22 February 2024
EMA/118494/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Keytruda

International non-proprietary name: Pembrolizumab

Procedure No. EMEA/H/C/003820/II/0134

Note

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

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List of abbreviations

Abbreviation	Definition
ADA	anti-drug antibodies
AE	adverse event
AEOSI	adverse event of special interest
AJCC	American Joint Committee on Cancer
APaT	all participants as treated
BICR	blinded, independent central review
BIPR	blinded, independent pathological review
CHMP	Committee for Medicinal Products for Human Use (EU)
CI	confidence interval
COVID-19	Coronavirus (SARS-CoV-2) disease 2019
CTCAE	Common Terminology Criteria for Adverse Events
DFS	disease-free survival
EC_{50}	half maximal effective concentration
ECOG	Eastern Cooperative Oncology Group
EFS	event-free survival
EGFR	epidermal growth factor receptor
EMA	European Medicines Agency (EU)
E-R	exposure response
EU	European Union
FAS	full analysis set
FDA	Food and Drug Administration (US)
HR	hazard ratio
IA1	interim analysis 1
IASLC	International Association for the Study of Lung Cancer
ICI	immune checkpoint inhibitors
IFN-γ	interferon gamma
IgG	immunoglobulin G
IL-2	interleukin-2
IPTW	inverse probability of treatment weighting
ITC	Indirect Treatment Comparison
ITT	intent-to-treat
KM	Kaplan-Meier
LS	least square
mAb	monoclonal antibody
mPR	major pathological response
NSCLC	non-small cell lung cancer
OS	overall survival

Abbreviation	Definition
pCR	pathological complete response
PD	progressive disease
PD-1	programmed cell death protein-1
PD-L1	programmed death-ligand 1
PD-L2	programmed death-ligand 2
PK	pharmacokinetics
PRO	patient reported outcomes
PT	Preferred Term
Q3W	every 3 weeks
Q6W	every 6 weeks
QoL	quality of life
RFS	recurrence-free survival
RSD	Reference Safety Dataset
SAE	serious adverse event
SAWP	Scientific Advice Working Party (EU)
SOC	system organ class
TNBC	triple negative breast cancer
TNFα	tumour necrosis factor alpha
TPS	tumour proportion score
UICC	Union for International Cancer Control
UK	United Kingdom
US	United States

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 March 2023 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 in combination with platinum-containing chemotherapy as neoadjuvant treatment, and then continued as monotherapy as adjuvant, treatment of resectable Stage II, IIIA, or IIIB (T3 4N2) non small cell lung carcinoma in adults for Keytruda based on study KEYNOTE-671, a phase III, randomized, double-blind trial of platinum doublet chemotherapy +/- pembrolizumab as neoadjuvant/adjuvant therapy for participants with resectable stage II, IIIA, and resectable IIIB (T3-4N2) non-small cell lung cancer. As a consequence, sections 4.1, 4.2, and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 41.1 of the RMP has also been submitted.

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

Information on paediatric requirements

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

At the time of submission of the application, the PIP P/0043/2018 was 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 9 November 2017 (EMA/CHMP/SAWP/726235/2017). 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

Timetable	Actual dates
Submission date	6 March 2023
Start of procedure:	25 March 2023
CHMP Rapporteur Assessment Report	26 May 2023
PRAC Rapporteur Assessment Report	26 May 2023
PRAC Outcome	8 June 2023
CHMP members comments	12 June 2023
Updated CHMP Rapporteur(s) (Joint) Assessment Report	15 June 2023
Request for supplementary information (RSI)	22 June 2023
CHMP Rapporteur Assessment Report	22 November 2023
CHMP members comments	04 December 2023
Updated CHMP Rapporteur Assessment Report	7 December 2023
Request for supplementary information (RSI)	14 December 2023
CHMP Rapporteur Assessment Report	30 January 2024
CHMP members comments	12 February 2024
Updated CHMP Rapporteur Assessment Report	N/A
Opinion	22 February 2024
An Oral explanation took place on:	21 February 2024
CHMP opinion:	22 February 2024

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

The scope of this variation is to extend the existing therapeutic indications for Keytruda to neoadjuvant/adjuvant treatment of NSCLC, based on the IA1 and IA2 results of the phase III study KEYNOTE-671.

Disease or condition

Early-stage NSCLC.

State the claimed the therapeutic indication

KEYTRUDA, in combination with platinum-containing chemotherapy as neoadjuvant treatment, and then continued as monotherapy as adjuvant treatment, is indicated for the treatment of resectable Stage II, IIIA, or IIIB (T3-4N2) non-small cell lung carcinoma in adults.

Epidemiology

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[1]. In EU, lung cancer is the second most common tumour for incidence in men and the third in women, while being the first cause of cancer-related mortality in men and second in women[2]. In the EU in 2020, the estimated incidence is more than 300.000 cases and the estimated mortality around 250.000[2].

Biologic features

NSCLC accounts for approximately 85% of all lung cancers, being adenocarcinoma and squamous cell carcinoma the most common histology subtypes[3]. Several genomic alterations have been identified, defining various molecular subtypes of NSCLC, for some of those targeted therapies are available.

Clinical presentation, diagnosis and stage/prognosis

At the time of diagnosis, approximately, 9% of patients have stage I disease, 4% stage II, 27% stage III, and 63% are stage IV according to the 8th ed of the UICC/IASLC lung cancer staging. Patients with clinical Stage IIIA and Stage IIIB disease each represent 12% of patients with NSCLC[4].

Management

Surgery

According to international guidelines, for patients with stage I to IIIA NSCLC, surgical resection is the standard treatment, which includes lobectomy, pneumonectomy, and mediastinal lymph node dissection/sampling depending on the extent of the disease and the cardiopulmonary reserve of the patient[5,6]. Patients with Stage IIIB disease are considered potentially operable if the metastases are limited to the N2 lymph nodes. In practice, fewer than 10% of patients with clinical Stage IIIB disease undergo surgery[6]. 5-year OS rates for patients with surgically treated NSCLC range from approximately 55% overall in stage I to 20% in stage IIIA[6].

Adjuvant therapy

Adjuvant chemotherapy should be offered to patients with resected stage IIB and III NSCLC and can be considered in patients with T2bN0, stage IIA resected primary tumour >4 cm[7], as it resulted in overall

[1] International Agency for Research on Cancer. Lung. Lyon (France): International Agency for Research on Cancer (IARC); 2020. 2 p. Available from: https://gco.iarc.fr/today/fact-sheets-cancers.
[2] ECIS - European Cancer Information System - https://ecis.jrc.ec.europa.eu/explorer (accessed 18 May 2023)
[3] National Cancer Institute. SEER Cancer Statistics Review 1975-2017: cancer of the lung and bronchus (invasive). Bethesda (MD): National Cancer Institute (NCI); 2020.
[4] 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.
[5] Postmus PE, Kerr KM, Oudkerk M, Senan S, Waller DA, Vansteenkiste J, et al. Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2017;28 Suppl 4:iv1-21. – E-update Published on 01 September 2021
[6] NCCN Guidelines Version 3.2023 NSCLC

5% absolute improvement in DFS and OS[7] [8]. Up to 4 cycles of a two-drug combination with cisplatin is preferable, being cisplatin-vinorelbine the regimen with most data available[7].

For patients whose tumours have EGFR exon 19 deletions or exon 21 L858R substitution mutations, osimertinib is approved and indicated as adjuvant treatment after complete tumour resection stage IB-IIIA[7] [9].

The recent study IMpower010 evaluating the anti-PD-L1 antibody atezolizumab demonstrated a statistically significant 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 (overall and PD-L1≥1%)[10]. The study resulted in FDA (Oct 2021) and EMA (Jun 2022) approval of Tecentriq as adjuvant treatment following surgery and platinum-based chemotherapy for adult patients with NSCLC whose tumours express PD-L1 ≥1% and ≥50%, respectively. At a pre-planned interim analysis for DFS with a median duration of survival follow-up of 32 months, HR was 0.66 (95%CI 0.50, 0.88) in the stage II-IIIA PD-L1≥1% population (median NE vs 35.3 months, 2y-DFS rate 74.6% vs 61%)[12,11].

KEYNOTE-091 study showed that adjuvant treatment with pembrolizumab monotherapy provides a statistically significant improvement in DFS compared with placebo in participants with Stage IB (T2a ≥4 cm), II and IIIA NSCLC (AJCC 7th ed.) following complete resection +/- adjuvant chemotherapy. At the second pre-planned interim analysis with median follow-up time of 35.6 months, DFS HR was 0.76 (95% CI 0·63–0·91), with median DFS 53.6 vs 42 months. 2y DFS rate was 67% vs 59%[12]. Based on the KEYNOTE-091 results, pembrolizumab was approved by the FDA in Jan 2023, and in the EU in Oct 2023, as adjuvant treatment following resection and platinum-based chemotherapy for adult patients with Stage IB (T2a ≥4 cm), II, or IIIA NSCLC.

Other phase 3 trials exploring anti-PD(L)1 in the adjuvant NSCLC setting are currently ongoing (CCTC-BR31 and MERMAID-1 and -2 with durvalumab, ANVIL with nivolumab).

Neoadjuvant therapy

Neoadjuvant chemotherapy has not been evaluated as extensively as postoperative one[7]. A meta-analysis of 15 randomized controlled studies showed that neoadjuvant chemotherapy significantly improves OS and RFS in resectable NSCLC as compared to surgery alone[13]. The benefit from pre-operative chemotherapy is overall similar to that attained with postoperative chemotherapy, with similar survival rates [8,14]. Pre-operative chemotherapy may provide benefits such as reduced tumour size and increased

[7] Artal Cortes A, Calera Urquizu L, Hernando Cubero J. Adjuvant chemotherapy in non-small cell lung cancer: state-of-the-art. Transl Lung Cancer Res 2015;4:191–197.
[8] Pignon JP, Tribodet H, Scagliotti GV, et al. Lung adjuvant cisplatin evaluation: a pooled analysis by the LACE Collaborative Group. J Clin Oncol. 2008 Jul 20;26(21):3552-9.
[9] Herbst RS, Wu YL, John T, et al. Adjuvant Osimertinib for Resected EGFR-Mutated Stage IB-IIIA Non-Small-Cell Lung Cancer: Updated Results From the Phase III Randomized ADAURA Trial. J Clin Oncol. 2023 Apr 1;41(10):1830-1840.
[10] 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.
[11] EPAR Tecentriq II/64 https://www.ema.europa.eu/documents/variation-report/tecentriq-h-c-h004143-ii-0064-epar-assessment-report-variation_en.pdf
[12] O'Brien M, Paz-Ares L, Marreaud S, et al; EORTC-1416-LCG/ETOP 8-15 – PEARLS/KEYNOTE-091 Investigators. Pembrolizumab versus placebo as adjuvant therapy for completely resected stage IB-IIIA non-small-cell lung cancer (PEARLS/KEYNOTE-091): an interim analysis of a randomised, triple-blind, phase 3 trial. Lancet Oncol. 2022 Oct;23(10):1274-1286.
[13] NSCLC Meta-analysis Collaborative Group. Preoperative chemotherapy for non-small-cell lung cancer: a systematic review and meta-analysis of individual participant data. Lancet. 2014 May 3;383(9928):1561-71.
[14] Lim E, Harris G, Patel A, Adachi I, Edmonds L, Song F. Preoperative versus postoperative chemotherapy in patients with resectable non-small cell lung cancer: systematic review and indirect comparison meta-analysis of randomized trials. J Thorac Oncol. 2009 Nov;4(11):1380-8.

operability. Additionally, in the post-operative setting comorbidities and incomplete recovery after surgery may make difficult to tolerate chemotherapy[15].

Recently, neoadjuvant treatment with nivolumab plus chemotherapy showed a statistically significant improvement in EFS and pCR compared to chemotherapy alone in CheckMate-816. Based on prespecified interim analysis 1 of EFS at a median follow-up of 29.5 months, DFS HR was 0.63 (97.38%CI 0.43, 0.91), median EFS 31.6 vs 20.8 months, 2y EFS rate 63.8% vs 45.3%. At the final analysis for pCR, this was 24% vs 2.2%[16]. The study led to FDA approval in Mar 2022 of nivolumab in combination with platinum-doublet chemotherapy in adult patients with resectable NSCLC (tumours ≥4 cm or node positive) in the neoadjuvant setting. Opdivo in combination with platinum-based chemotherapy as neoadjuvant treatment was later approved in the EU in June 2023, but limited to tumours with PD-L1 expression ≥ 1%.

Neoadjuvant/Adjuvant (Perioperative) Therapy

There are currently no approved therapies for neoadjuvant/adjuvant treatment regimens for early-stage NSCLC.

This strategy is however currently investigated in clinical trials with anti-PD(L)1 drugs. The phase 2 NADIM II study showed longer 24-month PFS (67.3% vs 52.6%; HR 0.56, 95%CI 0.28, 1.15) and 24-month OS (85.3% vs 64.8%; HR 0.37, 95%CI 0.14, 0.93) for neoadjuvant nivolumab in combination with carboplatin/paclitaxel followed by adjuvant nivolumab compared with neoadjuvant chemotherapy alone[17]. Recently, 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 planned interim analysis of after a median EFS follow-up of 11.7 months[18]. Positive results were also reported for the peri-operative strategy neoadjuvant nivolumab + chemotherapy followed by surgery and adjuvant nivolumab (nivolumab + chemotherapy/nivolumab) in the phase III Checkmate-77T at its pre-specified interim analyses (EFS HR 0.58 [0.42–0.81]; P = 0.00025, median not reached [28.9 mo–not reached] vs 18.4 mo [13.6–28.1])[19]. Other clinical trials exploring the perioperative strategy are currently ongoing (e.g. Impower030 with atezolizumab).

2.1.2. About the product

Pembrolizumab is a 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 tumour regression and, ultimately, immune rejection. In vitro and in vivo experiences have shown that PD-1 and PD-L1 blockade using a mAb can result in activation of antitumour T-cells and subsequent tumour regression. In T-cell activation assays using human donor blood cells, the EC50 was in the range of 0.1 to 0.3 nM. Pembrolizumab also modulates the level of IL-2, TNFα, IFNγ, and other cytokines. The antibody potentiates existing immune responses in the presence of antigen only; it does not non-specifically activate T-cells.

[15] Felip E, Rosell R, Maestre JA, Rodríguez-Paniagua JM, et al; Spanish Lung Cancer Group. Preoperative chemotherapy plus surgery versus surgery plus adjuvant chemotherapy versus surgery alone in early-stage non-small-cell lung cancer. J Clin Oncol. 2010 Jul 1;28(19):3138-45.
[16] Forde PM, Spicer J, Lu S, Provencio M, Mitsudomi T, Awad MM, et al. Neoadjuvant nivolumab plus chemotherapy in resectable lung cancer. N Engl J Med. 2022 May 26;386(21):1973-85.
[17] Provencio M, Serna R, Nadal E, Glez Larriba JL, Martinez-Marti A, Bernabe R, et al. Progression free survival and overall survival in NADIM II study [abstract]. Presented at: International Association for the Study of Lung Cancer (IASLC) 2022 World Conference on Lung Cancer (WCLC); 2022 Aug 6-9; Vienna (Austria). J Thorac Oncol. 2022 Sep;17(9 suppl): S2-3.
[18] Heymach JV, Harpole D, Mitsudomi T, et al; AEGEAN Investigators. Perioperative Durvalumab for Resectable Non-Small-Cell Lung Cancer. N Engl J Med. 2023 Nov 2;389(18):1672-1684. Epub 2023 Oct 23.
[19] Cascone T, Awad MM, Spicer JD, et al. LBA1 CheckMate 77T: Phase III study comparing neoadjuvant nivolumab (NIVO) plus chemotherapy (chemo) vs neoadjuvant placebo plus chemo followed by surgery and adjuvant NIVO or placebo for previously untreated, resectable stage II–IIIb NSCLC. Ann Oncol. Volume 34, SUPPLEMENT 2, S1295, October 2023.

At the time of the submission of this application, Keytruda has been granted approval for at least 1 indication in approximately 100 countries. In the EU, it was granted first approval on 17-JUL-2015, and it is now approved in several tumour types as monotherapy or in combination with other agents (chemotherapy, TKI, other MoAb). Specifically in the NSCLC setting, pembrolizumab is approved in the advanced/metastatic disease in 1L as monotherapy (PD-L1 TPS ≥50%) or in combination with chemotherapy (regardless PD-L1), as well as in 2L as monotherapy (PD-L1 TPS ≥1%). An indication in the adjuvant NSCLC setting, based on results from study KEYNOTE-091 was approved by CHMP in September 2023(EMEA/H/C/003820/II/0121).

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

An overview of the pembrolizumab **clinical development program** in resectable early-stage NSCLC is provided in the table below:

Study Number (Status)	Design	Population	Dosage, Regimen	Primary Efficacy Endpoint(s)
KEYNOTE-091 (ongoing)	A Phase 3, randomized, triple-blinded, placebo-controlled, multicenter study to evaluate the efficacy and safety of pembrolizumab vs placebo in participants with Stage IB (T2a ≥4 cm), II, or IIIA NSCLC who have undergone complete resection with or without standard adjuvant chemotherapy.	Approximately 1180 participants with early-stage NSCLC, who have undergone complete resection, were planned to be randomized in a 1:1 ratio to receive adjuvant treatment of either pembrolizumab 200 mg or placebo Q3W for 18 treatment cycles (~1 year).	200 mg Q3W for pembrolizumab; Q3W for placebo	- DFS in the PD-L1 TPS ≥50% subgroup - DFS in the overall study population
KEYNOTE-671 (ongoing)	A Phase 3, randomized, double-blind study of platinum doublet chemotherapy with or without pembrolizumab as neoadjuvant/adjuvant therapy for participants with resectable Stage II, IIIA, and resectable IIIB (T3-4N2) NSCLC.	Approximately 786 participants with Stage II, IIIA, or IIIB (N2) NSCLC were planned to be randomized in a 1:1 ratio to receive neoadjuvant pembrolizumab plus platinum doublet chemotherapy followed by surgery and adjuvant pembrolizumab, or neoadjuvant placebo plus platinum doublet chemotherapy followed by surgery and adjuvant placebo.	200 mg Q3W for pembrolizumab; Q3W for placebo; cisplatin (75 mg/m^2 Q3W), gemcitabine (1000 mg/m^2 Q3W), and pemetrexed (500 mg/m^2 Q3W) for chemotherapy	- EFS - OS
Abbreviations: DFS=disease-free survival; EFS=event-free survival; NSCLC=non-small cell lung cancer; OS=overall survival; Q3W=every 3 weeks; TPS=tumor proportion score				

The MAH received **Scientific Advice** from CHMP in 2017. The study plan was considered overall acceptable with regard to patient population, stratification factors, control arm, and endpoints. EFS was considered an acceptable primary endpoint in this setting if provided together, at least, a non-detrimental effect in OS. The CHMP noted that the current design would not allow disentangling the relative contribution of the neo-adjuvant and adjuvant part, and while the adjuvant therapy trial KEYNOTE-091 may provide further information, it will not be possible to extrapolate and address the main question on whether neo-adjuvant treatment in itself might be sufficient or whether any specific length of adjuvant treatment is required to optimize the treatment. It was also noted the heterogeneity of the patient population in terms of e.g. stage, histology, biomarkers expression, that the B/R will need to be discussed in the most relevant subgroups, making it very important to provide adequately mature follow-up data with good representations of various subgroups, in order to appropriately evaluate the effect in the target population.

2.1.4. General comments on compliance with GCP

The Applicant stated that KEYNOTE-671 study was conducted in accordance with local and/or national regulation, ICH GCP, and the ethical principles that have their origin in the Declaration of Helsinki regarding IEC review, informed consent, and the protection of human participants in biomedical research. The Applicant informed that GCP compliance issues were noted for one of the clinical site in US, which was then closed (see Conduct of the study below). Based on the assessment of the dossier, no issues that may lead to request a GCP inspection have been noted.

2.2. Non-clinical aspects

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

2.2.1. Ecotoxicity/environmental risk assessment

Keytruda is a protein and is therefore exempt from the ERA requirements. This is compliant to 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.

Table 1: Tabular overview of clinical studies

KEYNOTE-671 (ongoing)	A Phase 3, randomized, double-blind study of platinum doublet chemotherapy with or without pembrolizumab as neoadjuvant/adjuvant therapy for participants with resectable Stage II, IIIA, and resectable IIIB (T3-4N2) NSCLC.	Approximately 786 participants with Stage II, IIIA, or IIIB (N2) NSCLC were planned to be randomized in a 1:1 ratio to receive neoadjuvant pembrolizumab plus platinum doublet chemotherapy followed by surgery and adjuvant pembrolizumab, or neoadjuvant placebo plus platinum doublet chemotherapy followed by surgery and adjuvant placebo.	200 mg Q3W for pembrolizumab; Q3W for placebo; cisplatin (75 mg/m^2 Q3W), gemcitabine (1000 mg/m^2 Q3W), and pemetrexed (500 mg/m^2 Q3W) for chemotherapy	- EFS - OS

2.3.2. Discussion on clinical pharmacology

The description of the pharmacology of pembrolizumab in combination with chemotherapy in metastatic/locally advanced settings and the characterization of pembrolizumab immunogenicity in adjuvant settings were included in previous submissions. These analyses showed that the PK and

immunogenicity of pembrolizumab are not impacted by concomitant chemotherapy and the ADA incidence rates for pembrolizumab in the adjuvant setting are similar to the ADA incidence rates observed in metastatic/locally advanced settings.

Pembrolizumab dosing regimen of 200 mg Q3W has been used in the pivotal KEYNOTE-671 study. In addition, the 400 mg Q6W dosing regimen was also approved in the EU for all adult monotherapy indications (EMEA/H/C/003820/II/0062) and for all adult indications in combination with other anticancer agents (EMEA/H/C/003820/II/0102), mainly supported by PK and E-R bridging using modelling and simulation analysis. No clinical data are currently available in Stage II or IIIA-B (T3-4N2) NSCLC at 400 mg Q6W. Overall, on the basis of the understanding of pembrolizumab clinical pharmacology and its flat E-R profiles over a 5-fold dose range, the safety and efficacy of the 400 mg Q6W dosing regimen is expected to be similar to the approved 200 mg Q3W (or 2 mg/kg Q3W) dosing regimen in all treatment settings and the MAH concluded that the 400 mg Q6W regimen is considered a suitable dosing option based on the expected similarity of PK exposures, target saturation, efficacy and safety profile with those for the approved dosing regimens of 200 mg Q3W or 2 mg/kg Q3W. As such, it is expected that the 400 mg Q6W dosing regimen would have a similar benefit-risk profile as the 200 mg Q3W (or 2 mg/kg Q3W) dosing regimen in the proposed extension of indication.

2.3.3. Conclusions on clinical pharmacology

No new PK data have been submitted, which is considered acceptable.

The 400 mg Q6W dosing regimen is considered a suitable dosing regimen option for the current extension of indication, based on the justification provided by the MAH.

2.4. Clinical efficacy

2.4.1. Dose response study

No dose-response studies were performed specifically for the sought indication.

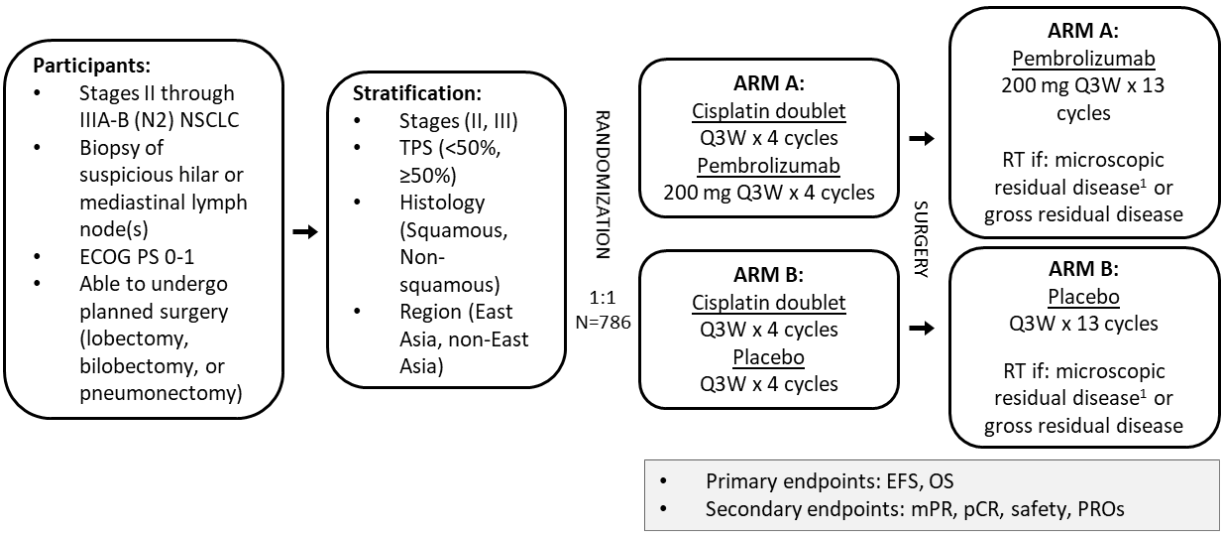
2.4.2. Main study

Title of Study

A Phase III, Randomized, Double-blind Trial of Platinum Doublet Chemotherapy +/− Pembrolizumab (MK-3475) as Neoadjuvant/Adjuvant Therapy for Participants with Resectable Stage II, IIIA, and Resectable IIIB (T3-4N2) Non-small Cell Lung Cancer (NSCLC) (**KEYNOTE-671**)

Methods

Figure 1: Study Design Schematic



ECOG = Eastern Cooperative Oncology Group; EFS = event-free survival; mPR = major pathological response; NSCLC = non-small cell lung cancer; OS = overall survival; pCR = pathological complete response; PRO = participant-reported outcomes; PS = performance scale; Q3W = every 3 weeks; RT = radiotherapy; TPS = tumor proportion score.

1. Primary tumor - positive margin at bronchus, pulmonary vessels, or structures abutting primary tumor. Mediastinal lymph node - extracapsular extension.

Study participants

Key inclusion criteria:

- Male/female participants at least 18 years with previously untreated and pathologically confirmed resectable Stage II, IIIA, or IIIB (N2) NSCLC (AJCC Version 8). Lymph node disease required pathologic confirmation, while T3 (rib destruction) disease required only radiographic documentation. A PET scan could be utilized as a surrogate for pathologic staging of N1 lymph nodes for participants with T2b and T4 tumours (the presence or absence of tumour in the N1 lymph nodes did not change the actual stage by which the participant was stratified). Similarly, biopsy confirmation of N2 disease was not required for pathologically confirmed T3N1 tumours and T4N0-1 tumours, as knowledge of the N2 status would not change the stage.

- Have available FFPE tumour tissue sample blocks for submission, if block not available have unstained slides for submission for central PD-L1 testing.
- Able to undergo protocol therapy, including necessary surgery.
- ECOG performance status of 0 to 1 within 10 days of randomization.
- Adequate organ function as defined in the study protocol.
- Female not pregnant or breastfeeding.
- Adequate contraceptive measures for male and WOCBP females as described in the study protocol.

Key exclusion criteria:

- Had one of the following tumour locations/types: NSCLC involving the superior sulcus, Large cell neuro-endocrine cancer, Sarcomatoid tumour.
- Had a history of (non-infectious) pneumonitis/interstitial lung disease that required steroids or had current pneumonitis/interstitial lung disease that required steroids.
- Had active autoimmune disease that had required systemic treatment in the past 2 years.
- Has a known history of human immunodeficiency virus (HIV) infection, hepatitis B (defined as HBsAg reactive) or known active Hepatitis C virus (defined as HCV RNA [qualitative] detected) infection; has a known history of active tuberculosis.
- Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy (>10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior the first dose of trial drug.
- Has a known additional malignancy that is progressing or requires active treatment within the past (5 years). Note: basal cell and squamous cell carcinoma of the skin, non-invasive bladder carcinoma, or any carcinoma in situ that have undergone potentially curative therapy are not excluded.
- Had received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent or with an agent directed to another co-inhibitory T-cell receptor (e.g., CTLA-4, OX-40, CD137).
- Had received prior systemic anticancer therapy including investigational agents for the current malignancy prior to randomization.

Additional details on the inclusion/exclusion criteria are available in the study protocol.

Biomarker – PD-L1 testing: For KEYNOTE-671, PD-L1 expression was determined using the PD-L1 IHC 22C3 pharmDx. LabCorp (ex-China) and Q2 Solutions (China) were the central laboratories for KN-671, with responsibility for all PD-L1 testing.

Patients with high risk of recurrence who are included in the therapeutic indication are reflective of the patient population with Stage II – IIIB (N2) according to the 8th edition staging system included in KEYNOTE-671 study, and are described by the following anatomical criteria: tumour size > 4 cm; or tumours of any size that are either accompanied by N1 or N2 status; or tumours that invade thoracic structures (directly invade the parietal pleura, chest wall, diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium, mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, oesophagus, vertebral body, carina); or tumours that involve a mainstem bronchus with tumour > 4 cm; or tumours > 4 cm that cause obstructive atelectasis that extends to the hilum; or tumours with separate nodule(s) in the same lobe or different ipsilateral lobe as the primary lung cancer.

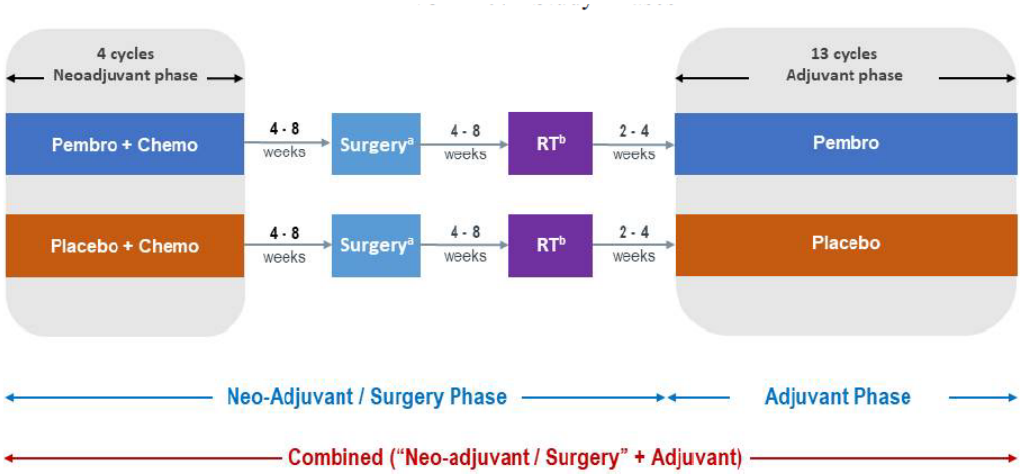
Treatments

Table 2: Study intervention

Arm Name	Intervention Name	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/Treatment Period	Use
Arm A	Pembrolizumab	25 mg/mL	200 mg	IV Infusion	Day 1 of each 21-day cycle for 4 cycles followed by surgery and 13 cycles	Test Product
Arm A	Cisplatin	1 mg/mL	75 mg/m^2	IV Infusion	Day 1 of each 21-day cycle for 4 cycles	Background Treatment
Arm A	Gemcitabine (squamous tumors)	1000 mg/vial	1000 mg/m^2	IV Infusion	Day 1 and Day 8 of each 21-day cycle for 4 cycles	Background Treatment
Arm A	Pemetrexed (nonsquamous tumors)	500 mg/vial	500 mg/m^2	IV Infusion	Day 1 of each 21-day cycle for 4 cycles	Background Treatment
Arm B	Normal saline	N/A	N/A	IV Infusion	Day 1 of each 21-day cycle for 4 cycles followed by surgery and 13 cycles	Placebo
Arm B	Cisplatin	1 mg/mL	75 mg/m^2	IV Infusion	Day 1 of each 21-day cycle for 4 cycles	Background Treatment
Arm B	Gemcitabine (squamous tumors)	1000 mg/vial	1000 mg/m^2	IV Infusion	Day 1 and Day 8 of each 21-day cycle for 4 cycles	Background Treatment
Arm B	Pemetrexed (nonsquamous tumors)	500 mg/vial	500 mg/m^2	IV Infusion	Day 1 of each 21-day cycle for 4 cycles	Background Treatment

N/A=not applicable; Q3W=every 3 weeks.

Table 3: KEYNOTE-671 study phases



NAC=neoadjuvant chemotherapy; RT=radiotherapy.

[a] If a participant did not undergo surgery due to refusal, physician decision, medical illness, or any reason other than local progression or metastatic disease, they were to receive RT and continue to the adjuvant phase.

[b] Only participants with microscopic residual disease or gross residual disease in the tumor bed after surgery were to undergo RT.

Neoadjuvant phase: The maximum interval from the first dose of neoadjuvant therapy to surgery is 20 weeks. If the participant receives fewer than 4 cycles of neoadjuvant therapy, she/he can remain in the study and should undergo surgery within 4-8 weeks following the last dose of protocol therapy and receive adjuvant therapy.

Adjuvant phase: Participants will receive up to 13 cycles of adjuvant therapy.

- Participants who do not have surgery should have radiotherapy (RT) followed by the adjuvant pembrolizumab/placebo treatment phase, and those should begin RT within 8 weeks of day 1 of the last chemotherapy cycle.

- Participants who do have surgery and do not receive RT must begin adjuvant pembrolizumab/placebo within 4-12 weeks following surgery.

- Participants who have surgery and RT must begin RT within 4-8 weeks following surgery. Adjuvant pembrolizumab/placebo must begin within 2-4 weeks following completion of RT. After surgery, only participants with microscopic or gross residual disease in the tumour bed after surgery were to undergo RT.

Objectives and outcomes/endpoints

The study has **dual primary endpoints EFS and OS** in the overall population, i.e. the study is considered positive if superiority in EFS **or** OS at an interim or final analysis is demonstrated.

Table 4: Primary objectives/endpoints

Primary Objective	Primary Endpoint
Objective: To evaluate event-free survival (EFS) by biopsy assessed by a local pathologist or by investigator-assessed imaging using RECIST 1.1. Hypothesis #1: NAC plus pembrolizumab followed by surgery and adjuvant pembrolizumab improves EFS by biopsy assessed by local pathologist or by investigator-assessed imaging using RECIST 1.1 compared to NAC plus placebo followed by surgery and adjuvant placebo.	EFS is defined as the time from randomization to the first of the following events: disease or local progression, inability to resect tumor, local or distant recurrence, or death.
Objective: To evaluate the overall survival (OS). Hypothesis #2: NAC plus pembrolizumab followed by surgery and adjuvant pembrolizumab improves OS compared to NAC plus placebo followed by surgery and adjuvant placebo.	OS is defined as the time from randomization to death due to any cause.

Event free survival definition:

EFS is defined as the time from randomization to the first of the following events:

- Radiographic disease progression per RECIST 1.1 (for participants who have not had or will not have surgery, or participants who have gross residual disease after an incomplete resection [R2 resection]);

- Local progression (primary tumour or regional lymph nodes) precluding planned surgery;

- Inability to resect the tumour;

- Local or distant recurrence (for participants who are disease free after surgery or participants with microscopic positive margins [R1 resection]);

- Death due to any cause.

Imaging and biopsy are investigator-assessed.

For radiographic progression/recurrence, the EFS event will be declared when:

- Only imaging is performed, and progression/recurrence confirmed.

- Only pathology is done, and progression/recurrence confirmed.

- Both pathology and imaging are done, and progression/recurrence confirmed (by at least one). In this case, whatever examination comes first, the first date is considered as the EFS event date.

In the event that biopsy is not diagnostic or does not reveal malignancy, the investigator should reassess the corresponding radiographic progression/recurrence.

Table 5: Secondary objectives/endpoints

Secondary Objectives	Secondary Endpoints
Objective: To evaluate the rate of major pathological response (mPR) assessed by blinded central laboratory pathologist following NAC ± pembrolizumab. Hypothesis #3: NAC plus pembrolizumab improves mPR rate assessed by blinded central laboratory pathologist compared to NAC plus placebo.	mPR is defined as ≤10% viable tumor cells in the resected primary tumor and all resected lymph nodes.
Objective: To evaluate the rate of pathological complete response (pCR) in the resected primary tumor and lymph nodes assessed by blinded central laboratory pathologist following NAC ± pembrolizumab. Hypothesis #4: NAC plus pembrolizumab improves pCR rate assessed by blinded central laboratory pathologist compared to NAC plus placebo.	pCR is defined as the absence of residual invasive cancer on hematoxylin and eosin stained slides of the resected lung specimen and lymph nodes following completion of neoadjuvant therapy (ie, ypT0/Tis ypN0).
Objective: To evaluate mean change from baseline in the neoadjuvant phase and in the adjuvant phase in global health status/quality of life (QoL) using the European Organization for Research and Treatment of Cancer (EORTC) QoL questionnaire (QLQ)-C30.	The QoL is based on the global health status/QoL scale (Items 29 and 30) of the EORTC QLQ-C30.
Objective: To evaluate the safety and tolerability of NAC plus pembrolizumab followed by surgery and adjuvant pembrolizumab.	• Participant experiencing AEs. • Participant discontinuing study drug due to AEs. • Participant experiencing perioperative complications.

Table 6: Exploratory objectives/endpoints

Tertiary/Exploratory	
• Objective: To evaluate changes in health-related QoL assessment from baseline in the neoadjuvant phase and in the adjuvant phase.	• Change from baseline in health-related QoL evaluated using the multi-item and single-item scales of EORTC QLQ-C30 and EORTC QLQ-LC13 scores: ○ Physical functioning (EORTC QLQC30 items 1-5) ○ Role functioning (EORTC QLQ C30, items 6-7) ○ Dyspnea (EORTC QLQC30 item 8) ○ Cough (EORTC QLQ-LC13 item 31) and ○ Chest pain (EORTC QLQ-LC13 item 40)
• Objective: To characterize health utilities in neoadjuvant and adjuvant phases using EQ-5D-5L.	• Health utilities assessed using EQ-5D-5L.
• Objective: To identify molecular (genomic, metabolic and/or proteomic) biomarkers that may be indicative of clinical response/resistance, safety, pharmacodynamic activity, and/or the mechanism of action of pembrolizumab plus chemotherapy used as neoadjuvant and in combination with pembrolizumab as adjuvant.	• The relationship between molecular biomarkers and clinical activity that may be indicative of clinical response/resistance, safety, pharmacodynamic activity, and/or the mechanism of action of the study treatments.

Tumour imaging assessment:

Baseline assessment: chest/abdomen CT scan must be performed within 28 days prior to randomization. Brain imaging is required for all participants at screening.

Neoadjuvant phase: for participants receiving all 4 cycles of neoadjuvant therapy, the first imaging assessment was performed 3 weeks after completion of 2 cycles, and the second imaging assessment took place 3 weeks after 4 cycles of preoperative therapy, before surgery. If the participant received fewer than 4 cycles, imaging schedule was adapted as defined in the protocol.

Adjuvant phase: following resection of lung cancer (+/- post-operative RT), participants must have new baseline imaging within 4 weeks prior to the start of adjuvant pembrolizumab/placebo.

Imaging in the adjuvant phase were performed every 16 weeks (±14 days).

End of treatment and follow-up: all participants discontinuing study treatment for any reason, including completion of 13 cycles of adjuvant treatment, should have tumour imaging performed at the time of treatment discontinuation. For participants who discontinue study treatment for reasons other than progressive disease or recurrence, every effort should be made to continue monitoring their disease status by tumour imaging every 16 weeks through the end of year 3, and then every 6 months for years 4 and 5. Imaging is required for participants who have started a new anticancer treatment. Once participants experience disease progression, imaging stopped and participants entered Survival Follow up.

All images were sent to a central imaging vendor.

Sample size

The study is event-driven and was planned to randomize approximately 786 participants in a 1:1 ratio into the pembrolizumab plus chemotherapy arm and the placebo plus chemotherapy arm.

This trial used dual-primary efficacy endpoints: 1) event-free survival (EFS) defined by investigator assessment and 2) overall survival (OS). Major pathological response (mPR) rate and pathological complete response (pCR) rate were evaluated as secondary endpoints and were defined by blinded central laboratory pathologist. For EFS, based on a target number of ~416 events at IA2 (i.e. FA for EFS), the study has power of 90.1% to detect a hazard ratio of 0.7 at α=0.01. Power is increased to 94.9% at α=0.025. For OS, based on a target number of ~ 386 deaths at FA, the study has power of 90% (α=0.0148) or 93.2% (α=0.025) to detect a hazard ratio of 0.7. The sample size and power calculation for EFS and OS were based on the following assumptions:

- EFS follows an exponential distribution with a median of 21 months for the control group and 30 months for the experimental group.

- OS follows an exponential distribution with a median of 34 months for the control group and 48.6 months for the experimental group.

- The hazard ratio for EFS and OS between the experimental and control groups is 0.7.

- The enrolment period is 36 months with a ramp up period of 6 months.

- The monthly drop-out rate is 1% for both EFS and OS.

Based on the 786 participants, there is 99.1% power to detect a difference in mPR rates at the allocated α=0.0001 assuming an underlying 22% mPR rate in the control group and 42% in the experimental group. There is 99.3% power to detect a difference in pCR rates at the allocated α=0.0001 assuming an underlying 8% pCR rate in the control group and 24% in the experimental group.

Randomisation

Treatment allocation/randomization occurred centrally using an interactive voice response system/ integrated web response system (IVRS/IWRS). Participants were randomly assigned in a 1:1 ratio in one of the two treatment arms of pembrolizumab + chemotherapy or placebo + chemotherapy, respectively.

Treatment randomization was stratified based on the following criteria:

1. Stage (II, III)

2. PD-L1 TPS (<50%, ≥50%)

3. Histology (Squamous, Non-squamous)

4. Region (East-Asia, non-East-Asia)

Blinding (masking)

KEYNOTE-671 study was conducted as a double-blind study under in-house blinding procedures. Pembrolizumab and placebo appeared identical so that the blind is maintained. The participant, the investigator and Sponsor personnel or delegate(s) who were involved in the study treatment administration or clinical evaluation of the participants were unaware of the group assignments.

The official, final database was not unblinded until medical/scientific review has been performed, protocol deviations have been identified, and data have been declared final and complete. Blinding to treatment assignment was maintained at all investigational sites. Treatment-level results of the planned interim analyses were provided by the external unblinded statistician to the DMC. Limited additional Sponsor personnel may be unblinded to the treatment level results of the interim analyses, if required, in order to act on the recommendations of the DMC (e.g., interaction with regulatory agencies). The extent to which individuals are unblinded with respect to results of interim analyses was to be documented by the external unblinded statistician. The DMC serves as the primary reviewer of the results of the interim analyses and to make recommendations for discontinuation of the study or modification to an EOC of the Sponsor. Depending on the recommendation of the DMC, the Sponsor may prepare a regulatory submission. If the DMC recommends modifications to the design of the protocol or discontinuation of the study, this EOC and limited additional Sponsor personnel may be unblinded to results at the treatment level in order to act on these recommendations. Prior to final study unblinding, the external unblinded statistician is not involved in any discussions regarding modifications to the protocol, statistical methods, identification of protocol deviations, or data validation efforts after the interim analyses.

Statistical methods

Protocol Amendments involving statistical methods

The protocol was subject to ten amendments, of which five were country specific and five were general amendments (see also "conduct of the study" below). The amendments listed below modified the SAP language as follows.

- Amendment No. 01 (11-Apr-2018): since new anti-cancer therapy was considered a confounding factor, it was added in the event scenarios of the censoring rule table. As per FDA requirements, the medians of EFS and OS for the experimental group were added.

- Amendment No. 03 (27-Aug-2018): some clarifications about the EFS definition, the small strata combination and censoring rules were updated. The age category for subgroup analysis was also updated to align with program-wide age category (≤65 and >65 were updated into <65 and ≥65).

- Amendment No. 05 (18-Jul-2019): the study population was updated to include stages IIA and resectable IIIB (N2); stratification levels for the variable "stage" and the corresponding subgroup definition were updated. Subgroup analysis for EGFR, ALK and type of surgery were also added. Subject enrolment was changed from 24 months to 36 months; consequently, timing of interim and final analyses, as well as the enrolment assumption, were updated. Finally, more details to general description of tiered approach in safety analyses section were added.

-Amendment No. 10 (24-Mar-2022): The primary objective was updated since the EFS was based on investigator assessment (see conduct of the study for rationale). As consequence, a sensitivity analysis for ESF evaluated by BICR was added. Based on blinded clinical data monitoring the OS events accrual was slower than expected, so the OS timing analysis was optimized and an additional IA was added (a total of 4 IA and 1 FA were planned). Multiplicity strategy was updated to be aligned with the updated interim analysis plan. The subgroup "type of surgery" was removed since it was not a baseline characteristic, and "smoking status" was added.

Interim Analyses

There were four planned interim efficacy analyses (IA) in addition to the final analysis (FA) for this study. The efficacy analyses in this submission are based on IA1 (cut-off date 29-Jul-2022). The analyses planned, endpoints evaluated, and drivers of timing are summarized in the table below:

Table 7: Planned analyses3

Analyses	Key Endpoints	Timing	Estimated Time after First Participant Randomized	Primary Purpose of Analysis
IA1	mPR rate pCR rate EFS OS*	~ 326 EFS events have been observed and ~ 5 months after last participant is randomized .	~48 months	• Demonstrate mPR rate superiority • Demonstrate pCR rate superiority • Interim evaluation of EFS superiority • Interim evaluation of OS superiority
IA2	EFS OS*	~ 416 EFS events have been observed.	~60 months	• Demonstrate EFS superiority • Interim evaluation of OS superiority
IA3	OS	~ 285 deaths have been observed.	~72 months	• Interim evaluation of OS superiority
IA4	OS	~ 340 deaths have been observed.	~84 months	• Interim evaluation of OS superiority
FA	OS	~ 386 deaths have been observed.	~96 months	• Demonstrate OS superiority

* The estimated observed OS events at IA1 and IA2 are approximately 159 and 225, respectively. Note that IA1 and IA2 are EFS event-driven, so there is no OS events count requirement to proceed with these 2 analyses.
Note that for IA3 and IA4, if the OS events accrue slower than expected, the Sponsor may conduct the analysis with additional 3 months of follow-up, or when the specified number of events is observed, whichever occurs first. If the final targeted OS events cannot be reached by the end of year 5 after last participant randomized, the final OS analysis will be conducted at the end of year 5 after last participant randomized at the latest.

Formal testing was conducted for the OS hypothesis while ESF was not formally tested at IA2 since the trial already met the success criterion for EFS at IA1. At time of IA2 a total of 254 OS events were observed (110 in the pembrolizumab arm and 144 in the placebo arm), resulting in 65.8% of information fraction.

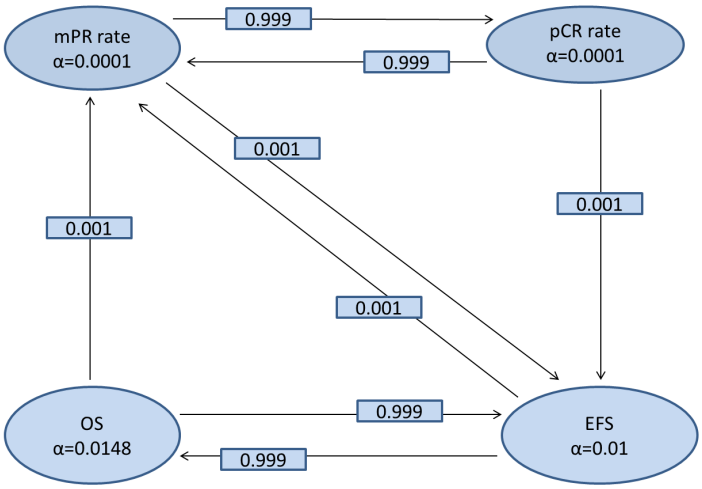
Results of the interim analyses were reviewed by the DMC. If the EFS or OS null hypothesis was rejected prior to the final analysis, the DMC could have recommended stopping the trial early for efficacy.

Error probabilities, adjustment for multiplicity

The overall Type I error rate was controlled at a 0.025 (one-sided) α level. The trial used the graphical method of Maurer and Bretz to provide multiplicity control for multiple hypotheses as well as interim efficacy

analyses; this method specifically extends previous graphical multiplicity methods to cases where individual hypotheses are tested in a group sequential fashion using an error spending approach.

Figure 2: type I error reallocation strategy (according to Protocol Amendment No. 10)



The initial one-sided α-allocation for each hypothesis in the ellipse representing the hypothesis. The initial weights for reallocation from each hypothesis to the others are represented in the boxes on the lines connecting hypotheses.

Major Pathological Response Rate: The trial initially allocates α=0.0001, one-sided, to test mPR rate. If the null hypothesis for pCR rate is rejected, its α=0.0001 is essentially fully reallocated to mPR rate hypothesis testing. Only data from IA1 were used to test the mPR rate. However, if the test does not reach statistical significance at IA1, the p-value from IA1 can be compared to an updated α-level if the null hypotheses for both EFS and OS are rejected at a later time. Power at the possible α-levels as well as the approximate treatment difference required to reach the bound (ΔmPR rate) are shown in the table below, assuming underlying 22% and 42% mPR rates in the control and experimental groups, respectively.

Table 8: Possible α-levels and approximate mPR rate difference required to demonstrate efficacy for mPR rate

A	~ΔmPR rate	Power
0.0001	12.38%	0.991
0.0002	11.78%	0.994
0.0249	6.53%	1.000
0.025	6.37%	1.000

Pathological Complete Response Rate: The trial initially allocates α=0.0001, one-sided, to test pCR rate. If the null hypothesis for mPR rate is rejected, its α=0.0001 is essentially fully reallocated to pCR rate hypothesis testing. Only data from IA1 were used to test the pCR rate. However, if the test does not reach statistical significance at IA1, the p-value from IA1 can be compared to an updated α-level if the null hypotheses for EFS, OS and mPR rate are all rejected at a later time. Power at the possible α-levels as well as the approximate treatment difference required to reach the bound (ΔpCR rate) are shown in the table below, assuming underlying 8% and 24% pCR rates in the control and experimental groups, respectively.

Table 9: Possible α-levels and approximate pCR rate difference required to demonstrate efficacy for pCR rate

A	~ Δ pCR rate	Power
0.0001	9.73%	0.993
0.0002	9.26%	0.996
0.025	5.13%	1.000

Event-free Survival: The trial initially allocates α=0.01, one-sided to test EFS. If the null hypothesis for OS is rejected, its α=0.0148 is essentially fully reallocated to EFS hypothesis testing. If the null hypotheses for mPR rate and pCR rate are both rejected, their accumulative α=0.0002 is fully reallocated to EFS hypothesis testing. The EFS null hypothesis may be tested at α=0.01 (if OS null hypothesis is not rejected, and not both of mPR and pCR null hypotheses are rejected), α=0.0102 (if both of mPR and pCR null hypotheses are rejected while OS null hypothesis is not), α=0.0248 (if OS null hypothesis is rejected while not both of mPR and pCR null hypotheses are rejected), or α=0.025 (if null hypotheses for mPR, pCR and OS are all rejected). Table 10 shows the boundary properties for α=0.01 and α=0.025 for the planned analysis testing of EFS, which were derived using a Lan-DeMets O'Brien-Fleming spending function. Note that the final row indicates the total power to reject the null hypothesis for EFS at each α-level. If the actual number of EFS events at the interim analyses differ from those specified in the table, the bounds will be adjusted using the Lan-DeMets O'Brien-Fleming spending function accordingly. If the OS null hypothesis is rejected at an interim or final analysis, the previously computed EFS test statistics for the EFS interim or final analyses may be re-evaluated versus the updated bounds considering the α reallocation from the OS hypothesis.

Table 10: Efficacy boundaries and properties for planned analyses of EFS

Analysis	Value	α = 0.01	α=0.025
IA1: 78%* N: 786 Events: 326 Month+: 48	Z statistics	2.6842	2.2772
	p (1-sided)§	0.0036	0.0114
	HR at boundI	0.7428	0.7770
	P (Cross) if HR = 1†	0.0036	0.0114
	P (Cross) if HR = 0.7#	0.7045	0.8264
IA2: N: 786 Events: 416 Month+: 60	Z statistics	2.3697	2.0207
	p (1-sided) §	0.0089	0.0217
	HR at boundI	0.7925	0.8201
	P (Cross) if HR = 1†	0.0100	0.0250
	P (Cross) if HR = 0.7#	0.9010	0.9495

*Percentage of total number of required events needed at each interim analysis.
§The nominal α for testing.
IThe approximate HR required to reach an efficacy bound.
†The probability of crossing a bound under the null hypothesis.
+The analysis timeline is projected based on blinded clinical data monitoring.
#The probability of crossing a bound under the alternative hypothesis.

Overall Survival: The OS hypothesis may be tested at α=0.0148 (if EFS null hypothesis is not rejected, and not both of mPR and pCR null hypotheses are rejected), α=0.0248 (if EFS null hypothesis is rejected while not both of mPR and pCR null hypotheses are rejected), or α=0.025 (if null hypotheses for mPR, pCR and EFS are all rejected). Table 11, shows the boundary properties for OS hypothesis testing, which

were derived using a Lan-DeMets O'Brien-Fleming spending function. If the actual number of OS events at the interim analyses differs from those specified in the table, the bounds will be adjusted using the Lan-DeMets O'Brien-Fleming spending function accordingly.

Table 11: Efficacy boundaries and properties for planned analyses of OS

Analysis	Value	α=0.0148	α=0.025
IA1: 41%* Events: 159 Month+: 48	Z statistics	3.6216	3.3023
	p(1-sided)§	0.0001	0.0005
	HR at bound%	0.5630	0.5922
	P(Cross) if HR = 1†	0.0001	0.0005
	P(Cross) if HR = 0.7#	0.0849	0.1458
IA2: 58%* Events: 225 Month+: 60	Z statistics	2.9968	2.7292
	p(1-sided)§	0.0014	0.0032
	HR at bound%	0.6706	0.6949
	P(Cross) if HR = 1†	0.0014	0.0033
	P(Cross) if HR = 0.7#	0.3759	0.4809
IA3: 74%* Events: 285 Month+: 72	Z statistics	2.6433	2.4075
	p(1-sided)§	0.0041	0.0080
	HR at bound%	0.7310	0.7518
	P(Cross) if HR = 1†	0.0046	0.0091
	P(Cross) if HR = 0.7#	0.6496	0.7334
IA4: 88%* Events: 340 Month+: 84	Z statistics	2.4109	2.1965
	p(1-sided)§	0.0080	0.0140
	HR at bound%	0.7699	0.7880
	P(Cross) if HR = 1†	0.0094	0.0169
	P(Cross) if HR = 0.7#	0.8183	0.8703
FA: Events: 386 Month+: 96	Z statistics	2.2666	2.0666
	p(1-sided)§	0.0117	0.0194
	HR at bound%	0.7939	0.8103
	P(Cross) if HR = 1†	0.0148	0.0250
	P(Cross) if HR = 0.7#	0.9004	0.9318

*Percentage of total number of required events needed at each interim analysis.
§The nominal α for testing.
%The approximate HR required to reach an efficacy bound.
†The probability of crossing a bound under the null hypothesis.
+The analysis timeline is projected based on blinded clinical data monitoring.
#The probability of crossing a bound under the alternative hypothesis.

Statistical Methods for Efficacy Analyses

The Intention-to-Treat (ITT) population served as the population for primary efficacy analyses. All randomized participants were included in this population. Participants were included in the treatment group to which they are randomized.

Table 12: Analysis Strategy for Key Efficacy Endpoints in KEYNOTE-671 IA1

Endpoint	Statistical Method	Analysis Population	Missing Data Approach
Primary/dual-primary Endpoints			
EFS	Test: Stratified Log-rank test to assess the treatment difference Estimation: Stratified Cox model with Efron's tie handling method to assess the magnitude of treatment difference	ITT	Censored at the last disease assessment
OS	Test: Stratified Log-rank test to assess the treatment difference Estimation: Stratified Cox model with Efron's tie handling method to assess the magnitude of treatment difference	ITT	Censored at the last known alive date
Secondary Endpoints			
mPR rate	Stratified Miettinen and Nurminen method with sample size weights	ITT	Participants with relevant data missing are considered non-responders
pCR rate	Stratified Miettinen and Nurminen method with sample size weights	ITT	Participants with relevant data missing are considered non-responders
EFS=event-free survival; ITT=intent to treat; mPR = major pathological response; OS=overall survival; pCR = pathological complete response.			

The non-parametric Kaplan-Meier method was used to estimate the EFS and OS curve in each treatment group. The treatment difference in EFS and OS was assessed by the stratified log-rank test. A stratified Cox proportional hazard model with Efron's method of tie handling was used to assess the magnitude of the treatment difference (i.e., hazard ratio) between the treatment arms. The hazard ratio (HR) and its 95% confidence interval (CI) from the stratified Cox model with Efron's method of tie handling and with a single treatment covariate was reported.

The same stratification factors used for randomization were applied to all stratified efficacy analyses, including stratified log-rank test, stratified Cox model, and stratified Miettinen and Nurminen method. In the event that some strata are of small size (< 5 event counts in one or more strata), they were pooled for analyses in a meaningful way.

The primary approach for EFS was based on investigator assessment. Sensitivity analyses by using the central review of imaging and biopsy were also conducted. In order to evaluate the robustness of the EFS endpoint, 2 sensitivity analyses with a different set of censoring rules were performed. The censoring rules for primary and sensitivity analyses are summarized in the table below:

Table 13: Censoring rules for primary and sensitivity analyses of EFS

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

The stratified Miettinen and Nurminen method was used for the comparison of the mPR rates and pCR rates between the two treatment groups. The difference in mPR and pCR rates and its 95% confidence interval from the stratified Miettinen and Nurminen method with strata weighting by sample size was reported.

The stratification factors used for randomization were applied to the analysis. The descriptive analysis of mPR and pCR based on all participants was performed after IA1. No formal hypothesis testing was conducted.

Subgroup analyses

To determine whether the treatment effect was consistent across various subgroups, the between-group treatment effect for the primary endpoint (with a nominal 95% CI) was estimated and plotted by treatment group within each category of the following classification variables: Tumor stage (II, III); TPS (<50%, ≥50%); Histology (squamous, non-squamous); Geographic region (East Asia, non-East Asia); Age category (<65, ≥65 years); Sex (female, male); Race (white, non-white); Smoking status (never, former, current); Known EGFR activating mutation status (Yes, No); ALK translocation status (Yes, No).

The consistency of the treatment effect was assessed descriptively via summary statistics by category for the classification variables listed below. If any level of a subgroup variable had fewer than 30 participants, above analysis could not be performed for that level of the subgroup variable. If a subgroup variable had two levels and one level of the subgroup variable had fewer than 30 participants, then this subgroup could not be displayed in the forest plot. The subgroup analyses for efficacy endpoints were conducted using unstratified methods. Country and/or region-specific subgroup (e.g., China, Japan, etc.) could also be analyzed per local registration needs.

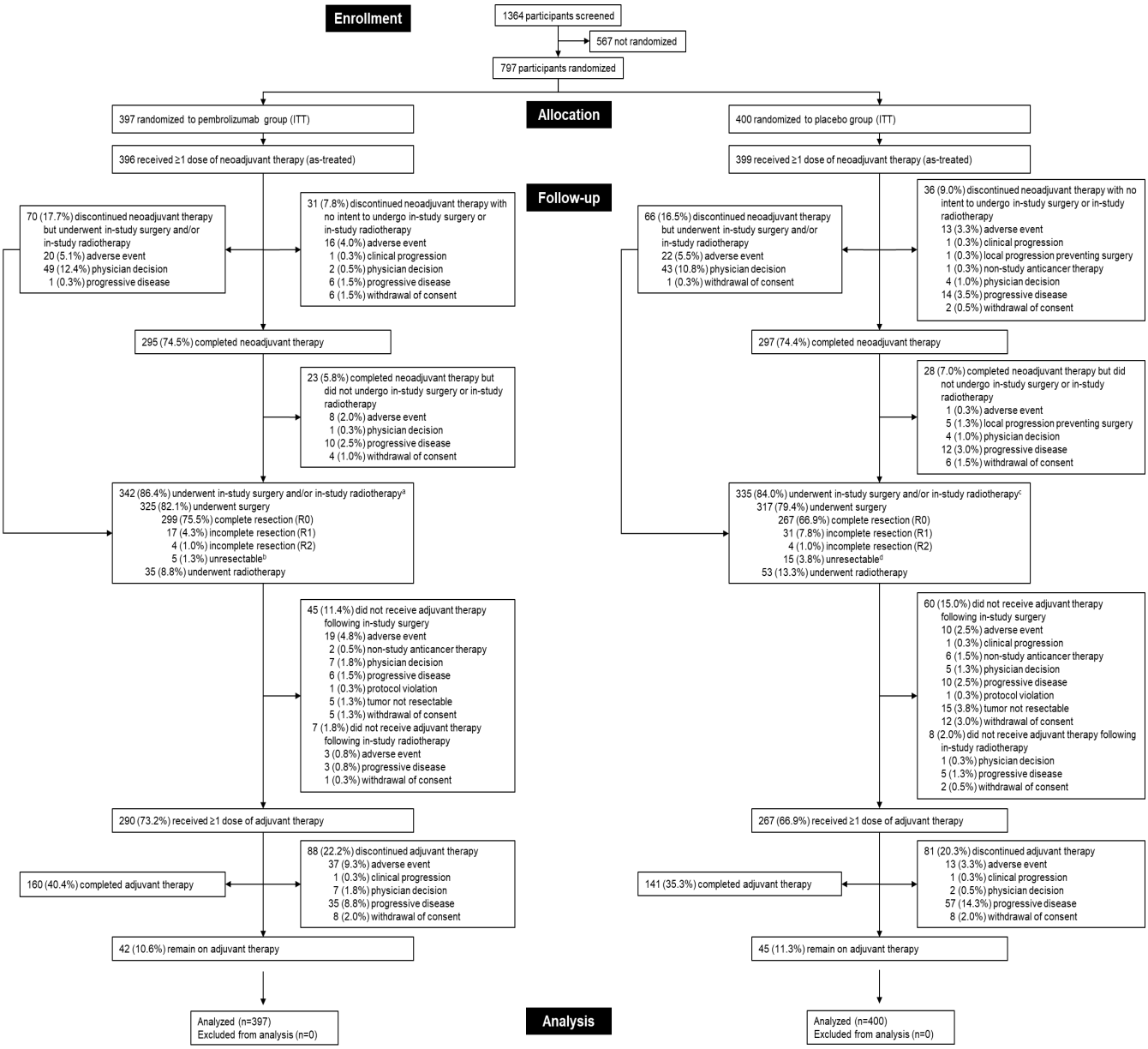
PRO analyses

Analyses of PRO endpoints were conducted using the PRO FAS population, defined as all randomized participants who had at least 1 PRO assessment available and received at least 1 dose of study intervention. Participants were analysed in the treatment arm to which they were randomized.

Results

Participant flow

Figure 3: KEYNOTE-671 Participant Flow Diagram - IA1



[a]307 participants underwent in-study surgery alone, 18 participants underwent both in-study surgery and in-study radiotherapy, and 17 participants underwent in-study radiotherapy alone; an additional 8 participants underwent off-study surgery.
[b]Includes 4 participants who underwent exploratory thoracotomy and 1 participant who underwent lobectomy but was found to have metastatic disease at the time of surgery.
[c]282 participants underwent in-study surgery alone, 35 participants underwent both in-study surgery and in-study radiotherapy, and 18 underwent in-study radiotherapy only; an additional 7 participants underwent off-study surgery.
[d]Includes 13 participants who underwent exploratory thoracotomy and 2 participants who underwent lobectomy but were found to have metastatic disease at the time of surgery.

A total of 1364 participants were screened, and 797 participants were randomized (pembrolizumab arm: 397; placebo arm: 400). Two participants (one in each arm) were randomized but not treated.

Of the 567 participants not randomized, the majority (565) due to not meeting inclusion or meeting exclusion criteria. The most frequent reasons for screen failure were not meeting inclusion criteria 1 (i.e.

on NSCLC criteria, 308/565=54.5%), followed by 7 (i.e. on tissue availability, 94/565=16.6%), and 2 (i.e. on able to undergo study procedures including surgery, 10%).

Patient disposition

Table 14: Disposition of participants

	Pembro + Chemo/Pembro		Placebo + Chemo/Placebo	
	n	(%)	n	(%)
Participants in population	397		400	
Status for Study Treatment (Neo-adjuvant/Surgery + Adjuvant)				
Started	396		399	
Completed	160	(40.4)	141	(35.3)
Discontinued	194	(49.0)	213	(53.4)
Adverse Event	83	(21.0)	37	(9.3)
Associated with COVID-19	3	(0.8)	0	(0.0)
Clinical Progression	2	(0.5)	3	(0.8)
Local Progression Preventing Surgery	0	(0.0)	6	(1.5)
Non-Study Anti-Cancer Therapy	2	(0.5)	7	(1.8)
Associated with COVID-19	0	(0.0)	1	(0.3)
Physician Decision	17	(4.3)	16	(4.0)
Associated with COVID-19	1	(0.3)	1	(0.3)
Progressive Disease	60	(15.2)	98	(24.6)
Protocol Violation	1	(0.3)	1	(0.3)
Associated with COVID-19	0	(0.0)	1	(0.3)
Tumor Found To Be Surgically Unresectable	5	(1.3)	15	(3.8)
Withdrawal By Subject	24	(6.1)	30	(7.5)
Associated with COVID-19	2	(0.5)	0	(0.0)
Participants Ongoing	42	(10.6)	45	(11.3)
Status for Trial				
Discontinued	83	(20.9)	112	(28.0)
Death	75	(18.9)	100	(25.0)
Associated with COVID-19	5	(1.3)	4	(1.0)
Lost To Follow-Up	1	(0.3)	1	(0.3)
Physician Decision	1	(0.3)	0	(0.0)
COVID-19 association unspecified, Subsequently died	1	(0.3)	0	(0.0)
Withdrawal By Subject	6	(1.5)	11	(2.8)
COVID-19 association unspecified, Subsequently died	0	(0.0)	1	(0.3)
Participants Ongoing	314	(79.1)	288	(72.0)

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.
Study treatment includes study medication, in-study surgery and in-study radiotherapy.
Completed indicates the completion of 13 cycles of adjuvant pembrolizumab/placebo.
Database Cutoff Date: 29JUL2022

Table 15: disposition of participants (by study phase)

	Pembro + Chemo/Pembro		Placebo + Chemo/Placebo	
	n	(%)	n	(%)
Participants in population	397		400	
Status of Study Medication (Neoadjuvant)				
Started	396		399	
Completed 4 Cycles Of Pembrolizumab/Placebo	295	(74.5)	297	(74.4)
Started Next Study Treatment	272	(68.7)	269	(67.4)
Without Intent To Receive Any Next Study Treatment	23	(5.8)	28	(7.0)
Adverse Event	8	(2.0)	1	(0.3)
Local Progression Preventing Surgery	0	(0.0)	5	(1.3)
Physician Decision	1	(0.3)	4	(1.0)
Progressive Disease	10	(2.5)	12	(3.0)
Withdrawal By Subject	4	(1.0)	6	(1.5)
Discontinued Without Receiving 4 Cycles Of Pembrolizumab/Placebo	101	(25.5)	102	(25.6)
Started Next Study Treatment	70	(17.7)	66	(16.5)
Adverse Event	20	(5.1)	22	(5.5)
Physician Decision	49	(12.4)	43	(10.8)
Progressive Disease	1	(0.3)	0	(0.0)
Withdrawal By Subject	0	(0.0)	1	(0.3)
Without Intent To Receive Any Next Study Treatment	31	(7.8)	36	(9.0)
Adverse Event	16	(4.0)	13	(3.3)
Clinical Progression	1	(0.3)	1	(0.3)
Local Progression Preventing Surgery	0	(0.0)	1	(0.3)
Non-Study Anti-Cancer Therapy	0	(0.0)	1	(0.3)
Physician Decision	2	(0.5)	4	(1.0)
Progressive Disease	6	(1.5)	14	(3.5)
Withdrawal By Subject	6	(1.5)	2	(0.5)
Status of in-study Surgery				
Started	325		317	
Complete Resection-R0	299	(92.0)	267	(84.2)
Incomplete Resection-R1	17	(5.2)	31	(9.8)
Incomplete Resection-R2	4	(1.2)	4	(1.3)
Status of in-study Surgery				
Unresectable	5	(1.5)	15	(4.7)
Discontinued Without Intent To Receive Any Next Study Treatment	45	(13.8)	60	(18.9)
Adverse Event	19	(5.8)	10	(3.2)
Clinical Progression	0	(0.0)	1	(0.3)
Non-Study Anti-Cancer Therapy	2	(0.6)	6	(1.9)
Physician Decision	7	(2.2)	5	(1.6)
Progressive Disease	6	(1.8)	10	(3.2)
Protocol Violation	1	(0.3)	1	(0.3)
Tumor Found To Be Surgically Unresectable	5	(1.5)	15	(4.7)
Withdrawal By Subject	5	(1.5)	12	(3.8)
Started Next Study Treatment	280	(86.2)	257	(81.1)
Status of in-study Radiotherapy				
Started	35		53	
Discontinued Without Intent To Receive Any Next Study Treatment	7	(20.0)	8	(15.1)
Adverse Event	3	(8.6)	0	(0.0)
Physician Decision	0	(0.0)	1	(1.9)
Progressive Disease	3	(8.6)	5	(9.4)
Withdrawal By Subject	1	(2.9)	2	(3.8)
Started Next Study Treatment	28	(80.0)	45	(84.9)
Status of Study Medication (Adjuvant)				
Started	290		267	
Completed	160	(55.2)	141	(52.8)
Discontinued	88	(30.3)	81	(30.3)
Adverse Event	37	(12.8)	13	(4.9)
Clinical Progression	1	(0.3)	1	(0.4)
Physician Decision	7	(2.4)	2	(0.7)
Progressive Disease	35	(12.1)	57	(21.3)
Withdrawal By Subject	8	(2.8)	8	(3.0)
Status of Study Medication (Adjuvant)				
Participants Ongoing	42	(14.5)	45	(16.9)

Study treatment includes study medication, in-study surgery and in-study radiotherapy.
Database Cutoff Date: 29JUL2022

Exposure

Table 16: Summary of drug exposure - combined phases (neo-adjuvant/surgery + adjuvant) (APaT Population)

	Pembro + Chemo/Pembro (N=396)	Placebo + Chemo/Placebo (N=399)
Study Days on Treatment (days)		
n	396	399
Mean (SD)	291.5 (153.2)	271.9 (155.2)
Median	332.0	315.0
Range	1.0 to 567.0	1.0 to 596.0
Study Days on Pembrolizumab/Placebo (days)		
n	396	399
Mean (SD)	283.5 (162.9)	262.5 (165.6)
Median	332.0	315.0
Range	1.0 to 567.0	1.0 to 596.0
Number of Administrations of Pembrolizumab/Placebo		
n	396	399
Mean (SD)	10.9 (5.9)	10.2 (5.9)
Median	12.0	10.0
Range	1.0 to 17.0	1.0 to 17.0
Treatment includes study drugs, in-study surgery and in-study radiotherapy. Database Cutoff Date: 29JUL2022		

Table 17: summary of drug exposure neo-adjuvant/surgery phase (APaT Population)

	Pembro + Chemo (N=396)	Placebo + Chemo (N=399)
Study Days on Treatment (days)		
Mean	105.9	107.9
Median	106.0	106.0
SD	40.1	43.8
Range	1.0 to 264.0	1.0 to 256.0
Study Days on Study Drugs (days)		
Mean	62.7	61.9
Median	65.0	66.0
SD	19.6	20.3
Range	1.0 to 107.0	1.0 to 107.0
Number of Cycles		
1	13 (3.3)	19 (4.8)
2	36 (9.1)	32 (8.0)
3	50 (12.6)	50 (12.5)
4	297 (75.0)	298 (74.7)
Mean	3.6	3.6
Median	4.0	4.0
SD	0.8	0.8
Range	1.0 to 4.0	1.0 to 4.0
Treatment includes neoadjuvant study medications, in-study surgery and in-study radiotherapy. Study drugs only include neoadjuvant study medications. Database Cutoff Date: 29JUL2022		

Table 18: Summary of drug administration by component neo-adjuvant/surgery phase (APaT)

	Pembro + Chemo (N=396)				Placebo + Chemo (N=399)			
	Pembrolizumab	Pemetrexed	Cisplatin	Gemcitabine	Placebo	Pemetrexed	Cisplatin	Gemcitabine
Study Days on Therapy(days)								
n	396	222	396	174	399	225	399	175
Mean (SD)	59.8 (19.3)	60.4 (18.6)	59.6 (19.1)	65.4 (20.6)	59.2 (19.5)	59.0 (17.9)	59.1 (19.6)	65.0 (23.3)
Median	64.0	64.0	64.0	71.0	64.0	64.0	64.0	71.0
Range	1.0 to 107.0	1.0 to 103.0	1.0 to 107.0	1.0 to 107.0	1.0 to 100.0	1.0 to 98.0	1.0 to 100.0	1.0 to 107.0
Number of Administrations								
n (%)	396	222	396	174	399	225	399	175
1	14 (3.5)	6 (2.7)	13 (3.3)	3 (1.7)	19 (4.8)	6 (2.7)	20 (5.0)	9 (5.1)
2	36 (9.1)	20 (9.0)	37 (9.3)	5 (2.9)	32 (8.0)	19 (8.4)	31 (7.8)	5 (2.9)
3	51 (12.9)	20 (9.0)	52 (13.1)	4 (2.3)	51 (12.8)	37 (16.4)	51 (12.8)	6 (3.4)
4	295 (74.5)	176 (79.3)	293 (74.0)	16 (9.2)	297 (74.4)	163 (72.4)	297 (74.4)	10 (5.7)
5	0 (0.0)	0 (0.0)	0 (0.0)	9 (5.2)	0 (0.0)	0 (0.0)	0 (0.0)	4 (2.3)
6	0 (0.0)	0 (0.0)	1 (0.3)	23 (13.2)	0 (0.0)	0 (0.0)	0 (0.0)	16 (9.1)
7	0 (0.0)	0 (0.0)	0 (0.0)	14 (8.0)	0 (0.0)	0 (0.0)	0 (0.0)	21 (12.0)
8	0 (0.0)	0 (0.0)	0 (0.0)	100 (57.5)	0 (0.0)	0 (0.0)	0 (0.0)	104 (59.4)
Mean (SD)	3.6 (0.8)	3.6 (0.8)	3.6 (0.8)	6.7 (1.8)	3.6 (0.8)	3.6 (0.8)	3.6 (0.8)	6.7 (2.1)
Median	4.0	4.0	4.0	8.0	4.0	4.0	4.0	8.0
Range	1.0 to 4.0	1.0 to 4.0	1.0 to 6.0	1.0 to 8.0	1.0 to 4.0	1.0 to 4.0	1.0 to 4.0	1.0 to 8.0
Database Cutoff Date: 29JUL2022								

Table 19: Summary of drug exposure adjuvant phase (participants who received the adjuvant pembrolizumab/placebo)

	Pembro (N=290)	Placebo (N=267)
Study Days on Study Drugs (days)		
n	290	267
Mean (SD)	201.5 (88.4)	195.2 (87.9)
Median	253.0	252.0
Range	1.0 to 336.0	1.0 to 387.0
Number of Administrations		
n	290	267
Mean (SD)	10.0 (4.0)	9.9 (4.0)
Median	13.0	13.0
Range	1.0 to 13.0	1.0 to 13.0
Treatment includes adjuvant pembrolizumab/placebo. Database Cutoff Date: 29JUL2022		

Surgery

Table 20: Surgery status

	Pembro + Chemo/Pembro		Placebo + Chemo/Placebo	
	n	(%)	n	(%)
Participants in population	397		400	
Not treated	1	(0.3)	1	(0.3)
With in-study surgery	325	(81.9)	317	(79.3)
Resectable	320	(80.6)	302	(75.5)
Complete Resection-R0	299	(75.3)	267	(66.8)
Incomplete Resection-R1	17	(4.3)	31	(7.8)
Incomplete Resection-R2	4	(1.0)	4	(1.0)
Unresectable	5	(1.3)	15	(3.8)
Without in-study surgery	71	(17.9)	82	(20.5)
Adverse Event	25	(6.3)	17	(4.3)
Clinical Progression	1	(0.3)	1	(0.3)
Local Progression Preventing Surgery	0	(0.0)	6	(1.5)
New Non-Study Anti-Cancer Therapy	0	(0.0)	1	(0.3)
Patient Refusal	4	(1.0)	3	(0.8)
Physician Decision	16	(4.0)	20	(5.0)
Progressive Disease	15	(3.8)	26	(6.5)
Withdrawal By Subject	10	(2.5)	8	(2.0)
With in-study surgery and in-study radiotherapy	18	(4.5)	35	(8.8)
Database Cutoff Date: 29JUL2022				

Table 21: type of surgery (participants who underwent surgery)

	Pembro + Chemo/Pembro		Placebo + Chemo/Placebo	
	n	(%)	n	(%)
Participants in population	325		317	
Surgery Procedure				
Lung bilobectomy	26	(8.0)	26	(8.2)
Lung lobectomy	256	(78.8)	238	(75.1)
Pneumonectomy	37	(11.4)	39	(12.3)
Thoracotomy	4	(1.2)	13	(4.1)
Lung wedge resection	1	(0.3)	0	(0.0)
Lung segmentectomy	1	(0.3)	0	(0.0)
Lymph node dissection	0	(0.0)	1	(0.3)
Database Cutoff Date: 29JUL2022				

Table 22: surgery outcome (participants who underwent surgery)

	Pembro + Chemo/Pembro		Placebo + Chemo/Placebo	
	n	(%)	n	(%)
Participants in population	325		317	
Surgery Outcome				
COMPLETE RESECTION-R0	299	(92.0)	267	(84.2)
INCOMPLETE RESECTION-R1	17	(5.2)	31	(9.8)
INCOMPLETE RESECTION-R2	4	(1.2)	4	(1.3)
UNRESECTABLE	5	(1.5)	15	(4.7)
Database Cutoff Date: 29JUL2022				

Radiotherapy

Per protocol, participants in either arm underwent RT if microscopic residual disease or gross residual disease was present. Radiotherapy was not allowed for participants with completely resected N2 disease in the absence of extracapsular spread. If the participant did not have surgery due to refusal, physician decision, medical illness, or any reason other than local progression or metastatic disease, the participant

should receive radiation therapy then continue to the adjuvant phase. Participants whose tumours were found to be unresectable during surgery were considered as an EFS event and, per protocol, discontinued all study treatments (including RT). Few patients in each arm did not received RT after R1/2 resections, and few were treated with RT after R0 resection; the justification provided by the Applicant for the above cases were considered acceptable.

Table 23: Surgery status (ITT population - participants who received in-study radiotherapy)

	Pembro + Chemo/Pembro		Placebo + Chemo/Placebo	
	n	(%)	n	(%)
Participants in population	35		53	
With in-study surgery	18	(51.4)	35	(66.0)
Complete Resection-R0	4	(11.4)	11	(20.8)
Incomplete Resection-R1	11	(31.4)	21	(39.6)
Incomplete Resection-R2	3	(8.6)	3	(5.7)
Without in-study surgery	17	(48.6)	18	(34.0)
Adverse Event	1	(2.9)	3	(5.7)
Patient Refusal	4	(11.4)	3	(5.7)
Physician Decision	12	(34.3)	12	(22.6)
Database Cutoff Date: 29JUL2022				

Post-study treatment

Table 24: Participants with subsequent oncologic therapies (incidence > 0% in one or more treatment groups) (ITT population)

	Pembro + Chemo/Pembro		Placebo + Chemo/Placebo	
	n	(%)	n	(%)
Participants in population	397		400	
with one or more subsequent oncologic therapies	68	(17.1)	149	(37.3)
with no subsequent oncologic therapies	329	(82.9)	251	(62.8)
ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS				
ANTINEOPLASTIC AGENTS	**68**	**(17.1)**	**149**	**(37.3)**
Afatinib	1	(0.3)	1	(0.3)
Afatinib Dimaleate	0	(0.0)	1	(0.3)
Ak 104	1	(0.3)	0	(0.0)
Alectinib	4	(1.0)	2	(0.5)
Alectinib Hydrochloride	1	(0.3)	0	(0.0)
Almonertinib	0	(0.0)	1	(0.3)
Amivantamab	0	(0.0)	1	(0.3)
Antineoplastic Agents	2	(0.5)	1	(0.3)
Atezolizumab	1	(0.3)	17	(4.3)
Bevacizumab	4	(1.0)	7	(1.8)
Brigatinib	2	(0.5)	0	(0.0)
Camrelizumab	1	(0.3)	1	(0.3)
Capmatinib	0	(0.0)	1	(0.3)
Carboplatin	28	(7.1)	67	(16.8)
Catequentinib Hydrochloride	0	(0.0)	2	(0.5)
Ceritinib	1	(0.3)	0	(0.0)
Cisplatin	9	(2.3)	18	(4.5)
Cyclophosphamide	0	(0.0)	2	(0.5)
Docetaxel	14	(3.5)	20	(5.0)
Doxorubicin	0	(0.0)	1	(0.3)
Durvalumab	3	(0.8)	13	(3.3)
Erlotinib Hydrochloride	1	(0.3)	1	(0.3)
Etoposide	5	(1.3)	9	(2.3)
Gefitinib	0	(0.0)	1	(0.3)
Gemcitabine	15	(3.8)	10	(2.5)
Gemcitabine Hydrochloride	1	(0.3)	1	(0.3)
Gimeracil;oteracil Potassium;tegafur	3	(0.8)	2	(0.5)
Icotinib Hydrochloride	0	(0.0)	4	(1.0)
Investigational Antineoplastic Drugs	2	(0.5)	3	(0.8)
Ipilimumab	1	(0.3)	5	(1.3)
Irinotecan	2	(0.5)	2	(0.5)
Lomustine	0	(0.0)	1	(0.3)
Methotrexate	0	(0.0)	1	(0.3)
Necitumumab	1	(0.3)	0	(0.0)
Nedaplatin	1	(0.3)	1	(0.3)
Nintedanib	1	(0.3)	2	(0.5)
Nivolumab	5	(1.3)	14	(3.5)
Osimertinib	4	(1.0)	6	(1.5)
Osimertinib Mesilate	2	(0.5)	5	(1.3)
Paclitaxel	16	(4.0)	49	(12.3)
Paclitaxel Nanoparticle Albumin-Bound	0	(0.0)	5	(1.3)
Pembrolizumab	9	(2.3)	39	(9.8)
Pemetrexed Disodium	7	(1.8)	18	(4.5)
Pemetrexed Disodium Heptahydrate	0	(0.0)	2	(0.5)
Ramucirumab	4	(1.0)	5	(1.3)
Regorafenib	0	(0.0)	1	(0.3)
Relatlimab	0	(0.0)	1	(0.3)
Sotorasib	3	(0.8)	0	(0.0)
Sunitinib Malate	0	(0.0)	1	(0.3)
Tegafur;uracil	1	(0.3)	0	(0.0)
Tislelizumab	0	(0.0)	2	(0.5)
Vibostolimab	0	(0.0)	1	(0.3)
Vincristine	0	(0.0)	1	(0.3)
Vinorelbine Tartrate	7	(1.8)	12	(3.0)
IMMUNOSTIMULANTS	**2**	**(0.5)**	**0**	**(0.0)**
Cancer Vaccines	1	(0.3)	0	(0.0)
Interleukins	1	(0.3)	0	(0.0)
IMMUNOSUPPRESSANTS	**0**	**(0.0)**	**1**	**(0.3)**
Methotrexate	0	(0.0)	1	(0.3)

Every participant is counted a single time for each applicable subsequent oncologic therapies . A participant with multiple subsequent oncologic therapies within a subsequent oncologic therapies category is counted a single time for that category.

A medication class or specific medication appears on this report only if its incidence meets the incidence criterion in the report title, after rounding.

Database Cutoff Date: 29JUL2022

In both arms, at IA1 patients received a median of 1 line of post-study treatment (range 1-5 in the pembrolizumab arm, and 1-6 in the placebo arm).

Recruitment

The study was conducted at 227 centres in 25 countries: Argentina, Australia, Belgium, Brazil, Canada, China, Estonia, France, Germany, Ireland, Italy, Japan, Latvia, Lithuania, Malaysia, Poland, Republic of Korea, Romania, Russia, South Africa, Spain, Taiwan, Ukraine, United Kingdom, and United States.

The first participant was randomized on 11-MAY-2018, the last on 15-DEC-2021.

This study is ongoing. The MAH submitted the results of the first planned interim analysis (IA1) with data cut-off 29-JUL-2022 (database lock 9-SEP-2022). In the overall population, median follow-up at IA1 was 21.4 months (range 0.4, 50.6 months). During the procedure, top-line results from the IA2 with data cut-off 10-JUL-2023 were also submitted, with median follow-up of 29.8 months (range 0.4-62.0 months).

Conduct of the study

Protocol amendments

Table 25: Protocol amendments for MK-3475-671

Document	Date of Issue	Overall Rationale
Amendment 10	24-MAR-2022	To change the definition of EFS event to utilize investigator assessment as opposed to central review in this double-blind trial.
Amendment 09	23-JUN-2021	The protocol was amended to specify continuation of imaging assessments for participants starting new anticancer therapy who have not yet progressed, incorporate country-specific requirements, and update the dose modification and toxicity management guidelines for immune-related AEs.
Amendment 08 (China Specific)	16-OCT-2020	The protocol was amended to address recommendations from China's regulatory authority regarding the sample size and duration of the Extension Portion of the study in China.
Amendment 07 (China Specific)	26-NOV-2019	The protocol was amended to add China extension and to clarify *EGFR/ALK* testing requirements.
Amendment 06 (Germany specific)	19-JUL-2019	The protocol was amended to align with the global amendment (671-05).
Amendment 05	18-JUL-2019	The protocol was amended to include Stages IIA and resectable IIIB (N2), to update stratification to Stage II vs Stage III, and to provide additional clarifications throughout the document in order to increase the pool of eligible participants.
Amendment 04 (Germany specific)	27-AUG-2018	The protocol was amended to align with the global amendment (671-03).
Amendment 03	27-AUG-2018	The protocol was amended to increase the maximum dose of radiotherapy for participants with gross residual disease after surgery or for those participants who do not have surgery, to add a new baseline scan prior to the start of adjuvant pembrolizumab/placebo, to align the SAP with the program standard and to provide additional clarifications throughout the document.
Amendment 02 (Germany specific)	01-MAY-2018	The protocol was amended to align HIV, HBV, HCV, TB, Amylase, Lipase, and pregnancy testing with regulatory requirements at German sites.
Amendment 01	11-APR-2018	The protocol was amended based on the input from the regulatory agency and to align with the pembrolizumab program standard.
Original protocol	07-NOV-2017	N/A

Protocol Amendment 10: Amendment 10 was implemented while this study was blinded and prior to IA1. In this Amendment, the MAH changed the EFS determination from "per BICR" to "per investigator assessment." This modification was made because the study was not designed to have a real-time verification of progression component and investigators are not aware of BICR read results. Under these conditions, imaging follow-up discontinuation, treatment discontinuation, and start of new anticancer therapy are all based on PD per investigator assessment and without a confirmation requirement from BICR. Therefore, to avoid a greater than expected censoring of the EFS endpoint, the MAH amended the definition of EFS to be based on investigator assessment instead of BICR. All BICR data continued to be collected for the sensitivity analysis.

Measures implemented by the MAH to manage key aspects of study conduct during the COVID-19 pandemic are summarized in the table below (implementation/end date shown in parentheses). Not all measures were implemented at all study sites due to differences in local conditions and impact of the pandemic.

Table 26: Measures implemented by the sponsor to manage study conduct during the COVID-19 pandemic for MK-3475-671

Process	Measure (Date Implemented)
Study site monitoring	• Modifications to the frequency of onsite and remote monitoring were allowed due to national and local travel restrictions and/or study site restrictions to onsite monitoring (21-MAR-2020). • Redacted/alternate methods for source data review and verification for critical data points in absence of remote access to electronic medical records were allowed under documented circumstances (06-MAR-2020). • Source data review and/or verification were completed to the extent possible before database lock (13-MAR-2020).
Protocol deviations	• Protocol deviations due to the COVID-19 pandemic were documented as such (20-MAR-2020).
AE reporting	• COVID-19 infection was to be reported following the protocol's AE and SAE reporting instructions.
Clinical supplies (including study intervention)	• An alternate location (eg, primary care center, pharmacy) for injectable and/or infusion administration of study intervention/other clinical supplies was allowed when participant travel was impacted, and administration could not be postponed (21-APR-2020).
Data management	• Study sites were queried, and responses documented about the relationship of the following to the COVID-19 pandemic (08-APR-2020): ○ Missing participant study visits and data. ○ Participants who discontinued study intervention and/or the study.
Clinical laboratory and other facilities	• Alternate clinical laboratory facilities were allowed for collection of samples for study participants unable to visit the study site (16-APR-2020). • Alternate imaging facilities and delayed schedules for study site and alternate facility imaging were allowed for protocol-required imaging (each to be reported as a protocol deviation) (24-MAR-2020).
Informed consent	• Oral confirmation of participant consent for amendments (eg, via telephone) was allowed when in-person discussion and signature was not possible (30-MAR-2020).
Home health care services	• Home health services could be used to perform protocol-specified activities (eg, physical examination, completion of participant questionnaires, sample collection) for study participants unable to visit the study site (31-MAR-2020).

Protocol deviations

Table 27: summary of important protocol deviations

	Pembro + Chemo/Pembro		Placebo + Chemo/Placebo	
	n	(%)	n	(%)
Participants in population	397		400	
with one or more important protocol deviations	40	(10.1)	48	(12.0)
with no important protocol deviations	357	(89.9)	352	(88.0)
Discontinuation Criteria	**2**	**(0.5)**	**2**	**(0.5)**
Participant developed trial specific discontinuation criteria but was not discontinued from the trial.	2	(0.5)	2	(0.5)
Inclusion/ Exclusion Criteria	**7**	**(1.8)**	**8**	**(2.0)**
Participant entered into the trial who did not have untreated, pathologically confirmed NSCLC or the correct tumor staging per protocol	4	(1.0)	5	(1.3)
Participant entered into the trial who was not resectable at baseline.	3	(0.8)	4	(1.0)
Prohibited Medications	**0**	**(0.0)**	**3**	**(0.8)**
Antineoplastic systemic chemotherapy, biologic therapy, immunotherapy, other investigational agents given while on treatment (unless allowed per protocol).	0	(0.0)	3	(0.8)
Safety Reporting	**22**	**(5.5)**	**23**	**(5.8)**
Participant had a reportable Safety Event and/or follow up Safety Event information that was not reported per the timelines outlined in the protocol.	22	(5.5)	23	(5.8)
Study Intervention	**8**	**(2.0)**	**12**	**(3.0)**
Participant received improper dose of radiotherapy of either <50 Gy or >70 Gy.	0	(0.0)	4	(1.0)
Participant underwent complete resection (with no extracapsular extension) and had radiotherapy as part of the study.	2	(0.5)	5	(1.3)
Participant was administered improperly stored study intervention that was deemed unacceptable for use.	4	(1.0)	1	(0.3)
Study Intervention	**8**	**(2.0)**	**12**	**(3.0)**
Participant was dispensed study intervention other than what was assigned in the allocation schedule, i.e. incorrect medication or potential cross-treatment.	1	(0.3)	3	(0.8)
Participant who received less than a lobectomy and continued to be treated in the study.	1	(0.3)	0	(0.0)
Trial Procedures	**1**	**(0.3)**	**4**	**(1.0)**
Surgical biopsy specimens sufficient for central read were not submitted.	1	(0.3)	4	(1.0)
Every participant is counted a single time for each applicable row and column. Database Cutoff Date: 29JUL2022				

Of the important protocol deviations, 3 were considered to be clinically important (entered trial even though the tumour was not considered resectable at baseline), 1 in the pembrolizumab arm and 2 in the control arm, respectively.

Important and not important protocol deviations associated with the pandemic were reported for 82 and 76 participants in the pembrolizumab and placebo arm, respectively, none considered clinically important.

No participant's data were excluded from analysis due to an important protocol deviation.

GCP compliance issues were noted for one site in US, where protocol deviations assessed for the 2 participants at this site were not considered to be clinically important. The site was closed, and FDA was informed. No protocol deviations were classified as a serious GCP compliance issue.

Baseline data

Table 28: Participant characteristics (ITT population)

	Pembro + Chemo/Pembro		Placebo + Chemo/Placebo		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	397		400		797	
Sex						
Male	279	(70.3)	284	(71.0)	563	(70.6)
Female	118	(29.7)	116	(29.0)	234	(29.4)
Age (Years)						
< 65	221	(55.7)	214	(53.5)	435	(54.6)
>= 65	176	(44.3)	186	(46.5)	362	(45.4)
Mean	62.7		63.6		63.1	
SD	8.5		8.1		8.3	
Median	63.0		64.0		64.0	
Range	26 to 83		35 to 81		26 to 83	
Race						
American Indian Or Alaska Native	1	(0.3)	0	(0.0)	1	(0.1)
Asian	124	(31.2)	125	(31.3)	249	(31.2)
Black Or African American	6	(1.5)	10	(2.5)	16	(2.0)
Multiple	3	(0.8)	10	(2.5)	13	(1.6)
Black Or African American White	3	(0.8)	10	(2.5)	13	(1.6)
White	250	(63.0)	239	(59.8)	489	(61.4)
Missing	13	(3.3)	16	(4.0)	29	(3.6)
Ethnicity						
Hispanic Or Latino	36	(9.1)	34	(8.5)	70	(8.8)
Not Hispanic Or Latino	329	(82.9)	333	(83.3)	662	(83.1)
Not Reported	18	(4.5)	25	(6.3)	43	(5.4)
Unknown	14	(3.5)	8	(2.0)	22	(2.8)
Age (Years)						
< 65	221	(55.7)	214	(53.5)	435	(54.6)
65 - 74	153	(38.5)	152	(38.0)	305	(38.3)
75 - 84	23	(5.8)	34	(8.5)	57	(7.2)
Region (EU vs Ex EU)						
EU	136	(34.3)	131	(32.8)	267	(33.5)
Ex EU	261	(65.7)	269	(67.3)	530	(66.5)
Region (East-Asia vs Non-East Asia)						

East-Asia	123	(31.0)	121	(30.3)	244	(30.6)
Non-East Asia	274	(69.0)	279	(69.8)	553	(69.4)
Overall Cancer Staging at Baseline						
II	118	(29.7)	121	(30.3)	239	(30.0)
III	279	(70.3)	279	(69.8)	558	(70.0)
PD-L1 Expression Level (50% cutoff)						
TPS>=50%	132	(33.2)	134	(33.5)	266	(33.4)
TPS<50%	265	(66.8)	266	(66.5)	531	(66.6)
PD-L1 Expression Level (1% cutoff)						
TPS>=1%	259	(65.2)	249	(62.3)	508	(63.7)
TPS<1%	138	(34.8)	151	(37.8)	289	(36.3)
PD-L1 Expression Level						
TPS >=50%	132	(33.2)	134	(33.5)	266	(33.4)
TPS =1-49%	127	(32.0)	115	(28.8)	242	(30.4)
TPS <1%	138	(34.8)	151	(37.8)	289	(36.3)
Smoking Status						
Never Smoker	54	(13.6)	47	(11.8)	101	(12.7)
Former Smoker	247	(62.2)	250	(62.5)	497	(62.4)
Current Smoker	96	(24.2)	103	(25.8)	199	(25.0)
Baseline ECOG						
0	253	(63.7)	246	(61.5)	499	(62.6)
1	144	(36.3)	154	(38.5)	298	(37.4)
Histology						
Squamous	171	(43.1)	173	(43.3)	344	(43.2)
Non-Squamous	226	(56.9)	227	(56.8)	453	(56.8)
EGFR Activating Mutation Status						
Yes	14	(3.5)	19	(4.8)	33	(4.1)
No	111	(28.0)	127	(31.8)	238	(29.9)
Unknown/Missing	272	(68.5)	254	(63.5)	526	(66.0)
ALK Translocation Status						
Yes	12	(3.0)	9	(2.3)	21	(2.6)
No	104	(26.2)	133	(33.3)	237	(29.7)
Unknown/Missing	281	(70.8)	258	(64.5)	539	(67.6)
Database Cutoff Date: 29JUL2022						

Table 29: Participant characteristics of staging (ITT population)

	Pembro + Chemo/Pembro		Placebo + Chemo/Placebo		Total	
	n	(%)	n	(%)	n	(%)
Detail Overall Cancer Staging at Baseline						
IIA	22	(5.5)	19	(4.8)	41	(5.1)
IIB	96	(24.2)	102	(25.5)	198	(24.8)
IIIA	217	(54.7)	224	(56.0)	441	(55.3)
IIIB	62	(15.6)	55	(13.8)	117	(14.7)
Database Cutoff Date: 10JUL2023						

The reported medical history conditions were generally balanced between the treatment arms (data not shown).

Numbers analysed

Table 30: Study population

	Pembro + Chemo/Pembro	Placebo + Chemo/Placebo	Total
Participants Screened			1364
Participants Randomized (Planned Treatment) (ITT)	397	400	797
Participants Randomized and Did not Receive Treatment	1	1	2
Participants Received Treatment (Actual Treatment) (APaT)	396	399	795
Participants Underwent In-Study Surgery	325	317	642
Participants Received In-Study Radiotherapy	35	53	88
Participants Received the Adjuvant Pembrolizumab/Placebo	290	267	557
Participants Died	76	101	177
Database Cutoff Date: 29JUL2022.			

Outcomes and estimation

Efficacy results from prespecified IA1 of KEYNOTE-671 are presented below, followed by topline efficacy results from IA2.

Table 31: Summary of KEYNOTE-671 primary results (Interim Analysis 1, CCOD 29 Jul 2022)

Endpoints (pembrolizumab vs. placebo)	Number of events observed (IF[a])	Median in months (95% CI)	Observed HR (95% CI)	P-value[b] crossing boundary	Observed P-value[b]	Outcome
EFS [c]	344 (82.7%)	NR (34.1, NR) vs. 17.0 (14.3, 22.0)	**0.58 (0.46, 0.72)**	0.00462	<0.00001	**Positive**
OS	177 (45.8%)	NR (NR, NR) vs. 45.5 (42.0, NR)	**0.73 (0.54, 0.99)**	0.00093	0.02124	**Not positive**, continue to be tested at next analyses

[a] Information fraction, the number of observed events / the required events for the EFS/OS final analysis.
[b] One-sided P-value
[c] Investigator assessed
Analyses of EFS and OS are based on stratified analyses.

Table 32: Summary of KEYNOTE-671 Secondary Endpoints (Interim Analysis 1, CCOD 29 Jul 2022)

Endpoints (pembrolizumab vs. placebo)	Observed difference in response rate (95% CI)	P-value[a] crossing boundary	Observed P-value[a]	Outcome
mPR	**19.2 (13.9, 24.7)**	0.0001	<0.00001	**Positive**
pCR	**14.2 (10.1, 18.7)**	0.0001	<0.00001	**Positive**

[a] One-sided P-value
Analyses of mPR and pCR are based on stratified analyses.

Primary endpoints

EFS

At IA1, EFS was formally tested with the multiplicity-adjusted, one-sided *p*-value boundary of 0.00462, and statistical significance was demonstrated.

Table 33: Analysis of event-free survival (primary censoring rule) based on investigator assessment (ITT population)

	Pembro + Chemo/Pembro (N=397)	Placebo + Chemo/Placebo (N=400)
Number of Events (%)	139 (35.0)	205 (51.3)
Number of Censored (%)	258 (65.0)	195 (48.8)
Kaplan-Meier Estimates (months)[a]		
Median (95% CI)	NR (34.1, NR)	17.0 (14.3, 22.0)
[Q1, Q3]	[11.0,]	[7.4,]
Person-months	7070.1	5709.7
Event Rate / 100 Person-months	2.0	3.6
vs Placebo + Chemo/Placebo		
Hazard Ratio (95% CI)[b]	0.58 (0.46, 0.72)	
p-value[c]	<0.00001	
EFS Rate at month 6 (%) (95% CI)	87.1 (83.3, 90.0)	79.7 (75.3, 83.4)
EFS Rate at month 12 (%) (95% CI)	73.2 (68.4, 77.4)	59.9 (54.6, 64.8)
EFS Rate at month 18 (%) (95% CI)	66.9 (61.7, 71.6)	49.0 (43.5, 54.4)
EFS Rate at month 24 (%) (95% CI)	62.4 (56.8, 67.5)	40.6 (34.8, 46.3)
EFS Rate at month 30 (%) (95% CI)	59.3 (53.3, 64.8)	37.2 (31.2, 43.2)
EFS Rate at month 36 (%) (95% CI)	56.3 (49.6, 62.4)	32.5 (25.8, 39.3)

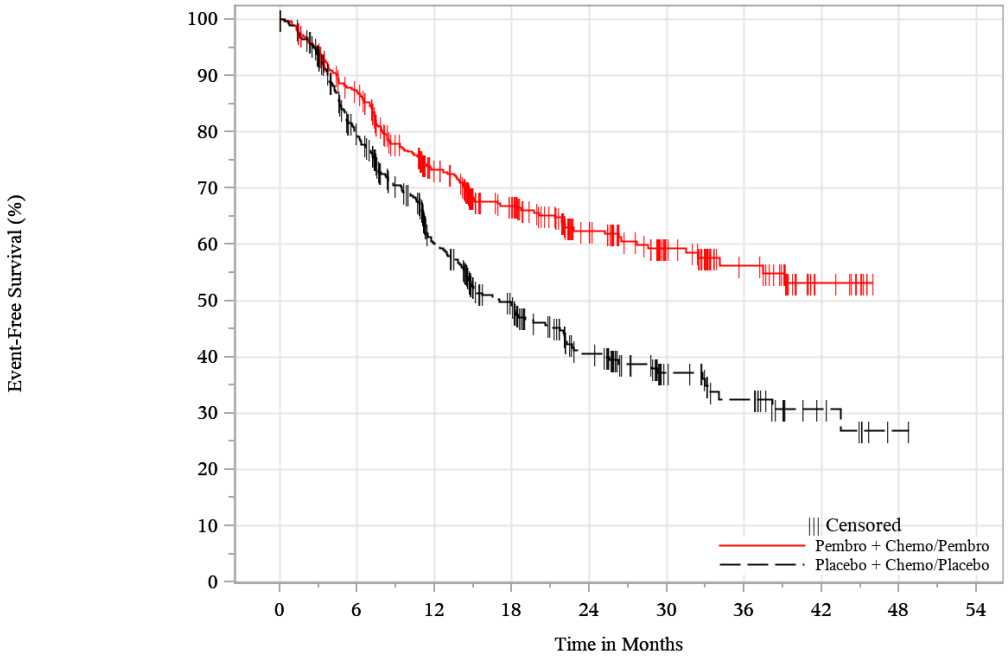
[a] From product-limit (Kaplan-Meier) method for censored data.

[b] Based on Cox regression model with treatment as a covariate stratified by Stage (II vs. III), TPS (>=50% vs. <50%), Histology (Squamous vs. Non-squamous) and Region (East-Asia vs. non-East Asia), where Region is collapsed for Stage II TPS >=50% Non-squamous and Stage II TPS >=50% Squamous.

[c] One-sided p-value based on log-rank test stratified by Stage (II vs. III), TPS (>=50% vs. <50%), Histology (Squamous vs. Non-squamous) and Region (East-Asia vs. non-East Asia), where Region is collapsed for Stage II TPS >=50% Non-squamous and Stage II TPS >=50% Squamous.

NR = Not reached. Database Cutoff Date: 29JUL2022

Figure 4: Kaplan-Meier plot of event-free survival (primary censoring rule) based on investigator assessment (ITT population)



Number of participants at risk

Pembro + Chemo/Pembro	397	330	236	172	117	72	42	11	0	0
Placebo + Chemo/Placebo	400	294	183	124	74	38	24	9	1	0

Database Cutoff Date: 29JUL2022

Table 34: disease status (ITT population)

	Pembro + Chemo/Pembro		Placebo + Chemo/Placebo	
	n	(%)	n	(%)
Participants in population	397		400	
Type of First Event in EFS Analysis				
No event	258	(65.0)	195	(48.8)
Event	139	(35.0)	205	(51.3)
Progression/Recurrence	94	(23.7)	155	(38.8)
Local Progression Preventing Surgery	0	(0.0)	6	(1.5)
Inability to resect the tumor	5	(1.3)	15	(3.8)
Death	40	(10.1)	29	(7.3)
Database Cutoff Date: 29JUL2022				

OS

OS was formally tested at IA1, but the observed p value did not cross the multiplicity-adjusted, one-sided p-value boundary of 0.00093. OS continued to be tested at the following IAs.

Table 35: Analysis of Overall Survival (ITT population)

	Pembro + Chemo/Pembro (N=397)	Placebo + Chemo/Placebo (N=400)
Number of Events (%)	76 (19.1)	101 (25.3)
Number of Censored (%)	321 (80.9)	299 (74.8)
Kaplan-Meier Estimates (months)[a]		
Median (95% CI)	NR (NR, NR)	45.5 (42.0, NR)
[Q1, Q3]	[42.9,]	[25.6,]
Person-months	9137.4	8692.4
Event Rate / 100 Person-months	0.8	1.2
vs Placebo + Chemo/Placebo		
Hazard Ratio (95% CI)[b]	0.73 (0.54, 0.99)	
p-value[c]	0.02124	
Rate at month 6 (%) (95% CI)	93.7 (90.8, 95.7)	95.2 (92.6, 96.9)
Rate at month 12 (%) (95% CI)	87.9 (84.3, 90.8)	87.9 (84.2, 90.8)
Rate at month 18 (%) (95% CI)	84.3 (80.2, 87.6)	82.8 (78.5, 86.4)
Rate at month 24 (%) (95% CI)	80.9 (76.2, 84.7)	77.6 (72.5, 81.9)
Rate at month 30 (%) (95% CI)	78.6 (73.5, 82.9)	69.3 (63.0, 74.8)
Rate at month 36 (%) (95% CI)	76.2 (70.4, 81.0)	62.7 (55.2, 69.3)

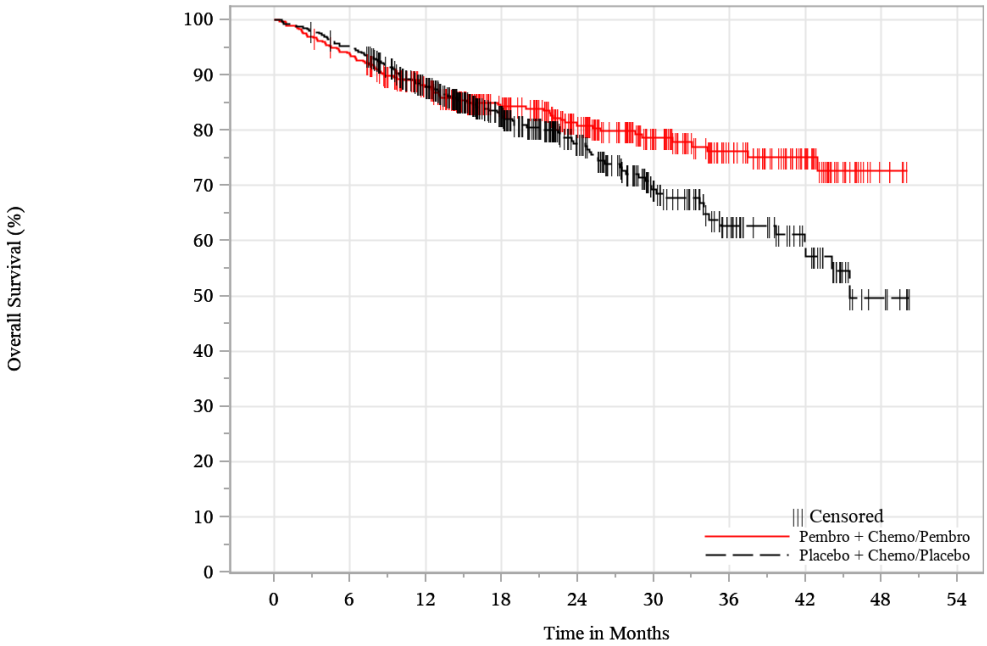
[a] From product-limit (Kaplan-Meier) method for censored data.

[b] Based on Cox regression model with treatment as a covariate stratified by Stage (II vs. III), TPS (>=50% vs. <50%), Histology (Squamous vs. Non-squamous) and Region (East-Asia vs. non-East Asia), where Region and Histology are collapsed for Stage II TPS >=50%;Region is collapsed for Stage III TPS >=50% Squamous and Stage II TPS<50% Non-squamous.

[c] One-sided p-value based on log-rank test stratified by Stage (II vs. III), TPS (>=50% vs. <50%), Histology (Squamous vs. Non-squamous) and Region (East-Asia vs. non-East Asia), where Region and Histology are collapsed for Stage II TPS >=50%; Region is collapsed for Stage III TPS >=50% Squamous and Stage II TPS<50% Non-squamous.

NR = Not reached. Database Cutoff Date: 29JUL2022

Figure 5: Kaplan-Meier Plot of Overall Survival (ITT population)



Number of participants at risk

Pembro + Chemo/Pembro	397	370	313	232	170	118	76	41	5	0
Placebo + Chemo/Placebo	400	379	316	225	153	91	54	30	6	0

Database Cutoff Date: 29JUL2022

Table 36: Piecewise Hazard Rate for Overall Survival (ITT population)

	Pembro + Chemo/Pembro (N=397)		Placebo + Chemo/Placebo (N=400)		
Month	Event	Rate	Event	Rate	Hazard Ratio[a]
(0-4]	16	0.010	12	0.008	1.35
(4-8]	19	0.013	16	0.011	1.21
(8-12]	12	0.009	19	0.014	0.64
(12-16]	10	0.009	12	0.011	0.82
16+	19	0.005	42	0.013	0.39

[a] Ratio of rate (Pembro + Chemo/Pembro vs. Placebo + Chemo/Placebo) in each interval.
The parenthesis "(" means the bound is not included in the time interval and the bracket "]" means the bound is included in the interval. Database Cutoff Date: 29JUL2022

Secondary endpoints

mPR

A statistically significant improvement in major pathologic response (mPR) based on blinded independent pathological review (BIPR) was seen in the pembrolizumab arm compared with the placebo arm at the IA1 (mPR was included in the multiplicity strategy).

Table 37: Analysis of Major Pathological Response based on BIPR assessment (ITT population)

Treatment	N	Number of mPR	mPR Rate (%) (95% CI)	Difference in % vs. Placebo + Chemo/Placebo	
				Estimate (95% CI)[a]	p-Value[b]
Pembro + Chemo/Pembro	397	120	30.2 (25.7, 35.0)	19.2 (13.9, 24.7)	<0.00001
Placebo + Chemo/Placebo	400	44	11.0 (8.1, 14.5)		

[a] Based on Miettinen & Nurminen method stratified by Stage (II vs. III), TPS (>=50% vs. <50%), Histology (Squamous vs. Non-squamous) and Region (East-Asia vs. non-East Asia).
[b] One-sided p-value for testing. H0: difference in % = 0 versus H1: difference in % > 0.
mPR= Major Pathological Response.
BIPR = Blinded independent pathologist review.
Database Cutoff Date: 29JUL2022.

pCR

A statistically significant improvement in pathological complete response (pCR) based on BIPR was seen in the pembrolizumab arm compared with the placebo arm at the IA1 (pCR was included in the multiplicity strategy).

Table 38: Analysis of Pathological Complete Response based on BIPR assessment (ITT population)

Treatment	N	Number of pCR	pCR Rate (%) (95% CI)	Difference in % vs. Placebo + Chemo/Placebo	
				Estimate (95% CI)[a]	p-Value[b]
Pembro + Chemo/Pembro	397	72	18.1 (14.5, 22.3)	14.2 (10.1, 18.7)	<0.00001
Placebo + Chemo/Placebo	400	16	4.0 (2.3, 6.4)		

[a] Based on Miettinen & Nurminen method stratified by Stage (II vs. III), TPS (>=50% vs. <50%), Histology (Squamous vs. Non-squamous) and Region (East-Asia vs. non-East Asia).
[b] One-sided p-value for testing. H0: difference in % = 0 versus H1: difference in % > 0.
pCR= Pathological Complete Responses.
BIPR = Blinded independent pathologist review.
Database Cutoff Date: 29JUL2022.

Patient-reported Outcomes

The baseline PRO assessment was defined as the neoadjuvant Cycle 1 assessment. The mean change from baseline in the neoadjuvant treatment phase was evaluated at the neoadjuvant Week 11 PRO assessment. At the database cutoff date (29-JUL-2022) within the adjuvant treatment phase, the Week 10 PRO assessment was selected as the primary timepoint for the mean change from baseline analysis to ensure that completion rates met approximately ≥60% and compliance rates met approximately ≥80% across the treatment groups. Compliance rates were defined as the percentage of participants completing the measure among those expected to complete the measure (i.e. not missing by design). Completion rates were defined as the percentage of participants who completed at least 1 item among all treated participants in the PRO analysis population. Nominal 2-sided p-values are reported.

For EORTC QLQ-C30, the completion rate was above 90% at baseline and similar in both the pembrolizumab arm and placebo arm (98.2% vs 98.2 %) and it was 87.1% vs 88.9% at Week 11 in the neoadjuvant phase and 68.1% vs 61.5% at Week 10 in the adjuvant phase. Similar completion and compliance rates were observed for EORTC QLQ-LC13 and EQ-5D-5L.

Secondary PRO Endpoint: Analysis of EORTC QLQ-C30 Global Health Status/Quality of Life (mean change from baseline in the neoadjuvant phase and in the adjuvant phase)

Global health status/QoL scores decreased relative to baseline showing deterioration in both pembrolizumab and placebo arm in the neoadjuvant phase; in the adjuvant phase, scores were stable relative to baseline in both the pembrolizumab and placebo arm. The empirical mean change from

baseline in global health status/QoL showed stable scores in both treatment arms over time across both the neoadjuvant and adjuvant phases.

Table 39: Analysis of change from baseline in EORTC QLQ-C30 Global Health Status/QoL to neoadjuvant week 11 (PRO FAS population)

	Baseline		Neoadjuvant Week 11		Change from Baseline to Neoadjuvant Week 11	
Treatment	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI)[a]
Pembro + Chemo/Pembro	388	73.48 (19.14)	344	64.10 (22.44)	390	-9.30 (-11.67, -6.94)
Placebo + Chemo/Placebo	390	72.78 (19.81)	353	62.23 (20.79)	395	-10.68 (-13.02, -8.34)
Pairwise Comparison					Difference in LS Means[a] (95% CI)	p-Value[a]
Pembro + Chemo/Pembro vs. Placebo + Chemo/Placebo					1.37 (-1.69, 4.44)	0.3794

[a] Based on a cLDA model with the PRO scores as the response variable with covariates for treatment by visit interaction and stratification factors (Stage (II vs. III), TPS (>=50% vs. <50%), Histology (Squamous vs. Non-squamous) and Region (East-Asia vs. non-East Asia)).

For baseline and Neoadjuvant Week 11, N is the number of participants in each treatment group with non-missing assessments at the specific time point; for change from baseline, N is the number of participants in the analysis population in each treatment group.

P-value is based on two-sided t test.

Database Cutoff Date: 29JUL2022

Table 40: Analysis of change from baseline in EORTC QLQ-C30 Global Health Status/QoL to adjuvant week 10 (PRO FAS population)

	Baseline		Adjuvant Week 10		Change from Baseline to Adjuvant Week 10	
Treatment	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI)[a]
Pembro + Chemo/Pembro	388	73.48 (19.14)	269	72.86 (17.89)	395	-1.51 (-3.67, 0.65)
Placebo + Chemo/Placebo	390	72.78 (19.81)	244	70.42 (17.47)	396	-3.81 (-6.05, -1.58)
Pairwise Comparison					Difference in LS Means[a] (95% CI)	p-Value[a]
Pembro + Chemo/Pembro vs. Placebo + Chemo/Placebo					2.31 (-0.52, 5.13)	0.1092

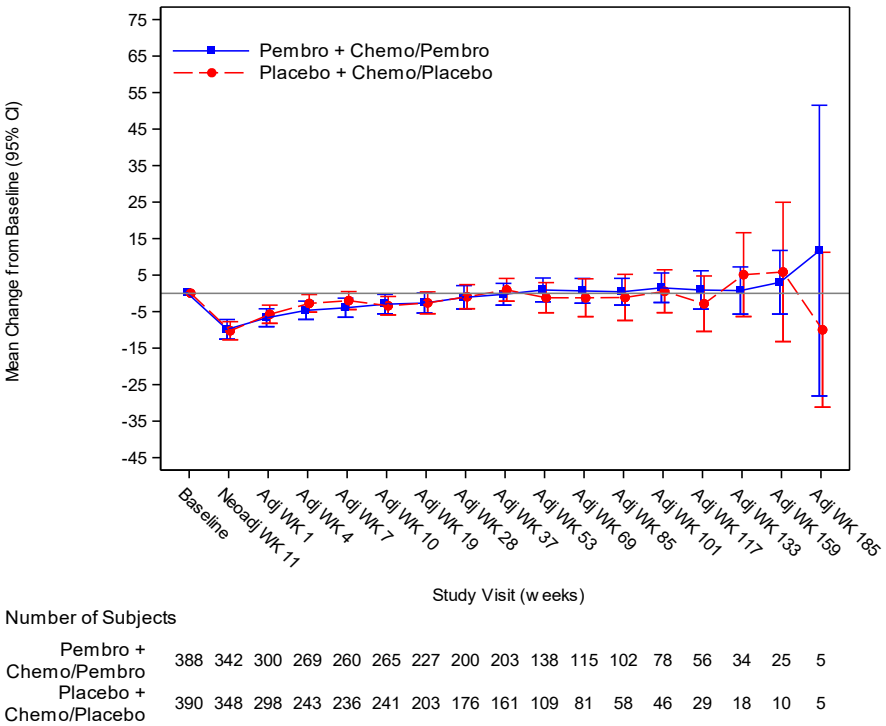
[a] Based on a cLDA model with the PRO scores as the response variable with covariates for treatment by visit interaction and stratification factors (Stage (II vs. III), TPS (>=50% vs. <50%), Histology (Squamous vs. Non-squamous) and Region (East-Asia vs. non-East Asia)).

For baseline and Adjuvant Week 10, N is the number of participants in each treatment group with non-missing assessments at the specific time point; for change from baseline, N is the number of participants in the analysis population in each treatment group.

P-value is based on two-sided t test.

Database Cutoff Date: 29JUL2022

Figure 6: 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)



Number of Subjects

Pembro + Chemo/Pembro	388	342	300	269	260	265	227	200	203	138	115	102	78	56	34	25	5
Placebo + Chemo/Placebo	390	348	298	243	236	241	203	176	161	109	81	58	46	29	18	10	5

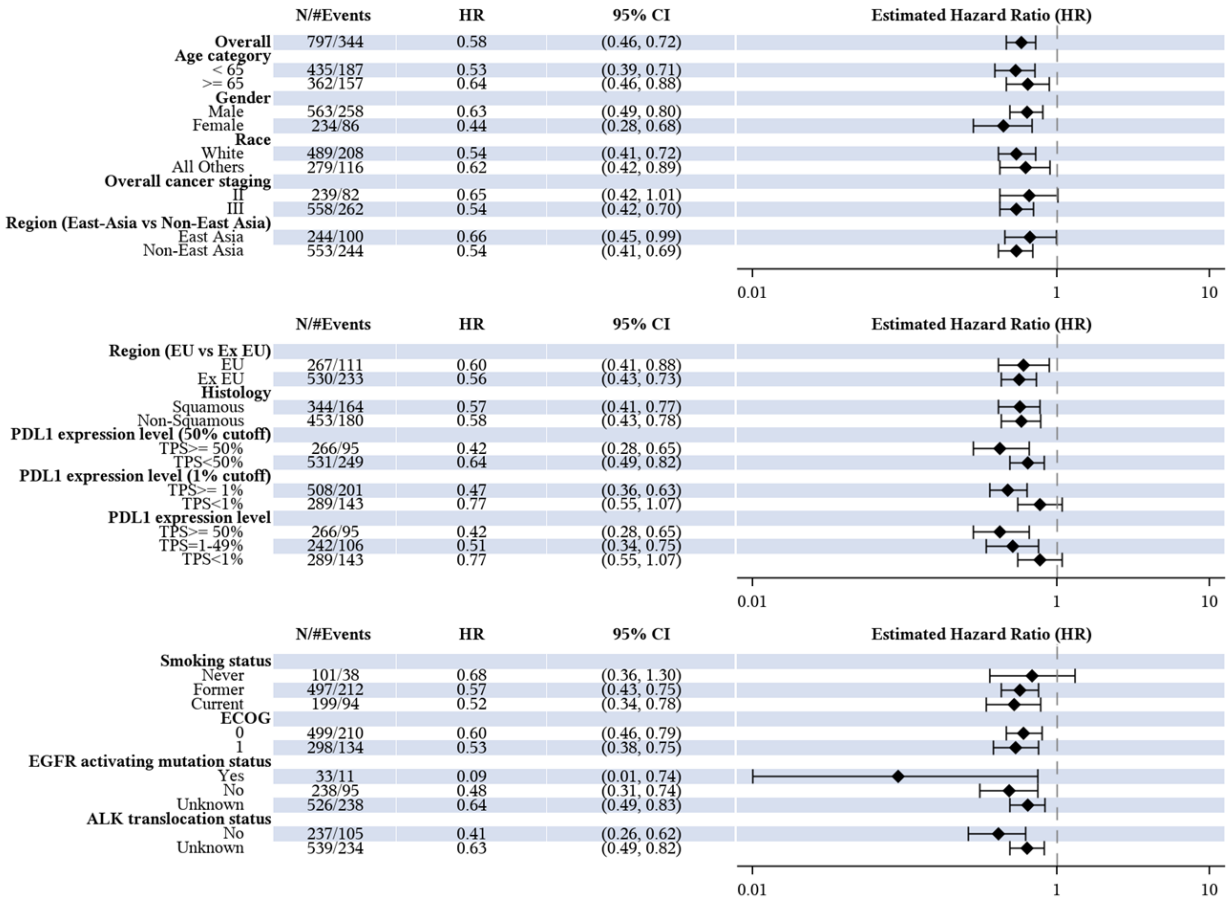
Database Cutoff Date: 29JUL2022
CI = confidence interval; Neoadj = neoadjuvant; Adj = adjuvant; WK = Week.

Ancillary analyses

Subgroup analyses

EFS subgroup analyses

Figure 7: Forest plot of EFS Hazard Ratio by subgroup factors (primary censoring rule) based on investigator assessment (ITT population)

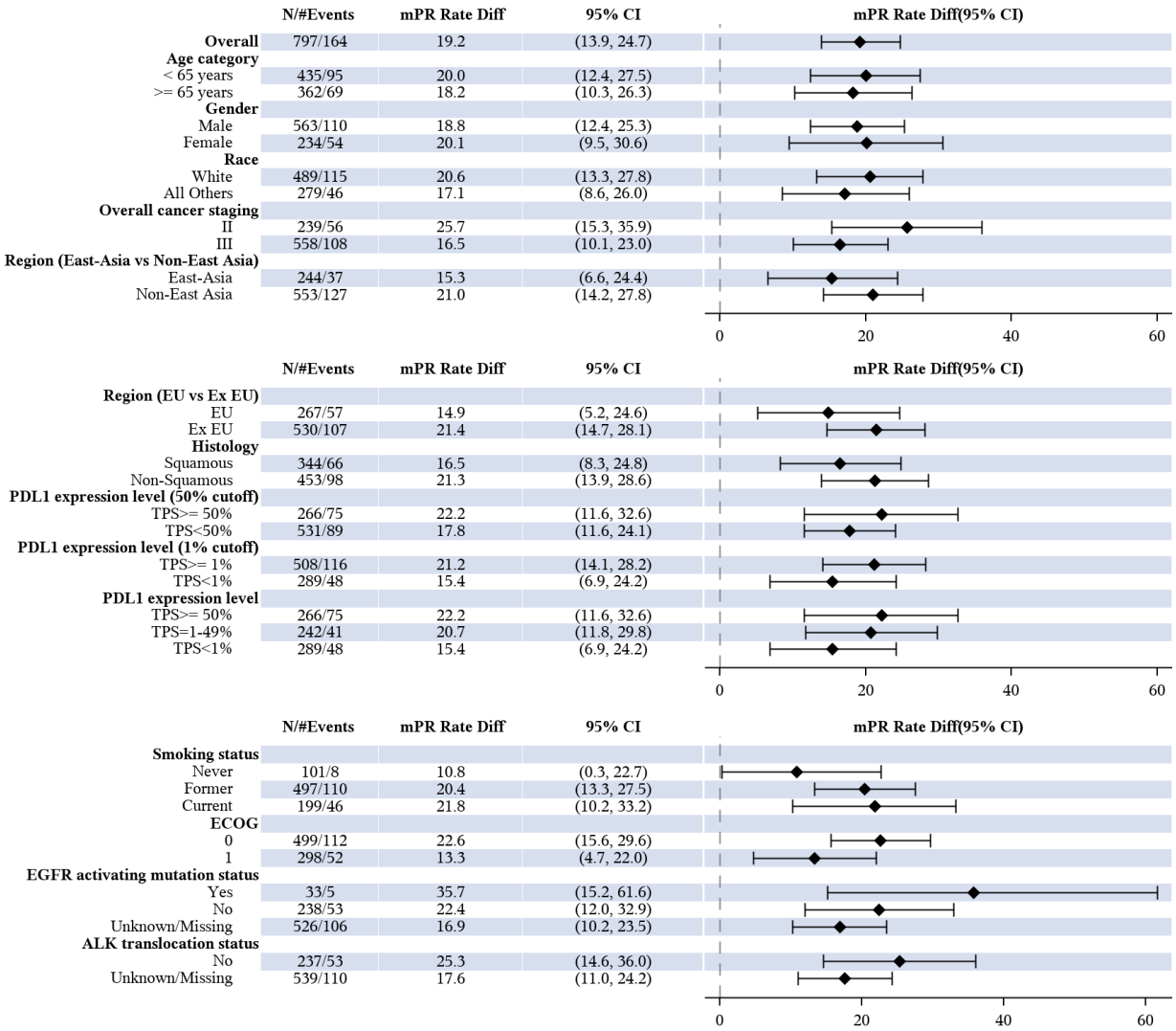


For overall population, analysis is based on stratified Cox regression model with treatment as a covariate.

For subgroups, analysis is based on unstratified Cox regression model with treatment as a covariate.
If a subgroup variable has two levels and one level of the subgroup has fewer than 30 participants, then this subgroup variable is not displayed in the plot. Database Cutoff Date: 29JUL2022

mPR subgroup analyses

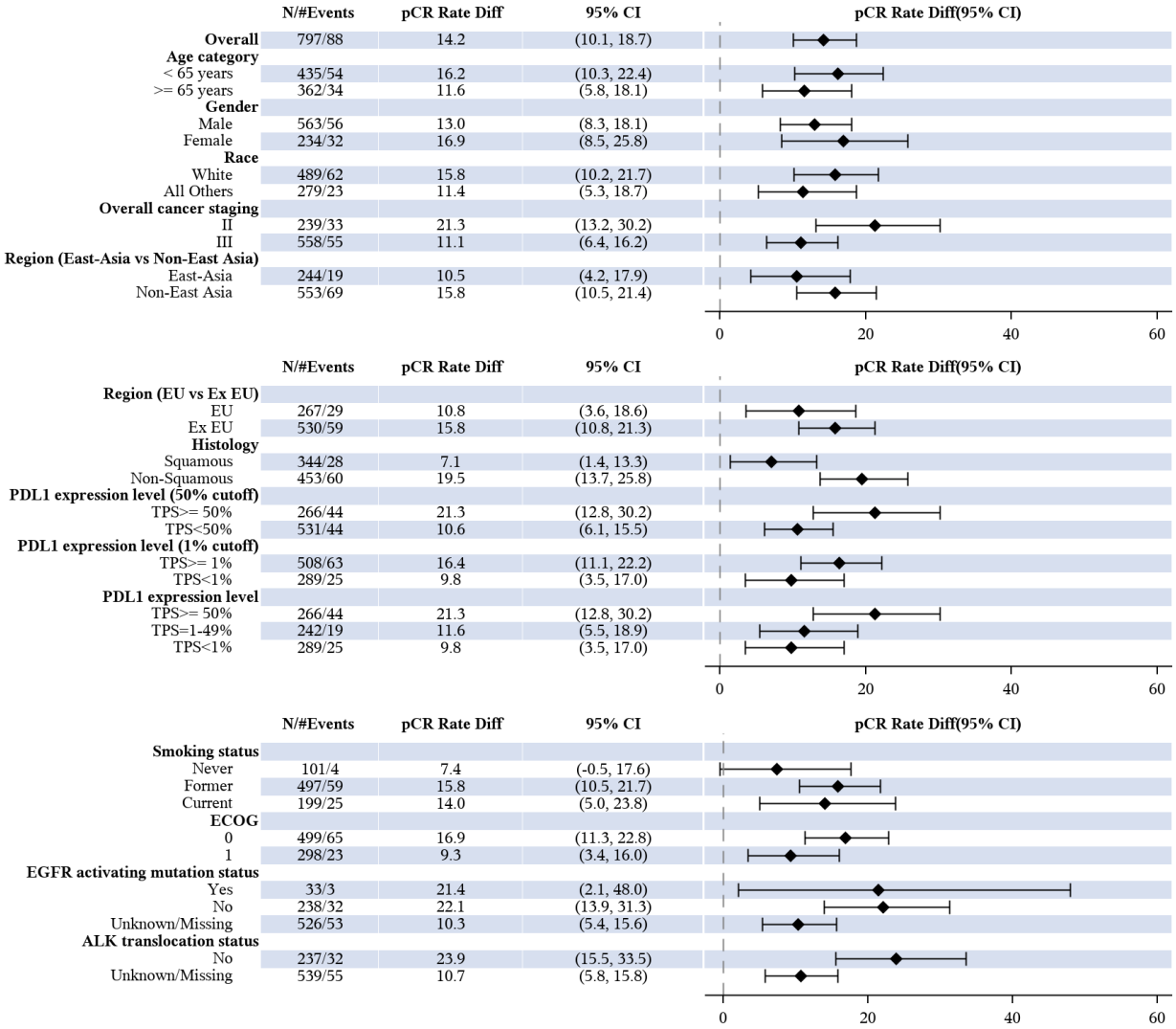
Figure 8: Forest plot of difference in mPR rate by subgroup factors based on BIPR assessment (ITT population)



Analysis (mPR difference and 95% CI) in the overall population is based on the stratified Miettinen & Nurminen method, analysis in the subgroups is based on the unstratified Miettinen & Nurminen method.
If a subgroup variable has two levels and one level of the subgroup has fewer than 30 participants, then this subgroup variable will not be displayed. Database Cutoff Date: 29JUL2022

pCR subgroup analyses

Figure 9: Forest Plot of difference in pCR rate by subgroup factors based on BIPR assessment (ITT population)



Analysis (pCR difference and 95% CI) in the overall population is based on the stratified Miettinen & Nurminen method, analysis in the subgroups is based on the unstratified Miettinen & Nurminen method.

If a subgroup variable has two levels and one level of the subgroup has fewer than 30 participants, then this subgroup variable will not be displayed. Database Cutoff Date: 29JUL2022

EFS pre-specified sensitivity analyses

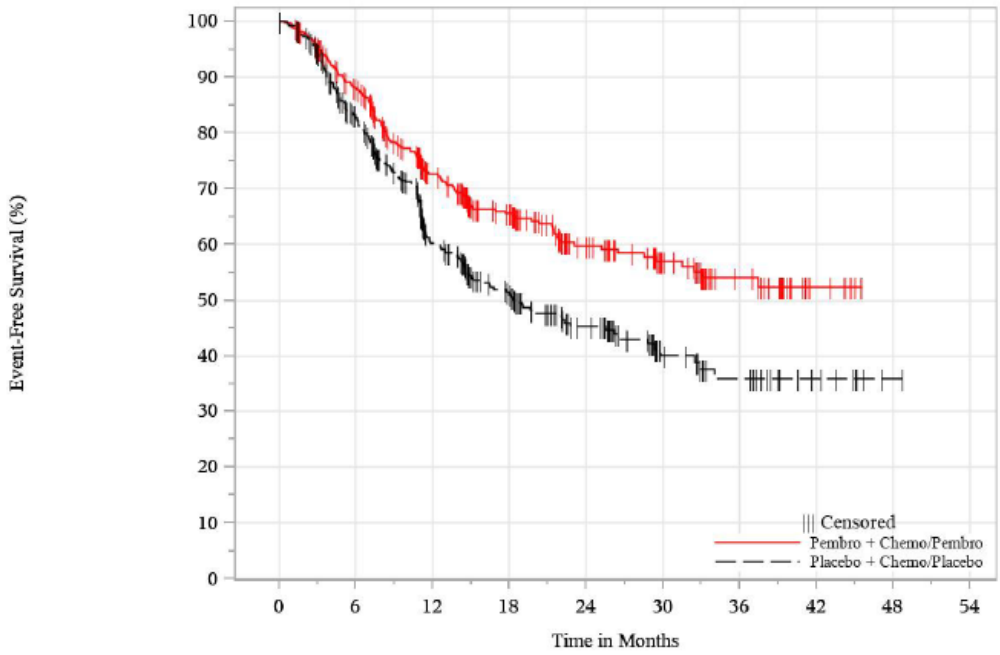
- A sensitivity analysis using **BICR assessment** was conducted using the same censoring rules as the primary analysis. The EFS HR was 0.66 (95% CI: 0.53, 0.83; p=0.00013)

Table 41: Analysis of EFS (primary censoring rule) based on BICR assessment

	Pembro + Chemo/Pembro (N=397)	Placebo + Chemo/Placebo (N=400)
Number of Events (%)	139 (35.0)	184 (46.0)
Number of Censored (%)	258 (65.0)	216 (54.0)
Kaplan-Meier Estimates (months)[a]		
Median (95% CI)	NR (31.5, NR)	18.4 (14.6, 26.2)
[Q1, Q3]	[11.0,]	[7.9,]
Person-months	6677.6	5613.3
Event Rate / 100 Person-months	2.1	3.3
vs Placebo + Chemo/Placebo		
Hazard Ratio (95% CI)[b]	0.66 (0.53, 0.83)	
p-value[c]	0.00013	
EFS Rate at month 6 (%) (95% CI)	87.9 (84.2, 90.8)	83.0 (78.8, 86.4)
EFS Rate at month 12 (%) (95% CI)	72.6 (67.6, 76.9)	60.2 (54.8, 65.2)
EFS Rate at month 18 (%) (95% CI)	65.6 (60.2, 70.4)	51.0 (45.3, 56.4)
EFS Rate at month 24 (%) (95% CI)	59.8 (53.9, 65.2)	45.4 (39.4, 51.1)
EFS Rate at month 30 (%) (95% CI)	57.0 (50.8, 62.7)	40.1 (33.5, 46.6)
EFS Rate at month 36 (%) (95% CI)	54.0 (47.2, 60.3)	36.0 (28.6, 43.4)

[a] From product-limit (Kaplan-Meier) method for censored data.
[b] Based on Cox regression model with treatment as a covariate stratified by Stage (II vs. III), TPS (>=50% vs. <50%), Histology (Squamous vs. Non-squamous) and Region (East-Asia vs. non-East Asia), where Region is collapsed for Stage II TPS >=50% Non-squamous and Stage II TPS >=50% Squamous.
[c] One-sided p-value based on log-rank test stratified by Stage (II vs. III), TPS (>=50% vs. <50%), Histology (Squamous vs. Non-squamous) and Region (East-Asia vs. non-East Asia), where Region is collapsed for Stage II TPS >=50% Non-squamous and Stage II TPS >=50% Squamous.
NR = Not reached.
BICR = Blinded Independent Central Review
Database Cutoff Date: 29JUL2022

Figure 10: Kaplan-Meier plot of EFS (primary censoring rule) based on BICR assessment (ITT population)



Number of participants at risk

Pembro + Chemo/Pembro	397	325	223	158	104	63	33	8	0	0
Placebo + Chemo/Placebo	400	299	173	117	72	35	22	9	1	0

Database Cutoff Date: 29JUL2022

The overall discordance rate between progression events (i.e. EFS events excluding death) per arm by BICR and investigator is similar between the two arms (pembrolizumab=12%; placebo=13%). Similar discordance rate is also observed between the two arms for EFS events (i.e. deaths included) by BICR and investigator (pembrolizumab and placebo =9%).

Planned **sensitivity analyses** results were consistent with the primary EFS analysis by investigator:

- events occurring after 2 consecutive missed disease assessments or after new anticancer therapy, if any, were censored at the last disease assessment prior to the earlier date of ≥2 consecutive missed disease assessments and new anti-cancer therapy: HR 0.58 (95% CI: 0.46, 0.72)

- initiation of new anticancer treatment considered as an EFS event: HR 0.57 (95% CI: 0.46, 0.70).

OS pre-specified sensitivity analysis

Table 42: Summary of restricted mean survival times (RMST) of Overall Survival (ITT population)

RMST based on Follow-up duration	Pembro + Chemo/Pembro (N=397)		Placebo + Chemo/Placebo (N=400)		Difference (95% CI) Pembro + Chemo/Pembro vs Placebo + Chemo/Placebo
	Number of Events	RMST	Number of Events	RMST	
6 months	25	5.82	19	5.87	-0.05 (-0.15 , 0.06)
12 months	47	11.25	47	11.36	-0.11 (-0.42 , 0.20)
18 months	59	16.39	63	16.48	-0.09 (-0.66 , 0.48)
24 months	67	21.38	75	21.29	0.09 (-0.78 , 0.96)
30 months	71	26.17	89	25.71	0.46 (-0.73 , 1.66)
36 months	74	30.81	96	29.70	1.12 (-0.45 , 2.68)
42 months	75	35.33	98	33.42	1.91 (-0.08 , 3.91)
48 months	76	39.72	101	36.62	3.10 (0.62 , 5.58)

RMST:Restricted mean survival time.
Database Cutoff Date: 29JUL2022

EFS by mPR and by pCR

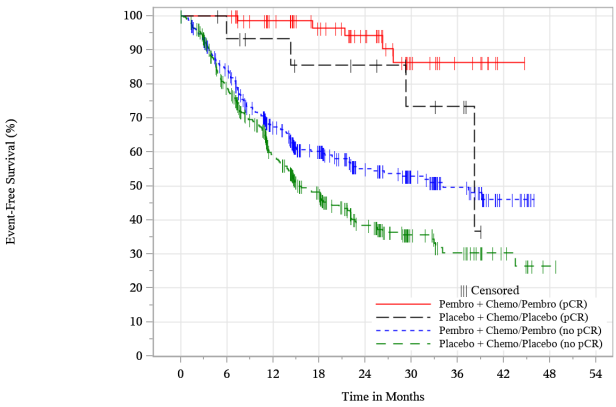
An exploratory unstratified subgroup analysis of EFS was performed among participants who achieved pCR and those participants who did not achieve pCR following neoadjuvant treatment.

Table 43: Analysis of event-free survival based on investigator assessment by pCR or mPR status (ITT population)

Status	Treatment	N	Number of Events (%)	Median (95% CI) (months)[a]	Hazard Ratio (95% CI)[b] vs Placebo + Chemo/Placebo
By pCR Status					
Y	Pembro + Chemo/Pembro	72	5 (6.9)	NR (NR, NR)	0.33 (0.09, 1.22)
	Placebo + Chemo/Placebo	16	4 (25.0)	38.2 (29.3, NR)	-
N	Pembro + Chemo/Pembro	325	134 (41.2)	34.1 (22.1, NR)	0.69 (0.55, 0.85)
	Placebo + Chemo/Placebo	384	201 (52.3)	15.2 (13.8, 19.6)	-
By mPR Status					
Y	Pembro + Chemo/Pembro	120	14 (11.7)	NR (NR, NR)	0.54 (0.24, 1.22)
	Placebo + Chemo/Placebo	44	10 (22.7)	NR (32.8, NR)	-
N	Pembro + Chemo/Pembro	277	125 (45.1)	22.1 (15.0, 39.2)	0.73 (0.58, 0.92)
	Placebo + Chemo/Placebo	356	195 (54.8)	14.5 (12.0, 18.1)	-

[a] From product-limit (Kaplan-Meier) method for censored data.
[b] Based on Cox regression model with treatment as a covariate.
NR = Not reached. Database Cutoff Date: 29JUL2022

Figure 11: Kaplan-Meier plot of Event-Free Survival (primary censoring rule) based on investigator assessment by pCR status (ITT population)

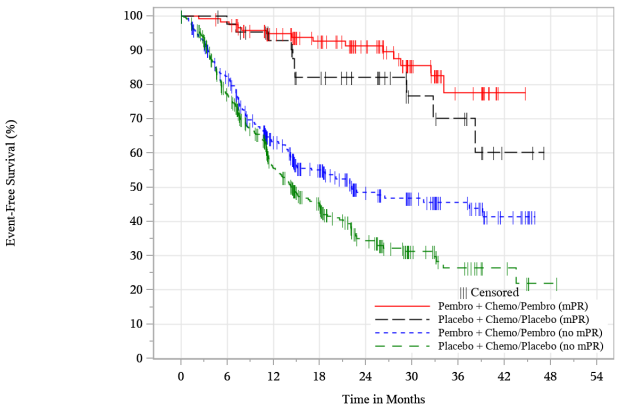


Number of participants at risk

Pembro + Chemo/Pembro (pCR)	72	72	59	46	33	15	8	1	0	0
Placebo + Chemo/Placebo (pCR)	16	14	12	10	9	5	4	0	0	0
Pembro + Chemo/Pembro (no pCR)	325	258	177	126	84	57	34	10	0	0
Placebo + Chemo/Placebo (no pCR)	384	280	171	114	65	33	20	9	1	0

Database Cutoff Date: 29JUL2022

Figure 12: Kaplan-Meier plot of Event-Free Survival (primary censoring rule) based on investigator assessment by mPR status (ITT population)



Number of participants at risk

Pembro + Chemo/Pembro (mPR)	120	117	99	79	60	30	15	1	0	0
Placebo + Chemo/Placebo (mPR)	44	42	36	28	22	12	10	2	0	0
Pembro + Chemo/Pembro (no mPR)	277	213	137	93	57	42	27	10	0	0
Placebo + Chemo/Placebo (no mPR)	356	252	147	96	52	26	14	7	1	0

Database Cutoff Date: 29JUL2022

TOP-LINE RESULTS OF INTERIM ANALYSIS 2 -DCO 10JUL2023

Table 44: Disposition of participants (ITT population) - IA2

	Pembro + Chemo/Pembro		Placebo + Chemo/Placebo	
	n	(%)	n	(%)
Participants in population	397		400	
Status for Study Treatment (Neo-adjuvant/Surgery + Adjuvant)				
Started	396		399	
Completed	191	(48.2)	174	(43.6)
Discontinued	205	(51.8)	225	(56.4)
Adverse Event	86	(21.7)	39	(9.8)
Associated with COVID-19	3	(0.8)	0	(0.0)
Clinical Progression	2	(0.5)	3	(0.8)
Local Progression Preventing Surgery	1	(0.3)	6	(1.5)
Non-Study Anti-Cancer Therapy	2	(0.5)	6	(1.5)
Associated with COVID-19	0	(0.0)	1	(0.3)
Physician Decision	22	(5.6)	17	(4.3)
Associated with COVID-19	1	(0.3)	1	(0.3)
Progressive Disease	62	(15.7)	106	(26.6)
Protocol Violation	1	(0.3)	1	(0.3)
Associated with COVID-19	0	(0.0)	1	(0.3)
Tumor Found To Be Surgically Unresectable	5	(1.3)	15	(3.8)
Withdrawal By Subject	24	(6.1)	32	(8.0)
Associated with COVID-19	2	(0.5)	0	(0.0)
Status for Trial				
Discontinued	121	(30.5)	153	(38.3)
Death	109	(27.5)	141	(35.3)
Associated with COVID-19	5	(1.3)	4	(1.0)
Lost To Follow-Up	2	(0.5)	0	(0.0)
Withdrawal By Subject	10	(2.5)	12	(3.0)
COVID-19 association unspecified, Subsequently died	1	(0.3)	3	(0.8)
Participants Ongoing	276	(69.5)	247	(61.8)

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.

Study treatment includes study medication, in-study surgery and in-study radiotherapy.

Completed indicates the completion of 13 cycles of adjuvant pembrolizumab/placebo.

Database Cutoff Date: 10JUL2023

Table 45: Summary of efficacy results for IA1 and IA2

Primary Endpoint	Overall Survival		Event-free Survival by Investigator	
	IA1	IA2	IA1	IA2
Events (IF)	177 (45.9%)	254 (65.8%)	344 (82.7%)	422
[a] Median (Months)	NR vs 45.5	NR vs 52.4	NR vs 17.0	47.2 vs 18.3
[b] HR (95% CI)	0.73 (0.54, 0.99)	0.72 (0.56, 0.93)	0.58 (0.46, 0.72)	0.59 (0.48, 0.72)
[c] P-value (1-sided)	0.02124	0.00517	<0.00001	Not Tested
Key Secondary Endpoint	Pathological Complete Response by BIPR		Major Pathological Response by BIPR	
	IA1	IA2	IA1	IA2
[c] Difference (95% CI)	14.2 (10.1, 18.7)	14.2 (10.1, 18.7)	19.2 (13.9, 24.7)	19.2 (13.9, 24.7)
[c] P-value (1-sided)	<.0.00001	Not Tested	<.0.00001	Not Tested

BIPR = blinded independent pathologic review; CI = confidence interval; HR = hazard ratio; IA = interim analysis; IF = information fraction; NR = not reached.
[a] From product-limit (Kaplan-Meier) method for censored data (pembrolizumab arm vs. placebo arm).
[b] Based on stratified Cox regression model with treatment as a covariate (pembrolizumab vs. placebo arm).
[c] For OS and EFS, observed one-sided p-value was based on stratified log-rank. For mPR and pCR, observed difference (95% CI) and one-sided p-value were based on stratified Miettinen & Nurminen method.
IA1 data cut date: 29Jul2022: IA2 data cut date: 10Jul2023.

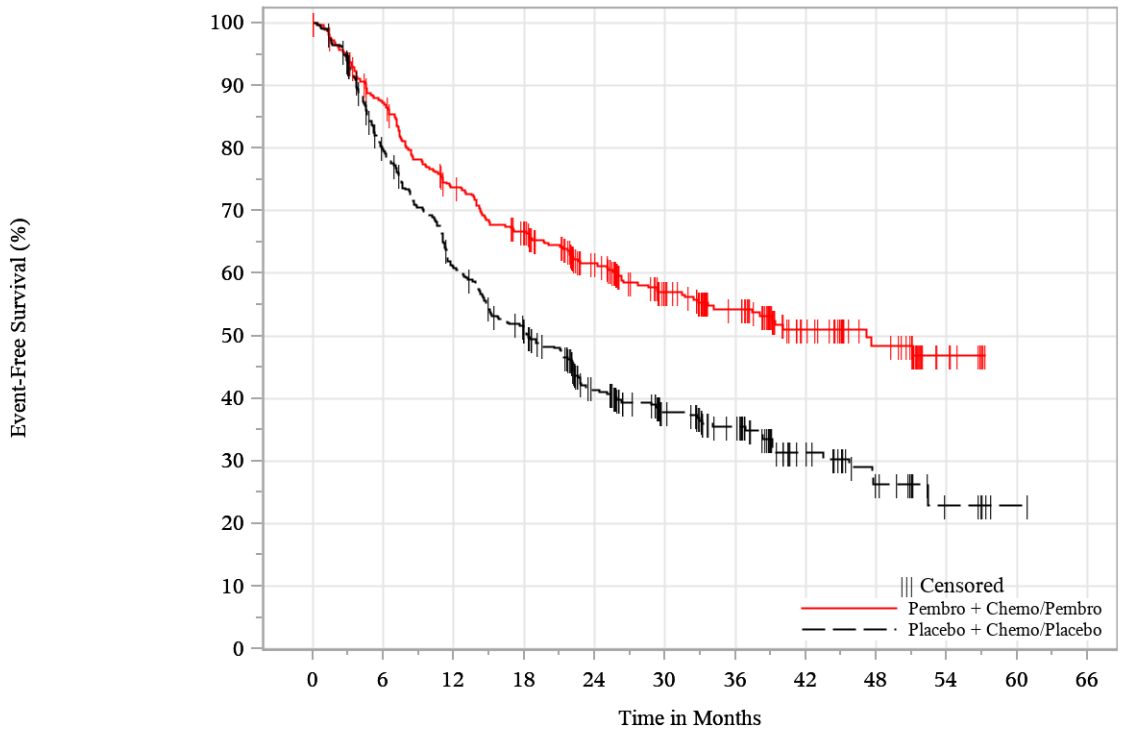
Table 46: Analysis of Event-Free Survival (primary censoring rule) based on investigator assessment (ITT population)

	Pembro + Chemo/Pembro (N=397)	Placebo + Chemo/Placebo (N=400)
Number of Events (%)	174 (43.8)	248 (62.0)
Number of Censored (%)	223 (56.2)	152 (38.0)
Kaplan-Meier Estimates (months)[a]		
Median (95% CI)	47.2 (32.9, NR)	18.3 (14.8, 22.1)
[Q1, Q3]	[11.0, NR]	[7.4, 52.4]
Person-months	9647.3	7684.5
Event Rate / 100 Person-months	1.8	3.2
vs Placebo + Chemo/Placebo		
Hazard Ratio (95% CI)[b]	0.59 (0.48, 0.72)	
p-value[c]	<0.00001	
EFS Rate at month 6 (%) (95% CI)	87.2 (83.5, 90.2)	79.9 (75.6, 83.5)
EFS Rate at month 12 (%) (95% CI)	73.8 (69.1, 77.9)	60.8 (55.8, 65.5)
EFS Rate at month 18 (%) (95% CI)	66.7 (61.7, 71.1)	51.1 (46.0, 55.9)
EFS Rate at month 24 (%) (95% CI)	61.5 (56.4, 66.2)	41.4 (36.3, 46.4)
EFS Rate at month 30 (%) (95% CI)	57.0 (51.7, 61.9)	37.8 (32.7, 42.8)
EFS Rate at month 36 (%) (95% CI)	54.3 (48.8, 59.4)	35.4 (30.3, 40.6)
EFS Rate at month 42 (%) (95% CI)	51.0 (45.1, 56.6)	31.3 (25.8, 36.9)
EFS Rate at month 48 (%) (95% CI)	48.4 (41.8, 54.7)	26.2 (20.0, 32.9)

[a] From product-limit (Kaplan-Meier) method for censored data.
[b] Based on Cox regression model with treatment as a covariate stratified by Stage (II vs. III), TPS (>=50% vs. <50%), Histology (Squamous vs. Non-squamous) and Region (East-Asia vs. non-East Asia), where Region is collapsed for Stage II TPS >=50% Non-squamous and Stage II TPS >=50% Squamous.
[c] One-sided p-value based on log-rank test stratified by Stage (II vs. III), TPS (>=50% vs. <50%), Histology (Squamous vs. Non-squamous) and Region (East-Asia vs. non-East Asia), where Region is collapsed for Stage II

TPS >=50% Non-squamous and Stage II TPS >=50% Squamous.
NR = Not reached.
Database Cutoff Date: 10JUL2023

Figure 13: Kaplan-Meier Plot of Event-Free Survival (primary censoring rule) based on investigator assessment (ITT Population)



Number of participants at risk

Pembro + Chemo/Pembro	397	339	282	250	196	142	102	62	37	10	0	0
Placebo + Chemo/Placebo	400	308	232	189	128	87	66	34	18	6	1	0

Database Cutoff Date: 10JUL2023

Table 47: Subgroup analysis of Event-free Survival (primary censoring rule) based on investigator assessment (ITT population)

	Pembro + Chemo/ Pembro (N=397)			Placebo + Chemo/ Placebo (N=400)			Pembro + Chemo/ Pembro vs Placebo + Chemo/ Placebo
	N	Number of Events	(%)	N	Number of Events	(%)	Hazard Ratio (95% CI)[a]
Overall	397	174	(43.8)	400	248	(62.0)	0.59 (0.48, 0.72)
Age category							
< 65	221	88	(39.8)	214	136	(63.6)	0.51 (0.39,0.67)
≥ 65	176	86	(48.9)	186	112	(60.2)	0.70 (0.52, 0.92)
Age category							
< 65	221	88	(39.8)	214	136	(63.6)	0.51 (0.39, 0.67)
65-74	153	71	(46.4)	152	91	(59.9)	0.68 (0.50, 0.93)
75-84	23	15	(65.2)	34	21	(61.8)	0.83 (0.43, 1.63)
Gender							

Male	279	127	(45.5)	284	178	(62.7)	0.62 (0.49, 0.78)
Female	118	47	(39.8)	116	70	(60.3)	0.52 (0.36, 0.75)
Race							
White	250	109	(43.6)	239	151	(63.2)	0.56 (0.44, 0.72)
All Others	134	57	(42.5)	145	85	(58.6)	0.63 (0.45, 0.88)
Overall cancer staging							
II	118	40	(33.9)	121	62	(51.2)	0.59 (0.40, 0.88)
III	279	134	(48.0)	279	186	(66.7)	0.58 (0.46, 0.72)
Detail Overall cancer staging							
IIA	22	7	(31.8)	19	9	(47.4)	0.59 (0.22, 1.58)
IIB	96	33	(34.4)	102	53	(52.0)	0.59 (0.38, 0.92)
IIIA	217	100	(46.1)	224	145	(64.7)	0.57 (0.44, 0.74)
IIIB	62	34	(54.8)	55	41	(74.5)	0.57 (0.36, 0.90)
Region (EU vs Ex EU)							
EU	136	59	(43.4)	131	79	(60.3)	0.60 (0.43, 0.85)
Ex EU	261	115	(44.1)	269	169	(62.8)	0.58 (0.46, 0.74)
Region (East-Asia vs Non-East Asia)							
East Asia	123	51	(41.5)	121	70	(57.9)	0.63 (0.44, 0.91)
Non-East Asia	274	123	(44.9)	279	178	(63.8)	0.57 (0.45, 0.72)
Histology							
Squamous	171	72	(42.1)	173	117	(67.6)	0.51 (0.38, 0.69)
Non-Squamous	226	102	(45.1)	227	131	(57.7)	0.66 (0.51, 0.86)
PDL1 expression level (50% cutoff)							
TPS≥ 50%	132	41	(31.1)	134	70	(52.2)	0.48 (0.33, 0.71)
TPS<50%	265	133	(50.2)	266	178	(66.9)	0.63 (0.51, 0.79)
PDL1 expression level							
TPS≥ 50%	132	41	(31.1)	134	70	(52.2)	0.48 (0.33, 0.71)
TPS=1-49%	127	55	(43.3)	115	76	(66.1)	0.52 (0.36, 0.73)
TPS<1%	138	78	(56.5)	151	102	(67.5)	0.75 (0.56, 1.01)
Smoking status							
Never	54	25	(46.3)	47	25	(53.2)	0.77 (0.44, 1.35)
Former	247	105	(42.5)	250	155	(62.0)	0.59 (0.46, 0.75)
Current	96	44	(45.8)	103	68	(66.0)	0.53 (0.36, 0.77)
ECOG							
0	253	105	(41.5)	246	150	(61.0)	0.57 (0.45, 0.74)
1	144	69	(47.9)	154	98	(63.6)	0.62 (0.46, 0.84)
EGFR activating mutation status							
Yes	14	5	(35.7)	19	13	(68.4)	0.32 (0.11, 0.91)
No	111	42	(37.8)	124	72	(58.1)	0.55 (0.38, 0.81)
Unknown/Missing	272	127	(46.7)	257	163	(63.4)	0.62 (0.49, 0.79)
ALK translocation status							
No	104	42	(40.4)	132	85	(64.4)	0.50 (0.35, 0.73)
Unknown/Missing	281	126	(44.8)	259	160	(61.8)	0.62 (0.49, 0.78)
EGFR OR ALK mutation							

EGFR or ALK yes	25	11	(44)	27	15	(55.6)	0.56 (0.25, 1.26)

[a] For overall population, analysis is based on stratified Cox regression model with treatment as a covariate. For subgroups, analysis is based on unstratified Cox regression model with treatment as a covariate.

If any level of a subgroup variable has fewer than 30 participants, subgroup analysis is not performed in that level of the subgroup variable.

Database Cutoff Date: 10JUL2023

Table 48: IA2 subgroup analyses of EFS by PD-L1 expression (ITT population)

PD-L1 Expression	Treatment	N	Number of Events (%)	Median[a] (months) (95% CI)	HR (95% CI) vs. Placebo
EFS per investigator assessment					
TPS>=50%	Pembro + Chemo/Pembro	132	41 (31.1)	NR (47.2, NR)	0.48 (0.33, 0.71)
	Placebo + Chemo/Placebo	134	70 (52.2)	26.3 (14.6, NR)	-
TPS=1-49%	Pembro + Chemo/Pembro	127	55 (43.3)	51.1 (26.5, NR)	0.52 (0.36, 0.73)
	Placebo + Chemo/Placebo	115	76 (66.1)	15.0 (11.1, 22.9)	-
TPS<1%	Pembro + Chemo/Pembro	138	78 (56.5)	22.8 (14.0, 32.5)	0.75 (0.56, 1.01)
	Placebo + Chemo/Placebo	151	102 (67.5)	17.9 (14.1, 21.4)	-

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

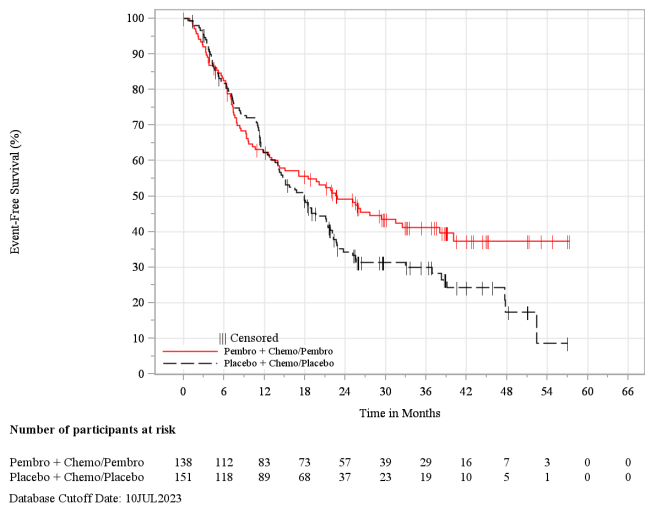
For subgroups, analysis is based on unstratified Cox regression model with treatment as a covariate.

NR = Not reached.

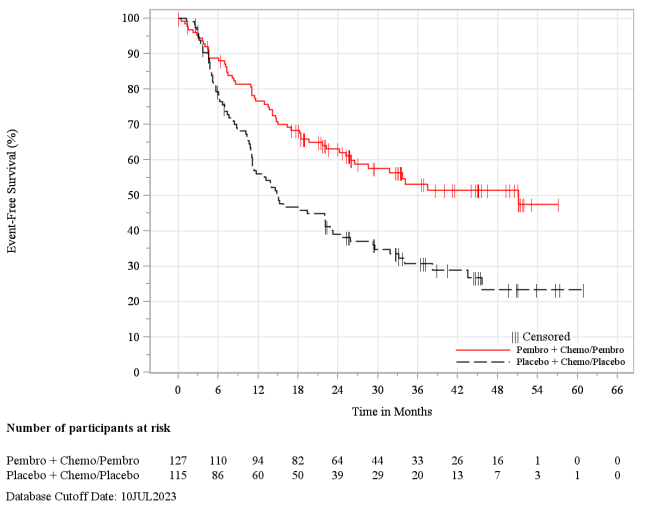
Database Cutoff Date: 10JUL2023

Figure 14: Kaplan-Meier plot of Event Free Survival by PD-L1 expression (ITT population)

TPS<1%



TPS=1-49%



TPS>=50%

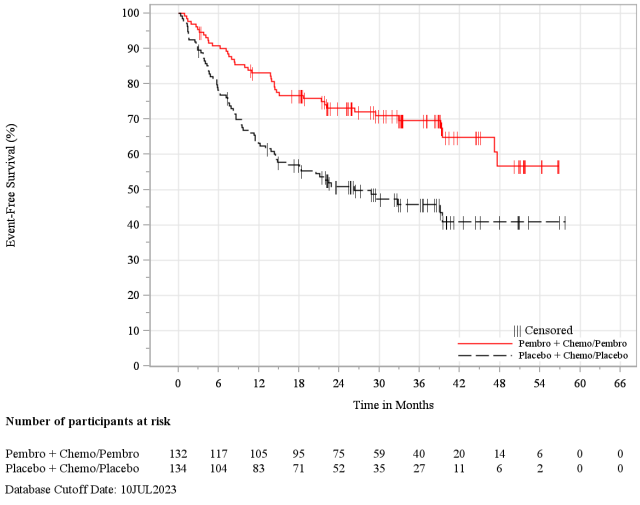


Table 49: Analysis of Overall Survival (ITT population)

	Pembro + Chemo/Pembro (N=397)	Placebo + Chemo/Placebo (N=400)
Number of Events (%)	110 (27.7)	144 (36.0)
Number of Censored (%)	287 (72.3)	256 (64.0)
Kaplan-Meier Estimates (months)[a]		
Median (95% CI)	NR (NR, NR)	52.4 (45.7, NR)
[Q1, Q3]	[29.3, NR]	[23.8, NR]
Person-months	12498.2	11697.2
Event Rate / 100 Person-months	0.9	1.2
vs Placebo + Chemo/Placebo		
Hazard Ratio (95% CI)[b]	0.72 (0.56, 0.93)	
p-value[c]	0.00517	
Rate at month 6 (%) (95% CI)	93.7 (90.8, 95.7)	95.2 (92.6, 96.9)
Rate at month 12 (%) (95% CI)	87.6 (84.0, 90.5)	87.7 (84.0, 90.5)
Rate at month 18 (%) (95% CI)	83.3 (79.3, 86.7)	80.9 (76.6, 84.4)
Rate at month 24 (%) (95% CI)	79.0 (74.6, 82.7)	74.7 (70.1, 78.7)
Rate at month 30 (%) (95% CI)	74.1 (69.2, 78.3)	68.4 (63.4, 73.0)
Rate at month 36 (%) (95% CI)	71.3 (66.2, 75.8)	64.0 (58.5, 68.9)
Rate at month 42 (%) (95% CI)	69.6 (64.3, 74.3)	60.5 (54.5, 66.0)
Rate at month 48 (%) (95% CI)	67.1 (61.1, 72.3)	51.5 (43.9, 58.6)

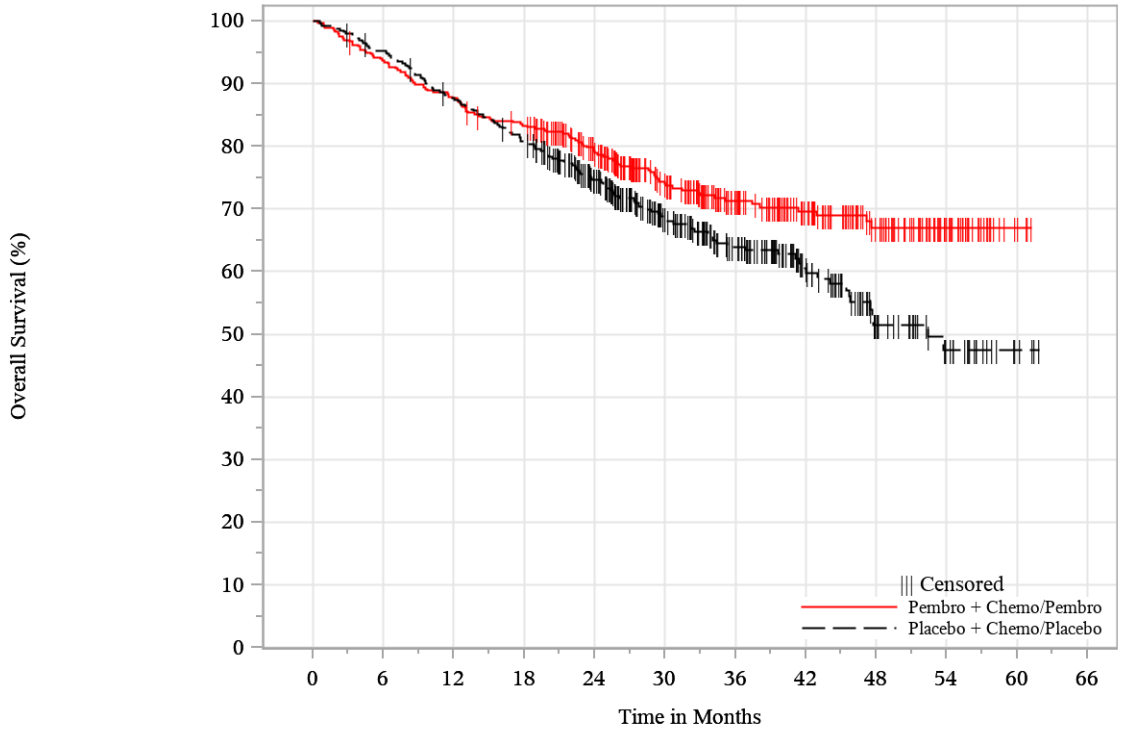
[a] From product-limit (Kaplan-Meier) method for censored data.

[b] Based on Cox regression model with treatment as a covariate stratified by Stage (II vs. III), TPS (>=50% vs. <50%), Histology (Squamous vs. Non-squamous) and Region (East-Asia vs. non-East Asia), where Region and Histology are collapsed for Stage II TPS >=50%; Region is collapsed for Stage III TPS >=50% Squamous and Stage II TPS<50% Non-squamous.

[c] One-sided p-value based on log-rank test stratified by Stage (II vs. III), TPS (>=50% vs. <50%), Histology (Squamous vs. Non-squamous) and Region (East-Asia vs. non-East Asia), where Region and Histology are collapsed for Stage II TPS >=50%; Region is collapsed for Stage III TPS >=50% Squamous and Stage II TPS<50% Non-squamous.

NR = Not reached.
Database Cutoff Date: 10JUL2023

Figure 15: Kaplan-Meier Plot of Overall Survival (ITT population)



Number of participants at risk

Pembro + Chemo/Pembro	397	371	347	327	277	205	148	108	69	32	4	0
Placebo + Chemo/Placebo	400	379	347	319	256	176	125	77	39	20	4	0

Database Cutoff Date: 10JUL2023

Table 50: Subgroup Analysis of Overall Survival (ITT population)

	Pembro + Chemo/ Pembro (N=397)			Placebo + Chemo/ Placebo (N=400)			Pembro + Chemo/ Pembro vs Placebo + Chemo/ Placebo
	N	Number of Events	(%)	N	Number of Events	(%)	Hazard Ratio (95% CI)[a]
Overall	397	110	(27.7)	400	144	(36.0)	0.72 (0.56, 0.93)
Age category							
< 65	221	54	(24.4)	214	82	(38.3)	0.57 (0.40, 0.80)
≥ 65	176	56	(31.8)	186	62	(33.3)	0.96 (0.67, 1.38)
Age category							
< 65	221	54	(24.4)	214	82	(38.3)	0.57 (0.40, 0.80)
65-74	153	47	(30.7)	152	50	(32.9)	0.97 (0.65, 1.44)
75-84	23	9	(39.1)	34	12	(35.3)	1.01 (0.43, 2.41)
Gender							
Male	279	89	(31.9)	284	114	(40.1)	0.73 (0.55, 0.96)
Female	118	21	(17.8)	116	30	(25.9)	0.69 (0.39, 1.20)

Race							
White	250	73	(29.2)	239	97	(40.6)	0.66 (0.49, 0.90)
All Others	134	34	(25.4)	145	39	(26.9)	0.93 (0.59, 1.48)
Overall cancer staging							
II	118	26	(22.0)	121	39	(32.2)	0.67 (0.41, 1.10)
III	279	84	(30.1)	279	105	(37.6)	0.74 (0.55, 0.98)
Detail Overall cancer staging							
IIA	22	5	(22.7)	19	6	(31.6)	0.75 (0.23, 2.47)
IIB	96	21	(21.9)	102	33	(32.4)	0.65 (0.38, 1.13)
IIIA	217	62	(28.6)	224	79	(35.3)	0.74 (0.53, 1.03)
IIIB	62	22	(35.5)	55	26	(47.3)	0.69 (0.39, 1.22)
Region (EU vs Ex EU)							
EU	136	39	(28.7)	131	45	(34.4)	0.81 (0.53, 1.24)
Ex EU	261	71	(27.2)	269	99	(36.8)	0.68 (0.50, 0.92)
Region (East-Asia vs Non-East Asia)							
East Asia	123	32	(26.0)	121	30	(24.8)	1.05 (0.64, 1.73)
Non-East Asia	274	78	(28.5)	279	114	(40.9)	0.63 (0.48, 0.85)
Histology							
Squamous	171	61	(35.7)	173	80	(46.2)	0.71 (0.51, 0.99)
Non-Squamous	226	49	(21.7)	227	64	(28.2)	0.73 (0.50, 1.06)
PDL1 expression level (50% cutoff)							
TPS≥ 50%	132	23	(17.4)	134	39	(29.1)	0.55 (0.33, 0.92)
TPS<50%	265	87	(32.8)	266	105	(39.5)	0.79 (0.60, 1.06)
PDL1 expression level							
TPS≥ 50%	132	23	(17.4)	134	39	(29.1)	0.55 (0.33, 0.92)
TPS=1-49%	127	35	(27.6)	115	44	(38.3)	0.69 (0.44, 1.07)
TPS<1%	138	52	(37.7)	151	61	(40.4)	0.91 (0.63, 1.32)
Smoking status							
Never	54	10	(18.5)	47	9	(19.1)	1.00 (0.41, 2.46)
Former	247	69	(27.9)	250	87	(34.8)	0.76 (0.56, 1.05)
Current	96	31	(32.3)	103	48	(46.6)	0.59 (0.38, 0.93)
ECOG							
0	253	62	(24.5)	246	77	(31.3)	0.74 (0.53, 1.03)
1	144	48	(33.3)	154	67	(43.5)	0.72 (0.50, 1.04)
EGFR activating mutation status							
Yes	14	1	(7.1)	19	5	(26.3)	0.24 (0.03, 2.03)
No	111	20	(18.0)	124	33	(26.6)	0.64 (0.37, 1.11)
Unknown	272	89	(32.7)	257	106	(41.2)	0.75 (0.56, 0.99)
ALK translocation status							
No	104	22	(21.2)	132	38	(28.8)	0.70 (0.41, 1.18)
Unknown	281	87	(31.0)	259	105	(40.5)	0.72 (0.54, 0.96)
EGFR OR ALK mutation							
EGFR or ALK yes	25	2	(8)	27	5	(18.5)	0.20 (0.02, 1.70)

[a] For overall population, analysis is based on stratified Cox regression model with treatment as a covariate. For subgroups, analysis is based on unstratified Cox regression model with treatment as a

covariate.

If any level of a subgroup variable has fewer than 30 participants, subgroup analysis is not performed in that level of the subgroup variable.

Database Cutoff Date: 10JUL2023

Table 51: IA2 Subgroup Analyses of OS by PD-L1 expression (ITT population)

PD-L1 Expression	Treatment	N	Number of Events (%)	Median[a] (months) (95% CI)	HR (95% CI) vs. Placebo
TPS>=50%	Pembro + Chemo/Pembro	132	23 (17.4)	NR (NR, NR)	0.55 (0.33, 0.92)
	Placebo + Chemo/Placebo	134	39 (29.1)	NR (NR, NR)	-
TPS=1-49%	Pembro + Chemo/Pembro	127	35 (27.6)	NR (NR, NR)	0.69 (0.44, 1.07)
	Placebo + Chemo/Placebo	115	44 (38.3)	47.6 (41.1, NR)	-
TPS<1%	Pembro + Chemo/Pembro	138	52 (37.7)	NR (41.4, NR)	0.91 (0.63, 1.32)
	Placebo + Chemo/Placebo	151	61 (40.4)	47.5 (36.9, 53.7)	-

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

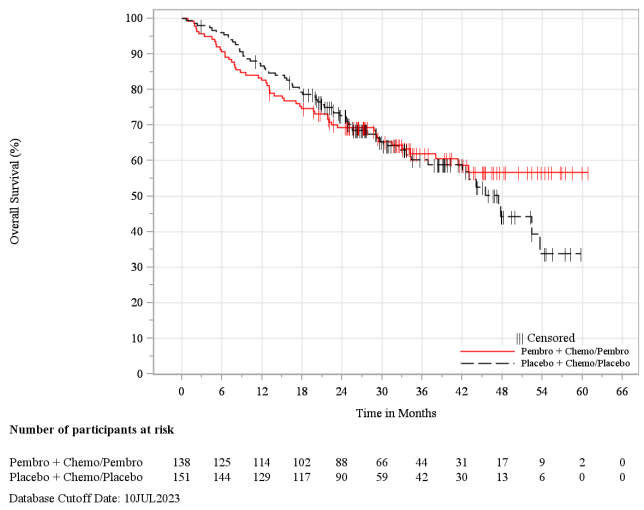
NR = Not reached.

For subgroups, analysis is based on unstratified Cox regression model with treatment as a covariate.

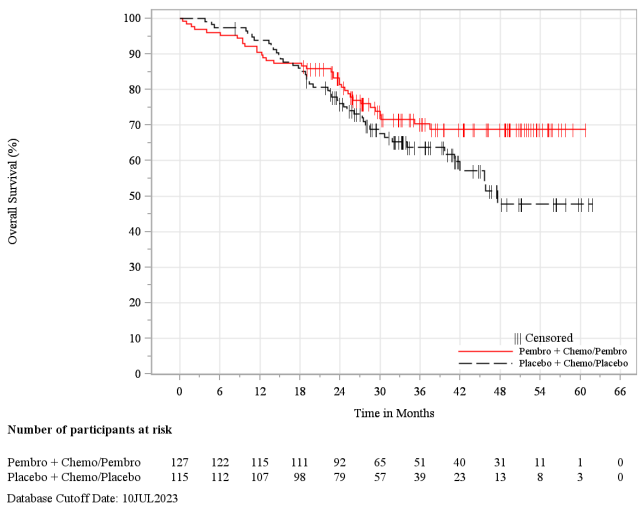
Database Cutoff Date: 10JUL2023

Figure 16: Kaplan-Meier Plot of Overall Survival by PD-L1 expression (ITT population)

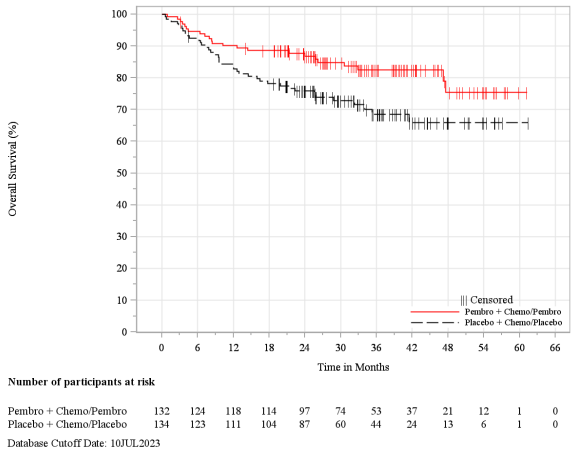
TPS<1%



TPS=1-49%



TPS>=50%



Summary of main study

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

Table 52: Summary of Efficacy for trial KEYNOTE-671

Title: A Phase III, Randomized, Double-blind Trial of Platinum Doublet Chemotherapy +/− Pembrolizumab (MK-3475) as Neoadjuvant/Adjuvant Therapy for Participants with Resectable Stage II, IIIA, and Resectable IIIB (T3-4N2) Non-small Cell Lung Cancer (NSCLC) (KEYNOTE-671)			
Study identifier	IND: 116,833, EudraCT: 2017-001832-21, NCT: 03425643		
Design	Phase 3, randomized, parallel assignment, placebo-controlled, double-blind, multicenter		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		First participant first visit 24-APR-2018; study ongoing not applicable not applicable
Hypothesis	Superiority		
Treatments groups	Pembrolizumab + neoadjuvant chemotherapy (NAC)/pembrolizumab N=397 randomized, 396 treated		**Neoadjuvant therapy prior to surgery:** 4 cycles of pembrolizumab 200 mg or placebo Q3W + cisplatin 75 mg/m2 Q3W + gemcitabine (squamous) 1000 mg/m2 on Days 1 and 8 of each 21-day cycle for 4 cycles + pemetrexed (non-squamous) 500 mg/m2 on Day 1 of each 21-day cycle for 4 cycles **Adjuvant therapy post-surgery:** 13 cycles of pembrolizumab 200 mg or placebo Q3W
	Placebo + NAC/placebo N = 400 randomized, 399 treated		
Endpoints and definitions	Dual primary endpoint	Event-free survival (EFS)	EFS is defined as the time from randomization to the first of the following events: radiographic disease progression or local progression precluding surgery, inability to resect tumour, local or distant recurrence, (including R1 or R2 resection), or death

	Dual primary endpoint	Overall survival (OS)	OS is defined as the time from randomization to death due to any cause
	Secondary endpoint	Major pathological response (mPR)	mPR is defined as ⩽10% viable tumour cells in the resected primary tumour and all resected lymph nodes text
	Secondary endpoint	Pathological complete response (pCR)	pCR is defined as the absence of residual invasive cancer on haematoxylin and eosin stained slides of the resected lung specimen and lymph nodes following completion of neoadjuvant therapy (i.e., ypT0/Tis ypN0).
Database lock	Interim Analysis 1: Data cutoff: 29-JUL-2022; database lock: 09-SEP-2022 Interim Analysis 2: Data cutoff: 10 Jul 2023		
Results and Analysis			
Analysis description	**Primary Analysis - EFS by investigator assessment at IA1** EFS was formally tested with the multiplicity-adjusted, one-sided p-value boundary of 0.00462 at IA1.		
Analysis population and time point description	Intent to treat (ITT) Interim analysis 1 (IA1); data cutoff 29-JUL-2022		
Descriptive statistics and estimate variability	Treatment group	Pembrolizumab + NAC/pembrolizumab	Placebo + NAC/placebo
	Number of subjects	397	400
	EFS (n events, %)	139 (35%)	205 (51.3%)
	EFS (median)	Not reached (NR)	17.0 months
	95% confidence interval (CI)	34.1, NR	14.3, 22.0
Effect estimate per comparison	EFS (dual Primary endpoint)	Comparison groups	Pembrolizumab + NAC/pembrolizumab Placebo + NAC/placebo
		Hazard ratio	0.58
		95% CI	0.46, 0.72
		P-value (log-rank test)	<0.00001
Analysis description	**Primary Analysis - OS at IA2** OS was formally tested at IA2 with the multiplicity-adjusted, one-sided p-value boundary of 0.005426		
Analysis population and time point description	Intent to treat Interim analysis 2 (IA2); data cutoff 10-JUL-2023		
Descriptive statistics and estimate variability	Treatment group	Pembrolizumab + NAC/pembrolizumab	Placebo + NAC/placebo
	Number of subjects	397	400
	OS (n events, %)	110 (27.7%)	144 (36.0%)
	OS (median)	NR	52.4 months

	95% confidence interval (CI)	NR, NR	45.7, NR
Effect estimate per comparison	OS (dual Primary endpoint)	Comparison groups	Pembrolizumab + NAC/pembrolizumab Placebo + NAC/placebo
		Hazard ratio	0.72
		95% CI	0.56, 0.93
		P-value (log-rank test)	0.00517
Notes	At IA1, the success criterion was met for one of the dual primary endpoints (EFS) in the ITT population, while OS was not statistically significant and was thus tested again at IA2.		
Analysis description	**Secondary Analysis - mPR assessed by blinded independent pathologic review at IA1**		
Analysis population and time point description	Intent to treat Interim analysis 1 (IA1); data cutoff 29-JUL-2022		
Descriptive statistics and estimate variability	Treatment group	Pembrolizumab + NAC/pembrolizumab	Placebo + NAC/placebo
	Number of subjects	397	400
	mPR rate	30.2%	11.0%
	95% confidence interval (CI)	25.7, 35.0	8.1, 14.5
Effect estimate per comparison	mPR (secondary endpoint)	Comparison groups	Pembrolizumab + NAC/pembrolizumab Placebo + NAC/placebo
		Estimated treatment difference	19.2%
		95% CI	13.9, 24.7
		P-value	<0.00001
Analysis description	**Secondary Analysis - pCR assessed by blinded independent pathologic review at IA1**		
Analysis population and time point description	Intent to treat Interim analysis 1 (IA1); data cutoff 29-JUL-2022		
Descriptive statistics and estimate variability	Treatment group	Pembrolizumab + NAC/pembrolizumab	Placebo + NAC/placebo
	Number of subjects	397	400
	pCR rate	18.1%	4.0%
	95% confidence interval (CI)	14.5, 22.3	2.3, 6.4
Effect estimate per comparison	pCR (secondary endpoint)	Comparison groups	Pembrolizumab + NAC/pembrolizumab Placebo + NAC/placebo

		Estimated treatment difference	14.2%
		95% CI	10.1, 18.7
		P-value	<0.00001
Notes	IA1: EFS was statistically significant. mPR and pCR were included in the multiplicity strategy and were statistically significant. OS was not statistically significant. IA2: OS was statistically significant. EFS was updated but not formally tested (as already significant at IA1)		

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

Indirect trial comparison (ITC) of pembrolizumab arms in KEYNOTE-671 and KEYNOTE-091 using patient-level data

To understand the contribution of pembrolizumab before surgery, the MAH performed an exploratory analysis of ITC for the pembrolizumab arms in KEYNOTE-671 and KEYNOTE-091 using patient-level data. Limitations of ITC were acknowledged, including:

- The 2 studies were different with respect to design and target population. The ITC would depend on the key assumption that the contribution of chemotherapy used before and after surgery is the same.
- Because randomization occurred at different time points relative to surgery, data collected prior to adjuvant treatment for KEYNOTE-671 may not sufficiently mirror the baseline status for KEYNOTE-091.
- The event definition in KEYNOTE-091 included second/new malignancies whereas KEYNOTE-671 did not.

Acknowledging the limitations above, ITC was performed based on the IPTW-ATT using propensity scores to balance baseline participant characteristics and to adjust for confounding for cross-trial comparisons. The analysis populations in both studies chosen for ITC consisted of participants treated with adjuvant pembrolizumab who received chemotherapy, had R0 resection, did not receive RT, had ECOG PS 0 or 1, and were disease-free before adjuvant pembrolizumab started. A total of 259 and 493 participants from the pembrolizumab arm in KEYNOTE-671 and KEYNOTE-091, respectively, were included in the analysis populations for the ITC. To achieve the same median follow-up, the data from KEYNOTE-091 were adjusted with a new analysis cutoff date by censoring the disease assessments and follow-up performed after this date. The propensity score was calculated using multivariate logistic regression as the probability of being treated with adjuvant pembrolizumab in KEYNOTE-671 versus KEYNOTE-091. The characteristics at baseline including race, gender, histology, smoking status, disease stage per AJCC eighth version (pathological stage), PD-L1 status, ECOG PS status and age, were known prognostic factors and potential confounders, and thus included as covariates in the logistic regression model. The inverse probability of treatment weights based on the propensity score were derived for each participant and used to balance the participant characteristics above. Participant characteristics were similar between the two pembrolizumab arms after weighting.

Table 53: Participant characteristics for the pembrolizumab arm in KEYNOTE-671 and KEYNOTE-091 after weighting

	3475-671		3475-091	
	n	(%)	n	(%)
Participants in population	249		253.9	
Sex				
Male	172	(69.1)	177.7	(70.0)

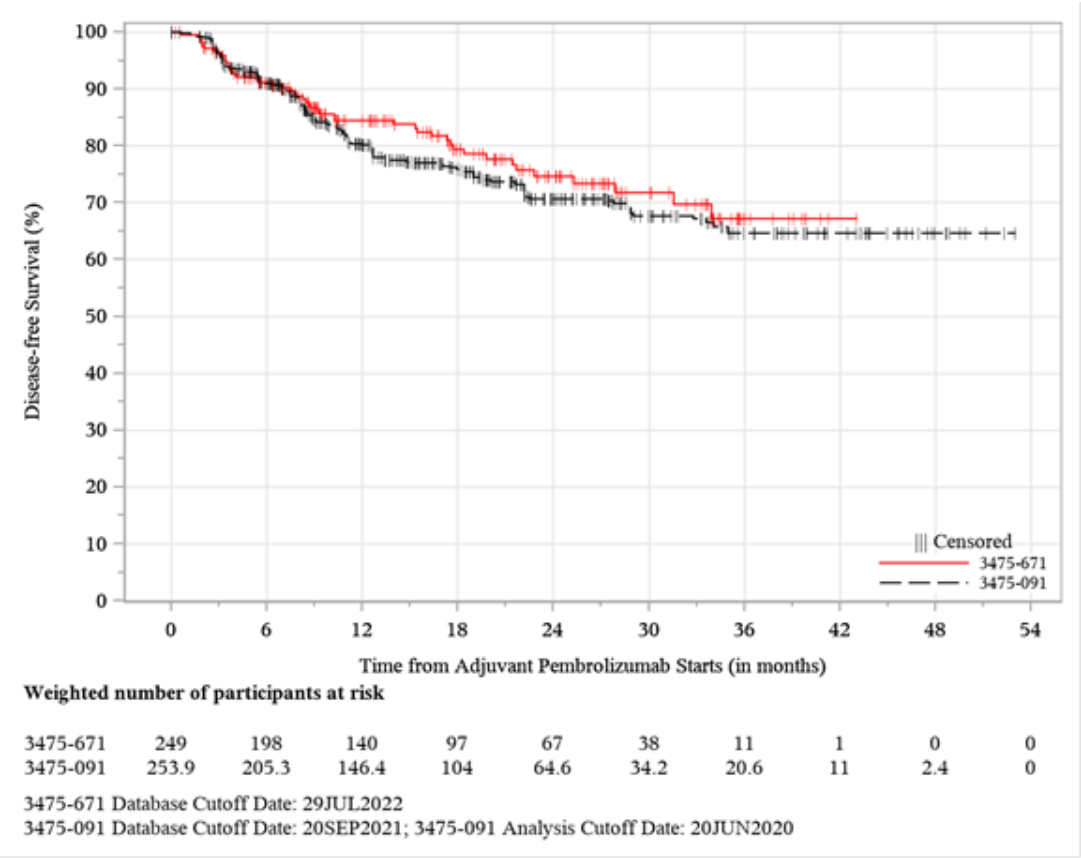
Female	77	(30.9)	76.2	(30.0)
Age (Years)				
Median	64.0		64.0	
Race				
Asian	87	(34.9)	89.8	(35.3)
All Others	162	(65.1)	164.1	(64.7)
Overall Cancer Staging at Baseline per AJCC V8				
IB			0.0	(0.0)
II	81	(32.5)	75.7	(29.8)
III	168	(67.5)	178.2	(70.2)
PD-L1 Expression Level				
TPS >=50%	87	(34.9)	92.6	(36.5)
TPS =1-49%	82	(32.9)	80.3	(31.6)
TPS <1%	80	(32.1)	81.0	(31.9)
Smoking Status				
Never Smoker	36	(14.5)	33.9	(13.4)
Former Smoker	154	(61.8)	160.9	(63.4)
Current Smoker	59	(23.7)	59.1	(23.3)
Baseline ECOG Prior to Adjuvant Pembrolizumab Starts				
0	130	(52.2)	133.1	(52.4)
1	119	(47.8)	120.8	(47.6)
Histology				
Non-Squamous	142	(57.0)	141.0	(55.5)
Squamous	107	(43.0)	112.9	(44.5)
3475-671 Database Cutoff Date: 29JUL2022				
3475-091 Database Cutoff Date: 20SEP2021				

The IPTW weights based on propensity score were then used in the weighted Cox model for DFS analysis to estimate the treatment effect adjusting for population imbalance across the 2 studies. Xie and Liu's method was used to estimate the adjusted DFS KM curves with IPTW. The time origin for the DFS analysis was the date when the adjuvant pembrolizumab treatment started.

With the median follow-up of 19.2 months since the adjuvant pembrolizumab started, the point estimate of population-adjusted DFS HR was 0.86 (95% CI: 0.60, 1.24) in favour of the pembrolizumab arm of KEYNOTE-671.

Given the limitations of the ITC approach described above, even in the context of available patient-level data, results should be interpreted with caution.

Figure 17: Adjusted Kaplan-Meier estimates of disease-free survival (population adjusted by weighting)



2.4.3. Discussion on clinical efficacy

The MAH for Keytruda is requesting an extension of indication for pembrolizumab as neoadjuvant/adjuvant (i.e. perioperative) treatment of early-stage NSCLC, based on the results of KEYNOTE-671 study.

Design and conduct of clinical studies

Keynote-671 is a phase III, multicenter, randomized, double-blind, placebo-controlled trial, which enrolled adult patients with resectable Stage II, IIIA, or IIIB (N2) NSCLC (AJCC 8th ed), not previously treated and able to undergo surgery. Inclusion/exclusion criteria are overall acceptable, in line with the ones commonly used in clinical trials with immune-checkpoint inhibitors, and considered adequately reflected in the SmPC. EGFR/ALK testing was not required for inclusion, but results of local testing were collected whenever available. This approach is acknowledged, as at the time of study start no targeted therapies were approved in early-stage NSCLC.

Patients received 4 cycles of neoadjuvant therapy with pembrolizumab 200 mg Q3W or placebo plus cisplatin-doublet chemotherapy (gemcitabine in squamous tumours or pemetrexed in non-squamous tumours). The chemotherapy backbone in the neoadjuvant phase is considered acceptable and in line with ESMO guidelines. After neoadjuvant treatment, patients underwent surgery. RT was given to patients who did no undergo surgery or who did not achieve complete resection (i.e. R1/R2). After surgery, patients were to receive adjuvant treatment with 13 cycles of pembrolizumab Q3W or placebo. The total duration of the treatment (neoadjuvant/surgery/(RT)/adjuvant) was around 12-18 months year overall.

The study has dual primary endpoints event free survival (EFS) and overall survival (OS) in the overall population, i.e. the study was considered positive if superiority in EFS or OS at an interim or final analysis is demonstrated. EFS was defined as the time from randomization to the first event between radiographic PD per RECIST 1.1, local progression precluding surgery, inability to resect tumour, local or distant recurrence after surgery, and death due to any cause. Imaging and biopsy were investigator-assessed. The definition of EFS is acceptable.

Major pathological response (mPR), defined as ≤10% viable tumour cells in the resected primary tumours and lymph nodes, and pathological complete response (pCR), i.e. ypT0/Tis ypN0, both defined by central laboratory pathologist where secondary endpoints, statistically tested under multiplicity adjustment.

Imaging schedule was well planned, and all patients underwent baseline imaging assessment before both neoadjuvant and adjuvant phase, that reduce the risk of difference between arms due to undetected metastases.

The study is event-driven. For EFS, based on a target number of ~416 events at IA2 (i.e. FA for EFS), the study has power of 90.1% to detect a HR of 0.7 at α=0.01. Power is increased to 94.9% at α=0.025. For OS, based on a target number of ~ 386 deaths at FA, the study has power of 90% (α=0.0148) or 93.2% (α=0.025) to detect a hazard ratio of 0.7. A total of approximately 786 participants were planned to be randomized. The sample size calculation is comprehensible and reproducible. None of the protocol amendments affected the sample size and power calculation.

Patients were randomly assigned 1:1 and stratified by stage (II, III), PD-L1 TPS (<50%, ≥50%), histology (squamous, non-squamous), and region (East-Asia, non-East-Asia). After the General Amendment No. 05, the study population was updated to include stages IIA and resectable IIIB (N2) (i.e. patients not resectable at presentation but that might become resectable with neoadjuvant therapy were not eligible for trial participation). The stratification levels for the variable "staging" were updated accordingly (IIB-IIIA were replaced by II vs III). This modification did not affect the randomization procedure and should not have inflated the balance of demographic and disease related characteristics at baseline between the 2 treatment groups, since the variable "staging" with two levels was already included in the original protocol. Amendment 10 changed the primary EFS endpoint from BICR to investigator assessment, just prior to IA1. The MAH's justification was that EFS based on investigator assessment was considered more consistent with medical practice. The change was deemed acceptable in the context of a double-blind study, also considering that EFS results by BICR have been provided as sensitivity analysis.

The blinding/unblinding procedure was well explained in the study protocol. No confirmed events of premature unblinding were reported for this study. The overall Type I error rate was controlled at a 0.025 (one-sided) α level. The graphical approach of Maurer and Bretz was applied to re-allocate alpha among the hypotheses for mPR rate, pCR rate, EFS and OS. Group sequential methods was used to allocate alpha among the interim and final analyses for the EFS and OS endpoints. There were four planned interim efficacy analyses (IA) in addition to the final analysis (FA) for this study: primary purpose of IA1 analysis was to demonstrate mPR and pCR superiority, as well as to interim evaluate EFS and OS superiority. IA2 is the final analysis for EFS and interim for OS superiority. The ITT population served as the population for the primary efficacy analyses. Statistical methods were well reported in the protocol and considered overall appropriate. Globally, all changes introduced in SAP should not have affected the consistency of study results.

Efficacy data and additional analyses

The MAH initially submitted the results of the IA1 with a data cut-off of 29 July 2022. Median follow-up duration at IA1 was 21.4 months, and the minimum time of follow up of the last patient enrolled was about 7 months.

A total of 397 and 400 patients were randomized to the pembrolizumab and control arm, respectively.

As compared to the pembrolizumab adjuvant pivotal trial KEYNOTE-091, the baseline characteristics of enrolled patients were overall comparable; the main difference is the tumour stage, being lower in the adjuvant study (stage II 30% in KN671 vs 60% in KN091). There were more Asian patients (30% vs 18%) and few more squamous histology (43% vs 35%) in KN0671 study. When considering the nivolumab study in the neoadjuvant setting Checkmate-816[20], there were less Asian patients in KN671 study, and differences in PD-L1 expression are noted (more negative patients and less high expressor in Checkmate-816), although it should be considered that different PD-L1 assays were used in the two studies.

Only one patient in each arm did not receive the planned treatment. Overall, 160 participants (40.4%) in the pembrolizumab arm and 141 (35.3%) in the placebo arm completed study treatment, while approximately 10% of patients in each arm were still receiving the adjuvant therapy at the data cut-off of IA1. The most frequent reason for treatment discontinuation overall was AEs in the pembrolizumab arm (21% vs 9.3%) and progressive disease in the placebo arm (15.2% vs 24.6%). In the neoadjuvant phase, about 25% of patients in each treatment arm did not complete 4 cycles of therapy, with similar exposure to drugs in the neoadjuvant phase in both groups. Reasons for discontinuing neoadjuvant treatment earlier than planned were however different in the two arms, being discontinuation for AEs more common in the pembrolizumab arm, while progressive disease in the control arm. Most patients underwent surgery similarly in both treatment arms (81.9% vs 79.3%), with few more patients in the comparator arm found unresectable during surgery.

The type of surgery and surgery outcome were generally consistent between treatment arms, but few more incomplete resections (R1+R2) were recorded in the comparator group. A total of 35 and 53 participants in the pembrolizumab and placebo arm, respectively, underwent radiotherapy. No safety signal was identified to suggest that in-study RT and the addition of pembrolizumab led to an increase of cardiopulmonary or haematological toxicity, although with the limit of small number of participants who received RT.

Adjuvant treatment was received by 73% vs 66.75% of patients in the pembrolizumab and the placebo arm, respectively: half of them completed the planned 13 cycles, while about 30% in both arms discontinued it. Again, discontinuation due to AEs was more common in the pembrolizumab arm, while discontinuation due to progressive disease was more common in the control arm. Subsequent oncologic therapies were more frequently received by patients in the placebo arm (17.1% vs 37.3%), as expected. At the time of IA2 data cut-off, no clear difference in ORR is observed between patients who received anti-PD(L)1 after rechallenge as compared to naïve patients, as well as no clear difference when using anti-PD(L)1 immediately post pembrolizumab or after different treatment in the meantime. However, the data limitation due to the analysis being based on post-randomization outcome, not evaluated/evaluable data in half of the patients, and overall limited number of patients, prevent making a conclusion over the use of anti-PD(L)1 at rechallenge.

A total of 10 protocol amendments were released. Of those, the most relevant is Amendment 5 leading to an enlargement of the eligible population during recruitment to include stages IIA and resectable IIIB (N2), while previously only Stage IIB or IIIA were eligible, treatment arms were well balanced with

[20] Forde PM, Spicer J, Lu S, Provencio M, Mitsudomi T, Awad MM, et al. Neoadjuvant nivolumab plus chemotherapy in resectable lung cancer. N Engl J Med. 2022 May 26;386(21):1973-85.

regard to substages, and the benefit of the addition of pembrolizumab appears consistent across tumour staging, thus not raising concern. Amendment 10 changed primary EFS endpoint from BICR to investigator assessment. EFS result by BICR has been provided as sensitivity analysis, and overall supports the investigator's assessment, and discordance rate between investigator and BICR was similar among the two arms, thus not raising concern. Additional prespecified sensitivity analyses for EFS were adequate to evaluate the robustness of EFS results, and showed consistent results with the primary EFS analysis.

Number of important protocol deviations were similar between treatment arms, and no concern is raised.

The baseline characteristics of participants in KEYNOTE-671 were overall balanced between the two treatment arms, with median age 64 years, mostly male (70.6%), White (about 60%), of those 33% from the EU. About 30% of participants were from Asia and most were former smoker (62.4%) and with an ECOG PS 0 (62.6%). Most patients had NSCLC stage III (70%), and more than half of the subjects (55%) had stage IIIA, while stage IIA were the least represented (5%). Adenocarcinoma was the most common histology (57%). PD-L1 expression, whose assessment was mandatory, indicated roughly one third of the population being TPS<1%, one third 1-49% and one third ≥50%. Assessment of molecular status (EGFR and ALK) was on the contrary not mandatory, and it is available only in about 30% of the population. Of those with known alterations, 33 patients had EGFR mutated tumour and 21 ALK mutated, equally distributed in the two arms. The MAH clarified that no additional biomarker analyses are planned for the time being.

At the IA1, treatment with pembrolizumab + chemotherapy/pembrolizumab resulted in a statistically significant improvement in EFS by investigator assessment compared to placebo + chemotherapy/placebo (HR: 0.58; 95% CI: 0.46, 0.72; p<0.00001); the median EFS was not reached for the pembrolizumab arm and was 17 months for the placebo arm. Higher rate of EFS events were reported in the comparator arm (35% vs 51.3%). More deaths were reported in the pembrolizumab arm as EFS events (40 vs 29); it is acknowledged that the overall difference between arms is <3% and may be an artifact due to small numbers, and that participants in the placebo arm have higher chance of disease progression/recurrence as first event and the overall number of OS events were higher in the placebo arm. EFS KM curves divide after approximately 4 months and remain clearly separated, although a very high rate of censoring is seen, and a plateau is not evident yet.

A statistically significant increase in mPR and pCR was also shown in the pembrolizumab arm as compared to the control arm (mPR 30.2% vs 11%; pCR 18.1% vs 4%). To date, pCR and mPR have not been specifically recognized as surrogate endpoint in early NSCLC nor yet incorporated in international guidelines e.g. to guide treatment decision. It is acknowledged that mPR and pCR are going in the same direction of EFS in this study, which is reassuring. Baseline characteristics of patients achieving and not achieving pCR and mPR were overall balanced between treatment arms, thus no specific baseline characteristics that markedly differ between patients who achieved pCR/mPR as compared to who did not achieve pCR/mPR can be identified. An exploratory unstratified subgroup analysis of EFS by participants who achieved pCR/mPR and those who did not achieve pCR/mPR following neoadjuvant treatment suggested overall better EFS outcome in patients who achieve pCR/mPR as compared to patients who did not achieve those. Treatment effect in patients who did and did not achieve pCR/mPR appears always in favour of the pembrolizumab arm. However, the limits of this analysis is that it is based on a post-randomization outcome, and that the number of patients/ events are low for patients with pCR/mPR, especially in the placebo arm.

PRO were also evaluated. Global health status/QoL scores decreased relative to baseline showing deterioration in both pembrolizumab and placebo arm in the neoadjuvant phase; in the adjuvant phase, scores were stable relative to baseline in both the pembrolizumab and placebo arm. The empirical mean

change from baseline in global health status/QoL showed stable scores in both treatment arms over time across both the neoadjuvant and adjuvant phases.

IA2 occurred approximately one year after IA1 (data cut-off 10-JUL-2023). Median FU at IA2 was 29.8 months (range 0.4-62 months). EFS was not formally tested, but a descriptive analysis showed consistency with prior result [EFS HR 0.59 (0.48, 0.72)] and EFS KM curves remain separated over time, which is encouraging. At the IA2 data cut-off there were no more patients under active treatment. Considering the duration of follow-up and the observed event rates for EFS, data are considered mature enough to assess the benefit with regard to a delay in recurrence. Although a plateau in EFS curves is not yet evident in the KM curves, the difference in EFS rate between the two treatment arms (e.g. 19% at 30 months) is considered clinically relevant.

While OS was not statistically significant at IA1, OS did reach statistical significance in the overall population at IA2 (HR 0.72, 95%CI 0.56-0.93), although only slightly crossing the boundary for declaring success (p=0.00517; p-value boundary = 0.005426). Median OS was not reached in the experimental arm vs 52.4 months in the control arm. OS events were recorded in 27.7% vs 36% of patients. High rate of censoring is observed in OS KM curves after month 18. OS KM curves are almost overlapping until month 16, then clearly dividing in favour of the pembrolizumab-containing arm, as also confirmed by piecewise Hazard Rate for OS which was in favour of the control arm up to month 8, then HR was <1 afterwards. The analysis of deaths occurring within the first 8 months (35 vs 28 in the experimental vs control arm) showed a higher rate of deaths due to disease progression in the placebo arm (22.9% vs 42.9%), thus faster progression with the addition of pembrolizumab is not suggested by available data. Also, deaths due to treatment-related AEs seems to be equally distributed (3 in each arm), although due to the small sample size the results should be interpreted with caution. A sensitivity analysis was performed for OS (at IA1) in case the proportional hazards assumption is not valid. The result of the RMST is consistent with the appearance of OS KM curve.

Results of pre-specified subgroup analyses showed overall consistent results across subgroups in the various endpoints.

With regard to the subgroup analyses by PD-L1 expression, the benefit for the addition of pembrolizumab was correlated with PD-L1 expression level, with improved outcomes across all endpoints EFS, OS and pCR/mPR in higher PD-L1 expressors subgroups. Following the principles expressed in EMA guideline on the investigation of subgroups in confirmatory clinical trials[21], exploring the consistency of the treatment effect across subgroups based on PD-L1 expression is of relevance in KEYNOTE-671 study, considering the existence of both a biological rationale and replication of the finding across several data sources, including accumulating (although still preliminary) evidence from similarly designed studies of anti-PD(L)1 in the peri-operative early stage NSCLC setting as KEYNOTE-671 (CheckMate-77T[22] and AEGEAN[23]).

The PD-L1 TPS<1% subgroup represent a relevant proportion of the population (approximately 36% of the ITT). While all patients were prospectively centrally evaluated for PD-L1 expression and the study was stratified by PD-L1 expression, the cut off used to stratify at randomization was 50% and not 1%. Evaluable baseline characteristics between the two treatment arms in the TPS<1% subset were overall

[21] EMA/CHMP/539146/2013 - Committee for Medicinal Products for Human Use (CHMP) - Guideline on the investigation of subgroups in confirmatory clinical trials
[22] Cascone T, Awad MM, Spicer JD et al. LBA1 CheckMate 77T: Phase III study comparing neoadjuvant nivolumab (NIVO) plus chemotherapy (chemo) vs neoadjuvant placebo plus chemo followed by surgery and adjuvant NIVO or placebo for previously untreated, resectable stage II–IIIb NSCLC. Ann Oncol October 2023. 34 (2): S1295.
[23] Heymach JV, Harpole D, Mitsudomi T, et al; AEGEAN Investigators. Perioperative Durvalumab for Resectable Non-Small-Cell Lung Cancer. N Engl J Med. 2023 Nov 2;389(18):1672-1684.

balanced thus not suggesting a relevant impact of differences in known prognostic/baseline factors in the results. However, a possible impact of unknown factors cannot be completely excluded.

In the TPS<1% subgroup, the EFS and OS point estimates were higher than in the other PD-L1 subgroups 1-49% and ≥50%, with EFS HR of 0.75 (95%CI 0.56, 1.01), and OS HR 0.91 (95%CI 0.63, 1.32), at IA2. EFS KM curves separate after month 12 in favour of pembrolizumab and separation is maintained in the long-term with the updated IA2 analysis, which is reassuring. With regard to OS, although the KM curves seem to cross up to month 24, the OS HR point estimate is however still in favour of the experimental arm and improved with longer follow-up time from 1.01 at IA1 to 0.91 at IA2, thus does not indicate a detriment in overall survival. However, as OS is considered still immature in this early-stage setting, the MAH should provide further updates on OS data at future analyses, included in subgroups by PD-L1 expression to reassure on survival results in the long term (REC).

Although the rate difference between the two arms (9.8% for pCR and 15.4% for mPR) was lower in the TPS<1% population compared to the subgroups expressing higher PD-L1 levels, an improvement with higher pCR and mPR with the addition of pembrolizumab was still observed in the TPS<1% group.

As KEYNOTE-671 findings by PD-L1 expression are considered of relevance for prescribers, EFS and OS results in the TPS<1%, 1-49% and ≥50% subgroups have been included in section 5.1 of the SmPC.

Justification of the peri-operative regimen

In order to justify the perioperative regimen in KEYNOTE-671 study, the MAH conducted exploratory unstratified subgroup analyses of EFS in participants who have and who have not achieved pCR/mPR in KEYNOTE-671 (described above), and an indirect trial comparison (ITC) between KEYNOTE-671 and KEYNOTE-91 studies based on patient level data. The ITC comparison was considered well conducted from a methodological perspective; no clear difference between the EFS curves is seen, although due to the limits of the ITC results should be interpreted with cautions. KEYNOTE-671 design however does not allow to disentangle the contribution of pembrolizumab to each treatment phase, and therefore whether neoadjuvant and/or adjuvant pembrolizumab are both needed. This would have been possible based on a different study design, such as with a second randomization after surgery, as already noted in the Scientific Advice, but this was not the case. Therefore, KEYNOTE-671 results may only be discussed in the context of an indication for pembrolizumab as neoadjuvant AND adjuvant treatment for NSCLC. While the exploratory analyses provided are of interest and acknowledged, such analyses should be interpreted with caution due to their limitations. Based on the overall available data, it is therefore not possible to conclude whether patients may benefit more from pembrolizumab in combination with platinum-containing chemotherapy as neoadjuvant treatment, and then continued as a single agent as adjuvant treatment, compared with purely neoadjuvant or adjuvant treatment.

2.4.4. Conclusions on the clinical efficacy

The phase III placebo-controlled KEYNOTE-671 study demonstrated statistically significant and clinically meaningful improvement in EFS according to investigator assessment in the ITT population at the IA1 for the perioperative treatment regimen of pembrolizumab in combination with platinum-containing chemotherapy as neoadjuvant treatment and continued as monotherapy in adjuvant treatment as compared to neoadjuvant chemotherapy in patients with resectable Stage II, IIIA, or IIIB (T3-4N2) NSCLC, confirmed with updated EFS analysis. Statistically significant improvement in mPR and pCR was also shown. Overall survival also reached statistical significance at IA2, although slightly crossing the p boundary for declaring success.

Higher benefit with the addition of pembrolizumab was seen with higher PD-L1 expression levels, which is considered biologically plausible and replicated in similar studies. Nonetheless, an EFS benefit was observed also in the PD-L1 TPS <1% subgroup. OS data were still immature, but did not indicate a detrimental effect and showed a trend for improvement with longer follow-up in TPS <1%. Further updates should be provided by the MAH post-approval to reassure on survival results in the long-term. Data by PD-L1 expression have been included in section 5.1 of the SmPC to inform prescribers.

The following measure is considered necessary to address issues related to efficacy: the MAH should provide updated OS data from KEYNOTE-671, including in subgroups by PD-L1 expression, at future analyses. (REC)

2.5. Clinical safety

Introduction

The safety profile of pembrolizumab in combination with platinum-containing chemotherapy as neoadjuvant treatment, and then continued as a single agent as adjuvant treatment, in the context of its intended use for the treatment of patients with resectable Stage II, IIIA, or IIIB (T3-4N2) NSCLC (as defined by the AJCC eighth edition), is based on safety data from KEYNOTE-671.

KEYNOTE-671 is an ongoing Phase 3, randomized, placebo-controlled with active treatment, double-blind study designed to evaluate the safety and efficacy of pembrolizumab in combination with platinum-containing chemotherapy as neoadjuvant treatment, and then continued as monotherapy as adjuvant treatment in participants with resectable Stage II, IIIA, or IIIB (T3-4N2) NSCLC.

NOTE: safety data of KEYNOTE-671 are presented at IA1 (data cutoff 29-JUL-2022), unless noted otherwise.

Patient exposure

As of the data cut-off (29-JUL-2022), 396 participants in the pembrolizumab arm and 399 in the placebo arm received at least 1 dose of study intervention.

The proportion of participants with duration of exposure ≥6 months and ≥12 months was higher in the pembrolizumab plus chemotherapy (72.7% and 46.7%, respectively) arm compared with the Pooled Pembrolizumab Combination Dataset (59.1% and 38.2%, respectively). The proportion of participants having ≥1 up to ≥7 administrations of pembrolizumab was similar in the pembrolizumab plus chemotherapy group compared with the Pooled Pembrolizumab Combination Dataset.

Table 54: Summary of drug exposure (APaT population)

	KN671 Pembrolizumab + Chemotherapy/ Pembrolizumab (N=396)	KN671 Placebo + Chemotherapy/Placebo (N=399)	Pooled Safety Dataset for Pembrolizumab + Chemotherapy[i] (N=3123)	Pembrolizumab Monotherapy Reference Safety Dataset[j] (N=7631)
Duration On Therapy (days)				
Mean	291.5	271.9	299.7	239.1
Median	332.0	315.0	240.0	176.0
SD	153.2	155.2	221.9	210.2

Range	1.0 to 567.0	1.0 to 596.0	1.0 to 1,461.0	1.0 to 1,157.0
Number of Cycles				
Mean	10.9	10.2	13.2	12.3
Median	12.0	10.0	11.0	9.0
SD	5.9	5.9	9.6	10.1
Range	1.0 to 17.0	1.0 to 17.0	1.0 to 68.0	1.0 to 59.0

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

Number of cycles for KN671 is calculated based on the number of administration of pembrolizumab/placebo.

[i] Includes all participants who received at least one dose of pembrolizumab in KN21 cohort A/C/G, KN189, KN407, KN048, KN590, KN355, KN826, KN522.

[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, KN024, KN013 cohort 3, KN087, KN204, KN045, KN052, KN164 - cohort A + B, KN177, KN012 cohort B and B2, KN040, KN042, KN048, KN054, KN055, KN716, KN564, KN158 (Cohort K).

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

Database cutoff date for Lung (KN671: 29JUL2022, KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEP2018, KN21 cohort A/C/G: 19AUG2019, KN407: 09MAY2019, KN189: 20MAY2019)

Database cutoff date for Hodgkin Lymphoma (KN013-cohort 3: 28SEP2018, KN087: 15MAR2021, KN204: 16JAN2020)

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

Database cutoff date for MSI-H CRC: (KN177: 19FEB2021)

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

Database cutoff date for RCC (KN564: 14JUN2021)

Database cutoff date for MSI-H tumors (KN164-cohort A + B: 09SEP2019, KN158 Cohort K: 05OCT2020)

Database cutoff date for Esophageal cancer (KN590: 02JUl2020)

Database cutoff date for Cervical (KN826: 03MAY2021)

Database cutoff date for TNBC (KN355: 11DEC2019, KN522: 23MAR2021)

Demographic and Other Characteristics of Study Population

Demographic and other baseline characteristics are reported in the figure below.

Table 55: Participant characteristics

	KN671 Pembrolizumab + Chemotherapy/ Pembrolizumab		KN671 Placebo + Chemotherapy/Placebo		Pooled Safety Dataset for Pembrolizumab + Chemotherapy[i]		Pembrolizumab Monotherapy Reference Safety Dataset[j]	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	396		399		3,123		7,631	
Sex								
Male	278	(70.2)	283	(70.9)	1,042	(33.4)	4,889	(64.1)
Female	118	(29.8)	116	(29.1)	2,081	(66.6)	2,742	(35.9)
Age (Years)								
<65	221	(55.8)	214	(53.6)	2,176	(69.7)	4,524	(59.3)
>=65	175	(44.2)	185	(46.4)	947	(30.3)	3,107	(40.7)
Mean	62.7		63.5		56.6		59.9	
SD	8.5		8.1		12.5		13.4	
Median	63.0		64.0		58.0		62.0	
Range	26 to 83		35 to 81		20 to 94		15 to 94	
Race								
American Indian Or Alaska Native	1	(0.3)	0	(0.0)	55	(1.8)	59	(0.8)
Asian	124	(31.3)	125	(31.3)	686	(22.0)	826	(10.8)
Black Or African American	6	(1.5)	10	(2.5)	108	(3.5)	146	(1.9)
Multiracial	3	(0.8)	10	(2.5)	64	(2.0)	86	(1.1)
Native Hawaiian Or Other Pacific Islander	0	(0.0)	0	(0.0)	2	(0.1)	5	(0.1)
White	249	(62.9)	239	(59.9)	2,088	(66.9)	5,838	(76.5)
Missing	13	(3.3)	15	(3.8)	120	(3.8)	671	(8.8)
Ethnicity								
Hispanic Or Latino	35	(8.8)	34	(8.5)	429	(13.7)	604	(7.9)
Not Hispanic Or Latino	329	(83.1)	332	(83.2)	2,502	(80.1)	6,064	(79.5)
Not Reported	18	(4.5)	25	(6.3)	105	(3.4)	808	(10.6)
Unknown	14	(3.5)	8	(2.0)	66	(2.1)	145	(1.9)
Missing	0	(0.0)	0	(0.0)	21	(0.7)	10	(0.1)
Age Class (Years)								
<65	221	(55.8)	214	(53.6)	2,176	(69.7)	4,524	(59.3)
65-74	152	(38.4)	151	(37.8)	767	(24.6)	2,173	(28.5)
75-84	23	(5.8)	34	(8.5)	175	(5.6)	824	(10.8)
>=85	0	(0.0)	0	(0.0)	5	(0.2)	110	(1.4)
ECOG Performance Status								
[0] Normal Activity	253	(63.9)	245	(61.4)	1,768	(56.6)	4,016	(52.6)
[1] Symptoms, but ambulatory	143	(36.1)	154	(38.6)	1,349	(43.2)	3,440	(45.1)
Other/Missing	0	(0.0)	0	(0.0)	6	(0.2)	175	(2.3)
Geographic Region								
EU	136	(34.3)	131	(32.8)	1,118	(35.8)	2,856	(37.4)
Ex-EU	260	(65.7)	268	(67.2)	2,005	(64.2)	4,775	(62.6)
Geographic Region 2								
East-Asia	123	(31.1)	121	(30.3)	637	(20.4)	713	(9.3)
Ex-East Asia	273	(68.9)	278	(69.7)	2,486	(79.6)	6,918	(90.7)

Adverse events

Table 56: Adverse Event summary (APaT population)

	KN671 Pembrolizumab + Chemotherapy/ Pembrolizumab		KN671 Placebo + Chemotherapy/Placebo		Pooled Safety Dataset for Pembrolizumab + Chemotherapy[i]		Pembrolizumab Monotherapy Reference Safety Dataset[j]	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	396		399		3,123		7,631	
with one or more adverse events	394	(99.5)	393	(98.5)	3,097	(99.2)	7,375	(96.6)
with no adverse event	2	(0.5)	6	(1.5)	26	(0.8)	256	(3.4)
with drug-related[a] adverse events	383	(96.7)	379	(95.0)	3,020	(96.7)	5,462	(71.6)
with toxicity grade 3-5 adverse events	256	(64.6)	212	(53.1)	2,479	(79.4)	3,514	(46.0)
with toxicity grade 3-5 drug-related adverse events	178	(44.9)	149	(37.3)	2,099	(67.2)	1,208	(15.8)
with serious adverse events	160	(40.4)	130	(32.6)	1,456	(46.6)	2,742	(35.9)
with serious drug-related adverse events	70	(17.7)	57	(14.3)	910	(29.1)	840	(11.0)
who died	25	(6.3)	14	(3.5)	160	(5.1)	346	(4.5)
who died due to a drug-related adverse event	4	(1.0)	3	(0.8)	49	(1.6)	42	(0.6)
discontinued any drug due to an adverse event	101	(25.5)	69	(17.3)	900	(28.8)	1,066	(14.0)
discontinued pembrolizumab or placebo	83	(21.0)	36	(9.0)	548	(17.5)	1,066	(14.0)
discontinued any chemotherapy	44	(11.1)	50	(12.5)	644	(20.6)	NA	
discontinued any drug due to a drug-related adverse event	74	(18.7)	53	(13.3)	747	(23.9)	639	(8.4)
discontinued pembrolizumab or placebo	55	(13.9)	22	(5.5)	405	(13.0)	639	(8.4)
discontinued any chemotherapy	32	(8.1)	44	(11.0)	537	(17.2)	NA	
discontinued any drug due to a serious adverse event	59	(14.9)	31	(7.8)	472	(15.1)	714	(9.4)
discontinued pembrolizumab or placebo	55	(13.9)	23	(5.8)	382	(12.2)	714	(9.4)
discontinued any chemotherapy	19	(4.8)	19	(4.8)	314	(10.1)	NA	
discontinued any drug due to a serious drug-related adverse event	35	(8.8)	19	(4.8)	343	(11.0)	347	(4.5)
discontinued pembrolizumab or placebo	33	(8.3)	12	(3.0)	261	(8.4)	347	(4.5)
discontinued any chemotherapy	9	(2.3)	16	(4.0)	221	(7.1)	NA	

Table 57: Exposure-adjusted Adverse Event summary (including multiple occurrences of events) (APaT population)

	Event Count and Rate (Events/100 person-months)[a]			
	KN671 Pembrolizumab + Chemotherapy/ Pembrolizumab	KN671 Placebo + Chemotherapy/Placebo	Pooled Safety Dataset for Pembrolizumab + Chemotherapy[i]	Pembrolizumab Monotherapy Reference Safety Dataset[j]
Number of subjects exposed	396	399	3123	7631
Total exposure[b] in person-months	4153.67	3928.05	34084.64	66844.27
Total events (rate)				
adverse events	6179 (148.76)	5335 (135.82)	66128 (194.01)	76878 (115.01)
drug-related[c] adverse events	3377 (81.30)	2940 (74.85)	40032 (117.45)	24542 (36.72)
toxicity grade 3-5 adverse events	639 (15.38)	462 (11.76)	9548 (28.01)	7463 (11.16)
toxicity grade 3-5 drug-related adverse events	363 (8.74)	288 (7.33)	6869 (20.15)	1770 (2.65)
serious adverse events	295 (7.10)	189 (4.81)	2903 (8.52)	4801 (7.18)
serious drug-related adverse events	113 (2.72)	70 (1.78)	1477 (4.33)	1093 (1.64)
adverse events leading to death	27 (0.65)	14 (0.36)	166 (0.49)	353 (0.53)
drug-related adverse events leading to death	4 (0.10)	3 (0.08)	50 (0.15)	42 (0.06)
adverse events resulting in drug discontinuation	134 (3.23)	97 (2.47)	1097 (3.22)	1165 (1.74)
drug-related adverse events resulting in drug discontinuation	98 (2.36)	69 (1.76)	907 (2.66)	703 (1.05)
serious adverse events resulting in drug discontinuation	69 (1.66)	37 (0.94)	534 (1.57)	753 (1.13)
serious drug-related adverse events resulting in drug discontinuation	40 (0.96)	21 (0.53)	386 (1.13)	363 (0.54)

Table 58: Adverse Event summary neo-adjuvant/surgery phase

	Pembro + Chemo		Placebo + Chemo	
	n	(%)	n	(%)
Participants in population	396		399	
with one or more adverse events	390	(98.5)	389	(97.5)
with no adverse event	6	(1.5)	10	(2.5)
with drug-related[a] adverse events	379	(95.7)	374	(93.7)
with toxicity grade 3-5 adverse events	236	(59.6)	202	(50.6)
with toxicity grade 3-5 drug-related adverse events	161	(40.7)	146	(36.6)
with serious adverse events	133	(33.6)	116	(29.1)
with serious drug-related adverse events	56	(14.1)	52	(13.0)
who died	21	(5.3)	11	(2.8)
who died due to a drug-related adverse event	3	(0.8)	3	(0.8)
discontinued any drug due to an adverse event	71	(17.9)	58	(14.5)
discontinued any chemotherapy	44	(11.1)	52	(13.0)
discontinued pembrolizumab or placebo	49	(12.4)	24	(6.0)
discontinued any drug due to a drug-related adverse event	49	(12.4)	47	(11.8)
discontinued any chemotherapy	32	(8.1)	46	(11.5)
discontinued pembrolizumab or placebo	28	(7.1)	16	(4.0)
discontinued any drug due to a serious adverse event	42	(10.6)	24	(6.0)
discontinued any chemotherapy	19	(4.8)	19	(4.8)
discontinued pembrolizumab or placebo	38	(9.6)	16	(4.0)
discontinued any drug due to a serious drug-related adverse event	23	(5.8)	16	(4.0)
discontinued any chemotherapy	9	(2.3)	16	(4.0)
discontinued pembrolizumab or placebo	21	(5.3)	9	(2.3)

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

Treatment includes neoadjuvant study medications, in-study surgery and in-study radiotherapy

Neo-adjuvant/surgery phase begins with the first neoadjuvant dose and continues until the first dose of adjuvant pembrolizumab/placebo.

Included adverse events in the neo-adjuvant/surgery phase. If there is no adjuvant pembrolizumab/placebo, non-serious adverse events up to 30 days of last treatment and serious adverse events up to 90 days of last treatment 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.

Drug includes pembrolizumab/placebo and chemotherapy.

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Table 59: Adverse Event summary adjuvant phase

	Pembro		Placebo	
	n	(%)	n	(%)
Participants in population	290		267	
with one or more adverse events	243	(83.8)	209	(78.3)
with no adverse event	47	(16.2)	58	(21.7)
with drug-related[a] adverse events	158	(54.5)	85	(31.8)
with toxicity grade 3-5 adverse events	57	(19.7)	34	(12.7)
with toxicity grade 3-5 drug-related adverse events	29	(10.0)	15	(5.6)
with serious adverse events	41	(14.1)	23	(8.6)
with serious drug-related adverse events	16	(5.5)	7	(2.6)
who died	4	(1.4)	3	(1.1)
who died due to a drug-related adverse event	1	(0.3)	0	(0.0)
discontinued drug due to an adverse event	36	(12.4)	13	(4.9)
discontinued drug due to a drug-related adverse event	29	(10.0)	7	(2.6)
discontinued drug due to a serious adverse event	17	(5.9)	7	(2.6)
discontinued drug due to a serious drug-related adverse event	12	(4.1)	3	(1.1)

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

Adjuvant phase begins with the first dose of adjuvant pembrolizumab/placebo.

Included adverse events in the adjuvant phase. Non-serious adverse events up to 30 days of last treatment and serious adverse events up to 90 days of last treatment 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.

Database Cutoff Date: 29JUL2022

Common Adverse Events

The frequency, type, and severity of AEs reported in the pembrolizumab arm were generally consistent with the established profile of pembrolizumab monotherapy and the known safety profile of the individual chemotherapy components. Overall, no new safety concerns were identified for pembrolizumab.

Table 60: Participants With Adverse Events by Decreasing Incidence (Incidence ≥ 10% in One or More Treatment Groups) (APaT Population)

	KN671 Pembrolizumab + Chemotherapy/ Pembrolizumab		KN671 Placebo + Chemotherapy/Placebo		Pooled Safety Dataset for Pembrolizumab + Chemotherapy[i]		Pembrolizumab Monotherapy Reference Safety Dataset[j]	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	396		399		3,123		7,631	
with one or more adverse events	394	(99.5)	393	(98.5)	3,097	(99.2)	7,375	(96.6)
with no adverse events	2	(0.5)	6	(1.5)	26	(0.8)	256	(3.4)
Nausea	228	(57.6)	212	(53.1)	1,695	(54.3)	1,534	(20.1)
Neutrophil count decreased	173	(43.7)	169	(42.4)	621	(19.9)	53	(0.7)
Anaemia	168	(42.4)	161	(40.4)	1,704	(54.6)	982	(12.9)
Constipation	153	(38.6)	145	(36.3)	1,107	(35.4)	1,179	(15.5)
Fatigue	125	(31.6)	100	(25.1)	1,197	(38.3)	2,368	(31.0)
Decreased appetite	114	(28.8)	100	(25.1)	850	(27.2)	1,312	(17.2)
White blood cell count decreased	112	(28.3)	101	(25.3)	464	(14.9)	70	(0.9)
Vomiting	82	(20.7)	68	(17.0)	885	(28.3)	945	(12.4)
Diarrhoea	77	(19.4)	73	(18.3)	1,071	(34.3)	1,678	(22.0)
Platelet count decreased	76	(19.2)	76	(19.0)	377	(12.1)	95	(1.2)
Dyspnoea	74	(18.7)	51	(12.8)	425	(13.6)	1,130	(14.8)
Cough	72	(18.2)	56	(14.0)	659	(21.1)	1,392	(18.2)
Blood creatinine increased	68	(17.2)	60	(15.0)	301	(9.6)	358	(4.7)
Rash	67	(16.9)	34	(8.5)	644	(20.6)	1,175	(15.4)
Procedural pain	62	(15.7)	61	(15.3)	76	(2.4)	60	(0.8)
Alanine aminotransferase increased	58	(14.6)	38	(9.5)	564	(18.1)	572	(7.5)
Asthenia	56	(14.1)	62	(15.5)	661	(21.2)	880	(11.5)
Pruritus	52	(13.1)	33	(8.3)	468	(15.0)	1,435	(18.8)
Dizziness	51	(12.9)	43	(10.8)	363	(11.6)	564	(7.4)
Insomnia	50	(12.6)	26	(6.5)	400	(12.8)	528	(6.9)
Hypomagnesaemia	49	(12.4)	40	(10.0)	235	(7.5)	184	(2.4)
Pyrexia	49	(12.4)	31	(7.8)	630	(20.2)	934	(12.2)
Aspartate aminotransferase increased	46	(11.6)	32	(8.0)	490	(15.7)	538	(7.1)
Chest pain	45	(11.4)	31	(7.8)	176	(5.6)	341	(4.5)
Alopecia	44	(11.1)	40	(10.0)	1,099	(35.2)	118	(1.5)
Hypothyroidism	44	(11.1)	7	(1.8)	434	(13.9)	937	(12.3)
Headache	42	(10.6)	41	(10.3)	572	(18.3)	946	(12.4)
Hyponatraemia	41	(10.4)	34	(8.5)	223	(7.1)	387	(5.1)
Stomatitis	41	(10.4)	34	(8.5)	451	(14.4)	201	(2.6)
Oedema peripheral	39	(9.8)	24	(6.0)	347	(11.1)	630	(8.3)
Back pain	36	(9.1)	24	(6.0)	365	(11.7)	847	(11.1)
Arthralgia	34	(8.6)	33	(8.3)	660	(21.1)	1,436	(18.8)
Dysgeusia	31	(7.8)	36	(9.0)	328	(10.5)	150	(2.0)
Hypokalaemia	31	(7.8)	38	(9.5)	335	(10.7)	324	(4.2)
Weight decreased	29	(7.3)	24	(6.0)	365	(11.7)	628	(8.2)
Hyperglycaemia	28	(7.1)	43	(10.8)	172	(5.5)	360	(4.7)
Urinary tract infection	21	(5.3)	15	(3.8)	343	(11.0)	511	(6.7)
Abdominal pain	19	(4.8)	18	(4.5)	323	(10.3)	674	(8.8)
Myalgia	16	(4.0)	12	(3.0)	361	(11.6)	575	(7.5)
Neuropathy peripheral	14	(3.5)	16	(4.0)	465	(14.9)	146	(1.9)
Peripheral sensory neuropathy	10	(2.5)	10	(2.5)	393	(12.6)	83	(1.1)
Neutropenia	2	(0.5)	1	(0.3)	1,111	(35.6)	82	(1.1)
Mucosal inflammation	1	(0.3)	2	(0.5)	363	(11.6)	111	(1.5)
Thrombocytopenia	1	(0.3)	1	(0.3)	572	(18.3)	117	(1.5)
Leukopenia	0	(0.0)	1	(0.3)	367	(11.8)	52	(0.7)

Drug-related Adverse Events

Between the pembrolizumab arm and the Pooled Pembrolizumab Combination Dataset, the incidence of participants with common drug-related AEs (>5% incidence) was generally similar for most PTs [Table 64]. Some chemotherapy-related AEs (anaemia, diarrhoea, alopecia, peripheral neuropathy, and neutropenia) were less common in the pembrolizumab arm compared with the Pooled Pembrolizumab Combination Dataset.

Between the pembrolizumab arm and the RSD (Reference Safety Dataset), the incidence of participants with drug-related AEs was similar for most PTs with the exception of the following events which were more common in the pembrolizumab arm: nausea, neutrophil count decreased, anaemia, white blood cell count decreased, constipation, decreased appetite, vomiting, platelet count decreased, blood creatinine increased, alanine aminotransferase increased, alopecia, and hypomagnesemia [Table 64]. Most of these events were likely associated with the addition of chemotherapy to pembrolizumab.

Table 61: Participants With Drug-Related Adverse Events by Decreasing Incidence (Incidence ≥ 5% in One or More Treatment Groups) (APaT Population)

	KN671 Pembrolizumab + Chemotherapy/ Pembrolizumab		KN671 Placebo + Chemotherapy/Placebo		Pooled Safety Dataset for Pembrolizumab + Chemotherapy[a]		Pembrolizumab Monotherapy Reference Safety Dataset[b]	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	396		399		3,123		7,631	
with one or more adverse events	383	(96.7)	379	(95.0)	3,020	(96.7)	5,462	(71.6)
with no adverse events	13	(3.3)	20	(5.0)	103	(3.3)	2,169	(28.4)
Nausea	215	(54.3)	204	(51.1)	1,513	(48.4)	675	(8.8)
Neutrophil count decreased	167	(42.2)	167	(41.9)	603	(19.3)	34	(0.4)
Anaemia	143	(36.1)	135	(33.8)	1,465	(46.9)	234	(3.1)
White blood cell count decreased	111	(28.0)	98	(24.6)	442	(14.2)	34	(0.4)
Fatigue	108	(27.3)	94	(23.6)	1,039	(33.3)	1,476	(19.3)
Constipation	106	(26.8)	100	(25.1)	509	(16.3)	184	(2.4)
Decreased appetite	91	(23.0)	88	(22.1)	661	(21.2)	525	(6.9)
Vomiting	75	(18.9)	58	(14.5)	693	(22.2)	248	(3.2)
Platelet count decreased	74	(18.7)	74	(18.5)	363	(11.6)	43	(0.6)
Blood creatinine increased	56	(14.1)	48	(12.0)	211	(6.8)	105	(1.4)
Diarrhoea	52	(13.1)	56	(14.0)	745	(23.9)	904	(11.8)
Alanine aminotransferase increased	51	(12.9)	31	(7.8)	454	(14.5)	336	(4.4)
Asthenia	45	(11.4)	55	(13.8)	522	(16.7)	491	(6.4)
Rash	45	(11.4)	26	(6.5)	496	(15.9)	884	(11.6)
Alopecia	40	(10.1)	40	(10.0)	1,072	(34.3)	57	(0.7)
Hypothyroidism	38	(9.6)	6	(1.5)	377	(12.1)	810	(10.6)
Pruritus	38	(9.6)	25	(6.3)	347	(11.1)	1,143	(15.0)
Aspartate aminotransferase increased	37	(9.3)	25	(6.3)	386	(12.4)	312	(4.1)
Hypomagnesaemia	35	(8.8)	22	(5.5)	141	(4.5)	37	(0.5)
Stomatitis	35	(8.8)	27	(6.8)	408	(13.1)	103	(1.3)
Dysgeusia	30	(7.6)	36	(9.0)	294	(9.4)	79	(1.0)
Malaise	29	(7.3)	27	(6.8)	130	(4.2)	55	(0.7)
Dizziness	24	(6.1)	22	(5.5)	130	(4.2)	120	(1.6)
Hyponatraemia	24	(6.1)	17	(4.3)	106	(3.4)	63	(0.8)
Tinnitus	24	(6.1)	23	(5.8)	74	(2.4)	7	(0.1)
Hiccups	22	(5.6)	29	(7.3)	73	(2.3)	10	(0.1)
Lymphocyte count decreased	20	(5.1)	19	(4.8)	112	(3.6)	64	(0.8)
Hypokalaemia	17	(4.3)	20	(5.0)	129	(4.1)	43	(0.6)
Headache	15	(3.8)	10	(2.5)	190	(6.1)	250	(3.3)
Pyrexia	13	(3.3)	12	(3.0)	291	(9.3)	314	(4.1)
Weight decreased	13	(3.3)	8	(2.0)	189	(6.1)	148	(1.9)
Neuropathy peripheral	12	(3.0)	13	(3.3)	409	(13.1)	54	(0.7)
Arthralgia	11	(2.8)	9	(2.3)	314	(10.1)	661	(8.7)
Myalgia	8	(2.0)	4	(1.0)	272	(8.7)	312	(4.1)
Peripheral sensory neuropathy	8	(2.0)	8	(2.0)	371	(11.9)	35	(0.5)
Epistaxis	5	(1.3)	4	(1.0)	155	(5.0)	6	(0.1)
Febrile neutropenia	3	(0.8)	2	(0.5)	250	(8.0)	0	(0.0)
Neutropenia	2	(0.5)	1	(0.3)	1,076	(34.5)	49	(0.6)
Thrombocytopenia	1	(0.3)	1	(0.3)	535	(17.1)	56	(0.7)
Leukopenia	0	(0.0)	1	(0.3)	345	(11.0)	32	(0.4)
Mucosal inflammation	0	(0.0)	1	(0.3)	330	(10.6)	57	(0.7)

All Grade 3 to 5 Adverse Events

The overall incidence of participants with Grade 3 to 5 AEs was smaller in the pembrolizumab arm compared with the Pooled Pembrolizumab Combination Dataset (64.6% vs 79.4%) [Table 65]. The higher proportions of participants with low neutrophil and platelet counts in the pembrolizumab arm are offset by higher incidences of drug-related neutropenia and thrombocytopenia in the Pooled Pembrolizumab Combination Dataset.

Exposure-adjusted rates of overall Grade 3 to 5 AEs were generally consistent in the pembrolizumab arm compared with Pooled Pembrolizumab Combination Dataset.

The incidence of Grade 3 to 5 AEs was 64.6% in the pembrolizumab arm and 46.0% in the RSD. The incidence of participants with Grade 3 to 5 AEs (>5% incidence) was generally similar except for chemotherapy-related AEs (neutrophil count decreased, anaemia, white blood cell count decreased, and platelet count decreased) that were more common in the pembrolizumab arm [Table 65]. After adjusting for exposure, overall rates were similar. Rates for most exposure-adjusted Grade 3 to 5 AEs were similar in the 2 groups with the exception of chemotherapy-related AEs (e.g. neutrophil count decreased, anaemia, and white blood cell count decreased) that were more common in the pembrolizumab arm.

Table 62: Participants with grade 3-5 adverse events by decreasing incidence (incidence ⩾ 5% in one or more treatment groups) (APaT Population)

	KN671 Pembrolizumab + Chemotherapy/ Pembrolizumab		KN671 Placebo + Chemotherapy/Placebo		Pooled Safety Dataset for Pembrolizumab + Chemotherapy[i]		Pembrolizumab Monotherapy Reference Safety Dataset[j]	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	396		399		3,123		7,631	
with one or more adverse events	256	(64.6)	212	(53.1)	2,479	(79.4)	3,514	(46.0)
with no adverse events	140	(35.4)	187	(46.9)	644	(20.6)	4,117	(54.0)
Neutrophil count decreased	85	(21.5)	78	(19.5)	443	(14.2)	10	(0.1)
Anaemia	39	(9.8)	27	(6.8)	620	(19.9)	275	(3.6)
White blood cell count decreased	22	(5.6)	22	(5.5)	218	(7.0)	5	(0.1)
Platelet count decreased	20	(5.1)	24	(6.0)	114	(3.7)	10	(0.1)
Fatigue	7	(1.8)	4	(1.0)	158	(5.1)	166	(2.2)
Febrile neutropenia	3	(0.8)	2	(0.5)	259	(8.3)	11	(0.1)
Neutropenia	1	(0.3)	1	(0.3)	722	(23.1)	21	(0.3)
Thrombocytopenia	1	(0.3)	1	(0.3)	201	(6.4)	23	(0.3)

Grade 3 to 5 Drug-related Adverse Events

Table 63: Participants With Grade 3-5 Drug-related Adverse Events by Decreasing Incidence (Incidence ≥ 5% in One or More Treatment Groups) (APaT Population)

	KN671 Pembrolizumab + Chemotherapy/ Pembrolizumab		KN671 Placebo + Chemotherapy/Placebo		Pooled Safety Dataset for Pembrolizumab + Chemotherapy[i]		Pembrolizumab Monotherapy Reference Safety Dataset[j]	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	396		399		3,123		7,631	
with one or more adverse events	178	(44.9)	149	(37.3)	2,099	(67.2)	1,208	(15.8)
with no adverse events	218	(55.1)	250	(62.7)	1,024	(32.8)	6,423	(84.2)
Neutrophil count decreased	82	(20.7)	78	(19.5)	428	(13.7)	6	(0.1)
Anaemia	29	(7.3)	22	(5.5)	524	(16.8)	33	(0.4)
White blood cell count decreased	21	(5.3)	22	(5.5)	211	(6.8)	2	(0.0)
Platelet count decreased	20	(5.1)	24	(6.0)	110	(3.5)	2	(0.0)
Febrile neutropenia	3	(0.8)	2	(0.5)	245	(7.8)	0	(0.0)
Neutropenia	1	(0.3)	1	(0.3)	710	(22.7)	13	(0.2)
Thrombocytopenia	1	(0.3)	1	(0.3)	185	(5.9)	11	(0.1)

Adverse Events of Special Interest

No new immune-related AEs causally associated with pembrolizumab were identified in the pembrolizumab arm when pembrolizumab was administered concurrently with neoadjuvant chemotherapy and followed by adjuvant pembrolizumab monotherapy. The frequency, severity, and types of AEOSIs observed in the pembrolizumab arm were generally consistent with the established safety profile of pembrolizumab.

The overall AEOSI profiles were similar between the pembrolizumab arm (25.3%) and the Pooled Pembrolizumab Combination Dataset (33.7%).

Table 64: Adverse Event Summary for AEOSI (APaT Population)

	KN671 Pembrolizumab + Chemotherapy/ Pembrolizumab		KN671 Placebo + Chemotherapy/Placebo		Pooled Safety Dataset for Pembrolizumab + Chemotherapy[i]		Pembrolizumab Monotherapy Reference Safety Dataset[j]	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	396		399		3,123		7,631	
with one or more adverse events	100	(25.3)	42	(10.5)	1,052	(33.7)	2,042	(26.8)
with no adverse event	296	(74.7)	357	(89.5)	2,071	(66.3)	5,589	(73.2)
with drug-related[a] adverse events	82	(20.7)	25	(6.3)	943	(30.2)	1,790	(23.5)
with toxicity grade 3-5 adverse events	23	(5.8)	6	(1.5)	326	(10.4)	523	(6.9)
with toxicity grade 3-5 drug-related adverse events	21	(5.3)	3	(0.8)	297	(9.5)	462	(6.1)
with serious adverse events	21	(5.3)	6	(1.5)	251	(8.0)	502	(6.6)
with serious drug-related adverse events	19	(4.8)	4	(1.0)	230	(7.4)	449	(5.9)
who died	1	(0.3)	0	(0.0)	9	(0.3)	13	(0.2)
who died due to a drug-related adverse event	1	(0.3)	0	(0.0)	9	(0.3)	13	(0.2)
discontinued any drug due to an adverse event	22	(5.6)	3	(0.8)	228	(7.3)	354	(4.6)
discontinued pembrolizumab or placebo	20	(5.1)	3	(0.8)	176	(5.6)	354	(4.6)
discontinued any chemotherapy	4	(1.0)	0	(0.0)	120	(3.8)	NA	
discontinued any drug due to a drug-related adverse event	20	(5.1)	3	(0.8)	224	(7.2)	349	(4.6)
discontinued pembrolizumab or placebo	19	(4.8)	3	(0.8)	172	(5.5)	349	(4.6)
discontinued any chemotherapy	3	(0.8)	0	(0.0)	118	(3.8)	NA	
discontinued any drug due to a serious adverse event	16	(4.0)	3	(0.8)	144	(4.6)	226	(3.0)
discontinued pembrolizumab or placebo	14	(3.5)	3	(0.8)	132	(4.2)	226	(3.0)
discontinued any chemotherapy	4	(1.0)	0	(0.0)	67	(2.1)	NA	
discontinued any drug due to a serious drug-related adverse event	14	(3.5)	3	(0.8)	141	(4.5)	224	(2.9)
discontinued pembrolizumab or placebo	13	(3.3)	3	(0.8)	129	(4.1)	224	(2.9)
discontinued any chemotherapy	3	(0.8)	0	(0.0)	65	(2.1)	NA	

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

For KN671, non-serious adverse events up to 30 days of last treatment and serious adverse events up to 90 days of last treatment are included, where treatment includes study medications, in-study surgery and in-study radiotherapy. 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.

Grades are based on NCI CTCAE version 4.03.

[i] Includes all participants who received at least one dose of pembrolizumab in KN21 cohort A/C/G, KN189, KN407, KN048, KN590, KN355, KN826, KN522.

[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, KN024, KN013 cohort 3, KN087, KN204, KN045, KN052, KN164 - cohort A + B, KN177, KN012 cohort B and B2, KN040, KN042, KN048, KN054, KN055, KN716, KN564, KN158 (Cohort K).

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

Database cutoff date for Lung (KN671: 29JUL2022, KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEP2018, KN21 cohort A/C/G: 19AUG2019, KN407: 09MAY2019, KN189: 20MAY2019)

Database cutoff date for Hodgkin Lymphoma (KN013-cohort 3: 28SEP2018, KN087: 15MAR2021, KN204: 16JAN2020)

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

Database cutoff date for MSI-H CRC: (KN177: 19FEB2021)

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

Database cutoff date for RCC (KN564: 14JUN2021)

Database cutoff date for MSI-H tumors (KN164-cohort A + B: 09SEP2019, KN158 Cohort K: 05OCT2020)

Database cutoff date for Esophageal cancer (KN590: 02JUl2020)

Database cutoff date for Cervical (KN826: 03MAY2021)

Database cutoff date for TNBC (KN355: 11DEC2019, KN522: 23MAR2021)

Table 65: Participants With Adverse Events of Special Interest by AEOSI Category (Incidence > 0% in One or More Treatment Groups) (APaT Population)

	KN671 Pembrolizumab + Chemotherapy/ Pembrolizumab		KN671 Placebo + Chemotherapy/Placebo		Pooled Safety Dataset for Pembrolizumab + Chemotherapy[i]		Pembrolizumab Monotherapy Reference Safety Dataset[j]	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	396		399		3,123		7,631	
with one or more adverse events	100	(25.3)	42	(10.5)	1,052	(33.7)	2,042	(26.8)
with no adverse events	296	(74.7)	357	(89.5)	2,071	(66.3)	5,589	(73.2)
Adrenal Insufficiency	**1**	**(0.3)**	**0**	**(0.0)**	**40**	**(1.3)**	**74**	**(1.0)**
Cholangitis Sclerosing	**0**	**(0.0)**	**0**	**(0.0)**	**2**	**(0.1)**	**0**	**(0.0)**
Colitis	**5**	**(1.3)**	**0**	**(0.0)**	**84**	**(2.7)**	**159**	**(2.1)**
Encephalitis	**0**	**(0.0)**	**0**	**(0.0)**	**5**	**(0.2)**	**5**	**(0.1)**
Guillain-Barre Syndrome	**0**	**(0.0)**	**1**	**(0.3)**	**2**	**(0.1)**	**6**	**(0.1)**
Hepatitis	**3**	**(0.8)**	**2**	**(0.5)**	**40**	**(1.3)**	**80**	**(1.0)**
Hyperthyroidism	**22**	**(5.6)**	**13**	**(3.3)**	**173**	**(5.5)**	**398**	**(5.2)**
Hypoparathyroidism	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(0.0)**	**1**	**(0.0)**
Hypophysitis	**2**	**(0.5)**	**0**	**(0.0)**	**28**	**(0.9)**	**52**	**(0.7)**
Hypothyroidism	**44**	**(11.1)**	**7**	**(1.8)**	**434**	**(13.9)**	**939**	**(12.3)**
Infusion Reactions	**5**	**(1.3)**	**6**	**(1.5)**	**246**	**(7.9)**	**165**	**(2.2)**
Myasthenic Syndrome	**1**	**(0.3)**	**0**	**(0.0)**	**1**	**(0.0)**	**8**	**(0.1)**
Myelitis	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**3**	**(0.0)**
Myocarditis	**1**	**(0.3)**	**0**	**(0.0)**	**8**	**(0.3)**	**9**	**(0.1)**
Myositis	**1**	**(0.3)**	**0**	**(0.0)**	**13**	**(0.4)**	**34**	**(0.4)**
Nephritis	**0**	**(0.0)**	**0**	**(0.0)**	**25**	**(0.8)**	**37**	**(0.5)**
Pancreatitis	**0**	**(0.0)**	**2**	**(0.5)**	**15**	**(0.5)**	**28**	**(0.4)**
Pneumonitis	**22**	**(5.6)**	**7**	**(1.8)**	**124**	**(4.0)**	**324**	**(4.2)**
Sarcoidosis	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(0.0)**	**20**	**(0.3)**
Severe Skin Reactions	**9**	**(2.3)**	**0**	**(0.0)**	**96**	**(3.1)**	**130**	**(1.7)**
Thyroiditis	**4**	**(1.0)**	**1**	**(0.3)**	**41**	**(1.3)**	**74**	**(1.0)**
Type 1 Diabetes Mellitus	**0**	**(0.0)**	**0**	**(0.0)**	**11**	**(0.4)**	**34**	**(0.4)**
Uveitis	**0**	**(0.0)**	**1**	**(0.3)**	**3**	**(0.1)**	**25**	**(0.3)**
Vasculitis	**0**	**(0.0)**	**2**	**(0.5)**	**23**	**(0.7)**	**5**	**(0.1)**

Adverse drug reactions

Section 4.8 of the SmPC was updated with safety information based on the most recent safety dataset for pembrolizumab in combination with chemotherapy, which includes KEYNOTE-671.

Table 69 encompasses the adverse reactions included in Table 2 of the SmPC with related frequency categories and incidence percentages from the latest pooled dataset from combination therapy (pembrolizumab plus chemotherapy) studies as follows:

• Non small cell lung cancer: KEYNOTE-021 (Cohorts A, C, and G), KEYNOTE-189 KEYNOTE-407, and KEYNOTE-671

• Head and neck squamous cell carcinoma: KEYNOTE-048

• Gastric, oesophageal or gastroesophageal cancer: KEYNOTE-590, KEYNOTE-811 and KEYNOTE-859

• Biliary Tract Cancer: KEYNOTE-966

• Triple negative breast cancer: KEYNOTE-355 and KEYNOTE-522

• Cervical cancer: KEYNOTE-826

Table 66: Adverse reactions in patients treated with pembrolizumab in combination with chemotherapy

		Combination Therapy (N=5183)	
		All AEs % (n)	Gr 3-5 AEs n
Infections and infestations			
Common	Pneumonia	7.4% (385)	215
Blood and lymphatic system disorders			
Very common	Anaemia	51.7% (2682)	950
Very common	Neutropenia	25.5% (1320)	809
Very common	Thrombocytopenia	13.7% (709)	228
Common	Febrile Neutropenia	5.6% (288)	278
Common	Leukopenia	8.7% (452)	163
Common	Lymphopenia	2.8% (145)	44
Uncommon	Eosinophilia	0.7% (34)	3
Rare	Haemolytic Anaemia	0.06% (3)	2
Rare	Immune Thrombocytopenia	0.06% (3)	2
Immune system disorders			
Common	Infusion Reactions[a]	6.9% (359)	64
Rare	Sarcoidosis	0.02% (1)	0
Endocrine disorders			
Very common	Hypothyroidism[b]	13.1% (680)	16
Common	Adrenal Insufficiency[c]	1.1% (58)	25
Common	Thyroiditis[d]	1.2% (61)	6
Common	Hyperthyroidism	5.2% (268)	5
Uncommon	Hypophysitis[e]	0.8% (40)	21
Rare	Hypoparathyroidism	0.04% (2)	0
Metabolism and nutrition disorders			
Very common	Hypokalaemia	11.3% (585)	183
Very common	Decreased Appetite	28.0% (1450)	115
Common	Hyponatraemia	7.9% (410)	172
Common	Hypocalcaemia	4.4% (227)	34
Uncommon	Type 1 Diabetes Mellitus[f]	0.3% (17)	16

		Combination Therapy (N=5183)	
		All AEs % (n)	Gr 3-5 AEs n
Psychiatric disorders			
Very common	Insomnia	10.7% (556)	6
Nervous system disorders			
Very common	Neuropathy Peripheral	13.9% (722)	53
Very common	Headache	13.8% (715)	15
Common	Dizziness	9.99% (518)	14
Common	Dysgeusia	8.8% (455)	3
Common	Lethargy	1.2% (60)	2
Uncommon	Encephalitis[g]	0.1% (7)	7
Uncommon	Epilepsy	0.1% (7)	3
Rare	Myasthenic Syndrome[h]	0.08% (4)	4
Rare	Guillain-Barre Syndrome[i]	0.04% (2)	2
Rare	Optic Neuritis	0.02% (1)	1
Eye disorders			
Common	Dry Eye	3.1% (161)	1
Rare	Uveitis[j]	0.096% (5)	0
Cardiac disorders			
Common	Cardiac Arrhythmia (Including Atrial Fibrillation)[k]	4.0% (206)	52
Uncommon	Myocarditis[l]	0.2% (10)	8
Uncommon	Pericardial Effusion	0.4% (22)	7
Uncommon	Pericarditis	0.1% (7)	2
Vascular disorders			
Common	Hypertension	6.4% (330)	142
Uncommon	Vasculitis[m]	0.6% (31)	4
Respiratory, thoracic and mediastinal disorders			
Very common	Dyspnoea	11.7% (608)	68
Very common	Cough	16.1% (836)	5

		Combination Therapy (N=5183)	
		All AEs % (n)	Gr 3-5 AEs n
Common	Pneumonitis[n]	4.2% (220)	81
Gastrointestinal disorders			
Very common	Diarrhoea	33.1% (1716)	206
Very common	Vomiting	28.3% (1467)	177
Very common	Nausea	51.9% (2689)	171
Very common	Abdominal Pain[o]	18.8% (975)	67
Very common	Constipation	32.4% (1677)	20
Common	Colitis[p]	2.7% (141)	71
Common	Gastritis[q]	2.0% (106)	8
Common	Dry Mouth	4.5% (233)	1
Uncommon	Pancreatitis[r]	0.4% (22)	17
Uncommon	Gastrointestinal Ulceration[s]	0.4% (23)	3
Rare	Small Intestinal Perforation	0.04% (2)	2
Hepatobiliary disorders			
Common	Hepatitis[t]	1.2% (64)	47
Rare	Cholangitis Sclerosing[u]	0.04% (2)	2
Skin and subcutaneous tissue disorders			
Very common	Alopecia	23.7% (1226)	6
Very common	Pruritus[v]	14.2% (737)	5
Very common	Rash[w]	21.2% (1098)	4
Common	Severe Skin Reactions[x]	2.6% (133)	114
Common	Erythema	3.6% (187)	3
Common	Dermatitis	1.5% (77)	3
Common	Dry Skin	5.3% (274)	2
Common	Dermatitis Acneiform	2.1% (109)	2
Common	Eczema	1.3% (65)	1
Uncommon	Psoriasis	0.6% (29)	4
Uncommon	Vitiligo[y]	0.5% (28)	0
Uncommon	Papule	0.2% (10)	0
Rare	Stevens-Johnson Syndrome	0.04% (2)	2
Rare	Lichenoid Keratosis[z]	0.096% (5)	1

		Combination Therapy (N=5183)	
		All AEs % (n)	Gr 3-5 AEs n
Rare	Erythema Nodosum	0.08% (4)	0
Rare	Hair Colour Changes	0.02% (1)	0
Musculoskeletal and connective tissue disorders			
Very common	Musculoskeletal Pain[aa]	13.9% (722)	37
Very common	Arthralgia	15.3% (791)	32
Common	Myositis[bb]	8.7% (450)	21
Common	Pain In Extremity	7.0% (362)	10
Common	Arthritis[cc]	1.6% (81)	8
Uncommon	Tenosynovitis[dd]	0.4% (19)	1
Rare	Sjogren's Syndrome	0.02% (1)	0
Renal and urinary disorders			
Common	Acute Kidney Injury	3.4% (178)	88
Uncommon	Nephritis[ee]	0.7% (35)	19
Uncommon	Cystitis Noninfective	0.2% (8)	0
General disorders and administration site conditions			
Very common	Fatigue	34.5% (1787)	246
Very common	Asthenia	18.7% (970)	160
Very common	Pyrexia	18.5% (961)	42
Common	Oedema[ff]	4.5% (232)	9
Common	Influenza Like Illness	2.6% (137)	2
Common	Chills	2.9% (152)	0
Investigations			
Very common	Alanine Aminotransferase Increased	17.5% (905)	163
Very common	Aspartate Aminotransferase Increased	17.2% (894)	134
Common	Blood Bilirubin Increased	5.3% (273)	49
Common	Blood Alkaline Phosphatase Increased	6.4% (331)	40
Common	Blood Creatinine Increased	9.7% (504)	29
Common	Hypercalcaemia	1.7% (87)	20

		Combination Therapy (N=5183)	
		All AEs % (n)	Gr 3-5 AEs n
Uncommon	Amylase Increased	0.6% (31)	9

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

a. Infusion Reactions (Anaphylactic Reaction, Cytokine Release Syndrome, Drug Hypersensitivity, Hypersensitivity, Infusion Related Hypersensitivity Reaction, Infusion Related Reaction, Serum Sickness)

b. Hypothyroidism (Hypothyroidism, Immune-Mediated Hypothyroidism)

c. Adrenal Insufficiency (Addison's Disease, Adrenal Insufficiency)

d. Thyroiditis (Autoimmune Thyroiditis, Silent Thyroiditis, Thyroid Disorder, Thyroiditis, Thyroiditis Acute)

e. Hypophysitis (Hypophysitis, Hypopituitarism)

f. Type 1 Diabetes Mellitus (Diabetic Ketoacidosis, Type 1 Diabetes Mellitus)

g. Encephalitis (Encephalitis, Encephalitis Autoimmune)

h. Myasthenic Syndrome (Myasthenia Gravis, Myasthenic Syndrome)

i. Guillain-Barre Syndrome (Demyelinating Polyneuropathy, Guillain-Barre Syndrome)

j. Uveitis (Iridocyclitis, Uveitis)

k. Cardiac Arrhythmia (Including Atrial Fibrillation) (Arrhythmia, Atrial Fibrillation, Atrial Flutter, Atrial Tachycardia, Atrioventricular Block, Atrioventricular Block First Degree, Atrioventricular Block Second Degree, Bundle Branch Block, Cardiac Flutter, Electrocardiogram Qt Prolonged, Electrocardiogram Repolarisation Abnormality, Extrasystoles, Heart Rate Irregular, Sinus Arrhythmia, Sinus Bradycardia, Sinus Node Dysfunction, Sinus Tachycardia, Supraventricular Extrasystoles, Supraventricular Tachycardia, Ventricular Arrhythmia, Ventricular Extrasystoles, Ventricular Tachycardia)

l. Myocarditis (Autoimmune Myocarditis, Myocarditis)

m. Vasculitis (Central Nervous System Vasculitis, Vasculitis)

n. Pneumonitis (Autoimmune Lung Disease, Immune-Mediated Lung Disease, Interstitial Lung Disease, Organising Pneumonia, Pneumonitis)

o. Abdominal Pain (Abdominal Discomfort, Abdominal Pain, Abdominal Pain Lower, Abdominal Pain Upper)

p. Colitis (Autoimmune Colitis, Colitis, Colitis Microscopic, Enterocolitis, Immune-Mediated Enterocolitis)

q. Gastritis (Gastritis, Gastritis Erosive)

r. Pancreatitis (Pancreatitis, Pancreatitis Acute)

s. Gastrointestinal Ulceration (Duodenal Ulcer, Gastric Ulcer)

t. Hepatitis (Autoimmune Hepatitis, Drug-Induced Liver Injury, Hepatitis, Immune-Mediated Hepatitis)

u. Cholangitis Sclerosing (Cholangitis Sclerosing, Immune-Mediated Cholangitis)

v. Pruritus (Pruritus, Pruritus Genital, Urticaria)

w. Rash (Genital Rash, Rash, Rash Erythematous, Rash Macular, Rash Maculo-Papular, Rash Papular, Rash Pruritic, Rash Vesicular)

x. Severe Skin Reactions (Cutaneous Vasculitis, Dermatitis Bullous, Dermatitis Exfoliative, Dermatitis Exfoliative Generalised, Erythema Multiforme, Pemphigoid, Pruritus, Rash, Rash Erythematous, Rash Maculo-Papular, Rash Pruritic, Rash Pustular, Stevens-Johnson Syndrome, Toxic Skin Eruption)

y. Vitiligo (Skin Depigmentation, Skin Hypopigmentation, Vitiligo)

z. Lichenoid Keratosis (Lichen Planus, Lichenoid Keratosis)

aa. Musculoskeletal Pain (Back Pain, Musculoskeletal Chest Pain, Musculoskeletal Discomfort, Musculoskeletal Pain, Musculoskeletal Stiffness, Torticollis)

bb. Myositis (Myalgia, Myopathy, Myositis, Polymyalgia Rheumatica, Rhabdomyolysis)

cc. Arthritis (Arthritis, Immune-Mediated Arthritis, Joint Effusion, Joint Swelling, Polyarthritis)

dd. Tenosynovitis (Synovitis, Tendon Pain, Tendonitis, Tenosynovitis)

ee. Nephritis (Autoimmune Nephritis, Immune-Mediated Nephritis, Nephritis, Tubulointerstitial Nephritis)

ff. Oedema (Eyelid Oedema, Face Oedema, Fluid Retention, Generalised Oedema, Lip Oedema, Localised Oedema, Oedema, Periorbital Oedema)

Includes all participants who received at least one dose of pembrolizumab combo therapy in KN021-A/C/G, KN048, KN189, KN355, KN407, KN522, KN590, KN811, KN826, KN859, KN966 and KN671.

Database cutoff date for NSCLC (KN671: 10JUL2023)

The list of studies and database cutoff dates for the aggregate safety dataset within this table are provided in the appendix of the memorandum in support of SmPC section 4.8.

Serious adverse event/deaths/other significant events

All serious adverse events

The overall incidence of participants with SAEs was generally similar in the pembrolizumab arm (40.4%) compared with the Pooled Pembrolizumab Combination Dataset (46.6%) with the most frequently reported SAEs in the pembrolizumab arm being pneumonia (5.3%), pulmonary embolism (2.3%), anemia (2.0%), and pyrexia (2.0%).

The most frequently reported SAEs in the pembrolizumab arm were generally consistent with the established profile of pembrolizumab monotherapy and the known safety profile of the individual chemotherapy components.

After adjusting for exposure, rates of SAEs by both SOC and PT were similar in the pembrolizumab and Pooled Pembrolizumab Combination Dataset.

The overall incidence of participants with SAEs was similar in the pembrolizumab arm and the placebo arm during the neoadjuvant/surgery phase (33.6% vs 29.1%) and the adjuvant phase (14.1% vs 8.6%). The SAEs observed for participants treated with pembrolizumab in the adjuvant phase were generally consistent with the known safety profile of pembrolizumab monotherapy, and no trend suggested any new safety concerns for pembrolizumab monotherapy.

Drug-related Serious Adverse Events

Table 67: Participants with drug-related serious adverse events by decreasing incidence (APaT Population)

	KN671 Pembrolizumab + Chemotherapy/ Pembrolizumab		KN671 Placebo + Chemotherapy/Placebo		Pooled Safety Dataset for Pembrolizumab + Chemotherapy[i]		Pembrolizumab Monotherapy Reference Safety Dataset[j]	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	396		399		3,123		7,631	
with one or more adverse events	70	(17.7)	57	(14.3)	910	(29.1)	840	(11.0)
with no adverse events	326	(82.3)	342	(85.7)	2,213	(70.9)	6,791	(89.0)
Anaemia	6	(1.5)	3	(0.8)	68	(2.2)	6	(0.1)
Aspartate aminotransferase increased	6	(1.5)	1	(0.3)	11	(0.4)	13	(0.2)
Neutrophil count decreased	6	(1.5)	1	(0.3)	11	(0.4)	0	(0.0)
Pneumonia	5	(1.3)	7	(1.8)	38	(1.2)	19	(0.2)
Alanine aminotransferase increased	4	(1.0)	1	(0.3)	11	(0.4)	12	(0.2)
Immune-mediated lung disease	4	(1.0)	1	(0.3)	0	(0.0)	3	(0.0)
Nausea	4	(1.0)	4	(1.0)	26	(0.8)	7	(0.1)
Pneumonitis	4	(1.0)	1	(0.3)	49	(1.6)	129	(1.7)
Acute kidney injury	3	(0.8)	3	(0.8)	36	(1.2)	19	(0.2)
Diarrhoea	3	(0.8)	3	(0.8)	34	(1.1)	44	(0.6)
Febrile neutropenia	3	(0.8)	0	(0.0)	208	(6.7)	0	(0.0)
Platelet count decreased	3	(0.8)	10	(2.5)	18	(0.6)	0	(0.0)
Pyrexia	3	(0.8)	0	(0.0)	39	(1.2)	22	(0.3)
Vomiting	3	(0.8)	1	(0.3)	30	(1.0)	9	(0.1)
Neutropenia	0	(0.0)	1	(0.3)	46	(1.5)	1	(0.0)
Thrombocytopenia	0	(0.0)	0	(0.0)	41	(1.3)	6	(0.1)

Deaths due to Adverse Events

No new safety signals for pembrolizumab were identified upon review of the fatal events in the pembrolizumab arm of the KEYNOTE-671 study.

Table 68: Participants with drug-related adverse events resulting in death by decreasing incidence (incidence > 0% in one or more treatment groups) (APaT Population)

	KN671 Pembrolizumab + Chemotherapy/ Pembrolizumab		KN671 Placebo + Chemotherapy/Placebo		Pooled Safety Dataset for Pembrolizumab + Chemotherapy[i]		Pembrolizumab Monotherapy Reference Safety Dataset[j]	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	396		399		3,123		7,631	
with one or more adverse events	4	(1.0)	3	(0.8)	49	(1.6)	42	(0.6)
with no adverse events	392	(99.0)	396	(99.2)	3,074	(98.4)	7,589	(99.4)
Atrial fibrillation	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Immune-mediated lung disease	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Pneumonia	1	(0.3)	1	(0.3)	3	(0.1)	4	(0.1)
Sudden cardiac death	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Acute coronary syndrome	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0)
Acute kidney injury	0	(0.0)	0	(0.0)	4	(0.1)	0	(0.0)
Autoinflammatory disease	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Bronchitis	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)
Cardiac arrest	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)
Cardiac failure	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)
Cardiac failure acute	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Cardio-respiratory arrest	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Cerebral ischaemia	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)
Death	0	(0.0)	0	(0.0)	3	(0.1)	3	(0.0)
Diarrhoea	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)
Disseminated intravascular coagulation	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Encephalitis autoimmune	0	(0.0)	0	(0.0)	2	(0.1)	0	(0.0)
Encephalopathy	0	(0.0)	0	(0.0)	1	(0.0)	1	(0.0)
Febrile neutropenia	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)
General physical health deterioration	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Guillain-Barre syndrome	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Haemorrhage	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)
Hepatic failure	0	(0.0)	0	(0.0)	2	(0.1)	0	(0.0)
Ileus paralytic	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Interstitial lung disease	0	(0.0)	0	(0.0)	2	(0.1)	1	(0.0)
Intestinal perforation	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)
Large intestine perforation	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Malignant neoplasm progression	0	(0.0)	0	(0.0)	0	(0.0)	4	(0.1)
Multiple organ dysfunction syndrome	0	(0.0)	0	(0.0)	2	(0.1)	0	(0.0)
Myocardial infarction	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Myocarditis	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Myositis	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Necrotising fasciitis	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)
Neutropenic sepsis	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)
Pneumonia klebsiella	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Pneumonitis	0	(0.0)	0	(0.0)	5	(0.2)	8	(0.1)
Pulmonary embolism	0	(0.0)	0	(0.0)	2	(0.1)	1	(0.0)
Pulmonary haemorrhage	0	(0.0)	1	(0.3)	1	(0.0)	0	(0.0)
Pulmonary sepsis	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)
Respiratory failure	0	(0.0)	0	(0.0)	1	(0.0)	2	(0.0)
Sepsis	0	(0.0)	0	(0.0)	5	(0.2)	1	(0.0)
Septic shock	0	(0.0)	0	(0.0)	5	(0.2)	0	(0.0)
Stevens-Johnson syndrome	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Sudden death	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Superior vena cava syndrome	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Tumour haemorrhage	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)
Urinary tract obstruction	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)

Post-Operative All-Cause Mortality

Within 30 days after in-study surgery the following number of participants died:

- In the pembrolizumab arm (n=6, 1.8%): Pulmonary embolism (n=2), Pulmonary sepsis (n=1), Septic shock (n=1), Respiratory failure (n=1), and Pulmonary haemorrhage (n=1) due to arterial injury during the surgery.
- In the placebo arm (n=2, 0.6%): Pneumonia (n=1) and Respiratory failure (n=1).

The fatal AEs in both treatment arms, occurring within 30 days after surgery, were assessed by the investigator **as related to the study procedure (surgery)** and not related to the study drugs.

Within 31 to 90 days after in-study surgery the following number of participants died:

- In the pembrolizumab arm (n=7, 2.2%): 3 from malignant neoplasm progression, 4 from the AEs: cardiac arrest (n=1), pulmonary haemorrhage (n=1), immune-mediated lung disease (n=1), and death (also reported as unexplained death as participant family declined to provide any

additional details and no autopsy was performed) (n=1). In the pembrolizumab arm all events were assessed by the investigator as **not related to surgery**.

One death due to atrial fibrillation occurred in the pembrolizumab arm during the adjuvant phase, one week after the last dose of pembrolizumab was given, on Cycle 5 of the adjuvant treatment. As reported in the narrative the participant was diagnosed with atrial fibrillation approximately 2 months prior to randomization and then was diagnosed with worsening of atrial fibrillation (Grade 4, onset 3 days before death), caused by hypercalcemia. The MAH considered that the cause of death for this participant was likely multifactorial.

One of the 4 AEs in this arm (immune-mediated lung disease) was assessed as related to pembrolizumab.

Laboratory findings

No new safety findings based on laboratory abnormalities were reported in the pembrolizumab arm.

The most frequently reported laboratory abnormalities were generally similar in the pembrolizumab arm and the pooled pembrolizumab combination dataset, and the majority were CTCAE Grade 1 to 2 toxicity.

The most frequently reported Grade 3 or 4 laboratory abnormalities were similar in the pembrolizumab arm and the Pooled Pembrolizumab Combination Dataset.

The most frequently reported Grade 3 or 4 laboratory abnormalities were generally similar in the pembrolizumab arm and the RSD with the exception of leukocytes decreased (pembrolizumab, 10.5%; RSD, 0.8%) and neutrophils decreased (pembrolizumab, 27.4%; RSD, 1.9%) which were more frequent in the pembrolizumab arm.

In KEYNOTE-671, there were 5 participants (3 in pembrolizumab arm and 2 in placebo arm) who met the criteria of ALT or AST $\geq 3 \times$ ULN and bilirubin $\geq 2 \times$ ULN and ALP $< 2 \times$ ULN.

In the pembrolizumab arm, LFT abnormalities were either resolving or resolved in all 3 participants after study treatment discontinuation. Two participants treated with pembrolizumab had investigator reported adverse events of drug-induced liver injury, but were determined not to meet the Hy's law predetermined criteria for hepatocellular injury upon review by the MAH.

Safety in special populations

Age

The AE profile based on age in the pembrolizumab arm was generally consistent with the Pooled Pembrolizumab Combination Dataset.

The AE profile in the pembrolizumab arm was similar between participants who were <65 years, 65 to 74 years, and 75 to 84 years with the exception of Grade 3 to 5 AEs, drug-related Grade 3 to 5 AEs, SAEs, and discontinuations of any drug due to an AE which were more frequent in participants ≥65 years of age [Table 70]. A similar pattern was observed between the age groups in the Pooled Pembrolizumab Combination Dataset and the RSD.

A summary of AEs by age groups shows that the proportion of participants in the pembrolizumab arm who experienced central nervous system events, cerebrovascular events, and infections was generally comparable across age groups (<65, 65 to 74, and 75 to 84 years). AEs related to falling and cardiovascular events were more frequent in the 75- to 84-year age group. Due to the small number of participants in the 75 to 84-year age group, these results should be interpreted with caution.

Table 69: Adverse Event Summary by Age Category (< 65, 65-74, 75-84, >=85 Years)

	KN671 Pembrolizumab + Chemotherapy/ Pembrolizumab								KN671 Placebo + Chemotherapy/Placebo							
	<65		65-74		75-84		>=85		<65		65-74		75-84		>=85	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	221		152		23		0		214		151		34		0	
with one or more adverse events	219	(99.1)	152	(100.0)	23	(100.0)	0	(0.0)	211	(98.6)	148	(98.0)	34	(100.0)	0	(0.0)
with no adverse event	2	(0.9)	0	(0.0)	0	(0.0)	0	(0.0)	3	(1.4)	3	(2.0)	0	(0.0)	0	(0.0)
with drug-related[a] adverse events	211	(95.5)	149	(98.0)	23	(100.0)	0	(0.0)	204	(95.3)	143	(94.7)	32	(94.1)	0	(0.0)
with toxicity grade 3-5 adverse events	129	(58.4)	109	(71.7)	18	(78.3)	0	(0.0)	102	(47.7)	91	(60.3)	19	(55.9)	0	(0.0)
with toxicity grade 3-5 drug-related adverse events	88	(39.8)	78	(51.3)	12	(52.2)	0	(0.0)	68	(31.8)	66	(43.7)	15	(44.1)	0	(0.0)
with serious adverse events	74	(33.5)	72	(47.4)	14	(60.9)	0	(0.0)	63	(29.4)	58	(38.4)	9	(26.5)	0	(0.0)
with serious drug-related adverse events	39	(17.6)	28	(18.4)	3	(13.0)	0	(0.0)	27	(12.6)	28	(18.5)	2	(5.9)	0	(0.0)
who died	7	(3.2)	18	(11.8)	0	(0.0)	0	(0.0)	5	(2.3)	4	(2.6)	5	(14.7)	0	(0.0)
who died due to a drug-related adverse event	1	(0.5)	3	(2.0)	0	(0.0)	0	(0.0)	1	(0.5)	1	(0.7)	1	(2.9)	0	(0.0)
discontinued any drug due to an adverse event	46	(20.8)	48	(31.6)	7	(30.4)	0	(0.0)	27	(12.6)	31	(20.5)	11	(32.4)	0	(0.0)
discontinued pembrolizumab or placebo	39	(17.6)	38	(25.0)	6	(26.1)	0	(0.0)	18	(8.4)	12	(7.9)	6	(17.6)	0	(0.0)
discontinued any chemotherapy	16	(7.2)	26	(17.1)	2	(8.7)	0	(0.0)	18	(8.4)	25	(16.6)	NA		NA	
discontinued any drug due to a drug-related adverse event	38	(17.2)	32	(21.1)	4	(17.4)	0	(0.0)	22	(10.3)	26	(17.2)	5	(14.7)	0	(0.0)
discontinued pembrolizumab or placebo	31	(14.0)	21	(13.8)	3	(13.0)	0	(0.0)	13	(6.1)	7	(4.6)	2	(5.9)	0	(0.0)
discontinued any chemotherapy	14	(6.3)	16	(10.5)	2	(8.7)	0	(0.0)	16	(7.5)	24	(15.9)	NA		NA	
discontinued any drug due to a serious adverse event	27	(12.2)	30	(19.7)	2	(8.7)	0	(0.0)	10	(4.7)	15	(9.9)	6	(17.6)	0	(0.0)
discontinued pembrolizumab or placebo	26	(11.8)	27	(17.8)	2	(8.7)	0	(0.0)	8	(3.7)	10	(6.6)	5	(14.7)	0	(0.0)
discontinued any chemotherapy	7	(3.2)	12	(7.9)	0	(0.0)	0	(0.0)	5	(2.3)	11	(7.3)	NA		NA	
discontinued any drug due to a serious drug-related adverse event	21	(9.5)	14	(9.2)	0	(0.0)	0	(0.0)	7	(3.3)	11	(7.3)	1	(2.9)	0	(0.0)
discontinued pembrolizumab or placebo	20	(9.0)	13	(8.6)	0	(0.0)	0	(0.0)	5	(2.3)	6	(4.0)	1	(2.9)	0	(0.0)
discontinued any chemotherapy	5	(2.3)	4	(2.6)	0	(0.0)	0	(0.0)	5	(2.3)	10	(6.6)	NA		NA	
Participants in population	2,176		767		175		5		4,524		2,173		824		110	
with one or more adverse events	2,158	(99.2)	760	(99.1)	174	(99.4)	5	(100.0)	4,364	(96.5)	2,097	(96.5)	805	(97.7)	109	(99.1)
with no adverse event	18	(0.8)	7	(0.9)	1	(0.6)	0	(0.0)	160	(3.5)	76	(3.5)	19	(2.3)	1	(0.9)
with drug-related[a] adverse events	2,107	(96.8)	742	(96.7)	167	(95.4)	4	(80.0)	3,231	(71.4)	1,552	(71.4)	594	(72.1)	85	(77.3)
with toxicity grade 3-5 adverse events	1,721	(79.1)	608	(79.3)	145	(82.9)	5	(100.0)	1,917	(42.4)	1,071	(49.3)	457	(55.5)	69	(62.7)
with toxicity grade 3-5 drug-related adverse events	1,464	(67.3)	520	(67.8)	111	(63.4)	4	(80.0)	629	(13.9)	391	(18.0)	163	(19.8)	25	(22.7)
with serious adverse events	935	(43.0)	415	(54.1)	102	(58.3)	4	(80.0)	1,457	(32.2)	839	(38.6)	387	(47.0)	59	(53.6)
with serious drug-related adverse events	592	(27.2)	255	(33.2)	60	(34.3)	3	(60.0)	451	(10.0)	265	(12.2)	105	(12.7)	19	(17.3)
who died	72	(3.3)	54	(7.0)	30	(17.1)	4	(80.0)	158	(3.5)	113	(5.2)	63	(7.6)	12	(10.9)
who died due to a drug-related adverse event	20	(0.9)	18	(2.3)	8	(4.6)	3	(60.0)	21	(0.5)	13	(0.6)	7	(0.8)	1	(0.9)
discontinued any drug due to an adverse event	567	(26.1)	259	(33.8)	70	(40.0)	4	(80.0)	554	(12.2)	327	(15.0)	168	(20.4)	17	(15.5)
discontinued pembrolizumab or placebo	332	(15.3)	159	(20.7)	53	(30.3)	4	(80.0)	554	(12.2)	327	(15.0)	168	(20.4)	17	(15.5)
discontinued any chemotherapy	387	(17.8)	198	(25.8)	55	(31.4)	4	(80.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued any drug due to a drug-related adverse event	493	(22.7)	205	(26.7)	46	(26.3)	3	(60.0)	333	(7.4)	206	(9.5)	92	(11.2)	8	(7.3)
discontinued pembrolizumab or placebo	261	(12.0)	112	(14.6)	29	(16.6)	3	(60.0)	333	(7.4)	206	(9.5)	92	(11.2)	8	(7.3)
discontinued any chemotherapy	344	(15.8)	157	(20.5)	33	(18.9)	3	(60.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued any drug due to a serious adverse event	270	(12.4)	147	(19.2)	51	(29.1)	4	(80.0)	366	(8.1)	214	(9.8)	120	(14.6)	14	(12.7)
discontinued pembrolizumab or placebo	210	(9.7)	122	(15.9)	46	(26.3)	4	(80.0)	366	(8.1)	214	(9.8)	120	(14.6)	14	(12.7)
discontinued any chemotherapy	167	(7.7)	105	(13.7)	38	(21.7)	4	(80.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued any drug due to a serious drug-related adverse event	211	(9.7)	100	(13.0)	29	(16.6)	3	(60.0)	177	(3.9)	113	(5.2)	52	(6.3)	5	(4.5)
discontinued pembrolizumab or placebo	154	(7.1)	80	(10.4)	24	(13.7)	3	(60.0)	177	(3.9)	113	(5.2)	52	(6.3)	5	(4.5)
discontinued any chemotherapy	129	(5.9)	70	(9.1)	19	(10.9)	3	(60.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

Sex

The AE profile in the pembrolizumab arm was generally similar between participants who were male and female.

Race

The AE profile in the pembrolizumab arm was generally similar between participants who were White and of other races with the exception of Grade 3 to 5 drug-related AEs which were more common in "other" races. A similar pattern was observed between the participants in the Pooled Pembrolizumab Combination Dataset. The AE profile in the RSD was generally similar between participants who were White and of other races.

A higher incidence of Grade 3 to 5 AEs, drug-related Grade 3 to 5 AEs, and discontinuations due to any drug were observed in the pembrolizumab arm (both White and other races) compared with the RSD.

ECOG Status

The proportion of participants in the pembrolizumab arm with an ECOG status of 0 who experienced AEs was similar to the proportion of participants with an ECOG status of 1. Compared with the Pooled Pembrolizumab Combination Dataset, for ECOG status of 0, a lower incidence of Grade 3 to 5 AEs and drug-related Grade 3 to 5 AEs was observed in the pembrolizumab arm; for ECOG status of 1, a lower incidence of Grade 3 to 5 AEs, drug-related Grade 3 to 5 AEs, SAEs, and drug-related SAEs was observed in the pembrolizumab arm.

Extrinsic Factors

Region

The proportion of EU participants in the pembrolizumab arm who experienced AEs was similar to the proportion of ex-EU participants.

Safety related to drug-drug interactions and other interactions

No dedicated DDI studies have been performed.

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. No impact of coadministered chemotherapy on pembrolizumab PK was observed in KEYNOTE-021 Cohort G.

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.

Use in Pregnancy and Lactation

There were no reports of pregnancy in KEYNOTE-671.

Overdose

No overdoses were reported in KEYNOTE-671.

Drug Abuse

Potential for drug abuse or dependence is not expected for an anti-PD-1 mAb. No reports of drug abuse with pembrolizumab have occurred.

Withdrawal and Rebound

No withdrawal or rebound effects are expected with an anti-PD-1 mAb. None have been observed in pembrolizumab clinical studies to date.

Effects on Ability to Drive or Operate Machinery or Impairment of Mental Ability

Impairment of cognitive ability is not expected from an anti-PD-1 mAb. No additional studies have been conducted to determine the effect of pembrolizumab on the impairment of mental function or the ability to drive or operate machinery.

Discontinuation due to adverse events

The types of AEs and incidence of participants with AEs leading to discontinuation of study drug were generally consistent with the established profile of pembrolizumab monotherapy and the known safety profile of the individual chemotherapy components.

Discontinuation of Any Study Drug

A similar percentage of participants in the pembrolizumab arm (25.5%) and Pooled Pembrolizumab Combination Dataset (28.8%) experienced AEs leading to discontinuation of any study drug. The most frequently reported (≥1%) AEs in the pembrolizumab arm were anaemia (1.5%), neutrophil count decreased (1.5%), AST increased (1.3%), pneumonitis (1.3%), pneumonia (1.0%), blood creatinine increased (1.0%), and diarrhoea (1.0%). The incidences of these events were within approximately 1 percentage point of those in the Pooled Pembrolizumab Combination Dataset.

Discontinuations of any study drug due to AEs were more common in the pembrolizumab arm (25.5%) compared with the RSD (14.0%). Differences were partly driven by higher incidences of chemotherapy-associated AEs (e.g., anaemia and laboratory AEs in the SOC of Investigations), and immune-mediated lung disorders (immune-mediated lung disease and interstitial lung disease) in the SOC of Respiratory, Thoracic, and Mediastinal Disorders.

Discontinuation of Pembrolizumab

A similar percentage of participants in the pembrolizumab arm (21.0%) and Pooled Pembrolizumab Combination Dataset (17.5%) experienced AEs leading to discontinuation of pembrolizumab. The most frequently reported (≥1%) AEs in the pembrolizumab arm were AST increased (1.3%), anaemia (1.0%), pneumonitis (1.0%), and diarrhoea (1.0%). The incidences of these events were within 1 percentage point of those in the Pooled Pembrolizumab Combination Dataset.

Discontinuations of pembrolizumab due to AEs were similar in the pembrolizumab arm (21.0%) and RSD (14.0%).

Discontinuation of Chemotherapy

A lower percentage of participants in the pembrolizumab arm (11.1%) experienced AEs leading to discontinuation of any chemotherapy compared with participants in the Pooled Pembrolizumab Combination Dataset (20.6%). The most frequently reported (≥1%) AE in the pembrolizumab arm was anaemia (1.5%), compared with an incidence of 0.6% in the Pooled Pembrolizumab Combination Dataset.

Drug-related Adverse Events Leading to Discontinuation of Study Drug

The types and incidences of drug-related AEs leading to discontinuation of study drug were generally consistent with the established profile of pembrolizumab monotherapy and the known safety profile of the individual chemotherapy components.

Discontinuation of Any Study Drug

A similar percentage of participants in the pembrolizumab arm (18.7%) and Pooled Pembrolizumab Combination Dataset (23.9%) experienced drug-related AEs leading to discontinuation of any study drug. The most frequently reported (≥1%) drug-related AEs leading to discontinuation in the pembrolizumab

arm were neutrophil count decreased (1.5%), anaemia (1.3%), pneumonitis (1.3%), diarrhoea (1.0%), and blood creatinine increased (1.0%). The incidences of these events were within 1 percentage point of those in the Pooled Pembrolizumab Combination Dataset.

Discontinuations of any study drug due to drug-related AEs were more common in the pembrolizumab arm (18.7%) compared with the RSD (8.4%). Differences were partly driven by higher incidences in the pembrolizumab arm of chemotherapy-associated AEs (e.g. anaemia and laboratory AEs in the SOC of Investigations).

Discontinuation of Pembrolizumab

A similar percentage of participants in the pembrolizumab arm (13.9%) and Pooled Pembrolizumab Combination Dataset (12.1%) experienced drug-related AEs leading to discontinuation of pembrolizumab. The most frequently reported (≥1%) drug-related AEs leading to discontinuation in the pembrolizumab arm were diarrhoea (1.0%) and AEs related to respiratory disorders: pneumonitis (1.0%), immune-mediated lung disease (0.5%) and interstitial lung disease (0.5%). The incidences of these events were within 1 percentage point of those in the Pooled Pembrolizumab Combination Dataset.

Discontinuations of pembrolizumab due to drug-related AEs were more common in the pembrolizumab arm (13.9%) compared with the RSD (8.2%).

Discontinuation of Chemotherapy

A smaller percentage of participants in the pembrolizumab arm (8.1%) experienced AEs leading to discontinuation of any chemotherapy compared with participants in the Pooled Pembrolizumab Combination Dataset (17.2%). The most frequently reported (≥1%) AEs in the pembrolizumab arm were neutrophil count decreased (1.5%) and anaemia (1.3%); incidences of these AEs in the Pooled Pembrolizumab Combination Dataset were 0.3% and 0.5%, respectively.

Drug-related Adverse Events Leading to Interruption of Study Drug

The types of AEs and incidence of participants with drug-related AEs leading to interruption of study drug were generally consistent with the established profile of pembrolizumab monotherapy and the known safety profile of the individual chemotherapy components.

Interruption of Any Study Drug

The proportion of participants with AEs leading to interruption of any study drug was smaller in the pembrolizumab group (33.3%) compared with the Pooled Pembrolizumab Combination Dataset (57.9%) By SOC and PT, the incidences of participants with AEs leading to interruption of study drug were generally similar (within 1 percentage point) in the 2 groups. A higher incidence of participants with drug-related neutrophil count decreased in the pembrolizumab arm was offset by higher incidences of drug-related neutropenia in the Pooled Pembrolizumab Combination Dataset.

Interruptions of any study drug due to drug-related AEs were more common in the pembrolizumab arm (33.3%) compared with the RSD (14.7%). Differences were largely driven by higher incidences in the pembrolizumab arm of chemotherapy-associated AEs (e.g. anaemia and laboratory AEs in the SOC of Investigations).

Interruption of Pembrolizumab

The proportion of participants with AEs leading to interruption of pembrolizumab was similar in the pembrolizumab group (28.8%) compared with the Pooled Pembrolizumab Combination Dataset (33.0%). By SOC and PT, the incidences of participants with AEs leading to interruption of pembrolizumab were similar (generally within 1 percentage point) in the 2 groups. A higher incidence of participants with drug-

related neutrophil count decreased in the pembrolizumab arm was offset by higher incidences of drug-related neutropenia in the Pooled Pembrolizumab Combination Dataset.

Interruptions of pembrolizumab due to drug-related AEs were more common in the pembrolizumab arm (28.8%) compared with the RSD (13.9%). Differences were largely driven by higher incidences in the pembrolizumab arm of chemotherapy-associated AEs (e.g. anaemia and laboratory AEs in the SOC of Investigations).

Interruption of Chemotherapy

The proportion of participants with AEs leading to interruption of chemotherapy was similar in the pembrolizumab group (26.8%) compared with the Pooled Pembrolizumab Combination Dataset (22.6%).

Immunogenicity

No new immunogenicity data are available.

Post marketing experience

No revocation or withdrawal of pembrolizumab registration for safety reasons has occurred in any country.

2.5.1. Discussion on clinical safety

The safety profile of pembrolizumab in combination with platinum-containing chemotherapy as neoadjuvant treatment, and then continued as a single agent as adjuvant treatment, in the context of its intended use for the treatment of patients with resectable Stage II, IIIA, or IIIB (T3-4N2) NSCLC (as defined by the AJCC eighth edition), is based on safety data from the ongoing study, KEYNOTE-671. Data provided are based on the first planned interim analysis (IA1). However, upon request an update of safety data on IA2 (data cutoff date 10-JUL-2023) with approximately 1 year of additional follow-up, has been presented. Overall, no significant differences in number and type of AEs were noted compared to the IA1 cutoff date. No additional drug-related fatal AEs in either study arm were reported. There were 2 additional Grade 5 events in IA2 compared with IA1: lung neoplasm malignant in the pembrolizumab arm and respiratory failure in the placebo arm.

The median drug exposure was similar between the pembrolizumab plus chemotherapy (332.0 days) compared to the placebo plus chemotherapy arm (315.0 days) in study KN671, but was longer if compared with the Pooled Pembrolizumab Combination Dataset (240.0 days), of note, the time needed for surgery and recovery was included in the duration of exposure (defined as the time from the first dose date to the last dose date). A similar median number of cycles was observed among different groups.

Overall, demographic characteristics are quite balanced between the two arms of the KN671 study, although a slightly lower number of elderly (75-84 years) was observed in pembrolizumab (5.8%) compared to placebo (8.5%) arm. When compared to pooled pembrolizumab combination dataset a higher number of male, >65 years of age and Asian was observed in the pembrolizumab arm.

Overall, the incidence of participants with common AEs are quite similar between the two study arms with some differences observed especially for rash (16.9% vs 8.5%), ALT increase (14.6% vs 9.5%), pruritus (13.1% vs 8.3%), insomnia (12.6% vs 6.5%), pyrexia (12.4% vs 7.8%) and hypothyroidism (11.1% vs 1.8%), which seem to be more frequent in the pembrolizumab arm compared to the placebo arm. However, the above-mentioned AEs are already reflected in the SmPC as ADRs and also reported with a similar rate in the RSD group, suggesting that they are known AEs of pembrolizumab. A higher incidence

of participants with neutrophil count decreased (43.7% vs 19.9%) and white blood cell count decreased (28.3% vs 14.9%) was observed when comparing the pembrolizumab arm with the Pooled Pembrolizumab Combination Dataset, while an opposite trend was seen for neutropenia (0.5% vs 35.6%, respectively) and leukopenia (0% vs 11.8%) However, when the PTs of neutrophil count decreased/neutropenia and white blood cell count decreased/leukopenia are pooled, the overall proportions of participants with low neutrophil and WBC counts are lower in study KEYNOTE-671 (44.2% and 28.3%, respectively) than in the Pooled Pembrolizumab Combination Dataset (55.5% and 26.7%, respectively). The terms of neutropenia, leukopenia, or thrombocytopenia are not defined in CTCAE v4.03 and were infrequently used in KEYNOTE-671 (reflecting a different choice of terms used by clinicians), with only 6 total instances in the pembrolizumab arm. Then the choice of terminology for decreased white blood cell and neutrophil counts was slightly different in KEYNOTE-671 from other MSD-sponsored studies. Similarly, the higher incidence of platelet count decreased noted in the pembrolizumab arm compared with Pooled Pembrolizumab Combination Dataset (19.2% vs 12.1%) was offset by the higher incidence of thrombocytopenia in the Pooled Pembrolizumab Combination Dataset (0.3% vs 18.3%).

In the adjuvant phase, the safety profile of the pembrolizumab arm compares unfavourably with the placebo arm. However, the incidence of patients with AEs (including also grade 3-5 AEs, SAEs, deaths) is overall lower compared to the neo-adjuvant/surgery phase, as expected due to the added chemotherapy treatment in this phase.

The incidence of participants with drug-related adverse events are overall similar among different groups. Some AEs (ALT and AST increase, asthenia, rash, hypothyroidism, pruritus), are reported with higher incidence in the pembrolizumab arm compared to the placebo arm, as described above.

Type and frequencies of AEOSI were overall similar among groups. The majority of AEOSI were mild or moderate with 5.3% of participants having a grade 3-5 drug-related AEs in pembrolizumab arm vs 0.8% in the placebo arm, as expected. Serious AEOSIs judged as related by the investigators occurred in a lower rate of participants (4.8%) in the pembrolizumab arm compared to the pooled safety database (7.4%) and RSD group (5.9%). One AEOSI lead to death (immune-mediated lung disease) in the pembrolizumab arm which was considered related to study drug. Immune-mediated lung disease is already reported in 4.4 section of the SmPC as immuno-related ADR, including severe and fatal cases. No cases of diabetes mellitus occurred.

The most frequently AEOSI reported in pembrolizumab arm with a higher incidence compared to the placebo arm were hypothyroidism (11.1% vs 1.8%), hyperthyroidism (5.6% vs 3.3%) and pneumonitis (5.6% vs 1.8%). They are already known ADRs of pembrolizumab and their frequency was similar between the pembrolizumab arm, the Pooled Pembrolizumab Combination Dataset and the RSD groups. A slightly higher incidence of pneumonitis was observed (5.6% in pembrolizumab arm compared to 4% in pooled pembrolizumab combination dataset), but appears consistent with the incidence observed in other studies for NSCLC (e.g. 5.9% in KEYNOTE-091 study).

The majority of AESIs in the pembrolizumab arm were resolved (42%), however 39% were not resolved and 17 % were resolving. Unresolved AESIs were mostly driven by hypothyroidism (59.1%), and hyperthyroidism 13.6%), which are known immuno-related ADR of pembrolizumab and these events are often managed with continued hormone therapy. The other unresolved AEOSI were: infusion reactions (1 case), myasthenic syndrome (1 case), pneumonitis (6 cases), severe skin reactions (2 cases), and thyroiditis (3 cases). These AEs are already reported in the SmPC as ADRs.

The incidence of participants presenting drug-related SAEs was similar or slightly higher in the pembrolizumab arm (17.7%) compared to the placebo arm (14.3%), but lower than the Pooled Pembrolizumab Combination Dataset (29.1%) The incidence of SAEs in the adjuvant phase was higher in the pembrolizumab arm (14.1%) compared with the placebo arm (8.6%), but lower than in the

neoadjuvant/surgery phase (33.6%). Moreover, it was similar to the rate of SAEs reported in the RSD group. Pneumonia was the most frequently reported SAE in the adjuvant phase.

Overall, 25 deaths (6.3%) were reported in the pembrolizumab arm, 160 (5.1%) in the Pooled Pembrolizumab Combination Dataset. Four (1.0%) deaths in the pembrolizumab arm (atrial fibrillation, immune-mediated lung disease, pneumonia, and sudden cardiac death) and 3 (0.8%) deaths in the placebo arm (pneumonia, acute coronary syndrome, and pulmonary hemorrhage) were judged as causally related to the study drugs (either pembrolizumab, placebo, or chemotherapy). Of those, 3 deaths in the pembrolizumab arm and 3 in the placebo arm occurred during the neoadjuvant/surgery phase. The one case of death due to atrial fibrillation occurred in the pembrolizumab arm during the adjuvant phase. Considering the available information, the CHMP shares the MAH conclusion that, the cause of death for this participant was likely multifactorial. A strong causality between administration of pembrolizumab and worsening of atrial fibrillation does not seem to be demonstrated and other conditions such as hypercalcemia, possible infection and signs of kidney failure, hypovolemia and dehydration, are all possible etiologies of worsening of atrial fibrillation and of the participant's death. Moreover, in the KEYNOTE-671 study, a similar proportion of participants experienced cardiac arrythmias in both treatment arms: 32 participants (8.1%) in the pembrolizumab arm and 33 participants (8.3%) in the placebo arm, with atrial fibrillation (n=14, 3.5% vs n=20, 5.0%), sinus tachycardia (n=10, 2.5% vs n=4, 1.0%) and arrythmia (n=2, 0.5% vs n=6, 1.5%) the most common arrythmias reported in the pembrolizumab and the placebo arms respectively. Other types of arrhythmias were reported in $\leqslant$0.3% of study participants.

Therefore, as atrial fibrillation is already reported in the SmPC as common ADR, no further update of the SmPC is deemed necessary at this time. Continued monitoring for arrhythmias and atrial fibrillation in particular through routine pharmacovigilance activities by the MAH remains expected.

Overall, no new safety signals leading to death for pembrolizumab seems to have been identified in the pembrolizumab arm of the KEYNOTE-671 study.

In the post-operative period in the pembrolizumab arm 6 patients died within 30 days after in-study surgery due to AEs which were considered not related to study drug and 7 patients died within 31 to 90 days due to AEs of which one (immune-mediated lung disease) was assessed as related to pembrolizumab.

Participants with adverse events resulting in pembrolizumab/placebo discontinuation in the Adjuvant Phase were higher in the pembrolizumab arm (12.4%) compared to the placebo arm (4.9%) with the most common AEs (>1%) being diarrhoea, aspartate aminotransferase increased and pneumonitis.

Overall, no new safety signals leading to the discontinuation were identified.

In order to better understand the impact of neoadjuvant pembrolizumab toxicity on the ability to undergo surgery, the number and type of AEs that led patients to be unfit for surgery was provided. A slightly higher rate of participants in the pembrolizumab arm [25 (6.3%)] compared with the placebo arm [17 (4.3%)] did not undergo in-study surgery due to adverse events. Some AEs such as acute kidney injury, death, interstitial lung disease and respiratory failure were reported in the pembrolizumab arm in 2 patients each. The other AEs were reported only in one patient each. Therefore, due to the low number of events, a clear trend of AEs as well as a clear correlation with pembrolizumab, cannot be identified.

With regard to age groups, grade 3-5 AEs, serious AEs and discontinuations of any drug due to an AE were generally more common in elderly (≥65 years of age) patients, as expected.

Regarding ECOG status, the proportion of participants in the pembrolizumab arm who experienced AEs was overall similar between an ECOG status of 0 and of 1.

The AE profile in the pembrolizumab arm was generally similar between participants who were white and of other races with the exception of Grade 3 to 5 drug-related AEs which were more common in "other" races (39.8% vs 53%).

Overall, the proportion of EU participants in the pembrolizumab arm who experienced AEs was similar or slightly higher (for some of the AEs) to the proportion of ex-EU participants. However, a similar trend was also observed in the placebo arm.

2.5.2. Conclusions on clinical safety

Overall, the safety profile of pembrolizumab with platinum-containing chemotherapy as neoadjuvant treatment, and then as monotherapy in adjuvant treatment, seems to be consistent with the known safety profile of pembrolizumab and similar to what observed in the pooled pembrolizumab combination dataset. The safety profile of the pembrolizumab arm compared unfavorably with the placebo arm in the adjuvant phase. However, the incidence of patients with AEs (including also grade 3-5 AEs, SAEs, deaths) is overall lower in the adjuvant phase than in the neo-adjuvant/surgery phase. No new safety signals were identified.

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 42, date of final sign off 21-Feb-2024) with this application. The (main) proposed RMP changes were the following:

- Addition of a new indication for pembrolizumab in combination with platinum-containing chemotherapy as neoadjuvant treatment, and then continued as monotherapy as adjuvant treatment, for the treatment of resectable Stage II, IIIA, or IIIB (T3 4N2) non-small cell lung carcinoma in adults.
- Addition of study KEYNOTE-671 in Modules SIII, SVII and SVIII.

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

The PRAC considered that the risk management plan version 42 is acceptable.

The CHMP endorsed the Risk Management Plan version 42 with the following content:

Safety concerns

Table 70: Summary of Safety Concerns

Summary of safety concerns	
Important identified risks	Immune-related 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 71: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety Concern	Risk minimisation Measures	Pharmacovigilance Activities
Important Identified Risks: Immune-Related Adverse Reactions		
Immune-related adverse reactions	Routine risk minimisation measures: • The risk of the immune-related adverse reactions associated with the use of pembrolizumab is described in the SmPC, Section 4.2, 4.4, 4.8 and appropriate advice is provided to the prescriber to minimize the risk. Additional risk minimisation measures: • Patient card	Routine pharmacovigilance activities Additional pharmacovigilance including: • Safety monitoring in all ongoing MAH-sponsored clinical trials for pembrolizumab in various tumour types
Important Potential Risks		
For hematologic malignancies: increased risk of severe complications of allogeneic SCT in patients who have previously received pembrolizumab	Routine risk minimisation measures: • For Hematologic malignancies: the increased risk of severe complications of allogeneic SCT in patients who have previously received pembrolizumab is described in the SmPC, Section 4.4, 4.8 and appropriate advice is provided to the prescriber to minimize the risk. No additional risk minimisation measures warranted	Routine pharmacovigilance activities Additional pharmacovigilance including: • Safety monitoring in the ongoing HL trial (KN204).
GVHD after pembrolizumab administration in patients with a history of allogeneic SCT	Routine risk minimisation measures: • GVHD after pembrolizumab administration in patients with a history of allogeneic SCT is described in the SmPC, Section 4.4 and appropriate advice is provided to the prescriber to minimize the risk. No additional risk minimisation measures warranted	Routine pharmacovigilance activities Additional pharmacovigilance including: • Safety monitoring in all ongoing MAH-sponsored clinical trials for pembrolizumab in various tumour 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 have been updated to include a new indication for Keytruda in combination with platinum-containing chemotherapy as neoadjuvant treatment, and then continued as monotherapy as adjuvant treatment, is indicated for the treatment of resectable non-small cell lung carcinoma at high risk of recurrence in adults; new treatment regimen and duration in the NSCLC peri operative setting; updated ADR frequencies in combination with chemotherapy, and in the NSCLC population; and results from study KEYNOTE 671. 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 in only one changes in the package leaflet for this submission in section 1. The key messages for the safe use of the medicinal product are however not impacted. Furthermore, the design, layout and format of the package leaflet will not be affected by the proposed revisions. Therefore, the proposed revision does not constitute significant changes that would require the need to conduct a new user consultation.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The MAH for Keytruda applied for the following extension of indication: "KEYTRUDA, in combination with platinum-containing chemotherapy as neoadjuvant treatment, and then continued as monotherapy adjuvant treatment, is indicated for the treatment of resectable Stage II, IIIA, or IIIB (T3-4N2) non-small cell lung carcinoma in adults."

The final wording of the indication was the following:

"KEYTRUDA, in combination with platinum-containing chemotherapy as neoadjuvant treatment, and then continued as monotherapy as adjuvant treatment, is indicated for the treatment of resectable non-small cell lung carcinoma at high risk of recurrence in adults (for selection criteria, see section 5.1)."

3.1.2. Available therapies and unmet medical need

Surgical resection is the standard treatment for stage I to IIIA early-stage resectable NSCLC. Patients with Stage IIIB disease are considered potentially operable if the metastases are limited to the N2 lymph nodes[24,25]. Adjuvant chemotherapy with up to 4 cycles of a cisplatin-based doublet should be offered to patients with resected stage IIB and III NSCLC and can be considered in patients with T2bN0, stage IIA

[24] Postmus PE, Kerr KM, Oudkerk M, Senan S, Waller DA, Vansteenkiste J, et al. Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2017;28 Suppl 4:iv1-21. – E-update Published on 01 September 2021.
[25] NCCN Guidelines Version 3.2023 NSCLC

resected primary tumour >4 cm. Neoadjuvant chemotherapy has been evaluated less extensively than adjuvant, although benefit is considered to be overall similar.

The only targeted therapy approved in early-stage NSCLC is osimertinib, indicated as adjuvant treatment in completely resected stage IB-IIIA EGFR positive NSCLC.

Immunotherapy was introduced recently in the treatment of early-stage NSCLC, with the approval in the EU of Tecentriq as adjuvant treatment following surgery and platinum-based chemotherapy in PD-L1 ≥50% NSCLC with no EGFR/ALK mutations. Keytruda was also approved as adjuvant treatment following resection and platinum-based chemotherapy. Further, neoadjuvant immunotherapy with nivolumab plus platinum-doublet chemotherapy was licenced in the EU.

The 5-year OS rates for surgically treated patients range from 55% overall in stage I to 20% in stage IIIA[26]. New therapies in the early stage setting able to prevent disease recurrence and improve cure rate and survival are needed.

3.1.3. Main clinical studies

The pivotal study for this application is KEYNOTE-671, a multicenter randomized double-blind phase III trial of pembrolizumab in combination with platinum-containing chemotherapy (4 cycles of pemetrexed [in non-squamous] or gemcitabine [in squamous], plus cisplatin) as neoadjuvant treatment and continued as single agent adjuvant treatment (13 cycles, for a systemic treatment duration of about 1 year in total) in adult patients with resectable Stage II, IIIA, or IIIB (N2) NSCLC (AJCC 8th ed), not previously treated and able to undergo surgery. EGFR/ALK testing was not required for inclusion. A total of 797 patients were randomized 1:1 stratified by stage, PD-L1 expression (50% cut-off), histology and region. EFS by investigator and OS were dual primary endpoints, pCR and mPR secondary endpoints. The MAH submitted the results of the IA1 with a data cut-off 29 July 2022, having a median follow-up of 23 months, and minimum follow up time of 7 months. Top-line results for the pre-planned IA2 with a data cut-off of 10 Jul 2023 and a median follow-up of 30 months have been provided during the procedure.

3.2. Favourable effects

- KEYNOTE-671 study showed a statistically significant improvement in the primary endpoint EFS based on investigator assessment for pembrolizumab in combination with platinum-containing chemotherapy as neoadjuvant treatment and then continued as single agent in adjuvant treatment relative to neoadjuvant chemotherapy plus placebo followed by adjuvant placebo, at the at the IA1: HR 0.58 (95%CI 0.46, 0.72, p<0.00001), number of events 35% vs 51.3%.

- The descriptive EFS update at IA2 was consistent with prior analysis, suggesting encouraging maintained benefit with longer follow-up. Although a plateau in EFS curves is not yet evident in the KM curves, the difference in EFS rates (e.g. 19% at 30 months) is considered clinically relevant. Considering the duration of follow-up and the observed event rates for EFS, together with the fact that there were no more patients on active treatment at IA2, data are considered mature enough to assess the benefit in EFS with regard to a delay in recurrence.

- EFS by BICR provided as sensitivity analyses supports EFS result by investigator assessment: HR 0.66 (95% CI: 0.53, 0.83).

[26] 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.

- Subgroup analyses showed overall a consistent effect across the pre-specified subgroups analysed (but PD-L1 is discussed separately).

- A statistically significant increase in the secondary endpoints pCR and mPR was shown at IA1: pCR 18.1% vs 4%, estimated difference of 14.2% (95%CI 10.1, 18.7, p<0.00001); mPR 30.2% vs 11%, estimated difference of 19.2% (95%CI 13.9, 24.7, p<0.00001).

- At the IA2, OS reached statistical significance, although only slightly crossing the boundary for declaring success (p=0.00517; p-value boundary = 0.005426). OS HR was 0.72 (95%CI 0.56, 0.93), with median OS not reached in the pembrolizumab arms vs 52.4 months in the comparator arm; OS events occurred in 27.7% of the patients in the pembrolizumab arm vs 36% of patients receiving the comparator.

3.3. Uncertainties and limitations about favourable effects

- KEYNOTE-671 as designed does not allow to disentangle the contribution of pembrolizumab to each treatment phase, and whether or not neoadjuvant and adjuvant pembrolizumab are both needed. Therefore, study results can only be discussed in the context of an overall peri-surgical strategy i.e. including neoadjuvant AND adjuvant treatment for NSCLC.

- Increased treatment effect with higher PD-L1 expression was observed, considered biologically plausible and replicated by external data. Higher point estimates in the PD-L1 <1% population are reported as compared to higher expression subgroups (EFS 0.75, OS 0.91), however EFS KM curves separation is maintained in the long-term in favour of the pembrolizumab arm at IA2 analysis. Although OS KM curves seem to cross up to month 24, the trend in OS from IA1 (HR 1.01) to IA2 (HR 0.91) does not indicate a detriment in OS. As OS is considered still immature in this early-stage setting, the MAH should provide further updates on OS data at future analyses, included in subgroups by PD-L1 expression to reassure on survival results in the long-term. (REC). In addition, data by PD-L1 expression have been included in section 5.1 of the SmPC to inform prescribers.

- Patients over 75 were only 7% of the ITT population (23 vs 34 patients), and some differences in distribution of baseline characteristics, possibly related to small numbers, are seen, including higher proportion with TPS <50% in the experimental arm that can influence the results. Although subgroup analyses at IA2 showed EFS 0.83 (0.43, 1.63) and OS 1.01 (0.43, 2.41), the sample size is too limited to draw conclusion in the elderly population. Wording in section 4.4 of the SmPC is already warning prescribers that pembrolizumab in combination with chemotherapy should be used with caution in patients ≥75 years after careful consideration of the potential benefit/risk on an individual basis.

3.4. Unfavourable effects

- Overall, the incidence of participants with common AEs were quite similar between the two study arms with some differences observed especially for the known ADRs of rash (16.9% vs 8.5%), ALT increase (14.6% vs 9.5%), pruritus (13.1% vs 8.3%), insomnia (12.6% vs 6.5%), pyrexia (12.4% vs 7.8%) and hypothyroidism (11.1% vs 1.8%), which seem to be more frequent in the pembrolizumab arm compared to placebo arm.

- The AEOSI most frequently reported in the pembrolizumab arm were hypothyroidism (11.1% vs 1.8%), hyperthyroidism (5.6% vs 3.3%) and pneumonitis (5.6% vs 1.8%). Serious AEOSIs judged as related by the investigators occurred in a lower rate of participants (4.8%) in pembrolizumab arm compared to pooled safety database (7.4%) and RSD group (5.9%). One AEOSI lead to death (immune-mediated lung disease) in the pembrolizumab arm and was considered related to pembrolizumab.

- The overall incidence of participants with SAEs was generally similar in the pembrolizumab arm (40.4%) compared with the Pooled Pembrolizumab Combination Dataset (46.6%) with the most frequently reported SAEs in the pembrolizumab arm being pneumonia (5.3%), pulmonary embolism (2.3%), anemia (2.0%), and pyrexia (2.0%).

- Overall, 25 deaths (6.3%) were reported in the pembrolizumab arm, 160 (5.1%) in the Pooled Pembrolizumab Combination Dataset. A total of 4 (1.0%) deaths in the pembrolizumab arm (atrial fibrillation, immune-mediated lung disease, pneumonia, and sudden cardiac death) and 3 (0.8%) deaths in the placebo arm (pneumonia, acute coronary syndrome, and pulmonary hemorrhage) were judged as causally related to the study drugs.

- Discontinuations of any study drug due to AEs were more common in the pembrolizumab arm (25.5%) compared with the RSD (14.0%), but were similar to those observed in Pooled Pembrolizumab Combination Dataset (28.8%). Participants with adverse events resulting in pembrolizumab/placebo discontinuation in the adjuvant Phase were more in pembrolizumab arm (12.4%) compared to placebo arm (4.9%) but similar to the RSD (14.0%).

- With regard to age groups, grade 3-5 AEs, serious AEs and discontinuations of any drug due to an AE were generally more common in elderly (≥65 years of age) patients, as expected.

3.5. Uncertainties and limitations about unfavourable effects

None

3.6. Effects Table

Table 72: Effects Table for Keytruda as neoadjuvant/adjuvant treatment of resectable NSCLC (study KEYNOTE-671, data cut-off: IA1 29 Jul 2022, IA2 10 Jul 2023)

Effect	Short description	Unit	Treatment Pembrolizumab +NACT → pembrolizumab	Control Placebo + NACT → placebo	Uncertainties / Strength of evidence	References
Favourable Effects						
EFS (IA1)	EFS is defined as the time from randomization to the first of the following events: disease or local progression, inability to resect tumour, local or distant recurrence, or death.	HR	HR 0.58 (95%CI 0.46, 0.72), p<0.00001		EFS reached statistical significance at IA1, updated EFS at IA2 showed consistent result; consistency of subgroups, supportive EFS by BICR	CSR KN-671 And MAH responses
OS (IA2)	OS was defined as the time from randomization to the date of death (whatever the cause).	HR	HR 0.72, 95% CI 0.56, 0.93, p=0.00517		Statistically significant at IA2/ p-value boundary only slightly crossed; piecewise HR in favour of the control arm within the first 8 months; OS trend in the PD-L1 <1% not detrimental, but to be further confirmed	

Effect	Short description	Unit	Treatment Pembrolizumab +NACT → pembrolizumab	Control Placebo + NACT → placebo	Uncertainties / Strength of evidence	References
					post-approval	
pCR (IA1)	Pathological complete response	%	18.1%	4%	Statistically significant/unclear clinical significance of the Δ pCR	
mPR (IA1)	Major pathological response	%	30.2%	11%,	Statistically significant/unclear clinical significance of the Δ mPR	
Unfavourable Effects						
	All AEs	%	99.5	98.5		CSR KN-671
	Grade 3-5 AEs	%	64.6	531		
	SAEs	%	4.04	32.6		
	Serious drug-related AEs	%	17.7	14.3		
	Deaths	%	6.3	3.5		

Abbreviations: EFS=event free survival; OS=overall survival; HR= Hazard Ratio; CI= confidence interval; IA= interim analysis; NR=not reached; AE=adverse event; SAE=serious adverse event; CSR=clinical study report.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

KEYNOTE-671 study, at the first pre-planned interim analysis (IA1) demonstrated statistically significant improvement in the primary endpoint EFS based on investigator assessment for pembrolizumab in combination with platinum-containing chemotherapy as neoadjuvant treatment then and continued as single agent as adjuvant treatment, relative to neoadjuvant chemotherapy plus placebo followed by adjuvant placebo, which was consistently observed at IA2 with updated EFS. EFS by BICR overall support the primary assessment by investigator. OS reached also statistical significance at the pre-planned analysis IA2, although only marginally crossing the pre-specified p-value boundary. Though OS data indicate a small benefit, they were still immature at this time point.

The two secondary endpoints pCR and mPR were both statistically significant at IA1. Although they are only relevant for the neoadjuvant phase and are not yet specifically recognized as surrogate endpoints in early NSCLC, results in the same direction of EFS are considered supportive.

Subgroup analyses showed overall consistent effect across subgroups, although a clear association of PD-L1 expression with all efficacy outcomes was noted, which is considered biologically plausible and replicated by preliminary external evidence from similar studies with anti-PD(L)1 in the early-stage NSCLC setting[27,28]. However, results in the PD-L1 TPS<1% subgroup (more than one third of the ITT population, not a stratification factor at randomization) suggest that the addition of pembrolizumab may still provide a benefit in EFS maintained with longer follow-up. OS data in this subgroup are difficult to interpret due to the limited event rates, although the improved OS HR estimate from IA1 to IA2 is

[27] Cascone T, Awad MM, Spicer JD et al. LBA1 CheckMate 77T: Phase III study comparing neoadjuvant nivolumab (NIVO) plus chemotherapy (chemo) vs neoadjuvant placebo plus chemo followed by surgery and adjuvant NIVO or placebo for previously untreated, resectable stage II–IIIb NSCLC. Ann Oncol October 2023. 34 (2): S1295.
[28] Heymach JV, Harpole D, Mitsudomi T, et al; AEGEAN Investigators. Perioperative Durvalumab for Resectable Non-Small-Cell Lung Cancer. N Engl J Med. 2023 Nov 2;389(18):1672-1684.

reassuring and does not indicate a detriment in survival. Updated OS analysis should be provided post-approval to further reassure on the long-term survival including by PD-L1 subgroups.

Overall, the safety profile of pembrolizumab with platinum-containing chemotherapy as neoadjuvant treatment, and then as monotherapy in adjuvant treatment, appears overall consistent with the known safety profile of pembrolizumab alone and in combination with chemotherapy agents. As already known, some long-term adverse event may occur, including in patients also potentially cured. Reassuringly, no new safety signals were identified.

It is considered a relevant limitation of KEYNOTE-671 that, due to the study design, it is not possible to disentangle the benefit and the need of pembrolizumab in the neoadjuvant and in the adjuvant phases. The MAH submitted some exploratory analysis and indirect comparison, which are however not able to overcome this deficiency. Therefore, the peri-operative treatment can only be assessed as a whole strategy.

The study design does not allow to disentangle the benefit of pembrolizumab used in the neoadjuvant and adjuvant phase. Although the MAH's attempt to justify the peri-operative regimen is appreciated, the exploratory EFS analysis by pCR/mPR and the indirect comparison between KEYNOTE-671 and KEYNOTE-091 are of interest but unfortunately do not allow to reach a definitive conclusion on this issue, therefore the peri-operative treatment strategy can only be considered as a whole.

3.7.2. Balance of benefits and risks

Efficacy in terms of EFS has been demonstrated in the ITT population. At the IA2, OS reached statistical significance, and, although marginally cross the p-boundary and still immature, this is supportive of the proposed indication. The treatment effect in terms of EFS and OS is more limited in the PD-L1 TPS<1% subgroup, but the overall data suggest that the addition of pembrolizumab may still provide a benefit in EFS maintained with longer follow-up, without indication of a detrimental effect in OS. Thus, an indication in all comers is considered justified. Section 5.1 has been adequately updated to include efficacy outcomes according to the different TPS expression levels.

3.7.3. Additional considerations on the benefit-risk balance

The wording of the indication was revised to align to previously EU approved indications in early stages solid tumours:

KEYTRUDA, in combination with platinum-containing chemotherapy as neoadjuvant treatment, and then continued as monotherapy as adjuvant treatment, is indicated for the treatment of resectable non-small cell lung carcinoma at high risk of recurrence in adults (for selection criteria, see section 5.1).

Additional information regarding the exact NSCLC staging with the TNM edition used in the pivotal study as well as the anatomical description of the extent of the disease is included in section 5.1 of the SmPC, to provide further details on the wording "high risk population" referred to in the indication.

3.8. Conclusions

The overall B/R of Keytruda as neoadjuvant/adjuvant treatment of resectable NSCLC is positive.

The following measure is considered necessary to address issues related to efficacy: the MAH should

provide updated OS data from KEYNOTE-671, including in subgroups by PD-L1 expression, at future analyses. (REC)

4. Recommendations

Outcome

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

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

Extension of indication to include in combination with platinum-containing chemotherapy as neoadjuvant treatment, and then continued as monotherapy as adjuvant, for the treatment of resectable non-small cell lung carcinoma at high risk of recurrence in adults ,for Keytruda based on study KEYNOTE-671, a phase III, randomized, double-blind trial of platinum doublet chemotherapy +/- pembrolizumab as neoadjuvant/adjuvant therapy for participants with resectable stage II, IIIA, and resectable IIIB (T3-4N2) non-small cell lung cancer. As a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 42 of the RMP has also been 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 and IIIB and to the Risk Management Plan are recommended.