Tremelimumab and durvalumab (NSCLC)

Benefit assessment according to §35a SGB V[1]

EXTRACT

Project: A23-29
A23-31

Version: 1.0

Status: 29 June 2023

[1] Translation of Sections I 1 to I 6 of the dossier assessment *Tremelimumab und Durvalumab (NSCLC) – Nutzenbewertung gemäß § 35a SGB V*. Please note: This document was translated by an external translator and is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

Publishing details

Publisher

Institute for Quality and Efficiency in Health Care

Topic

Tremelimumab and durvalumab (NSCLC) – Benefit assessment according to §35a SGB V

Commissioning agency

Federal Joint Committee

Commission awarded on

3 April 2023

Internal Project No.

A23-29 | A23-31

Address of publisher

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Patient and family involvement

No feedback was received in the framework of the present dossier assessment.

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Keywords

Durvalumab, Tremelimumab, Carcinoma – Non-Small-Cell Lung, Benefit Assessment, NCT03164616, NCT02142738, NCT02220894, NCT03215706

Part I: Benefit assessment

I Table of contents

I List of tables[2]

Page

[2] Table numbers start with “2” as numbering follows that of the full dossier assessment.

I List of figures

Page

I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
ALK	anaplastic lymphoma kinase
AM-RL	Arzneimittel-Richtlinie (Pharmaceutical Directive)
BRAF	rapidly accelerated fibrosarcoma – isoform B
CTCAE	Common Terminology Criteria for Adverse Events
ECOG-PS	Eastern Cooperative Oncology Group Performance Status
EGFR	epidermal growth factor receptor
EORTC	European Organization for Research and Treatment of Cancer
EPAR	European Public Assessment Report
EQ-5D	European Quality of Life – 5 Dimensions
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
KRAS	Kirsten rat sarcoma viral oncogene homologue
MET	mesenchymal-epithelial transition factor
NSCLC	non-small cell lung cancer
PD-L1	programmed death ligand 1
PFS	progression-free survival
PGIC	Patient Global Impression of Change
PRO-CTCAE	Patient-Reported Outcome – Common Terminology Criteria for Adverse Events
QLQ-C30	Quality of Life Questionnaire – Cancer 30
QLQ-LC13	Quality of Life Questionnaire – Lung Cancer 13
RCT	randomized controlled trial
ROS1	c-ros oncogene 1
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics
VAS	visual analogue scale

I 1 Executive summary of the benefit assessment

Background

In accordance with § 35a Social Code Book (SGB V), the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of tremelimumab (in combination with durvalumab and platinum-based chemotherapy) and of durvalumab (in combination with tremelimumab and platinum-based chemotherapy). The dossier was sent to IQWiG on 3 April 2023.

Research question

The aim of this report is to assess the added benefit of tremelimumab (in combination with durvalumab and platinum-based chemotherapy) and durvalumab (in combination with tremelimumab and platinum-based chemotherapy) compared with the appropriate comparator therapy (ACT) for the first-line treatment of adults with metastatic non-small cell lung cancer (NSCLC) with no sensitizing epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) positive mutations. Below, the combinations to be assessed are referred to as tremelimumab + durvalumab + platinum-containing chemotherapy.

The research questions shown in Table 2 were derived from the ACT specified by the G-BA.

Table 2: Research questions of the benefit assessment of tremelimumab + durvalumab + platinum-based chemotherapy (multipage table)

Research question	**Therapeutic indication**	**ACT**[a, b]
1	Adult patients with metastatic NSCLC with PD-L1 expression ≥ 50% and no sensitizing EGFR mutations or ALK-positive mutations[c]; first-line treatment[d]	▪ **Pembrolizumab as monotherapy** or ▪ atezolizumab as monotherapy or ▪ cemiplimab as monotherapy or ▪ nivolumab in combination with ipilimumab and 2 cycles of platinum-based chemotherapy (only for patients with ECOG-PS 0–1) or ▪ pembrolizumab in combination with carboplatin and either paclitaxel or nab-paclitaxel (only for patients with ECOG-PS 0–1 and squamous NSCLC) or ▪ pembrolizumab in combination with pemetrexed and platinum-containing chemotherapy (only for patients with ECOG-PS 0–1 and non-squamous NSCLC) or ▪ atezolizumab in combination with bevacizumab, paclitaxel, and carboplatin (only for patients with ECOG-PS 0–1 and non-squamous NSCLC) or ▪ atezolizumab in combination with nab-paclitaxel and carboplatin (only for patients with ECOG-PS 0–1 and non-squamous NSCLC)

Table 2: Research questions of the benefit assessment of tremelimumab + durvalumab + platinum-based chemotherapy (multipage table)

Research question	Therapeutic indication	ACT[a, b]
2	Adult patients with metastatic NSCLC with PD-L1 expression < 50% and no sensitizing EGFR mutations or ALK-positive mutations[c]; first-line treatment[d]	▪ Pembrolizumab in combination with pemetrexed and platinum-containing chemotherapy (only for patients with ECOG-PS 0–1 and non-squamous NSCLC) or ▪ pembrolizumab in combination with carboplatin and either paclitaxel or nab-paclitaxel (only for patients with ECOG-PS 0–1 and squamous NSCLC) or ▪ atezolizumab as monotherapy (only for patients with PD-L1 expression ≥ 10% in tumour-infiltrating immune cells) or ▪ atezolizumab in combination with bevacizumab, paclitaxel, and carboplatin (only for patients with ECOG-PS 0–1 and non-squamous NSCLC) or ▪ atezolizumab in combination with nab-paclitaxel and carboplatin (only for patients with ECOG-PS 0–1 and non-squamous NSCLC) or ▪ **nivolumab in combination with ipilimumab and 2 cycles of platinum-based chemotherapy (only for patients with ECOG-PS 0–1)** or ▪ carboplatin in combination with a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed[e]; only for patients with ECOG-PS 2) or ▪ carboplatin in combination with nab-paclitaxel (only for patients with ECOG-PS 2)

a. Presented is the respective ACT specified by the G-BA. In cases where the G-BA's specification of the ACT allowed the company to select a comparator from several options, the respective choice of the company is printed in **bold**.
b. A sole comparison against a treatment option which represents a comparator therapy for only part of the patient population is usually not sufficient to demonstrate added benefit for the overall population.
c. Patient population without genomic EGFR mutations or ALK-positive mutations, as designated by the G-BA when it determined the ACT. In the present benefit assessment, the wording according to the SPC was used.
d. For the present therapeutic indication, it is assumed as per G-BA that there is neither an indication for definitive radiochemotherapy nor for definitive local therapy. In addition, it is assumed that molecularly stratified therapy (directed against BRAF, KRAS, G12C, METex14, RET, or ROS1) is not an option for the patients at the time of treatment with tremelimumab in combination with durvalumab and platinum-based chemotherapy.
e. See Pharmaceutical Directive Annex VI to Section K.

Table 2: Research questions of the benefit assessment of tremelimumab + durvalumab + platinum-based chemotherapy (multipage table)

Research question	Therapeutic indication	ACT[a, b]
ACT: appropriate comparator therapy; ALK: anaplastic lymphoma kinase; BRAF: rapidly accelerated fibrosarcoma – isoform B; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; EGFR: epidermal growth factor receptor; G-BA: Federal Joint Committee; KRAS: Kirsten rat sarcoma viral oncogene homologue; MET: mesenchymal-epithelial transition factor; METex14: MET gene exon 14; NSCLC: non-small cell lung cancer; PD-L1: programmed death ligand 1; RET: rearranged during transfection; ROS1: c-ros oncogene 1; SPC: Summary of Product Characteristics		

In the present benefit assessment, the following terms are used for the patient populations of the 2 research questions:

- patients with programmed death ligand-1 (PD-L1) expression ≥ 50%
- patients with PD-L1 expression < 50%

The company followed the G-BA's specification of the ACT. For research question 1, the company selected pembrolizumab monotherapy. For research question 2, it chose nivolumab in combination with ipilimumab and 2 cycles of platinum-based chemotherapy (hereafter referred to as nivolumab + ipilimumab + platinum-based chemotherapy). Regarding research question 2, however, the company disregards the fact that the selected option represents an ACT only for patients with Eastern Cooperative Oncology Group Performance Status (ECOG-PS) 0–1. Concerning research question 2, conclusions on added benefit can therefore be drawn only for patients with ECOG-PS 0–1.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data presented by the company in the dossier.

Research question 1: PD-L1 expression ≥ 50%

Study pool and study design

Concurring with the company, the check of completeness of the study pool found no relevant study for a direct comparison of tremelimumab + durvalumab + platinum-containing chemotherapy versus pembrolizumab in the present therapeutic indication.

Therefore, the company presented an adjusted indirect comparison according to Bucher for the assessment of tremelimumab + durvalumab + platinum-containing chemotherapy in comparison with pembrolizumab using the common comparator of platinum-based chemotherapy. Concurring with the company, the benefit assessment used platinum-based chemotherapy as the common comparator for an adjusted indirect comparison. Regarding the adjusted indirect comparison, the company identified the POSEIDON study on the

intervention side and the KEYNOTE-024 study, the KEYNOTE-042 study, and its extension study KEYNOTE-042-China on the pembrolizumab side. Concurring with the company, the KEYNOTE-042-China study has been disregarded below, as no patient characteristics of the relevant subpopulation (with PD-L1 expression ≥ 50%) are available, and thus its similarity with the other studies of the indirect comparison cannot be assessed.

POSEIDON study: tremelimumab + durvalumab + platinum-based chemotherapy

The POSEIDON study is an open-label, 3-arm randomized controlled trial (RCT) comparing tremelimumab + durvalumab + platinum-based chemotherapy, durvalumab + platinum-based chemotherapy, and platinum-based chemotherapy. The study included adult patients with histologically or cytologically confirmed NSCLC (stage IV) without EGFR mutation or ALK translocation whose tumours exhibited PD-L1 expression. The inclusion criteria additionally required patients to be in good general health (ECOG-PS ≥ 1) and to be ineligible for curative surgery or radiotherapy. Prior chemotherapy or other systemic therapies for metastatic NSCLC were disallowed. In patients with squamous histology or patients with known Kirsten rat sarcoma viral oncogene homologue (KRAS) mutation of the tumour, EGFR or ALK testing was not required.

The POSEIDON study included a total of 1013 patients, randomized in a 1:1:1 ratio either to treatment with tremelimumab + durvalumab + platinum-based chemotherapy (N = 338), durvalumab + platinum-based chemotherapy (N = 338), or to treatment with platinum-based chemotherapy alone (N = 337).

Tremelimumab and durvalumab in combination with platinum-based chemotherapy was administered largely as per Summary of Product Characteristics (SPC).

In the comparator arm, platinum-based chemotherapy was administered for 4 to 6 cycles upon the investigator's discretion. For patients with non-squamous NSCLC, the treatment options for platinum-based chemotherapy comprised pemetrexed + cisplatin or pemetrexed + carboplatin; those for patients with squamous NSCLC were gemcitabine + cisplatin or gemcitabine + carboplatin. Furthermore, patients were allowed to receive nab-paclitaxel + carboplatin irrespective of tumour histology. The selection was made by the investigator on an individualized basis prior to randomization. The platinum-based chemotherapies were administered largely as per requirements of the respective SPCs or the Pharmaceutical Directive (AM-RL) for off-label use (Annex VI of Section K).

In patients with non-squamous histology who received pemetrexed chemotherapy and exhibited no disease progression, maintenance therapy with pemetrexed (every 4 weeks in the intervention arm and every 3 or 4 weeks in the comparator arm) was allowed in both study arms from Cycle 5 (Week 12) upon the investigator's discretion.

In both study arms, treatment continued until either disease progression, unacceptable toxicity, treatment discontinuation upon the physician's or patient's discretion, or until the start of new antineoplastic therapy.

Primary outcomes of the study were progression-free survival (PFS) and overall survival. Patient-relevant secondary outcomes were outcomes on morbidity, health-related quality of life, and AEs.

The POSEIDON study's relevant subpopulation relevant for the present research question 1 comprises patients with PD-L1 expression of the tumour ≥ 50% (101 patients in the intervention arm and 97 patients in the comparator arm).

The POSEIDON study comprises a global cohort and one referred to as China cohort. As per study protocol, all patients randomized into the China cohort before the 1st visit of the last patient of the global cohort were to also be included in the analyses of the global cohort. However, the final study report, an addendum to the study report as well as the results in Module 4 A contain the results of the global cohort excluding the Chinese patients. Hence, the company departed from its study protocol. The company did not cite any reasons for excluding the Chinese patients. In addition, the company failed to report whether results are already available for the China cohort. The population of Chinese patients is generally relevant for the present benefit assessment.

For the global cohort, it is unclear how many Chinese patients who had already been recruited were excluded from the analyses. Based on the planning (1000 patients in the global cohort and a maximum of 180 additional Chinese patients), the data from a maximum of 15% of all included patients are missing. Given the available evidence, using the global cohort without the Chinese patients is deemed justifiable.

Studies KEYNOTE-024 and KEYNOTE-042: pembrolizumab

KEYNOTE-024

KEYNOTE-024 is an open-label RCT comparing pembrolizumab versus a platinum-based combination chemotherapy. The study included adult patients with histologically or cytologically confirmed metastatic NSCLC without EGFR mutation or ALK translocation and with tumour PD-L1 expression ≥ 50%. Patients had to be in good general health (ECOG-PS ≤ 1). Prior systemic antineoplastic treatment for the metastatic stage was disallowed.

The KEYNOTE-024 study included a total of 305 patients, randomized in a 1:1 ratio either to treatment with pembrolizumab monotherapy (N = 154) or to 1 of 5 possible treatment options as platinum-based combination chemotherapy (N = 151). The treatment options were as follows: pemetrexed + cisplatin, pemetrexed + carboplatin, gemcitabine + cisplatin, gemcitabine + carboplatin, or paclitaxel + carboplatin, with the combination with pemetrexed

representing an option only for patients with non-squamous histology. Prior to randomization, an investigator specified on an individual basis which treatment was suitable for each patient.

The administration of pembrolizumab concurred with the requirements of the SPC. The platinum-based chemotherapies as well were administered as per requirements of the respective SPCs or the AM-RL for off-label use (Annex VI of Section K). In the KEYNOTE-024 study, the platinum component of the chemotherapy was administered for a maximum of 4 to 6 cycles. Thereafter, patients with non-squamous histology were allowed – and recommended – to receive maintenance treatment with pemetrexed.

Patients were treated until either disease progression, occurrence of unacceptable side effects, or discontinuation of the study as decided by the investigator or the patient.

PFS was the primary outcome of the study. Patient-relevant secondary outcomes were overall survival as well as outcomes on morbidity, health-related quality of life, and AEs.

The KEYNOTE-024 population relevant for the present research question comprises all randomized patients.

KEYNOTE-042

The KEYNOTE-042 study is an open-label RCT. The study compared pembrolizumab versus a combination of carboplatin and either paclitaxel or pemetrexed. A total of 1274 patients were randomly allocated in a 1:1 ratio to the intervention arm (pembrolizumab: N = 637) or to the comparator arm (N = 637). The study included adults with histologically or cytologically confirmed diagnosis of NSCLC exhibiting locally advanced or metastatic tumours with PD-L1 expression ≥ 1%. Prior systemic treatment was not allowed in the study. The included patients had to have an ECOG-PS of 0 or 1. Prior to randomization, an investigator decided which treatment option (pemetrexed + carboplatin or paclitaxel + carboplatin) would be suitable for each individual patient in the event of randomization to the comparator arm; however, the combination with pemetrexed was an option only for patients with non-squamous histology.

Patients in the intervention arm received pembrolizumab in accordance with the SPC. The platinum-based chemotherapies (pemetrexed + carboplatin or paclitaxel + carboplatin) were likewise administered as per requirements of the SPCs or the AM-RL for off-label use (Annex VI of Section K). In the KEYNOTE-042 study, patients with non-squamous histology received carboplatin for a maximum of 4 to 6 cycles. After at least 4 cycles, patients with non-squamous histology were allowed – and recommended – to receive maintenance treatment with pemetrexed.

Patients were treated until disease progression, complete response, occurrence of unacceptable side effects, or study discontinuation as decided by the investigator or the patient.

The study's primary outcome was overall survival. Patient-relevant secondary outcomes were AEs.

The KEYNOTE-042 study's subpopulation relevant for the present research question 1 comprises patients with tumour PD-L1 expression ≥ 50% (299 patients in the pembrolizumab arm and 300 patients in the comparator arm).

Similarity of the studies for the indirect comparison

In total, the 3 studies POSEIDON, KEYNOTE-024, and KEYNOTE-042 exhibit some differences in study and patient characteristics and particularly in the common comparator of platinum-based chemotherapy. Certain aspects cannot be adequately assessed due to some of the data being missing (treatment and observation periods, subsequent therapies). Overall, the similarity assumption required for indirect comparisons is not rejected.

Risk of bias

The risk of bias across outcomes for the studies POSEIDON, KEYNOTE-024, and KEYNOTE-024 was rated as low in each case.

In the present scenario, an indirect comparison can be conducted only for the outcome of overall survival. The outcome-specific risk of bias for overall survival was rated as low in each study.

Results

On the basis of the available information, no more than hints, e.g. of an added benefit, can be determined for all outcomes.

Mortality

Overall survival

The adjusted indirect comparison showed no statistically significant difference between the treatment groups for the outcome of overall survival. This results in no hint of an added benefit of tremelimumab + durvalumab + platinum-based chemotherapy in comparison with pembrolizumab; an added benefit is therefore not proven.

Morbidity

Symptoms, health status

For the symptoms outcomes surveyed with the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30), the EORTC Quality of Life

Questionnaire – Lung Cancer 13 (QLQ-LC13) as well as for the outcome of health status, surveyed with the European Quality of Life 5 Dimensions (EQ-5D) visual analogue scale (VAS) and the Patient Global Impression of Change (PGIC), no suitable data are available on 1 side of the indirect comparison (POSEIDON study). Therefore, it is impossible to conduct an indirect comparison for the outcomes surveyed with these instruments. For the outcomes of the morbidity category, this results in no hint of an added benefit of tremelimumab + durvalumab + platinum-based chemotherapy in comparison with pembrolizumab; an added benefit is therefore not proven for these outcomes.

Health-related quality of life

On 1 side of the indirect comparison (POSEIDON study), no suitable data are available for the outcomes of the category of health-related quality of life, recorded with the EORTC QLQ-C30. Therefore, an indirect comparison is not possible for these outcomes. For the outcomes of the health-related quality of life category, this results in no hint of an added benefit of tremelimumab + durvalumab + platinum-based chemotherapy in comparison with pembrolizumab; an added benefit is therefore not proven for these outcomes.

Side effects

No data on side effects were available for the relevant subpopulation of the KEYNOTE-042 study. Furthermore, no analyses of the side effects outcomes are available for the indirect comparison based on the KEYNOTE-024 and POSEIDON studies.

Serious adverse events (SAEs), discontinuation due to AEs

For the outcomes of SAEs and discontinuation due to AEs, data are available for only 1 study (POSEIDON or KEYNOTE-024) on both sides of the adjusted indirect comparison. Due to the high risk of bias at the outcome level, the prerequisites for drawing conclusions on added benefit with sufficient certainty of results from an adjusted indirect comparison were not met. For the outcomes of SAEs and discontinuation due to AEs, this results in no hint of an added benefit of tremelimumab + durvalumab + platinum-based chemotherapy in comparison with pembrolizumab; an added benefit is therefore not proven for these outcomes.

Severe AEs

For the outcome of severe AEs, no data on the employed data cutoff are available on 1 side of the indirect comparison. Therefore, an indirect comparison is not possible for these outcomes. For the outcome of severe AEs, this results in no hint of an added benefit of tremelimumab + durvalumab + platinum-based chemotherapy in comparison with pembrolizumab; an added benefit is therefore not proven.

Patient-Reported Outcome – Common Terminology Criteria for Adverse Events (PRO-CTCAE)

The outcome of PRO-CTCAE was surveyed only in the POSEIDON study. For this outcome, this results in no hint of an added benefit of tremelimumab + durvalumab + platinum-based chemotherapy in comparison with pembrolizumab; an added benefit is therefore not proven.

Immune-related AEs

For the outcome of immune-related AEs, Module 4 A lacks an analysis of the between-study comparability of operationalizations of immune-related AEs. In the present assessment, no indirect comparison was carried out for the outcome due to data being insufficient for a similarity check of the operationalizations. For this outcome, this results in no hint of an added benefit of tremelimumab + durvalumab + platinum-based chemotherapy in comparison with pembrolizumab; an added benefit is therefore not proven.

Research question 2: PD-L1 expression < 50%

Study pool and study design

Concurring with the company, the check of completeness of the study pool found no study for a direct comparison of tremelimumab + durvalumab + platinum-containing chemotherapy versus nivolumab + ipilimumab + platinum-based chemotherapy in the present therapeutic indication.

Therefore, the company presented an adjusted indirect comparison according to Bucher for the assessment of tremelimumab + durvalumab + platinum-containing chemotherapy in comparison with nivolumab + ipilimumab + platinum-based chemotherapy using the common comparator of platinum-based chemotherapy. Concurring with the company, the benefit assessment used platinum-based chemotherapy as the common comparator for an adjusted indirect comparison. Regarding the adjusted indirect comparison, the company identified the POSEIDON study on the intervention side and the CA209-9LA study on the nivolumab + ipilimumab + platinum-based chemotherapy side.

POSEIDON study: tremelimumab + durvalumab + platinum-based chemotherapy

The description of the POSEIDON study can be found under research question 1.

The POSEIDON study's subpopulation relevant for the present research question 2 comprises patients with tumour PD-L1 expression < 50% (237 patients in the intervention arm and 240 patients in the comparator arm).

CA209-9LA study: nivolumab + ipilimumab + 2 cycles of platinum-based chemotherapy

The CA209-9LA study is an ongoing, open-label, multicentre RCT comparing nivolumab + ipilimumab + platinum-based chemotherapy versus platinum-based chemotherapy.

The study included adult patients with squamous and non-squamous stage IV NSCLC without EGFR mutation or ALK translocation and ECOG-PS ≤ 1 irrespective of PD-L1 expression. No prior systemic therapy of stage IIIB or IV NSCLC was allowed.

EGFR testing of the tumour tissue was conducted only in patients with non-squamous histology. The study excluded any patients with unknown or indeterminable EGFR status. Testing for ALK translocations was not mandatory, but patients with known ALK translocation were excluded from the study.

The CA209-9LA study included a total of 719 patients, randomized in a 1:1 ratio to treatment with either nivolumab + ipilimumab + platinum-based chemotherapy (N = 361) or platinum-based chemotherapy alone (N = 358). The type of chemotherapy was dependent on the histology of the tumour: patients with squamous histology received carboplatin in combination with paclitaxel, while patients with non-squamous histology received either cisplatin or carboplatin in combination with pemetrexed. The platinum component was chosen by the investigator before randomization on the basis of eligibility criteria not described in more detail by the company.

The use of the study medication in both study arms largely follows the specifications of the respective SPCs or guidelines.

In the comparator arm, up to 4 cycles of chemotherapy were administered; afterwards, patients with non-squamous histology and no disease progression were allowed to receive maintenance therapy with pemetrexed from Cycle 5.

Treatment was administered until disease progression, unacceptable intolerance, withdrawal of consent, or reaching of the maximum duration of therapy.

Primary outcome of the CA209-9LA study was overall survival. Secondary patient-relevant outcomes were from the morbidity and side effects categories.

The CA209-9LA study's subpopulation relevant for the present research question comprises patients with tumour PD-L1 expression < 50% (262 patients in the intervention arm and 235 patients in the comparator arm).

Similarity of the studies for the indirect comparison

Similarity is a key prerequisite for studies to be taken into account in the adjusted indirect comparison. The 2 studies POSEIDON and CA209-9LA share a very similar study design. Differences exist between the 2 studies in the common comparator of platinum-based chemotherapy. The main difference between the relevant subpopulations of the POSEIDON and CA209-9LA studies lies in the patient characteristics for the family origin trait. The proportion of patients of White family origin is significantly lower in the POSEIDON study

compared to the CA209-9LA study. The characteristic of family origin represents a relevant effect modifier in the present data constellation, especially due to the qualitative effect modification in the POSEIDON study. Overall, the central assumption of between-study similarity for the indirect comparison is rejected. Thus, the data presented by the company for research question 2 are unsuitable for the benefit assessment.

Results

The data presented by the company are unsuitable for drawing conclusions on added benefit of tremelimumab + durvalumab + platinum-based chemotherapy compared with the ACT in adult patients with metastatic NSCLC with PD-L1 expression < 50% without sensitising EGFR mutations or ALK-positive mutations in first-line therapy. This results in no hint of an added benefit of tremelimumab + durvalumab + platinum-based chemotherapy in comparison with the ACT; an added benefit is therefore not proven.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

On the basis of the results presented, the probability and extent of added benefit of the drug combination tremelimumab + durvalumab + platinum-based chemotherapy in comparison with the ACT are assessed as follows:

Research question 1: PD-L1 expression ≥ 50%

Overall, based on the adjusted indirect comparison using the common comparator of platinum-based chemotherapy, neither favourable nor unfavourable effects were found for tremelimumab + durvalumab + platinum-based chemotherapy compared to pembrolizumab. However, it should be noted that usable results with sufficient certainty of results for an indirect comparison are available only for the outcome of overall survival. There is no hint of an added benefit of tremelimumab + durvalumab + platinum-based chemotherapy for this outcome because the indirect comparison shows no statistically significant difference. For the outcomes of the morbidity and health-related quality of life categories, no data suitable for an indirect comparison are available. For the outcomes of the side effects category, the certainty of results requirement for conducting an adjusted indirect comparison is not met. Moreover, the differences regarding maintenance therapy in the platinum-based chemotherapies of the common comparators must be taken into account when interpreting

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) “proof”, (2) “indication”, (3) “hint”, or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [1,2].

the results on the side effects outcomes. It should be noted that subgroup analyses for the assessment of added benefit are missing.

In summary, for patients with metastatic NSCLC with PD-L1 expression ≥ 50% without sensitising EGFR mutations or ALK-positive mutations in first-line therapy, there is no hint of an added benefit of tremelimumab + durvalumab + platinum-based chemotherapy compared to pembrolizumab; an added benefit is therefore not proven.

Research question 2: PD-L1 expression < 50%

The data presented by the company are unsuitable for drawing conclusions on the added benefit of tremelimumab + durvalumab + platinum-based chemotherapy compared with the ACT in adult patients with metastatic NSCLC with PD-L1 expression < 50% without sensitising EGFR mutations or ALK-positive mutations in first-line therapy. This results in no hint of an added benefit of tremelimumab + durvalumab + platinum-based chemotherapy in comparison with the ACT; an added benefit is therefore not proven.

In summary, for patients with metastatic NSCLC with PD-L1 expression < 50% without sensitising EGFR mutations or ALK-positive mutations in first-line therapy, there is no hint of an added benefit of tremelimumab + durvalumab + platinum-based chemotherapy compared to nivolumab + ipilimumab + platinum-based chemotherapy; an added benefit is therefore not proven.

Table 3 shows a summary of the probability and extent of added benefit of tremelimumab + durvalumab + platinum-based chemotherapy.

Table 3: Tremelimumab + durvalumab + platinum-based chemotherapy – probability and extent of added benefit (multipage table)

Research question	**Therapeutic indication**	**ACT**[a]	**Probability and extent of added benefit**
1	Adult patients with metastatic NSCLC with PD-L1 expression ≥ 50% with no sensitizing EGFR mutations or ALK-positive mutations[c]; first-line treatment[d]	▪ **Pembrolizumab as monotherapy** or ▪ atezolizumab as monotherapy or ▪ cemiplimab as monotherapy or ▪ nivolumab in combination with ipilimumab and 2 cycles of platinum-based chemotherapy (only for patients with ECOG-PS 0–1) or ▪ pembrolizumab in combination with carboplatin and either paclitaxel or nab-paclitaxel (only for patients with ECOG-PS 0–1 and squamous NSCLC) or ▪ pembrolizumab in combination with pemetrexed and platinum-containing chemotherapy (only for patients with ECOG-PS 0–1 and non-squamous NSCLC) or ▪ atezolizumab in combination with bevacizumab, paclitaxel, and carboplatin (only for patients with ECOG-PS 0–1 and non-squamous NSCLC) or ▪ atezolizumab in combination with nab-paclitaxel and carboplatin (only for patients with ECOG-PS 0–1 and non-squamous NSCLC)	Added benefit not proven[e]

Table 3: Tremelimumab + durvalumab + platinum-based chemotherapy – probability and extent of added benefit (multipage table)

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
2	Adult patients with metastatic NSCLC with PD-L1 expression < 50% and no sensitizing EGFR mutations or ALK-positive mutations[c]; first-line treatment[d]	▪ Pembrolizumab in combination with pemetrexed and platinum-containing chemotherapy (only for patients with ECOG-PS 0–1 and non-squamous NSCLC) or ▪ pembrolizumab in combination with carboplatin and either paclitaxel or nab-paclitaxel (only for patients with ECOG-PS 0–1 and squamous NSCLC) or ▪ atezolizumab as monotherapy (only for patients with PD-L1 expression ≥ 10% in tumour-infiltrating immune cells) or ▪ atezolizumab in combination with bevacizumab, paclitaxel, and carboplatin (only for patients with ECOG-PS 0–1 and non-squamous NSCLC) or ▪ atezolizumab in combination with nab-paclitaxel and carboplatin (only for patients with ECOG-PS 0–1 and non-squamous NSCLC) or ▪ **nivolumab in combination with ipilimumab and 2 cycles of platinum-based chemotherapy (only for patients with ECOG-PS 0–1)** or ▪ carboplatin in combination with a third-generation cytostatic (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed[f]; only for patients with ECOG-PS 2) or ▪ carboplatin in combination with nab-paclitaxel (only for patients with ECOG-PS 2)	Added benefit not proven[e]

Table 3: Tremelimumab + durvalumab + platinum-based chemotherapy – probability and extent of added benefit (multipage table)

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
a. Presented is the respective ACT specified by the G-BA. In cases where the G-BA's specification of the ACT allowed the company to select a comparator from several options, the respective choice of the company is printed in **bold**. b. A sole comparison against a treatment option which represents a comparator therapy for only part of the patient population is usually not sufficient to demonstrate added benefit for the overall population. c. Patient population without genomic EGFR mutations or ALK-positive mutations, as designated by the G-BA when it determined the ACT. The present benefit assessment uses the wording according to the SPC. d. For the present therapeutic indication, it is assumed as per G-BA that there is neither an indication for definitive radiochemotherapy nor for definitive local therapy. In addition, it is assumed that molecularly stratified therapy (directed against BRAF, KRAS, G12C, METex14, RET, or ROS1) is not an option for the patients at the time of treatment with tremelimumab in combination with durvalumab and platinum-based chemotherapy. e. Only patients with an ECOG-PS of 0 or 1 were included in the indirect comparison studies. f. See Pharmaceutical Directive Annex VI to Section K. ACT: appropriate comparator therapy; ALK: anaplastic lymphoma kinase; BRAF: rapidly accelerated fibrosarcoma – isoform B; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; EGFR: epidermal growth factor receptor; G-BA: Federal Joint Committee; KRAS: Kirsten rat sarcoma viral oncogene homologue; MET: mesenchymal-epithelial transition factor; METex14: Met gene exon 14; NSCLC: non-small cell lung cancer; PD-L1: programmed death ligand 1; RET: rearranged during transfection; ROS1: c-ros oncogene 1; SPC: Summary of Product Characteristics			

The approach for the derivation of an overall conclusion on added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

I 2 Research question

The aim of this report is to assess the added benefit of tremelimumab (in combination with durvalumab and platinum-based chemotherapy) and durvalumab (in combination with tremelimumab and platinum-based chemotherapy) compared with the ACT for the first-line treatment of adults with metastatic NSCLC with no sensitizing EGFR mutations or ALK positive mutations. Below, the combination to be assessed is referred to as tremelimumab + durvalumab + platinum-containing chemotherapy.

The research questions shown in Table 4 were derived from the ACT specified by the G-BA.

Table 4: Research questions for the benefit assessment of tremelimumab + durvalumab + platinum-based chemotherapy (multipage table)

Research question	Therapeutic indication	ACT[ab]
1	Adult patients with metastatic NSCLC with PD-L1 expression ≥ 50% with no sensitizing EGFR mutations or ALK-positive mutations[c]; first-line treatment[d]	▪ **Pembrolizumab as monotherapy** or ▪ atezolizumab as monotherapy or ▪ cemiplimab as monotherapy or ▪ nivolumab in combination with ipilimumab and 2 cycles of platinum-based chemotherapy (only for patients with ECOG-PS 0–1) or ▪ pembrolizumab in combination with carboplatin and either paclitaxel or nab-paclitaxel (only for patients with ECOG-PS 0–1 and squamous NSCLC) or ▪ pembrolizumab in combination with pemetrexed and platinum-containing chemotherapy (only for patients with ECOG-PS 0–1 and non-squamous NSCLC) or ▪ atezolizumab in combination with bevacizumab, paclitaxel, and carboplatin (only for patients with ECOG-PS 0–1 and non-squamous NSCLC) or ▪ atezolizumab in combination with nab-paclitaxel and carboplatin (only for patients with ECOG-PS 0–1 and non-squamous NSCLC)

Table 4: Research questions for the benefit assessment of tremelimumab + durvalumab + platinum-based chemotherapy (multipage table)

Research question	Therapeutic indication	ACT[ab]
2	Adult patients with metastatic NSCLC with PD-L1 expression < 50% and no sensitizing EGFR mutations or ALK-positive mutations[c]; first-line treatment[d]	▪ Pembrolizumab in combination with pemetrexed and platinum-containing chemotherapy (only for patients with ECOG-PS 0–1 and non-squamous NSCLC) or ▪ pembrolizumab in combination with carboplatin and either paclitaxel or nab-paclitaxel (only for patients with ECOG-PS 0–1 and squamous NSCLC) or ▪ atezolizumab as monotherapy (only for patients with PD-L1 expression ≥ 10% in tumour-infiltrating immune cells) or ▪ atezolizumab in combination with bevacizumab, paclitaxel, and carboplatin (only for patients with ECOG-PS 0–1 and non-squamous NSCLC) or ▪ atezolizumab in combination with nab-paclitaxel and carboplatin (only for patients with ECOG-PS 0–1 and non-squamous NSCLC) or ▪ **nivolumab in combination with ipilimumab and 2 cycles of platinum-based chemotherapy (only for patients with ECOG-PS 0–1)** or ▪ carboplatin in combination with a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed[e]; only for patients with ECOG-PS 2) or ▪ carboplatin in combination with nab-paclitaxel (only for patients with ECOG-PS 2)

a. Presented is the respective ACT specified by the G-BA. In cases where the G-BA's specification of the ACT allowed the company to select a comparator from several options, the respective choice of the company is printed in **bold**.
b. A sole comparison against a treatment option which represents a comparator therapy for only part of the patient population is usually not sufficient to demonstrate added benefit for the overall population.
c. Patient population without genomic EGFR mutations or ALK-positive mutations, as designated by the G-BA when it determined the ACT. The present benefit assessment uses the wording according to the SPC.
d. For the present therapeutic indication, it is assumed as per G-BA that there is neither an indication for definitive radiochemotherapy nor for definitive local therapy. In addition, it is assumed that molecularly stratified therapy (directed against BRAF, KRAS, G12C, METex14, RET, or ROS1) is not an option for the patients at the time of treatment with tremelimumab in combination with durvalumab and platinum-based chemotherapy.
e. See Pharmaceutical Directive Annex VI to Section K [3].

ACT: appropriate comparator therapy; ALK: anaplastic lymphoma kinase; BRAF: rapidly accelerated fibrosarcoma – isoform B; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; EGFR: epidermal growth factor receptor; G-BA: Federal Joint Committee; KRAS: Kirsten rat sarcoma viral oncogene homologue; MET: mesenchymal-epithelial transition factor; METex14: Met gene exon 14; NSCLC: non-small cell lung cancer; PD-L1: programmed death ligand 1; RET: rearranged during transfection; ROS1: c-ros oncogene 1; SPC: Summary of Product Characteristics

In the present benefit assessment, the following terms are used for the patient populations of the 2 research questions:

- patients with PD-L1 expression ≥ 50%
- patients with PD-L1 expression < 50%

The company followed the G-BA's specification of the ACT. For research question 1, the company selected pembrolizumab monotherapy. For research question 2, it chose nivolumab in combination with ipilimumab and 2 cycles of platinum-based chemotherapy (hereafter referred to as nivolumab + ipilimumab + platinum-based chemotherapy). Regarding research question 2, however, the company disregards the fact that the selected option represents an ACT only for patients with Eastern Cooperative Oncology Group Performance Status (ECOG-PS) 0–1. Concerning research question 2, conclusions on added benefit can therefore be drawn only for patients with ECOG-PS 0–1.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data presented by the company in the dossier.

I 3 Research question 1: PD-L1 expression ≥ 50%

I 3.1 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on tremelimumab + durvalumab + platinum-containing chemotherapy (as of 23 January 2023)
- bibliographic search on tremelimumab + durvalumab + platinum-containing chemotherapy (last search 23 January 2023)
- search in trial registries / trial results databases on tremelimumab + durvalumab + platinum-containing chemotherapy (last search on 23 January 2023)
- search on the G-BA website on tremelimumab + durvalumab + platinum-containing chemotherapy (last search on 23 January 2023)
- bibliographical literature search on the ACT (last search on 24 January 2023)
- search in trial registries / trial results databases for studies on the ACT (last search on 24 January 2023)
- search on the G-BA website for the ACT (last search on 24 January 2023)

To check the completeness of the study pool:

- search in trial registries for studies on tremelimumab + durvalumab (last search on 21 April 2023); for search strategies, see I Appendix A of the full dossier assessment
- search in trial registries for studies on pembrolizumab (last search on 24 April 2023); for search strategies, see I Appendix A of the full dossier assessment

Concurring with the company, the check of completeness of the study pool found no relevant study for a direct comparison of tremelimumab + durvalumab + platinum-containing chemotherapy versus pembrolizumab in the present therapeutic indication.

The company therefore presents an adjusted indirect comparison according to Bucher [4] for the assessment of tremelimumab + durvalumab + platinum-containing chemotherapy compared to pembrolizumab via the common comparator platinum-based chemotherapy.

The check of the study pool did not identify any additional relevant study for the adjusted indirect comparison presented by the company.

I 3.1.1 Studies included

Concurring with the company, the benefit assessment used platinum-based chemotherapy as the common comparator for an adjusted indirect comparison.

The studies listed in the following table were included in the benefit assessment.

Table 5: Study pool – RCT, indirect comparison: tremelimumab + durvalumab + platinum-based chemotherapy versus pembrolizumab: research question 1 (PD-L1 expression ≥ 50%)

Study	Study category			Available sources		
	Study for the approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	CSR (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication and other sources[c] (yes/no [citation])
Tremelimumab + durvalumab + platinum-based chemotherapy vs. platinum-based chemotherapy						
D419MC00004 (POSEIDON[d])	Yes	Yes	No	Yes [5,6]	Yes [7-9]	Yes [10,11]
Pembrolizumab vs. platinum-based chemotherapy						
KEYNOTE-024	No	No	Yes	No	Yes [12,13]	Yes [14-23]
KEYNOTE-042	No	No	Yes	No	Yes [24,25]	Yes [17-20,26-30]
KEYNOTE-042-China	No	No	Yes	No	Yes [31]	Yes [32]

a. Study for which the company was sponsor.
b. References of trial registry entries and any available reports on the study design and/or results listed in the trial registries.
c. Other sources: documents from the search on the G-BA website and other publicly available sources.
d. In the following tables, the study is referred to by this acronym.

CSR: clinical study report; G-BA: Federal Joint Committee; PD-L1: programmed death ligand 1; RCT: randomized controlled trial

The study pool includes the RCT POSEIDON for tremelimumab + durvalumab + platinum-based chemotherapy and the RCTs KEYNOTE-024 and KEYNOTE-042 for pembrolizumab. In addition, the study pool of the present assessment includes the KEYNOTE-042-China study. The extension study KEYNOTE-042-China was conducted using the same study protocol as the KEYNOTE-042 study. The company states that for the KEYNOTE-042-China study, no information is available on the patient characteristics of the relevant subpopulation (with PD-L1 expression ≥ 50%), and it therefore disregards the study in the indirect comparison. This approach is appropriate because including the KEYNOTE-042-China study in the indirect comparison requires, among other things, sufficient similarity of the patient populations between the studies used in the indirect comparison. The similarity cannot be tested without the information on the relevant subpopulation. The KEYNOTE-042-China study is therefore disregarded below.

The POSEIDON study comprises a global cohort and one referred to as China cohort. After recruitment of the global cohort (approximately 1000 patients), recruitment was to be closed at all sites, with the exception of the sites in China, where patient recruitment was allowed to continue. Chinese patients were enrolled based on the requirements of the Chinese regulatory authorities. As per study protocol, a total of 180 patients were to be randomised for the China cohort. They were to have been enrolled at the latest before the last patient in the global cohort had the last visit. As per study protocol, all patients randomized into the China cohort before the 1st visit of the last patient of the global cohort were to also be included in the analyses of the global cohort. However, the final study report, an addendum to the study report as well as the results in Module 4 A present the results of the global cohort excluding the Chinese patients. Hence, the company departed from its study protocol. The company did not cite any reasons for excluding the Chinese patients. In addition, the company failed to report whether results are already available for the China cohort. The population of Chinese patients is generally relevant for the present benefit assessment.

For the global cohort, it is unclear how many Chinese patients who had already been recruited were excluded from the analyses. Based on the planning (1000 patients in the global cohort and a maximum of 180 additional Chinese patients), the data from a maximum of 15% of all included patients are missing. Given the available evidence, using the global cohort without the Chinese patients is deemed justifiable.

The indirect comparison is shown schematically in Figure 1.

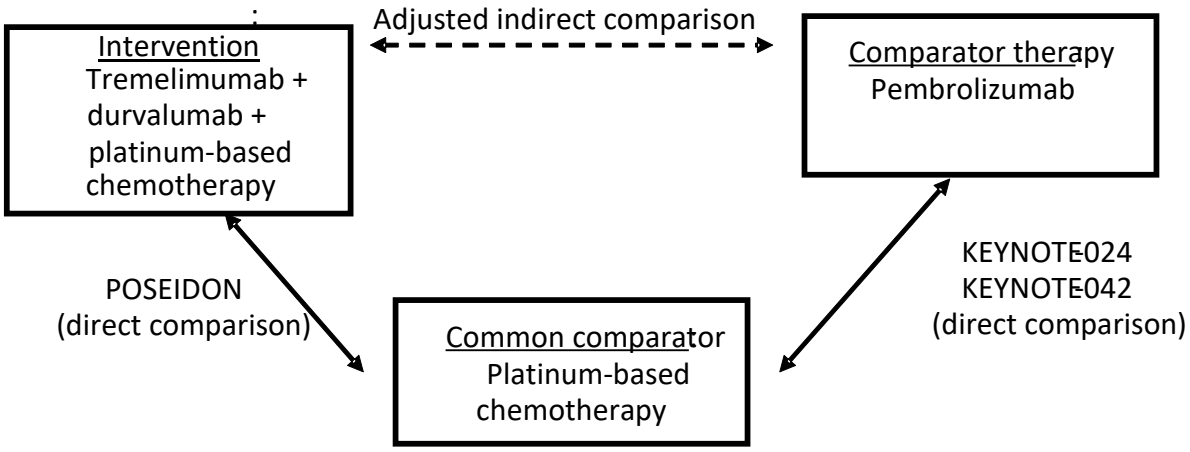

Figure 1: Study pool for the indirect comparison of tremelimumab + durvalumab + platinum-based chemotherapy versus the ACT of pembrolizumab: research question 1 (PD-L1 expression ≥ 50%)

I 3.1.2 Study characteristics

Table 6 and Table 7 describe the studies used for the benefit assessment.

Table 6: Characteristics of the included studies – RCT, indirect comparison: tremelimumab + durvalumab + platinum-based chemotherapy versus pembrolizumab: research question 1 (PD-L1 expression ≥ 50%) (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
Tremelimumab + durvalumab + platinum-based chemotherapy vs. platinum-based chemotherapy						
POSEIDON	RCT, open-label, parallel	Adults[b] with histologically or cytologically confirmed NSCLC (stage IV), confirmed PD-L1-expressing tumour, no EGFR mutation and no ALK translocation, ECOG-PS ≤ 1, without previous systemic therapy (first-line treatment)[c]	▪ Tremelimumab + durvalumab + platinum-based chemotherapy (N = 338) ▪ Durvalumab + platinum-based chemotherapy (N = 338)[d] ▪ Platinum-based chemotherapy (N = 337) of which relevant subpopulation with PD-L1 expression ≥ 50%: ▪ Tremelimumab + durvalumab + platinum-based chemotherapy (n = 101) ▪ Platinum-based chemotherapy (n = 97)	▪ Screening: 28 days prior to the start of treatment ▪ Treatment: until disease progression[e], unacceptable toxicity, discontinuation of therapy at the decision of the physician or patient, start of new antineoplastic therapy ▪ Observation[f]: outcome-specific, maximum until death	142 centres in: Brazil, Bulgaria, Germany, Hong Kong, Hungary, Japan, Mexico, Peru, Poland, Russia, South Africa, South Korea, Taiwan, Thailand, Ukraine, United States, United Kingdom, Vietnam 06/2017 – ongoing[g] <u>Data cutoffs:</u> ▪ 24/07/2019 (final analysis for PFS) ▪ 12/03/2021 (final analysis for OS)[h] ▪ 25/10/2021[i] ▪ 11/03/2022[j]	▪ Primary: PFS, overall survival ▪ Secondary: symptoms, health status, health-related quality of life, AEs

Table 6: Characteristics of the included studies – RCT, indirect comparison: tremelimumab + durvalumab + platinum-based chemotherapy versus pembrolizumab: research question 1 (PD-L1 expression ≥ 50%) (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
Pembrolizumab vs. platinum-based chemotherapy						
KEYNOTE-024	RCT, open-label, parallel	Adults with histologically or cytologically confirmed NSCLC stage IV, PD-L1-expressing tumour (TPS ≥ 50%)[k], no EGFR mutation and no ALK translocation, ECOG-PS ≤ 1, without previous systemic therapy[l]	▪ Pembrolizumab (N = 154) ▪ Platinum-based chemotherapy (N = 151)	▪ Screening: 30 days prior to the start of treatment ▪ Treatment: until progression (or beyond, as long as the patient benefits), unacceptable side effects, study discontinuation due to investigator or patient decision, achievement of a complete response or after a maximum of 35 cycles of pembrolizumab[m] ▪ Observation: outcome-specific[f], at maximum until death (for the outcome of overall survival)	142 centres in: Australia, Austria, Belgium, Canada, France, Germany, Hungary, Ireland, Israel, Italy, Japan, Netherlands, New Zealand, Spain, United Kingdom, United States 09/2014–05/2016[n] Data cutoffs: ▪ 9/05/2016 ▪ 10/07/2017 (final analysis on overall survival) ▪ 1/06/2020: (analysis of 5-year overall survival)	▪ Primary: PFS ▪ Secondary: overall survival, morbidity, health-related quality of life, AEs

Table 6: Characteristics of the included studies – RCT, indirect comparison: tremelimumab + durvalumab + platinum-based chemotherapy versus pembrolizumab: research question 1 (PD-L1 expression ≥ 50%) (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
KEYNOTE-042	RCT, open-label, parallel-group	Adults with histologically or cytologically confirmed locally advanced or metastatic NSCLC, PD-L1-expressing tumour (TPS ≥ 1%), no EGFR mutation and no ALK translocation, ECOG-PS ≤ 1, without prior systemic therapy[l]	▪ Pembrolizumab (N = 637) ▪ Platinum-based chemotherapy (N = 637) of which relevant subpopulation[k]: ▪ Pembrolizumab (n = 299) ▪ Platinum-based chemotherapy (n = 300)	▪ Screening: 30 days prior to the start of treatment ▪ Treatment: until progression, unacceptable side effects, study discontinuation due to investigator or patient decision, achievement of a complete response, or after a maximum of 35 cycles of pembrolizumab[m] ▪ Observation: outcome-specific[f], at maximum until death (for the outcome of overall survival)	A total of 196 centres in Argentina, Brazil, Bulgaria, Canada, Chile, China, Columbia, Czech Republic, Estonia, Guatemala, Hong Kong, Hungary, Japan, Latvia, Lithuania, Malaysia, Mexico, Peru, Philippines, Poland, Portugal, Romania, Russia, South Africa, South Korea, Sweden, Switzerland, Taiwan, Thailand, Turkey, Ukraine, Vietnam 11/2014–09/2022 Data cutoffs: ▪ 26/02/2018 ▪ 4/09/2018 (final PFS analysis)	Primary: overall survival Secondary: AEs

Table 6: Characteristics of the included studies – RCT, indirect comparison: tremelimumab + durvalumab + platinum-based chemotherapy versus pembrolizumab: research question 1 (PD-L1 expression ≥ 50%) (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]

a. Primary outcomes comprise information without regard to its relevance for this benefit assessment. Secondary outcomes include information only on relevant available outcomes for this benefit assessment.
b. ≥ 18 years; for patients in Japan ≥ 20 years.
c. Without prior chemotherapy or other systemic therapies for metastatic NSCLC.
d. This arm is irrelevant for the assessment and is not presented in the following tables.
e. Patients with confirmed radiological progression who, in the opinion of the investigator, continued to benefit from treatment were allowed to continue to receive durvalumab as monotherapy; no information is available on how many patients continued treatment after progression.
f. Outcome-specific information is provided in Table 8.
g. Planned end of study according to information provided by the company in Module 4 A: 28/05/2025.
h. Planned to occur after 532 deaths in the total population of the 2 study arms durvalumab + platinum-based chemotherapy and platinum-based chemotherapy.
i. Non-predefined data cutoff (see Section I 3.1.2, text below).
j. Non-predefined data cutoff (see Section I 3.1.2, text below); after the predefined final OS analysis of 12/03/2021, protocol version 6 dated 9/07/2021 added a subsequent follow-up survey of the outcome of overall survival (approximately 1 year after the predefined analysis); however, the analysis of the data collected for the 11/03/2022 data cutoff is not deemed predefined in the present benefit assessment (see following continuous text on data cutoffs).
k. Patients with high expression of PD-L1 in NSCLC, without EGFR mutation, and without ALK translocation (WT; TPS ≥ 50%, PD-L1 immunohistochemistry test 22C3 test).
l. Without prior systemic therapy of metastatic NSCLC stage (KEYNOTE-024) or of advanced or metastatic NSCLC stage (KEYNOTE-042).
m. Patients in the pembrolizumab arm (KEYNOTE-024 and KEYNOTE-042) were allowed to interrupt treatment after a complete confirmed response or after reaching the maximum number of treatment cycles for pembrolizumab and to restart treatment with pembrolizumab at the investigator's discretion following subsequent confirmed progression (if certain requirements for the previous treatment duration and disease status were met) ("second course phase"). It is safe to assume that only < 5% of the patients in the entire study population (KEYNOTE-024 and KEYNOTE-042) reached the "second course phase".
n. Due to the superiority of pembrolizumab over platinum-based chemotherapy in overall survival, the study was terminated at the time of the data cutoff of the 2nd interim analysis (9/05/2016). This 2nd data cutoff was prospectively planned to occur after reaching 175 events for the outcome PFS. All patients in the treatment arm with solely platinum-based chemotherapy were offered to switch to the pembrolizumab arm.

AE: adverse event; ALK: anaplastic lymphoma kinase; ECOG-PS: Eastern Cooperative Oncology Group - Performance Status; EGFR: epidermal growth factor receptor; n: relevant subpopulation; N: number of randomised patients; NSCLC: non-small cell lung cancer; PD-L1: programmed death ligand 1; PFS: progression-free survival; RCT: randomised controlled trial; TPS: tumour proportion score; WT: wild type

Table 7: Characteristics of the intervention – RCT, indirect comparison: tremelimumab + durvalumab + platinum-based chemotherapy versus pembrolizumab: research question 1 (PD-L1 expression ≥ 50%) (multipage table)

Study	Intervention	Comparison
Tremelimumab + durvalumab + platinum-based chemotherapy vs. platinum-based chemotherapy		
POSEIDON	Squamous and non-squamous histology: ▪ Tremelimumab[a] 75 mg/kg BW i.v. 4 cycles of 3 weeks each (Weeks 0, 3, 6 and 9, each on Day 1), plus a 5th dose at Week 16 (in parallel with durvalumab administration) + ▪ Durvalumab[a] 1500 mg/kg BW i.v. 4 cycles of 3 weeks each (Weeks 0, 3, 6 and 9, each on Day 1), and every 4 weeks from Cycle 5 (Week 12) + Histology-dependent platinum-based chemotherapy[b, c] for 4 cycles of 3 weeks each: ▪ Squamous and non-squamous histology: nab-paclitaxel 100 mg/m² BSA i.v. on Days 1, 8, 15 of each 21-day cycle and carboplatin (AUC 5 or 6) i.v. on Day 1 of each 21-day cycle ▪ Squamous histology[d]: Gemcitabine 1000 mg/m² or 1250 mg/m² BSA i.v. on Day 1 and Day 8 of each 21-day cycle and cisplatin 75 mg/m² BSA i.v. on Day 1 of each 21-day cycle or Gemcitabine 1000 mg/m² or 1250 mg/m² BSA i.v. on Day 1 and Day 8 of each 21-day cycle and carboplatin (AUC 5 or 6) i.v. on Day 1 of each 21-day cycle ▪ Non-squamous histology[d]: pemetrexed 500 mg/m² BSA i.v. and carboplatin (AUC 5 or 6) i.v. on Day 1 of each 21-day cycle or Pemetrexed 500 mg/m² BSA i.v. and cisplatin 75mg/m² BSA i.v. on Day 1 of each 21-day cycle If tremelimumab ± durvalumab or chemotherapy was discontinued, the continued administration of the other component was allowed. Re-treatment[e]: Patients who exhibited radiological progression after 5 cycles of continued durvalumab monotherapy and who, in the opinion of the investigator, continued to benefit from treatment, were allowed to receive re-treatment with tremelimumab + durvalumab.	Histology-dependent platinum-based chemotherapy[b] for 4 cycles[f] of 3 weeks each: ▪ Squamous and non-squamous histology: nab-paclitaxel 100mg/m² BSA i.v. on Days 1, 8, 15 of each 21-day cycle and carboplatin (AUC 5 or 6) i.v. on Day 1 of each 21-day cycle ▪ Squamous histology[d]: Gemcitabine 1000 mg/m² or 1250 mg/m² BSA i.v. on Day 1 and Day 8 of each 21-day cycle and cisplatin 75 mg/m² BSA i.v. on Day 1 of each 21-day cycle or Gemcitabine 1000 mg/m² or 1250 mg/m² BSA i.v. on Day 1 and Day 8 of each 21-day cycle and carboplatin (AUC 5 or 6) i.v. on Day 1 of each 21-day cycle ▪ Non-squamous histology[d]: Pemetrexed 500 mg/m² BSA i.v. and carboplatin (AUC 5 or 6) i.v. on Day 1 of each 21-day cycle) or Pemetrexed 500 mg/m² BSA i.v. and cisplatin 75 mg/m² BSA i.v. on Day 1 of each 21-day cycle

Table 7: Characteristics of the intervention – RCT, indirect comparison: tremelimumab + durvalumab + platinum-based chemotherapy versus pembrolizumab: research question 1 (PD-L1 expression ≥ 50%) (multipage table)

Study	Intervention	Comparison
	For patients with non-squamous tumour histology who received pemetrexed chemotherapy and had no disease progression, maintenance therapy with pemetrexed 500 mg/m^2 BSA i.v. on Day 1 of each cycle (every 4 weeks in the intervention arm and every 3 or 4 weeks in the comparator arm) was allowed from Cycle 5 (Week 12) at the investigator's discretion.	
	Dose adjustments ▪ As per SPC or local standards, dose adjustments were allowed only for chemotherapy; dose reduction of durvalumab or tremelimumab was not allowed. ▪ Treatment interruption due to toxicity was allowed.	
	Disallowed prior treatment ▪ Chemotherapy or other systemic therapy for metastatic NSCLC[g] ▪ Immune-mediated therapy (e.g.: other anti-CTLA-4, anti-PD-1, or anti-PD-L2 antibodies) ▪ Radiotherapy[h] **Disallowed concomitant treatment** ▪ Chemotherapy, radiotherapy, immunotherapy, biological or hormone therapy <u>Only for the treatment arm tremelimumab + durvalumab + platinum-based chemotherapy</u> ▪ Immunosuppressants (e.g. systemic corticosteroids at a dose > 10 mg prednisone or equivalent) ▪ Sunitinib ▪ EGFR tyrosine kinase inhibitors	

Table 7: Characteristics of the intervention – RCT, indirect comparison: tremelimumab + durvalumab + platinum-based chemotherapy versus pembrolizumab: research question 1 (PD-L1 expression ≥ 50%) (multipage table)

Study	Intervention	Comparison
Pembrolizumab vs. platinum-based chemotherapy		
KEYNOTE-024	Pembrolizumab 200 mg i.v. on Day 1 of a 21-day cycle	Platinum-based combination chemotherapy[b] for 4 to 6 cycles: <u>Induction phase (4 to 6 cycles)</u> Only non-squamous: Pemetrexed 500 mg/m^2 BSA, i.v., on Day 1 of a 21-week cycle + Cisplatin 75 mg/m^2 BSA i.v. or carboplatin AUC of 5 or 6 mg/mL/min i.v., each on Day 1 of a 21-day cycle Non-squamous and squamous: Gemcitabine 1250 mg/m^2 BSA, i.v., Days 1 and 8 of a 21-day cycle + Cisplatin 75mg/m^2 BSA i.v., Day 1 of a 21-day cycle or carboplatin AUC of 5 or 6 mg/mL/min i.v., Day 1 of a 21-day cycle or Paclitaxel 200 mg/m^2 BSA, i.v., on Day 1 of a 21-week cycle + Carboplatin AUC of 5 or 6 mg/mL/min i.v., Day 1 of a 21-day cycle <u>Maintenance phase</u> Only non-squamous: after at least 4 cycles of carboplatin + pemetrexed, cisplatin + pemetrexed or paclitaxel + carboplatin, further treatment with pemetrexed 500 mg/m^2 BSA, i.v., on Day 1 of a 21-day cycle at the investigator's discretion
	Dose adjustments ▪ Pembrolizumab: no dose adjustment allowed (according to the SPC); interruption allowed in case of side effects ▪ Chemotherapy: dose adjustments allowed according to the SPC	

Table 7: Characteristics of the intervention – RCT, indirect comparison: tremelimumab + durvalumab + platinum-based chemotherapy versus pembrolizumab: research question 1 (PD-L1 expression ≥ 50%) (multipage table)

Study	Intervention	Comparison
	Prior treatment ▪ Chemotherapy and/or radiotherapy as part of neoadjuvant or adjuvant treatment; the last treatment had to have taken place at least 6 months before the diagnosis of metastatic disease **Pre-treatment not permitted** ▪ Systemic therapy for stage IV NSCLC ▪ CD137 agonists, anti-PD-1, anti-PD-L1, anti PD-L2, and CTLA-4 therapeutic antibodies or immune checkpoint inhibitors **Disallowed concomitant treatment** ▪ Immunotherapies other than pembrolizumab ▪ Other chemotherapies ▪ Surgery for symptom and tumour control ▪ Live vaccines ▪ Corticosteroids except for treating AEs or when used as premedication for a platinum-based combination chemotherapy used in the study ▪ Bisphosphonates or anti-RANK-L inhibitors[i]	
KEYNOTE-042	Pembrolizumab 200 mg i.v. on Day 1 of a 21-day cycle	Carboplatin-based combination chemotherapy[b] for 4 to a maximum of 6 cycles: <u>Induction phase (4 to 6 cycles)</u> Only non-squamous: Pemetrexed 500 mg/m^2 BSA, i.v., Day 1 of a 21-day cycle + Carboplatin AUC of 5 or 6 mg/mL/min i.v., Day 1 of a 21-day cycle Non-squamous and squamous: Paclitaxel 200 mg/m^2 BSA, i.v., Day 1 of a 21-day cycle + Carboplatin AUC of 5 or 6 mg/mL/min i.v., Day 1 of a 21-day cycle <u>Maintenance phase</u> Only non-squamous: after at least 4 cycles of platinum-based combination chemotherapy, further treatment with pemetrexed 500 mg/m^2 BSA, i.v., on Day 1 of a 21-day cycle at the investigator's discretion

Table 7: Characteristics of the intervention – RCT, indirect comparison: tremelimumab + durvalumab + platinum-based chemotherapy versus pembrolizumab: research question 1 (PD-L1 expression ≥ 50%) (multipage table)

Study	Intervention	Comparison
	Dose adjustments ▪ Pembrolizumab: no dose adjustment allowed (treatment interruption or discontinuation allowed) ▪ Chemotherapy: dose adjustments allowed according to the SPC	
	Prior treatment ▪ Adjuvant or neoadjuvant therapy; the last treatment had to be administered at least 6 months prior to the development of the metastatic disease **Disallowed prior treatment** ▪ Systemic therapy for the advanced or metastatic NSCLC stage ▪ CD137 agonists, anti-PD-1, anti-PD-L1, anti PD-L2 and CTLA-4 therapeutic antibodies or immune checkpoint inhibitors **Disallowed concomitant treatment** ▪ Other chemotherapies or immunotherapies ▪ Surgery for symptom or tumour control ▪ Radiotherapy ▪ Live vaccines ▪ Corticosteroids except for the treatment of AEs or used as premedication of a chemotherapy used in the study	

a. Weight-based dosing for patients weighing ≤ 30 kg: 20 mg/kg BW for durvalumab and 1 mg/kg BW for tremelimumab until a weight of > 30 kg is reached.
b. The platinum-based combination chemotherapy was selected individually for each patient by the investigator prior to randomisation.
c. If platinum-based chemotherapy was discontinued due to treatment-related toxicities, therapy with durvalumab or durvalumab + tremelimumab was allowed to be continued at the discretion of the investigator (if AE grade ≤ 2).
d. Patients were allowed to switch between cisplatin therapy and carboplatin therapy at any time due to intolerance.
e. A total of 11 patients of the total intervention-arm population received re-treatment at the final data cutoff on 12/03/2021.
f. Administration of chemotherapy was allowed for up to 6 cycles if clinically indicated in the investigator's opinion.
g. Patients who had previously received platinum-containing adjuvant, neoadjuvant, or definitive chemoradiotherapy for advanced disease were included in the study if progression occurred > 12 months after the end of the last therapy.
h. Excluded was definitive radiotherapy ≥ 12 months prior to study inclusion, palliative radiotherapy of the brain with appropriate criteria for stability or absence of symptoms, and palliative irradiation of painful bone lesions (accounting for a maximum of 30% of the bone marrow).
i. These therapies were allowed to be continued in the study only if the treatment started before study enrolment.

AE: adverse event; AUC: area under the curve; BSA: body surface area; CD137: Cluster of Differentiation 137; CTLA-4: cytotoxic T-lymphocyte-associated protein 4; EGFR: Epidermal Growth Factor Receptor; i.v.: intravenous; NSCLC: non-small cell lung cancer; PD-1: programmed death protein 1; PD-L1/2: programmed death ligand 1/2; RANK-L: receptor activator of NF-κB ligand; RCT: randomised controlled trial; SPC: Summary of Product Characteristics

Study design

Study with tremelimumab + durvalumab + platinum-based chemotherapy: POSEIDON

The POSEIDON study is an open-label, 3-arm RCT comparing tremelimumab + durvalumab + platinum-based chemotherapy, durvalumab + platinum-based chemotherapy, and platinum-based chemotherapy. The study included adult patients with histologically or cytologically confirmed NSCLC (stage IV) without EGFR mutation or ALK translocation whose tumours exhibited PD-L1 expression. The inclusion criteria additionally required patients to be in good general health (ECOG-PS ≥ 1) and to be ineligible for curative surgery or radiotherapy. Prior chemotherapy or other systemic therapies for metastatic NSCLC were disallowed. In patients with squamous histology or patients with known KRAS mutation of the tumour, EGFR or ALK testing was not required.

PD-L1 expression of tumour tissue was determined by immunohistochemistry using the SP263 assay.

The POSEIDON study included a total of 1013 patients, randomized in a 1:1:1 ratio either to treatment with tremelimumab + durvalumab + platinum-based chemotherapy (N = 338), durvalumab + platinum-based chemotherapy (N = 338), or to treatment with platinum-based chemotherapy alone (N = 337). Randomisation was stratified by PD-L1 status (≥ 50%, < 50%), disease stage (IVA, IVB), and tumour histology (squamous, non-squamous). For the present benefit assessment, only the arms tremelimumab + durvalumab + platinum-based chemotherapy and platinum-based chemotherapy are relevant.

The administration of tremelimumab and durvalumab in combination with platinum-based chemotherapy is largely in line with the SPCs [33,34]. For durvalumab treatment beyond progression, see the body of text below.

In the comparator arm, platinum-based chemotherapy was administered for 4–6 cycles at the investigator's discretion. For patients with non-squamous NSCLC, the treatment options for platinum-based chemotherapy comprised pemetrexed + cisplatin or pemetrexed + carboplatin; those for patients with squamous NSCLC were gemcitabine + cisplatin or gemcitabine + carboplatin. Furthermore, patients were allowed to receive nab-paclitaxel + carboplatin irrespective of tumour histology. The selection was made by the investigator on an individualized basis prior to randomization. The platinum-based chemotherapies were administered as far as possible as per the requirements of the respective SPCs [35-39] or the AM-RL on off-label use (Annex VI to Section K [3]). Gemcitabine was allowed be administered in a dosage of 1000 or 1250 mg, but the SPC only provides for a dosage of 1000 mg in combination with cisplatin. Information on the number of patients by type of therapy in the comparator arm can be found in Table 12.

In patients with non-squamous histology who received pemetrexed chemotherapy and exhibited no disease progression, maintenance therapy with pemetrexed (every 4 weeks in the intervention arm and every 3 or 4 weeks in the comparator arm) was allowed in both study arms from Cycle 5 (Week 12) upon the investigator's discretion.

In both study arms, treatment continued until disease progression, unacceptable toxicity, treatment discontinuation upon the physician's or patient's discretion, or until the start of new antineoplastic therapy. Patients whose x-rays showed progression and were judged by the investigator to benefit from treatment were, with some limitations, permitted to continue receiving durvalumab as monotherapy. There is no information in the study documents on how many patients were treated with durvalumab monotherapy beyond progression. Furthermore, patients who experienced progression after 5 cycles of continued durvalumab monotherapy and who, in the investigator's opinion, continued to benefit from treatment, were allowed to receive re-treatment with tremelimumab + durvalumab. According to the information provided by the company in Module 4 A, this affected 10 patients in the study's intervention arm. Switching patients from the comparator arm to the intervention arm was not allowed. There were no restrictions regarding the administration of subsequent therapies.

Primary outcomes of the study were PFS and overall survival. Patient-relevant secondary outcomes were outcomes on morbidity, health-related quality of life, and AEs.

POSEIDON study subpopulation relevant for research question 1

The POSEIDON subpopulation relevant for the present research question 1 comprises patients with tumour PD-L1 expression ≥ 50% (101 patients in the intervention arm and 97 patients in the comparator arm).

Studies with pembrolizumab: KEYNOTE-024 and KEYNOTE-042

KEYNOTE-024

As already described in the dossier assessments A17-06, A19-30, and A21-69 [15,17,19], the KEYNOTE-024 study is an open-label RCT comparing pembrolizumab versus platinum-based combination chemotherapy. The study included adult patients with histologically or cytologically confirmed metastatic NSCLC without EGFR mutation or ALK translocation and with tumour PD-L1 expression ≥ 50%. Patients had to be in good general health (ECOG-PS ≤ 1). Prior systemic antineoplastic treatment for the metastatic stage was disallowed.

The KEYNOTE-024 study included a total of 305 patients, randomized in a 1:1 ratio to treatment with either pembrolizumab monotherapy (N = 154) or to 1 of 5 possible treatment options as platinum-based combination chemotherapy (N = 151). The treatment options were as follows: pemetrexed + cisplatin, pemetrexed + carboplatin, gemcitabine + cisplatin, gemcitabine + carboplatin, or paclitaxel + carboplatin, with the combination with pemetrexed

representing an option only for patients with non-squamous histology. Prior to randomization, an investigator specified on an individual basis which treatment was suitable for each patient. Randomization was stratified by histology (squamous, non-squamous), geographical region (East Asia, not East Asia), and ECOG-PS (0, 1).

In the study, the PD-L1 expression of the tumour tissue was determined by means of immunohistochemistry using the 22C3 assay.

The administration of pembrolizumab was in line with the SPC [40]. The maximum treatment duration for pembrolizumab was 35 cycles. In the KEYNOTE-024 study, none of the participants reached this duration. The platinum-based chemotherapies were administered as far as possible as per the respective SPC [35-39,41] or the AM-RL on off-label use (Annex VI to Section K [3]). In the KEYNOTE-024 study, the platinum component of the chemotherapy was administered for a maximum of 4 to 6 cycles. Thereafter, patients with non-squamous histology were allowed – and recommended – to receive maintenance treatment with pemetrexed. Information on the number of patients by type of chemotherapy in the comparator arm can be found in Table 12.

Patients were treated until either disease progression, occurrence of unacceptable side effects, or discontinuation of the study as decided by the investigator or the patient. After disease progression, suitable patients in the comparator arm were allowed to switch to monotherapy with pembrolizumab. The approval of pembrolizumab specifies this treatment option after prior chemotherapy. There was no further limitation regarding subsequent therapies.

PFS was the primary outcome of the study. Patient-relevant secondary outcomes were overall survival as well as outcomes on morbidity, health-related quality of life, and AEs.

The KEYNOTE-024 population relevant for the present research question comprises all randomized patients.

KEYNOTE-042

As already described in dossier assessments A19-30, A19-31, and A21-69 [17,19,26], the KEYNOTE-042 study is an open-label RCT. The study compared pembrolizumab versus a combination of carboplatin and either paclitaxel or pemetrexed. A total of 1274 patients were randomly allocated in a 1:1 ratio to the intervention arm (pembrolizumab: N = 637) or to the comparator arm (N = 637). Randomisation was stratified by ECOG-PS (0, 1), histology (squamous, non-squamous), PD-L1 expression (≥ 50%, 1% to 49%), and geographical region (East Asia, not East Asia). The study included adults with histologically or cytologically confirmed diagnosis of NSCLC exhibiting locally advanced or metastatic tumours with PD-L1 expression ≥ 1%. Prior systemic treatment was not allowed in the study. For patients who had

received adjuvant or neoadjuvant therapy, treatment had to be terminated at least 6 months prior to the development of metastases. The included patients had to have an ECOG-PS of 0 or 1. Prior to randomization, an investigator decided which treatment option (pemetrexed + carboplatin or paclitaxel + carboplatin) would be suitable for each individual patient in the event of randomization to the comparator arm; however, the combination with pemetrexed was an option only for patients with non-squamous histology.

In the study, the PD-L1 expression of the tumour tissue was determined by means of immunohistochemistry using the 22C3 assay.

Patients in the intervention arm received pembrolizumab in accordance with the requirements of the SPC [40]. The maximum treatment duration was 35 cycles. In the KEYNOTE-042 study, this duration was achieved by only about 7% of patients in the total study population. The platinum-based chemotherapies (pemetrexed + carboplatin or paclitaxel + carboplatin) were administered as per requirements of the respective SPC [35-38,41,42] or the AM-RL on off-label use (Annex VI to Section K [3]). In the KEYNOTE-042 study, patients with non-squamous histology received carboplatin for a maximum of 4 to 6 cycles. After at least 4 cycles, patients with non-squamous histology were allowed – and recommended – to receive maintenance treatment with pemetrexed. Information on the number of patients by type of therapy in the comparator arm can be found in Table 12.

Patients were treated until either disease progression, complete response, occurrence of unacceptable side effects, or study discontinuation as decided by the investigator or the patient.

After discontinuation of the study medication (e.g. due to disease progression), the patients in both treatment arms were allowed to receive subsequent therapies. There were no limitations regarding the type of subsequent therapy. The study design did not explicitly provide for a treatment switch from the ACT to pembrolizumab monotherapy after disease progression.

The study's primary outcome was overall survival. Patient-relevant secondary outcomes were AEs.

Relevant subpopulation of the KEYNOTE-042 study

The KEYNOTE-042 study's subpopulation relevant for the present research question 1 comprises patients with tumour PD-L1 expression ≥ 50% (299 patients in the pembrolizumab arm and 300 patients in the comparator arm).

Data cutoffs

The predefined data cutoffs of all 3 studies (POSEIDON, KEYNOTE-024, and KEYNOTE-042) are used for the assessment.

POSEIDON study

For the POSEIDON study, the company's Module 4 A presents results from 3 different data cutoffs, depending on the patient-relevant outcome:

- Data cutoff of 12 March 2021: for the patient-reported outcomes of the morbidity and health-related quality of life categories
- Data cutoff of 25 October 2021: for the outcomes on AEs, discontinuation due to AEs, and severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3)
- Data cutoff of 11 March 2022: for the outcomes on overall survival and serious adverse events (SAEs)

The company's Module 4 A does not explain or justify the selection of different data cutoffs for the analysis of the different outcomes.

The present benefit assessment uses the results from the 12 March 2021 data cutoff for all outcomes. This data cutoff was chosen because, as per study documents, it represents the predefined final data cutoff for overall survival. Accordingly, the results from this data cutoff are included in the study report for the outcome of overall survival (as well as for the other patient-relevant outcomes of the present benefit assessment). The European Public Assessment Report (EPAR) likewise uses only the 12 March 2021 data cutoff for overall survival, and no information is available on requested or planned further data cutoffs [10].

For the results presented by the company on the 2 data cutoffs of 25 October 2021 (for [severe] AEs and discontinuation due to AEs) and 11 March 2022 (overall survival and SAEs), it is not clear from the study documents whether they were predefined or, if subsequently defined, how they were specifically triggered.

For the 11 March 2022 data cutoff, it should be noted that it was implemented 1 year after the predefined final data cutoff for overall survival (12 March 2021) and the results for overall survival and for SAEs are available in an addendum to the study report (dated 25 May 2022). Version 6 of the study protocol dated 9 July 2021, i.e. after the data cutoff of the final analysis, newly specified that overall survival was to be followed up for approximately 1 year after the final data cutoff. However, it is not clear from the information provided whether and when the data collected for this outcome or other outcomes (such as SAEs) will be analysed.

KEYNOTE-024 and KEYNOTE-042 studies

For the KEYNOTE-024 study, the 2nd interim analysis from 9 May 2016 is used. Due to the superiority of pembrolizumab in terms of overall survival, all patients in the comparator arm had the option to switch to pembrolizumab monotherapy after this data cutoff.

For the KEYNOTE-042 study, the 2nd interim analysis dated 26 February 2018 is used because the overall survival results were final at this time.

Planned duration of follow-up observation

Table 8 shows the planned duration of patient follow-up observation for the individual outcomes.

Table 8: Planned duration of follow-up observation – RCT, indirect comparison: tremelimumab + durvalumab + platinum-based chemotherapy versus pembrolizumab: research question 1 (PD-L1 expression ≥ 50%) (multipage table)

Comparison **Study** **Outcome category** **Outcome**	**Planned follow-up observation**
Tremelimumab + durvalumab + platinum-based chemotherapy vs. platinum-based chemotherapy	
POSEIDON	
Mortality	
Overall survival	▪ At the longest until end of study
Morbidity	
Symptoms (EORTC QLQ-C30 and EORTC QLQ-LC13)	▪ Until 2nd disease progression or death (whichever came first)
Health status (EQ-5D VAS, PGIC)	▪ Until 2nd disease progression or death (whichever came first)
Health-related quality of life (EORTC QLQ-C30)	▪ Until 2nd disease progression or death (whichever came first)
Side effects	
all outcomes of the side effects category (except PRO-CTCAE)	▪ Until 90 days after discontinuation of the study medication
PRO-CTCAE	▪ Until 2nd disease progression or death (whichever came first)
Pembrolizumab vs. platinum-based chemotherapy	
KEYNOTE-024	
Mortality	
Overall survival	▪ Until death
Morbidity	
Symptoms (EORTC QLQ-C30 and EORTC QLQ-LC13), health status (EQ-5D VAS)	▪ Until 30 days after the last dose of the study medication ▪ If treatment ends before progression: until progression or start of new antineoplastic therapy
Health-related quality of life (EORTC QLQ-C30)	▪ Until 30 days after the last dose of the study medication ▪ If treatment ends before progression: until progression or start of new antineoplastic therapy
Side effects	
AEs	▪ Until 30 days after the last dose of the study medication
SAEs and immune-related AEs	▪ Until 90 days after the last dose of the study medication (or until 30 days after the last dose of the study medication if new antineoplastic treatment was initiated, whichever occurred first)

Table 8: Planned duration of follow-up observation – RCT, indirect comparison: tremelimumab + durvalumab + platinum-based chemotherapy versus pembrolizumab: research question 1 (PD-L1 expression ≥ 50%) (multipage table)

Comparison **Study** **Outcome category** **Outcome**	**Planned follow-up observation**
KEYNOTE-042	
Mortality	
Overall survival	▪ Until death
Morbidity	▪ Not recorded
Health-related quality of life	▪ Not recorded
Side effects	
AEs	▪ Until 30 days after the last dose of the study medication or until initiation of a new antineoplastic treatment (whichever occurred first)
SAEs and immune-related AEs	▪ Until 90 days after the last dose of the study medication (or until 30 days after the last dose of the study medication if new antineoplastic treatment was initiated, whichever occurred first)

AE: adverse event; EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: European Quality of Life – 5 Dimensions; PGIC: Patient Global Impression of Change; PRO-CTCAE: Patient-Reported Outcome – Common Terminology Criteria for Adverse Events; QLQ-C30: Quality of Life Questionnaire – Cancer 30; QLQ-LC13: Quality of Life Questionnaire – Lung Cancer 13; RCT: randomised controlled trial; SAE: serious adverse event; VAS: visual analogue scale

Outcomes on morbidity and health-related quality of life were collected only in the POSEIDON and KEYNOTE-024 studies. The observation times for these outcomes have been systematically shortened in both studies. In the POSEIDON study, these were collected up to the 2nd disease progression, in the KEYNOTE-024 study, up to 30 days after the last dose of study medication or, in the case of end of treatment before progression, up to progression or start of a new antineoplastic therapy.

The observation times for the side effects outcomes are likewise systematically shortened in all 3 studies because they were collected only for the period of treatment with the study medication (plus 90 days in the POSEIDON study or 30 days [AE] or 90 days [SAEs] in the KEYNOTE-024 and KEYNOTE-042 studies).

Drawing a reliable conclusion on the total study period or the time to patient death, however, would require surveying these outcomes for the total period, as was done for survival.

Study population

Table 9 shows the characteristics of the patients in the relevant subpopulation of the included studies.

Table 9: Characteristics of the study populations as well as study/treatment discontinuation – RCT, indirect comparison: tremelimumab + durvalumab + platinum-based chemotherapy versus pembrolizumab: research question 1 (PD-L1 expression ≥ 50%) (multipage table)

Study Characteristic Category	Study with tremelimumab + durvalumab		Studies with pembrolizumab			
	POSEIDON		KEYNOTE-024		KEYNOTE-042	
	Tremelimumab + durvalumab + platinum-based chemotherapy	Platinum-based chemotherapy	Pembrolizumab	Platinum-based chemotherapy	Pembrolizumab	Platinum-based chemotherapy
	N[a] = 101	N[a] = 97	N[a] = 154	N[a] = 151	N[a] = 299	N[a] = 300
Age [years]						
Mean (SD)	62 (9)	63 (9)	64 (10)	65 (10)	ND	ND
Median [min; max]	62 [34; 81]	64 [39; 80]	65 [33; 90]	66 [8; 85]	65 [33; 90]	66 [38; 85]
Sex [F/M], %	27/73	29/71	40/60	37/63	31/69	30/70
Family origin, n (%)						
White	55 (54)	44 (45)	125 (81)	126 (83)	ND	ND
Asian	32 (32)	45 (46)	25 (16)	21 (14)	ND	ND
Other	14 (14)	8 (8)	2 (1)[b]	4 (3)[b]	ND	ND
Unknown	0 (0)	0 (0)	2 (1)	0 (0)	ND	ND
Geographical region, n (%)						
Europe	41 (41)	35 (36)	ND	ND	71 (24)	66 (22)
Rest of the world	60 (59)	62 (64)	ND	ND	228 (76)	234 (78)
Smoking status, n (%)						
Active	19 (19)	17 (18)	34 (22)	31 (21)	57 (19)	59 (20)
Former	58 (57)	58 (60)	115 (75)	101 (67)	178 (60)	174 (58)
Never	24 (24)	21 (22)	5 (3)	19 (13)	64 (21)	67 (22)
Missing	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)

Table 9: Characteristics of the study populations as well as study/treatment discontinuation – RCT, indirect comparison: tremelimumab + durvalumab + platinum-based chemotherapy versus pembrolizumab: research question 1 (PD-L1 expression ≥ 50%) (multipage table)

Study Characteristic Category	Study with tremelimumab + durvalumab		Studies with pembrolizumab			
	POSEIDON		KEYNOTE-024		KEYNOTE-042	
	Tremelimumab + durvalumab + platinum-based chemotherapy	Platinum-based chemotherapy	Pembrolizumab	Platinum-based chemotherapy	Pembrolizumab	Platinum-based chemotherapy
	N[a] = 101	N[a] = 97	N[a] = 154	N[a] = 151	N[a] = 299	N[a] = 300
ECOG-PS, n (%)						
0	30 (30)	37 (38)	54 (35)	53 (35)	96 (32)	91 (30)
1	71 (70)	59 (61)	99 (64)	98 (65)	203 (68)	209 (70)
Unknown	0 (0)	1 (1)	1 (< 1)	0 (0)	0 (0)	0 (0)
Histology, n %						
Squamous	36 (36)	32 (33)	29 (19)	27 (18)	107 (36)	114 (38)
Non-squamous	65 (64)	64 (66)	125 (81)	124 (82)	192 (64)	186 (62)
Missing	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Brain metastases, n (%)	10 (10)	11 (11)	18 (12)	10 (7)	19 (6)	15 (5)
Disease status, n (%)						
IIIB	0 (0)	0 (0)	1 (< 1)	1 (< 1)	ND	ND
IV	100 (100)[b]	96 (99)[b]	153 (99)	150 (99)	ND	ND
IVA	48 (48)	46 (47)	ND	ND	ND	ND
IVB	53 (52)	50 (52)	ND	ND	ND	ND
Missing	0 (0)	1 (1)	0 (0)	0 (0)	ND	ND
Disease status, n (%)						
Locally advanced	0 (0)	0 (0)	ND	ND	27 (9)	35 (12)
Metastatic	101 (100)	96 (99)	ND	ND	272 (91)	265 (88)
Missing	0 (0)	1 (1)	ND	ND	0 (0)	0 (0)

Table 9: Characteristics of the study populations as well as study/treatment discontinuation – RCT, indirect comparison: tremelimumab + durvalumab + platinum-based chemotherapy versus pembrolizumab: research question 1 (PD-L1 expression ≥ 50%) (multipage table)

Study Characteristic Category	Study with tremelimumab + durvalumab		Studies with pembrolizumab			
	POSEIDON		KEYNOTE-024		KEYNOTE-042	
	Tremelimumab + durvalumab + platinum-based chemotherapy	Platinum-based chemotherapy	Pembrolizumab	Platinum-based chemotherapy	Pembrolizumab	Platinum-based chemotherapy
	N[a] = 101	N[a] = 97	N[a] = 154	N[a] = 151	N[a] = 299	N[a] = 300
Number of metastases at baseline, mean (SD) or median [min; max]	ND	ND	ND	ND	ND	ND
Metastasis, n (%)						
M0	11 (11)	1 (1)	1 (< 1)	1 (< 1)	ND	ND
M1	3 (3)	2 (2)	29 (19)	34 (23)	ND	ND
M1A	36 (36)	35 (36)	47 (31)	41 (27)	ND	ND
M1B	18 (18)	17 (18)	77 (50)	74 (49)	ND	ND
M1C	33 (33)	41 (42)	0 (0)	0 (0)	ND	ND
MX	0 (0)	0 (0)	0 (0)	1 (1)	ND	ND
Missing	0 (0)	1 (1)	0 (0)	0 (0)	ND	ND
Time since initial diagnosis [months]						
Mean (SD)	ND	ND	5.7 (13.4)	6.2 (23.7)	ND	ND
Median [min; max]	ND	ND	1.7 [0.7; 114.8]	1.7 [0.5; 230.8]	ND	ND
Previous therapies, n (%)						
Adjuvant	ND	ND	6 (4)	3 (2)	8 (3)	4 (1)
Neoadjuvant	ND	ND	3 (2)	1 (< 1)	1 (< 1)	5 (2)
Previous radiotherapies, n (%)	12 (12)	8 (8)	ND	ND	40 (13)	39 (13)

Table 9: Characteristics of the study populations as well as study/treatment discontinuation – RCT, indirect comparison: tremelimumab + durvalumab + platinum-based chemotherapy versus pembrolizumab: research question 1 (PD-L1 expression ≥ 50%) (multipage table)

Study Characteristic Category	Study with tremelimumab + durvalumab		Studies with pembrolizumab			
	POSEIDON		KEYNOTE-024		KEYNOTE-042	
	Tremelimumab + durvalumab + platinum-based chemotherapy	Platinum-based chemotherapy	Pembrolizumab	Platinum-based chemotherapy	Pembrolizumab	Platinum-based chemotherapy
	N[a] = 101	N[a] = 97	N[a] = 154	N[a] = 151	N[a] = 299	N[a] = 300
Treatment discontinuation, n (%)[c]	83 (84)	92 (99)[d]	80 (52)	106 (70)	217 (73)	194 (65)
Study discontinuation, n (%)[e]	71 (70)	87 (90)	47 (31)	69 (46)	ND	ND

a. Number of randomized patients. Values which are based on different patient numbers are marked in the corresponding line if the deviation is relevant.
b. Institute's calculation.
c. Common reasons for treatment discontinuation in the intervention vs. comparator arm were:
- POSEIDON study (data cutoff 21/03/2021): worsening of the disease (57.6% vs. ND), adverse event (21.2% vs. ND), patient decision (4.0% vs. ND).
- KEYNOTE-024 study: disease progression (33.1% vs. 46%), adverse event (11.0% vs. 10.7%), death (3.9% vs. 6%), investigator decision (<1% vs. 4.7%), treatment completed (0% vs. 19.3%).
- KEYNOTE-042 study: radiological progression (42.3 vs. 36.7%), adverse events (20.5% vs. 15.7%), clinical progression (7.7% vs. 9.8%).

d. Presumably includes discontinuation of pemetrexed as maintenance therapy; patients who have reached the maximum dose of chemotherapy and are not receiving pemetrexed were presumably also counted as patients discontinuing treatment.
e. Common reasons for study discontinuation in the intervention vs. comparator arm were:
- POSEIDON study (data cutoff 12/03/2021): based on all patients who received at least 1 dose of study medication (intervention arm N = 99; comparator arm N = 93): death (69.3% vs. 83.5%), withdrawal of patient consent (1.0% vs. 6.2%)
- KEYNOTE-024 and KEYNOTE-042 studies: ND

ECOG-PS: European Cooperative Oncology Group Performance Status; f: female; m: male; max: maximum; min: minimum; n: number of patients in the category; N: number of randomized patients; ND: no data; PD-L1: programmed death ligand 1; RCT: randomized controlled trial; SD: standard deviation

Information on the patient characteristics of interest is not available for all 3 studies. Nevertheless, based on the available information, the populations are deemed to be sufficiently comparable both between the POSEIDON, KEYNOTE-024, and KEYNOTE-042 studies and between the treatment arms in each of the individual studies.

The median age of the patients included in the subpopulations of the POSEIDON, KEYNOTE-024, and KEYNOTE-042 studies used for the assessment was between approximately 62 and 66 years, depending on the study and study arm, and the patients were predominantly male. Almost all of the patients were in stage IV (POSEIDON, KEYNOTE-024) or in the metastatic stage (KEYNOTE-042). The proportion of patients with brain metastases was comparable between the studies and ranged between 5% and 12%, depending on the study and study arm.

The proportion of patients of White family origin was approximately 50% in the POSEIDON study and approximately 80% in the KEYNOTE-024 study; no information on family origin is available for the relevant subpopulation of the KEYNOTE-024 study. Unlike for research question 2, the studies show no evidence of a relevant or qualitative effect modification for this characteristic (for a more detailed explanation, see Section I 3.1.3).

Overall, the patient populations of the 3 studies are sufficiently similar with regard to patient characteristics and are thus suitable for an indirect comparison in terms of the similarity test.

A major difference between the studies' results from the different treatment options of platinum-based chemotherapy in the respective comparator arms. This aspect is addressed in Section I 3.1.3 when describing the between-study similarity of the common comparator of platinum-based combination chemotherapy.

Treatment duration and observation period

Table 10 shows patients' mean and median treatment durations as well as the mean and median observation period for individual outcomes.

Table 10: Information on the course of the study – RCT, indirect comparison: tremelimumab + durvalumab + platinum-based chemotherapy versus pembrolizumab: research question 1 (PD-L1 expression ≥ 50%) (multipage table)

Comparison **Study** **Outcome category** **Treatment component / outcome**	**Tremelimumab + durvalumab + platinum-based chemotherapy or pembrolizumab**	**Platinum-based chemotherapy**
Tremelimumab + durvalumab + platinum-based chemotherapy vs. platinum-based chemotherapy		
POSEIDON (data cutoff 12/03/2021)	N[a] = 99	N[a] = 93
Treatment duration [months][b]		
Total		
Median [min; max]	7.4 [0.2; 43.7]	4.1 [0.2; 34.5]
Mean (SD)	13.7 (12.5)	5.5 (5.8)
Tremelimumab		
Median [min; max]	4.6 [0.2; 8.3]	–
Mean (SD)	4.3 (1.5)	–
Durvalumab		
Median [min; max]	7.4 [0.2; 43.7]	–
Mean (SD)	13.6 (12.5)	–
Platinum-based chemotherapy		
Median [min; max]	3.7 [0.2; 43.7]	4.1 [0.2; 34.5]
Mean (SD)	9.1 (11.1)	5.5 (5.8)
Observation period [months]		
Overall survival[c]	ND[d]	
Morbidity		
Symptoms (EORTC QLQ-C30, EORTC QLQ-LC13), health status (EQ-5D VAS)		
Median [min; max]	8.4 [0.1; 42.9]	4.7 [0; 33.4]
Mean (SD)	ND	
Health status (PGIC)[e]		
Median [min; max]	9 [0.7; 42.9]	5.9 [0.7; 33.4]
Mean (SD)	ND	
Health-related quality of life (EORTC QLQ-C30)		
Median [min; max]	8.4 [0.1; 42.9]	4.7 [0; 33.4]
Mean (SD)	ND	
Side effects	ND[f]	

Table 10: Information on the course of the study – RCT, indirect comparison: tremelimumab + durvalumab + platinum-based chemotherapy versus pembrolizumab: research question 1 (PD-L1 expression ≥ 50%) (multipage table)

Comparison **Study** **Outcome category** **Treatment component / outcome**	**Tremelimumab + durvalumab + platinum-based chemotherapy or pembrolizumab**	**Platinum-based chemotherapy**
Pembrolizumab vs. platinum-based chemotherapy		
KEYNOTE-024 (9/05/2016 data cutoff)	N[a] = 154	N[a] = 150
Treatment duration [months]		
Median [min; max]	7.0 [0.0; 18.7]	3.5 [0.0; 16.8]
Mean (SD)	6.8 (4.8)	4.0 (3.5)
Observation period	ND	
KEYNOTE-042 (26/02/2018 data cutoff)	N[a] = 299	N[a] = 300
Treatment duration	ND	
Observation period	ND	

a. Number of analysed patients. Values which are based on different patient numbers are marked in the corresponding line if the deviation is relevant.
b. The company's data are based on weeks, while some calculations are shown in months.
c. The observation duration was calculated as the time from randomisation to the date of the respective event or until censoring.
d. No information for the predefined final data cutoff of 12/03/2021; for data cutoff 11/03/2022: median [min; max] (intervention arm vs. comparator arm): 15.93 [0.3; 55.8] vs. 10.61 [0; 55.8] months.
e. Data based on 96 patients (intervention arm) vs. 80 patients (comparator arm).
f. No data for the predefined final data cutoff of 12/03/2021; 25/10/2021 data cutoff: median [min; max] (intervention arm vs. comparator arm): 9 months [0.3; 55.6] vs. 5.7 months [0.2; 46.6]; observation duration was calculated as the time from the first dose of study medication to the earliest time of occurrence of the following data: 90 days after the last dose of study medication, date of start of first subsequent therapy, or date of death.

EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: European Quality of Life – 5 Dimensions; max: maximum; min: minimum; N: number of patients evaluated; ND: no data; PD-L1: programmed death ligand 1; PGIC: Patient Global Impression of Change; QLQ-C30: Quality of Life Questionnaire – Cancer 30; QLQ-LC13: Quality of Life Questionnaire – Lung Cancer 13; RCT: randomised controlled trial; SD: standard deviation; VAS: visual analogue scale

Treatment duration data are available only for the 2 studies POSEIDON and KEYNOTE-024. In the POSEIDON and KEYNOTE-024 studies, the median total treatment duration in the intervention arm was approximately 1.8 times (POSEIDON trial) or 2 times (KEYNOTE-024 trial) as long as in the respective comparator arm. The treatment durations of the intervention arms and the comparator arms were comparable between the studies. No data on treatment duration are available for the KEYNOTE-042 study.

Data on observation durations are available only for the POSEIDON study, and only for the patient-reported outcomes of the morbidity and health-related quality of life categories. For

the KEYNOTE-024 and KEYNOTE-042 studies, no information at all is available on the observation period for all patient-relevant outcomes.

Regarding the patient-reported outcomes of the POSEIDON study, the observation durations in the intervention arm were 1.5 to 1.8 times longer than in the comparator arm.

For overall survival and the side effects outcomes, no information is available on the observation durations for the employed 12 March 2021 data cutoff. However, this has no consequences for the indirect comparison of the 3 studies. Assuming proportional hazards, the observation duration does not affect the point estimate of the effect on overall survival in the case of the analysis method chosen here for the indirect comparison (Cox proportional hazards model). For side effects, the observation duration of the POSEIDON study as well as for the KEYNOTE-024 study can be estimated from the data on the median treatment duration because AEs were to be surveyed for 90 days (POSEIDON study) and 30 days (KEYNOTE-024 study), with SAEs being surveyed for 90 days (both studies) after the last study medication. Thus, like the analysed differences in treatment durations, the observation durations for the side effects in both studies are longer in the intervention arm than in the comparator arm.

Overall, the missing data make it impossible to analyse the similarity of the KEYNOTE-042 study to the 2 other studies with regard to treatment duration and the similarity of the 3 studies with regard to observation duration. For side effects, however, the POSEIDON and KEYNOTE-024 studies exhibit similar treatment durations and thus similar follow-up times. Therefore, these 2 studies can be assumed to have comparable observation durations for side effects.

Subsequent therapies

Table 11 shows the subsequent therapies patients received after discontinuing the study medication.

Table 11: Information on subsequent antineoplastic therapies – RCT, indirect comparison: tremelimumab + durvalumab + platinum-based chemotherapy versus pembrolizumab: research question 1 (PD-L1 expression ≥ 50%)

Study **Drug class** **Drug**	**Patients with subsequent therapy n (%)**	
	Tremelimumab + durvalumab + platinum-based chemotherapy or pembrolizumab	**Platinum-based chemotherapy**
Tremelimumab + durvalumab + platinum-based chemotherapy vs. platinum-based chemotherapy		
POSEIDON (data cutoff 12/03/2021)	N = 99	N = 93
Total	34 (34.3)	61 (65.6)
Systemic treatment	28 (28.3)	58 (62.4)
Chemotherapy	26 (26.3)	32 (34.4)
Immunotherapy	3 (3.0)	37 (39.8)
Targeted therapy	5 (5.1)	4 (4.3)
Radiotherapy	11 (11.1)	15 (16.1)
Pembrolizumab vs. platinum-based chemotherapy		
KEYNOTE-024 (data cut 9/05/2016)	154	151
Total[a]	35 (22.7)	91 (60.3)[b]
Switch to pembrolizumab	NA	66 (43.7)
KEYNOTE-042	ND[c]	

a. No information is available on the type of therapy.
b. Institute's calculation.
c. Only data on the total population are available. Information on the relevant subpopulation with a PD-L1 expression of the tumour ≥ 50% is missing.

n: number of patients with subsequent therapy; N: number of patients evaluated; NA: not applicable; ND: no data; PD-L1: programmed death ligand 1; RCT: randomised controlled trial

In the POSEIDON study's relevant subpopulation, 34% of the patients in the intervention arm and 66% of the patients in the comparator arm received at least 1 subsequent antineoplastic therapy. Of these, the majority of patients received systemic therapy. In the comparator arm, 40% of patients received immunotherapy as a subsequent therapy, most frequently pembrolizumab monotherapy (n = 17, 18.3% based on the relevant subpopulation). Targeted therapies were used in approximately 5% of participants in both study arms (based on the relevant subpopulation).

Comparative data on subsequent therapies for the relevant subpopulations are only available for the POSEIDON study and the KEYNOTE-024 study. The available data on subsequent therapies show that when comparing the POSEIDON and KEYNOTE-024 studies, the proportion of intervention arm patients with subsequent therapies is slightly higher in the POSEIDON study (34% versus 23%), and the proportions are of a similar magnitude in the comparator arms (66% versus 60%). However, complete information on the therapy types is

available only for the POSEIDON study. For the KEYNOTE-024 study, the available information shows only that among the 91 patients who received subsequent therapy, 66 patients switched to pembrolizumab monotherapy.

No information on subsequent therapies received by the relevant subpopulation was available for the KEYNOTE-042 study. At the time point of the 26 February 2018 data cutoff, the proportion of patients with antineoplastic subsequent therapy from among the entire subpopulation was 37.7% (N = 240) in the intervention arm and 44.0% (N = 280) in the comparator arm. In the comparator arm, 28 patients (4.4%) had switched to pembrolizumab monotherapy.

Due to the incomplete information on subsequent therapies in the studies KEYNOTE-024 and KEYNOTE-042, the similarity of these studies to the POSEIDON study with regard to subsequent therapies cannot be adequately assessed. Overall, however, there is basically no doubt in terms of subsequent therapies that both studies are similar enough to subject them to an adjusted indirect comparison.

I 3.1.3 Similarity of the studies for the indirect comparison

Below, central aspects concerning the studies' similarity for conducting an adjusted indirect comparison are discussed beyond the study characteristics described in Section I 3.1.2.

Study design

The 3 included studies are multicentre, open-label RCTs with comparable study designs and comparable inclusion and exclusion criteria (see Table 6 and Table 7).

The time periods during which the studies were conducted differ slightly but do not fundamentally call into question the studies' similarity required for an adjusted indirect comparison. The KEYNOTE-024 and KEYNOTE-042 studies were initiated in September and November 2014, respectively, and the data cutoffs taken into account in this assessment are from 2016 (KEYNOTE-024 study) and 2018 (KEYNOTE-042 study). The POSEIDON study started in 2017, with the employed data cutoff being from 2021. Regarding the comparability of the 3 studies' observation durations, see explanation below Table 10 in Section I 3.1.2.

Patient characteristics

Table 9 presents information on patient characteristics of the 3 studies POSEIDON, KEYNOTE-024, and KEYNOTE-042. The patient populations of the 3 studies' relevant subpopulations are sufficiently comparable with the exception of the characteristic of family origin. The proportion of patients of White family origin is markedly lower in the POSEIDON study than in the KEYNOTE-024 study (approximately 50% versus approximately 80%). No family origin data is available for the relevant subpopulation of the KEYNOTE-042 study. Due to these differing proportions, the relevance of family origin was assessed for the similarity

test to determine whether it was a relevant effect modifier in the relevant subpopulations of the POSEIDON and KEYNOTE-024 studies.

For the relevant subpopulation of the POSEIDON study, no subgroup analyses for the characteristic of family origin are available, but they are available for the characteristic of region, with the categories of Europe / North America versus rest of the world. The absence of subgroup analyses for the characteristic of family origin is not adequate, especially because the company presents these for research question 2 and this characteristic was prespecified in the POSEIDON study. However, given the available data, the characteristic of region can serve as an approximation for the characteristic of family origin to investigate any effect modification. No relevant effect modification for overall survival was found between patients from Europe / North America and patients from the rest of the world for the 11 March 2022 data cutoff analysed by the company – and no subgroup analyses were available for the 12 March 2021 data cutoff used in the benefit assessment. For the study KEYNOTE-024, subgroup analyses are available for the characteristic of skin colour, with the categories White versus Non-White. In this study, too, no relevant effect modification by this characteristic is shown for the outcome overall survival for the population relevant in the present assessment. No data on subgroup analyses are available for the relevant subpopulation of the KEYNOTE-042 study.

A general analysis of the available data on the characteristics of region or skin colour, which are deemed approximations for the characteristic of family origin , in the relevant subpopulations of the POSEIDON and KEYNOTE-024 studies reveals that the similarity assumption for the studies' populations is not rejected for research question 1 because no relevant effect modifications are shown for these characteristics. For research question 2, in contrast, the studies show clues for a relevant or qualitative effect modification for the characteristic of family origin (see Sections I 4.1.2 and I 4.1.3).

Assays used to determine PD-L1 status

In all 3 analysed studies, immunohistochemistry assays were used to determine PD-L1 status. The POSEIDON study used the SP263 assay, and the KEYNOTE-024 and KEYNOTE-042 studies, the 22C3 assay. Moderate to high concordance between the 2 assays has been found [43].

Molecular testing for the presence of mutations in tumour tissue

EGFR mutation and ALK translocation

All 3 studies enrolled patients with no EGFR mutation and no ALK translocation in the tumour tissue. Prior testing of the tumour tissue was to be carried out in patients with non-squamous carcinoma. In patients with squamous cell carcinoma, the study protocols of the 3 studies did not require testing for these mutations/translocations. The POSEIDON study likewise did not require testing in case of the known presence of a KRAS mutation in the tumour tissue.

According to the current S3 guideline, molecular pathological testing is to be carried out for all therapeutically relevant molecular changes including EGFR mutations and ALK translocations in the tumour tissue of patients with stage IV NSCLC [44]. Unlike previous versions of this guideline [45], this updated guideline does not impose a restriction to non-squamous cell carcinomas. In light of the rare occurrence of EGFR mutations and ALK translocations in squamous cell NSCLC and the proportionally smaller share of patients with squamous cell NSCLC in the individual studies, the lack of testing in squamous cell carcinoma presumably does not call into question the similarity or relevance of the study populations. Furthermore, the POSEIDON study's lack of testing of EGFR and ALK status in patients with KRAS mutation does not call into question the relevance of the POSEIDON study population because KRAS mutation and EGFR or ALK mutation are typically mutually exclusive [46,47].

Other mutations

According to the G-BA's guidance on the ACT, molecularly stratified therapy (against rapidly accelerated fibrosarcoma – isoform B [BRAF], KRAS G12C, mesenchymal-epithelial transition factor [MET]ex14, rearranged during transfection [RET] or c-ros oncogene 1 [ROS1]) is assumed not to be an option for patients at the time of therapy with tremelimumab in combination with durvalumab and platinum-based chemotherapy. The 3 studies did not implement general testing for the mutations mentioned in the G-BA's guidance. While the POSEIDON study conducted KRAS testing in a subpopulation, no such information can be found in Module 4 A for the 2 other studies. The relevance of the study populations or subpopulations is not called into question despite the lack of molecular testing of the mutations mentioned because the BRAF, METex14, RET, or ROS1 mutations are rare [48], with the most common being in a range < 20% (KRAS G12C) [49]. Furthermore, the guideline does not recommend targeted therapy for patients with KRAS G12C mutation at the time of therapy with tremelimumab (first line). Sotorasib is not recommended until the second line of treatment [44].

Similarity of the common comparator

For the present indirect comparison, the company chose "platinum-based chemotherapy" as the common comparator. In the 3 included studies, POSEIDON, KEYNOTE-024, and KEYNOTE-042, this involves different platinum-based combination chemotherapies. All 3 studies had them selected individually for each patient by the investigator prior to randomisation. The chemotherapies selected are not identical between the 3 studies.

Table 12 shows which platinum-based chemotherapies the patients in the comparator arms of the 3 trials received. The following information is based on the studies' relevant subpopulations.

Table 12: Distribution of platinum-based combination chemotherapy regimens and maintenance therapies in the relevant comparator arms (common comparators) of the POSEIDON, KEYNOTE-024, and KEYNOTE-042 trials: research question 1 (PD-L1 expression ≥ 50%) (multipage table)

Study with tremelimumab + durvalumab + platinum-based chemotherapy	**Studies with pembrolizumab**	
POSEIDON (N = 97)[a]	**KEYNOTE-024 (N = 151)**	**KEYNOTE-042 (N = 300)**
Non-squamous histology[b, c]		
n = 64 (66%)	**n = 124 (82%)**	**n = 186 (62%)**
Pemetrexed + ▪ Cisplatin: 8 (12.5%[d]) ▪ Carboplatin: 51 (79.7%[d])	Pemetrexed + ▪ Cisplatin: 36 (29.0%)[d] ▪ Carboplatin: 66 (53.2%[d])	Pemetrexed + carboplatin: ▪ ND for the relevant subpopulation
Maintenance therapy with pemetrexed: ▪ 36 (56.3%)[d]	Maintenance therapy with pemetrexed: ▪ 46 (37.1%)[d] Gemcitabine + ▪ Cisplatin: 4 (3.2%) ▪ Carboplatin 5 (4.0%[d])	Maintenance therapy with pemetrexed: ▪ ND for the relevant subpopulation
Nab-paclitaxel + carboplatin: ▪ see under squamous and non-squamous cell	Paclitaxel + carboplatin: ▪ 12 (9.7%[d])	Paclitaxel + carboplatin: ▪ ND for the relevant subpopulation

Table 12: Distribution of platinum-based combination chemotherapy regimens and maintenance therapies in the relevant comparator arms (common comparators) of the POSEIDON, KEYNOTE-024, and KEYNOTE-042 trials: research question 1 (PD-L1 expression ≥ 50%) (multipage table)

Study with tremelimumab + durvalumab + platinum-based chemotherapy	**Studies with pembrolizumab**	
POSEIDON (N = 97)[a]	**KEYNOTE-024 (N = 151)**	**KEYNOTE-042 (N = 300)**
Squamous cell histology[b, e]		
n = 32 (33%)	**n = 27 (18%)**	**n = 114 (38%)**
Gemcitabine + ▪ Cisplatin: 6 (18.8%[d]) ▪ Carboplatin: 23 (71.9%[d]) Nab-paclitaxel + carboplatin: ▪ See under squamous and non-squamous cell	Gemcitabine + ▪ Cisplatin: 7 (25.9%) ▪ Carboplatin: 15 (55.6%) Paclitaxel + carboplatin: ▪ 5 (18.5%)	Paclitaxel + carboplatin: ▪ 114 (100%[d])
Squamous and non-squamous histology[b,f]		
▪ Nab-paclitaxel + carboplatin: 5 (5.2%[d])		
Total[f]		
▪ Cisplatin: 14 (14.4%)[d] ▪ Carboplatin: 79 (81.4%)[d]	▪ Cisplatin: 47 (31.1%) ▪ Carboplatin: 103 (68.2%)	▪ Carboplatin: 300 (100%)

a. Four patients did not receive any therapy.
b. For 1 patient, information on histology is missing.
c. Percentages based on patients with non-squamous histology.
b. Institute's calculation.
e. Percentages based on patients with squamous histology.
f. Percentages based on patients of the entire comparator arm.

n: Patients with respective histology; N: number of randomised patients of the relevant (sub-)populations; ND: no data

Platinum component of the common comparator

All patients included in the studies were to receive platinum-containing therapy with cisplatin or carboplatin. Table 12 shows that carboplatin was used in about 80% of patients in the POSEIDON study's comparator arm and in about 70% of patients in the KEYNOTE-024 study. In the KEYNOTE-042 study, only carboplatin was administered.

Chemotherapy component of the common comparator

With the exception of 5 patients who received nab-paclitaxel regardless of histology, the POSEIDON study restricted patients with non-squamous histology to only pemetrexed alongside the platinum component. In the KEYNOTE-024 study, gemcitabine or paclitaxel was allowed to be administered even in case of non-squamous histology, but it was shown that

the majority of patients received pemetrexed (82%). This information is missing for the relevant subpopulation of the KEYNOTE-042 study.

With the exception of the 5 patients mentioned above who received nab-paclitaxel regardless of histology, the POSEIDON study restricted patients with squamous cell histology to only gemcitabine alongside the platinum component. In the KEYNOTE-024 study, paclitaxel was also allowed to be administered, but most patients (81%) were given gemcitabine. In the KEYNOTE-042 study, patients with squamous histology qualified only to receive paclitaxel.

In the KEYNOTE-024 study, a total of 17 out of 151 patients (11%) with both squamous and non-squamous histology received paclitaxel.

Maintenance therapy in the common comparator

All 3 studies were intended for pemetrexed maintenance therapy to be administered only to patients with non-squamous histology. In the POSEIDON study, 56% of these patients received pemetrexed maintenance therapy, compared to only 37% in the KEYNOTE-024 study. In the KEYNOTE-042 study, the administration of maintenance therapy was at the discretion of the investigator and was recommended. No information was available for the relevant subpopulation.

Summary

The differences described between the platinum-based chemotherapies administered in the 3 studies – (i) paclitaxel almost exclusively on the comparator side of the indirect comparison, (ii) maintenance therapy more frequently with pemetrexed on the intervention side compared to the KEYNOTE-024 study, (iii) exclusive use of carboplatin as the platinum component in the KEYNOTE-042 study, and (iv) lack of information on the platinum-based chemotherapies used in the KEYNOTE-042 study for the relevant subpopulation – do not fundamentally call into question the similarity of the common comparators for the indirect comparison. These differences were taken into account in the interpretation of the results of the side effects outcomes.

Summary of the similarity of the studies used in the indirect comparison

Similarity is a key prerequisite for studies to be included in the adjusted indirect comparison. The 3 studies POSEIDON, KEYNOTE-024, and KEYNOTE-042 share a very similar study design. Their patient populations are also sufficiently similar. Some differences between the POSEIDON, KEYNOTE-024, and KEYNOTE-042 studies exist, particularly regarding the common comparator of platinum-based chemotherapy. Certain aspects cannot be adequately assessed due to certain missing data (duration of treatment and observation, subsequent therapies; see Table 10 and Table 11). Overall, the similarity assumption for the indirect comparison is not rejected. However, the described between-study differences in platinum-based

chemotherapies are taken into account when interpreting the results on the side effects outcomes.

The homogeneity assumption is another key prerequisite for taking into account studies in the adjusted indirect comparison. For the tremelimumab + durvalumab side, an investigation of homogeneity was not possible because only 1 study is available. Regarding the 2 included studies on pembrolizumab, the metaanalytical summary checked heterogeneity for the patient-relevant outcomes for which an indirect comparison is possible. No heterogeneity was found for the results of this outcome (see I Appendix C of the full dossier assessment).

I 3.1.4 Risk of bias across outcomes (study level)

Table 13 shows the risk of bias across outcomes (risk of bias at study level).

Table 13: Risk of bias across outcomes (study level) – RCT, indirect comparison: tremelimumab + durvalumab + platinum-based chemotherapy versus pembrolizumab: research question 1 (PD-L1 expression ≥ 50%)

Comparison Study	Adequate random sequence generation	Allocation concealment	Blinding		Nonselective reporting	Absence of additional aspects	Risk of bias at study level
			Patients	Treatment providers			
Tremelimumab + durvalumab + platinum-based chemotherapy vs. platinum-based chemotherapy							
POSEIDON	Yes	Yes	No	No	Yes	Yes	Low
Pembrolizumab + platinum-based chemotherapy							
KEYNOTE-024	Yes	Yes	No	No	Yes	Yes	Low
KEYNOTE-042	Yes	Yes	No	No	Yes	Yes	Low

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

The risk of bias across outcomes was rated as low for the studies included.

Limitations resulting from the open-label study design are described in Section I 3.2.2 under outcome-specific risk of bias.

Transferability of the study results to the German health care context

The company's Module 4 A presents the transferability of the study results separately for the individual studies.

In the POSEIDON study, the population of patients with NSCLC is reportedly generally comparable to the epidemiological characteristics of patients with this indication in Germany. The company bases this conclusion on demographic characteristics such as sex and age, smoking status, and tumour histology. Furthermore, the company argues that, at the time the POSEIDON study was designed and started, relevant guidelines recommended platinum-based chemotherapy in combination with a third-generation cytostatic drug as first-line therapy for patients with metastatic NSCLC without treatable mutations or translocations. Thus, in the company's view, the comparator therapy administered in the POSEIDON study corresponded to those administered in the German health care context at the time. Overall, the relevant subpopulations of patients with PD-L1 expression ≥ 50% (research question 1) and < 50% (research question 2) are comparable to the patient population in Germany, so that the respective study results are transferable to the German health care context.

For the KEYNOTE-024 and KEYNOTE-042 studies, the company first describes the general patient characteristics of the relevant populations in both studies. In these studies as well, the population of patients with NSCLC is reportedly largely comparable to the epidemiological characteristics of patients with this therapeutic indication in Germany. The company draws this conclusion based on demographic characteristics such as sex and age, smoking status, and tumour histology. It reports that when the study design was conceived and the KEYNOTE-024 and KEYNOTE-042 studies started, the administered comparator therapies corresponded to those used in German health care context at the time. Overall, the relevant patient populations in these 2 studies are reportedly likewise comparable to the patient population in Germany, so that the results of the studies are transferable to the German health care context.

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

I 3.2 Results on added benefit

I 3.2.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment:

- Mortality
  - overall survival
- Morbidity
  - symptoms surveyed using the EORTC QLQ-C30 and EORTC QLQ-LC13
  - health status surveyed with the EQ-5D VAS and the PGIC
- Health-related quality of life
  - surveyed with the EORTC QLQ-C30
- Side effects
  - SAEs
  - severe AEs (CTCAE grade ≥ 3)
  - discontinuation due to AEs
  - PRO-CTCAE
  - immune-related AEs
  - other specific AEs, if any

The patient-relevant outcomes selected for the indirect comparison differ from those selected by the company.

Table 14 shows the outcomes for which data are available in the included studies and states whether an indirect comparison is possible based on the available data.

Table 14: Matrix of the outcomes – RCT, indirect comparison: tremelimumab + durvalumab + platinum-based chemotherapy versus pembrolizumab: research question 1 (PD-L1 expression ≥ 50%)

Comparison / Study	Outcomes										
	Overall survival	Symptoms (EORTC QLQ-C30, QLQ-LC13)	Health status (PGIC)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30)	SAEs	Severe AEs[a]	Discontinuation due to AEs	PRO-CTCAE	Immune-related AEs	Further specific AEs
Tremelimumab + durvalumab + platinum-based chemotherapy vs. platinum-based chemotherapy											
POSEIDON	Yes	No[b]	No[b]	No[b]	No[b]	Yes	No[b]	Yes	Yes	Yes	No[c]
Pembrolizumab vs. platinum-based chemotherapy											
KEYNOTE-024	Yes	Yes	No[d]	Yes	Yes	Yes	Yes	Yes	No[d]	Yes	No[c]
KEYNOTE-042	Yes	No[d]	No[d]	No[d]	No[d]	No[e]	No[e]	No[e]	No[d]	No[e]	No[c]
Indirect comparison possible	Yes	No[f]	No[f]	No[f]	No[f]	No[g]	No[g]	No[g]	No[f]	No[h]	No[c]

a. Severe AEs are operationalized as CTCAE grade ≥ 3.
b. No suitable data (see body of text below).
c. The prerequisite concerning the certainty of results for conducting an adjusted indirect comparison is not met (see Section I 3.2.2). Therefore, no further specific AEs are selected.
d. Outcome not recorded.
e. No data available for the relevant subpopulation.
f. Not feasible because no (suitable) data are available for at least 1 side of the indirect comparison.
g. The prerequisite concerning the certainty of results for conducting an adjusted indirect comparison is not met (see Section I 3.2.2).
h. For the outcome, no indirect comparison is feasible in the present assessment due to insufficient information for a similarity check of the operationalizations (see body of text below).

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: European Quality of Life – 5 Dimensions; PD-L1: programmed death ligand 1; PGIC: Patient Global Impression of Change; PRO-CTCAE: Patient-Reported Outcome – Common Terminology Criteria for Adverse Events; QLQ-C30: Quality of Life Questionnaire – Cancer 30; QLQ-LC13: Quality of Life Questionnaire – Lung Cancer 13; RCT: randomised controlled trial; SAE: serious adverse event; VAS: visual analogue scale

Morbidity and health-related quality of life

For the outcomes of the categories of morbidity and health-related quality of life, surveyed with the EORTC QLQ-C30, EORTC QLQ-LC13, EQ-5D VAS, and PGIC, no suitable data were available in the POSEIDON study. This is due to the fact that the study arms differ in terms of their representation of treatment-related burden over the course of the cycle from the PRO survey. This is explained below.

According to the study documents, the PRO surveys in the POSEIDON study are conducted every 3 weeks (at Weeks 0, 3, 6, 9) for the first 4 cycles of treatment and every 4 weeks (at Weeks 12, 16, 20, etc.) from Cycle 5 onwards.

In the intervention arm, the PRO data are thus always collected at the beginning of a cycle because the study medication was also administered every 3 weeks for the first 4 cycles and every 4 weeks thereafter (including maintenance therapy with pemetrexed).

In the comparator arm, the PRO survey is also conducted synchronously with the administration of the medication in the first 4 cycles. After 4 cycles, however, comparator arm patients were allowed to continue chemotherapy for a further 2 cycles at 3-week intervals at the investigator's discretion. In the POSEIDON subpopulation relevant to the present research question, the proportion of comparator arm participants who received ≥ 5 cycles of chemotherapy was 58%. According to the study report, the PRO survey conducted during these additional 1 to 2 cycles was not synchronized with the 3-week medication dosing cycle and instead used 4-week intervals. Optionally, pemetrexed maintenance therapy (from Cycle 5) was allowed to be administered at 3-week instead of 4-week intervals. It is unclear how many comparator arm participants received pemetrexed maintenance therapy at 3-week intervals. As per study protocol, the PRO survey was carried out using 4-week intervals in these patients as well. Overall, for the patient population which received ≥ 5 cycles or pemetrexed maintenance therapy at 3-week intervals, it is thus safe to assume that the PRO survey from the 5th cycle onwards did not take place at the beginning of a cycle, unlike in the intervention arm. For the comparator arm, it is therefore unclear how many patients from Cycle 5 onwards took the PRO surveys not at the start of the cycle (as in the intervention arm) but instead during the treatment cycle. As a result, the PRO data do not fairly represent treatment-related burden over the course of the cycle between the study arms.

In the present situation, the PRO data from the POSEIDON study are therefore deemed unusable. Thus, no suitable data are available for the outcomes collected with the EORTC QLQ-C30, EORTC QLQ-LC13, EQ-5D, and PGIC on 1 side of the indirect comparison. Therefore, conducting an indirect comparison is not possible for these outcomes. Regarding the outcome of health status, surveyed by the PGIC, it should be noted that it was surveyed only in the POSEIDON study.

Due to the studies using different data collection times, the company disregards the PRO data for the indirect comparison. Notwithstanding the company's failure to elaborate on the lack of comparability of the data collection times, potential differences in data collection times between studies in the indirect comparison do not per se prevent the use of the data for the indirect comparison.

Side effects

For the 12 March 2021 data cutoff, the POSEIDON study provides no data regarding the relevant subpopulation in the side effects category. For the outcomes SAEs and discontinuation due to AEs, but not for severe AEs, the data from the data cutoffs submitted by the company in Module 4 A might be used as a substitute (for further explanation, see Table 16).

No results on side effects are available for the relevant subpopulation of the KEYNOTE-042 study. Results are available only separately for patients with squamous cell carcinoma (limited to stage IV and assigned to carboplatin/paclitaxel therapy prior to randomisation) and non-squamous cell carcinoma (limited to stage IV and assigned to carboplatin/pemetrexed therapy prior to randomisation). These results cover only just under 50% of the relevant subpopulation and are therefore disregarded in the present assessment.

Immune-related AEs

The company does not present any indirect comparisons for the outcome of immune-mediated AEs because it deems a comparison to not be meaningful due to the study-specific definition of the studies included in the indirect comparison. A review comparing how immune-mediated AEs are operationalized across different studies is missing. Given that the information for evaluating the similarity of outcome operationalization across studies is insufficient, no indirect comparison is conducted in the current assessment.

I 3.2.2 Risk of bias

Table 15 describes the risk of bias for the results of the relevant outcomes.

Table 15: Risk of bias across outcomes and outcome-specific risk of bias – RCT, indirect comparison: tremelimumab + durvalumab + platinum-based chemotherapy versus pembrolizumab: research question 1 (PD-L1 expression ≥ 50%)

Comparison Study	Study level	Outcomes										
		Overall survival	Symptoms (EORTC QLQ-C30, QLQ-LC13)	Health status (PGIC)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30)	SAEs	Severe AEs[a]	Discontinuation due to AEs	PRO-CTCAE	Immune-related AEs	Further specific AEs
Tremelimumab + durvalumab + platinum-based chemotherapy vs. platinum-based chemotherapy												
POSEIDON	L	L	-[b]	-[b]	-[b]	-[b]	H[c]	-[b]	H[e]	-[d]	-[f]	-[g]
Pembrolizumab vs. platinum-based chemotherapy												
KEYNOTE-024	L	L	-[d]	-[h]	-[d]	-[d]	H[c]	H[c]	H[e]	-[h]	-[f]	-[g]
KEYNOTE-042	L	L	-[h]	-[h]	-[h]	-[h]	-[i]	-[i]	-[i]	-[h]	-[i]	-[g]

a. Severe AEs are operationalized as CTCAE grade ≥ 3.
b. No suitable data (see Section I 3.2.1).
c. Different observation durations between treatment arms or high proportion of incomplete observations, for potentially informative reasons.
d. Not assessed because no (suitable) data are available for at least 1 side of the indirect comparison (see Section I 3.2.1).
e. Lack of blinding in subjective recording of outcomes.
f. Not assessed because no indirect comparison is feasible for the outcome due to insufficient information for a similarity check of the operationalizations (see Section I 3.2.1).
g. Therefore, no further specific AEs are selected.
h. Outcome not recorded.
i. No data for relevant subpopulation.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: European Quality of Life – 5 Dimensions; H: high; L: low; PD-L1: programmed death ligand 1; PGIC: Patient Global Impression of Change; PRO-CTCAE: Patient-Reported Outcome – Common Terminology Criteria for Adverse Events; QLQ-C30: Quality of Life Questionnaire – Cancer 30; QLQ-LC13: Quality of Life Questionnaire – Lung Cancer 13; RCT: randomised controlled trial; SAE: serious adverse event; VAS: visual analogue scale

The risk of bias across outcomes is assessed as low for the POSEIDON, KEYNOTE-024, and KEYNOTE-042 studies as well as for the results for the outcome of overall survival.

The risk of bias for the results of the PRO outcomes from the categories of morbidity and health-related quality of life was not assessed because no data (outcome of health status surveyed using PGIC) or no suitable data (outcomes collected using the EORTC QLQ-C30, EORTC QLQ-LC13, and EQ-5D VAS) were available for at least 1 side of the indirect comparison (see Section I 3.2.1).

For the results on the outcomes of SAEs (POSEIDON and KEYNOTE-024) and severe AEs (KEYNOTE-024), the risk of bias at study level is rated as high. This is due to the different observation durations between treatment arms or high proportion of incomplete observations for potentially informative reasons. For the results on the outcome of discontinuation due to AEs, the high risk of bias in these 2 studies results from the lack of blinding in the presence of subjective recording of outcomes. In the POSEIDON study, no data are available for the outcome of severe AEs for the data cutoff used (see Section I 3.2.1). Following this assessment, a high risk of bias can also be assumed for the results of the specific AEs. Therefore, in the present situation, no specific AE were selected.

For the KEYNOTE-042 study, the risk of bias for the outcomes on SAEs, severe AEs, and discontinuation due to AEs was not assessed because no data were available for the relevant subpopulation.

For the results of the outcomes of PRO-CTCAE and immune-mediated AEs, the risk of bias was not assessed because data are available only on 1 side of the indirect comparison or no indirect comparison is feasible due to insufficient information being available for a similarity test of the operationalizations.

If only 1 study is available on 1 side of an indirect comparison and results of individual outcomes of this study have a high risk of bias, the certainty of results required to conduct an adjusted indirect comparison is insufficient. Thus, sufficiently reliable data for conducting an adjusted indirect comparison are not available for any of the outcomes of the side effects category for which usable data are available in the individual studies. An indirect comparison is therefore carried out only for the outcome of overall survival.

I 3.2.3 Results

Table 16 summarises the results comparing tremelimumab + durvalumab + platinum-based chemotherapy versus pembrolizumab in adult patients with metastatic NSCLC with PD-L1 expression ≥ 50% with no sensitising EGFR mutations or ALK-positive mutations in first-line therapy (research question 1). Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier.

Available Kaplan-Meier curves for the overall survival outcome and side effects outcomes are provided in I Appendix B of the full dossier assessment. In the present research question, no Kaplan-Meier curve is available for the outcome of overall survival of the POSEIDON study.

For the POSEIDON study, no results on common AEs are available regarding the relevant subpopulation for the final data cutoff of 12 March 2021. Common AEs for the KEYNOTE-024 study can be found in benefit assessment A17-06 [15]. No results on common AEs are available for the relevant subpopulation of the KEYNOTE-042 study.

Table 16: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, indirect comparison: tremelimumab + durvalumab + platinum-based chemotherapy versus pembrolizumab: research question 1 (PD-L1 expression ≥ 50%) (multipage table)

Outcome category **Outcome** **Comparison** **Study**	**Tremelimumab + durvalumab + platinum-based chemotherapy or pembrolizumab**		**Platinum-based chemotherapy**		**Between-group difference**
	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**
Mortality					
Overall survival					
Tremelimumab + durvalumab + platinum-based chemotherapy vs. platinum-based chemotherapy					
POSEIDON (12/03/2021 data cutoff)	101	ND69 (68.3)	97	ND80 (82.5)	0.65 [0.47; 0.89]; ND[a]
Pembrolizumab vs. platinum-based chemotherapy					
KEYNOTE-024 (9/05/2016 data cutoff)	154	NR 44 (28.6)	151	NR [9.4; NC] 64 (42.4)	0.60 [0.41; 0.89]; 0.010[b]
KEYNOTE-042 (26/02/2018 data cutoff)	299	20.0 [15.4; 24.9]; ND	300	12.2 [10.4; 14.2]; ND	0.69 [0.56; 0.85]< 0.001[b]
Total					0.67 [0.56; 0.80] < 0.001[c]
Indirect comparison using common comparators[d]: **tremelimumab + durvalumab + platinum-based chemotherapy vs. pembrolizumab**					0.97 [0.67; 1.41]; 0.873[e]
Morbidity					
Symptoms (EORTC QLQ-C30, QLQ-LC13)	No suitable data for the indirect comparison[f]				
Health status (PGIC)	No suitable data for the indirect comparison[f]				
Health status (EQ-5D VAS)	No suitable data for the indirect comparison[f]				
Health-related quality of life (EORTC QLQ-C30)	No suitable data for the indirect comparison[f]				

Table 16: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, indirect comparison: tremelimumab + durvalumab + platinum-based chemotherapy versus pembrolizumab: research question 1 (PD-L1 expression ≥ 50%) (multipage table)

Outcome category **Outcome** **Comparison** **Study**	**Tremelimumab + durvalumab + platinum-based chemotherapy or pembrolizumab**		**Platinum-based chemotherapy**		**Between-group difference**
	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**
Side effects					
AEs (supplementary information)					
Tremelimumab + durvalumab + platinum-based chemotherapy vs. platinum-based chemotherapy					
POSEIDON[g]	99	0.1 [0.1; 0.3] 98 (99.0)	93	0.2 [0.1; 0.3] 88 (94.6)	–
Pembrolizumab vs. platinum-based chemotherapy					
KEYNOTE-024 (9/05/2016 data cutoff)	154	1.1 [0.7; 1.7] 148 (96.1)	150	0.6 [0.4; 0.9] 145 (96.7)	–
KEYNOTE-042 (26/02/2018 data cutoff)[h]	299	ND	300	ND	ND
SAEs					
Tremelimumab + durvalumab + platinum-based chemotherapy vs. platinum-based chemotherapy					
POSEIDON[i]	99	15.4 [7.2; NC] 47 (47.5)	93	18.3 [6.8; NC] 37 (39.8)	0.92 [0.59; 1.43]; 0.697[a]
Pembrolizumab vs. platinum-based chemotherapy					
KEYNOTE-024 (9/05/2016 data cutoff)	154	54.1 [27.1; NC] 68 (44.2)	150	65.4 [23.1; NC] 66 (44.0)	1.00 [0.71; 1.41]; 0.994[b]
KEYNOTE-042 (26/02/2018 data cutoff)[h]	299	ND	300	ND	ND
Indirect comparison using common comparators[d]:					
tremelimumab + durvalumab + platinum-based chemotherapy vs. pembrolizumab					–[j]

Table 16: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, indirect comparison: tremelimumab + durvalumab + platinum-based chemotherapy versus pembrolizumab: research question 1 (PD-L1 expression ≥ 50%) (multipage table)

Outcome category **Outcome** **Comparison** **Study**	**Tremelimumab + durvalumab + platinum-based chemotherapy or pembrolizumab**		**Platinum-based chemotherapy**		**Between-group difference**
	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**
Severe AEs (CTCAE grade ≥ 3)					
Tremelimumab + durvalumab + platinum-based chemotherapy vs. platinum-based chemotherapy					
POSEIDON[k]	No suitable data for the indirect comparison				
Pembrolizumab vs. platinum-based chemotherapy					
KEYNOTE-024 (9/05/2016 data cutoff)	154	27.1 [18.1; 44.4] 82 (53.2)	150	5.9 [4.4; 9.0] 109 (72.7)	0.49 [0.36; 0.66]; < 0.001[b]
KEYNOTE-042 (26/02/2018 data cutoff)[h]	299	ND	300	ND	ND
Indirect comparison using common comparators[d]:					–[l]
tremelimumab + durvalumab + platinum-based chemotherapy vs. pembrolizumab					
Discontinuation due to AEs					
Tremelimumab + durvalumab + platinum-based chemotherapy vs. platinum-based chemotherapy					
POSEIDON[g, m]	99	NR [16.4; NC] 31 (31.3)	93	NR 16 (17.2)	1.31 [0.72; 2.50]; 0.385[a]
Pembrolizumab vs. platinum-based chemotherapy					
KEYNOTE-024 (9/05/2016 data cutoff)	154	NR 14 (9.1)	150	NR 21 (14.0)	0.60 [0.31; 1.19]; 0.144[b]
KEYNOTE-042 (26/02/2018 data cutoff)[h]	299	ND	300	ND	ND
Indirect comparison using common comparators[d]:					
tremelimumab + durvalumab + platinum-based chemotherapy vs. pembrolizumab					–[j]
PRO-CTCAE	No suitable data for the indirect comparison[f]				
Immune-related AEs	No suitable data for the indirect comparison[f]				

Table 16: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, indirect comparison: tremelimumab + durvalumab + platinum-based chemotherapy versus pembrolizumab: research question 1 (PD-L1 expression ≥ 50%) (multipage table)

Outcome category **Outcome** **Comparison** **Study**	**Tremelimumab + durvalumab + platinum-based chemotherapy or pembrolizumab**		**Platinum-based chemotherapy**		**Between-group difference**
	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**

a. HR, 95% CI: unstratified Cox proportional hazards model; p-value: unstratified log-rank test.
b. HR, 95% CI: Cox proportional hazards model, stratified by geographic region, ECOG-PS and histology; p-value from Wald test (KEYNOTE-024) or log-rank test (KEYNOTE-042).
c. Meta-analysis calculated using a fixed effects model.
d. Indirect comparison according to Bucher [4].
e. Institute's calculation (effect, CI, p-value).
f. For an explanation, see Section I 3.2.1.
g. For the predefined final data cutoff of 12/03/2021, no data are available from the relevant subpopulation. The data from the dossier are used because the information on the total population does not differ in a relevant way between the final predefined data cutoff and the data cutoff submitted by the company in the dossier (25/10/2021).
h. These analyses are available only separately for patients with squamous cell carcinoma (limited to stage IV and assigned to carboplatin/paclitaxel therapy prior to randomisation) and non-squamous cell carcinoma (limited to stage IV and assigned to carboplatin/pemetrexed therapy prior to randomisation) and comprise only slightly less than 50% of the relevant subpopulation.
i. For the predefined final data cutoff of 12/03/2021, no data are available from the relevant subpopulation. Since the information on the total population is identical between the final predefined data cutoff and the data cutoff submitted by the company in the dossier (22/03/2022), the data from the dossier are used.
j. The certainty of results required for conducting an adjusted indirect comparison is not met.
k. For the predefined final data cutoff of 12/03/2021, no data are available from the relevant subpopulation. The number of patients with events at the 25/10/2021 data cutoff reported in the dossier differs relevantly from the number of patients in the predefined final data cutoff.
l. Not feasible because no (suitable) data are available for at least 1 side of the indirect comparison.
m. Module 4 A contains no information on the operationalization, but according to the study documents, it can be assumed to involve the discontinuation of at least 1 active substance component.

AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; ECOG-PS: European Cooperative Oncology Group Performance Status; EORTC: European Organization for Research and Treatment of Cancer; EQ-5D: European Quality of Life 5 Dimensions; HR: hazard ratio; N: number of analysed patients; n: number of patients with (at least 1) event; NC: not calculable; ND: no data; NR: not reached; PD-L1: programmed death ligand 1; PGIC: Patient Global Impression of Change; PRO-CTCAE: Patient-Reported Outcome – Common Terminology Criteria for Adverse Events; QLQ-C30: Quality of Life Questionnaire - Cancer 30; QLQ-LC13: Quality of Life Questionnaire - Lung Cancer 13; RCT: randomised controlled trial; SAE: serious adverse event; VAS: visual analogue scale

On the basis of the available information, no more than hints, e.g. of an added benefit, can be determined for all outcomes.

Mortality

Overall survival

The adjusted indirect comparison showed no statistically significant difference between the treatment groups for the outcome of overall survival. This results in no hint of an added benefit of tremelimumab + durvalumab + platinum-based chemotherapy in comparison with pembrolizumab; an added benefit is therefore not proven.

Morbidity

Symptoms, health status

For the symptoms outcomes surveyed with the EORTC QLQ-C30 and EORTC QLQ-LC13 as well as for the outcome of health status surveyed with the EQ-5D VAS and the PGIC, no suitable data were available on 1 side of the indirect comparison (POSEIDON study) (see Section I 3.2.1). Therefore, it is impossible to conduct an indirect comparison for the outcomes surveyed with these instruments. For the outcomes of the morbidity category, this results in no hint of an added benefit of tremelimumab + durvalumab + platinum-based chemotherapy in comparison with pembrolizumab; an added benefit is therefore not proven for these outcomes.

Health-related quality of life

For the outcomes of the category health-related quality of life surveyed with the EORTC QLQ-C30, no suitable data are available on 1 side of the indirect comparison (POSEIDON study) (see Section I 3.2.1). Therefore, conducting an indirect comparison is not possible for these outcomes. For the outcomes of the health-related quality of life category, this results in no hint of an added benefit of tremelimumab + durvalumab + platinum-based chemotherapy in comparison with pembrolizumab; an added benefit is therefore not proven for these outcomes.

Side effects

No side effects data were available for the relevant subpopulation of the KEYNOTE-042 study. These are available only separately for patients with squamous cell carcinoma (limited to stage IV and assigned to carboplatin/paclitaxel therapy prior to randomisation) and non-squamous cell carcinoma (limited to stage IV and assigned to carboplatin/pemetrexed therapy prior to randomisation) and comprise only slightly less than 50% of the relevant subpopulation. Furthermore, no data are available on the indirect comparison of the KEYNOTE-024 and POSEIDON studies for the side effects outcomes.

SAEs, discontinuation due to AEs

For the outcomes of SAEs and discontinuation due to AEs, data are available for only 1 study (POSEIDON or KEYNOTE-024) on both sides of the adjusted indirect comparison. Due to the high risk of bias at the outcome level, the prerequisites for drawing conclusions on added benefit with sufficient certainty of results from an adjusted indirect comparison were not met. In addition, the differences with regard to maintenance therapies in the common comparator arms (platinum-based chemotherapy) must be taken into account. For the outcomes of SAEs and discontinuation due to AEs, this results in no hint of an added benefit of tremelimumab + durvalumab + platinum-based chemotherapy in comparison with pembrolizumab; an added benefit is therefore not proven for these outcomes.

Severe AEs

For the outcome of severe AEs, no data from the data cutoff used are available on 1 side of the indirect comparison. Therefore, an indirect comparison is not possible for these outcomes. For the outcome of severe AEs, this results in no hint of an added benefit of tremelimumab + durvalumab + platinum-based chemotherapy in comparison with pembrolizumab; an added benefit is therefore not proven.

PRO-CTCAE

The outcome of PRO-CTCAE was surveyed only in the POSEIDON study. For this outcome, this results in no hint of an added benefit of tremelimumab + durvalumab + platinum-based chemotherapy in comparison with pembrolizumab; an added benefit is therefore not proven.

Immune-related AEs

For the outcome of immune-related AEs, Module 4 A lacks an analysis of the between-study comparability of operationalizations of immune-related AEs. In the present assessment, no indirect comparison was carried out for the outcome due to insufficient data for a similarity check of the operationalizations. For this outcome, this results in no hint of an added benefit of tremelimumab + durvalumab + platinum-based chemotherapy in comparison with pembrolizumab; an added benefit is therefore not proven.

I 3.2.4 Subgroups and other effect modifiers

The company's dossier does not present any subgroup analyses for the indirect comparison. The company reasons that the reliability of indirect comparisons is already limited even when based on the overall population and that subgroup analyses based on indirect comparisons can therefore no longer be meaningfully interpreted. The approach is not appropriate. Assessing added benefit requires subgroup analyses even in case of adjusted indirect comparisons. For the 12 March 2021 data cutoff used in the present dossier assessment, no subgroup analyses are available regarding the outcome of overall survival. It is unclear whether there is an effect modification for the outcome of overall survival in the present

indirect comparison. Due to the lack of subgroup analyses for the indirect comparison, no conclusions can be drawn on potential effect modifications for the comparison of tremelimumab + durvalumab + platinum-based chemotherapy versus pembrolizumab.

I 3.3 Probability and extent of added benefit

The probability and extent of added benefit at outcome level are derived below, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of IQWiG [1].

The approach for deriving an overall conclusion on the added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

I 3.3.1 Assessment of added benefit at outcome level

The extent of the respective added benefit at outcome level is estimated from the results presented in Section I 3.2 (see Table 17).

Table 17: Extent of added benefit at the outcome level: tremelimumab + durvalumab + platinum-based chemotherapy versus pembrolizumab: research question 1 (PD-L1 expression ≥ 50%) (multipage table)

Observation period **Outcome category** **Outcome**	**Tremelimumab + durvalumab + platinum-based chemotherapy vs. pembrolizumab** **Quantile of time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Outcomes observed over the entire study duration		
Mortality		
Overall survival	ND vs. NR or 20.0 HR: 0.97 [0.67; 1.41]; 0.873[c]	Lesser/added benefit not proven
Outcomes with shortened observation period		
Morbidity		
Symptoms (EORTC QLQ-C30, QLQ-LC13)	No suitable data[d]	Lesser/added benefit not proven
Health status (PGIC)	No suitable data[d]	Lesser/added benefit not proven
Health status (EQ-5D VAS)	No suitable data[d]	Lesser/added benefit not proven
Health-related quality of life		
Health-related quality of life (EORTC QLQ-C30)	No suitable data[d]	Lesser/added benefit not proven
Side effects		
SAEs	No suitable data[e]	Greater/lesser harm not proven
Severe AEs (CTCAE grade ≥ 3)	No suitable data[d]	Greater/lesser harm not proven
Discontinuation due to AEs	No suitable data[e]	Greater/lesser harm not proven
PRO-CTCAE	No suitable data[d]	Greater/lesser harm not proven
Immune-related AEs	No suitable data[f]	Greater/lesser harm not proven
Other specific AEs	No suitable data[g]	Greater/lesser harm not proven

Table 17: Extent of added benefit at the outcome level: tremelimumab + durvalumab + platinum-based chemotherapy versus pembrolizumab: research question 1 (PD-L1 expression ≥ 50%) (multipage table)

Observation period **Outcome category** **Outcome**	**Tremelimumab + durvalumab + platinum-based chemotherapy vs. pembrolizumab** **Quantile of time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
a. Probability provided if there is a statistically significant and relevant effect. b. Depending on the outcome category, the effect size is estimated using different limits based on the upper limit of the confidence interval (CI_u). c. Institute's calculation (effect, CI, p-value). d. Indirect comparison not feasible because no (suitable) data are available for at least 1 side of the indirect comparison. e. The requirement for the certainty of results to perform an adjusted indirect comparison is not met. f. Indirect comparison not feasible due to information being insufficient for a similarity check of the operationalizations. g. The standard for certainty of results required for conducting an adjusted indirect comparison is not met. Therefore, no further specific AEs are selected. AE: adverse event; CI: confidence interval; CI_U: upper limit of the confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; PD-L1: programmed death ligand 1; PGIC: Patient Global Impression of Change; PRO-CTCAE: patient-reported outcome -- Common Terminology Criteria for Adverse Events; QLQ-C30: Quality of Life Questionnaire - Cancer 30; QLQ-LC13: Quality of Life Questionnaire - Lung Cancer 13; RCT: randomised controlled trial; SAE: serious adverse event; VAS: visual analogue scale		

I 3.3.2 Overall conclusion on added benefit

Table 18 summarizes the results taken into account in the overall conclusion on the extent of added benefit.

Table 18: Favourable and unfavourable effects from the assessment of tremelimumab + durvalumab + platinum-based chemotherapy versus pembrolizumab: research question 1 (PD-L1 expression ≥ 50%)

Favourable effects	**Unfavourable effects**
—	—
For the outcomes of the categories of morbidity, health-related quality of life, and side effects, no data suitable for indirect comparison are available. PD-L1: programmed death-ligand-1	

Overall, based on the adjusted indirect comparison via the common comparator of platinum-based chemotherapy, there are neither favourable nor unfavourable effects of

tremelimumab + durvalumab + platinum-based chemotherapy compared to pembrolizumab. However, it should be noted that usable results with sufficient certainty of results for an indirect comparison are available only for the outcome of overall survival. There is no hint of an added benefit of tremelimumab + durvalumab + platinum-based chemotherapy for this outcome because the indirect comparison shows no statistically significant difference. For the outcomes of the morbidity and health-related quality of life categories, no data suitable for an indirect comparison are available. For the outcomes of the side effects category, the standard for certainty of results required for conducting an adjusted indirect comparison is not met. Moreover, the differences regarding maintenance therapy in the platinum-based chemotherapies of the common comparators must be taken into account when interpreting the results on the side effects outcomes. Additionally, subgroup analyses for the assessment of added benefit are missing.

In summary, for patients with metastatic NSCLC with PD-L1 expression ≥ 50% without sensitising EGFR mutations or ALK-positive mutations in first-line therapy, there is no hint of an added benefit of tremelimumab + durvalumab + platinum-based chemotherapy compared to pembrolizumab; an added benefit is therefore not proven.

The assessment described above concurs with the company’s assessment.

I 4 Research question 2: PD-L1 expression < 50%

I 4.1 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on tremelimumab + durvalumab + platinum-containing chemotherapy (as of 23 January 2023)
- bibliographic search on tremelimumab + durvalumab + platinum-containing chemotherapy (last search 23 January 2023)
- search in trial registries / trial results databases on tremelimumab + durvalumab + platinum-containing chemotherapy (last search on 23 January 2023)
- search on the G-BA website on tremelimumab + durvalumab + platinum-containing chemotherapy (last search on 23 January 2023)
- bibliographical literature search on the ACT (last search on 24 January 2023)
- search in trial registries / trial results databases for studies on the ACT (last search on 24 January 2023)
- search on the G-BA website for the ACT (last search on 24 January 2023)

To check the completeness of the study pool:

- search in trial registries for studies on tremelimumab + durvalumab (last search on 21 April 2023); for search strategies, see I Appendix A of the full dossier assessment
- search in trial registries for studies on nivolumab + ipilimumab (last search on 21 April 2023); for search strategies, see I Appendix A of the full dossier assessment

Concurring with the company, the check of completeness of the study pool found no study for the direct comparison of tremelimumab + durvalumab + platinum-containing chemotherapy versus nivolumab +ipilimumab + platinum-based chemotherapy in the present therapeutic indication.

The company therefore presents an adjusted indirect comparison according to Bucher [4] for the assessment of tremelimumab + durvalumab + platinum-based chemotherapy versus nivolumab + ipilimumab + platinum-based chemotherapy via the common comparator of platinum-based chemotherapy.

As supplementary information, the company presents a direct comparison of the POSEIDON study comparing tremelimumab + durvalumab + platinum-containing chemotherapy versus

platinum-based chemotherapy in patients with NSCLC with PD-L1 expression < 50%. The direct comparison is not relevant for the present benefit assessment because the ACT has not been implemented.

The check of the study pool did not identify any additional relevant study for the adjusted indirect comparison presented by the company.

I 4.1.1 Studies included

Concurring with the company, the benefit assessment used platinum-based chemotherapy as the common comparator for an adjusted indirect comparison.

The studies listed in the following table were included in the benefit assessment.

Table 19: Study pool – RCT, indirect comparison: tremelimumab + durvalumab + platinum-based chemotherapy versus nivolumab + ipilimumab + platinum-based chemotherapy: research question 2 (PD-L1 expression < 50%)

Study	Study category			Available sources		
	Study for the approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	Clinical study report (CSR) (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication and other sources[c] (yes/no [citation])
Tremelimumab + durvalumab + platinum-based chemotherapy vs. platinum-based chemotherapy						
D419MC00004 (POSEIDON[d])	Yes	Yes	No	Yes [5,6]	Yes [7-9]	Yes [10,11]
Nivolumab + ipilimumab + platinum-based chemotherapy vs. platinum-based chemotherapy						
CA209-9LA	No	No	Yes	No	Yes [50-52]	Yes [53-56]

a. Study for which the company was sponsor.
b. References of trial registry entries and any available reports on the study design and/or results listed in the trial registries.
c. Other sources: documents from the search on the G-BA website and other publicly available sources.
d. In the following tables, the study is referred to by this acronym.

G-BA: Federal Joint Committee; PD-L1: programmed death ligand 1; RCT: randomized controlled trial

The study pool concurs with that of the company.

The study pool includes the RCT POSEIDON for tremelimumab + durvalumab + platinum-based chemotherapy and the RCT CA209-9LA for nivolumab + ipilimumab + platinum-based chemotherapy.

The indirect comparison is shown schematically Figure 2.

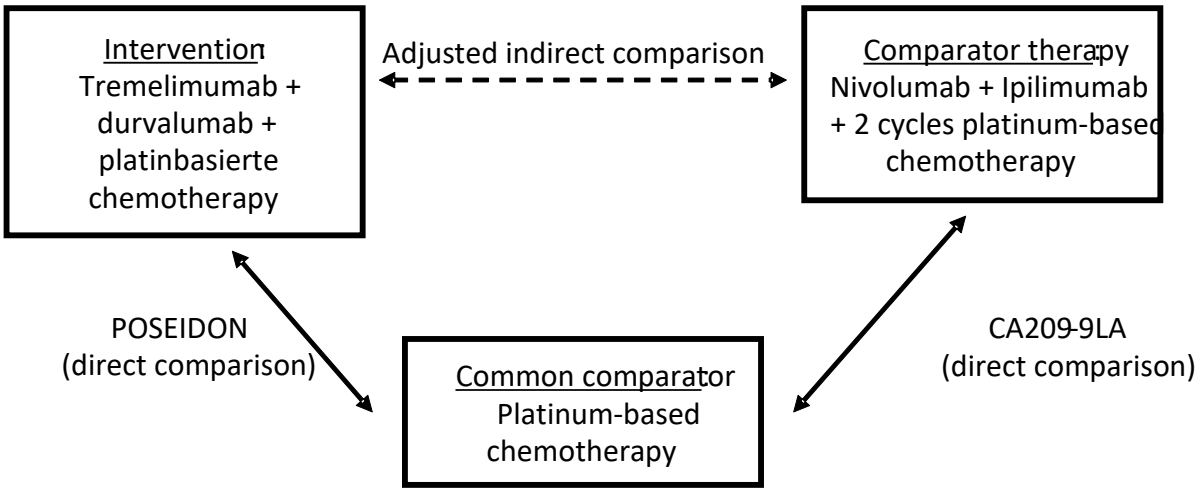

Figure 2: Study pool for the indirect comparison of tremelimumab + durvalumab + platinum-based chemotherapy versus the ACT of nivolumab + ipilimumab + platinum-based chemotherapy: research question 2 (PD-L1 expression < 50%)

I 4.1.2 Study characteristics

Table 20 and Table 21 describe the studies used for the benefit assessment.

Table 20: Characteristics of the included studies – RCT, indirect comparison: tremelimumab + durvalumab + platinum-based chemotherapy versus nivolumab + ipilimumab + platinum-based chemotherapy: research question 2 (PD-L1 expression < 50%) (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
Tremelimumab + durvalumab + platinum-based chemotherapy vs. platinum-based chemotherapy						
POSEIDON	RCT, open-label, parallel-group	Adults[b] with histologically or cytologically confirmed NSCLC (stage IV), confirmed PD-L1-expressing tumour, with no EGFR mutation or ALK translocation, with ECOG-PS ≤ 1, without previous systemic therapy (first-line treatment)[c]	▪ Tremelimumab + durvalumab + platinum-based chemotherapy (N = 338) ▪ Durvalumab + platinum-based chemotherapy (N = 338)[d] ▪ Platinum-based chemotherapy (N = 337) of which relevant subpopulation with PD-L1 expression < 50%: ▪ Tremelimumab + durvalumab + platinum-based chemotherapy (n = 237) ▪ Platinum-based chemotherapy (n = 240)	▪ Screening: 28 days prior to the start of treatment ▪ Treatment: until disease progression[e], unacceptable toxicity, discontinuation of therapy at the decision of the physician or patient, start of new antineoplastic therapy ▪ Observation[f]: outcome-specific, maximum until death	142 centres in: Brazil, Bulgaria, Germany, Hong Kong, Hungary, Japan, Mexico, Peru, Poland, Russia, South Africa, South Korea, Taiwan, Thailand, Ukraine, United Kingdom, United States, Vietnam 06/2017 – ongoing[g] <u>Data cutoffs:</u> ▪ 24/07/2019 (final analysis for PFS) ▪ 12/03/2021 (final analysis for OS)[h] ▪ 25/10/2021[i] ▪ 11/03/2022[j]	▪ Primary: PFS, overall survival ▪ Secondary: symptoms, health status, health-related quality of life, AEs

Table 20: Characteristics of the included studies – RCT, indirect comparison: tremelimumab + durvalumab + platinum-based chemotherapy versus nivolumab + ipilimumab + platinum-based chemotherapy: research question 2 (PD-L1 expression < 50%) (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
Nivolumab + ipilimumab + platinum-based chemotherapy vs. platinum-based chemotherapy						
CA209-9LA	RCT, open-label, parallel-group	Adults with histologically confirmed non-squamous or squamous NSCLC stage IIIB[k] or IV with no EGFR mutation or ALK translocation and with an ECOG-PS ≤ 1, without prior systemic therapy[l]	▪ Nivolumab + ipilimumab + platinum-based chemotherapy (N = 361) ▪ Platinum-based chemotherapy (N = 358) of which relevant subpopulation (PD-L1 expression < 50%): ▪ Nivolumab + ipilimumab + platinum-based chemotherapy (n = 262) ▪ Platinum-based chemotherapy (n = 235)	▪ Screening: ND ▪ Treatment: until either disease progression, unacceptable toxicity, discontinuation of therapy as decided by the physician or patient, or reaching the maximum duration of therapy (24 months for nivolumab + ipilimumab) ▪ Observation[f]: outcome-specific, at most until either death, discontinuation of participation in the study, or end of study	103 centres in Argentina, Australia, Belgium, Brazil, Canada, Chile, China, France, Germany, Ireland, Italy, Japan, Mexico, Poland, Romania, Russia, Spain, United Kingdom, United States 8/2017–ongoing Data cutoffs: 03/10/2019[m] 09/03/2020[n]	▪ Primary: overall survival ▪ Secondary: symptoms, health status, AEs

Table 20: Characteristics of the included studies – RCT, indirect comparison: tremelimumab + durvalumab + platinum-based chemotherapy versus nivolumab + ipilimumab + platinum-based chemotherapy: research question 2 (PD-L1 expression < 50%) (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]

a. Primary outcomes comprise information without regard to its relevance for this benefit assessment. Secondary outcomes only include information on relevant available outcomes for this benefit assessment.
b. ≥ 18 years; for patients in Japan ≥ 20 years.
c. Without prior chemotherapy or other systemic therapies for metastatic NSCLC.
d. This arm is irrelevant for the assessment and is not presented in the following tables.
e. Patients with confirmed radiological progression who, in the opinion of the investigator, continued to benefit from treatment were allowed to continue to receive durvalumab as monotherapy; no information is available on how many patients continued treatment after progression.
f. Outcome-specific information is provided in Table 22.
g. Planned end of study according to information provided by the company in Module 4 A: 28/05/2025.
h. Planned to occur after 532 deaths in the total population of the 2 study arms durvalumab + platinum-based chemotherapy and platinum-based chemotherapy.
i. Non-predefined data cutoff (see Section I 4.1.2, text below).
j. Non-predefined data cutoff (see Section I 4.1.2, text below); after the predefined final OS analysis of 12/03/2021, protocol version 6 dated 9/07/2021 added a subsequent follow-up survey of the outcome of overall survival (approximately 1 year after the predefined analysis); however, the analysis of the data collected for the 11/03/2022 data cutoff is not deemed predefined in the present benefit assessment (see following continuous text on data cutoffs).
k. A total of 94% of the patients in the subpopulation relevant to the present study were in stage IV.
l. Based on NSCLC stage IIIB or IV, respectively.
m. Planned to be carried out after the occurrence of 322 deaths.
n. Planned to be carried out after the occurrence of 402 deaths.

AE: adverse event; ALK: anaplastic lymphoma kinase; AM-RL: Pharmaceutical Directive; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; EGFR: epidermal growth factor receptor; n: relevant subpopulation; N: number of randomised (included) patients; ND: no data; NSCLC: non-small cell lung cancer; PD-L1: programmed death ligand 1; RCT: randomised controlled trial

Table 21: Characteristics of the intervention – RCT, indirect comparison: tremelimumab + durvalumab + platinum-based chemotherapy versus nivolumab + ipilimumab + platinum-based chemotherapy: research question 2 (PD-L1 expression < 50%) (multipage table)

Study	Intervention	Comparison
Tremelimumab + durvalumab + platinum-based chemotherapy vs. platinum-based chemotherapy		
POSEIDON	See information on characteristics for research question 1 (PD-L1 expression ≥ 50%) in Table 7	
Nivolumab + ipilimumab + platinum-based chemotherapy vs. platinum-based chemotherapy		
CA209-9LA	Nivolumab 360 mg i.v. every 3 weeks for a maximum of 24 months + Ipilimumab 1 mg/kg BW i.v. every 6 weeks for a maximum of 24 months + Histology-dependent chemotherapy for a maximum of 2 cycles of 3 weeks each: ▪ Squamous histology: Carboplatin AUC 6 i.v.+ paclitaxel 200 mg/m² BSA, i. v., Day 1 of each cycle ▪ Non-squamous histology[a]: Cisplatin 75 mg/m² BSA i.v. + pemetrexed 500 mg/m² BSA i.v. on Day 1 of each cycle or Carboplatin AUC 5– 6 i.v.+ pemetrexed 500 mg/m² BSA, i. v. on Day 1 of each cycle	Histology-dependent chemotherapy for a maximum of 4 cycles of 3 weeks each: ▪ Squamous histology: carboplatin AUC 6 i.v.+ paclitaxel 200 mg/m² BSA, i. v. on Day 1 of each cycle ▪ Non-squamous histology[a]: cisplatin 75 mg/m² BSA i.v. + pemetrexed 500 mg/m² BSA i.v. on Day 1 of each cycle or Carboplatin AUC 5–6 i.v.+ pemetrexed 500 mg/m² BSA, i. v. on Day 1 of each cycle
	▪ When nivolumab was discontinued, ipilimumab therapy also had to be stopped. When ipilimumab was discontinued, continuation of nivolumab was allowed. ▪ When ipilimumab or nivolumab was discontinued, continuation of chemotherapy was allowed until 2 cycles were reached (and vice versa).	For patients with non-squamous histology and no disease progression, maintenance therapy with pemetrexed 500 mg/m² BSA i.v. on Day 1 of each cycle was allowed at the investigator's discretion.
	▪ Interval extension between doses due to toxicity was allowed. Dose adjustments were allowed only for chemotherapy. ▪ Premedication for the administration of chemotherapy was carried out in accordance with the SPC or local standards.	

Table 21: Characteristics of the intervention – RCT, indirect comparison: tremelimumab + durvalumab + platinum-based chemotherapy versus nivolumab + ipilimumab + platinum-based chemotherapy: research question 2 (PD-L1 expression < 50%) (multipage table)

Study	Intervention	Comparison
	Disallowed prior treatment ▪ Systemic antineoplastic therapy as primary therapy for stage IIIB or IV NSCLC ▪ Systemic immunosuppressive agents within 14 days prior to the start of study medication (with the exception of systemic glucocorticoids < 10 mg/day prednisone equivalent) **Allowed prior treatment** ▪ Chemotherapy (adjuvant and neoadjuvant) and radiotherapy in early stage or locally advanced stage NSCLC up to ≥ 6 months prior to study inclusion ▪ Palliative radiotherapy of metastases outside the CNS up to ≥ 14 days before the start of study medication ▪ Treatment of CNS metastases: either discontinuation of glucocorticoid therapy or stable or reduced dose to ≤ 10 mg/day prednisone or equivalent ≥ 2 weeks before starting study medication ▪ Major surgery ≥ 14 days before the start of study medication **Concomitant treatment** ▪ Inhaled, topical, ocular, intraarticular, and intranasal glucocorticoids ▪ Glucocorticoids for adrenal replacement therapy > 10 mg prednisone equivalent ▪ < 3 weeks of glucocorticoids for prophylaxis of allergic reactions or for treatment of non-autoimmune diseases ▪ Bisphosphonates and RANK-L inhibitors for the prevention or reduction of skeletal events due to bone metastases if the therapy was already started before the start of the study medication ▪ Palliative radiotherapy[b] and surgical resection of symptomatic bone, skin, or CNS lesions ▪ Palliative treatment of lesions causing haemoptysis	

a. As part of chemotherapy, a platinum-based combination chemotherapy was selected individually for each patient by the investigator prior to randomisation.
b. Ipilimumab and nivolumab were to be paused 1 week before, during, and after radiotherapy.

AUC: area under the curve; BSA: body surface area; BW: body weight; CNS: central nervous system; i. v.: intravenous; NSCLC: non-small cell lung cancer; PD-L1: programmed death ligand 1; RANK-L: receptor activator of NF-κB ligand; RCT: randomised controlled trial

Study design

Study with tremelimumab + durvalumab + platinum-based chemotherapy: POSEIDON

A description of the POSEIDON study can be found in Section I 3.1.2.

Relevant subpopulation of the POSEIDON study for research question 2

The POSEIDON study's subpopulation relevant for the present research question 2 comprises patients with tumour PD-L1 expression < 50% (237 patients in the intervention arm and 240 patients in the comparator arm).

Study with nivolumab + ipilimumab + 2 cycles of platinum-based chemotherapy: CA209-9LA

The CA209-9LA study is an ongoing, open-label, multicentre RCT comparing nivolumab + ipilimumab + platinum-based chemotherapy versus platinum-based chemotherapy.

The study included adult patients with squamous and non-squamous stage IV NSCLC with no EGFR mutation or ALK translocation and ECOG-PS ≤ 1 irrespective of PD-L1 expression. The inclusion criteria of the CA209-9LA study additionally included patients in stage IIIB without the possibility of curative therapy. However, this only applied to 2% of the patients included. Patients with untreated brain metastases were excluded from the study. No prior systemic therapy of stage IIIB or IV NSCLC was allowed.

PD-L1 expression of tumour tissue was determined by a central laboratory using a DAKO immunohistochemistry kit (28-8 pharmDx assay) during the screening phase.

EGFR testing of the tumour tissue was conducted only in patients with non-squamous histology. The study excluded any patients with unknown or indeterminable EGFR status. Testing for ALK translocations was not mandatory, but patients with known ALK translocation were excluded from the study.

The CA209-9LA study included a total of 719 patients, randomized in a 1:1 ratio to treatment with either nivolumab + ipilimumab + platinum-based chemotherapy (N = 361) or to only platinum-based combination chemotherapy (N = 358). The type of chemotherapy was dependent on the histology of the tumour: patients with squamous histology received carboplatin in combination with paclitaxel, while patients with non-squamous histology received either cisplatin or carboplatin in combination with pemetrexed. The platinum component was chosen by the investigator before randomization on the basis of eligibility criteria not described in more detail by the company.

Randomisation was stratified by PD-L1 expression (≥ 1% versus < 1%), tumour histology (squamous histology versus non-squamous histology), and sex (male versus female). For stratification purposes, patients with non-quantifiable PD-L1 status (tumours with non-measurable PD-L1 expression or insufficient sample quality for PD-L1 expression determination) were assigned to the population with PD-L1 expression < 1%.

The company conducting the CA209-9LA [53] study reports that in addition to this global study, there is a sub-study in China. Module 4 of the dossier does not present any data for this substudy. According to the trial registry entry [51], the study was to be completed in January 2023.

In both study arms, the use of the study medication complies with the requirements of the respective SPC or guidelines [35,37,38,42,44,57]. Only the 200 mg/m^2 dose of paclitaxel specified in the study protocol for patients with squamous histology deviates slightly from the requirements of the SPC, which specifies 175 mg/m^2 for the combination with cisplatin [41]. The SPCs do not contain any further information on the combination of paclitaxel or pemetrexed with carboplatin.

The maximum treatment duration for nivolumab + ipilimumab is 24 months.

In the comparator arm, up to 4 cycles of chemotherapy were administered; afterwards, patients with non-squamous histology and no disease progression were allowed to receive maintenance therapy with pemetrexed from Cycle 5. It is unclear how many patients in the relevant subpopulation received maintenance therapy with pemetrexed. Information on the number of patients by type of therapy in the comparator arm can be found in Table 26.

Treatment was administered until either disease progression, unacceptable intolerance, withdrawal of consent, or reaching of the maximum duration of therapy. Under certain conditions, continuation of treatment was allowed even beyond disease progression at the discretion of the investigator. Switching patients from the comparator arm to treatment with nivolumab + ipilimumab after disease progression was not allowed. There were no restrictions regarding subsequent therapies.

Primary outcome of the CA209-9LA study was overall survival. Secondary patient-relevant outcomes were from the morbidity and side effects categories.

Relevant subpopulation of the CA209-9LA study

The CA209-9LA study's subpopulation relevant for the present research question comprises patients with tumour PD-L1 expression < 50% (262 patients in the intervention arm and 235 patients in the comparator arm). This subpopulation was analysed in Addendum A21-57 to Commission A20-118 [54].

Data cutoffs

For both studies (POSEIDON and CA209-9LA), the pre-specified cutoffs were used for the assessment.

POSEIDON study

For the POSEIDON study, the predefined final data cutoff for overall survival dated 12 March 2021 is used for all outcomes in this benefit assessment. For the assessment of the other data cutoffs submitted by the company in Module 4 A, see Section I 3.1.2 on research question 1.

Study CA209-9LA

For study CA209-9LA, 2 data cutoffs are available:

- 1st data cutoff from 3 October 2019: interim analysis on overall survival, planned to be implemented after 322 events
- 2nd data cut from 9 March 2020: final analysis on overall survival, planned to be implemented after 402 events

For the benefit assessment, the predefined final analysis for the 9 March 2020 data cutoff is used.

Planned duration of follow-up observation

Table 22 shows the planned duration of patient follow-up observation for the individual outcomes.

Table 22: Planned duration of follow-up observation – RCT, indirect comparison: tremelimumab + durvalumab + platinum-based chemotherapy versus nivolumab + ipilimumab + platinum-based chemotherapy: research question 2 (PD-L1 expression < 50%)

Comparison **Study** **Outcome category** **Outcome**	**Planned follow-up observation**
Tremelimumab + durvalumab + platinum-based chemotherapy vs. platinum-based chemotherapy	
POSEIDON	See information on planned duration of follow-up observation for research question 1 (PD-L1 expression ≥ 50%) in Table 8
Nivolumab + ipilimumab + platinum-based chemotherapy vs. platinum-based chemotherapy	
CA209-9LA	
Mortality	
Overall survival	▪ Until death, withdrawal of consent, lost-to-follow-up, or end of study
Morbidity	
Symptoms (LCSS ASBI)	▪ 35 and 115 days after the last study medication
Health status (EQ-5D VAS)	▪ 35 and 115 days after the last study medication, thereafter every 3 months in the 1st year, thereafter every 6 months
Health-related quality of life	▪ Not recorded
Side effects	
All outcomes in the side effects category	▪ 100 days after the last study medication

EQ-5D: European Quality of Life – 5 Dimensions; LCSS ASBI: Lung Cancer Symptom Scale - Average Symptom Burden Index; PD-L1: programmed death ligand 1; RCT: randomised controlled trial; VAS: visual analogue scale

The observation times for the outcomes on morbidity and health-related quality of life are systematically shortened in the POSEIDON study because they were collected only until the 2nd disease progression.

In the CA209-9LA study, symptoms were likewise surveyed for a shortened period, up to 115 days after the last study medication, using the Lung Cancer Symptom Scale – Average Symptom Burden Index (LCSS ASBI). In the CA209-9LA study, only health status (EQ-5D VAS) was assessed over the complete study period.

The observation times for the side effects outcomes were systematically shortened in both studies because they were collected only for the period of treatment with the study medication (plus 90 days in the POSEIDON study or 100 days in the CA209-9LA study).

Drawing a reliable conclusion on the total study period or the time to patient death, however, would require surveying these outcomes for the total period, as was done for survival.

Study population

Table 23 shows the characteristics of the patients in the relevant subpopulations of the included studies.

Table 23: Characteristics of the study populations as well as study/treatment discontinuation – RCT, indirect comparison: tremelimumab + durvalumab + platinum-based chemotherapy versus nivolumab + ipilimumab + platinum-based chemotherapy: research question 2 (PD-L1 expression < 50%) (multipage table)

Study Characteristic / **Category**	**Study with tremelimumab + durvalumab**		**Study with nivolumab + ipilimumab**	
	POSEIDON		**CA209-9LA**	
	Tremelimumab + durvalumab + platinum-based chemotherapy	**Platinum-based chemotherapy**	**Nivolumab + ipilimumab + platinum-based chemotherapy**	**Platinum-based chemotherapy**
	N[a] = 237	**N[a] = 240**	**N[a] = 262**	**N[a] = 235**
Age [years]				
Mean (SD)	63 (10)	63 (10)	64 (8)	63 (10)
Sex [F/M], %	18/82	25/75	27/73	29/71
Family origin, n (%)				
White	150 (63)	135 (56)	234 (89)	203 (86)
Black or African American	6 (3)	7 (3)	3 (1)	4 (2)
Asian	67 (28)	83 (35)	23 (9)	22 (9)
Other	14 (6)	15 (6)	2 (< 1)	6 (3)
Geographical region, n (%)				
Western Europe / North America / Eastern Europe	139 (59)	125 (52)	180 (69)	158 (67)
Asia	52 (22)	62 (26)	21 (8)	22 (9)
Rest of the world (incl. Japan)	46 (19)	53 (22)	61 (23)	55 (23)
Smoking status, n (%)				
Active/former	202 (85)	182 (76)	229 (87)	205 (87)
Never	35 (15)	58 (24)	33 (13)	30 (13)
ECOG-PS, n (%)				
0	80 (34)	82 (34)	89 (34)	77 (33)
1	157 (66)	158 (66)	172 (65)	158 (67)
Missing	0 (0)	0 (0)	1 (< 1)	0 (0)
Histology, n (%)				
Squamous	88 (37)	90 (38)	81 (31)	75 (32)
Non-squamous	149 (63)	150 (63)	181 (69)	160 (68)
Brain metastases, n (%)	23 (10)	34 (14)	45 (17)	35 (15)

Table 23: Characteristics of the study populations as well as study/treatment discontinuation – RCT, indirect comparison: tremelimumab + durvalumab + platinum-based chemotherapy versus nivolumab + ipilimumab + platinum-based chemotherapy: research question 2 (PD-L1 expression < 50%) (multipage table)

Study Characteristic / Category	Study with tremelimumab + durvalumab		Study with nivolumab + ipilimumab	
	POSEIDON		CA209-9LA	
	Tremelimumab + durvalumab + platinum-based chemotherapy	Platinum-based chemotherapy	Nivolumab + ipilimumab + platinum-based chemotherapy	Platinum-based chemotherapy
	N[a] = 237	N[a] = 240	N[a] = 262	N[a] = 235
Disease stage, n (%)				
IIIA	1 (< 1)	0 (0)	ND	ND
IIIB	1 (< 1)	0 (0)	ND	ND
IV	235 (99)[b]	240 (100)[b]	243 (93)	222 (94)
IVA	123 (52)	120 (50)	ND	ND
IVB	112 (47)	120 (50)	ND	ND
Recurrent to metastatic disease	ND	ND	19 (7)	13 (6)
Disease status, n (%)				
Locally advanced	0 (0)	0 (0)	ND	ND
Metastatic	236 (> 99)	240 (100)	ND	ND
Missing	1 (< 1)	0 (0)	ND	ND
PD-L1 status, n (%)				
≥ 1%	112 (47)	110 (46)	127 (48)	106 (45)
< 1%	125 (53)	130 (54)	135 (52)	129 (55)
Number of metastases at baseline, mean (SD) or median [min; max]	ND	ND	ND	ND
Metastasis, n (%)				
M0	33 (14)	28 (12)	ND	ND
M1	5 (2)	8 (3)	ND	ND
M1A	76 (32)	68 (28)	ND	ND
M1B	43 (18)	49 (20)	ND	ND
M1C	79 (33)	87 (36)	ND	ND
MX	0 (0)	0 (0)	ND	ND
Missing	1 (< 1)	0 (0)	ND	ND
Time since initial diagnosis [months], mean (SD or median [min; max])	ND	ND	ND	N D

Table 23: Characteristics of the study populations as well as study/treatment discontinuation – RCT, indirect comparison: tremelimumab + durvalumab + platinum-based chemotherapy versus nivolumab + ipilimumab + platinum-based chemotherapy: research question 2 (PD-L1 expression < 50%) (multipage table)

Study Characteristic Category	**Study with tremelimumab + durvalumab**		**Study with nivolumab + ipilimumab**	
	POSEIDON		**CA209-9LA**	
	Tremelimumab + durvalumab + platinum-based chemotherapy	**Platinum-based chemotherapy**	**Nivolumab + ipilimumab + platinum-based chemotherapy**	**Platinum-based chemotherapy**
	N[a] = 237	**N[a] = 240**	**N[a] = 262**	**N[a] = 235**
Prior therapies, n (%)				
Adjuvant	ND	ND	ND	ND
Neoadjuvant	ND	ND	ND	ND
Prior radiotherapies, n (%)	38 (16)	44 (18)	ND	ND
Treatment discontinuation, n (%)[c]	217 (94)	235 (99)[d]	209 (80)	149 (66)
Study discontinuation, n (%)[e]	202 (85)	225 (94)	42 (16)	33 (15)

a. Number of randomized patients. Values which are based on different patient numbers are marked in the corresponding line if the deviation is relevant.
b. Institute's calculation.
c. Common reasons for treatment discontinuation in the intervention vs. comparator arm were:
- POSEIDON study (21/03/2021 data cutoff): worsening of the disease (69.0% vs. ND), adverse event (18.5% vs. ND), patient decision (5.2% vs. ND).
- CA209-9LA study: progression (48.1% vs. 47.6%) and toxicity of study medication (20.8% vs. 7.9%).

d. Presumably also includes discontinuation of pemetrexed; patients who have reached the maximum dose of chemotherapy and are not receiving pemetrexed were presumably also counted as treatment discontinuers.
e. Common reasons for study discontinuation in the intervention vs. comparator arm were:
- POSEIDON study (12/03/2021 data cutoff): based on all patients who received at least 1 dose of study medication (intervention arm N = 232; comparator arm N = 238): death (81.4% vs. 89.2%).
- CA209-9LA study: based on all patients who received at least 1 dose of the study medication (intervention arm N = 260; comparator arm N = 227). The most common reason for study discontinuation in both treatment arms was death (15.0% vs. 12.8%).

ECOG-PS: European Cooperative Oncology Group Performance Status; f: female; m: male; max: maximum; min: minimum; n: number of patients in the category; N: number of randomized patients; ND: no data; PD-L1: programmed death 1 ligand 1; RCT: randomized controlled trial; SD: standard deviation

The POSEIDON and CA209-9LA studies do not provide data on all patient characteristics of interest. Based on the available information, conclusions can nevertheless be drawn about the similarity of the patient populations between the 2 studies.

The patients included in the relevant subpopulations from the POSEIDON and CA209-9LA studies were on average about 63 years old and predominantly male. The patients in both

studies were almost all in disease stage IV. The proportion of patients with brain metastases was comparable between the studies and ranged between 10% and 17%, depending on the study and study arm.

A major difference is the lower proportion of patients of White family origin in the POSEIDON study compared to the CA209-9LA study. It equals 60% in the POSEIDON study and 88% in the CA209-9LA study, each based on both study arms. The group of patients of Non-White family origin included Asian, Black/African American, and other patient groups, with the Asian group making up the largest proportion in both studies. The proportion of Asian patients was higher in the POSEIDON study than in the CA209-9LA study (31% versus 9%).

Overall, the patient populations of the 2 studies are sufficiently comparable, with the exception of the family origin characteristic. See Section I 4.1.3 regarding the relevance of the differences in the family origin characteristic among the patient populations of the POSEIDON and CA209-9LA studies with regard to the similarity test for the indirect comparison.

Treatment duration and observation period

Table 24 shows the mean and median treatment durations of the patients and the mean and median observation periods for individual outcomes.

Table 24: Information on the course of the study – RCT, indirect comparison: tremelimumab + durvalumab + platinum-based chemotherapy versus nivolumab + ipilimumab + platinum-based chemotherapy: research question 2 (PD-L1 expression < 50%) (multipage table)

Comparison **Study** **Outcome category** **Treatment component / outcome**	**Tremelimumab + durvalumab + platinum-based chemotherapy or nivolumab + ipilimumab + platinum-based chemotherapy**	**Platinum-based chemotherapy**
Tremelimumab + durvalumab + platinum-based chemotherapy vs. platinum-based chemotherapy		
POSEIDON (12/03/2021 data cutoff)	N[a] = 231	N[a] = 240
Treatment duration [months][b]		
Total		
Median [min; max]	6.7 [0.5; 40.2]	4.1 [0.2; 42.3]
Mean (SD)	10.4 (10.3)	6.1 (7)
Tremelimumab		
Median [min; max]	4.6 [0.5; 8.7]	–
Mean (SD)	4 (1.7)	–
Durvalumab		
Median [min; max]	6.4 [0.5; 40.2]	–
Mean (SD)	10.2 (10.2)	–
Platinum-based chemotherapy		
Median [min; max]	3.4 [0.5; 39.6]	4.1 [0.2; 42.3]
Mean (SD)	7.7 (8.9)	6.1 (7)
Observation period [months]		
Overall survival[c]	ND[d]	
Morbidity		
Symptoms (EORTC QLQ-C30, EORTC QLQ-LC13), health status (EQ-5D VAS)		
Median [min; max]	6.6 [0; 40.0]	4.7 [0; 41.7]
Mean (SD)	ND	
Health status (PGIC)[e]		
Median [min; max]	8.1 [0.7; 40.0]	5.4 [0.7; 41.7]
Mean (SD)	ND	
Health-related quality of life (EORTC QLQ-C30)		
Median [min; max]	6.6 [0; 40.0]	4.7 [0; 41.7]
Mean (SD)	ND	
Side effects	ND[f]	

Table 24: Information on the course of the study – RCT, indirect comparison: tremelimumab + durvalumab + platinum-based chemotherapy versus nivolumab + ipilimumab + platinum-based chemotherapy: research question 2 (PD-L1 expression < 50%) (multipage table)

Comparison **Study** **Outcome category** **Treatment component / outcome**	**Tremelimumab + durvalumab + platinum-based chemotherapy or nivolumab + ipilimumab + platinum-based chemotherapy**	**Platinum-based chemotherapy**
Nivolumab + ipilimumab + platinum-based chemotherapy vs. platinum-based chemotherapy		
CA209-9LA (9/03/2020 data cutoff)	N = 260[h]	N = 227[h]
Treatment duration [months]		
Median [min; max]	5.6 [0.0; 23.5]	2.4 [0.0; 22.8]
Mean (SD)	7.6 (ND)	4.4 (ND)
Observation period [months]		
Overall survival		
Median [min; max]	14.1 [0.2; 27.2]	10.2 [0.1; 26.7]
Mean (SD)	13 (6.7)	10.9 (6.5)
Morbidity		
Symptoms (LCSS ASBI)	ND	
Health status (EQ-5D VAS)	ND	
Health-related quality of life	Outcome not recorded	
Side effects	ND	

a. Number of analysed patients. Values which are based on different patient numbers are marked in the corresponding line if the deviation is relevant.
b. The company's data are based on weeks, while the Institute's calculations are shown in months.
c. The observation duration was calculated as the time from randomisation to the date of the respective event or until censoring.
d. No information for the predefined final data cutoff of 12/03/2021; for 11/03/2022 data cutoff: median [min; max] (intervention arm vs. comparator arm): 13.1 [0.4; 55] vs. 11.4 [0.1; 55] in months.
e. Data based on 210 patients (intervention arm) vs. 214 patients (comparator arm).
f. No data for the predefined final data cutoff of 12/03/2021; for the 25/10/2021 data cutoff: median [min; max] (intervention arm vs. comparator arm): 7.8 [0.4; 52.3] vs. 5.6 [0.2; 53.6] in months; observation duration was calculated as the time from the first dose of study medication to the earliest time of occurrence of the following: 90 days after the last dose of study medication, date of start of first subsequent therapy, or date of death.
g. All patients who received at least 1 dose of the study medication.

EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: European Quality of Life – 5 Dimensions; LCSS ASBI: Lung Cancer Symptom Scale – Average Symptom Burden Index; QLQ-C30: Quality of Life Questionnaire – Cancer 30; QLQ-LC13: Quality of Life Questionnaire – Lung Cancer 13; max: maximum; min: minimum; N: number of randomised patients; ND: no data; PD-L1: programmed death ligand 1; PGIC: Patient Global Impression of Change; RCT: randomised controlled trial; SD: standard deviation; VAS: visual analogue scale

In the POSEIDON and CA209-9LA studies, the median treatment durations in the intervention arm were approximately 1.6 times (POSEIDON trial) and 2.3 times (KEYNOTE-024 trial) as long as in the respective comparator arm. Overall, the median treatment durations in the POSEIDON study were longer than in the CA209-9LA study.

Data on observation durations in the POSEIDON study are available only for the patient-reported outcomes of morbidity and health-related quality of life. For these outcomes, the observation durations were longer in the intervention arm than in the comparator arm. For overall survival and the side effects outcomes, no information is available on the observation durations for the data cutoff used.

For the CA209-9LA study, data on observation durations are available only for the outcome of overall survival. The mean observation durations were 13 months in the intervention arm and 11 months in the comparator arm.

For side effects, the observation duration of the POSEIDON and CA209-9LA studies can be estimated from the data on median treatment duration because all AE outcomes were to be recorded for 90 days (POSEIDON study) and 100 days (CA209-9LA study) after the last dose of the study medication. Thus, analogous to the analysed differences in treatment durations, the observation durations for the side effects in both studies are longer in the intervention arm than in the comparator arm, and overall, the median observation durations are longer in the POSEIDON study than in the CA209-9LA study.

Overall, the median treatment duration in the POSEIDON study is longer than in the CA209-9LA study. Presumably, this is due to the fact that although chemotherapy was planned to be administered for 4 cycles in both studies, the POSEIDON study allowed administration for up to a maximum of 6 cycles if clinically indicated in the investigator's opinion. In total, 58% of comparator-arm participants of the POSEIDON subpopulation relevant for the present research question received ≥ 5 cycles of chemotherapy. Due to missing data, it is impossible to assess the between-study similarity in observation durations.

Subsequent therapies

Table 25 shows the subsequent therapies patients received after discontinuing the study medication.

Table 25: Information on antineoplastic subsequent therapies – RCT, indirect comparison: tremelimumab + durvalumab + platinum-based chemotherapy versus nivolumab + ipilimumab + platinum-based chemotherapy: research question 2 (PD-L1 expression < 50%)

Study **Drug class** **Drug**	**Patients with subsequent therapy n (%)**	
	Tremelimumab + durvalumab + platinum-based chemotherapy or nivolumab + ipilimumab + platinum-based chemotherapy	**Platinum-based chemotherapy**
Tremelimumab + durvalumab + platinum-based chemotherapy vs. platinum-based chemotherapy		
POSEIDON (data cutoff : 12/03/2021)	N = 231	N = 240
Total	102 (44.2)	142 (59.2)
Systemic treatment	93 (40.3)	136 (56.7)
Chemotherapy	81 (35.1)	90 (37.5)
Immunotherapy	18 (7.8)	75 (31.3)
Targeted therapy	9 (3.9)	15 (6.3)
Radiotherapy	37 (16.0)	50 (20.8)
Other	3 (1.3)	6 (2.5)
Nivolumab + ipilimumab + platinum-based chemotherapy vs. platinum-based chemotherapy		
CA209-9LA (data cutoff: 9/03/2020)	N = 262	N = 235
Total	94 (35.9)	108 (46.0)
Systemic treatment	81 (30.9)	96 (40.9)
Chemotherapy	78 (29.8)	56 (23.8)
Immunotherapy	13 (5.0)	68 (28.9)
Targeted therapy	15 (5.7)	10 (4.3)
Experimental drugs	1 (0.4)	3 (1.3)
Radiotherapy	31 (11.8)	34 (14.5)

n: number of patients with subsequent therapy; N: number of patients analysed; PD-L1: programmed death ligand 1; RCT: randomised controlled trial

In the POSEIDON study's relevant subpopulation, 44% of the patients in the intervention arm and 59% of the patients in the comparator arm received at least 1 subsequent antineoplastic therapy. Of these patients, the majority received systemic subsequent therapy (40% versus 57% based on the relevant subpopulation), most frequently chemotherapy. According to the information provided in the study documents, the most commonly used chemotherapeutic agent was docetaxel. In the comparator arm, the most commonly used immunotherapies were nivolumab and pembrolizumab. Targeted therapies were in the 1-digit range in both study arms (4% versus 6% based on the relevant subpopulation).

Among the CA209-9LA study's relevant subpopulation, 36% of the patients in the intervention arm and 46% of the patients in the comparator arm received at least 1 subsequent antineoplastic therapy. In this study, the most commonly used subsequent therapies in the

intervention arm were likewise chemotherapies, most commonly carboplatin and docetaxel. In the comparator arm, immunotherapies were used slightly more often than chemotherapies (29% versus 24%). Again, as in the POSEIDON study, the most commonly used immunotherapies were nivolumab and pembrolizumab. Targeted therapies were used as subsequent therapy in about 5% of both study arms.

Overall, in terms of subsequent therapy, both studies are unquestionably similar enough to subject them to an adjusted indirect comparison

I 4.1.3 Similarity of the studies for the indirect comparison

In the following, central aspects concerning the similarity of the studies for conducting an adjusted indirect comparison are discussed beyond the study characteristics described in Section I 4.1.2.

Study design

Both included studies are multicentre, open-label RCTs with comparable study designs. The studies use similar inclusion and exclusion criteria (see Table 20 and Table 21). The period of study implementation is also comparable. Both studies started in 2017, and the analysed data cutoffs are from March 2021 (POSEIDON study) and March 2020 (CA209-9LA study). See Table 24 regarding the comparability of the 2 studies' observation durations.

Patient characteristics

With the exception of the characteristic of family origin, the relevant subpopulations of the POSEIDON and CA209-9LA studies are sufficiently comparable (see Table 23). As described under patient characteristics, the proportion of patients of White family origin is significantly lower in the POSEIDON study than in the CA209-9LA study (60% versus 88%, each in both arms). In both studies, the largest group of patients of Non-White family origin are Asian patients. The proportion of Asian patients was higher in the POSEIDON study than in the CA209-9LA study (31% versus 9%).

Due to these different proportions, the relevance of family origin was assessed for the similarity test to determine whether it was a relevant effect modifier.

For the relevant subpopulation of the POSEIDON study, subgroup analyses for overall survival are available only for the data cutoff 11 March 2022, but not for the employed prespecified data cutoff of 12 March 2021. At the 11 March 2022 data cutoff, a statistically significant effect modification with marked qualitative differences between the results for Asian and non-Asian patients is shown. For Asian patients, there is a statistically significant disadvantage of tremelimumab + durvalumab compared to platinum-based chemotherapy (HR: 1.45; 95% CI: [1.03; 2.06]), whereas for non-Asian patients, there is a statistically significant advantage (HR: 0.57; 95% CI: [0.45; 0.72]).

In the CA209-9LA study, subgroup analyses are available for the characteristic of family origin, with the categories of White versus Asian. In the relevant subpopulation, the outcome of overall survival showed a benefit of nivolumab + ipilimumab compared to platinum-based chemotherapy for both Asian patients and patients of White family origin, although this benefit was more pronounced for Asian patients (HR: 0.19; 95% CI: [0.05; 0.69] versus HR: 0.67; 95% CI: [0.53; 0.84]). However, there was no statistically significant effect modification (p = 0.058) for the characteristic of family origin.

Overall, the characteristic of family origin in the present data constellation thus represents a relevant effect modifier, especially due to the qualitative effect modification in the POSEIDON study. In the overall picture of the available data on the characteristic of family origin for the relevant subpopulations of the POSEIDON and CA209-9LA studies, the assumption of similarity of the patient populations between the studies is therefore rejected for research question 2. This differs from research question 1, where there the studies show no evidence of a relevant or qualitative effect modification for the characteristic of family origin.

Assays used to determine PD-L1 status

In both studies, immunohistochemistry assays were used to determine PD-L1 status. The POSEIDON study used the SP263 assay, while the CA209-9LA study used the 28-8 pharmDX assay. Moderate to high concordance between the 2 assays has been found [43].

Molecular testing of tumour tissue for the presence of mutations

EGFR mutation and ALK translocation

The POSEIDON and CA209-9LA studies included patients with no EGFR mutation and no ALK translocation. In both studies, prior testing of the tumour tissue should be carried out in patients with non-squamous carcinoma. In patients with squamous cell carcinoma, testing of the tumour tissue was not required. In the CA209-9LA study, only the presence of an EGFR mutation was investigated, while testing of the ALK status was not planned. However, if patients were known to have an ALK translocation in the tumour tissue, they were excluded from the study. In the POSEIDON study, EGFR and ALK status testing was also foregone in case of the known presence of a KRAS mutation in the tumour tissue.

According to the current S3 guideline, molecular pathological testing is to be carried out for all therapeutically relevant molecular changes including EGFR mutations and ALK translocations in the tumour tissue of patients with stage IV NSCLC [44]. Unlike previous versions of this guideline [45], this updated guideline does not impose a restriction to non-squamous cell carcinomas. Due to the rarity of EGFR mutations in squamous cell NSCLC and ALK mutations (across histologies) [48] as well as the lower proportion of patients with squamous cell NSCLC in the 2 studies, the lack of EGFR testing of the tumour tissue in

squamous cell carcinoma and the lack of ALK translocation testing in the CA209-9LA study presumably do not call into question the similarity or relevance of the study populations.

Other mutations

The evaluation of the G-BA's note on the ACT regarding molecularly stratified therapy (directed against BRAF, KRAS G12C, METex14, RET, or ROS1) which presents an option for the study population as described under research question 1 applies equally to this research question (see Section I 3.1.3). The CA209-9LA study likewise did not test for the mutations mentioned in the G-BA's note.

Similarity of the common comparator

For the present indirect comparison, the company chose “platinum-based chemotherapy” as the common comparator. In both analysed studies, POSEIDON and CA209-9LA, this includes different platinum-based combination chemotherapies. In both studies, they were selected individually for each patient by the investigator prior to randomisation. The selected chemotherapies are not identical between both studies.

Table 26 shows which platinum-based chemotherapies were received by the patients in the comparator arms of the 2 studies. The information below is based on the studies’ relevant subpopulations.

Table 26: Distribution of platinum-based combination chemotherapy regimens and maintenance therapies in the relevant comparator arms (common comparators) of the POSEIDON and CA209-9LA studies: research question 2 (PD-L1 expression < 50%)

Study with tremelimumab + durvalumab + platinum-based chemotherapy	**Study with nivolumab + ipilimumab + platinum-based chemotherapy**
POSEIDON (N = 240)	**CA209-9LA (N = 235)[a]**
Non-squamous histology[b]	
n = 150 (63%)	**n = 160 (68%)**
Pemetrexed + ▪ Cisplatin: 25 (16.7%[c]) ▪ Carboplatin: 120 (80.0%[c]) Maintenance therapy with pemetrexed: ▪ 95 (63.3%)[c] Nab-paclitaxel + carboplatin: ▪ See under squamous and non-squamous cell	Pemetrexed + ▪ Cisplatin: 49 (30.6%[c]) ▪ Carboplatin: 103 (64.4%[c]) Maintenance therapy with pemetrexed: ▪ ND for the relevant subpopulation
Squamous histology[d]	
n = 90 (38%)	**n = 75 (32%)**
Gemcitabine + ▪ Cisplatin: 14 (15.6%[c]) ▪ Carboplatin: 69 (76.7%[c]) Nab-paclitaxel + carboplatin: ▪ See under squamous and non-squamous cell	Paclitaxel + carboplatin: ▪ 73 (97.3%[c])
Squamous and non-squamous histology[e]	
▪ nab-paclitaxel + carboplatin: 12 (5.0%)	
Total[e]	
▪ Cisplatin: 39 (16.3%)[c] ▪ Carboplatin: 201 (83.8%) [c]	▪ Cisplatin: 49 (20.9%) ▪ Carboplatin: 176 (74.9%) [c]

a. According to the company, in the comparator arm, 1 patient was treated with carboplatin, cisplatin, and pemetrexed and 1 patient with carboplatin, paclitaxel, and pemetrexed; no information on platinum-based chemotherapy is available for 8 patients.
b. Percentages based on patients with non-squamous histology.
c. Institute's calculation.
d. Percentages based on patients with squamous histology.
e. Percentages based on patients of the entire comparator arm.

n: Patients with respective histology; N: number of randomised patients of the relevant (sub-)populations; ND: no data

Platinum component of the common comparator

Table 26 shows that cisplatin and carboplatin were used in a similar proportion of patients in the comparator arms of the POSEIDON and CA209-9LA studies.

Chemotherapy component of the common comparator

In the POSEIDON and CA209-9LA studies, patients with non-squamous tumour histology were allowed to receive only pemetrexed in addition to the platinum component, with the exception of 12 patients in the POSEIDON study who received nab-paclitaxel regardless of histology.

A marked difference between the 2 studies exists in the chemotherapy component for patients with squamous histology. In the POSEIDON study, these patients received only gemcitabine in addition to the platinum component – with the exception of the 12 patients mentioned above who received nab-paclitaxel regardless of histology. In the CA209-9LA study, patients with squamous histology were restricted to paclitaxel.

Maintenance treatment in the common comparator

Maintenance therapy with pemetrexed was planned in both studies only in the case of non-squamous histology. In the POSEIDON study, 63% of these patients received pemetrexed maintenance therapy. In the CA209-9LA study, data on the proportion of patients receiving maintenance therapy are missing for the relevant subpopulation.

Summary

The described differences between the platinum-based chemotherapies of the POSEIDON and CA209-9LA studies – (i) predominant administration of gemcitabine in the POSEIDON study versus administration of paclitaxel in the CA209-9LA study in patients with squamous histology as well as (ii) lack of information on the frequency of maintenance therapy in the CA209-9LA study among the relevant subpopulation – do not in themselves lead to a fundamental questioning of the similarity of the common comparators for the indirect comparison.

Summary of the similarity of the studies in the indirect comparison

Similarity is a key prerequisite for studies to be included in the adjusted indirect comparison. The 2 studies POSEIDON and CA209-9LA share a very similar study design. Differences exist between the 2 studies in the common comparator of platinum-based chemotherapy. The main difference between the relevant subpopulations of the POSEIDON and CA209-9LA studies lies in the patient characteristics for the family origin characteristic. The proportion of patients of White family origin is significantly lower in the POSEIDON study compared to the CA209-9LA study. The characteristic of family origin represents a relevant effect modifier in the present data constellation, especially due to the qualitative effect modification in the POSEIDON study. Overall, the central assumption of between-study similarity for the indirect comparison is rejected. Thus, the data presented by the company for research question 2 are not suitable for the benefit assessment.

I 4.2 Results on added benefit

The data presented by the company are unsuitable for drawing conclusions on the added benefit of tremelimumab + durvalumab + platinum-based chemotherapy compared with the ACT in adult patients with metastatic NSCLC with PD-L1 expression < 50% without sensitising EGFR mutations or ALK-positive mutations in first-line therapy. This results in no hint of an added benefit of tremelimumab + durvalumab + platinum-based chemotherapy in comparison with the ACT; an added benefit is therefore not proven.

I 4.3 Probability and extent of the added benefit

The data presented by the company are unsuitable for drawing conclusions on the added benefit of tremelimumab + durvalumab + platinum-based chemotherapy compared with the ACT in adult patients with metastatic NSCLC with PD-L1 expression < 50% without sensitising EGFR mutations or ALK-positive mutations in first-line therapy. This results in no hint of an added benefit of tremelimumab + durvalumab + platinum-based chemotherapy in comparison with the ACT; an added benefit is therefore not proven.

The assessment of the added benefit is in line with the company's assessment. In the latter, the company uses the submitted indirect comparison for assessing the added benefit.

I 5 Probability and extent of the added benefit – summary

Table 27 summarizes the result of the assessment of added benefit for tremelimumab + durvalumab + platinum-based chemotherapy in comparison with the ACT.

Table 27: Tremelimumab + durvalumab + platinum-based chemotherapy – probability and extent of added benefit (multipage table)

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
1	Adult patients with metastatic NSCLC with PD-L1 expression ≥ 50% with no sensitizing EGFR mutations or ALK-positive mutations[c]; first-line treatment[d]	▪ **Pembrolizumab as monotherapy** or ▪ atezolizumab as monotherapy or ▪ cemiplimab as monotherapy or ▪ nivolumab in combination with ipilimumab and 2 cycles of platinum-based chemotherapy (only for patients with ECOG-PS 0–1) or ▪ pembrolizumab in combination with carboplatin and either paclitaxel or nab-paclitaxel (only for patients with ECOG-PS 0–1 and squamous NSCLC) or ▪ pembrolizumab in combination with pemetrexed and platinum-containing chemotherapy (only for patients with ECOG-PS 0–1 and non-squamous NSCLC) or ▪ atezolizumab in combination with bevacizumab, paclitaxel, and carboplatin (only for patients with ECOG-PS 0–1 and non-squamous NSCLC) or ▪ atezolizumab in combination with nab-paclitaxel and carboplatin (only for patients with ECOG-PS 0–1 and non-squamous NSCLC)	Added benefit not proven[e]

Table 27: Tremelimumab + durvalumab + platinum-based chemotherapy – probability and extent of added benefit (multipage table)

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
2	Adult patients with metastatic NSCLC with PD-L1 expression < 50% with no sensitizing EGFR mutations or ALK-positive mutations[c]; first-line treatment[d]	▪ Pembrolizumab in combination with pemetrexed and platinum-containing chemotherapy (only for patients with ECOG-PS 0–1 and non-squamous NSCLC) or ▪ pembrolizumab in combination with carboplatin and either paclitaxel or nab-paclitaxel (only for patients with ECOG-PS 0–1 and squamous NSCLC) or ▪ atezolizumab as monotherapy (only for patients with PD-L1 expression ≥ 10% in tumour-infiltrating immune cells) or ▪ atezolizumab in combination with bevacizumab, paclitaxel, and carboplatin (only for patients with ECOG-PS 0–1 and non-squamous NSCLC) or ▪ atezolizumab in combination with nab-paclitaxel and carboplatin (only for patients with ECOG-PS 0–1 and non-squamous NSCLC) or ▪ **nivolumab in combination with ipilimumab and 2 cycles of platinum-based chemotherapy (only for patients with ECOG-PS 0–1)** or ▪ Carboplatin in combination with a third-generation cytostatic (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed[f]; only for patients with ECOG-PS 2) or ▪ Carboplatin in combination with nab-paclitaxel (only for patients with ECOG-PS 2)	Added benefit not proven[e]

Table 27: Tremelimumab + durvalumab + platinum-based chemotherapy – probability and extent of added benefit (multipage table)

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit

a. Presented is the respective ACT specified by the G-BA. In cases where the G-BA's specification of the ACT allowed the company to select a comparator from several options, the respective choice of the company is printed in **bold**.
b. A sole comparison against a treatment option which represents a comparator therapy for only part of the patient population is usually not sufficient to demonstrate added benefit for the overall population.
c. Patient population without genomic EGFR mutations or ALK-positive mutations, as designated by the G-BA when it determined the ACT. The present benefit assessment uses the wording according to the SPC.
d. For the present therapeutic indication, it is assumed as per G-BA that there is neither an indication for definitive radiochemotherapy nor for definitive local therapy. In addition, it is assumed that molecularly stratified therapy (directed against BRAF, KRAS, G12C, METex14, RET, or ROS1) is not an option for the patients at the time of treatment with tremelimumab in combination with durvalumab and platinum-based chemotherapy.
e. Only patients with an ECOG-PS of 0 or 1 were included in the indirect comparison studies.
f. See Pharmaceutical Directive Annex VI to Section K [3].

ACT: appropriate comparator therapy; ALK: anaplastic lymphoma kinase; BRAF: rapidly accelerated fibrosarcoma – isoform B; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; EGFR: epidermal growth factor receptor; G-BA: Federal Joint Committee; KRAS: Kirsten rat sarcoma viral oncogene homologue; MET: mesenchymal-epithelial transition factor; METex14: met gene exon 14; NSCLC: non-small cell lung cancer; PD-L1: programmed death ligand 1; RET: rearranged during transfection; ROS1: c-ros oncogene 1; SPC: Summary of Product Characteristics

The approach for the derivation of an overall conclusion on added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

I 6 References for English extract

Please see full dossier assessment for full reference list.

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

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