	6	0	0	0
Placebo	165	140	121	114	109	101	70	59	28	27	7	2	0	0	0

Database Cutoff Date: 24JAN2023

TPS >= 1%



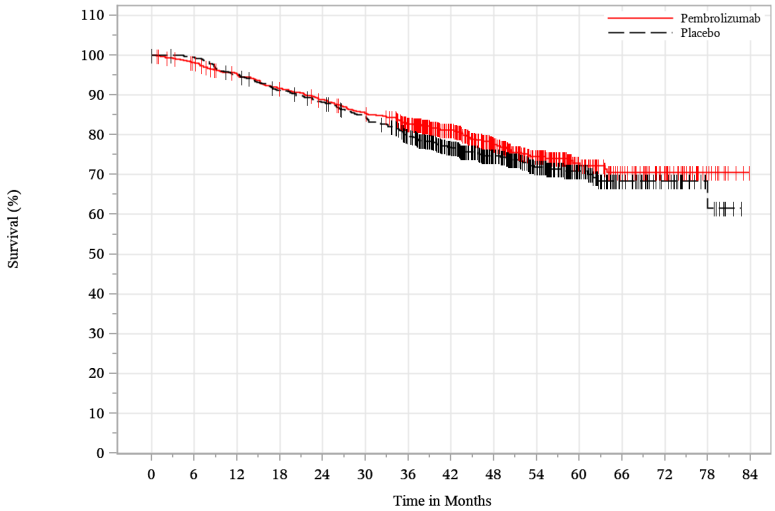
Number of participants at risk

Pembrolizumab	357	304	265	241	213	198	132	117	60	54	18	13	2	1	0
Placebo	355	299	250	226	210	193	130	112	48	45	12	4	1	0	0

Database Cutoff Date: 24JAN2023

Figure 13: Kaplan-Meier Estimates of Overall Survival (Primary Analysis) (ITT Population) - IA3

Overall population

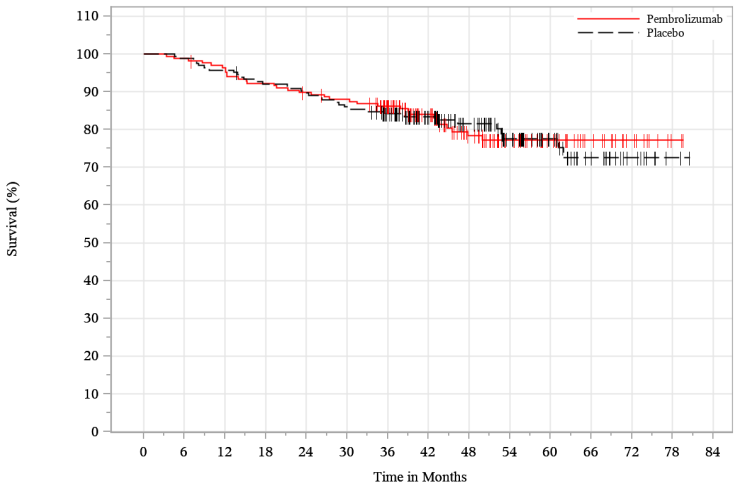


Number of participants at risk

Pembrolizumab	590	573	549	528	510	488	446	357	262	185	109	71	42	13	0
Placebo	587	582	556	530	510	485	433	342	256	177	99	59	36	9	0

Database Cutoff Date: 24JAN2023

TPS >= 50%

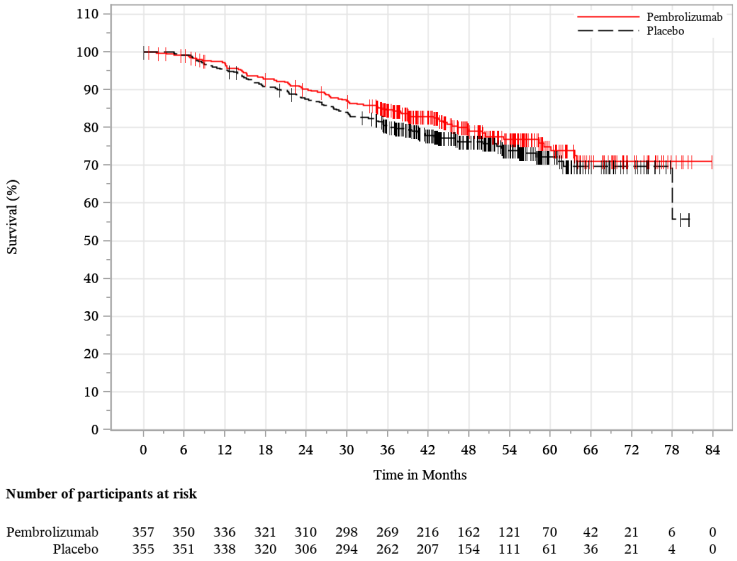


Number of participants at risk

Pembrolizumab	168	166	161	154	149	145	131	101	74	53	35	21	11	2	0
Placebo	165	163	158	151	147	141	128	99	76	53	35	21	10	3	0

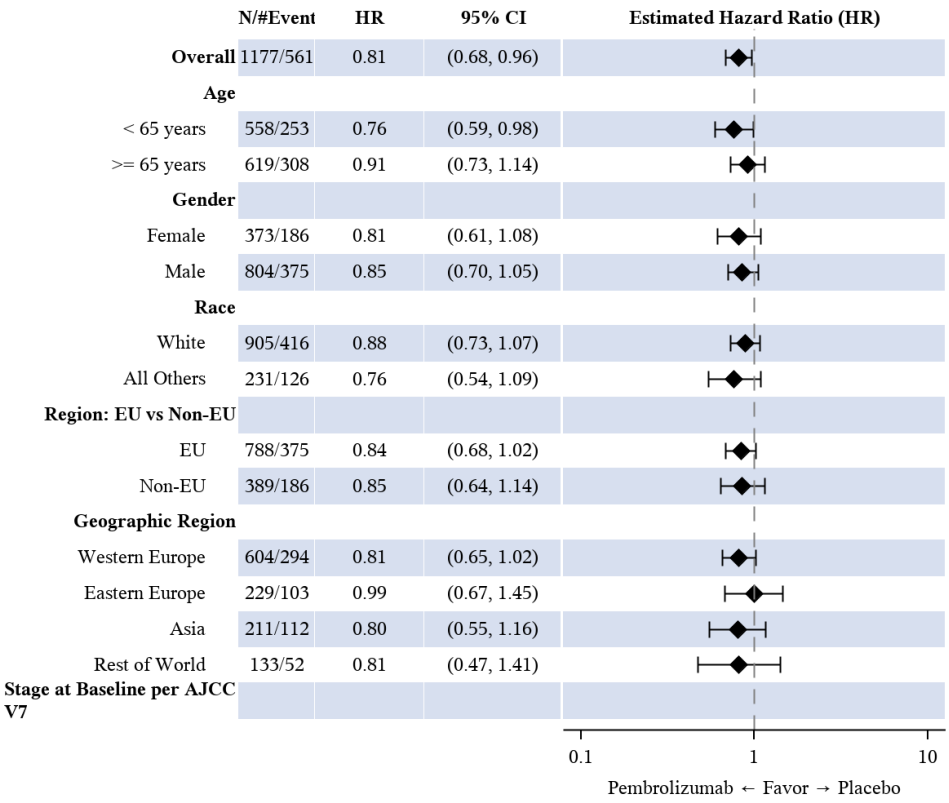
Database Cutoff Date: 24JAN2023

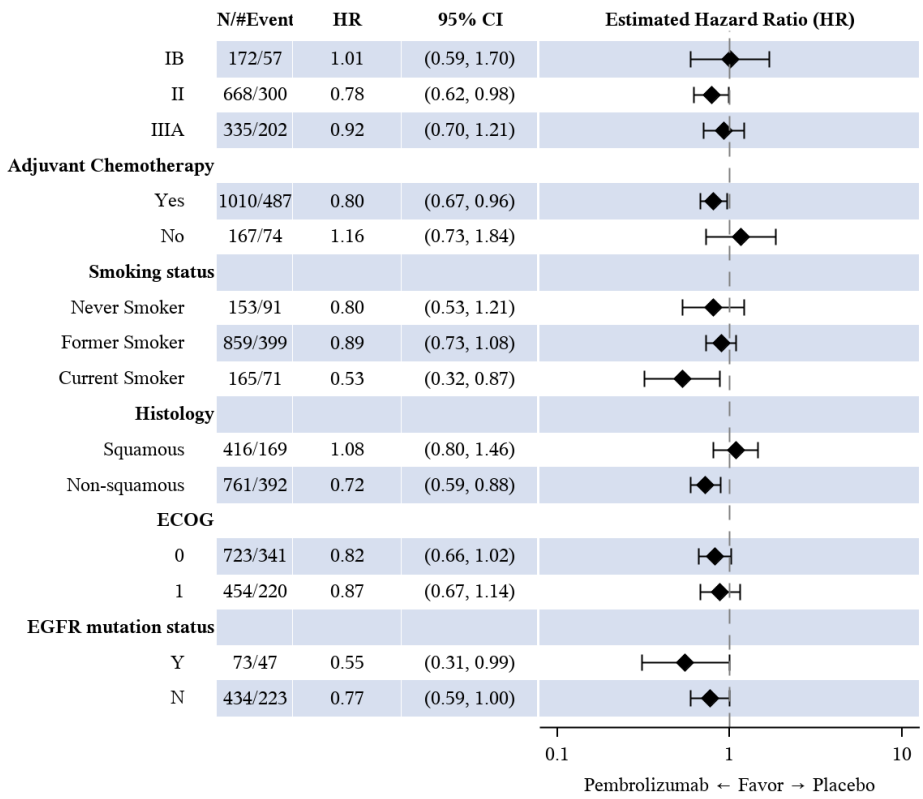
TPS >= 1%

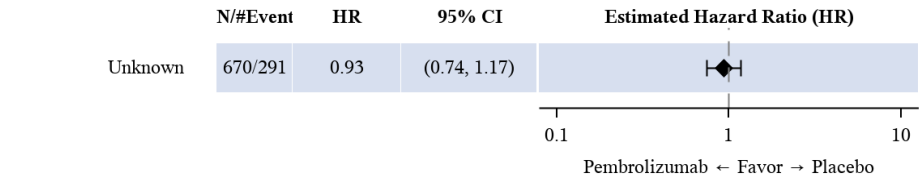


Database Cutoff Date: 24JAN2023

Figure 14: Forest Plot of DFS Hazard Ratio by Subgroup Factors (ITT Population) – IA3





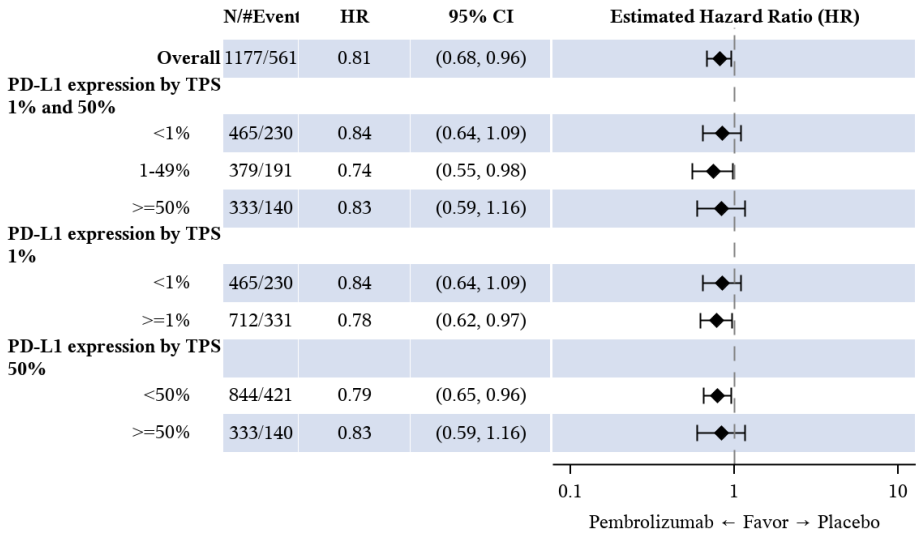


[1] For overall population, analysis is based on multivariate Cox regression model with treatment adjusted by the following covariates: stage (IB vs. II vs. IIIA), PD-L1 status (>=50% vs. 1-49% vs. <1%), adjuvant chemotherapy (yes vs. no), region (Western Europe vs. Eastern Europe vs. Rest of World vs. Asia), histology (squamous vs. non-squamous), and smoking status (never vs. former/current). For subgroups, analysis is based on Cox regression model with treatment as a covariate.

[2] If a subgroup variable has two levels and one level of the subgroup meets any criteria below, then this subgroup variable will not be displayed: (1) if the number of participants in a category of a subgroup variable is less than 50, (2) the number of events in a category of a subgroup variable is zero in one treatment arm, (3) the number of events in a category of a subgroup variable is less than 5 in the pooled arms.

Database Cutoff Date: 24JAN2023

Figure 15: Forest Plot of DFS Hazard Ratio by PD-L1 Expression (ITT Population) – IA3



For overall population and the PD-L1 subgroup, analysis is based on multivariate Cox regression model with treatment adjusted by the following covariates: stage (IB vs. II vs. IIIA), PD-L1 status (>=50% vs. 1-49% vs. <1%), adjuvant chemotherapy (yes vs. no), region (Western Europe vs. Eastern Europe vs. Rest of World vs. Asia), histology (squamous vs. non-squamous), and smoking status (never vs. former/current).
Database Cutoff Date: 24JAN2023

RESULTS IN THE POPULATION WITH ADJUVANT CHEMOTHERAPY

By inclusion criteria, adjuvant chemotherapy was not mandatory but considered for patients with stage IB (T ≥ 4 cm) and strongly recommended for stage II and IIIA, and was administered according to national and local guidelines. Adjuvant chemotherapy yes/no was a stratification factor. Overall, 86% of patients received adjuvant chemotherapy before pembrolizumab/placebo, this percentage was overall similar across subgroup by PD-L1 expression, and balanced between treatment arms.

All results below are based on the IA3.

Table 31: IA3 Analysis of Disease-Free Survival (Primary Censoring Rule) - Multivariate Analysis - ITT population – with adjuvant chemotherapy

Treatment	N	Number of Events (%)	Person-Months	Event Rate/100 Person-Months	Median DFS[a] (Months) (95% CI)	DFS Rate at Month 12 in %[a] (95% CI)	vs. Placebo	
							Hazard Ratio[b] (95% CI)[b]	p-Value[c]
Pembrolizumab	506	225 (44.5)	15754.5	1.4	53.8 (46.2, 70.4)	78.7 (74.8, 82.1)	0.76 (0.64, 0.91)	0.00150
Placebo	504	262 (52.0)	14614.8	1.8	40.5 (32.9, 47.4)	71.0 (66.8, 74.7)	---	---

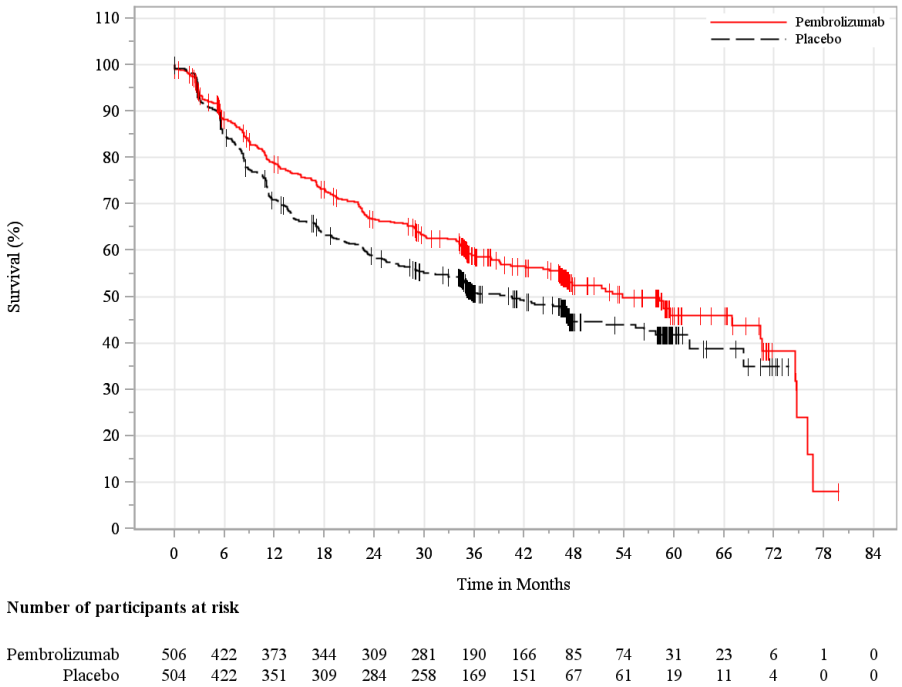
[a] From product-limit (Kaplan-Meier) method for censored data.

[b] Based on the multivariate Cox regression model with treatment adjusted by the following covariates: stage (IB vs. II vs. IIIA), PD-L1 status (≥50% vs. 1-49% vs. <1%), region (Western Europe vs. Eastern Europe vs. Rest of World vs. Asia), histology (squamous vs. non-squamous), and smoking status (never vs. former/current).

[c] One-sided p-value based on the Wald Test in the multivariate Cox regression model.

Database Cutoff Date: 24JAN2023

Figure 16: IA3 Kaplan-Meier Estimates of Disease-Free Survival (Primary Censoring Rule) (ITT population – with adjuvant chemotherapy)



Database Cutoff Date: 24JAN2023

Results of DFS based on the univariate Cox model were similar (HR 0.80; 95%CI 0.67, 0.96).

Table 32: IA3 Analysis of Overall Survival - Multivariate Analysis - (ITT Population – with adjuvant chemotherapy)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/100 Person-Months	Median OS[a] (Months) (95% CI)	OS Rate at Month 12 in %[a] (95% CI)	vs. Placebo	
							Hazard Ratio[b] (95% CI)[b]	p-Value[c]
Pembrolizumab	506	113 (22.3)	22810.0	0.5	Not Reached (., .)	95.6 (93.4, 97.1)	0.79 (0.62, 1.01)	0.03224
Placebo	504	138 (27.4)	22313.1	0.6	Not Reached (., .)	95.0 (92.7, 96.6)	---	---

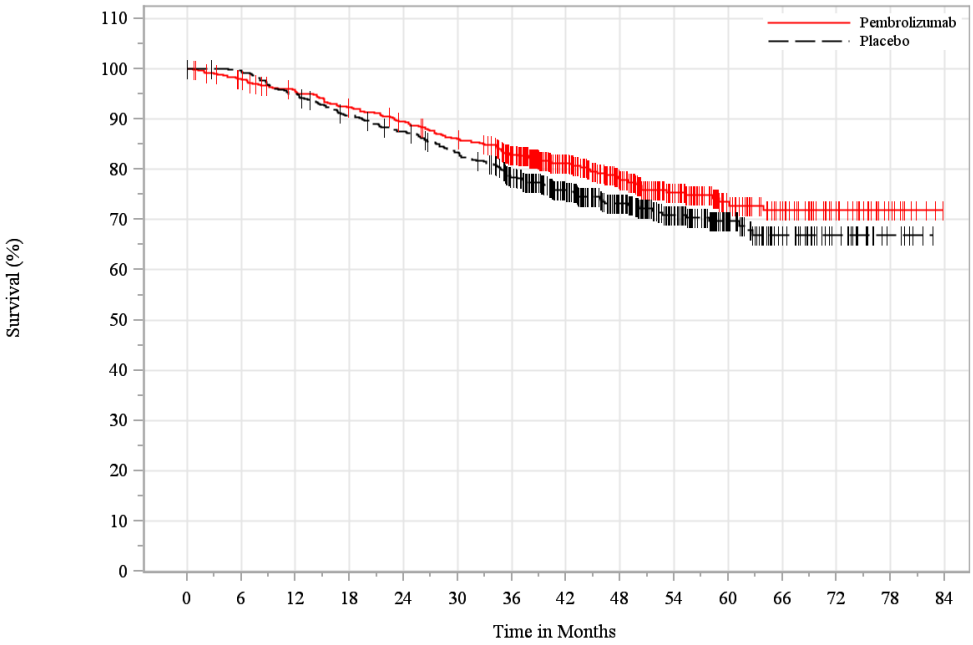
[a] From product-limit (Kaplan-Meier) method for censored data.

[b] Based on the multivariate Cox regression model with treatment adjusted by the following covariates: stage (IB vs. II vs. IIIA), PD-L1 status (≥50% vs. 1-49% vs. <1%), region (Western Europe vs. Eastern Europe vs. Rest of World vs. Asia), histology (squamous vs. non-squamous), and smoking status (never vs. former/current).

[c] One-sided p-value based on the Wald Test in the multivariate Cox regression model.

Database Cutoff Date: 24JAN2023

Figure 17: IA3 Kaplan-Meier Estimates of Overall Survival (ITT population – with adjuvant chemotherapy)



Number of participants at risk

Pembrolizumab	506	490	472	455	439	420	379	302	221	155	96	64	38	12	0
Placebo	504	500	477	452	435	411	362	288	219	148	83	50	30	7	0

Database Cutoff Date: 24JAN2023

Table 33: Subgroup Analysis of Disease-free Survival - Multivariate Analysis (ITT Population with adjuvant chemotherapy)

	Pembrolizumab (N=506)			Placebo (N=504)			Pembrolizumab vs. Placebo
	N	Number (%) of Events		N	Number (%) of Events		Hazard Ratio (95% CI)[a]
Overall	**506**	**225**	**(44.5)**	**504**	**262**	**(52.0)**	**0.76 (0.64,0.91)**
Age Category							
< 65 years	264	113	(42.8)	252	129	(51.2)	0.75 (0.58, 0.97)
>= 65 years	242	112	(46.3)	252	133	(52.8)	0.75 (0.58, 0.98)
Age Category							
< 65 years	264	113	(42.8)	252	129	(51.2)	0.75 (0.58, 0.97)
65 - 74 years	211	95	(45.0)	222	113	(50.9)	0.77 (0.58, 1.02)
75 - 84 years	31	17	(54.8)	30	20	(66.7)	0.70 (0.35, 1.39)
Age Category							
< 70 years	384	166	(43.2)	382	195	(51.0)	0.76 (0.62, 0.94)
>= 70 years	122	59	(48.4)	122	67	(54.9)	0.73 (0.51, 1.06)
Age Category							
< 75 years	475	208	(43.8)	474	242	(51.1)	0.77 (0.63, 0.92)
>= 75 years	31	17	(54.8)	30	20	(66.7)	0.70 (0.35, 1.39)
Gender							
M	339	149	(44.0)	347	175	(50.4)	0.81 (0.65, 1.02)
F	167	76	(45.5)	157	87	(55.4)	0.70 (0.51, 0.96)
Race							
White	387	167	(43.2)	392	194	(49.5)	0.80 (0.65, 0.98)
All Others	98	49	(50.0)	94	58	(61.7)	0.67 (0.45, 1.01)
Region: EU vs non-EU							
EU	343	153	(44.6)	342	178	(52.0)	0.76 (0.61, 0.95)
Non-EU	163	72	(44.2)	162	84	(51.9)	0.75 (0.55, 1.04)
Geographic Region							
Western Europe	261	117	(44.8)	266	141	(53.0)	0.75 (0.58, 0.96)
Eastern Europe	105	49	(46.7)	96	46	(47.9)	0.84 (0.56, 1.26)
Rest of World	53	17	(32.1)	55	23	(41.8)	0.75 (0.38, 1.44)
Asia	87	42	(48.3)	87	52	(59.8)	0.71 (0.47, 1.08)
Stage at Baseline per AJCC V7							
IB	60	19	(31.7)	57	21	(36.8)	0.66 (0.33, 1.33)
II	283	114	(40.3)	295	143	(48.5)	0.73 (0.57,0.94)
IIIA	163	92	(56.4)	150	96	(64.0)	0.82 (0.61,1.09)
Smoking status							
Never Smoker	80	46	(57.5)	57	38	(66.7)	0.72 (0.46, 1.14)
Former Smoker	362	157	(43.4)	375	187	(49.9)	0.81 (0.65, 1.00)
Current Smoker	64	22	(34.4)	72	37	(51.4)	0.45 (0.25, 0.79)
Histology							
Squamous	157	57	(36.3)	184	75	(40.8)	0.85 (0.60, 1.20)
Non-squamous	349	168	(48.1)	320	187	(58.4)	0.72 (0.59, 0.89)
ECOG							
0	326	145	(44.5)	292	148	(50.7)	0.76 (0.61, 0.96)
1	180	80	(44.4)	212	114	(53.8)	0.77 (0.57,1.03)
EGFR mutation status							
N	190	90	(47.4)	192	109	(56.8)	0.75 (0.56, 1.00)
Y	36	20	(55.6)	30	24	(80.0)	0.44 (0.22, 0.87)
Unknown	280	115	(41.1)	282	129	(45.7)	0.80 (0.62, 1.04)
PD-L1 expression							
<1%	198	92	(46.5)	198	108	(54.5)	0.75 (0.56, 0.99)
1-49%	165	76	(46.1)	165	91	(55.2)	0.70 (0.51, 0.96)
>=50%	143	57	(39.9)	141	63	(44.7)	0.83 (0.57, 1.19)
PD-L1 expression by TPS 1%							
TPS <1%	198	92	(46.5)	198	108	(54.5)	0.75 (0.56, 0.99)
TPS >=1%	308	133	(43.2)	306	154	(50.3)	0.76 (0.60, 0.96)
PD-L1 expression by TPS 50%							
TPS <50%	363	168	(46.3)	363	199	(54.8)	0.72 (0.59, 0.89)
TPS >=50%	143	57	(39.9)	141	63	(44.7)	0.83 (0.57, 1.19)

[a] For overall population and all subgroups, analysis is based on multivariate Cox regression model with treatment adjusted by the following covariates: stage (IB vs. II vs. IIIA), PD-L1 status (≥50% vs. 1-49% vs. <1%), region (Western Europe vs. Eastern Europe vs. Rest of World vs. Asia), histology (squamous vs. non-squamous), and smoking status (never vs. former/current).
If the number of participants in a category of a subgroup variable is less than 50 (except EGFR mutation status), or the number of events in a category of a subgroup variable is zero in one treatment arm, or the number of events in a category of a subgroup variable is less than 5 in the pooled arms, the subgroup analysis will not be performed for this category of the subgroup variable.
Database Cutoff Date: 24JAN2023.

Table 34: IA3 Subgroup Analysis of Overall Survival - Multivariate Analysis (ITT Population with adjuvant chemotherapy)

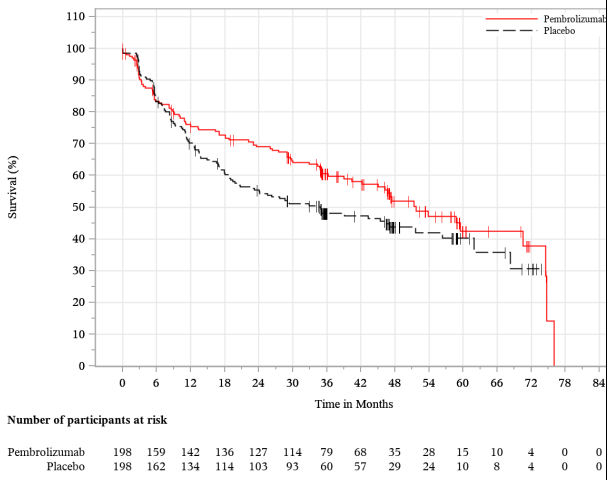
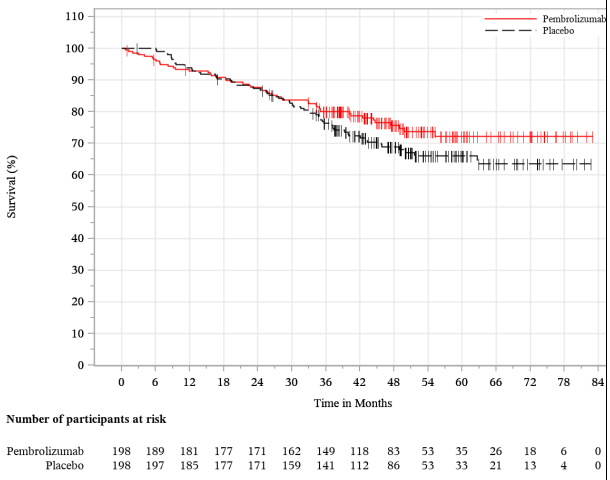
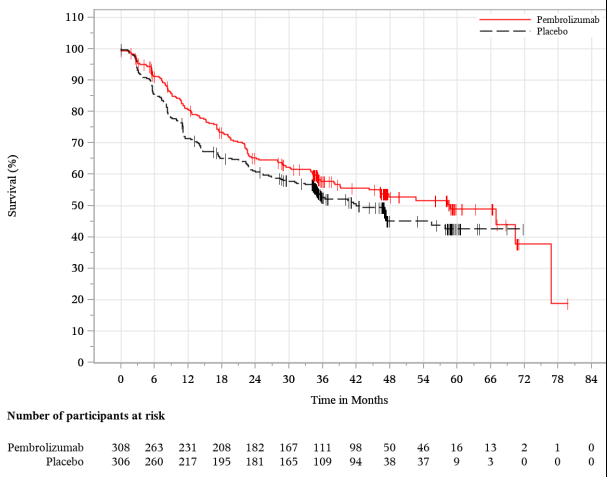
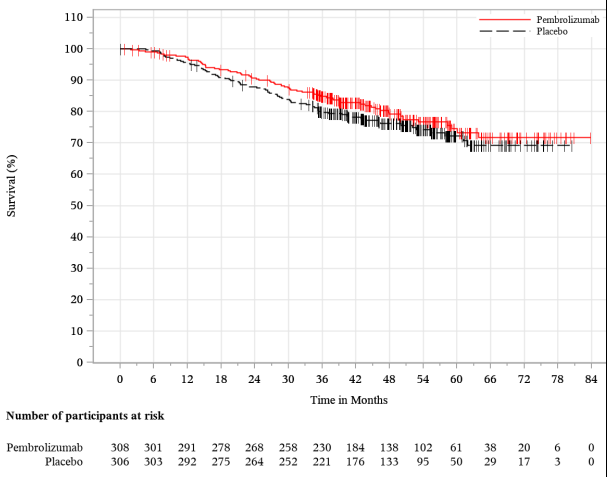
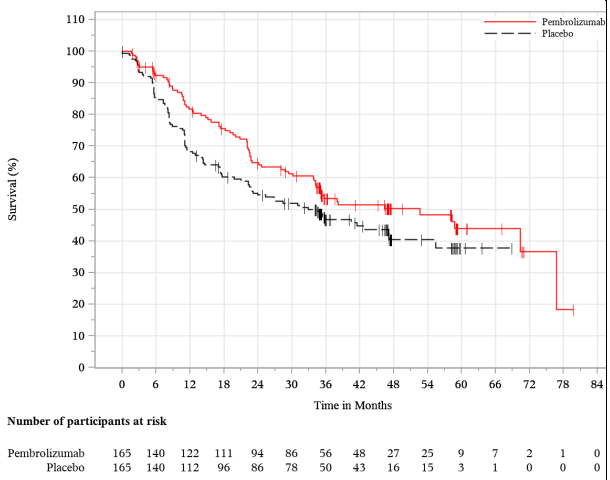
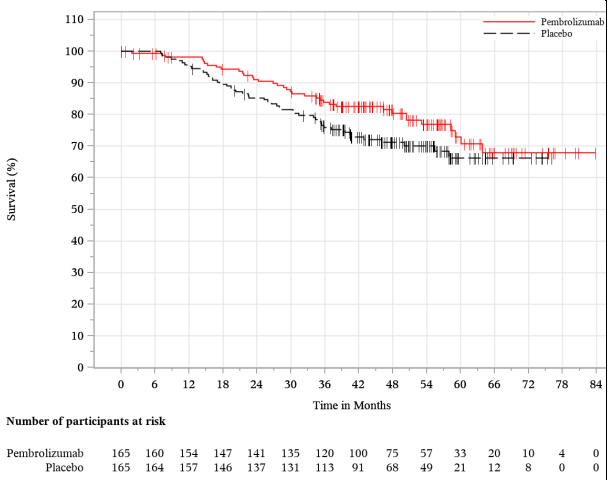
	Pembrolizumab (N=506)			Placebo (N=504)			Pembrolizumab vs. Placebo
	N	Number of Events	(%)	N	Number of Events	(%)	Hazard Ratio (95% CI)[a]
Overall	**506**	**113**	**(22.3)**	**504**	**138**	**(27.4)**	**0.79 (0.62, 1.01)**
Age Category							
< 65 years	264	55	(20.8)	252	58	(23.0)	0.90 (0.62, 1.30)
>= 65 years	242	58	(24.0)	252	80	(31.7)	0.70 (0.50, 0.99)
Age Category							
< 65 years	264	55	(20.8)	252	58	(23.0)	0.90 (0.62, 1.30)
65 - 74 years	211	43	(20.4)	222	68	(30.6)	0.61 (0.41, 0.90)
75 - 84 years	31	15	(48.4)	30	12	(40.0)	1.23 (0.55, 2.72)
Age Category							
< 70 years	384	77	(20.1)	382	94	(24.6)	0.80 (0.59, 1.09)
>= 70 years	122	36	(29.5)	122	44	(36.1)	0.70 (0.44, 1.11)
Age Category							
< 75 years	475	98	(20.6)	474	126	(26.6)	0.75 (0.58, 0.98)
>= 75 years	31	15	(48.4)	30	12	(40.0)	1.23 (0.55, 2.72)
Gender							
M	339	82	(24.2)	347	94	(27.1)	0.88 (0.65, 1.18)
F	167	31	(18.6)	157	44	(28.0)	0.65 (0.40,1.03)
Race							
White	387	87	(22.5)	392	111	(28.3)	0.77 (0.58, 1.03)
All Others	98	21	(21.4)	94	23	(24.5)	0.80 (0.43, 1.51)
Region: EU vs non-EU							
EU	343	82	(23.9)	342	97	(28.4)	0.82 (0.61, 1.11)
Non-EU	163	31	(19.0)	162	41	(25.3)	0.69 (0.43, 1.11)
Geographic Region							
Western Europe	261	57	(21.8)	266	71	(26.7)	0.81 (0.57, 1.14)
Eastern Europe	105	31	(29.5)	96	34	(35.4)	0.81 (0.50, 1.32)
Rest of World	53	8	(15.1)	55	16	(29.1)	0.52 (0.22, 1.23)
Asia	87	17	(19.5)	87	17	(19.5)	1.01 (0.51, 1.99)
Stage at Baseline per AJCC V7							
IB	60	9	(15.0)	57	12	(21.1)	0.60 (0.24, 1.55)
II	283	60	(21.2)	295	76	(25.8)	0.81 (0.58, 1.14)
IIIA	163	44	(27.0)	150	49	(32.7)	0.78 (0.51, 1.18)
Smoking status							
Never Smoker	80	18	(22.5)	57	18	(31.6)	0.70 (0.35, 1.37)
Former Smoker	362	84	(23.2)	375	100	(26.7)	0.85 (0.64,1.14)
Current Smoker	64	11	(17.2)	72	20	(27.8)	0.61 (0.29,1.31)
Histology							
Squamous	157	34	(21.7)	184	48	(26.1)	0.76 (0.49, 1.19)
Non-squamous	349	79	(22.6)	320	90	(28.1)	0.79 (0.59, 1.07)
ECOG							
0	326	70	(21.5)	292	70	(24.0)	0.86 (0.62, 1.20)
1	180	43	(23.9)	212	68	(32.1)	0.72 (0.49, 1.06)
EGFR mutation status							
N	190	46	(24.2)	192	51	(26.6)	0.91 (0.60, 1.36)
Y	36	6	(16.7)	30	12	(40.0)	0.35 (0.13, 0.98)
Unknown	280	61	(21.8)	282	75	(26.6)	0.78 (0.56, 1.10)
PD-L1 expression							
<1%	198	48	(24.2)	198	62	(31.3)	0.78 (0.53, 1.14)
1-49%	165	36	(21.8)	165	48	(29.1)	0.69 (0.45, 1.08)
>=50%	143	29	(20.3)	141	28	(19.9)	0.93 (0.55, 1.57)
PD-L1 expression by TPS 1%							
TPS <1%	198	48	(24.2)	198	62	(31.3)	0.78 (0.53, 1.14)
TPS >=1%	308	65	(21.1)	306	76	(24.8)	0.79 (0.57, 1.10)
PD-L1 expression by TPS 50%							
TPS <50%	363	84	(23.1)	363	110	(30.3)	0.74 (0.55, 0.98)
TPS >=50%	143	29	(20.3)	141	28	(19.9)	0.93 (0.55, 1.57)

[a] For overall population and all subgroups, analysis is based on multivariate Cox regression model with treatment adjusted by the following covariates: stage (IB vs. II vs. IIIA), PD-L1 status (≥50% vs. 1-49% vs. <1%), region (Western Europe vs. Eastern Europe vs. Rest of World vs. Asia), histology (squamous vs. non-squamous), and smoking status (never vs. former/current).

If the number of participants in a category of a subgroup variable is less than 50 (except EGFR mutation status), or the number of events in a category of a subgroup variable is zero in one treatment arm, or the number of events in a category of a subgroup variable is less than 5 in the pooled arms, the subgroup analysis will not be performed for this category of the subgroup variable.

Database Cutoff Date: 24JAN2023.

Figure 18: IA3 Kaplan-Meier Estimates by PD-L1 - ITT population – with adjuvant chemotherapy

DFS (primary censoring rule)	OS (primary analysis)
TPS < 1%	**TPS < 1%**
	
TPS >= 1%	**TPS >= 1%**
	
TPS = 1-49%	**TPS = 1-49%**
	
TPS >= 50%	**TPS >= 50%**

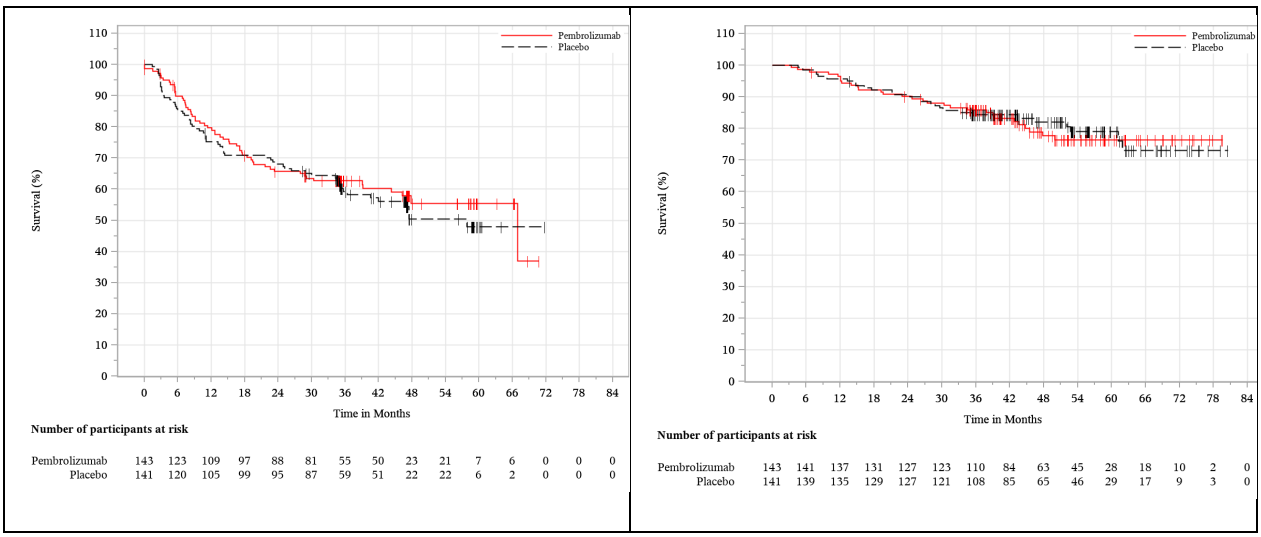
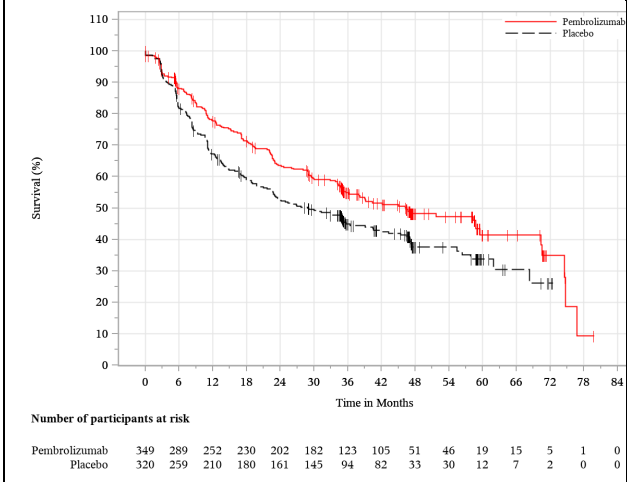
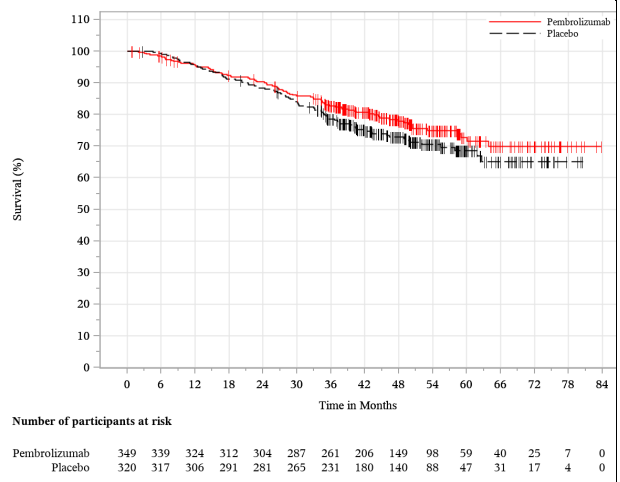
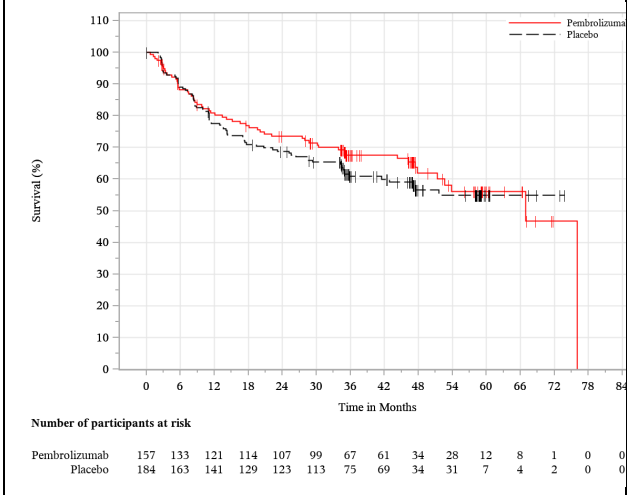
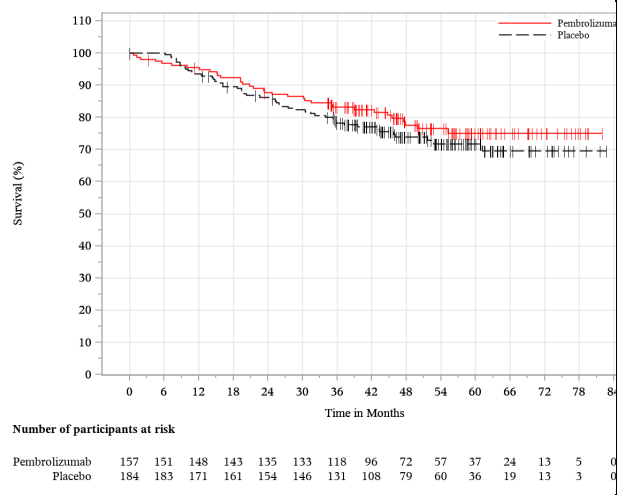


Figure 19: IA3 Kaplan-Meier Estimates <u>by histology</u> - ITT population – with adjuvant chemotherapy

DFS (primary censoring rule)	OS (primary analysis)
Non-squamous histology	**Non-squamous histology**
	
Squamous histology	**Squamous histology**
	

Summary of main study

The following table summarises the efficacy results from the main study supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 35: S**ummary of Efficacy for trial KEYNOTE-091**

Title: A randomized, phase 3 trial with anti-PD-1 monoclonal antibody pembrolizumab (MK-3475) versus placebo for patients with early stage NSCLC after resection and completion of standard adjuvant therapy (PEARLS) KEYNOTE-091			
Study identifier	P091V01MK3475 (IND: 116,833, EudraCT: 2015-000575-27, NCT: 02504372, Intergroup Study: EORTC-1416-LCG, ETOP Trial Number: ETOP-8-15)		
Design	Phase 3, two-arm, multicentre, triple-blinded, randomized, placebo-controlled study		
	Duration of main phase:		The first patient first visit was 10-NOV-2015; the study is ongoing.
	Duration of Run-in phase:		not applicable
	Duration of Extension phase:		not applicable
Hypothesis	Superiority		
Treatments groups	Pembrolizumab		200 mg IV infusion Q3W for up to 18 cycles (approximately 1 year), 590 participants were randomized.
	Placebo		Normal saline solution dosed and administered in the same manner as the investigational product, 587 participants were randomized.
Endpoints and definitions	Dual Primary endpoint	Disease-free survival (DFS), overall study population	DFS was defined as the time from randomization to either the date of disease recurrence or death (whatever the cause) as assessed by the investigator. Recurrence of disease was defined as local regional recurrence, a distant (metastatic) recurrence, or a second primary cancer. Occurrence of a second extra-pulmonary malignancy was considered to be an event.
	Dual Primary endpoint	DFS, PD-L1 TPS ⩾50%	DFS
	Secondary endpoint	DFS, PD-L1 TPS ⩾1%	DFS
	Secondary endpoint	overall survival (OS), overall study population	OS was defined as the time from randomization to the date of death (whatever the cause).
	Secondary endpoint	OS, PD-L1 TPS ⩾50%	OS
	Secondary endpoint	OS, PD-L1 TPS ⩾1%	OS
Database lock	The last patient last visit was 20-SEP-2021, which was the data cutoff		
Results and Analysis			
Analysis description	**Primary Analysis – DFS, overall study population** DFS in the overall study population was prespecified and formally tested with the multiplicity-adjusted, one-sided p-value boundary of 0.00564.		
Analysis population and time point description	Intent-to-treat (ITT) population (overall study population) Interim Analysis 2 (IA2; data cut-off 20-SEP-2021)		

Descriptive statistics and estimate variability	Treatment group	Pembrolizumab	Placebo
	Number of subjects	590	587
	DFS, overall study population (median)	53.6 months	42.0 months
	95% confidence interval (CI)	39.2, not reached (NR)	31.3, NR
Effect estimate per comparison	Dual Primary endpoint	Comparison groups	Pembrolizumab Placebo
		Hazard ratio (HR)	0.76
		95% CI	0.63, 0.91
		P-value	0.00143
Notes	At IA2, the success criterion was met for one of the dual primary endpoints of DFS in the overall study population. The result was statistically significant compared with the prespecified p-value boundary. The dual primary endpoint DFS in PD-L1 ≥50% population was tested at IA2 but was not statistically significant, thus was retested at IA3 (see below).		
Analysis description	**Dual Primary Analysis – DFS, PD-L1 TPS ⩾50%** DFS in the TPS ⩾50% subgroup was prespecified and formally retested at IA3 with the multiplicity-adjusted, one-sided p-value boundary of 0.01038.		
Analysis population and time point description	ITT population (PD-L1 TPS ⩾50%) **Interim Analysis 3 (IA3; data cut-off 24-JAN-2023) (FA for DFS)**		
Descriptive statistics and estimate variability	Treatment group	Pembrolizumab	Placebo
	Number of subjects	168	165
	DFS, PD-L1 TPS ⩾50%) (median)	67	47.6
Effect estimate per comparison	Dual Primary endpoint	Comparison groups	Pembrolizumab Placebo
		HR	0.83
		95% CI	0.59, 1.16
		P-value	0.13499
Notes	At IA3, the DFS in the TPS ≥50% subgroup was not statistically significant.		
Analysis description	**Secondary analysis – DFS, PD-L1 TPS ⩾1%** DFS in the TPS ⩾1% subgroup was prespecified but could not be formally tested because the protocol multiplicity strategy requires a statistically significant DFS in the TPS ⩾50% subgroup to be demonstrated first, which was not showed at IA2.		
Analysis description	**Secondary analysis – OS, overall study population** The OS in the overall study population was prespecified; given DFS was statistically significant in the overall study population, OS in the overall study population was formally tested with the multiplicity-adjusted p-value.		
Analysis population and time point description	ITT population (overall study population) IA3 (data cutoff 24-JAN-2023)		
Descriptive statistics and estimate variability	Treatment group	Pembrolizumab	Placebo
	Number of subjects	590	587
	OS, overall study population (median)	NR	NR

Effect estimate per comparison	Secondary endpoint	Comparison groups	Pembrolizumab Placebo
		HR	0.87
		95% CI	0.69, 1.10
		P-value	0.11792
Notes	The observed p-value did not cross the prespecified p-value boundary at IA2 and also at IA3 and will continue to be tested at the next analysis.		
Analysis description	**Secondary analysis – OS, PD-L1 TPS ⩾50%** The OS in the TPS ⩾50% subgroup was prespecified; given DFS was statistically significant in the overall study population, OS in participants with PD L1 TPS ⩾50% NSCLC was formally tested		
Analysis population and time point description	ITT population (PD-L1 TPS ⩾50%) IA3 (data cutoff 24-JAN-2023)		
Descriptive statistics and estimate variability	Treatment group	Pembrolizumab	Placebo
	Number of subjects	168	165
	OS, PD-L1 TPS ⩾50% (median)	NR	NR
	95% CI	NR, NR	NR, NR
Effect estimate per comparison	Secondary endpoint	Comparison groups	Pembrolizumab Placebo
		HR	0.93
		95% CI	0.57, 1.50
		P-value	0.3778
Notes	The observed p-value did not cross the prespecified p-value boundary at IA2 and at IA3 and will continue to be tested at the next analysis.		
Analysis description	**Secondary analysis – OS, PD-L1 TPS ⩾1%** The OS in the TPS ⩾1% subgroup was prespecified but was not formally tested at IA2 given that a statistically significant OS in participants with TPS ⩾50% was not demonstrated.		

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

Not performed

Clinical studies in special populations

See subgroup analyses according to age groups (tables 56 and 57).

2.4.3. Discussion on clinical efficacy

The MAH for Keytruda initially sought the following extension of indication: "KEYTRUDA as monotherapy is indicated for the adjuvant treatment of adults with Stage IB (T2a ≥ 4 cm), II or IIIA non-small cell lung carcinoma who have undergone complete resection." During the procedure, the MAH updated the requested indication to "KEYTRUDA as monotherapy is indicated for the adjuvant treatment of adults with non-small cell lung carcinoma who are at high risk of recurrence following complete resection and platinum-based chemotherapy (for selection criteria, see section 5.1)".

Design and conduct of clinical studies

The pivotal study is KEYNOTE-091/PEARLS study (EORTC-1416/ETOP-8-15), a randomized, phase 3 trial testing adjuvant pembrolizumab after primary surgical resection (R0) of NSCLC, and adjuvant chemotherapy if indicated. Patients were eligible regardless of the mutational profile of the tumour or histology, as well as regardless of PD-L1 status, which was assessed centrally as TPS score with IHC 22C3 antibody (IUO). Tumours were to be stage IB with T≥4 cm, II-IIIA NSCLC according to AJCC staging 7th in place at the time of study start (2015). Adjuvant chemotherapy was not mandatory but recommended according to guidelines. Overall, the inclusion/exclusion criteria are detailed and well define the population under study.

Patients received 18 cycles every 3 weeks of pembrolizumab/placebo (i.e. one year of treatment). Baseline imaging was performed to confirm no evidence of disease, and imaging assessment was continued initially every 12 weeks during treatment. This is considered acceptable.

Dual primary endpoints were DFS in the ITT and in the strongly PD-L1 positive (TPS≥50%) populations, as assessed by investigator.

Sample size calculation and power for DFS and OS endpoints was correctly conducted. Randomization was well conducted and stratified by stage, adjuvant chemotherapy, PD-L1 status and regions, which are considered appropriate, although it is unclear why histology (squamous vs non-squamous) was not used as stratification factor. The study was conducted in triple blind, with the exception of the pharmacist, which is considered acceptable. The statistical methods were generally adequate and well described.

Overall, the study appears well conducted. Collaterally, a problem in data transfer from EORTC to sponsor due to the incompatible date formatting were found, although related only to the protocol deviations' data listing and it's reassuring that the MAH confirmed that this problem did not affect any other dataset, with no impact on any analysis results.

Efficacy data and additional analyses

The MAH initially submitted the results of the interim analysis 2 (data cut-off 20 Sept 2021). A total of 1177 patients were randomized (590 in the pembrolizumab group and 587 in the placebo group).

It should be noted that less patients in the pembrolizumab group were able to complete the treatment as planned as compared to placebo (51.7% vs 65.6%), with higher rate of treatment discontinuation, the main reason being progressive disease in the placebo arm (12.4% vs 21.9%), and study drug toxicity in the pembrolizumab arm (19.8% vs 3.8%). Regarding the latter, the AEs leading to pembrolizumab discontinuation were however in line with pembrolizumab's known safety profile, and the incidence of discontinuations due to drug-related AEs was similar in the KEYNOTE-091 safety dataset and the reference dataset for pembrolizumab in an adjuvant setting (see also Clinical safety section), as well as also with other anti-PD(L)1 agents in the same adjuvant NSCLC setting (IMpower010 ~18%[20]).

At the IA2, median FU was 32.4 months (range 0.6, 68). All patients had either completed 1 year of treatment or discontinued treatment. The minimum follow-up time of the last patient randomized to the data cut-off date of IA2 was 16.5 months (at least 6 months after completion of 1 year of treatment), which is of importance in an adjuvant setting.

In the ITT and in the PD-L1 TPS≥50% populations (including approximately 30% of patients), baseline characteristics are consistent, and balanced between treatment arms. A slight difference is however

[20] EMA/667840/2022 EPAR CHMP Assessment Report Tecentriq EMEA/H/C/004143/II/0064

noted in histology distribution in the ITT (squamous histology 32.5 vs 38.2%), more marked in some PD-L1 subgroup. It would have been preferred if KEYNOTE-091 was stratified by histology. In addition, due to the unknown EGFR mutational status in 57% of the enrolled population, any analysis on EGFR mutated NSCLC is speculative at present. The MAH confirmed that no further biomarker analysis of EGFR status is planned in this study. In line with the SA, the CHMP considered the patient population to be heterogeneous, and noted that the impact on the final indication of any potential contrasting results will be a matter of assessment at time of evaluation.

At the interim analysis 2, statistical significance was reached for DFS in the overall population. With 36% and 44% of DFS event in pembrolizumab and placebo arm, respectively, DFS HR was 0.76, 95% CI: 0.63, 0.91; p=0.00143, median DFS 53.6 vs 42 months, DFS rate at month 12 78.7% vs 71.6%. With the results of IA2, the CHMP concluded that it was not yet possible to assess the cure rate (if any in NSCLC) in the context of an adjuvant setting (see also EMA anticancer guideline[21]). The tendence of DFS KM curves to converge was considered not particularly reassuring, although curves were hardly interpretable after month 16 due to high rate of censoring, thus not able to support the assumption of an increased cure rate for pembrolizumab. It might be expected that generally most of the recurrence will occur within 5 years after NSCLC resection. It was acknowledged that the largest difference of events rates between both treatment arms was due to a lower event rate of distant metastasis in the pembrolizumab arm (11.5% vs 17.2%). However, a higher rate of death as first DFS event was observed in the pembrolizumab arm (27 vs 12). Of those, 11 vs 5 were deaths related to treatment emergent AEs, and 4 vs 0 was due to treatment-related AEs. The MAH's explanation that participants receiving placebo have more chances of disease recurrence or new malignancy as the first event can be followed. The possibility for fatal treatment-related events with pembrolizumab, also in an adjuvant setting, can occur and should be considered. It is reassuring that the overall total number of deaths in the pembrolizumab group was however lower than that observed in the placebo group (98 [16.6%] vs 111 [18.9%]).

Contrary to ITT, DFS in the subgroup with higher PD-L1 expression TPS≥50% (dual primary endpoint) was not statistically significant at IA2 (HR 0.82, 95% CI: 0.57, 1.18; p=0.13639). The lack of statistical success in the PD-L1 TPS ≥50% subpopulation, with better results in lower PD-L1 expressors 1-49% (DFS HR 0.67, 95%CI 0.48, 0.92) were unexpected, as of limited biological plausibility and inconsistent with respect to accumulating evidence for immunotherapy. It cannot be excluded that imbalances in histology distribution in the ITT (squamous histology 32.5 vs 38.2%), more marked in some PD-L1 subgroup, had a role in the unexpected results of this study. No convincing explanation to this observation was provided. This was noted.

OS was also not considered very helpful in taking any decision based on IA2: OS HR was 0.87 (95%CI 0.67, 1.15) in the ITT population, and 0.92 (95%CI 0.52, 1.62) in the high PD-L1 expressor subgroup, with overlapping KM curves in both populations, yet of difficult interpretation due to low number of events and high censoring from month 18 onwards. No further support can be expected from other intermediate endpoints (e.g. DMFS or DFS2), as the MAH confirmed that those data have not been collected.

In order to clarify the unexpected results in the PD-L1 subgroups, the MAH was requested to discuss also the PD-L1 assay: based on the information provided, no concern was raised about PD-L1 determination.

Based on the IA2 results, the CHMP concluded that biological plausibility and external validity of the DFS data according to PD-L1 expression were put into question and uncertainties on KEYNOTE-091 results prevented to grant an unrestricted indication. Further, although in the overall population OS HR point estimate was <1 with KM curves almost overlapping, OS data was considered immature to draw

[21] EMA/CHMP/205/95 Rev.6 Guideline on the clinical evaluation of anticancer medicinal products.

any conclusions. As such, it was decided to wait for more mature data of IA3 (i.e. final DFS analysis and more mature OS) for any regulatory decision, to alleviate those uncertainties and to allow more confidence on the ITT results as well as possibly on subgroups, especially given the adjuvant setting.

Patients reported outcomes were assessed as an exploratory endpoint. The global health status/quality of life score of the EORTC QLQ-30 did not show meaningful change with pembrolizumab as compared to placebo.

The CHMP raised concern over the results in the population having squamous histology (35%), as no benefit from the use of pembrolizumab over placebo was suggested in DFS (HR 1.08, 95%CI 0.77, 1.50) or in OS (HR 1.09, 95%CI 0.70, 1.71), while benefit of adjuvant pembrolizumab seemed driven by non-squamous histology. The lack of stratification by histology was considered an issue: baseline characteristics by histology showed some differences as compared to the ITT population, such as more males, fewer never smokers and fewer EGFR mutated (all expected) and less PD-L1 negative, as well as some differences within the squamous histology between treatment arms such as age and ECOG performance status (in favour of the pembrolizumab arm) and disease stage. According to the MAH, DFS result in the squamous histology was driven by the TPS ≥50% population (HR 1.86, 95% CI: 0.92, 3.77), which was not expected and may be due, in part, to the better-than-expected DFS in participants receiving placebo in this population.

At IA2, subgroup analysis by EGFR status showed in the ITT population benefit of pembrolizumab over placebo regardless of EGFR expression but higher in known EGFR mutated tumours. Although treatment arms were overall balanced in EGFR mutated patients, data were of difficult interpretation as EGFR mutational status was unknown for about 60% of study participants. Data in ALK positive disease were far more limited, with only 14 participants with ALK rearrangement (7 in each arm), as ALK mutation status was unknown in 64% of participants. To conclude, overall data may suggest an activity of pembrolizumab in the adjuvant setting regardless of EGFR mutation. For ALK positive disease, no conclusion can be drawn.

To date, targeted therapy is approved and indicated in EGFR mutated NSCLC tumours in the adjuvant setting, although this was not the case when the study started. The clinical relevance of adjuvant pembrolizumab in mutated tumours is unclear, especially when the changed treatment landscape is considered. It would have been preferred if further biomarker analysis of EGFR status in KEYNOTE-091 was planned by the MAH. The IA3 data confirmed however a numerically favourable trend in DFS (HR 0.44, 95%CI 0.22, 0.87) and OS (HR 0.35, 95%CI 0.13, 0.98) in patients with EGFR positive NSCLC, acknowledging the large confidence intervals due to the small sample size. Therefore, no reason is found to explicitly exclude EGFR mutated tumours from the adjuvant indication. The information that testing for genomic tumour aberrations/oncogenic drivers was not mandatory for enrolment, as well as the number of patients with EGFR positive/negative/undetermined status have been included in the SmPC section 5.1.

Patients who did not receive prior adjuvant chemotherapy did not show apparent benefit for adjuvant treatment with pembrolizumab as compared to placebo. Acknowledging that this subgroup was a minority (84 vs 83, approximately 15% of the ITT population), adjuvant chemotherapy was a stratification factor, thus strengthening the data. No imbalances are observed with regard to prior adjuvant chemotherapy among study arms, received by approximately 86% of participants in both treatment arms. The most common agents used were cisplatin/vinorelbine, carboplatin/vinorelbine, and carboplatin/paclitaxel. The median duration of exposure to prior adjuvant chemotherapy and median number of cycles (4) was similar in both treatment groups. Patients who did not receive adjuvant chemotherapy were older (although ECOG was similar), slightly more Asian, with lower disease stage, and more squamous histology. Overall, about 14% of patients with stage II disease and approximately 6% of patients with stage IIIA did not receive adjuvant chemotherapy. It might be

reasonable to assume that the investigator's choice of avoiding adjuvant chemotherapy had been based on differences in baseline characteristics that are likely not fully reportable.

In the population of participants who did not receive adjuvant chemotherapy, at IA2 DFS HR was 1.21 (95% CI: 0.73, 2.03), contrary to patients who received adjuvant chemotherapy (HR 0.73, 95%CI 0.60, 0.89). When broken down by PD-L1 subgroups, results in patients not receiving prior adjuvant chemotherapy should be interpreted with caution due to small numbers. The MAH did not elaborate on any possible explanation for the observed lack of effect in patients who did not receive adjuvant treatment, and it was unclear how to interpret such data, acknowledging the limited number of patients who did not receive adjuvant treatment.

Stage (according to AJCC 7th ed) was a stratification factor. Overall, a trend toward more limited benefit in the higher stage (IIIA) was observed, which seems counterintuitive. However, maturity progresses differently across prognostic subgroups, and there are still fewer events in the IB stage for a conclusive assessment.

The assessment of IA2 results did not allow the CHMP to conclude a positive benefit/risk of one year of adjuvant pembrolizumab vs placebo in a broad population, or to restrict the indication to best performing subgroup(s) with reasonable degree of confidence. As a result, more mature results were requested, corresponding to the pre-planned IA3 data (i.e. final analysis for DFS).

The IA3 results (data cut-off date 24-Jan-2023) provided by the MAH, included patients with a median FU of 46.7 months, approximately 13 months longer compared with IA2; the minimum follow-up of the last patient randomized was 32 months i.e. about 1.7 year after the end of 1-year adjuvant treatment.

DFS in the overall population was updated (but not statistically tested, as already significant at IA2) (HR 0.81; 95%CI 0.68-0.96; 45% vs 51% of DFS events). Although HR point estimate was slightly worse than IA2 (from 0.76 to 0.81), confidence interval was still below the unity. DFS in TPS≥50% was tested at IA3 but again did not reach statistical significance (HR 0.83; 95%CI 0.59-1.16), as well as OS in the overall population (HR 0.87; 95%CI 0.69-1.10; p=0.118; 23% vs 27% of OS events) and in the TPS≥50% (HR 0.93; 95%CI 0.57-1.50 p=0.38). It can be concluded that results are overall consistent with IA2 data.

Also, the results of the DFS subgroup analyses at IA3 are consistent with IA2, with no subgroup driving the results. Most of the subgroups have confidence interval crossing 1, with HR point estimate >1 in squamous disease, no prior adjuvant chemotherapy, and stage IB.

With the submission of IA3 data, the MAH decided to seek a more limited indication by excluding patients who have not received previous adjuvant chemotherapy treatment. The MAH has justified the new proposal as IA2 and IA3 data were consistent, because limiting the population to those patients receiving adjuvant chemotherapy, the DFS HR point estimates for all subgroups were <1. Baseline characteristics of the newly proposed population treated with adjuvant chemotherapy (85% of the overall population) are balanced between treatment arms, being "adjuvant chemotherapy yes/no" a stratification factor. At IA3, the results in the population with adjuvant chemotherapy are numerically more favourable as compared to the ITT:

- DFS HR 0.76 (95%CI 0.64, 0.91), 44% vs 52 % events, medians 54 vs 40 months, DFS rate at 24 months 67% vs 59%. KM curves open after month 6 and remain separated with apparently constant distance.

- OS HR 0.79 (95%CI 0.62, 1.01), 22% vs 27% events, medians NR in either arm, pembrolizumab curve is marginally higher than placebo after 12 months but uninterpretable after month 36.

In the population treated with adjuvant chemotherapy, DFS HR point estimates for subgroups are all <1, although the same trend seen in the ITT is generally observed, e.g. worse outcome in PD-L1≥50% than in PD-L1<50%, and worse estimates in squamous histology rather than in the non-squamous. Regarding subgroups analysis for OS, HR point estimates for subgroups are all <1, with the exception of patients over 75 years. No subgroups appear to drive the results.

While it is agreed that the subgroup of patients who did not receive adjuvant chemotherapy showed negative DFS trend (HR 1.16; 95%CI 0.73, 1.84), biological plausibility of the choice of this patient population is not discussed and not clear. External evidence may however support the proposed population, as adjuvant Tecentriq in NSCLC was approved after adjuvant chemotherapy only, although the replication of findings is not fully evaluable as study IMpower010 enrolled only patients who have received prior adjuvant chemotherapy, differently from KEYNOTE-091. From a statistical perspective, however, adjuvant chemotherapy yes/no was a stratification factor, and pre-specified subgroup analyses, which strengthened the result.

Uncertainty remains in terms of OS maturity. The MAH will submit updated OS data as part of the imposed PAES (see Annex II). In addition, the MAH will submit data on treatment post-progression, and particularly on the uptake and activity of anti-PD(L)1 in patients previously treated with adjuvant pembrolizumab.

2.4.4. Conclusions on the clinical efficacy

KEYNOTE-091 study showed, at the IA2, statistically significant improvement in DFS for pembrolizumab over placebo when used for one year duration as adjuvant treatment after complete NSCLC resection in the ITT population. The results of the more mature IA3 confirmed IA2 data, providing reassurance that the benefit of adjuvant pembrolizumab can be maintained with longer follow-up.

The indication was restricted to patients who have been treated with prior adjuvant chemotherapy excluding a (small) subgroup of patients not receiving prior adjuvant chemotherapy in whom DFS detriment cannot be excluded. The overall results in the population after adjuvant chemotherapy suggest a relevant DFS benefit and positive OS trend for pembrolizumab vs placebo. In addition, this population will be aligned with indications of other medicines from the same class approved in the adjuvant NSCLC setting.

Uncertainty remains in terms of OS maturity. The MAH will submit updated OS data as part of the imposed PAES (see Annex II). In addition, the MAH will submit data on treatment post-progression, and particularly on the uptake and activity of anti-PD(L)1 in patients previously treated with adjuvant pembrolizumab.

The following measure is considered necessary to address issues related to clinical efficacy:

Post-authorisation efficacy study (PAES): in order to further characterise the efficacy of Keytruda for the adjuvant treatment of adults with non-small cell lung carcinoma who are at high risk of recurrence, the MAH should submit the results of the final OS analysis of study KEYNOTE-091. The MAH should submit updated data on treatment post-progression, and particularly on the uptake and activity of anti-PD(L)1 in patients previously treated with adjuvant pembrolizumab.

2.5. Clinical safety

Introduction

General safety profile

Pembrolizumab is most commonly associated with immune related adverse reactions. Most of these, including severe reactions, resolved following initiation of appropriate medical therapy or withdrawal of pembrolizumab.

When used as **monotherapy**, the most frequent adverse reactions with pembrolizumab were fatigue (30%) and diarrhoea (22%). The majority of adverse reactions reported for monotherapy were of Grades 1 or 2 severity. The most serious adverse reactions were immune-related adverse reactions and severe infusion-related reactions. The incidences of immune-related adverse reactions were 36.9% all Grades and 8.7% for Grades 3-5 for monotherapy in the adjuvant setting and 24.5% all Grades and 6.3% for Grades 3-5 in the metastatic setting.

Safety Datasets used in the present submission

Safety results for pembrolizumab are presented for the following 4 datasets:

- **KEYNOTE-091 Pembrolizumab** Dataset (N=580): Stage IB (T2a ≥4 cm), Stage II, or Stage IIIA NSCLC who participated in KEYNOTE-091 treated with adjuvant pembrolizumab monotherapy.
- **KEYNOTE-091 Placebo** Dataset (N=581): Stage IB (T2a ≥4 cm), Stage II, or Stage IIIA NSCLC who participated in KEYNOTE-091 treated with placebo.
- **Pembrolizumab Monotherapy RSD** [EU] (N=6185): The 6185 pembrolizumab-treated participants from the RSD consists of 2076 participants with advanced melanoma and 2022 participants with NSCLC (with pembrolizumab used as first-line treatment). In addition, this dataset includes participants with cHL, urothelial cancer, CRC, HNSCC. This dataset represents the established safety profile for pembrolizumab monotherapy.
- **Cumulative Reference Safety Dataset** (N=10,997): Participants from the Safety Dataset, the RSD, and participants treated with pembrolizumab in the studies listed in the footnotes of the data tables in this document and the ISS comprise the Cumulative Running Safety Dataset.

NOTE: safety data of KEYNOTE-091 are presented at IA2 (data cutoff 20-SEP-2021), unless noted otherwise.

Patient exposure

KEYNOTE-091 is an ongoing study. As of the data cutoff on 20-SEP-2021, n=1161 participants had received at least one dose of study treatment, including 580 in the pembrolizumab group and 581 in the placebo group. No participants were still receiving treatment. Thus, drug exposure was not changed at IA3 (data cut-off 24-Jan-2023). Pembrolizumab/placebo was given for up to 1 year.

The following table shows a summary on drug exposure.

Table 36: **summary of drug exposure (APaT population)**

	KN091 Data for Pembrolizumab (N=580)	KN091 Data for Placebo (N=581)	Reference Safety Dataset for Pembrolizumab[i] (N=6185)	Cumulative Running Safety Dataset for Pembrolizumab[j] (N=10997)
Duration On Therapy (months)				
Mean	8.7	10.0	7.5	7.5
Median	11.7	11.8	4.9	5.1
SD	4.50	3.59	7.03	6.92
Range	0.03 to 18.86	0.03 to 18.10	0.03 to 30.62	0.03 to 40.05
Number of Administrations				
Mean	12.8	14.9	12.0	11.7
Median	17.0	18.0	8.0	8.0
SD	6.22	4.97	10.43	10.08
Range	1.00 to 18.00	1.00 to 19.00	1.00 to 59.00	1.00 to 59.00

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

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

[j] 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 cohorts B ,B2, C and D, KN013 cohorts 3 and 4A, P017, KN024, KN028 cohorts B4, C1 and A4, KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN057, KN059 cohorts 1 and 3, KN061, KN062, KN087, KN091, KN158 cohorts E, G, TMB-H and K, KN164 cohorts A and B, KN170, KN177, KN180, KN181, KN204, KN224, KN361, KN427, KN564, KN629 and KN716.

Pembrolizumab Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 03APR2020, KN716: 21JUN2021)

Pembrolizumab Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEPT2018, KN091: 20SEP2021)

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

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

Pembrolizumab Database cutoff date for cHL (KN013-Cohort 3: 28SEP2018, KN087: 15MAR2021, KN204: 16JAN2020)

Pembrolizumab Database cutoff date for Bladder (KN012-Urothelial: 01SEP2015, KN045: 26OCT2017, KN052: 26SEP2018, KN057: 24MAY2019, KN361: 29APR2020)

Pembrolizumab Database cutoff date for Colorectal (KN164-Cohorts A and B: 09SEP2019, KN177: 19FEB2020)

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

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

Pembrolizumab Database cutoff date for HCC (KN224: 05JUN2019)

Pembrolizumab Database cutoff date for MCC (P017: 06FEB2018)

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

Pembrolizumab Database cutoff date for Renal Cell Carcinoma (KN427 Cohort A: 07SEP2018, KN564: 14JUN2021)

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

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

Pembrolizumab Database cutoff date for MSI-H (KN158: 05OCT2020)

Pembrolizumab Database cutoff date for CSCC (KN629: 29JUL2020)

The following table shows the distribution of patients by drug exposure duration categories:

Table 37: drug exposure by duration (APaT population)

	KN091 Data for Pembrolizumab (N=580)			KN091 Data for Placebo (N=581)			Reference Safety Dataset for Pembrolizumab[i] (N=6185)			Cumulative Running Safety Dataset for Pembrolizumab[j] (N=10997)		
	n	(%)	Person-years	n	(%)	Person-years	n	(%)	Person-years	n	(%)	Person-years
Duration of exposure												
>0 m	580	(100.0)	(418.7)	581	(100.0)	(485.7)	6,185	(100.0)	(3,875.4)	10,997	(100.0)	(6,856.5)
>=1 m	538	(92.8)	(417.4)	569	(97.9)	(485.3)	5,314	(85.9)	(3,846.7)	9,378	(85.3)	(6,800.5)
>=3 m	461	(79.5)	(403.9)	525	(90.4)	(476.4)	3,860	(62.4)	(3,604.5)	6,877	(62.5)	(6,386.9)
>=6 m	397	(68.4)	(380.1)	472	(81.2)	(455.6)	2,808	(45.4)	(3,222.1)	5,058	(46.0)	(5,726.9)
>=9 m	353	(60.9)	(352.4)	431	(74.2)	(430.1)	2,131	(34.5)	(2,811.1)	4,002	(36.4)	(5,084.1)

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

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

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

[j] 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 cohorts B ,B2, C and D, KN013 cohorts 3 and 4A, P017, KN024, KN028 cohorts B4, C1 and A4, KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN057, KN059 cohorts 1 and 3, KN061, KN062, KN087, KN091, KN158 cohorts E, G, TMB-H and K, KN164 cohorts A and B, KN170, KN177, KN180, KN181, KN204, KN224, KN361, KN427, KN564, KN629 and KN716.

Pembrolizumab Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 03APR2020, KN716: 21JUN2021)

Pembrolizumab Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEPT2018, KN091: 20SEP2021)

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

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

Pembrolizumab Database cutoff date for cHL (KN013-Cohort 3: 28SEP2018, KN087: 15MAR2021, KN204: 16JAN2020)

Pembrolizumab Database cutoff date for Bladder (KN012-Urothelial: 01SEP2015, KN045: 26OCT2017, KN052: 26SEP2018, KN057: 24MAY2019, KN361: 29APR2020)

Pembrolizumab Database cutoff date for Colorectal (KN164-Cohorts A and B: 09SEP2019, KN177: 19FEB2020)

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

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

Pembrolizumab Database cutoff date for HCC (KN224: 05JUN2019)

Pembrolizumab Database cutoff date for MCC (P017: 06FEB2018)

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

Pembrolizumab Database cutoff date for Renal Cell Carcinoma (KN427 Cohort A: 07SEP2018, KN564: 14JUN2021)

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

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

Pembrolizumab Database cutoff date for MSI-H (KN158: 05OCT2020)

Pembrolizumab Database cutoff date for CSCC (KN629: 29JUL2020)

Adverse events

Baseline characteristics

Table 38: participant characteristics (APaT population)

	KN091 Data for Pembrolizumab		KN091 Data for Placebo		Reference Safety Dataset for Pembrolizumab[i]		Cumulative Running Safety Dataset for Pembrolizumab[j]	
	n	(%)	n	(%)	n	(%)	n	(%)
Age Class (Years)								
<65	281	(48.4)	272	(46.8)	3,587	(58.0)	6,233	(56.7)
65-74	245	(42.2)	243	(41.8)	1,797	(29.1)	3,333	(30.3)
75-84	51	(8.8)	64	(11.0)	694	(11.2)	1,253	(11.4)
>=85	3	(0.5)	2	(0.3)	107	(1.7)	178	(1.6)
ECOG Performance Status								
[0] Normal Activity	375	(64.7)	339	(58.3)	2,942	(47.6)	5,570	(50.7)
[1] Symptoms, but ambulatory	205	(35.3)	242	(41.7)	3,069	(49.6)	5,110	(46.5)
Other/Missing	0	(0.0)	0	(0.0)	174	(2.8)	317	(2.9)
Geographic Region								
EU	388	(66.9)	387	(66.6)	2,217	(35.8)	4,209	(38.3)
Ex-EU	192	(33.1)	194	(33.4)	3,968	(64.2)	6,788	(61.7)
Geographic Region 2								
East Asia	106	(18.3)	105	(18.1)	595	(9.6)	1,441	(13.1)
Ex-East Asia	474	(81.7)	476	(81.9)	5,590	(90.4)	9,556	(86.9)

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

[j] 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 cohorts B ,B2, C and D, KN013 cohorts 3 and 4A, P017, KN024, KN028 cohorts B4, C1 and A4, KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN057, KN059 cohorts 1 and 3, KN061, KN062, KN087, KN091, KN158 cohorts E, G, TMB-H and K, KN164 cohorts A and B, KN170, KN177, KN180, KN181, KN204, KN224, KN361, KN427, KN564, KN629 and KN716.

Pembrolizumab Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 03APR2020, KN716: 21JUN2021)
Pembrolizumab Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEPT2018, KN091: 20SEP2021)
Pembrolizumab Database cutoff date for HNSCC (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)
Pembrolizumab Database cutoff date for Gastric (KN012-Gastric: 26APR2016, KN059-Cohorts 1 and 3: 08AUG2018, KN061: 26OCT2017, KN062: 26MAR2019)
Pembrolizumab Database cutoff date for cHL (KN013-Cohort 3: 28SEP2018, KN087: 15MAR2021, KN204: 16JAN2020)
Pembrolizumab Database cutoff date for Bladder (KN012-Urothelial: 01SEP2015, KN045: 26OCT2017, KN052: 26SEP2018, KN057: 24MAY2019, KN361: 29APR2020)
Pembrolizumab Database cutoff date for Colorectal (KN164-Cohorts A and B: 09SEP2019, KN177: 19FEB2020)
Pembrolizumab Database cutoff date for PMBCL (KN013-Cohort 4A: 04AUG2017. KN170: 07MAY2020)
Pembrolizumab Database cutoff date for Cervical (KN028-Cohort B4: 20FEB2017, KN158-Cohort E: 27JUN2019)
Pembrolizumab Database cutoff date for HCC (KN224: 05JUN2019)
Pembrolizumab Database cutoff date for MCC (P017: 06FEB2018)
Pembrolizumab Database cutoff date for Esophageal (KN028: 31JAN2018, KN180: 30JUL2018, KN181: 15OCT2018)
Pembrolizumab Database cutoff date for Renal Cell Carcinoma (KN427 Cohort A: 07SEP2018, KN564: 14JUN2021)
Pembrolizumab Database cutoff date for SCLC (KN028-Cohort C1: 31JUL2018, KN158-Cohort G: 27JUN2019)
Pembrolizumab Database cutoff date for TMB-H (KN158: 27JUN2019)
Pembrolizumab Database cutoff date for MSI-H (KN158: 05OCT2020)
Pembrolizumab Database cutoff date for CSCC (KN629: 29JUL2020)

AEs

Table 39: Adverse event summary (APaT population)

	KN091 Data for Pembrolizumab		KN091 Data for Placebo		Reference Safety Dataset for Pembrolizumab[i]		Cumulative Running Safety Dataset for Pembrolizumab[j]	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	580		581		6,185		10,997	
with one or more adverse events	556	(95.9)	529	(91.0)	5,989	(96.8)	10,597	(96.4)
with no adverse event	24	(4.1)	52	(9.0)	196	(3.2)	400	(3.6)
with drug-related[a] adverse events	436	(75.2)	305	(52.5)	4,366	(70.6)	7,689	(69.9)
with toxicity grade 3-5 adverse events	198	(34.1)	150	(25.8)	2,984	(48.2)	5,178	(47.1)
with toxicity grade 3-5 drug-related adverse events	88	(15.2)	25	(4.3)	975	(15.8)	1,761	(16.0)
with serious adverse events	142	(24.5)	90	(15.5)	2,371	(38.3)	3,984	(36.2)
with serious drug-related adverse events	68	(11.7)	13	(2.2)	701	(11.3)	1,227	(11.2)
who died	11	(1.9)	6	(1.0)	321	(5.2)	542	(4.9)
who died due to a drug-related adverse event	4	(0.7)	0	(0.0)	39	(0.6)	74	(0.7)
discontinued drug due to an adverse event	115	(19.8)	34	(5.9)	832	(13.5)	1,508	(13.7)
discontinued drug due to a drug-related adverse event	98	(16.9)	20	(3.4)	444	(7.2)	907	(8.2)
discontinued drug due to a serious adverse event	49	(8.4)	14	(2.4)	598	(9.7)	1,007	(9.2)
discontinued drug due to a serious drug-related adverse event	34	(5.9)	4	(0.7)	265	(4.3)	488	(4.4)

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

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

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

For KN091, Adverse Events of Special Interest (AEOSI) up to 90 days of last dose are included.

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

[j] 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 cohorts B ,B2, C and D, KN013 cohorts 3 and 4A, P017, KN024, KN028 cohorts B4, C1 and A4, KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN057, KN059 cohorts 1 and 3, KN061, KN062, KN087, KN091, KN158 cohorts E, G, TMB-H and K, KN164 cohorts A and B, KN170, KN177, KN180, KN181, KN204, KN224, KN361, KN427, KN564, KN629 and KN716.

Pembrolizumab Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 03APR2020, KN716: 21JUN2021)

Pembrolizumab Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEPT2018, KN091: 20SEP2021)

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

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

Pembrolizumab Database cutoff date for cHL (KN013-Cohort 3: 28SEP2018, KN087: 15MAR2021, KN204: 16JAN2020)

Pembrolizumab Database cutoff date for Bladder (KN012-Urothelial: 01SEP2015, KN045: 26OCT2017, KN052: 26SEP2018, KN057: 24MAY2019, KN361: 29APR2020)

Pembrolizumab Database cutoff date for Colorectal (KN164-Cohorts A and B: 09SEP2019, KN177: 19FEB2020)

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

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

Pembrolizumab Database cutoff date for HCC (KN224: 05JUN2019)

Pembrolizumab Database cutoff date for MCC (P017: 06FEB2018)

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

Pembrolizumab Database cutoff date for Renal Cell Carcinoma (KN427 Cohort A: 07SEP2018, KN564: 14JUN2021)

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

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

Pembrolizumab Database cutoff date for MSI-H (KN158: 05OCT2020)

Pembrolizumab Database cutoff date for CSCC (KN629: 29JUL2020)

Source: [ISS: adam-adsl; adae]

Table 40: Exposure-adjusted adverse event summary (including multiple occurrences of events) APaT population)

	Event Count and Rate (Events/100 person-months)[a]			
	KN091 Data for Pembrolizumab	KN091 Data for Placebo	Reference Safety Dataset for Pembrolizumab[i]	Cumulative Running Safety Dataset for Pembrolizumab[j]
Number of subjects exposed	580	581	6185	10997
Total exposure[b] in person-months	5596.37	6400.56	52032.15	92405.52
Total events (rate)				
adverse events	4151 (74.17)	3633 (56.76)	64171 (123.33)	106365 (115.11)
drug-related[c] adverse events	1533 (27.39)	915 (14.30)	20041 (38.52)	32767 (35.46)
toxicity grade 3-5 adverse events	312 (5.58)	229 (3.58)	6478 (12.45)	11285 (12.21)
toxicity grade 3-5 drug-related adverse events	113 (2.02)	35 (0.55)	1467 (2.82)	2627 (2.84)
serious adverse events	217 (3.88)	130 (2.03)	4264 (8.19)	6986 (7.56)
serious drug-related adverse events	81 (1.45)	16 (0.25)	971 (1.87)	1633 (1.77)
adverse events leading to death	13 (0.23)	6 (0.09)	328 (0.63)	553 (0.60)
drug-related adverse events leading to death	6 (0.11)	0 (0.00)	39 (0.07)	76 (0.08)
adverse events resulting in drug discontinuation	130 (2.32)	42 (0.66)	904 (1.74)	1635 (1.77)
drug-related adverse events resulting in drug discontinuation	108 (1.93)	26 (0.41)	481 (0.92)	987 (1.07)
serious adverse events resulting in drug discontinuation	57 (1.02)	15 (0.23)	635 (1.22)	1058 (1.14)

serious drug-related adverse events resulting in drug discontinuation	40 (0.71)	5 (0.08)	279 (0.54)	513 (0.56)

[a] Event rate per 100 person-months of exposure=event count *100/person-months of exposure.
[b] Drug exposure is defined as the time from the first dose date to the earlier of the last dose date + 30 or the database cut-off date.
[c] Determined by the investigator to be related to the drug.
MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
For KN091, Adverse Events of Special Interest (AEOSI) up to 90 days of last dose are included.
Grades are based on NCI CTCAE version 4.03.
For KN054, grade changes and changes in relationship or seriousness for the same adverse event are counted as separate episodes.
[i] 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 cohorts B and B2, KN013 cohort 3, KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN087, KN177 and KN204.
[j] 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 cohorts B ,B2, C and D, KN013 cohorts 3 and 4A, P017, KN024, KN028 cohorts B4, C1 and A4, KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN057, KN059 cohorts 1 and 3, KN061, KN062, KN087, KN091, KN158 cohorts E, G, TMB-H and K, KN164 cohorts A and B, KN170, KN177, KN180, KN181, KN204, KN224, KN361, KN427, KN564, KN629 and KN716.
Pembrolizumab Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 03APR2020, KN716: 21JUN2021)
Pembrolizumab Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEPT2018, KN091: 20SEP2021)
Pembrolizumab Database cutoff date for HNSCC (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)
Pembrolizumab Database cutoff date for Gastric (KN012-Gastric: 26APR2016, KN059-Cohorts 1 and 3: 08AUG2018, KN061: 26OCT2017, KN062: 26MAR2019)
Pembrolizumab Database cutoff date for cHL (KN013-Cohort 3: 28SEP2018, KN087: 15MAR2021, KN204: 16JAN2020)
Pembrolizumab Database cutoff date for Bladder (KN012-Urothelial: 01SEP2015, KN045: 26OCT2017, KN052: 26SEP2018, KN057: 24MAY2019, KN361: 29APR2020)
Pembrolizumab Database cutoff date for Colorectal (KN164-Cohorts A and B: 09SEP2019, KN177: 19FEB2020)
Pembrolizumab Database cutoff date for PMBCL (KN013-Cohort 4A: 04AUG2017. KN170: 07MAY2020)
Pembrolizumab Database cutoff date for Cervical (KN028-Cohort B4: 20FEB2017, KN158-Cohort E: 27JUN2019)
Pembrolizumab Database cutoff date for HCC (KN224: 05JUN2019)
Pembrolizumab Database cutoff date for MCC (P017: 06FEB2018)
Pembrolizumab Database cutoff date for Esophageal (KN028: 31JAN2018, KN180: 30JUL2018, KN181: 15OCT2018)
Pembrolizumab Database cutoff date for Renal Cell Carcinoma (KN427 Cohort A: 07SEP2018, KN564: 14JUN2021)
Pembrolizumab Database cutoff date for SCLC (KN028-Cohort C1: 31JUL2018, KN158-Cohort G: 27JUN2019)
Pembrolizumab Database cutoff date for TMB-H (KN158: 27JUN2019)
Pembrolizumab Database cutoff date for MSI-H (KN158: 05OCT2020)
Pembrolizumab Database cutoff date for CSCC (KN629: 29JUL2020)

Source: [ISS: adam-adsl; adae]

The most frequently reported (incidence >15%) AEs were weight increased, pruritus, hypothyroidism, arthralgia, diarrhoea, and fatigue (as shown in the table below).

Table 41: Participants with adverse events by decreasing incidence of preferred term (incidence ≥10% in one or more treatment groups) (APaT population)

	KN091 Data for Pembrolizumab		KN091 Data for Placebo		Reference Safety Dataset for Pembrolizumab[i]		Cumulative Running Safety Dataset for Pembrolizumab[j]	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	580		581		6,185		10,997	
with one or more adverse events	556	(95.9)	529	(91.0)	5,989	(96.8)	10,597	(96.4)
with no adverse events	24	(4.1)	52	(9.0)	196	(3.2)	400	(3.6)
Weight increased	133	(22.9)	168	(28.9)	209	(3.4)	417	(3.8)
Pruritus	125	(21.6)	74	(12.7)	1,111	(18.0)	1,992	(18.1)
Hypothyroidism	120	(20.7)	27	(4.6)	699	(11.3)	1,316	(12.0)
Arthralgia	108	(18.6)	75	(12.9)	1,148	(18.6)	1,924	(17.5)
Diarrhoea	106	(18.3)	83	(14.3)	1,295	(20.9)	2,279	(20.7)
Fatigue	96	(16.6)	89	(15.3)	1,967	(31.8)	3,205	(29.1)
Cough	87	(15.0)	98	(16.9)	1,200	(19.4)	1,861	(16.9)
Hypertension	67	(11.6)	74	(12.7)	318	(5.1)	585	(5.3)
Dyspnoea	66	(11.4)	72	(12.4)	1,020	(16.5)	1,496	(13.6)
Hyperthyroidism	62	(10.7)	17	(2.9)	261	(4.2)	583	(5.3)
Nausea	52	(9.0)	37	(6.4)	1,282	(20.7)	2,114	(19.2)
Rash	49	(8.4)	29	(5.0)	936	(15.1)	1,515	(13.8)
Back pain	45	(7.8)	46	(7.9)	709	(11.5)	1,205	(11.0)
Headache	45	(7.8)	46	(7.9)	747	(12.1)	1,175	(10.7)
Asthenia	44	(7.6)	32	(5.5)	692	(11.2)	1,262	(11.5)
Decreased appetite	41	(7.1)	27	(4.6)	1,181	(19.1)	1,951	(17.7)
Constipation	35	(6.0)	41	(7.1)	1,032	(16.7)	1,729	(15.7)
Pyrexia	32	(5.5)	34	(5.9)	802	(13.0)	1,300	(11.8)
Vomiting	28	(4.8)	21	(3.6)	784	(12.7)	1,338	(12.2)
Anaemia	25	(4.3)	18	(3.1)	872	(14.1)	1,526	(13.9)

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

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

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

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

For KN091, Adverse Events of Special Interest (AEOSI) up to 90 days of last dose are included.

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

[j] 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 cohorts B ,B2, C and D, KN013 cohorts 3 and 4A, P017, KN024, KN028 cohorts B4, C1 and A4, KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN057, KN059 cohorts 1 and 3, KN061, KN062, KN087, KN091, KN158 cohorts E, G, TMB-H and K, KN164 cohorts A and B, KN170, KN177, KN180, KN181, KN204, KN224, KN361, KN427, KN564, KN629 and KN716.

Pembrolizumab Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 03APR2020, KN716: 21JUN2021)

Pembrolizumab Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEPT2018, KN091: 20SEP2021)

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

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

Pembrolizumab Database cutoff date for cHL (KN013-Cohort 3: 28SEP2018, KN087: 15MAR2021, KN204: 16JAN2020)

Pembrolizumab Database cutoff date for Bladder (KN012-Urothelial: 01SEP2015, KN045: 26OCT2017, KN052: 26SEP2018, KN057: 24MAY2019, KN361: 29APR2020)

Pembrolizumab Database cutoff date for Colorectal (KN164-Cohorts A and B: 09SEP2019, KN177: 19FEB2020)

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

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

Pembrolizumab Database cutoff date for HCC (KN224: 05JUN2019)

Pembrolizumab Database cutoff date for MCC (P017: 06FEB2018)

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

Pembrolizumab Database cutoff date for Renal Cell Carcinoma (KN427 Cohort A: 07SEP2018, KN564: 14JUN2021)

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

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

Pembrolizumab Database cutoff date for MSI-H (KN158: 05OCT2020)

Pembrolizumab Database cutoff date for CSCC (KN629: 29JUL2020)

The following table shows data about drug-related AEs.

Table 42: Participants with drug-related adverse events by decreasing incidence of preferred term (incidence ≥5% in one or more treatment groups) (APaT population)

	KN091 Data for Pembrolizumab		KN091 Data for Placebo		Reference Safety Dataset for Pembrolizumab[i]		Cumulative Running Safety Dataset for Pembrolizumab[j]	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	580		581		6,185		10,997	
with one or more adverse events	436	(75.2)	305	(52.5)	4,366	(70.6)	7,689	(69.9)
with no adverse events	144	(24.8)	276	(47.5)	1,819	(29.4)	3,308	(30.1)
Hypothyroidism	114	(19.7)	19	(3.3)	605	(9.8)	1,153	(10.5)
Pruritus	104	(17.9)	60	(10.3)	871	(14.1)	1,559	(14.2)
Diarrhoea	74	(12.8)	47	(8.1)	681	(11.0)	1,200	(10.9)
Fatigue	61	(10.5)	53	(9.1)	1,216	(19.7)	1,952	(17.8)
Hyperthyroidism	54	(9.3)	15	(2.6)	231	(3.7)	515	(4.7)
Arthralgia	52	(9.0)	29	(5.0)	488	(7.9)	855	(7.8)
Rash maculo-papular	38	(6.6)	13	(2.2)	166	(2.7)	346	(3.1)
Rash	35	(6.0)	17	(2.9)	702	(11.4)	1,135	(10.3)
Alanine aminotransferase increased	33	(5.7)	24	(4.1)	254	(4.1)	476	(4.3)
Pneumonitis	33	(5.7)	12	(2.1)	242	(3.9)	374	(3.4)
Nausea	29	(5.0)	14	(2.4)	561	(9.1)	864	(7.9)
Asthenia	26	(4.5)	18	(3.1)	376	(6.1)	670	(6.1)
Decreased appetite	22	(3.8)	10	(1.7)	479	(7.7)	732	(6.7)

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

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

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

For KN091, Adverse Events of Special Interest (AEOSI) up to 90 days of last dose are included.

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

[j] 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 cohorts B ,B2, C and D, KN013 cohorts 3 and 4A, P017, KN024, KN028 cohorts B4, C1 and A4, KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN057, KN059 cohorts 1 and 3, KN061, KN062, KN087, KN091, KN158 cohorts E, G, TMB-H and K, KN164 cohorts A and B, KN170, KN177, KN180, KN181, KN204, KN224, KN361, KN427, KN564, KN629 and KN716.

Pembrolizumab Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 03APR2020, KN716: 21JUN2021)

Pembrolizumab Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEPT2018, KN091: 20SEP2021)

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

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

Pembrolizumab Database cutoff date for cHL (KN013-Cohort 3: 28SEP2018, KN087: 15MAR2021, KN204: 16JAN2020)

Pembrolizumab Database cutoff date for Bladder (KN012-Urothelial: 01SEP2015, KN045: 26OCT2017, KN052: 26SEP2018, KN057: 24MAY2019, KN361: 29APR2020)

Pembrolizumab Database cutoff date for Colorectal (KN164-Cohorts A and B: 09SEP2019, KN177: 19FEB2020)

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

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

Pembrolizumab Database cutoff date for HCC (KN224: 05JUN2019)

Pembrolizumab Database cutoff date for MCC (P017: 06FEB2018)

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

Pembrolizumab Database cutoff date for Renal Cell Carcinoma (KN427 Cohort A: 07SEP2018, KN564: 14JUN2021)

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

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

Pembrolizumab Database cutoff date for MSI-H (KN158: 05OCT2020)

Pembrolizumab Database cutoff date for CSCC (KN629: 29JUL2020)

The following table shows the proportion of patients with grade 3-5 AEs by decreasing incidence.

Table 43: Participants with Grade 3-5 adverse events by decreasing incidence of preferred term (incidence ≥1% in one or more treatment groups) (APaT population)

	KN091 Data for Pembrolizumab		KN091 Data for Placebo		Reference Safety Dataset for Pembrolizumab[i]		Cumulative Running Safety Dataset for Pembrolizumab[j]	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	580		581		6,185		10,997	
with one or more adverse events	198	(34.1)	150	(25.8)	2,984	(48.2)	5,178	(47.1)
with no adverse events	382	(65.9)	431	(74.2)	3,201	(51.8)	5,819	(52.9)
Hypertension	35	(6.0)	32	(5.5)	113	(1.8)	210	(1.9)
Pneumonia	12	(2.1)	7	(1.2)	255	(4.1)	379	(3.4)
Dyspnoea	8	(1.4)	7	(1.2)	133	(2.2)	201	(1.8)
Hyponatraemia	8	(1.4)	6	(1.0)	161	(2.6)	255	(2.3)
Diarrhoea	7	(1.2)	2	(0.3)	91	(1.5)	160	(1.5)
Pneumonitis	7	(1.2)	4	(0.7)	89	(1.4)	125	(1.1)
Weight increased	6	(1.0)	9	(1.5)	11	(0.2)	26	(0.2)
Alanine aminotransferase increased	4	(0.7)	3	(0.5)	67	(1.1)	143	(1.3)
Arthralgia	4	(0.7)	1	(0.2)	59	(1.0)	87	(0.8)
Colitis	4	(0.7)	1	(0.2)	64	(1.0)	106	(1.0)
Hypokalaemia	4	(0.7)	0	(0.0)	62	(1.0)	107	(1.0)
Urinary tract infection	4	(0.7)	3	(0.5)	74	(1.2)	142	(1.3)
Anaemia	3	(0.5)	3	(0.5)	247	(4.0)	485	(4.4)
Asthenia	3	(0.5)	3	(0.5)	61	(1.0)	125	(1.1)
Pulmonary embolism	3	(0.5)	4	(0.7)	94	(1.5)	142	(1.3)
Acute kidney injury	2	(0.3)	0	(0.0)	56	(0.9)	105	(1.0)
Aspartate aminotransferase increased	2	(0.3)	4	(0.7)	70	(1.1)	158	(1.4)
Hyperglycaemia	2	(0.3)	2	(0.3)	67	(1.1)	128	(1.2)
Back pain	1	(0.2)	0	(0.0)	66	(1.1)	108	(1.0)
Blood alkaline phosphatase increased	1	(0.2)	0	(0.0)	52	(0.8)	110	(1.0)
Decreased appetite	1	(0.2)	1	(0.2)	74	(1.2)	130	(1.2)
Fatigue	1	(0.2)	3	(0.5)	150	(2.4)	241	(2.2)
Abdominal pain	0	(0.0)	1	(0.2)	51	(0.8)	116	(1.1)
Dehydration	0	(0.0)	0	(0.0)	64	(1.0)	106	(1.0)
Pleural effusion	0	(0.0)	1	(0.2)	69	(1.1)	105	(1.0)

Every participant is counted a single time for each applicable row and column.
A specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
For KN091, Adverse Events of Special Interest (AEOSI) up to 90 days of last dose are included.
[i] 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 cohorts B and B2, KN013 cohort 3, KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN087, KN177 and KN204.
[j] 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 cohorts B ,B2, C and D, KN013 cohorts 3 and 4A, P017, KN024, KN028 cohorts B4, C1 and A4, KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN057, KN059 cohorts 1 and 3, KN061, KN062, KN087, KN091, KN158 cohorts E, G, TMB-H and K, KN164 cohorts A and B, KN170, KN177, KN180, KN181, KN204, KN224, KN361, KN427, KN564, KN629 and KN716.
Pembrolizumab Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 03APR2020, KN716: 21JUN2021)
Pembrolizumab Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEPT2018, KN091: 20SEP2021)
Pembrolizumab Database cutoff date for HNSCC (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)
Pembrolizumab Database cutoff date for Gastric (KN012-Gastric: 26APR2016, KN059-Cohorts 1 and 3: 08AUG2018, KN061: 26OCT2017, KN062: 26MAR2019)
Pembrolizumab Database cutoff date for cHL (KN013-Cohort 3: 28SEP2018, KN087: 15MAR2021, KN204: 16JAN2020)
Pembrolizumab Database cutoff date for Bladder (KN012-Urothelial: 01SEP2015, KN045: 26OCT2017, KN052: 26SEP2018, KN057: 24MAY2019, KN361: 29APR2020)
Pembrolizumab Database cutoff date for Colorectal (KN164-Cohorts A and B: 09SEP2019, KN177: 19FEB2020)
Pembrolizumab Database cutoff date for PMBCL (KN013-Cohort 4A: 04AUG2017. KN170: 07MAY2020)
Pembrolizumab Database cutoff date for Cervical (KN028-Cohort B4: 20FEB2017, KN158-Cohort E: 27JUN2019)
Pembrolizumab Database cutoff date for HCC (KN224: 05JUN2019)
Pembrolizumab Database cutoff date for MCC (P017: 06FEB2018)
Pembrolizumab Database cutoff date for Esophageal (KN028: 31JAN2018, KN180: 30JUL2018, KN181: 15OCT2018)
Pembrolizumab Database cutoff date for Renal Cell Carcinoma (KN427 Cohort A: 07SEP2018, KN564: 14JUN2021)
Pembrolizumab Database cutoff date for SCLC (KN028-Cohort C1: 31JUL2018, KN158-Cohort G: 27JUN2019)
Pembrolizumab Database cutoff date for TMB-H (KN158: 27JUN2019)
Pembrolizumab Database cutoff date for MSI-H (KN158: 05OCT2020)
Pembrolizumab Database cutoff date for CSCC (KN629: 29JUL2020)

The most frequently reported (incidence ≥1%) Grade 3 to 5 drug-related AEs in the KEYNOTE-091 Pembrolizumab Dataset were pneumonitis and diarrhea. There were no Grade 3 to 5 drug-related AEs reported more frequently in the KEYNOTE-091 Pembrolizumab Dataset than in the RSD.

Table 44: Participants with Grade 3-5 drug-related adverse events by decreasing incidence of preferred term (incidence ≥1% in one or more treatment groups) (APaT population)

	KN091 Data for Pembrolizumab		KN091 Data for Placebo		Reference Safety Dataset for Pembrolizumab[i]		Cumulative Running Safety Dataset for Pembrolizumab[j]	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	580		581		6,185		10,997	
with one or more adverse events	88	(15.2)	25	(4.3)	975	(15.8)	1,761	(16.0)
with no adverse events	492	(84.8)	556	(95.7)	5,210	(84.2)	9,236	(84.0)
Pneumonitis	7	(1.2)	3	(0.5)	84	(1.4)	118	(1.1)
Diarrhoea	6	(1.0)	1	(0.2)	60	(1.0)	103	(0.9)
Fatigue	1	(0.2)	3	(0.5)	66	(1.1)	108	(1.0)

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

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

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

For KN091, Adverse Events of Special Interest (AEOSI) up to 90 days of last dose are included.

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

[j] 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 cohorts B ,B2, C and D, KN013 cohorts 3 and 4A, P017, KN024, KN028 cohorts B4, C1 and A4, KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN057, KN059 cohorts 1 and 3, KN061, KN062, KN087, KN091, KN158 cohorts E, G, TMB-H and K, KN164 cohorts A and B, KN170, KN177, KN180, KN181, KN204, KN224, KN361, KN427, KN564, KN629 and KN716.

Pembrolizumab Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 03APR2020, KN716: 21JUN2021)

Pembrolizumab Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEPT2018, KN091: 20SEP2021)

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

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

Pembrolizumab Database cutoff date for cHL (KN013-Cohort 3: 28SEP2018, KN087: 15MAR2021, KN204: 16JAN2020)

Pembrolizumab Database cutoff date for Bladder (KN012-Urothelial: 01SEP2015, KN045: 26OCT2017, KN052: 26SEP2018, KN057: 24MAY2019, KN361: 29APR2020)

Pembrolizumab Database cutoff date for Colorectal (KN164-Cohorts A and B: 09SEP2019, KN177: 19FEB2020)

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

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

Pembrolizumab Database cutoff date for HCC (KN224: 05JUN2019)

Pembrolizumab Database cutoff date for MCC (P017: 06FEB2018)

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

Pembrolizumab Database cutoff date for Renal Cell Carcinoma (KN427 Cohort A: 07SEP2018, KN564: 14JUN2021)

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

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

Pembrolizumab Database cutoff date for MSI-H (KN158: 05OCT2020)

Pembrolizumab Database cutoff date for CSCC (KN629: 29JUL2020)

Source: [ISS: adam-adsl; adae]

The most frequently reported (incidence ≥1%) Grade 3 to 5 drug-related AEs in the KEYNOTE-091 Pembrolizumab Dataset were pneumonitis and diarrhea as shown in the table below. There were no Grade 3 to 5 drug-related AEs reported more frequently in the KEYNOTE-091 Pembrolizumab Dataset than in the RSD.

AEOSIs are immune-related events and infusion-related reactions associated with pembrolizumab (showed in the next two tables).

Table 45: Adverse event summary for AEOSI (APaT population)

	KN091 Data for Pembrolizumab		KN091 Data for Placebo		Reference Safety Dataset for Pembrolizumab[i]		Cumulative Running Safety Dataset for Pembrolizumab[j]	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	580		581		6,185		10,997	
with one or more adverse events	226	(39.0)	75	(12.9)	1,577	(25.5)	2,874	(26.1)
with no adverse event	354	(61.0)	506	(87.1)	4,608	(74.5)	8,123	(73.9)
with drug-related[a] adverse events	214	(36.9)	53	(9.1)	1,367	(22.1)	2,538	(23.1)
with toxicity grade 3-5 adverse events	46	(7.9)	11	(1.9)	405	(6.5)	738	(6.7)
with toxicity grade 3-5 drug-related adverse events	45	(7.8)	9	(1.5)	351	(5.7)	656	(6.0)
with serious adverse events	47	(8.1)	9	(1.5)	405	(6.5)	698	(6.3)
with serious drug-related adverse events	46	(7.9)	7	(1.2)	359	(5.8)	629	(5.7)
who died	2	(0.3)	0	(0.0)	11	(0.2)	24	(0.2)
who died due to a drug-related adverse event	2	(0.3)	0	(0.0)	11	(0.2)	24	(0.2)
discontinued drug due to an adverse event	59	(10.2)	9	(1.5)	256	(4.1)	502	(4.6)
discontinued drug due to a drug-related adverse event	59	(10.2)	9	(1.5)	252	(4.1)	497	(4.5)
discontinued drug due to a serious adverse event	23	(4.0)	3	(0.5)	172	(2.8)	302	(2.7)
discontinued drug due to a serious drug-related adverse event	23	(4.0)	3	(0.5)	170	(2.7)	300	(2.7)

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

For KN091, Adverse Events of Special Interest (AEOSI) up to 90 days of last dose are included. For all other studies, non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.

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

[j] 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 cohorts B ,B2, C and D, KN013 cohorts 3 and 4A, P017, KN024, KN028 cohorts B4, C1 and A4, KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN057, KN059 cohorts 1 and 3, KN061, KN062, KN087, KN091, KN158 cohorts E, G, TMB-H and K, KN164 cohorts A and B, KN170, KN177, KN180, KN181, KN204, KN224, KN361, KN427, KN564, KN629 and KN716.

Pembrolizumab Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 03APR2020, KN716: 21JUN2021)

Pembrolizumab Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEPT2018, KN091: 20SEP2021)

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

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

Pembrolizumab Database cutoff date for cHL (KN013-Cohort 3: 28SEP2018, KN087: 15MAR2021, KN204: 16JAN2020)

Pembrolizumab Database cutoff date for Bladder (KN012-Urothelial: 01SEP2015, KN045: 26OCT2017, KN052: 26SEP2018, KN057: 24MAY2019, KN361: 29APR2020)

Pembrolizumab Database cutoff date for Colorectal (KN164-Cohorts A and B: 09SEP2019, KN177: 19FEB2020)

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

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

Pembrolizumab Database cutoff date for HCC (KN224: 05JUN2019)

Pembrolizumab Database cutoff date for MCC (P017: 06FEB2018)

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

Pembrolizumab Database cutoff date for Renal Cell Carcinoma (KN427 Cohort A: 07SEP2018, KN564: 14JUN2021)

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

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

Pembrolizumab Database cutoff date for MSI-H (KN158: 05OCT2020)

Pembrolizumab Database cutoff date for CSCC (KN629: 29JUL2020)

Source: [ISS: adam-adsl; adae]

Table 46: Exposure-adjusted adverse event of special interest summary (including multiple occurrences of events) (APaT population)

	Event Count and Rate (Events/100 person-months)[a]			
	KN091 Data for Pembrolizumab	KN091 Data for Placebo	Reference Safety Dataset for Pembrolizumab[i]	Cumulative Running Safety Dataset for Pembrolizumab[j]
Number of subjects exposed	580	581	6185	10997
Total exposure[b] in person-months	5596.37	6400.56	52032.15	92405.52
Total events (rate)				
adverse events	320 (5.72)	85 (1.33)	2268 (4.36)	4121 (4.46)
drug-related[c] adverse events	296 (5.29)	61 (0.95)	1950 (3.75)	3591 (3.89)
toxicity grade 3-5 adverse events	51 (0.91)	11 (0.17)	482 (0.93)	858 (0.93)
toxicity grade 3-5 drug-related adverse events	49 (0.88)	9 (0.14)	418 (0.80)	759 (0.82)
serious adverse events	52 (0.93)	10 (0.16)	478 (0.92)	803 (0.87)
serious drug-related adverse events	50 (0.89)	8 (0.12)	426 (0.82)	723 (0.78)
adverse events leading to death	2 (0.04)	0 (0.00)	11 (0.02)	24 (0.03)
drug-related adverse events leading to death	2 (0.04)	0 (0.00)	11 (0.02)	24 (0.03)
adverse events resulting in drug discontinuation	62 (1.11)	9 (0.14)	262 (0.50)	515 (0.56)
drug-related adverse events resulting in drug discontinuation	62 (1.11)	9 (0.14)	258 (0.50)	510 (0.55)
serious adverse events resulting in drug discontinuation	26 (0.46)	3 (0.05)	177 (0.34)	312 (0.34)
serious drug-related adverse events resulting in drug discontinuation	26 (0.46)	3 (0.05)	175 (0.34)	310 (0.34)

[a] Event rate per 100 person-months of exposure=event count *100/person-months of exposure.
[b] Drug exposure is defined as the time from the first dose date to the earlier of the last dose date + 30 or the database cut-off date.
[c] Determined by the investigator to be related to the drug.
MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
For KN091, Adverse Events of Special Interest (AEOSI) up to 90 days of last dose are included.
Grades are based on NCI CTCAE version 4.03.
For KN054, grade changes and changes in relationship or seriousness for the same adverse event are counted as separate episodes.
[i] 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 cohorts B and B2, KN013 cohort 3, KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN087, KN177 and KN204.
[j] 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 cohorts B ,B2, C and D, KN013 cohorts 3 and 4A, P017, KN024, KN028 cohorts B4, C1 and A4, KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN057, KN059 cohorts 1 and 3, KN061, KN062, KN087, KN091, KN158 cohorts E, G, TMB-H and K, KN164 cohorts A and B, KN170, KN177, KN180, KN181, KN204, KN224, KN361, KN427, KN564, KN629 and KN716.
Pembrolizumab Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 03APR2020, KN716: 21JUN2021)
Pembrolizumab Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEPT2018, KN091: 20SEP2021)
Pembrolizumab Database cutoff date for HNSCC (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)
Pembrolizumab Database cutoff date for Gastric (KN012-Gastric: 26APR2016, KN059-Cohorts 1 and 3: 08AUG2018, KN061: 26OCT2017, KN062: 26MAR2019)
Pembrolizumab Database cutoff date for cHL (KN013-Cohort 3: 28SEP2018, KN087: 15MAR2021, KN204: 16JAN2020)
Pembrolizumab Database cutoff date for Bladder (KN012-Urothelial: 01SEP2015, KN045: 26OCT2017, KN052: 26SEP2018, KN057: 24MAY2019, KN361: 29APR2020)
Pembrolizumab Database cutoff date for Colorectal (KN164-Cohorts A and B: 09SEP2019, KN177: 19FEB2020)
Pembrolizumab Database cutoff date for PMBCL (KN013-Cohort 4A: 04AUG2017. KN170: 07MAY2020)
Pembrolizumab Database cutoff date for Cervical (KN028-Cohort B4: 20FEB2017, KN158-Cohort E: 27JUN2019)
Pembrolizumab Database cutoff date for HCC (KN224: 05JUN2019)
Pembrolizumab Database cutoff date for MCC (P017: 06FEB2018)
Pembrolizumab Database cutoff date for Esophageal (KN028: 31JAN2018, KN180: 30JUL2018, KN181: 15OCT2018)
Pembrolizumab Database cutoff date for Renal Cell Carcinoma (KN427 Cohort A: 07SEP2018, KN564: 14JUN2021)
Pembrolizumab Database cutoff date for SCLC (KN028-Cohort C1: 31JUL2018, KN158-Cohort G: 27JUN2019)
Pembrolizumab Database cutoff date for TMB-H (KN158: 27JUN2019)
Pembrolizumab Database cutoff date for MSI-H (KN158: 05OCT2020)
Pembrolizumab Database cutoff date for CSCC (KN629: 29JUL2020)

Source: [ISS: adam-adsl; adae]

The next table shows the number of patients with AEOSI by Category and Preferred Term.

Table 47: Participants with adverse events of special interest by AEOSI category and preferred term (Incidence >0% in one or more treatment groups) (APaT population)

	KN091 Data for Pembrolizumab		KN091 Data for Placebo		Reference Safety Dataset for Pembrolizumab[i]		Cumulative Running Safety Dataset for Pembrolizumab[j]	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	580		581		6,185		10,997	
with one or more adverse events	226	(39.0)	75	(12.9)	1,577	(25.5)	2,874	(26.1)
with no adverse events	354	(61.0)	506	(87.1)	4,608	(74.5)	8,123	(73.9)
Adrenal Insufficiency	**10**	**(1.7)**	**0**	**(0.0)**	**52**	**(0.8)**	**106**	**(1.0)**
Adrenal insufficiency	10	(1.7)	0	(0.0)	47	(0.8)	94	(0.9)
Addison's disease	0	(0.0)	0	(0.0)	2	(0.0)	4	(0.0)
Adrenocortical insufficiency acute	0	(0.0)	0	(0.0)	2	(0.0)	2	(0.0)
Primary adrenal insufficiency	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Secondary adrenocortical insufficiency	0	(0.0)	0	(0.0)	2	(0.0)	5	(0.0)
Colitis	**14**	**(2.4)**	**5**	**(0.9)**	**122**	**(2.0)**	**226**	**(2.1)**
Colitis	14	(2.4)	5	(0.9)	104	(1.7)	192	(1.7)
Immune-mediated enterocolitis	1	(0.2)	0	(0.0)	4	(0.1)	7	(0.1)
Autoimmune colitis	0	(0.0)	0	(0.0)	4	(0.1)	8	(0.1)
Colitis microscopic	0	(0.0)	0	(0.0)	4	(0.1)	4	(0.0)
Enterocolitis	0	(0.0)	0	(0.0)	8	(0.1)	17	(0.2)
Enterocolitis haemorrhagic	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Encephalitis	**0**	**(0.0)**	**0**	**(0.0)**	**4**	**(0.1)**	**8**	**(0.1)**
Encephalitis	0	(0.0)	0	(0.0)	3	(0.0)	6	(0.1)
Encephalitis autoimmune	0	(0.0)	0	(0.0)	1	(0.0)	2	(0.0)
Guillain-Barre Syndrome	**0**	**(0.0)**	**0**	**(0.0)**	**4**	**(0.1)**	**8**	**(0.1)**
Axonal neuropathy	0	(0.0)	0	(0.0)	1	(0.0)	1	(0.0)
Demyelinating polyneuropathy	0	(0.0)	0	(0.0)	1	(0.0)	1	(0.0)
Guillain-Barre syndrome	0	(0.0)	0	(0.0)	2	(0.0)	6	(0.1)
Hepatitis	**10**	**(1.7)**	**4**	**(0.7)**	**60**	**(1.0)**	**121**	**(1.1)**
Immune-mediated hepatitis	4	(0.7)	2	(0.3)	2	(0.0)	9	(0.1)
Hepatitis	3	(0.5)	1	(0.2)	25	(0.4)	49	(0.4)
Autoimmune hepatitis	2	(0.3)	0	(0.0)	26	(0.4)	52	(0.5)
Drug-induced liver injury	2	(0.3)	1	(0.2)	7	(0.1)	12	(0.1)
Hepatitis acute	0	(0.0)	0	(0.0)	1	(0.0)	1	(0.0)
Hyperthyroidism	**62**	**(10.7)**	**17**	**(2.9)**	**261**	**(4.2)**	**583**	**(5.3)**
Hyperthyroidism	62	(10.7)	17	(2.9)	261	(4.2)	583	(5.3)
Hypophysitis	**7**	**(1.2)**	**0**	**(0.0)**	**38**	**(0.6)**	**73**	**(0.7)**
Hypophysitis	6	(1.0)	0	(0.0)	23	(0.4)	46	(0.4)
Hypopituitarism	1	(0.2)	0	(0.0)	14	(0.2)	25	(0.2)
Lymphocytic hypophysitis	0	(0.0)	0	(0.0)	1	(0.0)	3	(0.0)
Hypothyroidism	**120**	**(20.7)**	**27**	**(4.6)**	**700**	**(11.3)**	**1,321**	**(12.0)**
Hypothyroidism	120	(20.7)	27	(4.6)	699	(11.3)	1,316	(12.0)
Autoimmune hypothyroidism	0	(0.0)	0	(0.0)	0	(0.0)	3	(0.0)
Myxoedema	0	(0.0)	0	(0.0)	1	(0.0)	2	(0.0)
Primary hypothyroidism	0	(0.0)	0	(0.0)	1	(0.0)	1	(0.0)
Infusion Reactions	**5**	**(0.9)**	**4**	**(0.7)**	**149**	**(2.4)**	**209**	**(1.9)**
Infusion related reaction	3	(0.5)	1	(0.2)	63	(1.0)	103	(0.9)
Hypersensitivity	2	(0.3)	3	(0.5)	47	(0.8)	59	(0.5)
Anaphylactic reaction	0	(0.0)	0	(0.0)	10	(0.2)	12	(0.1)
Anaphylactoid reaction	0	(0.0)	0	(0.0)	1	(0.0)	1	(0.0)
Cytokine release syndrome	0	(0.0)	0	(0.0)	8	(0.1)	9	(0.1)
Drug hypersensitivity	0	(0.0)	0	(0.0)	22	(0.4)	28	(0.3)
Myasthenic Syndrome	**0**	**(0.0)**	**0**	**(0.0)**	**3**	**(0.0)**	**9**	**(0.1)**
Myasthenia gravis	0	(0.0)	0	(0.0)	1	(0.0)	5	(0.0)
Myasthenic syndrome	0	(0.0)	0	(0.0)	2	(0.0)	4	(0.0)
Myelitis	**0**	**(0.0)**	**0**	**(0.0)**	**2**	**(0.0)**	**3**	**(0.0)**
Myelitis	0	(0.0)	0	(0.0)	1	(0.0)	1	(0.0)
Myelitis transverse	0	(0.0)	0	(0.0)	1	(0.0)	2	(0.0)
Myocarditis	**5**	**(0.9)**	**1**	**(0.2)**	**7**	**(0.1)**	**16**	**(0.1)**
Myocarditis	5	(0.9)	1	(0.2)	7	(0.1)	16	(0.1)
Myositis	**1**	**(0.2)**	**0**	**(0.0)**	**21**	**(0.3)**	**49**	**(0.4)**
Myopathy	1	(0.2)	0	(0.0)	4	(0.1)	9	(0.1)
Myositis	0	(0.0)	0	(0.0)	14	(0.2)	34	(0.3)
Necrotising myositis	0	(0.0)	0	(0.0)	1	(0.0)	1	(0.0)
Polymyositis	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Rhabdomyolysis	0	(0.0)	0	(0.0)	2	(0.0)	5	(0.0)

	KN091 Data for Pembrolizumab		KN091 Data for Placebo		Reference Safety Dataset for Pembrolizumab[i]		Cumulative Running Safety Dataset for Pembrolizumab[j]	
	n	(%)	n	(%)	n	(%)	n	(%)
Nephritis	**4**	**(0.7)**	**0**	**(0.0)**	**25**	**(0.4)**	**55**	**(0.5)**
Nephritis	4	(0.7)	0	(0.0)	4	(0.1)	21	(0.2)
Acute kidney injury	0	(0.0)	0	(0.0)	2	(0.0)	2	(0.0)
Autoimmune nephritis	0	(0.0)	0	(0.0)	3	(0.0)	8	(0.1)
Glomerulonephritis	0	(0.0)	0	(0.0)	1	(0.0)	1	(0.0)
Glomerulonephritis acute	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Glomerulonephritis membranous	0	(0.0)	0	(0.0)	1	(0.0)	1	(0.0)
Nephrotic syndrome	0	(0.0)	0	(0.0)	1	(0.0)	2	(0.0)
Renal failure	0	(0.0)	0	(0.0)	2	(0.0)	2	(0.0)
Tubulointerstitial nephritis	0	(0.0)	0	(0.0)	11	(0.2)	17	(0.2)
Pancreatitis	**2**	**(0.3)**	**2**	**(0.3)**	**21**	**(0.3)**	**41**	**(0.4)**
Pancreatitis	2	(0.3)	2	(0.3)	17	(0.3)	36	(0.3)
Autoimmune pancreatitis	0	(0.0)	0	(0.0)	1	(0.0)	1	(0.0)
Pancreatitis acute	0	(0.0)	0	(0.0)	4	(0.1)	5	(0.0)
Pneumonitis	**40**	**(6.9)**	**17**	**(2.9)**	**288**	**(4.7)**	**455**	**(4.1)**
Pneumonitis	34	(5.9)	16	(2.8)	263	(4.3)	402	(3.7)
Interstitial lung disease	5	(0.9)	1	(0.2)	25	(0.4)	48	(0.4)
Immune-mediated lung disease	1	(0.2)	0	(0.0)	0	(0.0)	5	(0.0)
Organising pneumonia	0	(0.0)	0	(0.0)	3	(0.0)	3	(0.0)
Sarcoidosis	**1**	**(0.2)**	**0**	**(0.0)**	**10**	**(0.2)**	**22**	**(0.2)**
Sarcoidosis	1	(0.2)	0	(0.0)	10	(0.2)	20	(0.2)
Cutaneous sarcoidosis	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Pulmonary sarcoidosis	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Severe Skin Reactions	**16**	**(2.8)**	**4**	**(0.7)**	**102**	**(1.6)**	**185**	**(1.7)**
Rash maculo-papular	3	(0.5)	0	(0.0)	17	(0.3)	33	(0.3)
Erythema multiforme	2	(0.3)	1	(0.2)	5	(0.1)	13	(0.1)
Pemphigoid	2	(0.3)	0	(0.0)	3	(0.0)	9	(0.1)
Rash	2	(0.3)	0	(0.0)	31	(0.5)	57	(0.5)
Dermatitis exfoliative generalised	1	(0.2)	0	(0.0)	2	(0.0)	4	(0.0)
Lichen planus	1	(0.2)	0	(0.0)	5	(0.1)	8	(0.1)
Pruritus	1	(0.2)	2	(0.3)	12	(0.2)	20	(0.2)
Rash erythematous	1	(0.2)	0	(0.0)	1	(0.0)	2	(0.0)
Rash pustular	1	(0.2)	0	(0.0)	1	(0.0)	4	(0.0)
Stevens-Johnson syndrome	1	(0.2)	0	(0.0)	3	(0.0)	5	(0.0)
Toxic skin eruption	1	(0.2)	0	(0.0)	4	(0.1)	6	(0.1)
Dermatitis bullous	0	(0.0)	1	(0.2)	8	(0.1)	10	(0.1)
Dermatitis exfoliative	0	(0.0)	0	(0.0)	5	(0.1)	5	(0.0)
Exfoliative rash	0	(0.0)	0	(0.0)	2	(0.0)	6	(0.1)
Oral lichen planus	0	(0.0)	0	(0.0)	1	(0.0)	2	(0.0)
Pemphigus	0	(0.0)	0	(0.0)	2	(0.0)	3	(0.0)
Pruritus genital	0	(0.0)	0	(0.0)	2	(0.0)	2	(0.0)
Rash pruritic	0	(0.0)	0	(0.0)	2	(0.0)	5	(0.0)
Skin necrosis	0	(0.0)	0	(0.0)	2	(0.0)	2	(0.0)
Thyroiditis	**6**	**(1.0)**	**1**	**(0.2)**	**60**	**(1.0)**	**99**	**(0.9)**
Thyroiditis	5	(0.9)	1	(0.2)	43	(0.7)	69	(0.6)
Autoimmune thyroiditis	1	(0.2)	0	(0.0)	16	(0.3)	27	(0.2)
Thyroid disorder	1	(0.2)	0	(0.0)	3	(0.0)	5	(0.0)
Immune-mediated thyroiditis	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Type 1 Diabetes Mellitus	**1**	**(0.2)**	**0**	**(0.0)**	**21**	**(0.3)**	**46**	**(0.4)**
Type 1 diabetes mellitus	1	(0.2)	0	(0.0)	17	(0.3)	34	(0.3)
Diabetic ketoacidosis	0	(0.0)	0	(0.0)	9	(0.1)	19	(0.2)
Fulminant type 1 diabetes mellitus	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Uveitis	**0**	**(0.0)**	**0**	**(0.0)**	**23**	**(0.4)**	**30**	**(0.3)**
Chorioretinitis	0	(0.0)	0	(0.0)	1	(0.0)	1	(0.0)
Iridocyclitis	0	(0.0)	0	(0.0)	4	(0.1)	5	(0.0)
Iritis	0	(0.0)	0	(0.0)	3	(0.0)	5	(0.0)
Uveitis	0	(0.0)	0	(0.0)	15	(0.2)	20	(0.2)
Vasculitis	**1**	**(0.2)**	**0**	**(0.0)**	**2**	**(0.0)**	**7**	**(0.1)**
Giant cell arteritis	1	(0.2)	0	(0.0)	0	(0.0)	3	(0.0)

	Event Count and Rate (Events/100 person-months)[a]			
	KN091 Data for Pembrolizumab	KN091 Data for Placebo	Reference Safety Dataset for Pembrolizumab[i]	Cumulative Running Safety Dataset for Pembrolizumab[j]
serious drug-related adverse events resulting in drug discontinuation	40 (0.71)	5 (0.08)	279 (0.54)	513 (0.56)

[a] Event rate per 100 person-months of exposure=event count *100/person-months of exposure.
[b] Drug exposure is defined as the time from the first dose date to the earlier of the last dose date + 30 or the database cut-off date.
[c] Determined by the investigator to be related to the drug.
MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
For KN091, Adverse Events of Special Interest (AEOSI) up to 90 days of last dose are included.
Grades are based on NCI CTCAE version 4.03.
For KN054, grade changes and changes in relationship or seriousness for the same adverse event are counted as separate episodes.
[i] 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 cohorts B and B2, KN013 cohort 3, KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN087, KN177 and KN204.
[j] 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 cohorts B ,B2, C and D, KN013 cohorts 3 and 4A, P017, KN024, KN028 cohorts B4, C1 and A4, KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN057, KN059 cohorts 1 and 3, KN061, KN062, KN087, KN091, KN158 cohorts E, G, TMB-H and K, KN164 cohorts A and B, KN170, KN177, KN180, KN181, KN204, KN224, KN361, KN427, KN564, KN629 and KN716.
Pembrolizumab Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 03APR2020, KN716: 21JUN2021)
Pembrolizumab Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEPT2018, KN091: 20SEP2021)
Pembrolizumab Database cutoff date for HNSCC (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)
Pembrolizumab Database cutoff date for Gastric (KN012-Gastric: 26APR2016, KN059-Cohorts 1 and 3: 08AUG2018, KN061: 26OCT2017, KN062: 26MAR2019)
Pembrolizumab Database cutoff date for cHL (KN013-Cohort 3: 28SEP2018, KN087: 15MAR2021, KN204: 16JAN2020)
Pembrolizumab Database cutoff date for Bladder (KN012-Urothelial: 01SEP2015, KN045: 26OCT2017, KN052: 26SEP2018, KN057: 24MAY2019, KN361: 29APR2020)
Pembrolizumab Database cutoff date for Colorectal (KN164-Cohorts A and B: 09SEP2019, KN177: 19FEB2020)
Pembrolizumab Database cutoff date for PMBCL (KN013-Cohort 4A: 04AUG2017. KN170: 07MAY2020)
Pembrolizumab Database cutoff date for Cervical (KN028-Cohort B4: 20FEB2017, KN158-Cohort E: 27JUN2019)
Pembrolizumab Database cutoff date for HCC (KN224: 05JUN2019)
Pembrolizumab Database cutoff date for MCC (P017: 06FEB2018)
Pembrolizumab Database cutoff date for Esophageal (KN028: 31JAN2018, KN180: 30JUL2018, KN181: 15OCT2018)
Pembrolizumab Database cutoff date for Renal Cell Carcinoma (KN427 Cohort A: 07SEP2018, KN564: 14JUN2021)
Pembrolizumab Database cutoff date for SCLC (KN028-Cohort C1: 31JUL2018, KN158-Cohort G: 27JUN2019)
Pembrolizumab Database cutoff date for TMB-H (KN158: 27JUN2019)
Pembrolizumab Database cutoff date for MSI-H (KN158: 05OCT2020)
Pembrolizumab Database cutoff date for CSCC (KN629: 29JUL2020)

Source: [ISS: adam-adsl; adae]

At the IA3, one additional patient with hepatitis and one additional patient with arthritis classified as AEOSI have been reported.

Serious adverse event/deaths/other significant events

SAEs

The most frequently reported SAEs in the KEYNOTE-091 Dataset were pneumonia, pneumonitis, and diarrhoea, as shown in the next table.

Table 48: Participants with serious adverse events by decreasing incidence of preferred term (incidence ≥1% in one or more treatment groups) (APaT population)

	KN091 Data for Pembrolizumab		KN091 Data for Placebo		Reference Safety Dataset for Pembrolizumab[i]		Cumulative Running Safety Dataset for Pembrolizumab[j]	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	580		581		6,185		10,997	
with one or more adverse events	142	(24.5)	90	(15.5)	2,371	(38.3)	3,984	(36.2)
with no adverse events	438	(75.5)	491	(84.5)	3,814	(61.7)	7,013	(63.8)
Pneumonia	13	(2.2)	9	(1.5)	257	(4.2)	376	(3.4)
Pneumonitis	12	(2.1)	4	(0.7)	126	(2.0)	180	(1.6)
Diarrhoea	7	(1.2)	1	(0.2)	63	(1.0)	102	(0.9)
Colitis	4	(0.7)	2	(0.3)	61	(1.0)	98	(0.9)
Dyspnoea	4	(0.7)	4	(0.7)	82	(1.3)	109	(1.0)
Pulmonary embolism	3	(0.5)	0	(0.0)	72	(1.2)	108	(1.0)
Urinary tract infection	3	(0.5)	2	(0.3)	59	(1.0)	110	(1.0)
Acute kidney injury	2	(0.3)	0	(0.0)	55	(0.9)	114	(1.0)
Anaemia	1	(0.2)	0	(0.0)	61	(1.0)	112	(1.0)
Pyrexia	1	(0.2)	3	(0.5)	75	(1.2)	108	(1.0)
Pleural effusion	0	(0.0)	0	(0.0)	83	(1.3)	118	(1.1)

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

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

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

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

For KN091, Adverse Events of Special Interest (AEOSI) up to 90 days of last dose are included.

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

[j] 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 cohorts B ,B2, C and D, KN013 cohorts 3 and 4A, P017, KN024, KN028 cohorts B4, C1 and A4, KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN057, KN059 cohorts 1 and 3, KN061, KN062, KN087, KN091, KN158 cohorts E, G, TMB-H and K, KN164 cohorts A and B, KN170, KN177, KN180, KN181, KN204, KN224, KN361, KN427, KN564, KN629 and KN716.

Pembrolizumab Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 03APR2020, KN716: 21JUN2021)

Pembrolizumab Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEPT2018, KN091: 20SEP2021)

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

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

Pembrolizumab Database cutoff date for cHL (KN013-Cohort 3: 28SEP2018, KN087: 15MAR2021, KN204: 16JAN2020)

Pembrolizumab Database cutoff date for Bladder (KN012-Urothelial: 01SEP2015, KN045: 26OCT2017, KN052: 26SEP2018, KN057: 24MAY2019, KN361: 29APR2020)

Pembrolizumab Database cutoff date for Colorectal (KN164-Cohorts A and B: 09SEP2019, KN177: 19FEB2020)

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

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

Pembrolizumab Database cutoff date for HCC (KN224: 05JUN2019)

Pembrolizumab Database cutoff date for MCC (P017: 06FEB2018)

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

Pembrolizumab Database cutoff date for Renal Cell Carcinoma (KN427 Cohort A: 07SEP2018, KN564: 14JUN2021)

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

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

Pembrolizumab Database cutoff date for MSI-H (KN158: 05OCT2020)

Pembrolizumab Database cutoff date for CSCC (KN629: 29JUL2020)

The most frequent Drug-related SAEs were (pembrolizumab vs placebo) Pneumonitis (2.1% vs 0.5%) and Diarrhoea (1.0% vs 0), in line with the frequency observed in the RDS.

DEATHS

In the present study 11 patients died in the pembrolizumab (1.9%) vs 6 (1.0%) in placebo (RSD: n=321, 5.2%) arm. In pembrolizumab arm, most of these cases were for cardiac causes (2 Myocarditis, 1 Myocardial infarction, 1 Myocardial ischaemia, and other cardiac generic conditions). Two other patients died by sepsis and other 2 by pulmonary infections.

The MAH considered 4 participants (in pembrolizumab arm) to have died due to drug-related AEs: myocarditis and cardiogenic shock in 1 participant; myocarditis and septic shock in 1 participant; and pneumonia and sudden death each in 1 participant.

Patient was with a history including (but not limited to) Sleep apnoea syndrome, Chronic obstructive pulmonary disease. From Days 40 to 46 and Days 56 to 63 (after pembrolizumab start), the participant experienced 2 separate events of lower respiratory tract infection (Grade 2), treated with antibiotics and corticosteroids. On Day 68 the participant had dyspnea and orthopnea and was hospitalized with the diagnosis respiratory tract infection (Grade 3) with bilateral interstitial pattern at the x-ray. On Day 74 a fibrobronchoscopy showed acute inflammation and infection by Stenotrophomonas maltophilia.

On Day 83 a CT showed an unspecified infiltrate and the participant was readmitted to the hospital with increased dyspnea and fever. Lab test showed increased WBC and neutrophils. On Day 88 pembrolizumab was discontinued in response to respiratory infection (last dose on Day 64). On Day 91 the participant died due to respiratory tract infection. The investigator considered respiratory tract infection not related to pembrolizumab.

Patient was with a history of atrial fibrillation and hypertension, who developed myocardial ischemia at Day 121 (after pembrolizumab start) after a total of 5 doses of pembrolizumab. The patient also developed pericardial effusion, at the same time, and the microbiological analysis revealed that the fluid was positive for Staphylococcus spp. The participant died due to myocardial ischemia on Day 121. The investigator considered myocardial ischemia not related to pembrolizumab.

Patient, according to the MAH, developed hypothyroidism. The table with his lab tests is shown below. The diagnosis of hypothyroidism was on day 43 and the start of treatment with thyroid hormone was on day 53. The patient died by sudden death after chest pain (no further information available).

Table 49: Participants With Adverse Events Resulting in Death by Decreasing Incidence of Preferred Term (ApaT Population)

	KN091 Data for Pembrolizumab		KN091 Data for Placebo		Reference Safety Dataset for Pembrolizumab[i]		Cumulative Running Safety Dataset for Pembrolizumab[j]	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	580		581		6,185		10,997	
with one or more adverse events	11	(1.9)	6	(1.0)	321	(5.2)	542	(4.9)
with no adverse events	569	(98.1)	575	(99.0)	5,864	(94.8)	10,455	(95.1)
Myocarditis	2	(0.3)	0	(0.0)	0	(0.0)	4	(0.0)
Cardiac arrest	1	(0.2)	0	(0.0)	9	(0.1)	15	(0.1)
Cardiac death	1	(0.2)	0	(0.0)	0	(0.0)	1	(0.0)
Cardiogenic shock	1	(0.2)	0	(0.0)	0	(0.0)	1	(0.0)
Completed suicide	1	(0.2)	0	(0.0)	3	(0.0)	7	(0.1)
Myocardial infarction	1	(0.2)	1	(0.2)	6	(0.1)	9	(0.1)
Myocardial ischaemia	1	(0.2)	0	(0.0)	0	(0.0)	1	(0.0)
Pneumonia	1	(0.2)	1	(0.2)	37	(0.6)	58	(0.5)
Respiratory tract infection	1	(0.2)	0	(0.0)	0	(0.0)	3	(0.0)
Sepsis	1	(0.2)	0	(0.0)	9	(0.1)	19	(0.2)
Septic shock	1	(0.2)	0	(0.0)	10	(0.2)	17	(0.2)
Sudden death	1	(0.2)	0	(0.0)	2	(0.0)	3	(0.0)
Aortic aneurysm rupture	0	(0.0)	1	(0.2)	0	(0.0)	0	(0.0)
Death	0	(0.0)	1	(0.2)	44	(0.7)	73	(0.7)
Pneumonia bacterial	0	(0.0)	1	(0.2)	0	(0.0)	0	(0.0)
Post procedural pneumonia	0	(0.0)	1	(0.2)	0	(0.0)	0	(0.0)

Table 50: Participants With Drug-Related Adverse Events Resulting in Death by Decreasing Incidence of Preferred Term (APaT Population)

	KN091 Data for Pembrolizumab	KN091 Data for Placebo	Reference Safety Dataset for	Cumulative Running Safety

					Pembrolizumab[i]		Dataset for Pembrolizumab[j]	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	580		581		6,185		10,997	
with one or more adverse events	4	(0.7)	0	(0.0)	39	(0.6)	74	(0.7)
with no adverse events	576	(99.3)	581	(100.0)	6,146	(99.4)	10,923	(99.3)
Myocarditis	2	(0.3)	0	(0.0)	0	(0.0)	4	(0.0)
Cardiogenic shock	1	(0.2)	0	(0.0)	0	(0.0)	1	(0.0)
Pneumonia	1	(0.2)	0	(0.0)	3	(0.0)	7	(0.1)
Septic shock	1	(0.2)	0	(0.0)	0	(0.0)	1	(0.0)
Sudden death	1	(0.2)	0	(0.0)	2	(0.0)	3	(0.0)

The AEs compared to other adjuvant setting are reported below.

Table 51: Adverse event summary (APaT population)

	KN091 Data for Pembrolizumab		KN091 Data for Placebo		Current Safety Dataset for Pembrolizumab in Adjuvant Setting[i]		Reference Safety Dataset for Pembrolizumab[j]	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	580		581		1,480		7,631	
with one or more adverse events	556	(95.9)	529	(91.0)	1,411	(95.3)	7,375	(96.6)
with no adverse event	24	(4.1)	52	(9.0)	69	(4.7)	256	(3.4)
with drug-related[a] adverse events	436	(75.2)	305	(52.5)	1,184	(80.0)	5,462	(71.6)
with toxicity grade 3-5 adverse events	198	(34.1)	150	(25.8)	455	(30.7)	3,514	(46.0)
with toxicity grade 3-5 drug-related adverse events	88	(15.2)	25	(4.3)	247	(16.7)	1,208	(15.8)
with serious adverse events	142	(24.5)	90	(15.5)	329	(22.2)	2,742	(35.9)
with serious drug-related adverse events	68	(11.7)	13	(2.2)	167	(11.3)	840	(11.0)
who died	11	(1.9)	6	(1.0)	4	(0.3)	346	(4.5)
who died due to a drug-related adverse event	4	(0.7)	0	(0.0)	0	(0.0)	42	(0.6)
discontinued drug due to an adverse event	115	(19.8)	34	(5.9)	258	(17.4)	1,066	(14.0)
discontinued drug due to a drug-related adverse event	98	(16.9)	20	(3.4)	230	(15.5)	639	(8.4)
discontinued drug due to a serious adverse event	49	(8.4)	14	(2.4)	115	(7.8)	714	(9.4)
discontinued drug due to a serious drug-related adverse event	34	(5.9)	4	(0.7)	92	(6.2)	347	(4.5)

[a] Determined by the investigator to be related to the drug.
MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
For KN091, Adverse Events of Special Interest (AEOSI) up to 90 days of last dose are included.
[i] Includes all participants who received at least one dose of pembrolizumab in KN054, KN716, KN564.
[j] Includes all participants who received at least one dose of Pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 cohort B and B2, KN013 cohort 3, KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN087, KN158, KN164, KN177, KN204, KN564 and KN716.
Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 03APR2020, KN716: 21JUN2021)
Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEP2018, KN091: 20SEP2021)
Database cutoff date for HNSCC (KN012 cohort B and B2: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)
Database cutoff date for cHL (KN013 cohort 3: 28SEP2018, KN087: 21MAR2019, KN204: 16JAN2020)
Database cutoff date for Bladder (KN045: 26OCT2017, KN052: 26SEP2018)
Database cutoff date for Colorectal (KN164: 09SEP2019, KN177: 19FEB2021, KN564: 14JUN2021)
Database cutoff date for MSI-H (KN158: 05OCT2020)

Laboratory findings

Laboratory Test	KN091 Data for Pembrolizumab (N=580) n	(%)	KN091 Data for Placebo (N=581) n	(%)	Reference Safety Dataset for Pembrolizumab[i] (N=6185) n	(%)	Cumulative Running Safety Dataset for Pembrolizumab[j] (N=10997) n	(%)
Alanine Aminotransferase Increased (Alanine aminotransferase increased)								
Participants with baseline and post-baseline measurements	578		579		5786		10258	
Grade 1	133	(23.0)	109	(18.8)	1196	(20.7)	2052	(20.0)
Grade 2	20	(3.5)	10	(1.7)	156	(2.7)	302	(2.9)
Grade 3	15	(2.6)	3	(0.5)	148	(2.6)	320	(3.1)
Grade 4	4	(0.7)	0	(0.0)	24	(0.4)	45	(0.4)
Grade 3-4	19	(3.3)	3	(0.5)	172	(3.0)	365	(3.6)
All Grades	172	(29.8)	122	(21.1)	1524	(26.3)	2719	(26.5)
Albumin Decreased (Hypoalbuminemia)								
Participants with baseline and post-baseline measurements	575		572		5698		9822	
Grade 1	100	(17.4)	54	(9.4)	1113	(19.5)	1758	(17.9)
Grade 2	15	(2.6)	8	(1.4)	787	(13.8)	1247	(12.7)
Grade 3	2	(0.3)	0	(0.0)	86	(1.5)	169	(1.7)
Grade 4	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Grade 3-4	2	(0.3)	0	(0.0)	86	(1.5)	169	(1.7)
All Grades	117	(20.3)	62	(10.8)	1986	(34.9)	3174	(32.3)
Alkaline Phosphatase Increased (Alkaline phosphatase increased)								
Participants with baseline and post-baseline measurements	578		579		5770		10233	
Grade 1	85	(14.7)	86	(14.9)	1091	(18.9)	1821	(17.8)
Grade 2	10	(1.7)	4	(0.7)	292	(5.1)	531	(5.2)

Grade 3	5	(0.9)	0	(0.0)	144	(2.5)	319	(3.1)
Grade 4	0	(0.0)	0	(0.0)	3	(0.1)	6	(0.1)
Grade 3-4	5	(0.9)	0	(0.0)	147	(2.5)	325	(3.2)
All Grades	100	(17.3)	90	(15.5)	1530	(26.5)	2677	(26.2)
Aspartate Aminotransferase Increased (Aspartate aminotransferase increased)								
Participants with baseline and post-baseline measurements	577		579		5782		10248	
Grade 1	137	(23.7)	105	(18.1)	1295	(22.4)	2184	(21.3)
Grade 2	16	(2.8)	6	(1.0)	208	(3.6)	393	(3.8)
Grade 3	10	(1.7)	5	(0.9)	139	(2.4)	328	(3.2)
Grade 4	6	(1.0)	0	(0.0)	33	(0.6)	59	(0.6)
Grade 3-4	16	(2.8)	5	(0.9)	172	(3.0)	387	(3.8)
All Grades	169	(29.3)	116	(20.0)	1675	(29.0)	2964	(28.9)
Bilirubin Increased (Blood bilirubin increased)								
Participants with baseline and post-baseline measurements	578		579		5761		10220	
Grade 1	30	(5.2)	36	(6.2)	356	(6.2)	606	(5.9)
Grade 2	12	(2.1)	4	(0.7)	177	(3.1)	324	(3.2)
Grade 3	2	(0.3)	0	(0.0)	77	(1.3)	171	(1.7)
Grade 4	4	(0.7)	0	(0.0)	19	(0.3)	56	(0.5)
Grade 3-4	6	(1.0)	0	(0.0)	96	(1.7)	227	(2.2)
All Grades	48	(8.3)	40	(6.9)	629	(10.9)	1157	(11.3)
Calcium Decreased (Hypocalcemia)								
Participants with baseline and post-baseline measurements	570		573		5766		10183	
Grade 1	73	(12.8)	61	(10.6)	1009	(17.5)	1701	(16.7)
Grade 2	8	(1.4)	6	(1.0)	253	(4.4)	467	(4.6)
Grade 3	0	(0.0)	1	(0.2)	34	(0.6)	61	(0.6)
Grade 4	1	(0.2)	0	(0.0)	54	(0.9)	76	(0.7)
Grade 3-4	1	(0.2)	1	(0.2)	88	(1.5)	137	(1.3)
All Grades	82	(14.4)	68	(11.9)	1350	(23.4)	2305	(22.6)
Calcium Increased (Hypercalcemia)								
Participants with baseline and post-baseline measurements	570		573		5760		10163	
Grade 1	73	(12.8)	64	(11.2)	496	(8.6)	894	(8.8)
Grade 2	4	(0.7)	1	(0.2)	68	(1.2)	110	(1.1)
Grade 3	1	(0.2)	1	(0.2)	41	(0.7)	61	(0.6)
Grade 4	0	(0.0)	1	(0.2)	72	(1.3)	110	(1.1)
Grade 3-4	1	(0.2)	2	(0.3)	113	(2.0)	171	(1.7)
All Grades	78	(13.7)	67	(11.7)	677	(11.8)	1175	(11.6)
Creatinine Increased (Creatinine increased)								
Participants with baseline and post-baseline measurements	578		579		5792		10253	
Grade 1	135	(23.4)	131	(22.6)	762	(13.2)	1521	(14.8)
Grade 2	25	(4.3)	25	(4.3)	280	(4.8)	569	(5.5)
Grade 3	3	(0.5)	1	(0.2)	59	(1.0)	113	(1.1)
Grade 4	0	(0.0)	0	(0.0)	24	(0.4)	45	(0.4)
Grade 3-4	3	(0.5)	1	(0.2)	83	(1.4)	158	(1.5)
All Grades	163	(28.2)	157	(27.1)	1125	(19.4)	2248	(21.9)
Glucose Decreased (Hypoglycemia)								
Participants with baseline and post-baseline measurements	564		556		5175		9552	
Grade 1	47	(8.3)	47	(8.5)	424	(8.2)	891	(9.3)
Grade 2	4	(0.7)	3	(0.5)	69	(1.3)	178	(1.9)
Grade 3	0	(0.0)	0	(0.0)	15	(0.3)	40	(0.4)
Grade 4	1	(0.2)	0	(0.0)	18	(0.3)	34	(0.4)
Grade 3-4	1	(0.2)	0	(0.0)	33	(0.6)	74	(0.8)
All Grades	52	(9.2)	50	(9.0)	526	(10.2)	1143	(12.0)
Glucose Increased (Hyperglycemia)								
Participants with baseline and post-baseline measurements	0		0		5193		9024	
Grade 1	0	(0.0)	0	(0.0)	1705	(32.8)	2795	(31.0)
Grade 2	0	(0.0)	0	(0.0)	654	(12.6)	1174	(13.0)

Laboratory Test	KN091 Data for Pembrolizumab (N=580) n	(%)	KN091 Data for Placebo (N=581) n	(%)	Reference Safety Dataset for Pembrolizumab[i] (N=6185) n	(%)	Cumulative Running Safety Dataset for Pembrolizumab[j] (N=10997) n	(%)
Glucose Increased (Hyperglycemia)								
Grade 3	0	(0.0)	0	(0.0)	230	(4.4)	407	(4.5)
Grade 4	0	(0.0)	0	(0.0)	37	(0.7)	81	(0.9)
Grade 3-4	0	(0.0)	0	(0.0)	267	(5.1)	488	(5.4)
All Grades	0	(0.0)	0	(0.0)	2626	(50.6)	4457	(49.4)
Hemoglobin Decreased (Anemia)								
Participants with baseline and post-baseline measurements	578		579		5349		9899	
Grade 1	54	(9.3)	40	(6.9)	1135	(21.2)	1919	(19.4)
Grade 2	21	(3.6)	16	(2.8)	865	(16.2)	1441	(14.6)
Grade 3	5	(0.9)	3	(0.5)	333	(6.2)	652	(6.6)
Grade 4	0	(0.0)	0	(0.0)	9	(0.2)	10	(0.1)
Grade 3-4	5	(0.9)	3	(0.5)	342	(6.4)	662	(6.7)
All Grades	80	(13.8)	59	(10.2)	2342	(43.8)	4022	(40.6)
Leukocytes Decreased (White blood cell decreased)								
Participants with baseline and post-baseline measurements	578		579		5809		10326	
Grade 1	38	(6.6)	35	(6.0)	526	(9.1)	900	(8.7)
Grade 2	7	(1.2)	6	(1.0)	172	(3.0)	304	(2.9)
Grade 3	0	(0.0)	2	(0.3)	19	(0.3)	43	(0.4)
Grade 4	0	(0.0)	0	(0.0)	26	(0.4)	43	(0.4)
Grade 3-4	0	(0.0)	2	(0.3)	45	(0.8)	86	(0.8)

All Grades	45	(7.8)	43	(7.4)	743	(12.8)	1290	(12.5)
Lymphocytes Decreased (Lymphocyte count decreased)								
Participants with baseline and post-baseline measurements	577		577		5469		9895	
Grade 1	73	(12.7)	36	(6.2)	645	(11.8)	1141	(11.5)
Grade 2	45	(7.8)	33	(5.7)	835	(15.3)	1406	(14.2)
Grade 3	12	(2.1)	9	(1.6)	462	(8.4)	763	(7.7)
Grade 4	0	(0.0)	0	(0.0)	95	(1.7)	163	(1.6)
Grade 3-4	12	(2.1)	9	(1.6)	557	(10.2)	926	(9.4)
All Grades	130	(22.5)	78	(13.5)	2037	(37.2)	3473	(35.1)
Platelets Decreased (Platelet count decreased)								
Participants with baseline and post-baseline measurements	578		579		5817		10314	
Grade 1	57	(9.9)	62	(10.7)	588	(10.1)	997	(9.7)
Grade 2	1	(0.2)	0	(0.0)	56	(1.0)	104	(1.0)
Grade 3	0	(0.0)	0	(0.0)	33	(0.6)	61	(0.6)
Grade 4	0	(0.0)	0	(0.0)	72	(1.2)	106	(1.0)
Grade 3-4	0	(0.0)	0	(0.0)	105	(1.8)	167	(1.6)
All Grades	58	(10.0)	62	(10.7)	749	(12.9)	1268	(12.3)
Potassium Decreased (Hypokalemia)								
Participants with baseline and post-baseline measurements	577		578		5772		10223	
Grade 1	46	(8.0)	41	(7.1)	636	(11.0)	1101	(10.8)
Grade 2	0	(0.0)	0	(0.0)	0	(0.0)	20	(0.2)
Grade 3	10	(1.7)	2	(0.3)	108	(1.9)	191	(1.9)
Grade 4	1	(0.2)	0	(0.0)	29	(0.5)	67	(0.7)
Grade 3-4	11	(1.9)	2	(0.3)	137	(2.4)	258	(2.5)
All Grades	57	(9.9)	43	(7.4)	773	(13.4)	1379	(13.5)
Potassium Increased (Hyperkalemia)								
Participants with baseline and post-baseline measurements	577		578		5772		10217	
Grade 1	118	(20.5)	113	(19.6)	745	(12.9)	1351	(13.2)
Grade 2	40	(6.9)	40	(6.9)	243	(4.2)	435	(4.3)
Grade 3	7	(1.2)	11	(1.9)	70	(1.2)	137	(1.3)
Grade 4	1	(0.2)	0	(0.0)	42	(0.7)	87	(0.9)
Grade 3-4	8	(1.4)	11	(1.9)	112	(1.9)	224	(2.2)
All Grades	166	(28.8)	164	(28.4)	1100	(19.1)	2010	(19.7)
Sodium Decreased (Hyponatremia)								
Participants with baseline and post-baseline measurements	578		579		5807		10267	
Grade 1	101	(17.5)	101	(17.4)	1603	(27.6)	2542	(24.8)
Grade 2	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Grade 3	18	(3.1)	9	(1.6)	397	(6.8)	670	(6.5)
Grade 4	3	(0.5)	3	(0.5)	88	(1.5)	153	(1.5)
Grade 3-4	21	(3.6)	12	(2.1)	485	(8.4)	823	(8.0)

Laboratory Test	KN091 Data for Pembrolizumab (N=580) n (%)		KN091 Data for Placebo (N=581) n (%)		Reference Safety Dataset for Pembrolizumab[i] (N=6185) n (%)		Cumulative Running Safety Dataset for Pembrolizumab[j] (N=10997) n (%)	
Sodium Decreased (Hyponatremia)								
All Grades	122	(21.1)	113	(19.5)	2088	(36.0)	3366	(32.8)

Only the highest reported grade of a given laboratory test is counted for the individual participant.
The number of participants with at least one baseline and post-baseline laboratory measurements is used as the denominator for the percentage calculation.
Grades are based on NCI CTCAE version 4.0.
[i] 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 cohorts B and B2, KN013 cohort 3, KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN087, KN177 and KN204.
[j] 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 cohorts B ,B2, C and D, KN013 cohorts 3 and 4A, P017, KN024, KN028 cohorts B4, C1 and A4, KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN057, KN059 cohorts 1 and 3, KN061, KN062, KN087, KN091, KN158 cohorts E, G, TMB-H and K, KN164 cohorts A and B, KN170, KN177, KN180, KN181, KN204, KN224, KN361, KN427, KN564, KN629 and KN716.
Pembrolizumab Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 03APR2020, KN716: 21JUN2021)
Pembrolizumab Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEPT2018, KN091: 20SEP2021)
Pembrolizumab Database cutoff date for HNSCC (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)
Pembrolizumab Database cutoff date for Gastric (KN012-Gastric: 26APR2016, KN059-Cohorts 1 and 3: 08AUG2018, KN061: 26OCT2017, KN062: 26MAR2019)
Pembrolizumab Database cutoff date for cHL (KN013-Cohort 3: 28SEP2018, KN087: 15MAR2021, KN204: 16JAN2020)
Pembrolizumab Database cutoff date for Bladder (KN012-Urothelial: 01SEP2015, KN045: 26OCT2017, KN052: 26SEP2018, KN057: 24MAY2019, KN361: 29APR2020)
Pembrolizumab Database cutoff date for Colorectal (KN164-Cohorts A and B: 09SEP2019, KN177: 19FEB2020)
Pembrolizumab Database cutoff date for PMBCL (KN013-Cohort 4A: 04AUG2017. KN170: 07MAY2020)
Pembrolizumab Database cutoff date for Cervical (KN028-Cohort B4: 20FEB2017, KN158-Cohort E: 27JUN2019)
Pembrolizumab Database cutoff date for HCC (KN224: 05JUN2019)
Pembrolizumab Database cutoff date for MCC (P017: 06FEB2018)
Pembrolizumab Database cutoff date for Esophageal (KN028: 31JAN2018, KN180: 30JUL2018, KN181: 15OCT2018)
Pembrolizumab Database cutoff date for Renal Cell Carcinoma (KN427 Cohort A: 07SEP2018, KN564: 14JUN2021)
Pembrolizumab Database cutoff date for SCLC (KN028-Cohort C1: 31JUL2018, KN158-Cohort G: 27JUN2019)
Pembrolizumab Database cutoff date for TMB-H (KN158: 27JUN2019)
Pembrolizumab Database cutoff date for MSI-H (KN158: 05OCT2020)
Pembrolizumab Database cutoff date for CSCC (KN629: 29JUL2020)

Source: [ISS: adam-adsl; adlbgrd]

Immunogenicity

The immunogenicity incidence rate of treatment emergent positive participants for pembrolizumab monotherapy as adjuvant treatment in participants with completely resected lymph node-positive stage III melanoma (KEYNOTE-054 / EORTC-1325-MG) or completely resected stages IB, II, or IIIA

NSCLC (KEYNOTE-091 / EORTC-1416-LCG) is 2.8% (30 out of 1053 evaluable participants). The historical incidence rate reported after pembrolizumab monotherapy is 2.1% (27 out of 1289 evaluable participants) (see next table). Overall, treatment-emergent ADA status in KEYNOTE-091 and KEYNOTE-054 is not found to affect pembrolizumab exposures. Without any impact on exposures, ADA status is not expected to impact on safety and efficacy.

Table 52: Summary of subject immunogenicity results after pembrolizumab adjuvant treatment (200 mg pembrolizumab Q3W), in participants with completely resected lymph node-positive Stage III melanoma (KEYNOTE-054/EORTC-1325-MG) or completely resected early stage NSCLC (KEYNOTE-091/EORTC-1416-LCG)

Pembrolizumab Therapy			
Immunogenicity status	**Total**	**Melanoma** KEYNOTE-054 / EORTC-1325-MG	**NSCLC** KEYNOTE-091 / EORTC-1416-LCG
Assessable participants[a]	1057	496	561
Inconclusive participants[b]	4	1	3
Evaluable participants[c]	**1053**	**495**	**558**
Negative[d]	1011 (96.0%)	473 (95.6%)	538 (96.4%)
Non-Treatment emergent positive[d]	12 (1.1%)	5 (1.0%)	7 (1.3%)
Neutralizing negative	9 (0.8%)	5 (1.0%)	4 (0.7%)
Neutralizing positive	3 (0.3%)	0	3 (0.5%)
Treatment emergent positive[d]	30 (2.8%)	17 (3.4%)	13 (2.3%)
Neutralizing negative	30 (2.8%)	17 (3.4%)	13 (2.3%)
Neutralizing positive	0	0	0

a: Included are participants with at least one ADA sample available after treatment with pembrolizumab
b: Inconclusive participants are the number of participants with no positive ADA samples present and the drug concentration in the last sample above the drug tolerance level.
c: Evaluable participants are the total number of negative and positive participants (non-treatment emergent and treatment emergent.
d: Denominator was total number of evaluable participants.

Safety in special populations

Age

The AE profile based on age (with a cutoff at 65 years) in the KEYNOTE-091 Pembrolizumab Dataset is shown in the table below.

Table 53: Adverse event summary by age category (<65, ≥65 years) (APaT population)

	KN091 Data for Pembrolizumab				KN091 Data for Placebo				Reference Safety Dataset for Pembrolizumab[i]				Cumulative Running Safety Dataset for Pembrolizumab[j]			
	<65		>=65		<65		>=65		<65		>=65		<65		>=65	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	281		299		272		309		3,587		2,598		6,233		4,764	
with one or more adverse events	267	(95.0)	289	(96.7)	250	(91.9)	279	(90.3)	3,469	(96.7)	2,520	(97.0)	5,998	(96.2)	4,599	(96.5)
with no adverse event	14	(5.0)	10	(3.3)	22	(8.1)	30	(9.7)	118	(3.3)	78	(3.0)	235	(3.8)	165	(3.5)
with drug-related[a] adverse events	210	(74.7)	226	(75.6)	147	(54.0)	158	(51.1)	2,521	(70.3)	1,845	(71.0)	4,316	(69.2)	3,373	(70.8)
with toxicity grade 3-5 adverse events	92	(32.7)	106	(35.5)	71	(26.1)	79	(25.6)	1,596	(44.5)	1,388	(53.4)	2,759	(44.3)	2,419	(50.8)
with toxicity grade 3-5 drug-related adverse events	43	(15.3)	45	(15.1)	11	(4.0)	14	(4.5)	495	(13.8)	480	(18.5)	886	(14.2)	875	(18.4)
with serious adverse events	62	(22.1)	80	(26.8)	44	(16.2)	46	(14.9)	1,236	(34.5)	1,135	(43.7)	2,059	(33.0)	1,925	(40.4)
with serious drug-related adverse events	29	(10.3)	39	(13.0)	6	(2.2)	7	(2.3)	371	(10.3)	330	(12.7)	623	(10.0)	604	(12.7)
who died	5	(1.8)	6	(2.0)	1	(0.4)	5	(1.6)	148	(4.1)	173	(6.7)	233	(3.7)	309	(6.5)
who died due to a drug-related adverse event	3	(1.1)	1	(0.3)	0	(0.0)	0	(0.0)	21	(0.6)	18	(0.7)	32	(0.5)	42	(0.9)
discontinued drug due to an adverse event	50	(17.8)	65	(21.7)	11	(4.0)	23	(7.4)	423	(11.8)	409	(15.7)	737	(11.8)	771	(16.2)
discontinued drug due to a drug-related adverse event	43	(15.3)	55	(18.4)	6	(2.2)	14	(4.5)	228	(6.4)	216	(8.3)	440	(7.1)	467	(9.8)
discontinued drug due to a serious adverse event	22	(7.8)	27	(9.0)	8	(2.9)	6	(1.9)	301	(8.4)	297	(11.4)	491	(7.9)	516	(10.8)

The following table shows the data about AEs in pembrolizumab and placebo arms with subcategories for patients >65 years (table truncated for brevity).

Table 54: Adverse event summary by age category (<65, 65-74, 75-84, ≥85 years) (APaT population)

	KN091 Data for Pembrolizumab								KN091 Data for Placebo							
	<65		65-74		75-84		>=85		<65		65-74		75-84		>=85	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	281		245		51		3		272		243		64		2	
with one or more adverse events	267	(95.0)	236	(96.3)	50	(98.0)	3	(100.0)	250	(91.9)	220	(90.5)	57	(89.1)	2	(100.0)
with no adverse event	14	(5.0)	9	(3.7)	1	(2.0)	0	(0.0)	22	(8.1)	23	(9.5)	7	(10.9)	0	(0.0)
with drug-related[a] adverse events	210	(74.7)	187	(76.3)	36	(70.6)	3	(100.0)	147	(54.0)	132	(54.3)	26	(40.6)	0	(0.0)
with toxicity grade 3-5 adverse events	92	(32.7)	87	(35.5)	18	(35.3)	1	(33.3)	71	(26.1)	58	(23.9)	20	(31.3)	1	(50.0)
with toxicity grade 3-5 drug-related adverse events	43	(15.3)	36	(14.7)	9	(17.6)	0	(0.0)	11	(4.0)	10	(4.1)	4	(6.3)	0	(0.0)
with serious adverse events	62	(22.1)	65	(26.5)	14	(27.5)	1	(33.3)	44	(16.2)	33	(13.6)	12	(18.8)	1	(50.0)
with serious drug-related adverse events	29	(10.3)	33	(13.5)	6	(11.8)	0	(0.0)	6	(2.2)	6	(2.5)	1	(1.6)	0	(0.0)
who died	5	(1.8)	5	(2.0)	1	(2.0)	0	(0.0)	1	(0.4)	4	(1.6)	1	(1.6)	0	(0.0)
who died due to a drug-related adverse event	3	(1.1)	1	(0.4)	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	50	(17.8)	48	(19.6)	17	(33.3)	0	(0.0)	11	(4.0)	17	(7.0)	6	(9.4)	0	(0.0)
discontinued drug due to a drug-related adverse event	43	(15.3)	42	(17.1)	13	(25.5)	0	(0.0)	6	(2.2)	11	(4.5)	3	(4.7)	0	(0.0)
discontinued drug due to a serious adverse event	22	(7.8)	22	(9.0)	5	(9.8)	0	(0.0)	8	(2.9)	5	(2.1)	1	(1.6)	0	(0.0)

	Reference Safety Dataset for Pembrolizumab[i]								Cumulative Running Safety Dataset for Pembrolizumab[j]							
	<65		65-74		75-84		>=85		<65		65-74		75-84		>=85	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	3,587		1,797		694		107		6,233		3,333		1,253		178	
with one or more adverse events	3,469	(96.7)	1,737	(96.7)	677	(97.6)	106	(99.1)	5,998	(96.2)	3,203	(96.1)	1,221	(97.4)	175	(98.3)
with no adverse event	118	(3.3)	60	(3.3)	17	(2.4)	1	(0.9)	235	(3.8)	130	(3.9)	32	(2.6)	3	(1.7)
with drug-related[a] adverse events	2,521	(70.3)	1,272	(70.8)	491	(70.7)	82	(76.6)	4,316	(69.2)	2,360	(70.8)	884	(70.6)	129	(72.5)
with toxicity grade 3-5 adverse events	1,596	(44.5)	928	(51.6)	392	(56.5)	68	(63.6)	2,759	(44.3)	1,629	(48.9)	688	(54.9)	102	(57.3)
with toxicity grade 3-5 drug-related adverse events	495	(13.8)	321	(17.9)	135	(19.5)	24	(22.4)	886	(14.2)	596	(17.9)	241	(19.2)	38	(21.3)
with serious adverse events	1,236	(34.5)	749	(41.7)	329	(47.4)	57	(53.3)	2,059	(33.0)	1,263	(37.9)	577	(46.0)	85	(47.8)
with serious drug-related adverse events	371	(10.3)	223	(12.4)	90	(13.0)	17	(15.9)	623	(10.0)	419	(12.6)	160	(12.8)	25	(14.0)
who died	148	(4.1)	106	(5.9)	55	(7.9)	12	(11.2)	233	(3.7)	184	(5.5)	105	(8.4)	20	(11.2)
who died due to a drug-related adverse event	21	(0.6)	12	(0.7)	5	(0.7)	1	(0.9)	32	(0.5)	26	(0.8)	14	(1.1)	2	(1.1)
discontinued drug due to an adverse event	423	(11.8)	255	(14.2)	138	(19.9)	16	(15.0)	737	(11.8)	488	(14.6)	252	(20.1)	31	(17.4)
discontinued drug due to a drug-related adverse event	228	(6.4)	142	(7.9)	67	(9.7)	7	(6.5)	440	(7.1)	310	(9.3)	142	(11.3)	15	(8.4)
discontinued drug due to a serious adverse event	301	(8.4)	181	(10.1)	103	(14.8)	13	(12.1)	491	(7.9)	319	(9.6)	173	(13.8)	24	(13.5)

[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.

For KN091, Adverse Events of Special Interest (AEOSI) up to 90 days of last dose are included.

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

Grades are based on NCI CTCAE version 4.03.

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

[j] 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 cohorts B ,B2, C and D, KN013 cohorts 3 and 4A, P017, KN024, KN028 cohorts B4, C1 and A4, KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN057, KN059 cohorts 1 and 3, KN061, KN062, KN087, KN091, KN158 cohorts E, G, TMB-H and K, KN164 cohorts A and B, KN170, KN177, KN180, KN181, KN204, KN224, KN361, KN427, KN564, KN629 and KN716.

Pembrolizumab Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 03APR2020, KN716: 21JUN2021)

Pembrolizumab Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEPT2018, KN091: 20SEP2021)

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

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

Pembrolizumab Database cutoff date for cHL (KN013-Cohort 3: 28SEP2018, KN087: 15MAR2021, KN204: 16JAN2020)

Pembrolizumab Database cutoff date for Bladder (KN012-Urothelial: 01SEP2015, KN045: 26OCT2017, KN052: 26SEP2018, KN057: 24MAY2019, KN361: 29APR2020)

Pembrolizumab Database cutoff date for Colorectal (KN164-Cohorts A and B: 09SEP2019, KN177: 19FEB2020)

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

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

Pembrolizumab Database cutoff date for HCC (KN224: 05JUN2019)

Pembrolizumab Database cutoff date for MCC (P017: 06FEB2018)

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

Pembrolizumab Database cutoff date for Renal Cell Carcinoma (KN427 Cohort A: 07SEP2018, KN564: 14JUN2021)

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

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

Pembrolizumab Database cutoff date for MSI-H (KN158: 05OCT2020)

Pembrolizumab Database cutoff date for CSCC (KN629: 29JUL2020)

Source: [ISS: adam-adsl; adae]

Gender

The next table shows the overall summary of AEs by gender in the different datasets.

Table 55: Adverse event summary by sex (Male, Female) (APaT population)

	KN091 Data for Pembrolizumab				KN091 Data for Placebo				Reference Safety Dataset for Pembrolizumab[i]				Cumulative Running Safety Dataset for Pembrolizumab[j]			
	M		F		M		F		M		F		M		F	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	394		186		397		184		4,039		2,146		7,259		3,738	
with one or more adverse events	374	(94.9)	182	(97.8)	358	(90.2)	171	(92.9)	3,908	(96.8)	2,081	(97.0)	6,964	(95.9)	3,633	(97.2)
with no adverse event	20	(5.1)	4	(2.2)	39	(9.8)	13	(7.1)	131	(3.2)	65	(3.0)	295	(4.1)	105	(2.8)
with drug-related[a] adverse events	295	(74.9)	141	(75.8)	195	(49.1)	110	(59.8)	2,826	(70.0)	1,540	(71.8)	5,008	(69.0)	2,681	(71.7)
with toxicity grade 3-5 adverse events	143	(36.3)	55	(29.6)	100	(25.2)	50	(27.2)	1,965	(48.7)	1,019	(47.5)	3,445	(47.5)	1,733	(46.4)
with toxicity grade 3-5 drug-related adverse events	56	(14.2)	32	(17.2)	13	(3.3)	12	(6.5)	662	(16.4)	313	(14.6)	1,205	(16.6)	556	(14.9)
with serious adverse events	103	(26.1)	39	(21.0)	65	(16.4)	25	(13.6)	1,580	(39.1)	791	(36.9)	2,680	(36.9)	1,304	(34.9)
with serious drug-related adverse events	46	(11.7)	22	(11.8)	7	(1.8)	6	(3.3)	473	(11.7)	228	(10.6)	844	(11.6)	383	(10.2)
who died	10	(2.5)	1	(0.5)	5	(1.3)	1	(0.5)	224	(5.5)	97	(4.5)	395	(5.4)	147	(3.9)
who died due to a drug-related adverse event	3	(0.8)	1	(0.5)	0	(0.0)	0	(0.0)	24	(0.6)	15	(0.7)	50	(0.7)	24	(0.6)
discontinued drug due to an adverse event	81	(20.6)	34	(18.3)	22	(5.5)	12	(6.5)	544	(13.5)	288	(13.4)	1,011	(13.9)	497	(13.3)
discontinued drug due to a drug-related adverse event	65	(16.5)	33	(17.7)	12	(3.0)	8	(4.3)	292	(7.2)	152	(7.1)	601	(8.3)	306	(8.2)
discontinued drug due to a serious adverse event	35	(8.9)	14	(7.5)	10	(2.5)	4	(2.2)	397	(9.8)	201	(9.4)	684	(9.4)	323	(8.6)
discontinued drug due to a serious drug-related adverse event	20	(5.1)	14	(7.5)	2	(0.5)	2	(1.1)	177	(4.4)	88	(4.1)	328	(4.5)	160	(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.

For KN091, Adverse Events of Special Interest (AEOSI) up to 90 days of last dose are included.

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

Grades are based on NCI CTCAE version 4.03.

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

[j] 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 cohorts B ,B2, C and D, KN013 cohorts 3 and 4A, P017, KN024, KN028 cohorts B4, C1 and A4, KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN057, KN059 cohorts 1 and 3, KN061, KN062, KN087, KN091, KN158 cohorts E, G, TMB-H and K, KN164 cohorts A and B, KN170, KN177, KN180, KN181, KN204, KN224, KN361, KN427, KN564, KN629 and KN716.

Pembrolizumab Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 03APR2020, KN716: 21JUN2021)

Pembrolizumab Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEPT2018, KN091: 20SEP2021)

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

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

Pembrolizumab Database cutoff date for cHL (KN013-Cohort 3: 28SEP2018, KN087: 15MAR2021, KN204: 16JAN2020)

Pembrolizumab Database cutoff date for Bladder (KN012-Urothelial: 01SEP2015, KN045: 26OCT2017, KN052: 26SEP2018, KN057: 24MAY2019, KN361: 29APR2020)

Pembrolizumab Database cutoff date for Colorectal (KN164-Cohorts A and B: 09SEP2019, KN177: 19FEB2020)

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

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

Pembrolizumab Database cutoff date for HCC (KN224: 05JUN2019)

Pembrolizumab Database cutoff date for MCC (P017: 06FEB2018)

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

Pembrolizumab Database cutoff date for Renal Cell Carcinoma (KN427 Cohort A: 07SEP2018, KN564: 14JUN2021)

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

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

Pembrolizumab Database cutoff date for MSI-H (KN158: 05OCT2020)

Pembrolizumab Database cutoff date for CSCC (KN629: 29JUL2020)

Race

The next table shows the overall summary of AEs by race.

Table 56: Adverse event summary by race (white, other, not applicable) (APaT population)

	KN091 Data for Pembrolizumab						KN091 Data for Placebo					
	White		Other		Not Applicable		White		Other		Not Applicable	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	442		117		21		450		113		18	
with one or more adverse events	422	(95.5)	114	(97.4)	20	(95.2)	411	(91.3)	100	(88.5)	18	(100.0)
with no adverse event	20	(4.5)	3	(2.6)	1	(4.8)	39	(8.7)	13	(11.5)	0	(0.0)
with drug-related[a] adverse events	334	(75.6)	85	(72.6)	17	(81.0)	238	(52.9)	51	(45.1)	16	(88.9)
with toxicity grade 3-5 adverse events	164	(37.1)	27	(23.1)	7	(33.3)	131	(29.1)	14	(12.4)	5	(27.8)
with toxicity grade 3-5 drug-related adverse events	71	(16.1)	15	(12.8)	2	(9.5)	20	(4.4)	4	(3.5)	1	(5.6)
with serious adverse events	116	(26.2)	22	(18.8)	4	(19.0)	81	(18.0)	8	(7.1)	1	(5.6)
with serious drug-related adverse events	54	(12.2)	12	(10.3)	2	(9.5)	10	(2.2)	3	(2.7)	0	(0.0)
who died	9	(2.0)	2	(1.7)	0	(0.0)	5	(1.1)	0	(0.0)	1	(5.6)
who died due to a drug-related adverse event	3	(0.7)	1	(0.9)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued drug due to an adverse event	96	(21.7)	14	(12.0)	5	(23.8)	26	(5.8)	8	(7.1)	0	(0.0)
discontinued drug due to a drug-related adverse event	80	(18.1)	14	(12.0)	4	(19.0)	14	(3.1)	6	(5.3)	0	(0.0)
discontinued drug due to a serious adverse event	40	(9.0)	7	(6.0)	2	(9.5)	13	(2.9)	1	(0.9)	0	(0.0)
discontinued drug due to a serious drug-related adverse event	25	(5.7)	7	(6.0)	2	(9.5)	4	(0.9)	0	(0.0)	0	(0.0)

	Reference Safety Dataset for Pembrolizumab[i]						Cumulative Running Safety Dataset for Pembrolizumab[j]					
	White		Other		Not Applicable		White		Other		Not Applicable	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	4,673		921		591		8,170		1,996		831	
with one or more adverse events	4,545	(97.3)	886	(96.2)	558	(94.4)	7,902	(96.7)	1,908	(95.6)	787	(94.7)
with no adverse event	128	(2.7)	35	(3.8)	33	(5.6)	268	(3.3)	88	(4.4)	44	(5.3)
with drug-related[a] adverse events	3,292	(70.4)	615	(66.8)	459	(77.7)	5,714	(69.9)	1,330	(66.6)	645	(77.6)
with toxicity grade 3-5 adverse events	2,334	(49.9)	448	(48.6)	202	(34.2)	3,983	(48.8)	902	(45.2)	293	(35.3)
with toxicity grade 3-5 drug-related adverse events	736	(15.8)	155	(16.8)	84	(14.2)	1,313	(16.1)	329	(16.5)	119	(14.3)
with serious adverse events	1,852	(39.6)	361	(39.2)	158	(26.7)	3,066	(37.5)	685	(34.3)	233	(28.0)
with serious drug-related adverse events	495	(10.6)	134	(14.5)	72	(12.2)	860	(10.5)	265	(13.3)	102	(12.3)
who died	255	(5.5)	63	(6.8)	3	(0.5)	426	(5.2)	104	(5.2)	12	(1.4)
who died due to a drug-related adverse event	29	(0.6)	10	(1.1)	0	(0.0)	49	(0.6)	22	(1.1)	3	(0.4)
discontinued drug due to an adverse event	625	(13.4)	129	(14.0)	78	(13.2)	1,136	(13.9)	251	(12.6)	121	(14.6)
discontinued drug due to a drug-related adverse event	306	(6.5)	71	(7.7)	67	(11.3)	641	(7.8)	162	(8.1)	104	(12.5)
discontinued drug due to a serious adverse event	464	(9.9)	101	(11.0)	33	(5.6)	763	(9.3)	184	(9.2)	60	(7.2)
discontinued drug due to a serious drug-related adverse event	191	(4.1)	50	(5.4)	24	(4.1)	336	(4.1)	106	(5.3)	46	(5.5)

[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.

For KN091, Adverse Events of Special Interest (AEOSI) up to 90 days of last dose are included.

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

Grades are based on NCI CTCAE version 4.03.

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

[j] 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 cohorts B ,B2, C and D, KN013 cohorts 3 and 4A, P017, KN024, KN028 cohorts B4, C1 and A4, KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN057, KN059 cohorts 1 and 3, KN061, KN062, KN087, KN091, KN158 cohorts E, G, TMB-H and K, KN164 cohorts A and B, KN170, KN177, KN180, KN181, KN204, KN224, KN361, KN427, KN564, KN629 and KN716.

Pembrolizumab Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 03APR2020, KN716: 21JUN2021)

Pembrolizumab Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEPT2018, KN091: 20SEP2021)

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

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

Pembrolizumab Database cutoff date for cHL (KN013-Cohort 3: 28SEP2018, KN087: 15MAR2021, KN204: 16JAN2020)

Pembrolizumab Database cutoff date for Bladder (KN012-Urothelial: 01SEP2015, KN045: 26OCT2017, KN052: 26SEP2018, KN057: 24MAY2019, KN361: 29APR2020)

Pembrolizumab Database cutoff date for Colorectal (KN164-Cohorts A and B: 09SEP2019, KN177: 19FEB2020)

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

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

Pembrolizumab Database cutoff date for HCC (KN224: 05JUN2019)

Pembrolizumab Database cutoff date for MCC (P017: 06FEB2018)

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

Pembrolizumab Database cutoff date for Renal Cell Carcinoma (KN427 Cohort A: 07SEP2018, KN564: 14JUN2021)

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

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

Pembrolizumab Database cutoff date for MSI-H (KN158: 05OCT2020)

Pembrolizumab Database cutoff date for CSCC (KN629: 29JUL2020)

Source: [ISS: adam-adsl; adae]

Pregnancy and lactation

There were no reports of pregnancy in KEYNOTE-091.

Pembrolizumab should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus. It is not known whether pembrolizumab is secreted in human milk. Because many drugs and IgG antibodies are secreted in human milk, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

ECOG status

The following table shows a summary of the AEs by ECOG status.

Table 57: Adverse event summary by ECOG status category (0, 1) (APaT population)

	KN091 Data for Pembrolizumab				KN091 Data for Placebo				Reference Safety Dataset for Pembrolizumab[i]				Cumulative Running Safety Dataset for Pembrolizumab[j]			
	[0] Normal Activity		[1] Symptoms, but ambulatory		[0] Normal Activity		[1] Symptoms, but ambulatory		[0] Normal Activity		[1] Symptoms, but ambulatory		[0] Normal Activity		[1] Symptoms, but ambulatory	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	375		205		339		242		2,942		3,069		5,570		5,110	
with one or more adverse events	358	(95.5)	198	(96.6)	307	(90.6)	222	(91.7)	2,852	(96.9)	2,970	(96.8)	5,363	(96.3)	4,929	(96.5)
with no adverse event	17	(4.5)	7	(3.4)	32	(9.4)	20	(8.3)	90	(3.1)	99	(3.2)	207	(3.7)	181	(3.5)
with drug-related[a] adverse events	282	(75.2)	154	(75.1)	169	(49.9)	136	(56.2)	2,223	(75.6)	2,048	(66.7)	4,148	(74.5)	3,336	(65.3)
with toxicity grade 3-5 adverse events	117	(31.2)	81	(39.5)	68	(20.1)	82	(33.9)	1,196	(40.7)	1,680	(54.7)	2,182	(39.2)	2,815	(55.1)
with toxicity grade 3-5 drug-related adverse events	54	(14.4)	34	(16.6)	12	(3.5)	13	(5.4)	446	(15.2)	499	(16.3)	860	(15.4)	836	(16.4)
with serious adverse events	86	(22.9)	56	(27.3)	43	(12.7)	47	(19.4)	930	(31.6)	1,347	(43.9)	1,634	(29.3)	2,196	(43.0)
with serious drug-related adverse events	46	(12.3)	22	(10.7)	6	(1.8)	7	(2.9)	336	(11.4)	348	(11.3)	613	(11.0)	574	(11.2)
who died	5	(1.3)	6	(2.9)	3	(0.9)	3	(1.2)	83	(2.8)	222	(7.2)	154	(2.8)	366	(7.2)
who died due to a drug-related adverse event	3	(0.8)	1	(0.5)	0	(0.0)	0	(0.0)	13	(0.4)	26	(0.8)	26	(0.5)	47	(0.9)
discontinued drug due to an adverse event	71	(18.9)	44	(21.5)	13	(3.8)	21	(8.7)	333	(11.3)	470	(15.3)	713	(12.8)	742	(14.5)
discontinued drug due to a drug-related adverse event	65	(17.3)	33	(16.1)	9	(2.7)	11	(4.5)	217	(7.4)	214	(7.0)	519	(9.3)	358	(7.0)
discontinued drug due to a serious adverse event	27	(7.2)	22	(10.7)	4	(1.2)	10	(4.1)	214	(7.3)	363	(11.8)	408	(7.3)	565	(11.1)
discontinued drug due to a serious drug-related adverse event	21	(5.6)	13	(6.3)	1	(0.3)	3	(1.2)	118	(4.0)	140	(4.6)	247	(4.4)	227	(4.4)

[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.

For KN091, Adverse Events of Special Interest (AEOSI) up to 90 days of last dose are included.

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

Grades are based on NCI CTCAE version 4.03.

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

[j] 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 cohorts B ,B2, C and D, KN013 cohorts 3 and 4A, P017, KN024, KN028 cohorts B4, C1 and A4, KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN057, KN059 cohorts 1 and 3, KN061, KN062, KN087, KN091, KN158 cohorts E, G, TMB-H and K, KN164 cohorts A and B, KN170, KN177, KN180, KN181, KN204, KN224, KN361, KN427, KN564, KN629 and KN716.

Pembrolizumab Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 03APR2020, KN716: 21JUN2021)

Pembrolizumab Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEPT2018, KN091: 20SEP2021)

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

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

Pembrolizumab Database cutoff date for cHL (KN013-Cohort 3: 28SEP2018, KN087: 15MAR2021, KN204: 16JAN2020)

Pembrolizumab Database cutoff date for Bladder (KN012-Urothelial: 01SEP2015, KN045: 26OCT2017, KN052: 26SEP2018, KN057: 24MAY2019, KN361: 29APR2020)

Pembrolizumab Database cutoff date for Colorectal (KN164-Cohorts A and B: 09SEP2019, KN177: 19FEB2020)

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

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

Pembrolizumab Database cutoff date for HCC (KN224: 05JUN2019)

Pembrolizumab Database cutoff date for MCC (P017: 06FEB2018)

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

Pembrolizumab Database cutoff date for Renal Cell Carcinoma (KN427 Cohort A: 07SEP2018, KN564: 14JUN2021)

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

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

Pembrolizumab Database cutoff date for MSI-H (KN158: 05OCT2020)

Pembrolizumab Database cutoff date for CSCC (KN629: 29JUL2020)

Source: [ISS: adam-adsl; adae]

Geographical region

The following table shows the summary of AEs by geographical region.

Table 58: Adverse event summary by region (EU, ex-EU) (APaT population)

	KN091 Data for Pembrolizumab				KN091 Data for Placebo				Reference Safety Dataset for Pembrolizumab[i]				Cumulative Running Safety Dataset for Pembrolizumab[j]			
	EU		Ex-EU		EU		Ex-EU		EU		Ex-EU		EU		Ex-EU	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	388		192		387		194		2,217		3,968		4,209		6,788	
with one or more adverse events	373	(96.1)	183	(95.3)	353	(91.2)	176	(90.7)	2,135	(96.3)	3,854	(97.1)	4,042	(96.0)	6,555	(96.6)
with no adverse event	15	(3.9)	9	(4.7)	34	(8.8)	18	(9.3)	82	(3.7)	114	(2.9)	167	(4.0)	233	(3.4)
with drug-related[a] adverse events	293	(75.5)	143	(74.5)	215	(55.6)	90	(46.4)	1,526	(68.8)	2,840	(71.6)	2,920	(69.4)	4,769	(70.3)
with toxicity grade 3-5 adverse events	147	(37.9)	51	(26.6)	118	(30.5)	32	(16.5)	1,022	(46.1)	1,962	(49.4)	1,931	(45.9)	3,247	(47.8)
with toxicity grade 3-5 drug-related adverse events	65	(16.8)	23	(12.0)	19	(4.9)	6	(3.1)	341	(15.4)	634	(16.0)	668	(15.9)	1,093	(16.1)
with serious adverse events	104	(26.8)	38	(19.8)	71	(18.3)	19	(9.8)	846	(38.2)	1,525	(38.4)	1,550	(36.8)	2,434	(35.9)
with serious drug-related adverse events	53	(13.7)	15	(7.8)	9	(2.3)	4	(2.1)	260	(11.7)	441	(11.1)	490	(11.6)	737	(10.9)
who died	7	(1.8)	4	(2.1)	4	(1.0)	2	(1.0)	113	(5.1)	208	(5.2)	208	(4.9)	334	(4.9)
who died due to a drug-related adverse event	3	(0.8)	1	(0.5)	0	(0.0)	0	(0.0)	11	(0.5)	28	(0.7)	26	(0.6)	48	(0.7)
discontinued drug due to an adverse event	92	(23.7)	23	(12.0)	21	(5.4)	13	(6.7)	287	(12.9)	545	(13.7)	626	(14.9)	882	(13.0)
discontinued drug due to a drug-related adverse event	77	(19.8)	21	(10.9)	12	(3.1)	8	(4.1)	166	(7.5)	278	(7.0)	400	(9.5)	507	(7.5)
discontinued drug due to a serious adverse event	38	(9.8)	11	(5.7)	11	(2.8)	3	(1.5)	205	(9.2)	393	(9.9)	401	(9.5)	606	(8.9)
discontinued drug due to a serious drug-related adverse event	25	(6.4)	9	(4.7)	4	(1.0)	0	(0.0)	98	(4.4)	167	(4.2)	202	(4.8)	286	(4.2)

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

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

For KN091, Adverse Events of Special Interest (AEOSI) up to 90 days of last dose are included.

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

Grades are based on NCI CTCAE version 4.03.

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

[j] 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 cohorts B ,B2, C and D, KN013 cohorts 3 and 4A, P017, KN024, KN028 cohorts B4, C1 and A4, KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN057, KN059 cohorts 1 and 3, KN061, KN062, KN087, KN091, KN158 cohorts E, G, TMB-H and K, KN164 cohorts A and B, KN170, KN177, KN180, KN181, KN204, KN224, KN361, KN427, KN564, KN629 and KN716.

Pembrolizumab Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 03APR2020, KN716: 21JUN2021)

Pembrolizumab Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEPT2018, KN091: 20SEP2021)

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

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

Pembrolizumab Database cutoff date for cHL (KN013-Cohort 3: 28SEP2018, KN087: 15MAR2021, KN204: 16JAN2020)

Pembrolizumab Database cutoff date for Bladder (KN012-Urothelial: 01SEP2015, KN045: 26OCT2017, KN052: 26SEP2018, KN057: 24MAY2019, KN361: 29APR2020)

Pembrolizumab Database cutoff date for Colorectal (KN164-Cohorts A and B: 09SEP2019, KN177: 19FEB2020)

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

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

Pembrolizumab Database cutoff date for HCC (KN224: 05JUN2019)

Pembrolizumab Database cutoff date for MCC (P017: 06FEB2018)

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

Pembrolizumab Database cutoff date for Renal Cell Carcinoma (KN427 Cohort A: 07SEP2018, KN564: 14JUN2021)

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

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

Pembrolizumab Database cutoff date for MSI-H (KN158: 05OCT2020)

Pembrolizumab Database cutoff date for CSCC (KN629: 29JUL2020)

Source: [ISS: adam-adsl; adae]

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. No preclinical pharmacokinetic studies were conducted to assess the propensity of pembrolizumab to be a victim or perpetrator of pharmacokinetic DDIs.

Studies evaluating pharmacodynamic drug interactions with pembrolizumab have not been conducted. However, as systemic corticosteroids may be used in combination with pembrolizumab to ameliorate potential side effects, the potential for a pharmacokinetic DDI with pembrolizumab as a victim was assessed as part of the population pharmacokinetic analysis. No relationship was observed between prolonged use of systemic corticosteroids and pembrolizumab exposure. Nevertheless, given the study design, exclusion criteria, and immunomodulatory mechanism of action, the use of systemic

corticosteroids (at doses greater than physiologic replacement), or other immunosuppressants before the start of pembrolizumab treatment, is not recommended. However, systemic corticosteroids, or other immunosuppressants, can be used during pembrolizumab treatment to treat immune-related adverse reactions.

Discontinuation due to adverse events

The proportions of participants who discontinued study medication due to a drug-related AE were higher in the KEYNOTE-091 Pembrolizumab Dataset than in the RSD. The higher incidence of discontinuation of study medication due to drug-related AEs may be explained by the approximately 2-fold longer duration of exposure in the KEYNOTE-091 Pembrolizumab Dataset compared with the RSD.

The number of patients who discontinued the drug due to AEs was higher in pembrolizumab than placebo (19.8% vs 5.9%) and also compared to the RSD (13.5%). Most, in both arms pembrolizumab and placebo, discontinued due to a drug-related AE (16.9% vs 3.4%). Those who discontinued due to a SAE were more frequent in pembrolizumab (8.4% vs 2.4%).

The most frequently reported AEs (incidence ≥5 participants) leading to treatment discontinuation in the KEYNOTE-091 Pembrolizumab Dataset were pneumonitis, diarrhoea, colitis, and hypothyroidism. Pneumonitis was reported in 3.6% of participants in the KEYNOTE-091 Pembrolizumab Dataset compared with 1.7% in the RSD. Diarrhoea was observed in 1.2% of participants in the KEYNOTE-091 Pembrolizumab Dataset compared with 0.2% in the RSD. Colitis was observed with a similar frequency in the KEYNOTE-091 Pembrolizumab Dataset and RSD.

The following table shows the most frequent causes of discontinuation (the table is truncated for brevity).

Table 59: Participants with adverse events resulting in treatment discontinuation by decreasing incidence of preferred term (incidence >0% in one or more treatment groups) (APaT population)

	KN091 Data for Pembrolizumab		KN091 Data for Placebo		Reference Safety Dataset for Pembrolizumab[i]		Cumulative Running Safety Dataset for Pembrolizumab[j]	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	580		581		6,185		10,997	
with one or more adverse events	115	(19.8)	34	(5.9)	832	(13.5)	1,508	(13.7)
with no adverse events	465	(80.2)	547	(94.1)	5,353	(86.5)	9,489	(86.3)
Pneumonitis	21	(3.6)	4	(0.7)	107	(1.7)	159	(1.4)
Diarrhoea	7	(1.2)	2	(0.3)	13	(0.2)	33	(0.3)
Colitis	5	(0.9)	1	(0.2)	29	(0.5)	55	(0.5)
Hypothyroidism	5	(0.9)	0	(0.0)	2	(0.0)	12	(0.1)
Hypophysitis	4	(0.7)	0	(0.0)	5	(0.1)	12	(0.1)
Interstitial lung disease	4	(0.7)	1	(0.2)	10	(0.2)	22	(0.2)
Hepatitis	3	(0.5)	0	(0.0)	9	(0.1)	23	(0.2)
Immune-mediated hepatitis	3	(0.5)	0	(0.0)	2	(0.0)	6	(0.1)
Myocarditis	3	(0.5)	1	(0.2)	4	(0.1)	10	(0.1)
Psoriasis	3	(0.5)	0	(0.0)	3	(0.0)	7	(0.1)
Adrenal insufficiency	2	(0.3)	0	(0.0)	4	(0.1)	18	(0.2)
Alanine aminotransferase increased	2	(0.3)	4	(0.7)	21	(0.3)	44	(0.4)
Anaemia	2	(0.3)	0	(0.0)	3	(0.0)	5	(0.0)
Aspartate aminotransferase increased	2	(0.3)	4	(0.7)	20	(0.3)	36	(0.3)
Autoimmune hepatitis	2	(0.3)	0	(0.0)	12	(0.2)	31	(0.3)
Dyspnoea	2	(0.3)	1	(0.2)	16	(0.3)	20	(0.2)
Fatigue	2	(0.3)	2	(0.3)	17	(0.3)	22	(0.2)
General physical health deterioration	2	(0.3)	0	(0.0)	10	(0.2)	16	(0.1)
Peripheral sensory neuropathy	2	(0.3)	1	(0.2)	2	(0.0)	4	(0.0)
Polymyalgia rheumatica	2	(0.3)	0	(0.0)	1	(0.0)	3	(0.0)
Sepsis	2	(0.3)	0	(0.0)	8	(0.1)	14	(0.1)
Acute kidney injury	1	(0.2)	0	(0.0)	8	(0.1)	20	(0.2)
Adenocarcinoma gastric	1	(0.2)	0	(0.0)	1	(0.0)	2	(0.0)
Alopecia	1	(0.2)	0	(0.0)	0	(0.0)	1	(0.0)
Arthritis	1	(0.2)	0	(0.0)	2	(0.0)	9	(0.1)
Atypical pneumonia	1	(0.2)	0	(0.0)	1	(0.0)	2	(0.0)
Azotaemia	1	(0.2)	0	(0.0)	0	(0.0)	1	(0.0)
Balanoposthitis	1	(0.2)	0	(0.0)	0	(0.0)	1	(0.0)
Blood creatinine increased	1	(0.2)	1	(0.2)	1	(0.0)	12	(0.1)
Cardiac failure congestive	1	(0.2)	0	(0.0)	1	(0.0)	2	(0.0)
Decreased appetite	1	(0.2)	0	(0.0)	2	(0.0)	5	(0.0)
Drug-induced liver injury	1	(0.2)	0	(0.0)	1	(0.0)	4	(0.0)
Erysipelas	1	(0.2)	0	(0.0)	0	(0.0)	1	(0.0)
Gastric cancer	1	(0.2)	0	(0.0)	2	(0.0)	3	(0.0)
Gastroenteritis	1	(0.2)	0	(0.0)	0	(0.0)	1	(0.0)
Giant cell arteritis	1	(0.2)	0	(0.0)	0	(0.0)	1	(0.0)

The following table shows the AEs resulting in **treatment interruption** by frequency (the table is truncated for brevity).

Table 60: Participants with adverse events resulting in treatment interruption by decreasing incidence of preferred term (incidence >0% in one or more treatment groups) (APaT population)

	KN091 Data for Pembrolizumab		KN091 Data for Placebo		Reference Safety Dataset for Pembrolizumab[i]		Cumulative Running Safety Dataset for Pembrolizumab[j]	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	580		581		6,185		10,997	
with one or more adverse events	221	(38.1)	145	(25.0)	1,596	(25.8)	2,972	(27.0)
with no adverse events	359	(61.9)	436	(75.0)	4,589	(74.2)	8,025	(73.0)
Hypothyroidism	20	(3.4)	1	(0.2)	36	(0.6)	81	(0.7)
Diarrhoea	19	(3.3)	6	(1.0)	127	(2.1)	225	(2.0)
Pneumonitis	18	(3.1)	5	(0.9)	91	(1.5)	144	(1.3)
Arthralgia	16	(2.8)	3	(0.5)	43	(0.7)	98	(0.9)
Bronchitis	10	(1.7)	7	(1.2)	25	(0.4)	46	(0.4)
Upper respiratory tract infection	10	(1.7)	8	(1.4)	46	(0.7)	68	(0.6)
Dyspnoea	9	(1.6)	6	(1.0)	49	(0.8)	84	(0.8)
Colitis	8	(1.4)	0	(0.0)	37	(0.6)	69	(0.6)
Fatigue	8	(1.4)	6	(1.0)	58	(0.9)	101	(0.9)
Alanine aminotransferase increased	7	(1.2)	4	(0.7)	82	(1.3)	148	(1.3)
Aspartate aminotransferase increased	7	(1.2)	4	(0.7)	72	(1.2)	144	(1.3)
Hyperthyroidism	7	(1.2)	0	(0.0)	15	(0.2)	44	(0.4)
Pneumonia	7	(1.2)	9	(1.5)	101	(1.6)	154	(1.4)
Rash	7	(1.2)	0	(0.0)	49	(0.8)	83	(0.8)
Rash maculo-papular	7	(1.2)	0	(0.0)	22	(0.4)	49	(0.4)
Arthritis	6	(1.0)	2	(0.3)	11	(0.2)	21	(0.2)
Blood creatinine increased	6	(1.0)	7	(1.2)	17	(0.3)	53	(0.5)
Influenza like illness	6	(1.0)	8	(1.4)	12	(0.2)	33	(0.3)
Lower respiratory tract infection	5	(0.9)	3	(0.5)	9	(0.1)	21	(0.2)
Myalgia	5	(0.9)	0	(0.0)	13	(0.2)	29	(0.3)
Pyrexia	5	(0.9)	6	(1.0)	36	(0.6)	71	(0.6)
Urinary tract infection	5	(0.9)	5	(0.9)	23	(0.4)	60	(0.5)
Vomiting	5	(0.9)	3	(0.5)	23	(0.4)	46	(0.4)
Gamma-glutamyltransferase increased	4	(0.7)	2	(0.3)	15	(0.2)	31	(0.3)
Interstitial lung disease	4	(0.7)	0	(0.0)	9	(0.1)	17	(0.2)
Nausea	4	(0.7)	2	(0.3)	25	(0.4)	44	(0.4)
Adrenal insufficiency	3	(0.5)	0	(0.0)	19	(0.3)	31	(0.3)
Anaemia	3	(0.5)	0	(0.0)	52	(0.8)	104	(0.9)
Back pain	3	(0.5)	0	(0.0)	15	(0.2)	27	(0.2)
Chronic obstructive pulmonary disease	3	(0.5)	1	(0.2)	14	(0.2)	21	(0.2)
Cough	3	(0.5)	7	(1.2)	27	(0.4)	56	(0.5)
Herpes zoster	3	(0.5)	4	(0.7)	12	(0.2)	25	(0.2)
Nasopharyngitis	3	(0.5)	5	(0.9)	13	(0.2)	24	(0.2)
Non-cardiac chest pain	3	(0.5)	2	(0.3)	0	(0.0)	3	(0.0)
Blood bilirubin increased	2	(0.3)	0	(0.0)	22	(0.4)	44	(0.4)
Cataract	2	(0.3)	0	(0.0)	1	(0.0)	4	(0.0)

Post marketing experience

The safety profile of pembrolizumab was summarized in the Periodic Safety Update Report covering the period 04-Sep-2020 through 03-Sep-2021, specifically Appendix 20.3 (Numbers of Adverse Drug Reactions by Preferred Term from Postauthorization Sources).

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 **known safety profile** of pembrolizumab is mainly characterised by immune-related adverse reactions, most of which resolved after appropriate medical therapy or withdrawal of pembrolizumab. When used as monotherapy, the most frequent known ADRs with pembrolizumab were fatigue (30%) and diarrhoea (22%). The majority of ADRs reported were of Grades 1 or 2 severity. The most serious

adverse reactions were immune-related ADRs and severe infusion-related reactions. The incidences of immune-related ADRs were 36.9% for all Grades and 8.7% for Grades 3-5 for monotherapy in the adjuvant setting, and 24.5% for all Grades and 6.3% for Grades 3-5 in the metastatic setting.

The **data** analysed in the present procedure come mainly from the study KEYNOTE-091 on patients affected by Stage IB (T2a ≥4 cm), Stage II, or Stage IIIA NSCLC, randomised to one of the two arms: 1) pembrolizumab (n=580, treated with adjuvant pembrolizumab monotherapy); 2) placebo (n=581). For comparison with the currently known safety profile, data from the pembrolizumab monotherapy RSD (n=6185, mainly patients with advanced melanoma or with NSCLC in first-line setting). A comparison versus the pooled pembrolizumab arms from other adjuvant settings has also been performed.

For the present study, the median of **exposure** to pembrolizumab was similar to placebo (11.7 vs 11.8 months), whereas the mean was markedly lower for pembrolizumab than placebo (8.7 vs 10.0 months). Also, the patients with exposure >6 months and >9 months were lower in pembrolizumab than in placebo (68.4% vs 81.2% and 60.9% vs 74.2%, respectively). All these data are consistent with higher discontinuation rate in pembrolizumab compared to placebo.

At **baseline**, more patients in the pembrolizumab arm had an ECOG status of 0 compared to placebo (64.7% vs 58.3%). In the RDS the number of patients with ECOG 0 was lower (47.6%).

Adverse events

Overall distribution: out of 580 patients in each arm, those with at least one AE were (pembrolizumab vs placebo) 95.9% vs 91.0%. More AEs were adjudicated as drug-related in pembrolizumab compared to placebo (75.2% vs 52.5%) but in line with RSD (70.6%). Many more grade 3-5 AEs were considered as drug-related in pembrolizumab compared to placebo (15.2% vs 4.3%), again in line with RSD. A similar trend was observed with serious drug-related AEs. More patients discontinued the drug in pembrolizumab than in placebo (19.8% vs 5.9%) or in RSD (13.5%): the figure compared to RSD could be explained by a better clinical/general condition of patients enrolled in the present study compared to the average RSD patient and, thus, to a higher probability that every deviation from this wellness condition is attributed to the drug (instead that to the disease). Patients who discontinued the treatment due to drug-related AEs were many more in pembrolizumab than in placebo (16.9% vs 3.4%) or in RSD (7.2%).

The **most frequently** reported **AEs** (incidence >15%) were weight increased, pruritus, hypothyroidism, arthralgia, diarrhoea, and fatigue (but weight increased was lower compared to placebo). Pruritus was more common in pembrolizumab (21.6% vs 12.7%) but in line with RSD (18.0%). Hypothyroidism was much more frequent in pembrolizumab than in placebo (20.7% vs 4.6%) and RSD (11.3%); a similar pattern was observed for Hyperthyroidism: more frequent in pembrolizumab than placebo (10.7% vs 2.9%) or RSD (4.2). The higher frequency compared to RSD is probably due to the lower exposure occurred in this latter dataset. Arthralgia was slightly more frequent with pembrolizumab but in line with RSD. Overall, the AEs were similar to what observed for the adjuvant-setting database (with the notable exception of deaths, see below).

Drug-related AEs: Hypothyroidism was the most frequent drug-related AE (pembrolizumab vs placebo: 19.7% vs 3.3%; RSD: 9.8%). A similar pattern was observed for drug-related hyperthyroidism (9.3% vs 3.7%). Pruritus was considered related to treatment more often in pembrolizumab than placebo (17.9% vs 10.3%) but with a similar proportion compared to RSD. A similar pattern was observed for diarrhoea. Rush was also more frequently related to treatment in pembrolizumab vs placebo (manually calculated adding related PTs: 12.6% vs 5.1%). Pneumonitis related to drug in pembrolizumab were more than twice as many as in placebo (5.7% vs 2.1%).

Grade 3-5 AEs: the number of subjects experiencing at least one grade 3-5 AE was higher with pembrolizumab compared to placebo (34.1% vs 25.8%) but lower compared to RSD (48.2%), as somewhat expected because of the more severe clinical conditions of patients in the latter dataset. The AEs which showed the biggest differences of prevalence between pembrolizumab and placebo were pneumonia/pneumonitis (3.3% vs 1.9%; RSD: 5.5%) and diarrhoea (1.2% vs 0.3%). It is noteworthy that hypothyroidism and hyperthyroidism, which were two frequent AEs, are not listed among the most frequent grade 3-5 AEs (just 1 case for each AE is reported). However, grade 3-5 hypocortisolism (that can be a life-threatening endocrine condition) was observed only in pembrolizumab (n=5, 0.9% vs n=0).

AEOSIs (immune-related events and infusion-related reactions): the number of patients with at least one AEOSI was higher in pembrolizumab than placebo (39.0% vs 12.9%) or RSD (25.5%). A similar pattern is observed for drug-related AEOSI (36.9% vs 9.1%; RSD: 22.1%). Also, when adjusted for the exposure, the incidence of AEOSI was higher in pembrolizumab compared to the RSD, probably because many of these events require some time to develop fully and to become clinically evident: thus, the shorter exposure of the RSD could have been insufficient for many of these events to emerge, resulting in a lower incidence in the RSD.

Hypothyroidism was much more frequent in pembrolizumab than in placebo (20.7% vs 4.6%) or in RSD (11.3%). Hyperthyroidism, too, was much more frequent with pembrolizumab than placebo (10.7% vs 2.9%) or RSD (4.2%). Adrenal insufficiency was observed only in pembrolizumab (n=10, 1.7%): it has been reassigned a frequency of "Common" at the 4.8 section of the SmPC; the frequency in the RSD was 0.8%. Hypophysitis was only observed in patients in pembrolizumab (n=7, 1.2%) and no cases were registered with placebo; the frequency in the RSD was 0.6%.

Hepatitis was more common in pembrolizumab than placebo (n=10, 1.7% vs n=4, 0.7%) and than RSD (1.0%). Myocarditis was more frequent in pembrolizumab compared to placebo (n=5, 0.9% vs n=1, 0.2%) and to RSD (n=7, 0.1%). Whilst the lower incidence of many immune-mediated AEs in the RSD can be attributed to a lower exposure in that dataset, the difference observed for myocarditis in pembrolizumab vs RSD (0.9% vs 0.1%) seems higher compared to other immune-related AEs (such as hepatitis). Immune-mediated myocarditis is a known AE associated to anti-PD-L1 therapies. It is difficult to assess the relationship between the cases of myocarditis observed in the study and the treatment because of the concomitant complications observed in some patients (such as sepsis). However, since the known causal relationship, it is not possible to exclude pembrolizumab as causal factor of these cases.

The most frequent **SAEs** (pembrolizumab vs placebo) were: pneumonia (2.2% vs 1.5%), pneumonitis (2.1% vs 0.7%), diarrhoea (1.2% vs 0.2%); the prevalence of these three AEs was not higher than what observed in the RSD. Pulmonary embolism was observed only in the pembrolizumab group (n=3, 0.5%) and none in the placebo (but the prevalence in the RSD was higher: 1.2%); however, only 3 subjects were involved, and therefore it is not possible to establish firmly whether embolism was related to the IMP or it was by chance. In general, SAEs were in line to what already known from the RSD, and the frequency was similar or lower in the current pembrolizumab arm compared to RSD.

Patients who **died** for AEs were almost double with pembrolizumab compared to placebo (1.9% vs 1.0%) but less than RSD (5.2%). Moreover, it must be kept in mind that the current setting is adjuvant therapy and, therefore, patients had ECOG status 0 or 1 (i.e. they were in relatively good general clinical conditions as compared to the metastatic setting). Compared to other approved adjuvant settings, there were more patients with fatal AEs in the current pembrolizumab arm than in the pooled pembrolizumab arms of the other adjuvant settings, n=11 (1.9%) vs n=4 (0.3%), and the cases considered drug-related were 4 (0.7%) vs 0. Therefore, at first glance a higher number of patients died in the pembrolizumab arm of the current trial compared to the other studies in the

adjuvant setting. However, when all the deaths in the current trial are considered (both those due to AEs and those counted as outcome events for efficacy evaluation) the number of patients who died in the pembrolizumab arm is lower compared to placebo (98, 16.6% vs 111, 18.9%). Therefore, an overall lower mortality has been registered in the pembrolizumab arm of the current study.

One patient with hyperthyroidism (high FT4, low TSH) was erroneously treated with thyroid hormone therapy. The patient died by sudden death, after chest pain, the day after the finding of a FT4 value more than 3 times higher than the upper normal value. The cause of death could be related to myocardial ischemia, for which a condition of hyperthyroidism is a known risk factor. However, from the data available it has not been possible to gather more information.

Regarding the **laboratory findings**, a grade 3-4 ALT increase was observed in more patients in pembrolizumab than placebo (3.3% vs 0.5%) but in line with RSD. Similar findings were seen for AST and bilirubin. Grade 3-4 Hypokalaemia was more frequent in pembrolizumab than placebo (1.9% vs 0.3%) but less than RSD. The other main laboratory findings were overall similar between the two arms and to the RSD.

Discontinuation of the IMP was higher with pembrolizumab compared to placebo and to the RSD. The latter finding can be due to the shorter exposure in the RSD. The most frequent cause of discontinuation was Pneumonitis: (pembrolizumab vs placebo) n=21 (3.6%) vs n=4 (0.7); pneumonitis is a well-known ADR to pembrolizumab. This cause was also more frequent in the pembrolizumab arm of the current study compared to the RSD (1.7%). Other AEs which caused discontinuation were Diarrhoea (1.2% vs 0.3%), Colitis (0.9% vs 0.2%), Hypothyroidism (0.9% vs 0). Autoimmune hepatitis was also more frequent in pembrolizumab than placebo (n=5, 0.9% vs n=0).

The most frequent cause of **treatment interruption** was Hypothyroidism which was more frequent in pembrolizumab than in placebo (3.4% vs 0.2%) and RSD. Again, the difference with the RSD could be due to a shorter exposure in the latter dataset. Other AEs leading to interruption were Diarrhoea (3.3% vs 1.0%) and pneumonitis (3.1% vs 1.5%). Other AEs with a high difference in frequency between the two arms were Arthralgia (2.8% vs 0.5%), Colitis (1.4% vs 0), Hyperthyroidism (1.2% vs 0), Rash (1.2% vs 0), Adrenal insufficiency (n=3, 0.5% vs 0): the latter event is not frequent but, since it is a possible life-threatening condition, deserves particular attention.

The MAH position that food and **DDI** are not anticipated to influence exposure to pembrolizumab, since it is an IgG antibody, is shared. In the same way, drugs that affect the cytochrome P450 enzymes, and other metabolizing enzymes, are not expected to interfere with the metabolism of pembrolizumab.

The **ADA** incidence rate in the present study was lower or comparable to what observed in a similar setting (adjuvant treatment of melanoma): 2.3% vs 3.4% respectively. The historical incidence rate of treatment emergent positive subjects reported for monotherapy is 2.1%, that is similar to what observed in the present study.

Relevant figures in section 4.8 of the SmPC were updated to incorporate safety data from this submission. More specifically, the incidences of immune-mediated adverse reactions for pembrolizumab as monotherapy was updated to 37% all Grades and 9% for Grades 3-5 for pembrolizumab monotherapy in the adjuvant setting and 25% all Grades and 6% for Grades 3-5 in the metastatic setting; In patients with NSCLC, pneumonitis occurred in 206 (6.1%), including Grade 2, 3, 4 or 5 cases in 92 (2.7%), 56 (1.7%), 16 (0.5%) and 9 (0.3%), respectively; In patients with melanoma, NSCLC and RCC treated with pembrolizumab monotherapy in the adjuvant setting (n=2,060), the incidence of hyperthyroidism was updated to 11.0%, the majority of which were Grade 1 or 2. In patients with melanoma, NSCLC and RCC treated with pembrolizumab monotherapy in the adjuvant setting (n=2,060), the incidence of hypothyroidism was updated to 18.5%, the majority of which were Grade 1 or 2.

Effects of intrinsic and extrinsic factors on safety

Regarding the **age**, on average, the number of AEs, drug-related AEs and grade 3-5 AEs in the pembrolizumab arm in patients >65 years was similar to that of patient <65 years, except for SAEs and discontinuation which were slightly more frequent in the category >65 years. This pattern seems slightly different than that observed in the RSD where also the overall number of AEs, drug-related AEs and grade 3-5 AEs was higher in the >65 years. The frequency of AEs seems to increase with age in patients >65 years, but the number of patients >85 years is very limited, and no conclusions can be gathered on this age group. In the range 75-84 years (about 50-60 patients in each arm in the current study) in the pembrolizumab arm, the number of AEs was not higher compared to the corresponding RSD age category, except for discontinuations due to AEs that were more frequent in the current pembrolizumab arm (but the small number of subjects prevents any further evaluation).

When analysed by **gender**, the overall number of patients with at least one AE in pembrolizumab arm was similar between male and female. However, more male patients had grade 3-5 AEs compared to female (36.3% vs 29.6%); but when only drug-related AEs are considered, these were similar between the two categories. A similar pattern can also be observed for SAEs. AEs with fatal outcome were more frequent in male vs female (n=10, 2.5% vs n=1, 0.5%) but the same happened in the placebo group (1.3% vs 0.5%), whereas in the RSD dataset this difference is much lower (5.5% vs 4.5%). However, it seems that male participants had more baseline risk factors than female participants (such as age, smoking history and pre-existing medical conditions) potentially leading to a worse outcome.

There are some differences observed in the frequency of AEs according to the **race** (divided into *white*, *other* and *not applicable*). For instance, patients who discontinued the drug due to AEs were more frequent in the *white* group than in the *other* group (21.7% vs 12.0%); however, the groups were unbalanced as to numerosity (442 vs 117 subjects enrolled, in pembrolizumab arm, in each category respectively) and in the RSD the differences were much less noticeable.

When patients with AEs were analysed by **geographical regions**, the number of patients in pembrolizumab arm with grade 3-5 AEs was higher in EU than in non-EU (37.9% vs 26.6%); a similar pattern is observed in the placebo arm but not in RSD where the distribution was similar. Drug-related grade 3-5 AEs, SAEs and discontinuation due to AEs were all more frequent in EU compared to non-EU, in both arms (pembrolizumab and placebo), whereas they had similar frequency in the RSD. It should be noted that the two groups (i.e. EU and non-EU) of the current study were of different size (388 vs 192 respectively). The EU patients seemed to have more risk factors at baseline compared to non-EU (slightly higher age, more smokers). This could have given EU patients a worse outcome.

When analysed by **ECOG status** there were no relevant differences between patients with ECOG status 0 and 1 in the pembrolizumab arm: the differences, if any, were small, in the expected direction (possible slightly higher frequency of AEs in ECOG 1), and in line with what observed in the placebo arm and in the RSD.

2.5.2. Conclusions on clinical safety

The safety profile of pembrolizumab is mainly characterised by immune-related adverse reactions. In the current study, overall, the number of AEs was higher in pembrolizumab compared to placebo but in line with the RSD. However, discontinuations due to AEs and the frequency of AEOSI (such as hypothyroidism and hyperthyroidism) were higher in pembrolizumab than RSD (but exposure was longer in the present study). The AEs most frequently reported were pruritus, hypothyroidism, arthralgia, diarrhoea, and fatigue. Death due to AEs was more commonly observed in pembrolizumab than placebo, and was slightly higher when compared to the pooled pembrolizumab arms from other adjuvant settings. Overall, no new particular safety concerns have arisen from the data submitted in

the current procedure, and the safety profile could be acceptable. However, considering the adjuvant setting and, thus, the relatively good clinical general condition of these patients, the observed higher mortality compared to placebo, and the higher discontinuation and higher AEOSI rate compared to RSD, will have to be taken into account in the definition of the B/R ratio (see 3.7.2).

2.5.3. PSUR cycle

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

2.6. Risk management plan

The MAH submitted an updated RMP version with this application.

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

The PRAC considered that the risk management plan version 39.2 is acceptable.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 39.2 with the following content:

Safety concerns

Table 61: Summary of Safety Concerns

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

Pharmacovigilance plan

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

Risk minimisation measures

Table 62: 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		

Table 62: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk minimisation Measures	Pharmacovigilance Activities
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
	Additional risk minimisation measures: Patient educational material	Additional pharmacovigilance including: • Safety monitoring in all ongoing MAH-sponsored clinical trials for pembrolizumab in various tumor types
Important Potential Risks		
For hematologic malignancies: increased risk of severe complications of allogeneic SCT in patients who have previously received pembrolizumab	Routine risk minimisation measures: • For Hematologic malignancies: the increased risk of severe complications of allogeneic SCT in patients who have previously received pembrolizumab is described in the SmPC, Section 4.4, 4.8 and appropriate advice is provided to the prescriber to minimize the risk.	Routine pharmacovigilance activities

Table 62: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

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

2.7. Update of the Product information

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

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons: There are two limited modifications and no other proposed changes to the content of the package leaflet; in particular the key messages for the safe use of the medicinal product are not impacted. Furthermore, the design, layout and format of the package leaflet will not be affected by the proposed revisions.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The final indication is "KEYTRUDA as monotherapy is indicated for the adjuvant treatment of adults with non-small cell lung carcinoma who are at high risk of recurrence following complete resection and platinum-based chemotherapy (for selection criteria, see section 5.1)".

3.1.2. Available therapies and unmet medical need

Platinum-based doublets is the mainstay of the systemic adjuvant treatment for resected NSCLC. Standard combinations are cisplatin and vinorelbine, but other combinations are commonly used in the clinical practice (etoposide, gemcitabine, pemetrexed, taxane)[22,23]. Regarding immunotherapy, atezolizumab was approved for the adjuvant treatment of NSCLC after resection and platinum-based chemotherapy at high risk of recurrence and PD-L1 expression on tumour cells (TC) ≥50% and who do not have EGFR mutant or ALK-positive NSCLC[24]. In mutated NSCLC, osimertinib was approved for the adjuvant treatment of stage IB-IIIA NSCLC limited to tumors with EGFR exon 19 deletions or exon 21 (L858R) substitution mutations[25].

3.1.3. Main clinical studies

KEYNOTE-091 (PEARLS study/EORTC-1416/ETOP-8-15) is a randomized Phase 3 trial with pembrolizumab versus placebo for patients with early-stage non-small cell lung cancer (NSCLC) Stage IB (T2a ≥ 4 cm), II or IIIA (AJCC 7th ed) after complete resection and completion of standard adjuvant chemotherapy (administered when recommended). The trial randomized 1170 patients 1:1 to receive pembrolizumab or placebo (triple blinded). Dual primary endpoints of the study were DFS in the ITT and in the PD-L1 TPS ≥50% subgroup. The MAH submitted the IA2 analysis (data cutoff of 20-SEP-2021), at a median follow-up of duration for participants of 33.3 months for the pembrolizumab group and 31.9 months for the placebo group. All patients have either discontinued or completed 1 year of adjuvant treatment. Results of the pre-specified IA3 analysis (data cut-off 24 Jan 2023) were also submitted during the procedure. At IA3, median follow-up was 46.7 months (approximately 13 months longer as compared to IA2).

3.2. Favourable effects

- In KEYNOTE-091 study, most of the population (86%, 506 vs 504 patients) received prior adjuvant chemotherapy which was a stratification factor and was balanced between treatment arms. At IA3, the results in the population with adjuvant chemotherapy are numerically more favourable as compared to the ITT, showing relevant DFS benefit maintained with longer follow up [DFS HR 0.76 (95%CI 0.64, 0.91), 44% vs 52 % events, medians 54 vs 40 months, DFS rate at 24 months 67%

[22] Postmus PE, Kerr KM, Oudkerk M, Senan S, Waller DA, Vansteenkiste J, Escriu C, Peters S; ESMO Guidelines Committee. Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2017 Jul 1;28(suppl_4):iv1-iv21.
[23] National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: non-small cell lung cancer; version 8.2020.
[24] EMA/667840/2022, EPAR Tecentriq CHMP Assessment report
[25] EMA/280219/2021, EPAR Tagrisso CHMP Assessment report

vs 59%], and numerical positive OS trend [OS HR 0.79 (95%CI 0.62, 1.01), 22% vs 27% events, medians NR in either arm]. In this population, DFS HR point estimates for subgroups are all <1, as well as for OS (with the exception of patients over 75 years). No subgroups appear to drive the results.

- IA3 data confirmed numerically favourable trends in DFS (HR 0.44, 95%CI 0.22, 0.87) and OS (HR 0.35, 95%CI 0.13, 0.98) in patients with EGFR positive NSCLC, acknowledging the large confidence intervals due to the small sample size. Therefore, patients with EGFR mutated tumours are not explicitly excluded from the adjuvant indication.

3.3. Uncertainties and limitations about favourable effects

- OS in the ITT and in the PD-L1 TPS ≥50% population did not reach statistical significance neither at IA2 nor at IA3, and could not formally be tested in PD-L1 TPS ≥1% (IA3 OS in all patients: HR 0.87, 95%CI 0.69, 1.10, p=0.11792, 23% vs 27% OS event; OS in TPS ≥50%: HR 0.93, 95%CI 0.57, 1.50, p= 0.3778, 20% vs 21% OS events). The MAH will submit the final OS analysis which will further characterise the efficacy of Keytruda in the intended indication (see Annex II).
- Some uncertainty remains in terms of the efficacy in the adjuvant treatment of adults with NSCLC, specifically on data on treatment post-progression, and particularly on the uptake and activity of anti-PD(L)1 in patients previously treated with adjuvant pembrolizumab. The MAH is expected to submit these data as part of a PAES (see Annex II).
- The population was not stratified for EGFR/ALK alterations, and the mutational status is unknown in about 60% of the overall population. The low number of positive patients is described in section 5.1 of the SmPC to highlight the limited data available. No further analysis of EGFR is planned in this study.

3.4. Unfavourable effects

- The most frequently reported AEs were weight increased, pruritus, hypothyroidism, arthralgia, diarrhoea, and fatigue. The number of subjects experiencing at least one grade 3-5 AE was higher with pembrolizumab compared to placebo but lower compared to RSD. The AEs which showed the greatest differences of prevalence between pembrolizumab and placebo were pneumonia/pneumonitis (3.3% vs 1.9%; RSD: 5.5%) and diarrhoea (1.2% vs 0.3%). Grade 3-5 hypocortisolism was observed only in pembrolizumab (5 cases, 0.9%).
- AEs of special interest were mainly immune-related events and infusion-related reactions: the number of patients with at least one AEOSI was higher in pembrolizumab than placebo (39.0% vs 12.9%) or RSD (25.5%). A similar pattern is observed for drug-related AEOSI. Even when adjusted for the exposure, the incidence of AEOSI was higher in pembrolizumab compared to the RSD. Hypothyroidism and hyperthyroidism were more frequent in pembrolizumab than both placebo and RSD. Adrenal insufficiency was observed in 10 patients with pembrolizumab vs 0 in placebo. Hypophysitis was only observed in patients in pembrolizumab (n=7, 1.2%). Hepatitis and myocarditis were more common in pembrolizumab than placebo or RSD.
- The most frequent SAEs (pembrolizumab vs placebo) were: pneumonia (2.2% vs 1.5%), pneumonitis (2.1% vs 0.7%), diarrhoea (1.2% vs 0.2%); the prevalence of these three AEs was similar (or lower) to what observed in the RSD. Pulmonary embolism was observed only in the pembrolizumab group (n=3, 0.5%) vs none in the placebo (but lower frequency compared to RSD).

In general, SAEs were in line to what already known from the RSD, and the frequency was similar or lower in the current pembrolizumab arm compared to RSD.

- Patients who died were almost double with pembrolizumab compared to placebo (1.9% vs 1.0%) but less than RSD (5.2%). However, it must be taken into account that RSD patients were, on average, affected by more advanced disease. Fatal AEs considered as related were more frequent in pembrolizumab than placebo but similar to RSD. Also, when compared to pembrolizumab in the other approved adjuvant settings, a higher number of fatal AEs were recorded (n=11, 1.9% vs n=4 0.3%).
- The safety profile was similar in patients >65 years and <65 years, except for SAEs and discontinuation which were slightly more frequent in >65 years.
- AEs with fatal outcome were more frequent in male vs female (n=10, 2.5% vs n=1, 0.5%) but the same happened in the placebo group (1.3% vs 0.5%). It seems that male patients had more risk factors at baseline (age, smoking).
- The number of patients in pembrolizumab arm with grade 3-5 AEs was higher in EU than in non-EU (37.9% vs 26.6%) and the same was observed in the placebo arm. A similar trend was observed for drug-related grade 3-5 AEs, for SAEs and for discontinuation due to AEs. It seems that EU patients had more risk factors at baseline (age, smoking).

3.5. Uncertainties and limitations about unfavourable effects

None

3.6. Effects Table

Table 63: Effects Table for Keytruda in adjuvant Stage IB(≥4cm)-IIIA NSCLC after complete resection and adjuvant chemotherapy (IA3, data cut-off: 24 Jan 2023)

Effects	Short description	Unit	Treatment Pembrolizumab (n=506) Vs Control Placebo (n=504)	Uncertainties / Strength of evidence	References
Favourable Effect					
DFS in patients with prior adjuvant chemotherapy	DFS was defined as the time from randomization to either the date of disease recurrence or death (whatever the cause) as assessed by the investigator.	Events % Median Months (95% CI)	44.5% vs 52% 53.8 (46.2, 70.4) vs 40.5 (32.9, 47.4) HR 0.76 (0.64, 0.91), p=0.00143	Relevant DFS benefit confirmed at IA3; prior chemotherapy stratification factor and prespecified subgroup analyses; all subgroups HRs <1	MAH's response to 2nd RSI
OS in patients with prior adjuvant chemotherapy	OS was defined as the time from randomization to the date of death (whatever the cause).	Events % Median Months (95% CI)	22.3% vs 27.4% NR vs NR HR 0.79 (0.62, 1.01; p=0.03224	Positive OS trend; prior chemotherapy stratification factor; all subgroups HRs<1 (except >75y) / still interim OS data	
Unfavourable Effects					
			Placebo / RSD	Patients in RSD had more severe disease	KEYNOTE 091 CSR
Patients with NO AEs		%	4.1	9.0 / 3.2	
Patients with drug-related AEs		%	75.2	52.5 / 70.6	
Patients with grade 3-5 AEs		%	34.1	25.8 / 48.2	
Patients with SAEs		%	24.5	15.5 / 38.3	
Deaths		n (%)	11 (1.9)	6 (1) / 321 (5.2)	
Deaths due to drug-related AEs		n (%)	4 (0.7)	0 / 39 (0.6)	
Hypothyroidism		%	20.7	4.6 / 11.3	
Hyperthyroidism		%	10.7	2.9 / 4.2	

Abbreviations: DFS=disease free survival; OS=overall survival; CI: confidence interval; IA: interim analysis; NR=not reached; AE=adverse event; SAE=serious adverse event; RSD=reference safety dataset; CSR=clinical study report.

Notes: One-sided p-value based on the Wald Test in the multivariate Cox regression model.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

KEYNOTE-091 showed at the IA2 a statistically significant improvement in DFS for one year of adjuvant pembrolizumab vs placebo in the overall population of patients with resected Stage IB (T2a≥ 4cm), II and IIIA (AJCC 7th ed) NSCLC in KEYNOTE-091 study. The results of IA3 (i.e. final DFS analysis) were consistent with IA2, reassuring on the stability of the benefit of pembrolizumab over placebo in the overall population with more mature data and longer follow-up (including relevant observation time after stopping treatment given the adjuvant setting), but showing also unclear less

favourable trends in some subgroups (for patients with squamous histology, PD-L1 TPS ≥ 50% and patients without prior adjuvant chemotherapy). The indication in patients with NSCLC at high risk of recurrence [Stage IB (T2a≥4 cm), II, or IIIA, as defined by the AJCC 7th edition] following complete resection of the lung tumour AND adjuvant platinum based chemotherapy is based on numerically more favourable results in the population who have received prior adjuvant chemotherapy as compared to the ITT, suggesting relevant DFS benefit and positive OS trend (with no current suggestion of detriment) for pembrolizumab vs placebo. In the population treated with prior adjuvant chemotherapy, DFS HR point estimates for subgroups are all <1, with no subgroups driving the results. Although the retrospective exclusion of patients without adjuvant chemotherapy subgroup can at least not be regarded as optimal as the MAH failed to provide a clear rationale, it is important that adjuvant treatment (received or not) had been a stratification factor and as such the subgroup analysis was pre-specified. The MAH will submit updated OS data as part of the imposed PAES (see Annex II). In addition, the MAH will submit data on treatment post-progression, and particularly on the uptake and activity of anti-PD(L)1 in patients previously treated with adjuvant pembrolizumab.

Overall, the safety profile in the current setting is similar to what is already known for pembrolizumab in general and pembrolizumab as adjuvant treatment. Higher discontinuations and higher AEOSI rate have been observed compared to the RSD; however, the exposure in the current study was longer than that in RSD, potentially explaining this finding. Discontinuations due to AEs was also overall similar to other studies using pembrolizumab or other anti-PD(L)1 agents with an adjuvant aim. While more fatal AEs were observed compared to patients receiving placebo and compared to the pembrolizumab in other approved adjuvant settings, when all the deaths (due to AEs and outcome events for efficacy evaluation) are counted, the number of patients who died in the pembrolizumab arm is lower compared to placebo.

3.7.2. Balance of benefits and risks

Adjuvant 1-year therapy with pembrolizumab resulted in an improved benefit over placebo that can be considered to outweigh the toxicities of the treatment in the indication of patients with high risk of recurrence [Stage IB (T2a≥4cm), II and IIIA, per AJCC 7th ed] NSCLC following resection and prior adjuvant platinum-based chemotherapy.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

3.8. Conclusions

The overall B/R of Keytruda is positive in the adjuvant treatment of patients with high risk of recurrence [Stage IB (T2a⩾4cm), II and IIIA, per AJCC 7th ed] NSCLC following resection and prior adjuvant platinum-based chemotherapy.

The following measures are considered necessary to address issues related to efficacy, in accordance with the Commission Delegated Regulation (EC) No 357/2014, (a) an initial efficacy assessment that is based on surrogate endpoints, which requires verification of the impact of the intervention on clinical outcome or disease progression or confirmation of previous efficacy assumptions:

Post-authorisation efficacy study (PAES): in order to further characterise the efficacy of Keytruda for the adjuvant treatment of adults with non-small cell lung carcinoma who are at high risk of recurrence, the MAH should submit the results of the final OS analysis of study KEYNOTE-091. The MAH should

submit updated data on treatment post-progression, and particularly on the uptake and activity of anti-PD(L)1 in patients previously treated with adjuvant pembrolizumab.

4. Recommendations

Outcome

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

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

Extension of indication to include Keytruda as monotherapy for the adjuvant treatment of adults with non-small cell lung carcinoma who are at high risk of recurrence following complete resection and platinum-based chemotherapy based on study KEYNOTE-091; an ongoing Phase 3, randomized, triple-blinded, placebo-controlled, multicentre study of pembrolizumab versus placebo in patients with early-stage NSCLC after resection and completion of standard adjuvant therapy. As a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are being updated and the Annex II and the Package Leaflet are updated in accordance. An updated RMP version 39.0 was also submitted.

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

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I, II and IIIB and to the Risk Management Plan are recommended.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk management plan (RMP)

The Marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

In addition, an updated RMP should be submitted:

At the request of the European Medicines Agency;

Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Obligation to conduct post-authorisation measures

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
Post-authorisation efficacy study (PAES): In order to further characterise the efficacy of Keytruda for the adjuvant treatment of adults with non-small cell lung carcinoma who are at high risk of recurrence, the MAH should submit the results of the final OS analysis of study KEYNOTE-091. The MAH should submit updated data on treatment post-progression, and particularly on the uptake and activity of anti-PD(L)1 in patients previously treated with adjuvant pembrolizumab – Final Study Report	3Q 2026

5. EPAR changes

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

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'Keytruda-H-C-003820-II-0121'