Pembrolizumab (NSCLC, neoadjuvant + adjuvant)

Addendum to Project A24-46 (dossier assessment)[1]

ADDENDUM

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
AJCC	American Joint Committee on Cancer
ALK	anaplastic lymphoma kinase
CTCAE	Common Terminology Criteria for Adverse-Events
EFS	event-free survival
EGFR	epidermal growth factor receptor
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
EORTC QLQ-LC13	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Lung Cancer 13
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HR	hazard ratio
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed-effects model with repeated measures
NSCLC	nicht kleinzelliges Lungenkarzinom
PD-L1	programmed death ligand 1
PRO	patient-reported outcome
PT	Preferred Term
RR	relative risk
SAE	serious adverse event
SAP	statistical analysis plan
SGB	Sozialgesetzbuch (Social Code Book)
SOC	System Organ Class
UICC	Union for International Cancer Control
VAS	visual analogue scale

1 Background

On 10 September 2024, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Project A24-46 (Pembrolizumab (NSCLC, neoadjuvant + adjuvant) – Benefit assessment according to §35a Social Code Book V) [1].

The commission comprises the assessment of the analyses presented by the pharmaceutical company (hereinafter referred to as "the company") in the commenting procedure [2], taking into account the information provided in the dossier [3]:

- study results for patients with programmed death ligand 1 (PD-L1) status < 1% (patient population b) of the KEYNOTE 671 study

The responsibility for the present assessment and the assessment result lies exclusively with IQWiG. The assessment is forwarded to the G-BA. The G-BA decides on the added benefit.

2 Assessment

As explained in detail in dossier assessment A24-46 [1], the KEYNOTE 671 study [4-7] was not used for the benefit assessment. Firstly, because only analyses of the total population of the KEYNOTE 671 study were available in the company's dossier. Secondly, because the G-BA's appropriate comparator therapy (ACT) for adults with resectable non-small cell lung cancer with tumour cell PD-L1 expression < 1% at high risk of recurrence was not implemented in the study. The ACT for pembrolizumab in combination with platinum-based chemotherapy for neoadjuvant treatment followed by pembrolizumab as monotherapy for adjuvant treatment in these patients is individualized treatment selected from:

- pre-operative (neoadjuvant) systemic chemotherapy selected from:
  - cisplatin in combination with a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed)

    and
  - carboplatin in combination with a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed) and
- simultaneous radiochemotherapy with platinum-based (cisplatin or carboplatin) combination chemotherapy

taking into account the tumour stage, the tumour histology, the presence of a Pancoast tumour and the feasibility of an R0 resection, as well as the prerequisites for the use of carboplatin.

Followed by adjuvant treatment:

- best supportive care

The decisive reason for the lack of implementation of the ACT given in the dossier assessment was the fact that in the neoadjuvant phase of the KEYNOTE 671 study, exclusively cisplatin in combination with gemcitabine was specified as treatment for patients with squamous non-small cell lung cancer (NSCLC) and cisplatin in combination with pemetrexed for patients with non-squamous NSCLC in the comparator arm. Thus, the investigators did not have a choice of several treatment options that would have enabled an individualized treatment decision for each patient.

In compliance with the commission, the results of the KEYNOTE 671 study for the subpopulation of adults with resectable NSCLC with tumour cell PD-L1 expression < 1% at high risk of recurrence; neoadjuvant and adjuvant therapy (hereinafter referred to as patients with tumour cell PD-L1 expression < 1%) are presented below.

2.1 Study results for patients with tumour cell PD-L1 expression < 1%

2.1.1 Study characteristics

A detailed characterization of the KEYNOTE 671 study can be found in dossier assessment A24-46 [1] and its Appendix B.

A total of 797 patients were included in the KEYNOTE 671 study. This included 289 (36%) patients with tumour cell PD-L1 expression < 1%, 138 patients in the intervention arm and 151 patients in the comparator arm.

Planned duration of follow-up observation

Table 1 shows the planned duration of patient follow-up observation for the individual outcomes.

Table 1: Planned duration of follow-up observation – RCT, direct comparison: pembrolizumab + platinum-based chemotherapya (neoadjuvant) + pembrolizumab (adjuvant) vs. placebo + platinum-based chemotherapya (neoadjuvant) + placebo (adjuvant) (patients with tumour cell PD-L1 expression < 1%)

Study **Outcome category** **Outcome**	**Planned follow-up observation**
KEYNOTE 671	
Mortality	
Overall survival	Until death, withdrawal of consent, or end of study
Morbidity	
Failure of the curative approach[b]	Until occurrence of an event relevant to the outcome, or until the end of study, or withdrawal of consent
Symptoms (EORTC QLQ-C30, EORTC QLQ-LC13)	Up to 5 years
Health status (EQ-5D VAS)	Up to 5 years
Health-related quality of life	
EORTC QLQ-C30	Up to 5 years
Side effects	
AEs	Up to 30 days after the last study medication
SAEs	Up to 90 days after the last study medication or 30 days after initiation of subsequent therapy, whichever occurred first

a. Cisplatin + gemcitabine (for squamous histology) or cisplatin + pemetrexed (for non-squamous histology).
b. Operationalized via event-free survival: includes the events: radiographic disease progression per RECIST 1.1 that prevents planned surgery; local progression (primary tumour or regional lymph nodes) precluding planned surgery; no surgery (for patients who switched to the adjuvant phase without surgery); inability to resect the tumour; not disease-free after surgery (patients with R1 or R2 resection); local or distant recurrence (for patients who are disease free after surgery [R0 resection]; death due to any cause.

AE: adverse event; EORTC: European Organisation for Research and Treatment of Cancer; PD-L1: programmed death ligand 1; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-LC13: Quality of Life Questionnaire-Lung Cancer 13; RCT: randomized controlled trial; RECIST: Response Evaluation Criteria in Solid Tumours; SAE: serious adverse event; VAS: visual analogue scale

In the KEYNOTE 671 study, the outcomes of overall survival, failure of the curative approach, and health status were recorded until death, end of the study or withdrawal of consent. The outcomes of health status and health-related quality of life were recorded for up to 5 years.

The observation times for the side effects outcomes are systematically shortened in the KEYNOTE 671 study, as they were recorded up to a maximum of 90 days after the last study medication. However, drawing a reliable conclusion on the total study period or the time to patient death would require recording these outcomes for the total period, as was done for survival and failure of the curative approach.

Characteristics of patients with tumour cell PD-L1 expression < 1%

Table 2 shows the characteristics of the patients with tumour cell PD-L1 expression < 1% in the KEYNOTE 671 study.

Table 2: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: pembrolizumab + platinum-based chemotherapy[a] (neoadjuvant) + pembrolizumab (adjuvant) vs. placebo + platinum-based chemotherapy[a] (neoadjuvant) + placebo (adjuvant) (patients with tumour cell PD-L1 expression < 1%) (multipage table)

Study **Characteristic** **Category**	**Pembrolizumab + platinum-based chemotherapy[a] (neoadjuvant) + pembrolizumab (adjuvant)** **N = 138**	**Placebo + platinum-based chemotherapy[a] (neoadjuvant) + placebo (adjuvant)** **N = 151**
KEYNOTE 671		
Age [years], mean (SD)	63 (8)	63 (8)
Age [years], n (%)		
< 65	75 (54)	77 (51)
≥ 65	63 (46)	74 (49)
Sex [F/M], %	30/70	27/73
ECOG Performance Status, n (%)		
0	86 (62)	96 (64)
1	52 (38)	55 (36)
Family origin, n (%)		
Asian	44 (32)	48 (32)
Black or African American	1 (< 1)	5 (3)
White	86 (62)	85 (56)
Multiple	2 (1)	8 (5)
Missing	5 (4)	5 (3)
Smoking status, n (%)		
Never smoker	22 (16)	20 (13)
Ex-smoker	82 (59)	93 (62)
Current smoker	34 (25)	38 (25)
Disease stage[b] at baseline, n (%)		
Stage II	43 (31)	51 (34)
Stage III	95 (69)	100 (66)
Tumour histology, n (%)		
Squamous cell carcinoma	60 (43)	66 (44)
Non-squamous cell carcinoma	78 (57)	85 (56)

Table 2: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: pembrolizumab + platinum-based chemotherapy[a] (neoadjuvant) + pembrolizumab (adjuvant) vs. placebo + platinum-based chemotherapy[a] (neoadjuvant) + placebo (adjuvant) (patients with tumour cell PD-L1 expression < 1%) (multipage table)

Study Characteristic Category	**Pembrolizumab + platinum-based chemotherapy[a] (neoadjuvant) + pembrolizumab (adjuvant) N = 138**	**Placebo + platinum-based chemotherapy[a] (neoadjuvant) + placebo (adjuvant) N = 151**
EGFR mutation status, n (%)		
Yes	5 (4)	8 (5)
No	41 (30)	48 (32)
Unknown/missing	92 (67)	95 (63)
ALK translocation status, n (%)		
Yes	0 (0)	2 (1)
No	40 (29)	47 (31)
Unknown/missing	98 (71)	102 (68)
Treatment discontinuation, n (%)[c]	81 (59)	85 (56)
Study discontinuation, n (%)[d]	56 (41)	65 (43)

a. Cisplatin + gemcitabine (for squamous histology) or cisplatin + pemetrexed (for non-squamous histology).
b. Staging according to UICC/AJCC, version 8 [8].
c. Common reasons for treatment discontinuation in the intervention arm vs. control arm were the following (percentages based on randomized patients): disease progression (25% vs. 23%), side effects (20% vs. 9%), withdrawal of consent (7% vs. 9%). In addition, 57 and 66 of the patients completed the therapy as planned.
d. The data include patients who died during the course of the study (intervention arm: 51 vs. control arm: 60).

AJCC: American Joint Committee on Cancer; ALK: anaplastic lymphoma kinase; ECOG: Eastern Cooperative Oncology Group; EGFR: epidermal growth factor receptor; F: female; M: male; n: number of patients in the category; N: number of patients; PD-L1: programmed death ligand 1; RCT: randomized controlled trial; SD: standard deviation; UICC: Union for International Cancer Control

Both treatment arms are largely similar in terms of the demographic and clinical characteristics of the patients with tumour cell PD-L1 expression < 1% in the KEYNOTE 671 study. The patients' mean age at study entry was 63 years, about 3 quarters of patients were male, and slightly more than half (62% and 56%) were of white family origin. About 2 thirds of patients were in Stage III according to the Union for International Cancer Control (UICC)/American Joint Committee on Cancer (AJCC) Classification 8; 1 third was in Stage II.

The proportion of patients who discontinued treatment or the study was balanced between the treatment arms. The 2 most common reasons for treatment discontinuation were disease

progression and side effects. Study discontinuation was almost exclusively due to the death of patients.

Information on the course of the study

Data on treatment durations and observation periods are not available for the relevant subpopulation of patients with tumour cell PD-L1 expression < 1%.

Information on subsequent therapies

Table 3 shows the first subsequent therapies patients received after discontinuation of the study medication.

Table 3: Information on first subsequent antineoplastic therapies – RCT, direct comparison: pembrolizumab + platinum-based chemotherapy[a] (neoadjuvant) + pembrolizumab (adjuvant) vs. placebo + platinum-based chemotherapy[a] (neoadjuvant) + placebo (adjuvant) (patients with tumour cell PD-L1 expression < 1%) (multipage table)

Study **Drug class** **Drug**	**Patients with subsequent therapy, n (%)**	
	Pembrolizumab + platinum-based chemotherapy[a] (neoadjuvant) + pembrolizumab (adjuvant) **N = 138**	**Placebo + platinum-based chemotherapy[a] (neoadjuvant) + placebo (adjuvant)** **N = 151**
KEYNOTE 671		
Radiation	13 (9.4)	20 (13.2)
Systemic therapy[b]	34 (24.6)	58 (38.4)
ALK inhibitors	1 (0.7)	1 (0.7)
Alectinib	0 (0)	1 (0.7)
Alectinib hydrochloride	1 (0.7)	0 (0)
EGFR tyrosine kinase inhibitors	3 (2.2)	8 (5.3)
Osimertinib	1 (0.7)	2 (1.3)
Osimertinib mesilate	1 (0.7)	2 (1.3)
Gefitinib	1 (0.7)	1 (0.7)
Icotinib hydrochloride	0 (0)	2 (1.3)
Afatinib dimaleate	0 (0)	1 (0.7)
Furmonertinib mesilate	0 (0)	1 (0.7)
Investigational preparations	0 (0)	1 (0.7)
Multiple	3 (2.2)	16 (10.6)
Paclitaxel	3 (2.2)	14 (9.3)
Bevacizumab	1 (0.7)	4 (2.6)
Other monoclonal antibodies and antibody conjugates	1 (0.7)	2 (1.3)
Ipilimumab	0 (0)	2 (1.3)
Cadonilimab	1 (0.7)	0 (0)
Other protein kinase inhibitors	1 (0.7)	1 (0.7)
Catequentinib hydrochloride	0 (0)	1 (0.7)
Tepotinib	1 (0.7)	0 (0)
PD-1/PD-L1 inhibitors	7 (5.1)	25 (16.6)
Pembrolizumab	4 (2.9)	8 (5.3)
Atezolizumab	1 (0.7)	7 (4.6)
Durvalumab	1 (0.7)	3 (2.0)
Nivolumab	0 (0)	4 (2.6)
Tislelizumab	0 (0)	3 (2.0)
Camrelizumab	1 (0.7)	0 (0)

Table 3: Information on first subsequent antineoplastic therapies – RCT, direct comparison: pembrolizumab + platinum-based chemotherapy[a] (neoadjuvant) + pembrolizumab (adjuvant) vs. placebo + platinum-based chemotherapy[a] (neoadjuvant) + placebo (adjuvant) (patients with tumour cell PD-L1 expression < 1%) (multipage table)

Study	**Patients with subsequent therapy, n (%)**	
Drug class **Drug**	**Pembrolizumab + platinum-based chemotherapy[a] (neoadjuvant) + pembrolizumab (adjuvant)** **N = 138**	**Placebo + platinum-based chemotherapy[a] (neoadjuvant) + placebo (adjuvant)** **N = 151**
Platinum compounds	13 (9.4)	31 (20.5)
Carboplatin	9 (6.5)	26 (17.2)
Cisplatin	4 (2.9)	5 (3.3)
Pyrimidine analogues	6 (4.3)	4 (2.6)
Gemcitabine	4 (2.9)	2 (1.3)
Gimeracil/oteracil (potassium)/tegafur	1 (0.7)	1 (0.7)
Gemcitabine hydrochloride	0 (0)	1 (0.7)
Tegafur/uracil	1 (0.7)	0 (0)
Taxanes	7 (5.1)	6 (4.0)
Docetaxel	6 (4.3)	2 (1.3)
Nanoparticle albumin-bound paclitaxel	1 (0.7)	4 (2.6)
Vinca alkaloids and analogues	1 (0.7)	3 (2.0)
Vinorelbine tartrate	1 (0.7)	2 (1.3)
Vincristine	0 (0)	1 (0.7)
Other[c]		
Doxorubicin	0 (0)	1 (0.7)
Cyclophosphamide	0 (0)	1 (0.7)
Lomustine	0 (0)	1 (0.7)
Sotorasib	2 (1.4)	0 (0)
Mitomycin	0 (0)	1 (0.7)
Denosumab	0 (0)	1 (0.7)
Other therapeutic products	1 (0.7)	0 (0)
Etoposide	1 (0.7)	3 (2.0)
Ramucirumab	2 (1.4)	1 (0.7)
Pemetrexed disodium	4 (2.9)	6 (4.0)

a. Cisplatin + gemcitabine (for squamous histology) or cisplatin + pemetrexed (for non-squamous histology).
b. This includes 2 vs. 5 patients (intervention vs. control) who received radiochemotherapy.
c. Drug classes that contain only one drug are summarized with the respective drug under "other".

ALK: anaplastic lymphoma kinase; EGFR: epidermal growth factor receptor n: number of patients with subsequent therapy; N: number of analysed patients; PD-1: programmed cell death protein 1; PD-L1: programmed death ligand 1; RCT: randomized controlled trial

The company presented data on the first subsequent therapy. The choice of subsequent antineoplastic therapies was not restricted in the KEYNOTE 671 study. In the subpopulation with tumour PD-L1 expression < 1%, 34% in the intervention arm and 52% in the comparator arm received at least one subsequent antineoplastic therapy (systemic and/or radiation therapy). Based on the data on the outcome of failure of the curative approach, death or no qualifying event occurred in 51% of patients in the intervention arm and 38% in the comparator arm. These patients therefore did not require any subsequent antineoplastic therapy. Assuming that patients with other qualifying events were generally eligible for subsequent antineoplastic therapy, only 70% of these patients in the intervention arm and 83% in the comparator arm received at least one subsequent therapy.

25% of the patients in the intervention arm and 38% of the patients in the comparator arm received systemic therapy. A variety of drugs were administered, most commonly platinum-based drugs (9% versus 21%) and PD-1/PD-L1 inhibitors (5% versus 17%). Based on the provided information it is not possible to assess whether the first subsequent therapies administered are adequate. This is explained below. According to the S3 guideline *Prevention, Diagnosis, Treatment and Follow-up of Lung Cancer* and the guideline of the German Society for Haematology and Medical Oncology, patients with advanced or metastatic NSCLC who do not have any treatable mutations and no contraindications to immune checkpoint inhibitors (in the present therapeutic indication, primarily PD-1/PD-L1 inhibitors) should receive systemic therapy with an immune checkpoint inhibitor or a combination of immune checkpoint inhibitor and chemotherapy in the first-line setting [9,10]. These recommendations are based on advantages in overall survival from the use of immune checkpoint inhibitors (also in combination with chemotherapy) in comparison with chemotherapy [9,10].

The information on the total population of the KEYNOTE 671 study shows that 108 patients in the comparator arm had distant metastases as their disease progressed. Of these, 46 (approx. 43%) received subsequent therapy with an immune checkpoint inhibitor. However, in accordance with the recommendations of the guidelines, it can be assumed that subsequent therapy using an immune checkpoint inhibitor would generally have been indicated for patients with distant metastases in the comparator arm [9,10]. For the subpopulation of patients with tumour PD-L1 expression < 1%, no data are available on the proportion of patients with distant metastases.

According to the current S3 guideline, molecular diagnostics for relevant driver mutations (epidermal growth factor receptor [EGFR], anaplastic lymphoma kinase [ALK]) should be carried out in patients with stage III tumours [9]. According to the information provided by the company, 67.5% of patients in the subpopulation with tumour cell PD-L1 expression < 1% were in tumour stage III. However, information on the molecular status was only available for 35.3%

(EGFR) and 30.8% (ALK) of patients at baseline, regardless of tumour stage. No information is available on whether further molecular diagnostics were performed after recurrence. It is therefore unclear whether all patients who could have benefited from a subsequent therapy directed against EGFR or ALK actually received such therapy.

Based on the available data, it is overall assumed that the subsequent systemic therapies administered do not adequately reflect the current standard of care after recurrence. On the one hand, this assessment is based on the low proportion of immune checkpoint inhibitors as subsequent therapy in the comparator arm of the total population and the lack of data for the subpopulation of patients with tumour PD-L1 expression < 1%. On the other hand, it can be assumed that a relevant proportion of patients in stage III were not diagnosed in accordance with the guidelines. Overall, the results for the outcome of overall survival are therefore not interpretable (see Section 2.1.2.1).

Risk of bias across outcomes

Table 4 shows the risk of bias across outcomes (risk of bias at study level).

Table 4: Risk of bias across outcomes (study level) – RCT, direct comparison: pembrolizumab + platinum-based chemotherapy[a] (neoadjuvant) + pembrolizumab (adjuvant) vs. placebo + platinum-based chemotherapy[a] (neoadjuvant) + placebo (adjuvant) (patients with tumour cell PD-L1 expression < 1%)

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patients	Treating staff			
KEYNOTE 671	Yes	Yes	Yes	Yes	Yes	Yes	Low

a. Cisplatin + gemcitabine (for squamous histology) or cisplatin + pemetrexed (for non-squamous histology).

PD-L1: programmed death ligand 1; RCT: randomized controlled trial

The risk of bias across outcomes was rated as low for the KEYNOTE 671 study.

Transferability of the study results to the German health care context

In the company's opinion, the results of the KEYNOTE 671 study are transferable to the German health care context. The company based its assertion on the characteristics of the investigated patient population, the study design, and the approval-compliant use of pembrolizumab and platinum-based chemotherapy. The company also stated that the

subgroups by region showed no important indication of a deviating efficacy or safety of pembrolizumab (in relation to the total population of the KEYNOTE 671 study).

The company did not provide any further information on the transferability of the study results to the German health care context.

2.1.2 Results

2.1.2.1 Presented outcomes

For patients with tumour cell PD-L1 expression < 1% in the KEYNOTE 671 study, the following patient-relevant outcomes should be presented:

- Mortality
  - overall survival
- Morbidity
  - failure of the curative approach
  - symptoms, recorded using European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) and European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Lung Cancer 13 (EORTC QLQ-LC13)
  - health status, recorded using the EQ-5D visual analogue scale (VAS)
- Health-related quality of life
  - health-related quality of life, recorded using EORTC QLQ-C30
- Side effects
  - serious adverse events (SAEs)
  - severe adverse events (AEs) (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3)
  - discontinuation due to AEs
  - immune-related SAEs
  - immune-related severe AEs
  - oedema peripheral (Preferred Term [PT], AE)
  - general disorders and administration site conditions (System Organ Class [SOC], SAE)

Table 5 shows the outcomes for which data were available in the KEYNOTE 671 study (patients with tumour PD-L1 expression < 1%).

Table 5: Matrix of outcomes – RCT, direct comparison: pembrolizumab + platinum-based chemotherapy[a] (neoadjuvant) + pembrolizumab (adjuvant) vs. placebo + platinum-based chemotherapy[a] (neoadjuvant) + placebo (adjuvant) (patients with tumour cell PD-L1 expression < 1%)

Study	Outcomes											
	Overall survival	Failure of the curative approach[b]	Symptoms (EORTC QLQ-C30, EORTC QLQ-LC13)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30)	SAEs	Severe AEs[c]	Discontinuation due to AEs	Immune-related SAEs[d]	Immune-related severe AEs[c, d]	Oedema peripheral (PT, AEs)	General disorders and administration site conditions (SOC, SAEs)
KEYNOTE 671	No[e]	Yes	No[f]	No[f]	No[f]	Yes	Yes	Yes	Yes	Yes	Yes	Yes

a. Cisplatin + gemcitabine (for squamous histology) or cisplatin + pemetrexed (for non-squamous histology).
b. Operationalized via event-free survival: includes the events: radiographic disease progression per RECIST 1.1 that prevents planned surgery; local progression (primary tumour or regional lymph nodes) precluding planned surgery; no surgery (for patients who switched to the adjuvant phase without surgery); inability to resect the tumour; not disease-free after surgery (patients with R1 or R2 resection); local or distant recurrence (for patients who are disease free after surgery [R0 resection]; death due to any cause.
c. Severe AEs are operationalized as CTCAE grade ≥ 3.
d. Presented in Module 4 A using a list of predefined PTs. The same definition is used for the subsequently submitted documents.
e. Data not interpretable; for justification, see body of text below.
f. No suitable data available; for justification, see text below.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; PD-L1: programmed death ligand 1; PT: Preferred Term; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-LC13: Quality of Life Questionnaire-Lung Cancer 13; RCT: randomized controlled trial; RECIST: Response Evaluation Criteria in Solid Tumours; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

Notes on outcomes

Results on overall survival not interpretable due to inadequate subsequent therapies

The overall survival of patients in the present therapeutic indication is composed of a phase of disease-free survival until recurrence and the subsequent stage of advanced and/or metastatic NSCLC.

An observed effect in the outcome of overall survival is not only influenced by the initial study treatment, but also by the subsequent antineoplastic therapies used after disease progression or recurrence [11-13]. In order for an observed effect in the outcome of overall survival to be interpreted meaningfully, adequate guideline-compliant subsequent treatment of patients

after progression or recurrence of the disease is therefore necessary, especially in the (neo-)adjuvant treatment setting.

Based on the available data, however, it is assumed that the subsequent systemic therapies administered do not adequately reflect the current standard of care after recurrence (see Section 2.1.1). Thus, the results on overall survival in the KEYNOTE 671 study cannot be interpreted overall. Irrespective of this, no statistically significant effects were shown for the outcome of overall survival (see Appendix C).

Failure of the curative treatment approach

In the present therapeutic indication, curative therapy is possible in principle. The infeasibility of the planned surgery or recurrence after R0 remission means that the curative treatment approach in this line of therapy has failed. In the present treatment situation, failure of the curative treatment approach in the current line of therapy is a patient-relevant event because, albeit possible in principle, cure is less likely to be achieved in a subsequent line of therapy. Failure of the curative treatment approach is therefore considered a patient-relevant outcome in this assessment.

The statistical analysis plan (SAP) of the KEYNOTE 671 study defined the outcome of event-free survival (EFS) as the time from randomization to the occurrence of one of the following events: radiographic disease progression per RECIST 1.1 (for patients who have not had or will not have surgery or patients 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 patients who are disease free after surgery [R0 resection] or patients with microscopic positive margins [R1 resection]), or death due to any cause.

In addition, the company presented a further operationalization of the EFS outcome in Module 4 A, referred to by the company as “post hoc adapted event-free survival”. The outcome was operationalized as time from randomization to occurrence of any of the following events:

- radiographic disease progression per RECIST 1.1 precluding planned surgery
- local progression (primary tumour or regional lymph nodes) precluding planned surgery
- no surgery (for patients who switched to the adjuvant phase without surgery)
- inability to resect the tumour
- not disease-free after surgery (patients with R1 or R2 resection)
- local or distant recurrence (for patients who are disease free after surgery [R0 resection])

- death due to any cause

The operationalization "post hoc adapted event-free survival" presented by the company post hoc differs from the prespecified operationalization primarily in that failure to achieve an R0 resection, i.e. that the patients were not disease-free after surgery and had an R1 or R2 resection, was also counted as event. In addition, the absence of surgery, i.e. the patients switched to the adjuvant phase without surgery, was counted as event.

It is unclear how the event "local progression (primary tumour or regional lymph nodes) precluding planned surgery" differs from the event "radiographic disease progression per RECIST 1.1", e.g. whether it was also determined radiographically. However, since the event "local progression (primary tumour or regional lymph nodes) precluding planned surgery" only occurred once, this uncertainty has no consequences.

Overall, the operationalization "post hoc adapted event-free survival" presented by the company post hoc is a comprehensive representation of the outcome of failure of the curative approach in comparison with the prespecified operationalization and is used in the present benefit assessment. In addition to the time to occurrence of an event (event-free survival, hazard ratio [HR]), the occurrence of the event (relative risk [RR]) is also relevant for the assessment.

Patient-reported outcomes on morbidity and health-related quality of life

The patient-reported outcomes (PROs) of symptoms (using EORTC QLQ-C30 and EORTC QLQ-LC13), health status (using EQ-5D VAS) and health-related quality of life (using EORTC QLQ-C30) were recorded on the KEYNOTE 671 study. However, the data presented by the company on the PROs cannot be interpreted meaningfully due to the long and potentially different recording-free periods between the neoadjuvant and adjuvant treatment phases and the strongly decreasing return rates. This is explained below.

Different lengths of recording-free periods between the neoadjuvant and adjuvant treatment phases

Figure 1 shows examples of possible recording-free periods for the PROs in the KEYNOTE 671 study.

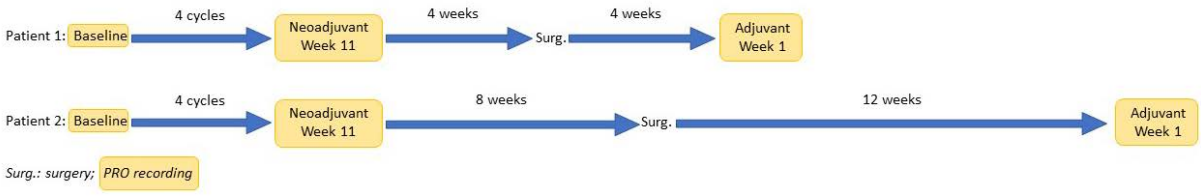

Figure 1: Examples of different lengths of recording-free periods between the neoadjuvant and adjuvant treatment phases in the KEYNOTE 671 study

According to the study protocol, the questionnaires were to be recorded on the first day of Cycle 1 and in the middle of Cycle 4 of the neoadjuvant treatment phase, as well as in Cycles 1, 2, 3, 4, 7, 10 and 13 of the adjuvant treatment phase, at treatment discontinuation, as part of the 30-day follow-up after treatment discontinuation, and as part of the further follow-up observation every 16 weeks in the second and third year and every 6 months in the fourth and fifth year.

No patient-reported outcomes were recorded in the period between the neoadjuvant and adjuvant treatment phases. This means that there was no recording for a period of at least 8 weeks, but even up to 20 weeks depending on the individual patient (see Figure 1). Even longer recording-free periods were possible for patients who received radiotherapy.

From a substantive perspective, this approach is not appropriate. The period between the neoadjuvant and adjuvant treatment phases is part of the study, so the PROs should be continuously recorded. Furthermore, there is no information available on how long this period actually was and whether it differed between the study arms.

Return rates

There was a strong decrease in return rates of the PRO questionnaires, which differed over the course of the observation. When assessing the return rates, there is also the uncertainty that the time points of recording cannot be presented on an absolute time scale (measured from the start of the study) and that there may therefore be (greatly) different time intervals between the individual patients.

Analyses presented by the company on PROs

In the comments, the company presented only continuous analyses using a mixed-effects model with repeated measures (MMRM) for the EORTC QLQ-C30, the EORTC QLQ-LC13 and the EQ-5D VAS. According to the company, the “spatial power” covariance matrix was used for the model, which presumably included the patient-specific time intervals of the recordings. In principle, it makes sense to take these into account in the model. However, more frequent recordings would be appropriate in this case. These should both reflect the period between the neoadjuvant and adjuvant treatment phases and allow temporal comparability of the patients.

In principle, responder analyses are also possible for these outcomes, which would be preferable according to the IQWiG *General Methods* [14].

Conclusion on the PROs

Overall, the lack of recording of PROs between the neoadjuvant and adjuvant treatment phases, the potentially different periods between these phases and the decreasing response

rates mean that the results on PROs cannot be interpreted meaningfully. The results are not presented.

Side effects

Effect measure

In the documents subsequently submitted, the company did not provide any information on the observation periods for the individual outcomes for the subpopulation of patients with tumour cell PD-L1 expression < 1%. However, based on the available observation periods for the total population and the discontinuation rates in the total population and the subpopulation, it is assumed that the observation period for the side effect outcomes is comparable between the treatment arms and that the RR is therefore suitable as an effect measure.

Immune-related AEs

In Module 4 A, the company presented analyses for SAEs and severe AEs under the term immune-related adverse events. According to the company, these outcomes were recorded using a predefined PT list. In the comments, the company presented results on serious and severe events of special interest, without describing these in more detail, for patients with tumour cell PD-L1 expression < 1%. It is assumed that the subsequently submitted documents are the outcomes defined in Module 4 A.

2.1.2.2 Risk of bias

Table 6 describes the risk of bias for the results of the relevant outcomes for patients with tumour cell PD-L1 expression < 1%.

Table 6: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: pembrolizumab + platinum-based chemotherapy[a] (neoadjuvant) + pembrolizumab (adjuvant) vs. placebo + platinum-based chemotherapy[a] (neoadjuvant) + placebo (adjuvant) (patients with tumour cell PD-L1 expression < 1%)

Study		Outcomes											
	Study level	Overall survival	Failure of the curative approach[b]	Symptoms (EORTC QLQ-C30, EORTC QLQ-LC13)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30)	SAEs	Severe AEs[c]	Discontinuation due to AEs	Immune-related SAEs[d]	Immune-related severe AEs[c, d]	Oedema peripheral (PT, AEs)	General disorders and administration site conditions (SOC, SAEs)
KEYNOTE 671	L	–[e]	L	–[f]	–[f]	–[f]	L	L	L	L	L	L	L

a. Cisplatin + gemcitabine (for squamous histology) or cisplatin + pemetrexed (for non-squamous histology).
b. Operationalized via event-free survival: includes the events: radiographic disease progression per RECIST 1.1 that prevents planned surgery; local progression (primary tumour or regional lymph nodes) precluding planned surgery; no surgery (for patients who switched to the adjuvant phase without surgery); inability to resect the tumour; not disease-free after surgery (patients with R1 or R2 resection); local or distant recurrence (for patients who are disease free after surgery [R0 resection]; death due to any cause.
c. Severe AEs are operationalized as CTCAE grade ≥ 3.
d. Presented in Module 4 A using a list of predefined PTs. The same definition is used for the subsequently submitted documents.
e. Data not interpretable; for justification, see Section 2.1.2.1.
f. No suitable data available; for justification, see Section 2.1.2.1.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; H: high; L: low; PD-L1: programmed death ligand 1; PT: Preferred Term; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-LC13: Quality of Life Questionnaire-Lung Cancer 13; RCT: randomized controlled trial; RECIST: Response Evaluation Criteria in Solid Tumours; SAE: serious adverse event; SOC: System Organ Class

For patients with tumour cell PD-L1 expression < 1%, the risk of bias for the outcomes of failure of the curative approach and side effects is rated as low in each case.

2.1.2.3 Results

Table 7 and Table 8 summarize the results of the comparison of pembrolizumab + platinum-based chemotherapy (neoadjuvant) + pembrolizumab (adjuvant) versus placebo + platinum-based chemotherapy (neoadjuvant) + placebo (adjuvant) in patients with tumour cell PD-L1 expression < 1%.

The Kaplan-Meier curves for the outcomes of overall survival and failure of the curative approach are shown in Appendix A.

Table 7: Results (mortality, morbidity, time to event) – RCT, direct comparison: pembrolizumab + platinum-based chemotherapy[a] (neoadjuvant) + pembrolizumab (adjuvant) vs. placebo + platinum-based chemotherapy[a] (neoadjuvant) + placebo (adjuvant) (patients with tumour cell PD-L1 expression < 1%) (multipage table)

Study **Outcome category** **Outcome**	**Pembrolizumab + platinum-based chemotherapy[a] (neoadjuvant) + pembrolizumab (adjuvant)**		**Placebo + platinum-based chemotherapy[a] (neoadjuvant) + placebo (adjuvant)**		**Pembrolizumab + platinum-based chemotherapy[a] (neoadjuvant) + pembrolizumab (adjuvant) vs. placebo + platinum-based chemotherapy[a] (neoadjuvant) + placebo (adjuvant)**
	N	**Median time to event in months [95% CI]** **Patients with event n (%)**	**N**	**Median time to event in months [95% CI]** **Patients with event n (%)**	**HR [95%-CI]; p-value[b]**
KEYNOTE 671					
Mortality					
Overall survival			No suitable data[c]		
Morbidity					
Failure of the curative approach[d]	138	13.1 [8.3; 26.3] 85 (61.6)	151	12.8 [9.4; 17.9] 107 (70.9)	0.81 [0.61; 1.08]; 0.150 RR [95% CI]; p-value 0.87 [0.74; 1.03]; 0.100
Death	138	– 18 (13.0)	151	– 13 (8.6)	–[e]
Local progression precluding planned surgery	138	– 0 (0)	151	– 1 (0.7)	–[e]
No R0 surgery	138	– 7 (5.1)	151	– 16 (10.6)	–[e]
No surgery[f]	138	– 17 (12.3)	151	– 12 (7.9)	–[e]
Disease progression per RECIST 1.1	138	– 6 (4.3)	151	– 6 (4.0)	–[e]
Recurrence	138	– 35 (25.4)	151	– 49 (32.5)	–[e]
Unresectable	138	– 2 (1.4)	151	– 10 (6.6)	–[e]

Table 7: Results (mortality, morbidity, time to event) – RCT, direct comparison: pembrolizumab + platinum-based chemotherapy[a] (neoadjuvant) + pembrolizumab (adjuvant) vs. placebo + platinum-based chemotherapy[a] (neoadjuvant) + placebo (adjuvant) (patients with tumour cell PD-L1 expression < 1%) (multipage table)

Study **Outcome category** **Outcome**	**Pembrolizumab + platinum-based chemotherapy[a] (neoadjuvant) + pembrolizumab (adjuvant)**		**Placebo + platinum-based chemotherapy[a] (neoadjuvant) + placebo (adjuvant)**		**Pembrolizumab + platinum-based chemotherapy[a] (neoadjuvant) + pembrolizumab (adjuvant) vs. placebo + platinum-based chemotherapy[a] (neoadjuvant) + placebo (adjuvant)**
	N	**Median time to event in months [95% CI]** **Patients with event n (%)**	**N**	**Median time to event in months [95% CI]** **Patients with event n (%)**	**HR [95%-CI]; p-value[b]**
Symptoms (EORTC QLQ-C30, EORTC QLQ-LC13)			No suitable data[g]		
Health status (EQ-5D VAS)			No suitable data[g]		
Health-related quality of life			No suitable data[g]		

a. Cisplatin + gemcitabine (for squamous histology) or cisplatin + pemetrexed (for non-squamous histology).
b. Effect, CI and p-value: Cox proportional hazards model, unclear whether stratification as described in Module 4 of the company (stratification factors: tumour stage [II vs. III], PD-L1 status [TPS < 50% vs. TPS ≥ 50%], histology [squamous vs. non-squamous] and region [East Asia vs. non-East Asia], with prespecified summary [depending on outcome, see Module 4 of the company] of characteristics due to low number of events) was also used here; p-value: Wald test.
c. For justification, see Section 2.1.2.1.
d. Operationalized via event-free survival: includes the events: radiographic disease progression per RECIST 1.1 that prevents planned surgery; local progression (primary tumour or regional lymph nodes) precluding planned surgery; no surgery (for patients who switched to the adjuvant phase without surgery); inability to resect the tumour; not disease-free after surgery (patients with R1 or R2 resection); local or distant recurrence (for patients who are disease free after surgery [R0 resection]; death due to any cause.
e. As only the qualifying events for the EFS are provided for the individual components, the effect estimates for the individual components are not shown.
f. Reasons for absence of surgery: physician decision, adverse event, withdrawal of consent or refusal by the patient, disease progression per RECIST 1.1, clinical progression and new cancer therapy not included in the study.
g. No suitable data available; for justification, see Section 2.1.2.1.

CI: confidence interval; EFS: event-free survival; HR: hazard ratio; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; NC: not calculable; PD-L1: programmed death ligand 1; RCT: randomized controlled trial; RECIST: Response Evaluation Criteria in Solid Tumours

Table 8: Results (side effects) – RCT, direct comparison: pembrolizumab + platinum-based chemotherapy[a] (neoadjuvant) + pembrolizumab (adjuvant) vs. placebo + platinum-based chemotherapy[a] (neoadjuvant) + placebo (adjuvant) (patients with tumour cell PD-L1 expression < 1%)

Study **Outcome category** **Outcome**	**Pembrolizumab + platinum-based chemotherapy[a] (neoadjuvant) + pembrolizumab (adjuvant)**		**Placebo + platinum-based chemotherapy[a] (neoadjuvant) + placebo (adjuvant)**		**Pembrolizumab + platinum-based chemotherapy[a] (neoadjuvant) + pembrolizumab (adjuvant) vs. placebo + platinum-based chemotherapy[a] (neoadjuvant) + placebo (adjuvant)**
	N	**Patients with event n (%)**	**N**	**Patients with event n (%)**	**RR [95% CI][b]; p-value[c]**
KEYNOTE 671					
Side effects					
AEs (supplementary information)	138	137 (99.3)	151	148 (98.0)	–
SAEs	138	58 (42.0)	151	48 (31.8)	1.32 [0.97; 1.79]; 0.074
Severe AEs[d]	138	89 (64.5)	151	87 (57.6)	1.12 [0.93; 1.35]; 0.256
Discontinuation due to AEs	138	37 (26.8)	151	26 (17.2)	1.56 [0.998; 2.43]; 0.0505
Immune-related SAEs[e]	138	9 (6.5)	151	2 (1.3)	4.92 [1.08; 22.39]; 0.022
Immune-related severe AEs[d, e]	138	8 (5.8)	151	3 (2.0)	2.92 [0.79; 10.78]; 0.096
Oedema peripheral (PT, AEs)	138	19 (13.8)	151	7 (4.6)	2.97 [1.29; 6.85]; 0.007
General disorders and administration site conditions (SOC, SAEs)	138	11 (8.0)	151	2 (1.3)	6.02 [1.36; 26.67]; 0.007

a. Cisplatin + gemcitabine (for squamous histology) or cisplatin + pemetrexed (for non-squamous histology).
b. Institute's calculation of RR and CI (asymptotic).
c. Institute's calculation (unconditional exact test, CSZ method according to [15]).
d. Operationalized as CTCAE grade ≥ 3.
e. Presented in Module 4 A using a list of predefined PTs. The same definition is used for the subsequently submitted documents.

AE: adverse event; CI: confidence interval; CSZ: convexity, symmetry, z-score; CTCAE: Common Terminology Criteria for Adverse Events; n: number of patients with (at least one) event; N: number of analysed patients; PD-L1: programmed death ligand 1; PT: Preferred Term; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SOC: System Organ Class

Mortality

Overall survival

The results for the outcome of overall survival are not interpretable (see Section 2.1.2.1).

Morbidity

Failure of the curative approach

No statistically significant difference between treatment groups was found for the outcome of failure of the curative treatment approach.

Symptoms (EORTC QLQ-C30 and EORTC QLQ-LC13) and health status (EQ-5D VAS)

No suitable data are available for the outcomes of symptoms (recorded using EORTC QLQ-C30 and EORTC QLQ-LC13) and health status (recorded using EQ-5D VAS) (for reasons, see Section 2.1.2.1).

Health-related quality of life (EORTC QLQ-C30)

No suitable data are available for the outcome of health-related quality of life (recorded using EORTC QLQ-C30) (for reasons, see Section 2.1.2.1).

Side effects

SAEs, severe AEs, and discontinuation due to AEs

There were no statistically significant differences between treatment groups for the outcomes of SAEs, severe AEs and discontinuation due to AEs.

Specific AEs

Immune-related SAEs, oedema peripheral (AEs), general disorders and administration site conditions (SAEs)

A statistically significant difference to the disadvantage of pembrolizumab + platinum-based chemotherapy (neoadjuvant) + pembrolizumab (adjuvant) compared with placebo + platinum-based chemotherapy (neoadjuvant) + placebo (adjuvant) was shown for each of the outcomes of immune-related SAEs, oedema peripheral, and general disorders and administration site conditions (SAEs).

Immune-related severe AEs

There was no statistically significant difference between treatment groups for the outcome of immune-related severe AEs.

2.1.2.4 Subgroups and other effect modifiers

For this addendum, the following potential effect modifiers are considered for patients with tumour PD-L1 expression < 1%:

- age (< 65 years versus ≥ 65 years)
- sex (female versus male)
- tumour stage (II versus III)

Interaction tests are performed when at least 10 patients per subgroup are included in the analysis. For binary data, there must also be at least 10 events in at least one subgroup.

Only the results with an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) are presented. In addition, subgroup results are presented only if there is a statistically significant and relevant effect in at least one subgroup.

No subgroup analyses are available for the population of patients with tumour PD-L1 expression < 1%.

2.1.3 Summary of the results

Overall, no advantages were shown for pembrolizumab + platinum-based chemotherapy (neoadjuvant) + pembrolizumab (adjuvant) compared with placebo + platinum-based chemotherapy (neoadjuvant) + placebo (adjuvant).

For the following outcomes, disadvantages were shown for pembrolizumab + platinum-based chemotherapy (neoadjuvant) + pembrolizumab (adjuvant) compared with placebo + platinum-based chemotherapy (neoadjuvant) + placebo (adjuvant):

- immune-related SAEs
- oedema peripheral (AEs)
- general disorders and administration site conditions (SAEs)

2.2 Summary

The conclusion on the added benefit of pembrolizumab in combination with platinum-based chemotherapy for neoadjuvant and subsequently as monotherapy for adjuvant treatment in comparison with the ACT specified by the G-BA for patients with tumour cell PD-L1 expression < 1% does not change in comparison with dossier assessment A24-46 [1].

Table 9 below shows the result of the benefit assessment of pembrolizumab in combination with platinum-based chemotherapy for neoadjuvant and subsequently as monotherapy for adjuvant treatment, taking into account both dossier assessment A24-46 and the present addendum.

Table 9: Pembrolizumab in combination with platinum-based chemotherapy (neoadjuvant) and subsequent monotherapy (adjuvant) – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
Adult patients with resectable non-small cell lung cancer with tumour cell PD-L1 expression < 1% at high risk of recurrence; neoadjuvant and adjuvant treatment	Neoadjuvant[b]: individualized treatment selected from ▪ pre-operative (neoadjuvant) systemic chemotherapy selected from ▫ cisplatin in combination with a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed) and ▫ carboplatin in combination with a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed) and ▪ simultaneous radiochemotherapy with platinum-based (cisplatin or carboplatin) combination chemotherapy taking into account the tumour stage, the tumour histology, the presence of a Pancoast tumour and the feasibility of an R0 resection, as well as the prerequisites for the use of carboplatin adjuvant: BSC[c]	Added benefit not proven

a. Presented is the respective ACT specified by the G-BA.
b. Comments of the G-BA:
- The ACT was determined in the present therapeutic indication on the condition that the decision in favour of neoadjuvant therapy was made in the present therapeutic indication.
- For the implementation of individualized therapy in a study of direct comparison, the investigator is expected to have a selection of several treatment options at disposal to permit an individualized treatment decision taking into account the listed criteria (multicomparator study). A rationale must be provided for the choice and any limitation of treatment options. The decision on individualized treatment with regard to the comparator therapy should be made before group allocation (e.g. randomization). This does not apply to necessary therapy adjustments during the course of the study (e.g. due to the onset of symptoms or similar reasons). If only a single-comparator study is submitted, the extent to which conclusions on a subpopulation can be derived will be examined as part of the benefit assessment.
- Cisplatin and carboplatin, each in combination with a third-generation cytostatic agent, are not approved for the neoadjuvant treatment of resectable NSCLC. The use of cisplatin or carboplatin in combination with vinorelbine, paclitaxel, docetaxel, gemcitabine, or pemetrexed is medically necessary for the neoadjuvant treatment of patients with NSCLC with tumour cell PD-L1 expression < 1%. According to the generally recognized state of medical knowledge in the therapeutic indication to be assessed, off-label use is considered the therapy standard.

c. BSC refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.

ACT: appropriate comparator therapy; BSC: best supportive care; G-BA: Federal Joint Committee; NSCLC: non-small cell lung cancer; PD-L1: programmed death ligand 1

The G-BA decides on the added benefit.

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The reference list contains citations provided by the company in which bibliographical information may be missing.

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Appendix A Kaplan-Meier curves (patients with tumour cell PD-L1 expression < 1%)

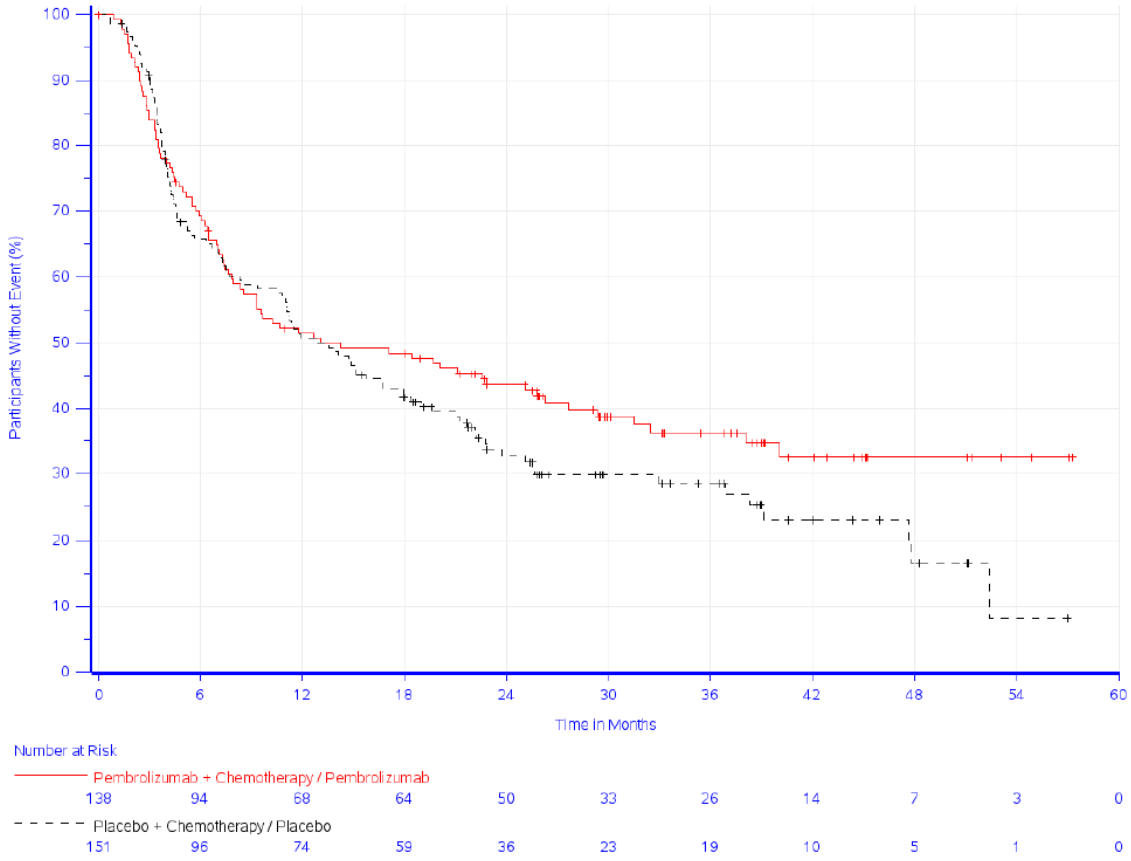

Figure 2: Kaplan-Meier curves for the outcome of failure of the curative treatment approach (post hoc adapted analysis) (KEYNOTE 671 study, patients with tumour cell PD-L1 expression < 1%)

Appendix B Results on side effects

For the overall rates of AEs, SAEs, and severe AEs (CTCAE grade ≥ 3), the following tables present events for SOCs and PTs according to the Medical Dictionary for Regulatory Activities (MedDRA), each on the basis of the following criteria:

- Overall rate of AEs (irrespective of severity): events that occurred in at least 10% of patients in one study arm
- Overall rates of severe AEs (CTCAE grade ≥ 3) and SAEs: events that occurred in at least 5% of patients in one study arm
- In addition, for all events irrespective of severity grade: events that occurred in at least 10 patients and in at least 1% of patients in one study arm

For the outcome of discontinuation due to AEs, a complete presentation of all events (SOCs/PTs) that resulted in discontinuation is provided.

Table 10: Common AEs[a] – RCT, direct comparison: pembrolizumab + platinum-based chemotherapy[b] (neoadjuvant) + pembrolizumab (adjuvant) vs. placebo + platinum-based chemotherapy[b] (neoadjuvant) + placebo (adjuvant) (patients with tumour cell PD-L1 expression < 1%) (multipage table)

Study	**Patients with event n (%)**	
SOC[c] **PT[c]**	**Pembrolizumab + platinum-based chemotherapy[b] (neoadjuvant) + pembrolizumab (adjuvant) N = 138**	**Placebo + platinum-based chemotherapy[b] (neoadjuvant) + placebo (adjuvant) N = 151**
KEYNOTE 671		
Overall AE rate	137 (99.3)	148 (98.0)
Blood and lymphatic system disorders	61 (44.2)	72 (47.7)
Anaemia	59 (42.8)	68 (45.0)
Cardiac disorders	19 (13.8)	21 (13.9)
Ear and labyrinth disorders	11 (8.0)	11 (7.3)
Endocrine disorders	19 (13.8)	5 (3.3)
Hypothyroidism	11 (8.0)	3 (2.0)
Eye disorders	9 (6.5)	13 (8.6)
Gastrointestinal disorders	104 (75.4)	112 (74.2)
Constipation	51 (37.0)	54 (35.8)
Diarrhoea	35 (25.4)	30 (19.9)
Dyspepsia	5 (3.6)	12 (7.9)
Nausea	72 (52.2)	73 (48.3)
Stomatitis	9 (6.5)	14 (9.3)
Vomiting	26 (18.8)	21 (13.9)
General disorders and administration site conditions	87 (63.0)	75 (49.7)
Asthenia	17 (12.3)	22 (14.6)
Chest pain	14 (10.1)	6 (4.0)
Fatigue	47 (34.1)	30 (19.9)
Malaise	8 (5.8)	11 (7.3)
Oedema peripheral	19 (13.8)	7 (4.6)
Pyrexia	19 (13.8)	11 (7.3)
Infections and infestations	60 (43.5)	53 (35.1)
COVID-19	5 (3.6)	10 (6.6)
Pneumonia	10 (7.2)	17 (11.3)
Upper respiratory tract infection	10 (7.2)	6 (4.0)
Injury, poisoning and procedural complications	39 (28.3)	56 (37.1)
Procedural pain	11 (8.0)	20 (13.2)
Wound complication	7 (5.1)	14 (9.3)

Table 10: Common AEs[a] – RCT, direct comparison: pembrolizumab + platinum-based chemotherapy[b] (neoadjuvant) + pembrolizumab (adjuvant) vs. placebo + platinum-based chemotherapy[b] (neoadjuvant) + placebo (adjuvant) (patients with tumour cell PD-L1 expression < 1%) (multipage table)

Study	**Patients with event n (%)**	
SOC[c] **PT[c]**	**Pembrolizumab + platinum-based chemotherapy[b] (neoadjuvant) + pembrolizumab (adjuvant) N = 138**	**Placebo + platinum-based chemotherapy[b] (neoadjuvant) + placebo (adjuvant) N = 151**
Investigations	93 (67.4)	109 (72.2)
Alanine aminotransferase increased	27 (19.6)	17 (11.3)
Aspartate aminotransferase increased	19 (13.8)	16 (10.6)
Blood creatinine increased	26 (18.8)	22 (14.6)
Lymphocyte count decreased	12 (8.7)	13 (8.6)
Neutrophil count decreased	54 (39.1)	67 (44.4)
Platelet count decreased	20 (14.5)	35 (23.2)
Weight decreased	11 (8.0)	9 (6.0)
White blood cell count decreased	42 (30.4)	38 (25.2)
Metabolism and nutrition disorders	73 (52.9)	79 (52.3)
Decreased appetite	32 (23.2)	42 (27.8)
Hyperglycaemia	16 (11.6)	18 (11.9)
Hyperkalaemia	11 (8.0)	9 (6.0)
Hypokalaemia	10 (7.2)	17 (11.3)
Hypomagnesaemia	15 (10.9)	10 (6.6)
Hyponatraemia	12 (8.7)	13 (8.6)
Musculoskeletal and connective tissue disorders	31 (22.5)	45 (29.8)
Arthralgia	11 (8.0)	14 (9.3)
Nervous system disorders	48 (34.8)	57 (37.7)
Dizziness	15 (10.9)	15 (9.9)
Dysgeusia	7 (5.1)	10 (6.6)
Headache	10 (7.2)	9 (6.0)
Psychiatric disorders	21 (15.2)	18 (11.9)
Insomnia	16 (11.6)	10 (6.6)

Table 10: Common AEs[a] – RCT, direct comparison: pembrolizumab + platinum-based chemotherapy[b] (neoadjuvant) + pembrolizumab (adjuvant) vs. placebo + platinum-based chemotherapy[b] (neoadjuvant) + placebo (adjuvant) (patients with tumour cell PD-L1 expression < 1%) (multipage table)

Study	**Patients with event n (%)**	
SOC[c] **PT[c]**	**Pembrolizumab + platinum-based chemotherapy[b] (neoadjuvant) + pembrolizumab (adjuvant) N = 138**	**Placebo + platinum-based chemotherapy[b] (neoadjuvant) + placebo (adjuvant) N = 151**
Renal and urinary disorders	21 (15.2)	24 (15.9)
Respiratory, thoracic and mediastinal disorders	79 (57.2)	79 (52.3)
Cough	23 (16.7)	27 (17.9)
Dyspnoea	24 (17.4)	18 (11.9)
Hiccups	9 (6.5)	14 (9.3)
Pneumothorax	8 (5.8)	11 (7.3)
Productive cough	3 (2.2)	15 (9.9)
Skin and subcutaneous tissue disorders	67 (48.6)	48 (31.8)
Alopecia	15 (10.9)	12 (7.9)
Pruritus	20 (14.5)	8 (5.3)
Rash	22 (15.9)	13 (8.6)
Vascular disorders	22 (15.9)	27 (17.9)
Hypertension	11 (8.0)	10 (6.6)

a. Events that occurred in ≥ 10 patients in at least one study arm.
b. Cisplatin + gemcitabine (for squamous histology) or cisplatin + pemetrexed (for non-squamous histology).
c. SOC and PT notation taken without adaptation from the company's comments.

AE: adverse event; COVID-19: coronavirus disease 2019; n: number of patients with at least one event; N: number of analysed patients; PD-L1: programmed death ligand 1; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class

Table 11: Common SAEs[a] – RCT, direct comparison: pembrolizumab + platinum-based chemotherapy[b] (neoadjuvant) + pembrolizumab (adjuvant) vs. placebo + platinum-based chemotherapy[b] (neoadjuvant) + placebo (adjuvant) (patients with tumour cell PD-L1 expression < 1%)

Study	**Patients with event n (%)**	
SOC[c] **PT[c]**	**Pembrolizumab + platinum-based chemotherapy[b] (neoadjuvant) + pembrolizumab (adjuvant) N = 138**	**Placebo + platinum-based chemotherapy[b] (neoadjuvant) + placebo (adjuvant) N = 151**
KEYNOTE 671		
Overall SAE rate	58 (42.0)	48 (31.8)
Cardiac disorders	9 (6.5)	4 (2.6)
General disorders and administration site conditions	11 (8.0)	2 (1.3)
Infections and infestations	16 (11.6)	15 (9.9)
Respiratory, thoracic and mediastinal disorders	17 (12.3)	12 (7.9)

a. Events that occurred in at least one study arm in ≥ 5% of patients.
b. Cisplatin + gemcitabine (for squamous histology) or cisplatin + pemetrexed (for non-squamous histology).
c. SOC and PT notation taken without adaptation from the company's comments.

n: number of patients with at least one event; N: number of analysed patients; PD-L1: programmed death ligand 1; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class

Table 12: Common severe AEs (CTCAE ≥ 3)[a] – RCT, direct comparison: pembrolizumab + platinum-based chemotherapy[b] (neoadjuvant) + pembrolizumab (adjuvant) vs. placebo + platinum-based chemotherapy[b] (neoadjuvant) + placebo (adjuvant) (patients with tumour cell PD-L1 expression < 1%)

Study	**Patients with event n (%)**	
SOC[c] **PT[c]**	**Pembrolizumab + platinum-based chemotherapy[b] (neoadjuvant) + pembrolizumab (adjuvant) N = 138**	**Placebo + platinum-based chemotherapy[b] (neoadjuvant) + placebo (adjuvant) N = 151**
KEYNOTE 671		
Overall rate of severe AEs (CTCAE grade ≥ 3)	89 (64.5)	87 (57.6)
Blood and lymphatic system disorders	12 (8.7)	11 (7.3)
Anaemia	9 (6.5)	11 (7.3)
Cardiac disorders	9 (6.5)	5 (3.3)
Gastrointestinal disorders	9 (6.5)	6 (4.0)
General disorders and administration site conditions	14 (10.1)	6 (4.0)
Infections and infestations	15 (10.9)	19 (12.6)
Investigations	44 (31.9)	46 (30.5)
Neutrophil count decreased	30 (21.7)	33 (21.9)
Platelet count decreased	7 (5.1)	11 (7.3)
White blood cell count decreased	8 (5.8)	10 (6.6)
Metabolism and nutrition disorders	16 (11.6)	15 (9.9)
Respiratory, thoracic and mediastinal disorders	19 (13.8)	14 (9.3)
Vascular disorders	8 (5.8)	10 (6.6)

a. Events that occurred in at least one study arm in ≥ 5% of patients.
b. Cisplatin + gemcitabine (for squamous histology) or cisplatin + pemetrexed (for non-squamous histology).
c. SOC and PT notation taken without adaptation from the company's comments.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; n: number of patients with at least one event; N: number of analysed patients; PD-L1: programmed death ligand 1; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class

Table 13: Discontinuations due to AEs – RCT, direct comparison: pembrolizumab + platinum-based chemotherapy[a] (neoadjuvant) + pembrolizumab (adjuvant) vs. placebo + platinum-based chemotherapy[a] (neoadjuvant) + placebo (adjuvant) (patients with tumour cell PD-L1 expression < 1%) (multipage table)

Study	**Patients with event n (%)**	
SOC[b] **PT[b]**	**Pembrolizumab + platinum-based chemotherapy[a] (neoadjuvant) + pembrolizumab (adjuvant) N = 138**	**Placebo + platinum-based chemotherapy[a] (neoadjuvant) + placebo (adjuvant) N = 151**
KEYNOTE 671		
Overall rate of discontinuations due to AEs	37 (26.8)	26 (17.2)
Blood and lymphatic system disorders	2 (1.4)	0 (0)
Anaemia	2 (1.4)	0 (0)
Cardiac disorders	1 (0.7)	1 (0.7)
Acute myocardial infarction	0 (0)	1 (0.7)
Myocarditis	1 (0.7)	0 (0)
Ear and labyrinth disorders	0 (0)	1 (0.7)
Hypoacusis	0 (0)	1 (0.7)
Endocrine disorders	1 (0.7)	0 (0)
Hypophysitis	1 (0.7)	0 (0)
Gastrointestinal disorders	1 (0.7)	2 (1.3)
Nausea	0 (0)	1 (0.7)
Oesophagitis	0 (0)	1 (0.7)
Upper gastrointestinal haemorrhage	1 (0.7)	0 (0)
General disorders and administration site conditions	3 (2.2)	3 (2.0)
Malaise	0 (0)	2 (1.3)
Death	1 (0.7)	0 (0)
Face oedema	1 (0.7)	0 (0)
Fatigue	0 (0)	1 (0.7)
Generalised oedema	1 (0.7)	0 (0)
Sudden cardiac death	1 (0.7)	0 (0)
Hepatobiliary disorders	1 (0.7)	0 (0)
Drug-induced liver injury	1 (0.7)	0 (0)

Table 13: Discontinuations due to AEs – RCT, direct comparison: pembrolizumab + platinum-based chemotherapy[a] (neoadjuvant) + pembrolizumab (adjuvant) vs. placebo + platinum-based chemotherapy[a] (neoadjuvant) + placebo (adjuvant) (patients with tumour cell PD-L1 expression < 1%) (multipage table)

Study	**Patients with event n (%)**	
SOC[b] **PT[b]**	**Pembrolizumab + platinum-based chemotherapy[a] (neoadjuvant) + pembrolizumab (adjuvant) N = 138**	**Placebo + platinum-based chemotherapy[a] (neoadjuvant) + placebo (adjuvant) N = 151**
Infections and infestations	3 (2.2)	4 (2.6)
COVID-19	1 (0.7)	0 (0)
Hepatitis A	0 (0)	1 (0.7)
Hepatitis C	0 (0)	1 (0.7)
Pneumonia	1 (0.7)	0 (0)
Pneumonia bacterial	1 (0.7)	0 (0)
Septic shock	1 (0.7)	0 (0)
Staphylococcal sepsis	0 (0)	1 (0.7)
Subcutaneous abscess	0 (0)	1 (0.7)
Systemic infection	0 (0)	1 (0.7)
Investigations	7 (5.1)	8 (5.3)
Neutrophil count decreased	2 (1.4)	4 (2.6)
Alanine aminotransferase increased	3 (2.2)	1 (0.7)
Aspartate aminotransferase increased	3 (2.2)	1 (0.7)
Blood creatinine increased	1 (0.7)	1 (0.7)
Glomerular filtration rate decreased	1 (0.7)	0 (0)
Platelet count decreased	0 (0)	1 (0.7)
Weight decreased	0 (0)	1 (0.7)
White blood cell count decreased	1 (0.7)	0 (0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.7)	0 (0)
Acute leukaemia	1 (0.7)	0 (0)
Nervous system disorders	3 (2.2)	4 (2.6)
Neuropathy peripheral	2 (1.4)	0 (0)
Cerebral haemorrhage	0 (0)	1 (0.7)
Cerebrovascular accident	1 (0.7)	0 (0)
Dizziness	0 (0)	1 (0.7)
Ischaemic cerebral infarction	0 (0)	1 (0.7)
Syncope	0 (0)	1 (0.7)

Table 13: Discontinuations due to AEs – RCT, direct comparison: pembrolizumab + platinum-based chemotherapy[a] (neoadjuvant) + pembrolizumab (adjuvant) vs. placebo + platinum-based chemotherapy[a] (neoadjuvant) + placebo (adjuvant) (patients with tumour cell PD-L1 expression < 1%) (multipage table)

Study	**Patients with event n (%)**	
SOC[b] **PT[b]**	**Pembrolizumab + platinum-based chemotherapy[a] (neoadjuvant) + pembrolizumab (adjuvant) N = 138**	**Placebo + platinum-based chemotherapy[a] (neoadjuvant) + placebo (adjuvant) N = 151**
Renal and urinary disorders	4 (2.9)	4 (2.6)
Renal failure	1 (0.7)	2 (1.3)
Acute kidney injury	1 (0.7)	1 (0.7)
Renal injury	1 (0.7)	1 (0.7)
Chronic kidney disease	1 (0.7)	0 (0)
Respiratory, thoracic and mediastinal disorders	11 (8.0)	3 (2.0)
Interstitial lung disease	2 (1.4)	1 (0.7)
Pulmonary embolism	1 (0.7)	1 (0.7)
Respiratory failure	2 (1.4)	0 (0)
Acute respiratory failure	0 (0)	1 (0.7)
Dyspnoea	1 (0.7)	0 (0)
Immune-mediated lung disease	1 (0.7)	0 (0)
Organising pneumonia	1 (0.7)	0 (0)
Pleural effusion	1 (0.7)	0 (0)
Pneumonitis	1 (0.7)	0 (0)
Pulmonary haemorrhage	1 (0.7)	0 (0)
Skin and subcutaneous tissue disorders	0 (0)	1 (0.7)
Rash	0 (0)	1 (0.7)
Vascular disorders	1 (0.7)	0 (0)
Hypertension	1 (0.7)	0 (0)

a. Cisplatin + gemcitabine (for squamous histology) or cisplatin + pemetrexed (for non-squamous histology).
b. SOC and PT notation taken without adaptation from the company's comments.

AE: adverse event; COVID-19: coronavirus disease 2019; n: number of patients with at least one event; N: number of analysed patients; PD-L1: programmed death ligand 1; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class

Appendix C Result and Kaplan-Meier curves for the outcome of overall survival

Table 14: Results (mortality, time to event) – RCT, direct comparison: pembrolizumab + platinum-based chemotherapy[a] (neoadjuvant) + pembrolizumab (adjuvant) vs. placebo + platinum-based chemotherapy[a] (neoadjuvant) + placebo (adjuvant) (research question 2: patients with tumour PD-L1 expression < 1%)

Study **Outcome category** **Outcome**	**Pembrolizumab + platinum-based chemotherapy[a] (neoadjuvant) + pembrolizumab (adjuvant)**		**Placebo + platinum-based chemotherapy[a] (neoadjuvant) + placebo (adjuvant)**		**Pembrolizumab + platinum-based chemotherapy[a] (neoadjuvant) + pembrolizumab (adjuvant) vs. placebo + platinum-based chemotherapy[a] (neoadjuvant) + placebo (adjuvant)**
	N	**Median time to event in months [95% CI]** **Patients with event n (%)**	**N**	**Median time to event in months [95% CI]** **Patients with event n (%)**	**HR [95%-CI]; p-value[b]**
KEYNOTE 671					
Mortality					
Overall survival	138	NA [41.4; NC] 52 (37.7)[c]	151	47.5 [36.9; 53.7] 61 (40.4)[c]	0.91 [0.63; 1.32]; 0.618

a. Cisplatin + gemcitabine (for squamous histology) or cisplatin + pemetrexed (for non-squamous histology).
b. Effect, CI and p-value: Cox proportional hazards model, unclear whether stratification as described in Module 4 of the company (stratification factors: tumour stage [II vs. III], PD-L1 status [TPS < 50% vs. TPS ≥ 50%], histology [squamous vs. non-squamous] and region [East Asia vs. non-East Asia], with prespecified summary [depending on outcome, see Module 4 of the company] of characteristics due to low number of events) was also used here; p-value: Wald test.
c. This includes one patient in each arm who had withdrawn consent before death; it is unclear why these 2 patients were included in the analysis.

CI: confidence interval; HR: hazard ratio; n: number of patients with (at least one) event; N: number of analysed patients; PD-L1: programmed death ligand 1; RCT: randomized controlled trial; TPS: Tumour Proportion Score

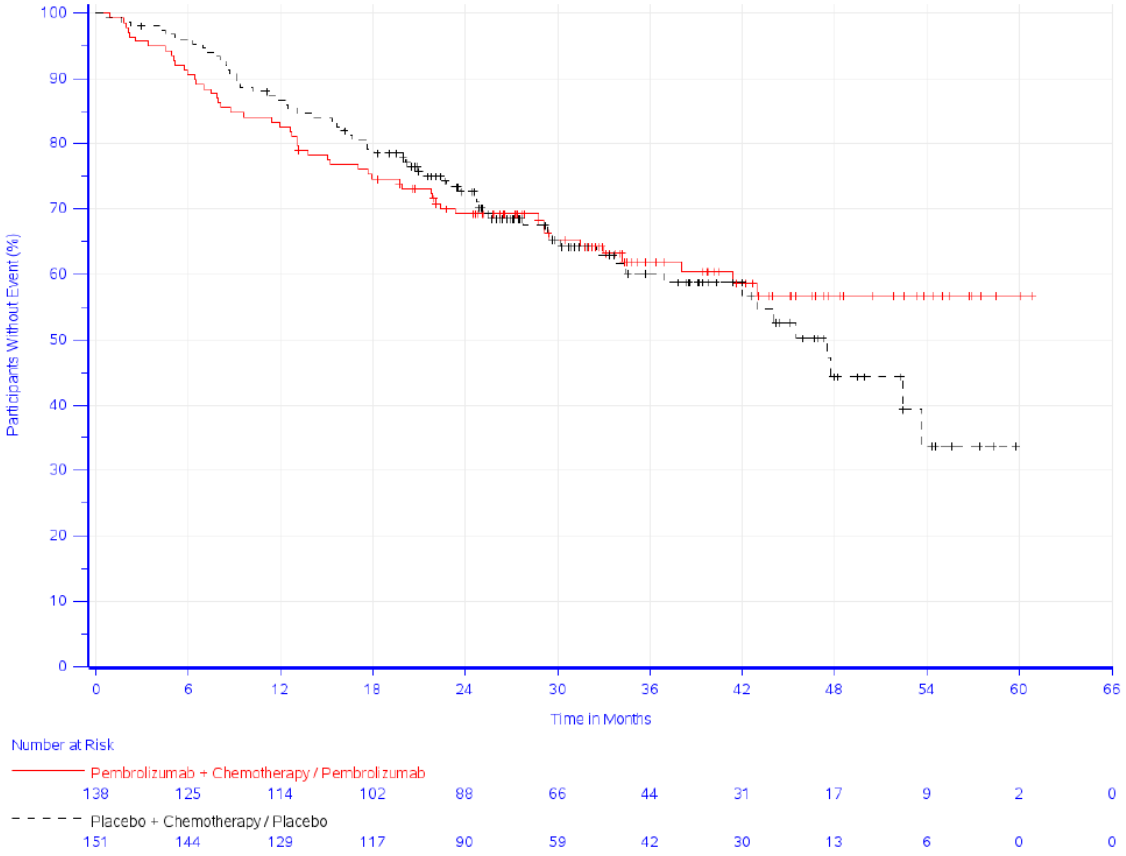

Figure 3: Kaplan-Meier curves for the outcome of overall survival (KEYNOTE 671 study, patients with tumour cell PD-L1 expression < 1%)