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Durvalumab (small cell lung cancer) –

Benefit assessment according to §35a Social Code Book V[1]

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Durvalumab (kleinzelliges Lungenkarzinom) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 23 December 2020). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

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

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
AESI	adverse events of special interest
BSA	body surface area
BSC	best supportive care
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EORTC	European Organisation for Research and Treatment of Cancer
EQ-5D	European Quality of Life-5 Dimensions
ES-SCLC	extensive-stage small cell lung cancer
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HR	hazard ratio
IPD	individual patient data
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MD	mean difference
MMRM	mixed-effects model with repeated measures
PCI	prophylactic cranial irradiation
PGIC	Patient Global Impression of Change
PRO	patient-reported outcome
PT	Preferred Term
QLQ-C30	Quality of Life Questionnaire-Core 30
QLQ-LC13	Quality of Life Questionnaire-Lung Cancer 13
RCT	randomized controlled trial
RECIST	Response Evaluation Criteria in Solid Tumours
RKI	Robert Koch Institute
SAE	serious adverse event
SAP	statistical analysis plan
SGB	Sozialgesetzbuch (Social Code Book)
SMD	standardized mean difference
SOC	System Organ Class
SPC	Summary of Product Characteristics

Abbreviation	Meaning
TNM	classification of malignant tumours (tumour size, lymph node involvement and metastases)
VAS	visual analogue scale
WHO PS	World Health Organization Performance Status

2 Benefit assessment

2.1 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 the drug durvalumab. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 28 September 2020.

Research question

The aim of the present report is the assessment of the added benefit of durvalumab in combination with etoposide and either carboplatin or cisplatin (hereinafter referred to as "durvalumab in combination with chemotherapy") in comparison with the appropriate comparator therapy (ACT) etoposide with either carboplatin or cisplatin (hereinafter referred to as "chemotherapy") in the first-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC).

The G-BA's specification of the ACT resulted in one research question, which is presented in the following Table 2.

Table 2: Research question of the benefit assessment of durvalumab + chemotherapy[a]

Therapeutic indication[b]	**ACT[c]**
Extensive-stage small cell lung cancer (ES-SCLC)	Cisplatin in combination with etoposide or carboplatin in combination with etoposide

a. Cisplatin in combination with etoposide or carboplatin in combination with etoposide.
b. For the present therapeutic indication, the G-BA assumes patients to have stage IV SCLC (in accordance with IASLC and UICC staging). Furthermore, the G-BA assumes that patients who have responded to previous chemotherapy[a] receive prophylactic whole brain radiation therapy. The administration of a total of at least 4 cycles of etoposide and cisplatin or carboplatin is adequate according to the G-BA.
c. Presentation of the respective ACT specified by the G-BA.

ACT: appropriate comparator therapy; ES-SCLC: extensive-stage small cell lung cancer; G-BA: Federal Joint Committee; IASLC: International Association for the Study of Lung Cancer; UICC: Union for International Cancer Control

The company followed the option specified by the G-BA and chose etoposide combined with either carboplatin or cisplatin as ACT.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) were used for the derivation of the added benefit. This concurs with the inclusion criterion of the company.

Results

One relevant study (CASPIAN) with 2 cohorts (Global and China) was available for the benefit assessment.

Study characteristics

The CASPIAN study is an ongoing, open-label RCT comparing durvalumab in combination with chemotherapy (intervention arm) versus chemotherapy (comparator arm). The study included adult patients with ES-SCLC who had not received prior systemic therapy in the ES-SCLC stage and who were eligible for platinum-based chemotherapy as first-line treatment for ES-SCLC. Patients with a history of radiotherapy to the chest (related to any stage) or planned consolidation chest radiotherapy were excluded. Patients with brain metastases were eligible for study inclusion provided they were either asymptomatic at baseline or previously treated and stable off steroids and anticonvulsants for at least 1 month before start of the study treatment. The general condition of the patients had to concur with an Eastern Cooperative Oncology Group Performance Status (ECOG PS) or a World Health Organization Performance Status (WHO PS) of 0 or 1. Therefore, there are no data for patients with symptomatic brain metastases and for patients with ECOG PS ≥ 2. 268 patients were randomly allocated to treatment with durvalumab in combination with chemotherapy, and 269 patients to treatment with chemotherapy.

In both cohorts, patients in the intervention arm received durvalumab for a total of 4 cycles, each followed by carboplatin or cisplatin. Etoposide was administered in 3 doses on days 1, 2 and 3 of each cycle. From cycle 5 onwards, treatment with durvalumab was continued as monotherapy (maintenance therapy). Patients in the comparator arm received a total of 4 cycles of chemotherapy following an identical regimen as in the intervention arm. In cycles 5 and 6, up to 2 additional cycles of chemotherapy could be administered at the discretion of the investigator. Administration of the drugs was largely in line with the recommendations of the guideline and the requirements of the Summary of Product Characteristics (SPC).

In addition, the patients received therapies within the scope of the permitted concomitant treatment, referred to as best supportive care (BSC) in the clinical study report (CSR), until progression.

Treatment was given until disease progression, unacceptable toxicity, initiation of other tumour therapy, withdrawal of consent, or death. At the discretion of the investigator, treatment could be continued beyond progression if there was still clinical benefit.

Primary outcome of the CASPIAN study was overall survival. Patient-relevant secondary outcomes were recorded in the categories of morbidity (symptoms, health status), health-related quality of life, and side effects.

Cohort in China

According to the company, patients from China and Taiwan were recruited for the purpose of the approval in China. Within this recruitment, 61 patients were randomly assigned to the intervention arm and 62 patients to the comparator arm. According to the study protocol, recruitment took place after completion of the recruitment phase of the global cohort into a separate cohort. The patients were treated in accordance with an identical study protocol and statistical analysis plan (SAP) as the global study population, but the data were analysed separately.

Inclusion of patients with brain metastases only in case of asymptomatic or previously treated brain metastases

10% of the patients in the global cohort and 15.5% of the patients in the cohort in China had brain metastases at baseline. However, only patients with asymptomatic or previously treated brain metastases were included in the CASPIAN study. It remains unclear whether the effects observed in the CASPIAN study can be transferred to the group of patients with symptomatic brain metastases.

Limitations of the study

The analyses of the results of the CASPIAN study were used for the benefit assessment. However, there are limitations; these uncertainties are described below.

- According to the S3 guideline, patients with ES-SCLC should receive 4 to 6 cycles of chemotherapy with etoposide and either carboplatin or cisplatin at the discretion of the treating physician. However, there is no evidence to show that 6 cycles versus 4 cycles of chemotherapy are superior in terms of mortality. In the CASPIAN study, chemotherapy in the intervention arm was limited to a maximum of 4 cycles, in compliance with the SPC of durvalumab. In the comparator arm, up to 2 additional doses of chemotherapy could be administered in cycles 5 and 6 at the discretion of the investigator. Overall, about 50% of the patients in the comparator arm received 6 cycles of chemotherapy. It is not clear from the study documents what criteria were used to select the patients who received 6 cycles of chemotherapy. It is therefore unclear whether a therapy with 6 cycles of chemotherapy was adequate for the patients or whether they were potentially overtreated in the study. It is possible that these patients would have received only 4 to 5 cycles of chemotherapy in the German health care context. The possible overtreatment in the comparator arm may affect the results of all patient-relevant outcomes.
- According to the S3 guideline, patients who have responded to first-line chemotherapy should receive subsequent prophylactic cranial irradiation (PCI). According to the study protocol, PCI was only allowed in the comparator arm if clinically indicated at the discretion of the investigator. In the intervention arm, no PCI was performed according to the study protocol. At 8.2% in the global cohort and 0% in the cohort in China, the proportion of patients who received PCI in the comparator arm of the CASPIAN study was low (in relation to the high proportion of patients without brain metastases at baseline

and the high response rate to chemotherapy). It is not clear from the study documents how many of these patients received PCI following chemotherapy or whether PCI was performed as subsequent therapy. It therefore remains questionable whether PCI was performed in the CASPIAN study in all patients for whom it would have been indicated.

- Consolidation and palliative thoracic radiotherapy (also referred to as "postsurgical thoracic radiotherapy") was disallowed in the CASPIAN study by the prohibition of chest radiotherapy in the study protocol in both arms until progression or initiation of subsequent therapy. In addition, patients with consolidation chest radiation therapy already planned at the beginning of the study were excluded from the study from the outset. According to the S3 guideline, there are indications that consolidation radiotherapy of the primary tumour can prolong survival time for some patients with very good remission of distant metastasis after completion of chemotherapy. Furthermore, the S3 guideline recommends at least considering the therapeutic indication for palliative radiotherapy of the primary tumour in patients with inadequate local tumour control, with chemotherapy-resistant superior vena cava syndrome, impending or existing complete atelectasis, or uncontrollable tumour infiltration into organs adjacent to the lungs. The general exclusion of this concomitant treatment in the CASPIAN study therefore does not seem justified.

Data cut-offs and available analyses

A meta-analysis based on individual patient data was available for the benefit assessment (IPD meta-analysis). The analysis was based on a fixed-effect model. The data cut-off from 27 January 2020 was included for the global cohort, and the data cut-off from 6 January 2020 for the cohort in China.

Risk of bias and certainty of conclusions

The risk of bias across outcomes was rated as low.

The risk of bias was rated as low for the outcome "overall survival", and as high for all other outcomes.

The limitations of the study described above overall led to a reduced certainty of conclusions. On the basis of the effects shown in the CASPIAN study, at most hints, e.g. of an added benefit, can therefore be derived for all outcomes.

Mortality

Overall survival

A statistically significant effect in favour of durvalumab was shown for the outcome "overall survival". This resulted in a hint of an added benefit of durvalumab + chemotherapy in comparison with chemotherapy.

Morbidity and health-related quality of life

There were no relevant group differences for the symptom outcomes, the outcome "health status" and the outcomes of health-related quality of life. This resulted in no hint of an added benefit of durvalumab in combination with chemotherapy in comparison with chemotherapy for any of these outcomes. An added benefit is therefore not proven. No usable data were available for the Patient Global Impression of Change (PGIC) instrument.

Side effects

SAEs

The event time analyses of the meta-analysis showed no statistically significant difference between the treatment arms for the outcome "serious adverse events (SAEs)".

There was an effect modification by the characteristic "brain metastases at baseline" for this outcome. For patients with brain metastases at baseline, there was a hint of lesser harm from durvalumab + chemotherapy in comparison with chemotherapy. For patients without brain metastases at baseline, in contrast, there was no added benefit.

Severe AEs (CTCAE grade ≥ 3) and discontinuation due to AEs

The event time analysis showed no statistically significant difference between the treatment arms for the outcomes "severe adverse events (AEs)" (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3) and "discontinuation due to AEs". This resulted in no hint of greater or lesser harm from durvalumab + chemotherapy in comparison with chemotherapy for each of these outcomes; greater or lesser harm is therefore not proven.

Specific AEs

Immune-related SAEs and severe AEs

There was statistically significant heterogeneity between the global cohort and the cohort in China for the outcome "immune-related SAEs". The event time analysis showed no statistically significant difference between the treatment arms in the global cohort. This resulted in no hint of greater or lesser harm from durvalumab + chemotherapy in comparison with chemotherapy for this outcome in the global cohort; greater or lesser harm is therefore not proven. No effect estimations, no Kaplan-Meier curves, and no p-values were available for immune-related SAEs for the cohort in China, so an assessment of the results was not possible. The use of another statistical test (e.g. non-stratified log-rank test) would allow testing for statistical significance between the treatment arms in the cohort in China. Since there was no statistically significant result in the global cohort, this remains without consequence, however.

The event time analysis showed no statistically significant difference between the treatment arms for the outcome "immune-related severe AEs" (CTCAE grade ≥ 3). There was an effect modification by the characteristic "sex", however. There was no hint of greater or lesser harm from durvalumab + chemotherapy in comparison with chemotherapy for men; greater or lesser harm is therefore not proven. For women, there was no effect estimation and no p-value

available for immune-related severe AEs (CTCAE grade ≥ 3), so an assessment of the results was not possible.

PRO-CTCAE

For the outcome "patient-reported outcome (PRO)-CTCAE", no usable analyses were available for the global cohort. The outcome was not recorded in the cohort in China. This resulted in no hint of an added benefit of durvalumab + chemotherapy in comparison with the ACT; an added benefit is therefore not proven.

Hypertension (PT, AEs [CTCAE grade ≥ 3]), blood and lymphatic system disorders (SOC, AEs [CTCAE grade ≥ 3])

The event time analyses showed a statistically significant difference between the treatment arms to the disadvantage of durvalumab + chemotherapy in comparison with chemotherapy for the outcome "hypertension" (Preferred Term [PT], AEs [CTCAE grade ≥ 3]). This resulted in a hint of greater harm of durvalumab + chemotherapy in comparison with chemotherapy.

The event time analyses showed a statistically significant difference between the treatment arms in favour of durvalumab + chemotherapy in comparison with chemotherapy for the outcome "blood and lymphatic system disorders" (System Organ Class [SOC], AEs [CTCAE grade ≥ 3]). In addition, there was an effect modification by the characteristic "brain metastases at baseline" for this outcome. For patients with brain metastases at baseline, there was a hint of lesser harm from durvalumab + chemotherapy in comparison with chemotherapy. For patients without brain metastases at baseline, in contrast, there was no added benefit.

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

The overall picture shows both positive and negative effects of durvalumab + chemotherapy in comparison with chemotherapy, in each case with the probability "hint".

On the positive side, there was a hint of considerable added benefit for the outcome "overall survival".

For patients with brain metastases at baseline, there was additionally a hint of lesser harm with the extent "considerable" for the outcome "SAEs" in the category of serious/severe side effects,

[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].

and a hint of lesser harm with the extent "major" for the outcome "blood and lymphatic system disorders" (category of serious/severe side effects).

On the side of negative effects, there was a hint of greater harm with the extent "considerable" for the outcome "hypertension" in the category of serious/severe side effects, which did not call into question the positive effect in overall survival, however.

For women, there was also a clear numerical disadvantage in the outcome "immune-related severe AEs" (category of serious/severe side effects). However, no usable effect estimation and no p-value allowing an assessment of statistical significance was available for women. Thus, it cannot be ruled out with certainty that there is greater harm from durvalumab affecting the overall conclusion on the added benefit for women. As a result, the overall extent of the added benefit for women was considered non-quantifiable.

In summary, there is a hint of considerable added benefit of durvalumab + chemotherapy in comparison with the ACT for men with extensive-stage small cell lung cancer. For women with extensive-stage small cell lung cancer, there is a hint of a non-quantifiable, at most considerable added benefit in comparison with the ACT.

Table 3 shows a summary of probability and extent of the added benefit of durvalumab.

Table 3: Durvalumab + chemotherapy[a] – probability and extent of added benefit

Therapeutic indication	**ACT[b]**	**Probability and extent of added benefit**
Extensive-stage small cell lung cancer (ES-SCLC)[c]	Cisplatin in combination with etoposide or carboplatin in combination with etoposide	▪ Men: ▫ hint of considerable added benefit ▪ Women: ▫ Hint of added benefit; extent "non-quantifiable", at most "considerable"
a. Cisplatin in combination with etoposide or carboplatin in combination with etoposide. b. Presentation of the respective ACT specified by the G-BA. c. The CASPIAN study only included patients with an ECOG PS of 0 or 1 and with asymptomatic or previously treated brain metastases. It remains unclear whether the observed effects can be transferred to patients with ECOG PS ≥ 2 or with symptomatic brain metastases. ACT: appropriate comparator therapy; ECOG PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee		

The G-BA decides on the added benefit.

2.2 Research question

The aim of the present report is the assessment of the added benefit of durvalumab in combination with etoposide and either carboplatin or cisplatin (hereinafter referred to as "durvalumab + chemotherapy") in comparison with the ACT etoposide with either carboplatin or cisplatin (hereinafter referred to as "chemotherapy") in the first-line treatment of adult patients with ES-SCLC.

The G-BA's specification of the ACT resulted in one research question, which is presented in the following Table 4.

Table 4: Research question of the benefit assessment of durvalumab + chemotherapy[a]

Therapeutic indication[b]	**ACT[c]**
Extensive-stage small cell lung cancer (ES-SCLC)	Cisplatin in combination with etoposide or carboplatin in combination with etoposide
a. Cisplatin in combination with etoposide or carboplatin in combination with etoposide. b. For the present therapeutic indication, the G-BA assumes patients to have stage IV SCLC (in accordance with IASLC and UICC staging). Furthermore, the G-BA assumes that patients who have responded to previous chemotherapy[a] receive prophylactic whole brain radiation therapy. The administration of a total of at least 4 cycles of etoposide and cisplatin or carboplatin is adequate according to the G-BA. c. Presentation of the respective ACT specified by the G-BA. ACT: appropriate comparator therapy; ES-SCLC: extensive-stage small cell lung cancer; G-BA: Federal Joint Committee; IASLC: International Association for the Study of Lung Cancer; UICC: Union for International Cancer Control	

The company followed the option specified by the G-BA and chose etoposide combined with either carboplatin or cisplatin as ACT.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs were used for the derivation of the added benefit. This concurs with the inclusion criterion of the company.

2.3 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 durvalumab + chemotherapy (status: 9 July 2020)
- bibliographical literature search on durvalumab + chemotherapy (last search on 22 July 2020)
- search in trial registries/trial results databases for studies on durvalumab + chemotherapy (last search on 23 July 2020)
- search on the G-BA website for durvalumab + chemotherapy (last search on 23 July 2020)

To check the completeness of the study pool:

- search in trial registries for studies on durvalumab + chemotherapy (last search on 1 October 2020)

The check did not identify any additional relevant studies.

2.3.1 Studies included

The study listed in the following table was included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: durvalumab + chemotherapy[a] vs. chemotherapy[a]

Study	Study category			Available sources		
	Study for the approval of the drug to be assessed (yes/no)	Sponsored study[b] (yes/no)	Third-party study (yes/no)	CSR (yes/no [citation])	Registry entries[c] (yes/no [citation])	Publication and other sources[d] (yes/no [citation])
D419QC00001 (CASPIAN[e])	Yes	Yes	No	Yes [3-5]	Yes [6-8]	Yes [9-12]

a. Cisplatin in combination with etoposide or carboplatin in combination with etoposide.
b. Study for which the company was sponsor.
c. Citation of the study registry entries and, if available, of the reports on study design and/or results listed in the study registries.
d. Other sources: EPAR.
e. In the following tables, the study is referred to with this abbreviated form.

CSR: clinical study report; EPAR: European Public Assessment Report; RCT: randomized controlled trial; vs.: versus

The CASPIAN study was used for the benefit assessment. The study pool concurs with that of the company.

2.3.2 Study characteristics

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

Table 6: Characteristics of the study included – RCT, direct comparison: durvalumab + chemotherapy[a] vs. chemotherapy[a] (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[b]
CASPIAN	RCT, parallel, open-label	Adults (≥ 18 years[c]) with untreated[d] extensive-stage small cell lung cancer (ES-SCLC), with WHO/ECOG PS 0 or 1	Global cohort[e]: ▪ durvalumab + chemotherapy[a] (N = 268) ▪ chemotherapy[a] (N = 269) ▪ durvalumab + tremelimumab + chemotherapy[a] (N = 268)[f] Cohort in China[e]: ▪ durvalumab + chemotherapy[a] (N = 61) ▪ chemotherapy[a] (N = 62) ▪ durvalumab + tremelimumab + chemotherapy[a] (N = 65)[f]	Screening: 21 days Treatment: ▪ Study medication for 4 cycles of 3 weeks ▪ From cycle 5: ▫ intervention arm: durvalumab monotherapy every 4 weeks ▫ comparator arm: up to 2 additional cycles of chemotherapy[a] at the investigator's discretion ▪ Treatment until disease progression or unacceptable intolerance, withdrawal of consent or until another discontinuation criterion was met ▪ Durvalumab and chemotherapy[a] could be continued beyond progression at the investigator's discretion if there was still clinical benefit. Chemotherapy[a] was limited to 4 cycles in the intervention arm and 6 cycles in the comparator arm. Observation[g]: ▪ outcome-specific, at most until death, withdrawal of consent or end of study[h]	Global cohort: 209 centres in Argentina, Austria, Brazil, Bulgaria, China[i], Czech Republic, France, Germany, Hungary, Israel, Italy, Japan, Netherlands, Poland, Romania, Russia, Slovakia, South Korea, Spain, Taiwan, Turkey, Ukraine and USA 4/2017–ongoing Data cut-offs: 11 March 2019[j] 27 January 2020[k] Cohort in China: 28 centres in China and Taiwan 5/2018–ongoing Data cut-off: 6 January 2020[l]	Primary: overall survival Secondary: symptoms, health status, health-related quality of life, AEs

Table 6: Characteristics of the study included – RCT, direct comparison: durvalumab + chemotherapy[a] vs. chemotherapy[a] (multipage table)

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

a. Cisplatin in combination with etoposide or carboplatin in combination with etoposide.
b. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes only include information on relevant available outcomes for this benefit assessment.
c. In Japan, patients had to be ≥ 20 years old at the time of screening.
d. Patients had to be untreated at the extensive stage.
e. A total of 2 patients were included in both the cohort in China and the global cohort. These patients were assigned to the cohort in China for the meta-analysis.
f. The arm is not relevant for the assessment and is no longer presented in the following tables.
g. Outcome-specific information is provided in Table 8.
h. The end of the study is planned after the last visit of the last patient (including cohort in China).
i. Only at 3 centres in China were patients included in the global cohort.
j. Interim analysis of overall survival (planned after about 318 events).
k. Final analysis of overall survival (planned after about 425 events).
l. Analysis of overall survival (planned after events in about 60% of the patients).

AE: adverse event; ECOG PS: Eastern Cooperative Oncology Group Performance Status; ES-SCLC: extensive-stage small cell lung cancer; N: number of randomized patients; RCT: randomized controlled trial; vs.: versus; WHO: World Health Organization

Table 7: Characteristics of the intervention – RCT, direct comparison: durvalumab + chemotherapy[a] vs. chemotherapy[a] (multipage table)

Study	Intervention	Comparison
CASPIAN	<u>4 cycles of 3 weeks</u> ▪ durvalumab 1500 mg[b] IV on day 1 of a cycle + ▪ etoposide 80–100 mg/m² BSA IV on days 1, 2 and 3 of a cycle + carboplatin, dosage to obtain an AUC: 5-6 mg/mL/min IV on day 1 of a cycle or cisplatin 75–80 mg/m² BSA IV on day 1	<u>4 cycles of 3 weeks</u> ▪ etoposide 80–100 mg/m² BSA IV on days 1, 2 and 3 of a cycle + carboplatin, dosage to obtain an AUC: 5-6 mg/mL/min IV on day 1 of a cycle or cisplatin 75–80 mg/m² BSA IV on day 1 Subsequently, up to 2 additional doses of etoposide + carboplatin/cisplatin (cycles 5 and 6) could be administered at the discretion of the investigator.
	<u>Maintenance therapy</u> from cycle 5 durvalumab monotherapy 1500 mg IV on day 1 of a 4-week cycle	<u>Maintenance therapy</u> none (but see below for permitted concomitant treatment)
	▪ Treatment was given until demonstration of disease progression in accordance with RECIST 1.1, but could be continued at the investigator's discretion if patients derived clinical benefit from the treatment[c]. ▪ Treatment interruptions due to toxicity were possible. Dose adjustments were only allowed for chemotherapy[a]. ▪ If one component of the study medication was discontinued due to toxicity, treatment with the other components could be continued until progression. ▪ Patients could switch between carboplatin and cisplatin at the investigator's discretion	

Table 7: Characteristics of the intervention – RCT, direct comparison: durvalumab + chemotherapy[a] vs. chemotherapy[a] (multipage table)

Study	Intervention	Comparison
	Non-permitted pretreatment ▪ systemic therapy of the ES-SCLC ▪ radiotherapy to the chest (radiotherapy outside the chest for palliative care [e.g. bone metastases] was allowed, but had to be completed before the first dose of study drug) ▪ immunotherapies and systemic immunosuppressive therapies within 14 days before the first dose of study medication (with the exception of systemic glucocorticoids < 10 mg/day prednisone equivalent) ▪ live vaccines within 30 days prior to the first dose of study medication **Permitted concomitant treatment** ▪ prophylactic cranial irradiation at the investigator's discretion **only in the comparator arm** ▪ antiemetics, antibiotics, haematopoietic factors, pain therapy, nutritional support, correction of metabolic disorders, optimized symptom control ▪ hormonal therapy for non-cancer-related diseases (e.g. hormone replacement therapy) **Non-permitted concomitant treatment** ▪ any radiotherapy for cancer treatment (except palliative radiotherapy outside the chest of non-target lesions; e.g. pain therapy for bone metastases) ▪ any concurrent chemotherapy, therapy with an investigational product, biological or hormonal therapy for cancer treatment ▪ live vaccines until 30 days after the last dose of study medication ▪ systemic immunosuppressive therapy in the intervention arm (with the exception of systemic glucocorticoids < 10 mg/day prednisone equivalent) ▪ herbs and natural remedies with possible immunomodulatory effects in the intervention arm	

a. Cisplatin in combination with etoposide or carboplatin in combination with etoposide.
b. Patients with a body weight ≤ 30 kg received durvalumab at a weight-dependent dose of 20 mg/kg.
c. Chemotherapy[a] was limited to 4 cycles in the intervention arm and 6 cycles in the comparator arm.

AUC: area under the curve; BSA: body surface area; ES-SCLC: extensive-stage small cell lung cancer; IV: intravenous; RCT: randomized controlled trial; RECIST: Response Evaluation Criteria in Solid Tumours; vs.: versus

The included CASPIAN study is an ongoing, open-label, 3-arm RCT. Only the comparison of 2 study arms – durvalumab in combination with chemotherapy (hereinafter referred to as "intervention arm") and chemotherapy (hereinafter referred to as "comparator arm") – is relevant for the present assessment. The third study arm, durvalumab + tremelimumab + chemotherapy, is not considered further in this benefit assessment.

The study included adult patients with ES-SCLC who had not received prior systemic therapy in the ES-SCLC stage and who were eligible for platinum-based chemotherapy as first-line treatment for ES-SCLC. Patients with a history of radiotherapy to the chest (related to any stage) or planned consolidation chest radiotherapy were excluded. Patients with brain metastases were only eligible for study inclusion provided their brain metastases were either asymptomatic at baseline or previously treated and stable off steroids and anticonvulsants for at least 1 month before start of the study treatment. Patients with suspected brain metastases at screening had to have a computed tomography or magnetic resonance imaging of the brain prior to study entry,

with magnetic resonance imaging being the preferred method. The general condition of the patients had to concur with an ECOG PS or a WHO PS of 0 or 1. Due to these criteria, there are no data from the CASPIAN study for patients with symptomatic brain metastases and for patients with ECOG PS ≥ 2.

A total of 805 patients were included in the global cohort and assigned to the treatment arms in a 1:1:1 randomization. 268 patients were randomly assigned to the intervention arm and 269 patients to the comparator arm. Randomization was stratified by the planned platinum-based chemotherapy at cycle 1 (cisplatin or carboplatin). The choice of platinum (carboplatin or cisplatin) was made by the investigator during the screening phase. In addition to this global cohort, there was a cohort in China with identical study protocol, which started later and was investigated separately. This cohort is described below.

In both cohorts, patients in the intervention arm received durvalumab for a total of 4 cycles, each followed by carboplatin or cisplatin. Etoposide was administered in 3 doses on days 1, 2 and 3 of each cycle. From cycle 5 onwards, treatment with durvalumab was continued as monotherapy (maintenance therapy). Patients in the comparator arm received a total of 4 cycles of chemotherapy following an identical regimen as in the intervention arm. In cycles 5 and 6, up to 2 additional cycles of chemotherapy could be administered at the discretion of the investigator. The dose of etoposide of 240 to 300 mg/m² body surface area (BSA) per cycle planned according to the study protocol deviates slightly from the recommendations of the S3 guideline, which specifies at least 300 mg/m² BSA etoposide [13]. Apart from this, the use of the drugs in both treatment arms largely corresponds to the recommendations of the guideline and specifications of the SPC [13-17].

In addition, the patients received therapies within the scope of the permitted concomitant treatment (see Table 7), referred to as BSC in the CSR, until progression. With the exception of the limitations listed below (concerning postsurgical thoracic radiotherapy and PCI), the permitted concomitant treatment was considered to be sufficient implementation of best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life (BSC).

Treatment was given until disease progression (determined by Response Evaluation Criteria in Solid Tumours [RECIST] version 1.1), unacceptable toxicity, initiation of other tumour therapy, withdrawal of consent, or death. At the discretion of the investigator, treatment could be continued beyond progression if there was still clinical benefit. Chemotherapy was limited to 4 cycles in the intervention arm and 6 cycles in the comparator arm, however.

Primary outcome of the CASPIAN study was overall survival. Patient-relevant secondary outcomes were recorded in the categories of morbidity, health-related quality of life, and side effects.

The patients underwent outcome-specific observation, at most until death, withdrawal of consent or end of the study. The study will be ended after the last visit of the last patient (including cohort in China).

Subpopulation of the CASPIAN study (cohort in China)

According to the company, 188 patients from China and Taiwan were additionally recruited for the purpose of the approval in China. Within this recruitment, 61 patients were randomly assigned to the intervention arm and 62 patients to the comparator arm. According to the study protocol, recruitment took place after completion of the recruitment phase of the global cohort into a separate cohort. Patients in China and Taiwan who had been enrolled before completion of the recruitment phase of the global cohort were included in the analyses of both the global cohort and the cohort in China. This applied to 2 patients. The patients in the cohort in China were treated in accordance with an identical study protocol and SAP as the global study population, but the data were analysed separately.

Inclusion of patients with brain metastases only in case of asymptomatic or previously treated brain metastases

10.1% of the patients in the global cohort and 15.4% of the patients in the cohort in China had brain metastases at baseline. However, only patients with asymptomatic or previously treated brain metastases were included in the CASPIAN study. At the start of the study, the patients already treated had to be stable off steroids and anticonvulsants for at least 1 month before start of the study treatment. Due to these limitations, patients with brain metastases are underrepresented in the CASPIAN study; no data are available from the CASPIAN study for patients with symptomatic brain metastases. Although therapy with PD-L1 inhibitors is not recommended for uncontrolled symptomatic brain metastases (e.g. with cerebral pressure signs), therapy with PD-L1 inhibitors is not excluded per se for controlled symptomatic brain metastases (e.g. by anticonvulsants) [18].

In summary, it therefore remains unclear whether the effects observed in the CASPIAN study can be transferred to the group of patients with symptomatic brain metastases.

Data cut-offs and available analyses

Two data cut-offs were planned in the global cohort:

- first data cut-off on 11 March 2019: interim analysis of overall survival (planned after about 318 events)
- second data cut-off on 27 January 2020: final analysis of overall survival (planned after about 425 events)

One data cut-off was planned in the cohort in China:

- 6 January 2020: analysis of overall survival (planned after events in about 60% of the patients)

A meta-analysis based on individual patient data was available for the benefit assessment (IPD meta-analysis). The analysis was based on a fixed-effect model. For this purpose, the company used the data cut-off from 27 January 2020 for the global cohort, and the data cut-off from 6 January 2020 for the cohort in China. For the meta-analysis, the company assigned the 2 patients included in the analysis of both cohorts to the cohort in China. The benefit assessment was based on the results of the meta-analysis; the results of the individual cohorts were only considered if there was important heterogeneity between the cohorts (p-value of the interaction test of cohort and treatment < 0.05). However, these heterogeneity tests were not available for the relevant analyses on the outcomes of morbidity and quality of life (see Section 2.4.1). The company also derived the added benefit on the basis of the results of the meta-analysis; this procedure is appropriate.

Limitations of the CASPIAN study

The analyses of the results of the CASPIAN study were used for the benefit assessment. However, there are limitations; these uncertainties are described below.

Administration of up to 6 cycles of chemotherapy possible in the comparator arm

According to the S3 guideline [13], patients with ES-SCLC should receive 4 to 6 cycles of chemotherapy with etoposide and either carboplatin or cisplatin at the discretion of the treating physician. However, there is no evidence to show that 6 cycles versus 4 cycles of chemotherapy are superior in terms of mortality [9,19]. In the CASPIAN study, chemotherapy in the intervention arm was limited to a maximum of 4 cycles. In the comparator arm, up to 2 additional doses of chemotherapy could be administered in cycles 5 and 6 at the discretion of the investigator. Overall, about 55% of the patients in the comparator arm received 6 cycles of chemotherapy [9]. It is not clear from the study documents what criteria were used to select the patients who received 6 cycles of chemotherapy. It is therefore unclear whether a therapy with 6 cycles of chemotherapy was adequate for the patients or whether they were potentially overtreated in the study. It is possible that these patients would have received only 4 to 5 cycles of chemotherapy in the German health care context [9,19,20]. In a study on another immunotherapy in the same therapeutic indication (study IMpower133 on atezolizumab), chemotherapy was also limited to a maximum of 4 cycles in the comparator arm [21,22].

It thus remains unclear whether the included patients in the comparator arm received adequate treatment in accordance with the German health care context. The possible overtreatment in the comparator arm may affect the results of all patient-relevant outcomes. The observed advantages of durvalumab regarding side effects (see Section 2.4.3) must be considered against the background that some patients in the comparator arm were treated with more cycles of chemotherapy than they might have received in Germany. The transferability to the German health care context is therefore not completely guaranteed.

Prophylactic cranial irradiation only allowed in the comparator arm

According to the S3 guideline [13] patients who have responded to first-line chemotherapy should receive subsequent PCI. According to the study protocol, PCI was only allowed in the comparator arm if clinically indicated at the discretion of the investigator. In the intervention arm, no PCI was performed according to the study protocol, where this was justified with the unknown risks of the combination of PCI with immunotherapy. However, in a concurrent study on another immunotherapy in the same therapeutic indication (study IMpower on atezolizumab), the use of PCI was also allowed in the intervention arm during maintenance therapy [21]. At 8.2% in the global cohort and 0% in the cohort in China, the proportion of patients who received PCI in the comparator arm of the CASPIAN study was low (in relation to the high proportion of patients without brain metastases at baseline and the high response rate to chemotherapy). It is not clear from the study documents how many of these patients received PCI following chemotherapy or whether PCI was performed as subsequent therapy.

In summary, it therefore remains questionable whether PCI was performed in the CASPIAN study in all patients for whom it would have been indicated. It cannot be ruled out that some of the patients were not treated adequately. Furthermore, due to the prohibition of PCI in the intervention arm, no data are available on the combined use of PCI and durvalumab.

Chest radiotherapy prohibited in both study arms, only radiotherapy outside the chest for palliative care allowed

Consolidation and palliative thoracic radiotherapy (also referred to as “postsurgical thoracic radiotherapy”) was disallowed in the CASPIAN study by the prohibition of chest radiotherapy in the study protocol in both arms until progression or initiation of subsequent therapy. In addition, patients with consolidation chest radiation therapy already planned at the beginning of the study were excluded from the study from the outset. According to the S3 guideline [13], there are indications that consolidation radiotherapy of the primary tumour can prolong survival time for some patients with very good remission of distant metastasis after completion of chemotherapy. Furthermore, the S3 guideline recommends at least considering the therapeutic indication for palliative radiotherapy of the primary tumour in patients with inadequate local tumour control, with chemotherapy-resistant superior vena cava syndrome, impending or existing complete atelectasis, or uncontrollable tumour infiltration into organs adjacent to the lungs. In contrast to the CASPIAN study, in a study on another immunotherapy in the same therapeutic indication (study IMpower on atezolizumab), palliative thoracic radiotherapy was allowed in both treatment arms [21]. The general exclusion of this concomitant treatment in the CASPIAN study therefore does not seem justified. In this context, the notably higher number of radiotherapies in the thoracic region performed as subsequent therapy in the comparator arm versus the intervention arm is also remarkable (in the global cohort, see Table 11). This might suggest that even before progression (or before initiation of subsequent therapy) this concomitant treatment would have been indicated as postsurgical thoracic radiotherapy, especially in the comparator arm.

In summary, the prohibition of chest radiotherapy in the CASPIAN study can thus be considered as a limitation of the BSC or of the non-drug treatment options.

Summary

Due to the limitations described above, only hints, e.g. of an added benefit, can be derived on the basis of the CASPIAN study (see Section 2.4.2).

Treatment duration and follow-up observation

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

Table 8: Planned duration of follow-up observation – RCT, direct comparison: durvalumab + chemotherapy[a] vs. chemotherapy[a]

Study **Outcome category** **Outcome**	**Planned follow-up observation**
CASPIAN	
Mortality	
Overall survival	▪ Until death or termination of study by the sponsor
Morbidity	▪ After progression until second progression or death (whichever occurred first)
Symptoms (EORTC QLQ-C30 and EORTC QLQ-LC13)	
Health status (EQ-5D VAS and PGIC)	
Health-related quality of life (EORTC QLQ-C30)	
Side effects	
AE outcomes	▪ 90 days after the last dose of the study medication or until initiation of a subsequent antineoplastic treatment (whichever occurred first) ▪ 90 days after the last dose of the study medication[b]
PRO-CTCAE	▪ After progression until second progression or death (whichever occurred first)

a. Cisplatin in combination with etoposide or carboplatin in combination with etoposide.
b. Planned according to study protocol to assess long-term side effects, but no results are available in the dossier.

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 Dimension; PGIC: Patient Global Impression of Change; PRO: patient-reported outcome; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-LC13: Quality of Life Questionnaire-Lung Cancer 13; RCT: randomized controlled trial; VAS: visual analogue scale; vs.: versus

The observation periods for the side effect outcomes are systematically shortened because they were only recorded for the period of treatment with the study medication (plus 90 days or until initiation of a subsequent antineoplastic treatment, whichever occurred first). To be able to draw a reliable conclusion on the total study period or the time until death of the patients, it would

be necessary, however, to record these outcomes over the total period of time, as was the case for survival. The effects of the systematically shortened observation periods for the present benefit assessment are addressed in Section 2.4.2.

According to the study protocol, additional analyses of the side effect outcomes were planned, which were to include all AEs up to 90 days after discontinuation of the study medication (regardless of the initiation of a subsequent therapy). However, the company did not present these analyses in the dossier.

For morbidity and health-related quality of life, it was planned to record data also after progression (until the second progression or death; whichever occurred first). However, data recorded after progression were only included in the responder analyses for the time to deterioration. However, the analyses submitted by the company using a mixed-effects model with repeated measures (MMRM) only take into account data up to progression or month 12 (whichever occurred earlier).

Characteristics of the study population

Table 9 shows the characteristics of the patients in the study included.

Table 9: Characteristics of the study populations – RCT, direct comparison: durvalumab + chemotherapy[a] vs. chemotherapy[a] (multipage table)

Study	CASPIAN – Global		CASPIAN – China	
Characteristic Category	Durvalumab + chemotherapy[a]	Chemotherapy[a]	Durvalumab + chemotherapy[a]	Chemotherapy[a]
	N[b] = 268	N[b] = 269	N[b] = 61	N[b] = 62
Age [years]				
Mean (SD)	62 (8)	62 (8)	61 (8)	61 (9)
Sex [F/M], %	29/71	32/68	15/85	16/84
Family origin, n (%)				
White	229 (85)	221 (82)	0 (0)	0 (0)
Black or African American	2 (1)	3 (1)	0 (0)	0 (0)
Asian	36 (13)	42 (16)	61 (100)	62 (100)
Other or missing	1 (< 1)	3 (1)[c]	0 (0)	0 (0)
Geographical region, n (%)				
Europe	198 (75[c])[d]	205 (77[c])[d]	0 (0)	0 (0)
Asia	35 (13[c])[d]	39 (15[c])[d]	61 (100)	62 (100)
North and South America	32 (12[c])[d]	22 (8[c])[d]	0 (0)	0 (0)
Body weight [kg]				
Mean (SD)	73.6 (15.9)	72.6 (15.1)	63.6 (11.1)	64.1 (11.4)
BMI [kg/m²]				
Mean (SD)	25.6 (4.7)	25.6 (4.8)	23.0 (3.4)	23.0 (3.2)
Smoking status, n (%)				
Active	120 (45)	126 (47)	13 (21)	11 (18)
Former	126 (47)	128 (48)	40 (66)	34 (55)
Never	22 (8)	15 (6)	8 (13)	17 (27)
ECOG PS, n (%)				
0	99 (37)	90 (33)	15 (25)	15 (24)
1	169 (63)	179 (67)	46 (75)	47 (76)
AJCC staging[e, f], n (%)				
III[g]	1 (< 1)	0 (0)	0 (0)	0 (0)
IIIA	5 (2)	3 (1)	1 (2)	0 (0)
IIIB	22 (8)	21 (8)	4 (7)	4 (6)
IV	240 (90)	245 (91)	56 (92)	58 (94)
Histology[e], n (%)				
Small cell carcinoma (neuroendocrine)	39 (15)	48 (18)	1 (2)	3 (5)
Small cell carcinoma (combined)[h]	229 (85)	220 (82)	60 (98)	59 (95)
Other	0 (0)	1 (< 1)	0 (0)	0 (0)
Brain metastases, n (%)	28 (10)	27 (10)	9 (15)	10 (16)
Liver metastases, n (%)	108 (40)	104 (39)	17 (28)	26 (42)
Prior cytotoxic chemotherapy[i], n (%)	3 (1)	3 (1)	0 (0)	0 (0)

Table 9: Characteristics of the study populations – RCT, direct comparison: durvalumab + chemotherapy[a] vs. chemotherapy[a] (multipage table)

Study Characteristic Category	CASPIAN – Global		CASPIAN – China	
	Durvalumab + chemotherapy[a]	Chemotherapy[a]	Durvalumab + chemotherapy[a]	Chemotherapy[a]
	N[b] = 268	N[b] = 269	N[b] = 61	N[b] = 62
Prior radiotherapy[i], n (%)				
Adjuvant	0 (0)	1 (< 1)	0 (0)	0 (0)
Palliative	8 (3)	8 (3)	0 (0)	0 (0)
Definitive	0 (0)	1 (< 1)	0 (0)	0 (0)
Treatment discontinuation, n (%)	Durvalumab: 233 (88) Chemotherapy[a]: 42 (16)	Chemotherapy[a]: 76 (29)	Durvalumab: 52 (85) Chemotherapy[a]: 8 (13)	Chemotherapy[a]: 20 (32)
Study discontinuation, n (%)	5 (2)[c]	13 (5)[c]	0 (0)	2 (3)[c]

a. Cisplatin in combination with etoposide or carboplatin in combination with etoposide.
b. Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
c. Institute's calculation.
d. Percentages based on the number of patients who received at least one dose of the study medication (safety population: durvalumab + chemotherapy[a] N = 265; chemotherapy[a] N = 266).
e. Histology and AJCC staging at diagnosis.
f. AJCC staging: stage IV combines stage IV/stage IVA/stage IVB from the eCRF.
g. For one patient with stage III, the TNM classification suggests stage IIIb.
h. The category of small cell carcinoma (combined) contains the categories of SCLC, SCC, SCC oat cell type/intermediate type/combined oat cell type from the eCRF.
i. Prior therapies can also cover diseases other than lung cancer.

AJCC: American Joint Committee on Cancer; BMI: body mass index; ECOG PS: Eastern Cooperative Oncology Group Performance Status; eCRF: electronic case report form; F: female; M: male; n: number of patients in the category; N: number of randomized patients; RCT: randomized controlled trial; SCC: small cell carcinoma; SCLC: small cell lung cancer; SD: standard deviation; TNM: classification of malignant tumours (tumour size, lymph node involvement and metastases); vs.: versus

The patient characteristics of the 2 cohorts (Global and China) were each largely balanced between the treatment arms. In the cohort in China, fewer patients in the intervention arm had never smoked (13% versus 27%) and fewer patients had liver metastases (28% versus 42%).

The mean age of the patients in the global cohort included in the CASPIAN study was 62 years, and most of them were male. More than 80% where white, the proportion of patients with Asian family origin was about 15%. About 2 thirds had an ECOG PS of 1, the ECOG PS of the other patients was 0. About 90% had no brain metastases. Only few patients had already received radiotherapy or chemotherapy before the start of the study.

By definition, the subpopulation of the cohort in China differed from the global cohort primarily in family origin. Whereas the cohort in China only included Asian patients, their proportion in the global cohort was only about 15%. Further differences were found in the distribution of sex, ECOG PS, histology, and smoking status. The biggest difference concerns smoking status.

Whereas 20% of the patients in the cohort in China were never smokers, this proportion in the global cohort was 7%.

Table 10 shows the mean/median treatment durations of the patients and the median observation periods for individual outcomes.

Table 10: Information on the course of the study – RCT, direct comparison: durvalumab + chemotherapy[a] vs. chemotherapy[a] (multipage table)

Study **Duration of the study phase** **Outcome category**	**Durvalumab + chemotherapy[a]**	**Chemotherapy[a]**
CASPIAN – Global	N[b] = 268	N[b] = 269
Treatment duration [months][c]		
Median [min; max]	6.4 [< 0.1; 32.0]	4.4 [< 0.1; 6.2]
Mean (SD)	8.9 (7.4)	3.8 (1.3)
Observation period [months][c]		
Overall survival		
Median [Q1; Q3]	12.7 [7.0; 20.8]	10.2 [6.6; 17.1]
Mean (SD)	ND	ND
Morbidity		
Symptoms (EORTC QLQ-C30)		
Median [min; max]	7.3 [< 0.1; 31.3]	4.8 [< 0.1; 28.6]
Mean (SD)	ND	ND
Symptoms (EORTC QLQ-LC13)		
Median [min; max]	7.4 [< 0.1; 31.3]	4.8 [< 0.1; 28.6]
Mean (SD)	ND	ND
Health status (EQ-5D VAS)		
Median [min; max]	7.5 [< 0.1; 31.3]	4.9 [< 0.1; 28.6]
Mean (SD)	ND	ND
Health status (PGIC)		
Median [min; max]	7.5 [0.7; 31.3]	4.9 [0.5; 28.6]
Mean (SD)	ND	ND
Health-related quality of life (EORTC QLQ-C30)		
Median [min; max]	7.3 [< 0.1; 31.3]	4.8 [< 0.1; 28.6]
Mean (SD)	ND	ND
Side effects		
AE outcomes		
Median [min; max]	6.9 [< 0.1; 31.9]	6.0 [< 0.1; 8.3]
Mean (SD)	ND	ND
PRO-CTCAE		
Median [min; max]	ND	ND
Mean (SD)	ND	ND

Table 10: Information on the course of the study – RCT, direct comparison: durvalumab + chemotherapy[a] vs. chemotherapy[a] (multipage table)

Study **Duration of the study phase** **Outcome category**	**Durvalumab + chemotherapy[a]**	**Chemotherapy[a]**
CASPIAN – China	N[b] = 61	N[b] = 62
Treatment duration [months][c]		
Median [min; max]	5.5 [0.4; 17.6]	4.4 [0.4; 5.8]
Mean (SD)	6.7 (4.1)	3.7 (1.4)
Observation period [months][c]		
Overall survival		
Median [Q1; Q3]	14.16 [8.51; 16.53]	10.8 [6.9; 14.5]
Mean (SD)	ND	ND
Morbidity		
Symptoms (EORTC QLQ-C30)		
Median [min; max]	6.1 [< 0.1; 17.4]	5.7 [< 0.1; 15.7]
Mean (SD)	ND	ND
Symptoms (EORTC QLQ-LC13)		
Median [min; max]	6.1 [< 0.1; 17.4]	5.7 [< 0.1; 15.7]
Mean (SD)	ND	ND
Health status (EQ-5D VAS)		
Median [min; max]	6.1 [< 0.1; 17.4]	5.7 [< 0.1; 15.7]
Mean (SD)	ND	ND
Health status (PGIC)		
Median [min; max]	6.3 [0.8; 17.4]	5.8 [0.7; 15.7]
Mean (SD)	ND	ND
Health-related quality of life (EORTC QLQ-C30)		
Median [min; max]	6.1 [< 0.1; 17.4]	5.7 [< 0.1; 15.7]
Mean (SD)	ND	ND
Side effects		
AE outcomes		
Median [min; max]	5.8 [0.4; 17.6]	5.3 [0.4; 7.4]
Mean (SD)	ND	ND
PRO-CTCAE		
Median [min; max]	ND	ND
Mean (SD)	ND	ND

a. Cisplatin in combination with etoposide or carboplatin in combination with etoposide.
b. Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
c. Institute's calculation from weeks or days into months.

CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: European Quality of Life-5 Dimensions; max: maximum; min: minimum; N: number of randomized patients; ND: no data; PGIC: Patient Global Impression of Change; PRO: patient-reported outcome; Q1: first quartile; Q3: third quartile; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-LC13: Quality of Life Questionnaire-Lung Cancer 13; RCT: randomized controlled trial; SD: standard deviation; VAS: visual analogue scale; vs.: versus

The median duration of treatment in the global cohort was 2 months longer in the intervention arm than in the comparator arm, and the difference was 1.1 months in the cohort in China. This is particular due to the fact that, in the intervention arm, continued treatment with durvalumab (maintenance therapy) was planned until the onset of disease progression, the occurrence of unacceptable intolerances, or at most until the end of the study, whereas patients in the comparator arm could be treated with chemotherapy for a maximum of 6 cycles (see Table 7).

The median observation period for the outcomes "overall survival" and "morbidity" is comparable between both study arms and the cohorts. For AEs, follow-up observation was only until 90 days after the last dose of study medication or until initiation of subsequent therapy (see Table 8). In the intervention arm, the study medication could be continued as durvalumab maintenance therapy after completion of chemotherapy, whereas in the comparator arm, the study medication could only be used for a maximum of 6 cycles of 21 days, and no subsequent maintenance therapy was given until progression. The differences in the treatment duration resulted in large differences in the observation periods for the side effects in individual patients. See Section 2.4.2 for the effects on the outcome-specific risk of bias.

Subsequent therapies

Switching from the comparator to the intervention arm after disease progression was not allowed. Module 4 A described that PCI in the intervention arm was also prohibited as a subsequent therapy; apart from that, there were no restrictions in the study documents regarding treatment after the end of the study medication. The proportion of patients receiving subsequent therapy was balanced between the treatment arms in both cohorts. The most frequent subsequent therapy given to the patients was cytotoxic chemotherapy. The proportion of chemotherapy and immunotherapy was comparable between the treatment arms in the global cohort. In the cohort in China, more patients in the intervention arm received cytotoxic chemotherapy as subsequent therapy (60.7% versus 43.3%).

In the global cohort, more patients in the comparator arm received thoracic radiotherapy as subsequent therapy (7.5% versus 17.5%). PCI was only performed in the comparator arm (8.2%). In the cohort in China, the ratio of thoracic radiotherapy was balanced between comparator arm and intervention arm; PCI was not performed in either treatment arm.

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

Table 11: Information on subsequent antineoplastic therapies – RCT, direct comparison: durvalumab + chemotherapy[a] vs. chemotherapy[a] (multipage table)

Study **Regimen** **Therapy**	**Patients with subsequent therapy n (%)**	
	Durvalumab + chemotherapy[a]	**Chemotherapy[a]**
CASPIAN – Global	N = 268	N = 269
Total	123 (45.9)	125 (46.5)
Cytotoxic chemotherapy	120 (44.8)	118 (43.9)
Single regimen	64 (23.9)	72 (26.8)
Platinum doublet	59 (22.0)	50 (18.6)
Other combination	30 (11.2)	31 (11.5)
Immunotherapy	6 (2.2)	17 (6.3)
Single IT regimen	1 (0.4)	5 (1.9)
IT + IT combination	2 (0.7)	3 (1.1)
IT + chemotherapy	1 (0.4)	3 (1.1)
Investigational preparation	3 (1.1)	7 (2.6)
Other	4 (1.5)	5 (1.9)
Radiotherapy	79 (29.5)	112 (41.6)
Brain	55 (20.5)	57 (21.2)
Thoracic region	20 (7.5)	47 (17.5)
Bone	15 (5.6)	11 (4.1)
PCI[b]	–	22 (8.2)
Other areas	7 (2.6)	3 (1.1)
Line of treatment		
Second line	122 (45.5)	125 (46.5)
Third line	51 (19.0)	49 (18.2)
> third line	16 (6.0)	13 (4.8)
CASPIAN – China	N = 61	N = 62
Total	40 (65.6)	40 (64.5)
Cytotoxic chemotherapy	37 (60.7)	27 (43.5)
Single regimen	18 (29.5)	14 (22.6)
Platinum doublet	17 (27.9)	12 (19.4)
Other combination	6 (9.8)	4 (6.5)
Immunotherapy	0 (0)	5 (8.1)
Single IT regimen	0 (0)	1 (1.6)
IT + chemotherapy	0 (0)	4 (6.5)
Other	6 (9.8)	15 (24.2)
TCM/herbal agents	3 (4.9)	4 (6.5)
Tyrosine kinase inhibitor	3 (4.9)	10 (16.1)
Other antineoplastic drugs	0 (0)	2 (3.2)

Table 11: Information on subsequent antineoplastic therapies – RCT, direct comparison: durvalumab + chemotherapy[a] vs. chemotherapy[a] (multipage table)

Study Regimen Therapy	Patients with subsequent therapy n (%)	
	Durvalumab + chemotherapy[a]	Chemotherapy[a]
Radiotherapy	17 (27.9)	17 (27.4)
Brain	10 (16.4)	7 (11.3)
Thoracic region	9 (14.8)	10 (16.1)
Bone	1 (1.6)	2 (3.2)
PCI[b]	0 (0)	0 (0)
Other areas	1 (1.6)	2 (3.2)
Line of treatment		
Second line	39 (63.9)	37 (59.7)
Third line	11 (18.0)	10 (16.1)
> third line	2 (3.3)	3 (4.8)
Not applicable[c]	4 (6.6)	3 (4.8)

a. Cisplatin in combination with etoposide or carboplatin in combination with etoposide.
b. PCI was only allowed in the chemotherapy arm; it is unclear which data on PCI from the comparator arm were included in the list of subsequent therapies, including whether data after completion of chemotherapy that occurred before progression were also included. The CSR for the global cohort also contains data on concomitant treatment with PCI after the end of chemotherapy, according to which 2 patients in the intervention arm received PCI, and no patient in the comparator arm.
c. Non-applicable entries are limited to drugs without a recognized line of treatment, for example traditional herbal drugs.

CSR: clinical study report; IT: immunotherapy; n: number of patients with subsequent therapy; N: number of analysed patients; PCI: prophylactic cranial irradiation; RCT: randomized controlled trial; TCM: traditional Chinese medicine; vs.: versus

Risk of bias across outcomes (study level)

Table 12 shows the risk of bias across outcomes (risk of bias at study level).

Table 12: Risk of bias across outcomes (study level) – RCT, direct comparison: durvalumab + chemotherapy[a] vs. chemotherapy[a]

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

a. Cisplatin in combination with etoposide or carboplatin in combination with etoposide.

RCT: randomized controlled trial; vs.: versus

The risk of bias across outcomes was rated as low for both cohorts. This concurs with the company's assessment.

Limitations resulting from the open-label study design are described in Section 2.4 with the outcome-specific risk of bias.

Transferability of the study results to the German health care context

Referring to registry data from the Robert Koch Institute (RKI) and the Association of German Tumour Centres [23-25], the company pointed out that the patient characteristics of the study population in the CASPIAN study largely reflect the situation in the German population with regard to family origin, the proportion of men and smoking status. According to the company, the median age of the included patients was slightly lower than in the German patient population, but comparable to the median age in similar clinical studies on small cell lung cancer [26,27]. The majority of patients were in stage IV of the disease according to the TNM classification of malignant tumours (tumour size, lymph node involvement and metastases). From the point of view of the company, the treatment in both study arms is in line with the treatment standard in the present therapeutic area. Almost all patients received the study medication as first-line therapy. The majority of the patients received carboplatin instead of cisplatin as part of their chemotherapy due to better tolerability [13,28].

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

2.4 Results on added benefit

2.4.1 Outcomes included

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

- Mortality
  - overall survival
- Morbidity
  - symptoms measured with the symptom scales of the instruments European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30) and Quality of Life Questionnaire-Lung Cancer 13 (QLQ-LC13)
  - health status measured with the European Quality of Life-5 Dimensions (EQ-5D) visual analogue scale (VAS)
  - health status measured with the PGIC
- Health-related quality of life
  - measured with the EORTC QLQ-C30 functional scales

- Side effects
  - SAEs
  - severe AEs (CTCAE grade ≥ 3)
  - discontinuation due to AEs
  - immune-related SAEs and severe AEs (CTCAE grade ≥ 3)
  - PRO-CTCAE
  - further specific AEs, if any

The choice of patient-relevant outcomes deviates from that of the company, which used further outcomes in the dossier (Module 4 A).

Table 13 shows for which outcomes data were available in the study included.

Table 13: Matrix of outcomes – RCT, direct comparison: durvalumab + chemotherapy[a] vs. chemotherapy[a]

Study	Outcomes												
	Overall survival	**Symptoms (EORTC QLQ-C30)**	**Symptoms (EORTC QLQ-LC13)**	**Health status (EQ-5D VAS)**	**Health status (PGIC)**	**Health-related quality of life (EORTC QLQ-C30)**	**SAEs**	**Severe AEs[b]**	**Discontinuation due to AEs**	**Immune-related SAEs[c]**	**Immune-related severe AEs[b, c]**	**PRO-CTCAE**	**Further specific AEs[d]**
CASPIAN – Global	Yes	Yes	Yes	Yes	No[e]	Yes	Yes	Yes	Yes	Yes	Yes	No[e]	Yes
CASPIAN – China	Yes	Yes	Yes	Yes	No[e]	Yes	Yes	Yes	Yes	Yes	Yes	No[f]	Yes

a. Cisplatin in combination with etoposide or carboplatin in combination with etoposide.
b. Operationalized as CTCAE grade ≥ 3.
c. The operationalization of AEs of special interest is used in each case.
d. The following events are considered (MedDRA coding): hypertension (PT, severe AEs [CTCAE grade ≥ 3]), blood and lymphatic system disorders (SOC, severe AEs [CTCAE grade ≥ 3]).
e. No usable data available; see Section 2.4.1 for reasons.
f. Outcome not recorded.

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; MedDRA: Medical Dictionary for Regulatory Activities; PGIC: Patient Global Impression of Change; PRO: patient-reported outcome; PT: Preferred Term; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-LC13: Quality of Life Questionnaire-Lung Cancer 13; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale; vs.: versus

Analyses presented in the dossier on the outcome categories of morbidity and health-related quality of life

Event time analyses on the instruments EORTC QLQ-C30, QLQ-LC13 and EQ-5D VAS

In its dossier, the company presented analyses for the outcomes "morbidity" and "health-related quality of life" for the time to first deterioration by 10 points (EORTC QLQ-C30 and QLQ-LC13) and by 7 and 10 points (EQ-5D VAS).

These were not used for the dossier assessment, as the company only provided data for the time to first deterioration up to cycle 6 (about 4.2 months). It justified this with the fact that the response rates to the questionnaires from cycle 7 onwards were below 70% (according to the calculations of the company).

In principle, the benefit assessment requires analyses that take into account all data recorded, if possible. The fact that, in the event time analyses, the company only included part of the available data in the analysis is not appropriate. The Goldman 2020 publication [10] presents event time analyses for the time to first deterioration by 10 points for the entire documentation period, but only based on an earlier data cut-off (11 March 2019). In addition, these analyses refer exclusively to the global cohort and therefore do not cover the entire study population relevant for the benefit assessment.

The benefit assessment would therefore require analyses of the time to first deterioration that take into account all recorded data with a response criterion of 15% [1,29] of the scale range.

In summary, the event time analyses presented in the dossier as well as in the publication by Goldman 2020 [10] were not usable for the benefit assessment and were not used because relevant data were not taken into account.

MMRM analyses on the instruments EORTC QLQ-C30, QLQ-LC13 and EQ-5D VAS

As supplementary information, the company presented MMRM analyses for the EORTC QLQ-C30 and QLQ-LC13 and the EQ-5D VAS in Module 4 A (Appendix 4 G). The CASPIAN study prespecified analyses to provide results for the mean change in symptoms from baseline to progression or month 12 (whichever occurred first). However, the analyses presented by the company in the dossier cover a period of 15 cycles in the course of the study, which corresponds to about 13 months without taking dose delays into account. The company did not provide any justification for this. The SAP also specified that documentation times with more than 75% of missing values (according to the calculation of the company) were excluded from the analysis; this corresponds to the information provided in Appendix 4 G.

As described in Table 8, the above instruments were followed up even until the second progression or death, whichever occurred earlier. In principle, analyses that take into account all recorded data are desirable for the assessment of the data on morbidity and health-related quality of life. In the present data situation, however, the analysis presented by the company (up to progression or up to month 12, whichever occurred earlier) was used, as it can be

estimated that an analysis with all recorded data (i.e. with the recordings starting in cycle 15) will not result in a relevant change of the observed results.

Lack of information on the heterogeneity of the results between the cohorts (heterogeneity tests) as well as subgroup analyses

The dossier provided no heterogeneity tests for the factor "cohort" for the MMRM analyses (EORTC QLQ-C30 and QLQ-LC13 and EQ-5D VAS). In addition, subgroup analyses are missing for these analyses.

Notes on the PRO-CTCAE instrument

Available analyses

According to the study protocol, recording of the PRO-CTCAE was planned in the CASPIAN study. The company selected 11 symptomatic AEs from the PRO-CTCAE system. The PRO-CTCAE was only recorded in countries where a translation of the questionnaire into the national language was available. Therefore, the CSR contained only analyses for 70 (intervention arm) and 65 (comparison arm) patients from the global cohort. Furthermore, the CSR provided only a descriptive presentation of the results (proportion of patients with AEs, partly subdivided according to severity). The company did not present these results in Module 4 A, and only mentioned the recording of the PRO-CTCAE in the Appendix.

General assessment of the PRO CTCAE system

The PRO-CTCAE system is a validated system for recording patient-reported symptomatic AEs [30-32]. According to Basch [30], in contrast to "laboratory-based events" (e.g. neutropenia) and "observable/measurable events" (e.g. retinal tear), symptomatic AEs (e.g. nausea) are suitable for the recording as PROs. The system comprises a total of 78 symptomatic AEs of the CTCAE system. Each symptomatic AE is assessed by 1 to 3 attributes (5 possible attributes in total [frequency, severity, interference with daily activities, presence of AE and amount]) so that the PRO-CTCAE consists of a total of 124 questions (items). The developers suggest that, depending on the therapeutic indication and the type of therapy, the symptoms relevant to the respective study situation should be selected a priori from the 78 symptoms when planning the study. The current version (Item Library Version 1.0 [33]) of the PRO-CTCAE additionally asks whether the patient has any other symptoms that he or she would like to name (if so, the severity of each symptom mentioned is requested). Moreover, there is currently no established procedure for the methods of analysis.

Overall, the PRO-CTCAE system is a valuable addition to the common recording and analysis of AEs and is generally included as a source of patient-relevant outcomes in benefit assessments. To exclude selective reporting, the choice of AEs should be prespecified in the study protocol. In addition, the choice should be comprehensible, e.g. by containing a recording of potential AEs of the drugs in the intervention and the control arm that is as complete as possible. Approaches to how a choice can be done are described in Tolstrup [34] and Taarnhoj

[35]. Analyses should also be determined a priori. First suggestions for possible methods of analysis can be found in the literature [36].

Assessment of the use and analysis of the PRO-CTCAE in the CASPIAN study

There is no detailed rationale in the study protocol (or CSR) for the choice of the 11 symptomatic AEs used from the PRO-CTCAE system. The company only described that AEs that were considered to be relevant to the study, the type of cancer and the cancer treatment were selected. The following AEs were prespecified in the study protocol:

- rash
- hand-foot syndrome (a rash of the hands or feet that can make the skin burn, peel, redden or hurt)
- itching
- swollen arms or legs
- abdominal pain
- numbness or tingling in the hands or feet
- dizziness
- mouth or throat sores
- dry mouth
- chills
- pain, swelling or redness at injection site from an infusion or syringe

The descriptive analyses of these AEs available in the CSR are not suitable for assessing the added benefit of durvalumab in combination with chemotherapy in comparison with the ACT. In order to assess the results of this outcome, analyses are needed that adequately take into account the different observation periods.

Analyses on health status (PGIC) additionally presented

In the dossier, the company submitted the following additional responder analyses for the PGIC at the time of analysis cycle 6 day 1 (for the global cohort and meta-analysis) and at the time of analysis cycle 7 day 1 (for the Chinese cohort):

- proportion of patients with improvement: answer option 1 or 2 (very much better, much better)
- proportion of patients with no change: answer option 3 or 4 or 5 (a little better, no change, a little worse)
- proportion of patients with deterioration: answer option 6 or 7 (much worse, very much worse)

The response criteria prespecified by the company in the SAP on the proportion of patients with improvement or deterioration are meaningful in terms of content. The company provided an effect estimation for the proportion of patients with improvement. For the analysis on deterioration, however, it only presented the proportion of patients with deterioration per study arm at the time of analysis chosen by the company. Due to the progressive course of the disease expected in the present therapeutic indication, an analysis of the deterioration of the health status is primarily relevant for the present benefit assessment, as the primary treatment goal is to delay the progression of the disease. An isolated consideration of the improvement is therefore not appropriate.

In addition, the consideration of a single documentation time carried out by the company is not considered to be meaningful. It is instead desirable for the benefit assessment that all recorded data are included in the analysis. A conceivable option for the PGIC would be a responder analysis of the time to deterioration, for example.

In summary, the analyses on the PGIC presented in the dossier are not usable and are therefore not presented in the benefit assessment.

2.4.2 Risk of bias

Table 14 describes the risk of bias for the results of the relevant outcomes.

Table 14: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: durvalumab + chemotherapy[a] vs. chemotherapy[a]

Study	Study level	Outcomes												
		Overall survival	Symptoms (EORTC QLQ-C30)	Symptoms (EORTC QLQ-LC13)	Health status (EQ-5D VAS)	Health status (PGIC)	Health-related quality of life (EORTC QLQ-C30)	SAEs	Severe AEs[b]	Discontinuation due to AEs	Immune-related SAEs[c]	Immune-related severe AEs[b, c]	PRO-CTCAE	Further specific AEs[d]
CASPIAN – Global	L	L	H[e, f]	H[e, f]	H[e, f]	–[g]	H[e, f]	H[h]	H[h]	H[h]	H[h]	H[h]	–[g]	H[h]
CASPIAN – China	L	L	H[e, f]	H[e, f]	H[e, f]	–[g]	H[e, f]	H[h]	H[h]	H[h]	H[h]	H[h]	–[i]	H[h]

a. Cisplatin in combination with etoposide or carboplatin in combination with etoposide.
b. Operationalized as CTCAE grade ≥ 3.
c. The operationalization of AEs of special interest is used in each case.
d. The following events are considered (MedDRA coding): hypertension (PT, severe AEs [CTCAE grade ≥ 3]), blood and lymphatic system disorders (SOC, severe AEs [CTCAE grade ≥ 3]).
e. Lack of blinding in subjective recording of outcomes.
f. Strong decrease and large differences in response rates; discrepancies between Module 4 A and Module 4 A Appendix 4-G.
g. No usable data available; see Section 2.4.1 for reasons.
h. Large difference in observation period between the treatment arms; potentially informative censorings.
i. Outcome not recorded.

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; MedDRA: Medical Dictionary for Regulatory Activities; PGIC: Patient Global Impression of Change; PRO: patient-reported outcome; PT: Preferred Term; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-LC13: Quality of Life Questionnaire-Lung Cancer 13; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale; vs.: versus

The risk of bias for the results of the outcome "overall survival" was rated as low. This concurs with the company's assessment.

Due to the increasingly high proportion of missing values, which differ between the treatment arms, and the open-label study design in subjective recording of outcomes, the risk of bias for the results of the outcomes "symptoms" (symptom scales of the EORTC QLQ-C30 and the EORTC-QLQ-LC13), "health status" (EQ-5D VAS), and "health-related quality of life" (functional scales of the EORTC QLQ-C30) was rated as high. The company also rated the risk of bias as high, but only took the open-label study design into account in the assessment. In addition, there was discrepant information on the response rates for this outcomes in Module 4 A (Section 4.3.1.3.1.5) and Module 4 A Appendix 4-G. Furthermore, values from cycle 1 (values before the first dose of study medication) were used as baseline values if no values from the start of the study were available (as planned in the SAP).

The risk of bias of the results of each of the following outcomes was rated as high: SAEs, severe AEs (CTCAE grade ≥ 3), immune-related SAEs, immune-related severe AEs (CTCAE grade ≥ 3); hypertension (PT, AEs [CTCAE grade ≥ 3]), and blood and lymphatic system disorders (SOC, AEs [CTCAE grade ≥ 3]). Side effect outcomes were only recorded for the period of treatment with the study medication (plus 90 days or until initiation of a subsequent antineoplastic treatment, whichever occurred first). Since the study medication in the intervention arm (i.e. primarily durvalumab maintenance therapy) could be given until disease progression, whereas the study medication in the comparator arm could only be given for a maximum of 6 cycles of 21 days, there are marked differences in the observation periods of the individual patients with potentially informative censoring for all outcomes mentioned.

The assessment deviates from that of the company, which derived a low risk of bias for the outcomes on SAEs, severe AEs (CTCAE grade ≥ 3), immune-related SAEs and immune-related severe AEs (CTCAE grade ≥ 3).

The risk of bias of the results of the outcome "discontinuation due to AEs" was rated as high due to the lack of blinding in subjective recording of outcomes. This concurs with the company's assessment.

Certainty of conclusions

The 2 cohorts included (Global and China) were considered as one study because of the comparable time of study start and overlapping patient populations. At most an indication, e.g. of an added benefit, can be derived on the basis of one study. However, there are uncertainties in the CASPIAN study. It is unclear whether the patients who received 6 cycles of chemotherapy in the comparator arm were adequately treated (see Section 2.3.2). Further uncertainties arise from the restrictions regarding consolidation and palliative thoracic radiotherapy and the PCI (see Section 2.3.2). These uncertainties lead overall to a reduced certainty of conclusions. On the basis of the effects shown in the CASPIAN study, at most hints, e.g. of an added benefit, can therefore be derived for all outcomes.

2.4.3 Results

Table 15 and Table 16 summarize the results of the comparison of durvalumab + chemotherapy in patients with extensive-stage small cell lung cancer. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier. In the case of 0 events in one treatment arm, the company did not calculate a suitable significance test such as the log-rank test.

Kaplan-Meier curves on event time analyses can be found in Appendix A of the full dossier assessment. Results on common AEs and immune-related AEs are presented in Appendix C and Appendix D of the full dossier assessment.

Table 15: Results (mortality, side effects) – RCT, direct comparison: durvalumab + chemotherapy[a] vs. chemotherapy[a] (multipage table)

Outcome category Outcome Study	Durvalumab + chemotherapy[a]		Chemotherapy[a]		Durvalumab + chemotherapy[a] vs. chemotherapy[a]
	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					
CASPIAN – Global	268	12.9 [11.3; 14.7] 210 (78.4)	269	10.5 [9.3; 11.2] 231 (85.9)	0.75 [0.63; 0.91]; 0.003[b]
CASPIAN – China	61	14.4 [12.3; NC] 35 (57.4)	62	10.9 [8.9; 14.0] 43 (69.4)	0.65 [0.41; 1.03]; 0.066[b]
Total[c, d]	328	13.4 [11.9; 14.7] 245 (74.7)	330	10.6 [9.5; 11.2] 273 (82.7)	0.74 [0.63; 0.88]; < 0.001[b]
Side effects					
AEs (supplementary information)					
CASPIAN – Global	265	0.3 [0.2; 0.3] 260 (98.1)	266	0.3 [0.2; 0.3] 258 (97.0)	–
CASPIAN – China	61	0.1 [0.1; 0.1] 61 (100.0)	62	0.1 [0.1; 0.1] 61 (98.4)	–
Total[c, d]	325	0.3 [0.2; 0.3] 320 (98.5)	327	0.2 [0.2; 0.3] 318 (97.2)	–
SAEs					
CASPIAN – Global	265	NA [21.6; NC] 85 (32.1)	266	NA 97 (36.5)	0.72 [0.53; 0.97]; 0.030[e]
CASPIAN – China	61	NA [3.9; NC] 26 (42.6)	62	NA 22 (35.5)	1.11 [0.63; 1.99]; 0.714[e]
Total[c, d]	325	NA [21.6; NC] 110 (33.8)	327	NA 119 (36.4)	0.78 [0.60; 1.02]; 0.067[f]
Severe AEs[g]					
CASPIAN – Global	265	0.7 [0.5; 1.0] 171 (64.5)	266	0.7 [0.5; 0.8] 173 (65.0)	0.98 [0.80; 1.21]; 0.873[e]
CASPIAN – China	61	0.1 [0.1; 0.2] 49 (80.3)	62	0.1 [0.1; 0.2] 49 (79.0)	0.99 [0.66; 1.47]; 0.954[e]
Total[c, d]	325	0.5 [0.3; 0.7] 219 (67.4)	327	0.5 [0.3; 0.7] 222 (67.9)	0.98 [0.81; 1.18]; 0.801[f]
Discontinuation due to AEs[h]					
CASPIAN – Global	265	NA 27 (10.2)	266	NA 25 (9.4)	0.90 [0.51; 1.59]; 0.718[e]
CASPIAN – China	61	NA 10 (16.4)	62	NA 7 (11.3)	1.27 [0.47; 3.54]; 0.639[e]
Total[c, d]	325	NA 37 (11.4)	327	NA 32 (9.8)	0.98 [0.60; 1.60]; 0.938[f]

Table 15: Results (mortality, side effects) – RCT, direct comparison: durvalumab + chemotherapy[a] vs. chemotherapy[a] (multipage table)

Outcome category Outcome Study	Durvalumab + chemotherapy[a]		Chemotherapy[a]		Durvalumab + chemotherapy[a] vs. chemotherapy[a]
	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
Immune-related AEs (supplementary information)					
CASPIAN – Global	265	21.6 [11.2; NC] 95 (35.8)	266	NA 60 (22.6)	–
CASPIAN – China	61	6.2 [4.9; NC] 28 (45.9)	62	NA 11 (17.7)	–
Total[c, d]	325	14.5 [10.4; NC] 123 (37.8)	327	NA 71 (21.7)	–
Immune-related SAEs					
CASPIAN – Global	265	NA 9 (3.4)	266	NA 8 (3.0)	0.70 [0.24; 1.99]; 0.504[e]
CASPIAN – China	61	NA 3 (4.9)	62	NA 0 (0)	ND[i]
Total[c, d]					Heterogeneity: p = 0.0497
Immune-related severe AEs[g]					
CASPIAN – Global	265	NA 12 (4.5)	266	NA 6 (2.3)	1.54 [0.57; 4.56]; 0.340[e]
CASPIAN – China	61	NA 2 (3.3)	62	NA 0 (0)	ND[i]
Total[c, d]	325	NA 14 (4.3)	327	NA 6 (1.8)	1.87 [0.72; 5.41]; 0.120[f]
PRO-CTCAE					
CASPIAN – Global			No usable data available[j]		
CASPIAN – China			Outcome not recorded		
Hypertension (PT, severe AEs[g])					
CASPIAN – Global	265	NA 8 (3.0)	266	NA 1 (0.4)	7.77 [1.42; 144.07]; 0.014[e]
CASPIAN – China	61	NA 3 (4.9)	62	NA 1 (1.6)	3.13 [0.40; 63.22]; 0.287[e]
Total[c, d]	325	NA 11 (3.4)	327	NA 2 (0.6)	5.46 [1.47; 35.28]; 0.009[f]

Table 15: Results (mortality, side effects) – RCT, direct comparison: durvalumab + chemotherapy[a] vs. chemotherapy[a] (multipage table)

Outcome category Outcome Study	Durvalumab + chemotherapy[a]		Chemotherapy[a]		Durvalumab + chemotherapy[a] vs. chemotherapy[a]
	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
Blood and lymphatic system disorders (SOC, severe AEs[g])					
CASPIAN – Global	265	NA 95 (35.8)	266	NA [2.5; NC] 125 (47.0)	0.71 [0.54; 0.92]; 0.010[e]
CASPIAN – China	61	NA [1.4; NC] 29 (47.5)	62	2.3 [0.7; NC] 34 (54.8)	0.78 [0.47; 1.28]; 0.332[e]
Total[c, d]	325	NA 124 (38.2)	327	4.0 [2.3; NC] 159 (48.6)	0.72 [0.57; 0.91]; 0.006[f]

a. Cisplatin in combination with etoposide or carboplatin in combination with etoposide.
b. HR [95% CI] from stratified Cox regression model, p-value based on stratified log-rank test; stratification by planned chemotherapy in cycle 1 (cisplatin vs. carboplatin); result for meta-analysis additionally stratified by cohort (Global vs. China).
c. Calculated from meta-analysis.
d. A total of 2 patients were included in both the cohort in China and the global cohort. These patients were assigned to the cohort in China for the meta-analysis.
e. HR [95% CI] from Cox regression model, p-value based on likelihood ratio test; result for meta-analysis stratified by cohort (Global vs. China).
f. HR [95% CI] from Cox regression model, p-value based on log-rank test; stratification by cohort (Global vs. China).
g. Operationalized as CTCAE grade ≥ 3.
h. Discontinuation of at least one drug component.
i. p-value based on likelihood ratio test not calculable.
j. See Section 2.4.1 for reasons.

AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; HR: hazard ratio; N: number of analysed patients; n: number of patients with (at least one) event; NA: not achieved; NC: not calculable; ND: no data; PRO: patient-reported outcome; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; vs.: versus

Table 16: Results (morbidity, health-related quality of life) – RCT, direct comparison: durvalumab + chemotherapy[a] vs. chemotherapy[a] (multipage table)

Outcome category Outcome Study	Durvalumab + chemotherapy[a]			Chemotherapy[a]			Durvalumab + chemotherapy[a] vs. chemotherapy[a]
	N[b]	Values at baseline mean (SD)	Mean change in the course of the study up to 12 months Mean[c] (SE)	N[b]	Values at baseline mean (SD)	Mean change in the course of the study up to 12 months Mean[c] (SE)	MD [95% CI][d]; p-value
Morbidity							
EORTC QLQ-C30 (symptom scales)[e]							
Fatigue							
CASPIAN – Global[f]	233	35.32 (24.59)	−7.47 (1.63)	233	37.14 (27.21)	−5.21 (1.84)	−2.27 [−5.52; 0.98]; 0.171
CASPIAN – China	58	26.05 (18.45)	−0.36 (2.12)	56	22.03 (17.60)	NC	NC
Total[g, h]	290	33.66 (23.76)	−6.78 (1.33)	288	34.25 (26.35)	−5.56 (1.51)	−1.22 [−4.08; 1.64]; 0.402
Nausea and vomiting							
CASPIAN – Global[f]	233	5.56 (13.75)	−0.65 (0.92)	233	6.94 (16.79)	1.54 (1.07)	−2.20 [−4.04; −0.35]; 0.020
CASPIAN – China	58	3.45 (10.71)	NC	56	2.87 (8.34)	NC	NC
Total[g, h]	290	5.17 (13.25)	0.62 (0.80)	288	6.13 (15.62)	2.40 (0.92)	−1.78 [−3.48; −0.08]; 0.040 Hedges' g[i]: −0.17 [−0.34; −0.01]
Pain							
CASPIAN – Global[f]	233	28.25 (26.73)	−11.75 (1.56)	233	29.52 (29.52)	−12.12 (1.81)	0.37 [−2.92; 3.65]; 0.827
CASPIAN – China	58	20.11 (22.89)	NC	56	21.26 (20.89)	NC	NC
Total[g, h]	290	26.73 (26.24)	−10.06 (1.27)	288	27.87 (28.25)	−10.81 (1.47)	0.75 [−2.10; 3.60]; 0.606
Dyspnoea							
CASPIAN – Global[f]	233	36.31 (28.73)	−12.69 (1.86)	233	38.50 (30.64)	−12.96 (2.16)	0.27 [−3.64; 4.19]; 0.891
CASPIAN – China	58	28.16 (24.02)	−9.82 (2.16)	56	25.86 (25.01)	NC	NC
Total[g, h]	290	34.87 (28.02)	−12.39 (1.54)	288	36.09 (30.07)	−11.81 (1.78)	−0.58 [−3.98; 2.82]; 0.737

Table 16: Results (morbidity, health-related quality of life) – RCT, direct comparison: durvalumab + chemotherapy[a] vs. chemotherapy[a] (multipage table)

Outcome category Outcome Study	Durvalumab + chemotherapy[a]			Chemotherapy[a]			Durvalumab + chemotherapy[a] vs. chemotherapy[a]
	N[b]	Values at baseline mean (SD)	Mean change in the course of the study up to 12 months Mean[c] (SE)	N[b]	Values at baseline mean (SD)	Mean change in the course of the study up to 12 months Mean[c] (SE)	MD [95% CI][d]; p-value
Insomnia							
CASPIAN – Global[f]	233	29.81 (31.68)	−13.51 (1.86)	233	33.88 (35.58)	−12.16 (2.13)	−1.35 [−5.10; 2.40]; 0.480
CASPIAN – China	58	17.24 (20.94)	NC	56	17.24 (19.98)	NC	NC
Total[g, h]	290	27.50 (30.31)	−10.96 (1.50)	288	30.68 (33.83)	−9.79 (1.71)	−1.17 [−4.39; 2.05]; 0.476
Appetite loss							
CASPIAN – Global[f]	233	24.12 (30.21)	−12.75 (1.66)	233	25.58 (32.49)	−7.42 (1.92)	−5.33 [−8.66; −2.00]; 0.002
CASPIAN – China	58	14.94 (24.32)	NC	56	20.11 (23.31)	NC	NC
Total[g, h]	290	22.44 (29.38)	−9.90 (1.36)	288	24.50 (31.03)	−5.74 (1.57)	−4.16 [−7.06; −1.27]; 0.005 Hedges' g[i]: −0.24 [−0.40; −0.07]
Constipation							
CASPIAN – Global[f]	233	12.20 (23.04)	−2.24 (1.57)	233	18.10 (29.48)	−3.87 (1.87)	1.63 [−1.84; 5.10]; 0.356
CASPIAN – China	58	10.92 (20.12)	−3.14 (1.99)	56	13.22 (18.67)	NC	NC
Total[g, h]	290	11.99 (22.52)	−2.23 (1.28)	288	17.00 (27.67)	−4.06 (1.54)	1.83 [−1.19, 4.84]; 0.235
Diarrhoea							
CASPIAN – Global[f]	233	4.88 (14.87)	−2.82 (0.74)	233	5.58 (15.99)	−1.22 (0.90)	−1.60 [−3.13; −0.07]; 0.041
CASPIAN – China	58	1.15 (6.14)	NC	56	2.30 (8.52)	NC	NC
Total[g, h]	290	4.18 (13.73)	−2.86 (0.57)	288	4.97 (14.92)	−1.49 (0.72)	−1.37 [−2.69; −0.05]; 0.043 Hedges' g[i] −0.17 [−0.33; −0.01]

Table 16: Results (morbidity, health-related quality of life) – RCT, direct comparison: durvalumab + chemotherapy[a] vs. chemotherapy[a] (multipage table)

Outcome category Outcome Study	Durvalumab + chemotherapy[a]			Chemotherapy[a]			Durvalumab + chemotherapy[a] vs. chemotherapy[a]
	N[b]	Values at baseline mean (SD)	Mean change in the course of the study up to 12 months Mean[c] (SE)	N[b]	Values at baseline mean (SD)	Mean change in the course of the study up to 12 months Mean[c] (SE)	MD [95% CI][d]; p-value
EORTC QLQ-LC13 (symptom scales)[d]							
Alopecia							
CASPIAN – Global[f]	232	1.90 (10.28)	15.83 (1.49)	232	2.99 (12.08)	21.68 (1.90)	−5.85 [−10.03; −1.68] 0.006
CASPIAN – China	58	6.32 (13.18)	NC	56	6.32 (13.18)	NC	NC
Total[g, h]	289	2.76 (11.03)	17.03 (1.25)	287	3.64 (12.36)	22.90 (1.60)	−5.88 [−9.48; −2.28]; 0.001 Hedges' g[i]: −0.27 [−0.43; −0.10]
Haemoptysis							
CASPIAN – Global[f]	232	6.26 (16.44)	−4.69 (0.52)	232	5.31 (14.28)	−4.68 (0.67)	−0.02 [−1.25, 1.22]; 0.981
CASPIAN – China	58	9.20 (17.43)	−7.69 (1.05)	56	8.62 (15.99)	NC	NC
Total[g, h]	289	6.84 (16.67)	−4.99 (0.43)	287	5.96 (14.68)	−4.64 (0.58)	−0.35 [−1.47; 0.78]; 0.544
Dysphagia							
CASPIAN – Global[f]	232	9.52 (20.69)	−4.72 (0.99)	232	9.39 (22.13)	−3.82 (1.21)	−0.90 [−3.16; 1.35]; 0.431
CASPIAN – China	58	9.20 (17.43)	NC	56	7.47 (18.78)	NC	NC
Total[g, h]	289	9.49 (20.12)	−4.25 (0.82)	287	9.05 (21.54)	−3.53 (1.01)	−0.73 [−2.70; 1.25]; 0.469
Dyspnoea							
CASPIAN – Global[f]	232	30.70 (23.49)	−8.66 (1.44)	232	31.75 (23.91)	−7.55 (1.62)	−1.12 [−3.97; 1.73]; 0.441
CASPIAN – China	58	27.78 (21.15)	−5.22 (1.56)	56	23.56 (20.51)	NC	NC
Total[g, h]	289	30.21 (23.07)	−7.63 (1.18)	287	30.13 (23.51)	−6.98 (1.32)	−0.65 [−3.13; 1.82]; 0.604

Table 16: Results (morbidity, health-related quality of life) – RCT, direct comparison: durvalumab + chemotherapy[a] vs. chemotherapy[a] (multipage table)

Outcome category Outcome Study	Durvalumab + chemotherapy[a]			Chemotherapy[a]			Durvalumab + chemotherapy[a] vs. chemotherapy[a]
	N[b]	Values at baseline mean (SD)	Mean change in the course of the study up to 12 months Mean[c] (SE)	N[b]	Values at baseline mean (SD)	Mean change in the course of the study up to 12 months Mean[c] (SE)	MD [95% CI][d]; p-value
Cough							
CASPIAN – Global[f]	232	41.50 (25.90)	−17.20 (1.68)	232	40.54 (26.44)	−16.95 (2.01)	−0.25 [−3.98; 3.48]; 0.895
CASPIAN – China	58	39.08 (24.29)	−20.15 (2.67)	56	36.21 (26.70)	NC	NC
Total[g, h]	289	40.95 (25.58)	−18.08 (1.41)	287	39.74 (26.54)	−17.18 (1.71)	−0.90 [−4.24; 2.44]; 0.596
Sore mouth							
CASPIAN – Global[f]	232	4.76 (14.78)	−0.84 (0.95)	232	−0.37 (1.15)	4.22 (13.34)	−0.47 [−2.53; 1.59]; 0.655
CASPIAN – China	58	4.02 (10.95)	NC	56	3.45 (10.24)	NC	NC
Total[g, h]	289	4.64 (14.12)	−0.25 (0.76)	287	4.08 (12.81)	0.04 (0.94)	−0.29 [−2.08; 1.49]; 0.749
Peripheral neuropathy							
CASPIAN – Global[f]	232	9.12 (21.41)	4.09 (1.65)	232	8.57 (19.42)	7.50 (2.03)	−3.41 [−7.38; 0.56]; 0.092
CASPIAN – China	58	7.47 (18.78)	−0.14 (1.70)	56	4.02 (12.61)	NC	NC
Total[g, h]	289	8.83 (20.94)	2.41 (1.34)	287	7.73 (18.41)	5.11 (1.65)	−2.71 [−6.09; 0.68]; 0.117
Pain (arm/shoulder)							
CASPIAN – Global[f]	232	16.87 (24.82)	−4.00 (1.45)	232	13.20 (24.76)	−4.69 (1.75)	0.69 [−2.62; 3.99]; 0.683
CASPIAN – China	58	18.97 (26.57)	NC	56	7.47 (14.02)	NC	NC
Total[g, h]	289	17.22 (25.16)	−3.61 (1.20)	287	12.03 (23.19)	−4.43 (1.47)	0.82 [−2.09; 3.73]; 0.580
Pain (chest)							
CASPIAN – Global[f]	232	22.72 (25.53)	−8.58 (1.58)	232	21.09 (25.15)	−8.38 (1.82)	−0.20 [−3.50; 3.10]; 0.906
CASPIAN – China	58	24.71 (30.31)	−6.74 (2.23)	56	20.11 (23.31)	NC	NC
Total[g, h]	289	23.18 (26.48)	−8.70 (1.28)	287	20.86 (24.81)	−8.66 (1.48)	−0.04 [−2.91; 2.83]; 0.980

Table 16: Results (morbidity, health-related quality of life) – RCT, direct comparison: durvalumab + chemotherapy[a] vs. chemotherapy[a] (multipage table)

Outcome category Outcome Study	Durvalumab + chemotherapy[a]			Chemotherapy[a]			Durvalumab + chemotherapy[a] vs. chemotherapy[a]
	N[b]	Values at baseline mean (SD)	Mean change in the course of the study up to 12 months Mean[c] (SE)	N[b]	Values at baseline mean (SD)	Mean change in the course of the study up to 12 months Mean[c] (SE)	MD [95% CI][d]; p-value
Pain (other)							
CASPIAN – Global[f]	232	21.36 (27.53)	−5.52 (1.70)	232	22.99 (30.06)	−4.79 (2.01)	−0.73 [−4.48; 3.03]; 0.703
CASPIAN – China	58	17.24 (22.72)	−4.34 (1.99)	56	19.54 (25.77)	NC	NC
Total[g, h]	289	20.64 (26.71)	−5.57 (1.37)	287	22.30 (29.32)	−5.18 (1.63)	−0.39 [−3.59; 2.81]; 0.811
Health status (EQ-5D VAS)							
CASPIAN – Global[f]	228	63.7 (19.91)	7.76 (1.28)	228	61.0 (20.43)	6.83 (1.44)	0.93 [−1.63; 3.49]; 0.477
CASPIAN – China	58	72.1 (17.93)	2.00 (1.58)	56	68.9 (22.04)	NC	NC
Total[g, h]	285	65.2 (19.80)	7.02 (1.06)	283	62.5 (20.97)	6.48 (1.17)	0.54 [−1.68; 2.76]; 0.631
Health-related quality of life[j]							
EORTC QLQ-C30 (functional scales)							
Global health status							
CASPIAN – Global[f]	233	56.06 (22.21)	11.23 (1.45)	233	54.08 (22.41)	9.30 (1.63)	1.93 [−0.92; 4.78]; 0.184
CASPIAN – China	58	60.78 (20.35)	6.15 (1.62)	56	61.21 (23.55)	NC	NC
Total[g, h]	290	56.88 (21.90)	10.42 (1.19)	288	55.52 (22.77)	9.17 (1.33)	1.24 [−1.25; 3.73]; 0.327
Physical functioning							
CASPIAN – Global[f]	233	72.22 (21.25)	7.01 (1.49)	233	70.67 (22.42)	5.95 (1.65)	1.07 [−1.83, 3.97]; 0.470
CASPIAN – China	58	81.95 (16.89)	−0.65 (1.49)	56	82.18 (16.68)	NC	NC
Total[g, h]	290	74.02 (20.82)	5.70 (1.21)	288	72.87 (21.93)	5.40 (1.33)	0.30 [−2.21; 2.81]; 0.815

Table 16: Results (morbidity, health-related quality of life) – RCT, direct comparison: durvalumab + chemotherapy[a] vs. chemotherapy[a] (multipage table)

Outcome category Outcome Study	Durvalumab + chemotherapy[a]			Chemotherapy[a]			Durvalumab + chemotherapy[a] vs. chemotherapy[a]
	N[b]	Values at baseline mean (SD)	Mean change in the course of the study up to 12 months Mean[c] (SE)	N[b]	Values at baseline mean (SD)	Mean change in the course of the study up to 12 months Mean[c] (SE)	MD [95% CI][d]; p-value
Role functioning							
CASPIAN – Global[f]	233	69.99 (29.99)	7.44 (1.88)	233	69.80 (31.13)	3.73 (2.09)	3.71 [0.10; 7.32]; 0.044
CASPIAN – China	58	79.02 (25.47)	−0.74 (2.31)	56	81.03 (25.26)	NC	NC
Total[g, h]	290	71.73 (29.41)	6.88 (1.56)	288	71.96 (30.43)	4.52 (1.72)	2.36 [−0.84; 5.56]; 0.148
Emotional functioning							
CASPIAN – Global[f]	233	73.71 (21.39)	10.04 (1.40)	233	71.73 (24.96)	8.79 (1.60)	1.25 [−1.66; 4.16]; 0.399
CASPIAN – China	58	84.63 (16.94)	1.31 (1.58)	56	85.34 (15.48)	NC	NC
Total[g, h]	290	75.83 (21.06)	8.23 (1.18)	288	74.28 (24.04)	7.98 (1.33)	0.24 [−2.32; 2.81]; 0.852
Cognitive functioning							
CASPIAN – Global[f]	233	87.06 (19.48)	2.34 (1.21)	233	86.94 (19.43)	−0.77 (1.39)	3.11 [0.61; 5.61]; 0.015
CASPIAN – China	58	90.23 (13.62)	−5.47 (1.65)	56	91.09 (13.69)	NC	NC
Total[g, h]	290	87.68 (18.56)	0.75 (1.03)	288	87.80 (18.51)	−1.02 (1.16)	1.77 [−0.44; 3.99]; 0.117
Social functioning							
CASPIAN – Global[f]	233	76.90 (27.44)	7.12 (1.70)	233	76.26 (27.49)	5.34 (1.90)	1.78 [−1.60; 5.16]; 0.302
CASPIAN – China	58	73.85 (24.80)	0.37 (2.67)	56	77.30 (24.92)	NC	NC
Total[g, h]	290	76.35 (26.99)	4.29 (1.42)	288	76.55 (26.98)	3.21 (1.58)	1.08 [−1.92; 4.08]; 0.478

Table 16: Results (morbidity, health-related quality of life) – RCT, direct comparison: durvalumab + chemotherapy[a] vs. chemotherapy[a] (multipage table)

Outcome category Outcome Study	Durvalumab + chemotherapy[a]			Chemotherapy[a]			Durvalumab + chemotherapy[a] vs. chemotherapy[a]
	N[b]	Values at baseline mean (SD)	Mean change in the course of the study up to 12 months Mean[c] (SE)	N[b]	Values at baseline mean (SD)	Mean change in the course of the study up to 12 months Mean[c] (SE)	MD [95% CI][d]; p-value
a. Cisplatin in combination with etoposide or carboplatin in combination with etoposide. b. Number of patients considered in the analysis for the calculation of the effect estimation; the values at baseline (possibly at other time points) may be based on other patient numbers. c. Least square estimations from an MMRM; data up to cycle 15/month 13 were included in the analyses (see Section 2.4.1). d. MMRM analysis of the mean difference over the first 15 cycles adjusted for visit, treatment*visit, value at baseline and value at baseline*visit, age (< 65 vs. ≥ 65 years), sex (male vs. female), smoking (smoker vs. non-smoker); no data for the cohort in China. e. Lower (decreasing) values indicate better symptoms; negative effects (intervention minus control) indicate an advantage for the intervention. f. Patients from one study centre in Ukraine were not considered due to incorrect data recording. These were 16 (information in the CSR) or 17 (information in the SAP) randomized patients. g. For the meta-analysis additionally adjusted for cohort (Global vs. China). h. A total of 2 patients were included in both the cohort in China and the global cohort. These patients were assigned to the cohort in China for the meta-analysis. i. Institute's calculations. j. Higher (increasing) values indicate better quality of life; positive effects (intervention minus control) indicate an advantage for the intervention. CI: confidence interval; CSR: clinical study report; EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: European Quality of Life-5 Dimensions; MD: mean difference; MMRM: mixed-effects model with repeated measures; N: number of analysed patients; NC: not calculable; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-LC13: Quality of Life Questionnaire-Lung Cancer 13; RCT: randomized controlled trial; SAP: statistical analysis plan; SD: standard deviation; SE: standard error; VAS: visual analogue scale; vs.: versus						

Based on the available data, at most hints, e.g. of an added benefit, can be determined for all outcomes (see Section 2.3.2 and Section 2.4.2).

Mortality

Overall survival

In the present benefit assessment, the results of time from randomization to death for any reason were used for the outcome "overall survival". A statistically significant effect in favour of durvalumab was shown for the outcome "overall survival". This resulted in a hint of an added benefit of durvalumab + chemotherapy in comparison with chemotherapy.

This deviates from the assessment of the company, which derived an indication of an added benefit.

Morbidity

Symptoms (symptom scales of EORTC QLQ-C30 and EORTC QLQ-LC13)

Operationalization

Symptom outcomes were recorded in the CASPIAN study using the symptom scales of the EORTC QLQ-C30 and the EORTC QLQ-LC13. The operationalization used for the present assessment was the mean change in comparison with the start of treatment until progression or month 12 (whichever occurred earlier) using MMRM analyses.

If there was a statistically significant mean difference (MD), a standardized mean difference (SMD) was used to assess clinical relevance. The company presented calculations for this, which it referred to as "Hedges' g". The results show discrepancies in statistical significance between the MD and the SMD. As it was not described how the calculation was carried out, the results were checked by calculations conducted by the Institute. For this purpose, an SMD analogous to Hedges' g was determined using the MD estimated from the MMRM analysis, the corresponding standard error as well as the respective sample sizes.

Results

For the symptom scales of the EORTC QLQ-C30, a statistically significant difference for the mean change in favour of durvalumab + chemotherapy was shown in each case for nausea and vomiting, appetite loss, and diarrhoea. For the EORTC QLQ-LC13 symptom scale of alopecia, there was also a significant difference in favour of durvalumab + chemotherapy. The SMD in form of Hedges' g was considered to check the relevance of these results. The 95% confidence interval (CI) was not fully outside the irrelevance range [−0,2; 0,2] for these 4 outcomes. Thus, for nausea and vomiting, appetite loss, diarrhoea and alopecia respectively, it cannot be deduced that the effect is relevant. This resulted in no hint of an added benefit of durvalumab + chemotherapy in comparison with chemotherapy for nausea and vomiting, appetite loss, diarrhoea, and alopecia; an added benefit is therefore not proven for these 4 symptom scales.

No statistically significant difference between the treatment arms was shown for the mean change for any of the other symptom scales of the EORTC QLQ-C30 and of the EORTC QLQ-LC13. This resulted in no hint of an added benefit of durvalumab + chemotherapy in comparison with chemotherapy for the other symptom scales; an added benefit is therefore not proven in each case.

This corresponds to the result of the assessment of the company, which, however, deviated from this for the EORTC QLQ-C30 and EORTC QLQ-LC13 by using the results for the time to deterioration by ≥ 10 points, but also did not derive an added benefit for any of the symptom scales.

Health status

EQ-5D VAS

Operationalization

For the outcome "health status" (recorded using the EQ-5D VAS), the mean change in comparison with the start of treatment until progression or month 12 (whichever occurred earlier) using MMRM analyses was used.

Results

There was no statistically significant difference between the treatment groups for the outcome "health status". This resulted in no hint of an added benefit of durvalumab + chemotherapy in comparison with chemotherapy for the outcome "health status"; an added benefit is therefore not proven.

This corresponds to the assessment of the company, which deviates from this for the EQ-5D VAS by using the results for the time to deterioration by ≥ 7 or ≥ 10 points, but also did not derive an added benefit.

Patient Global Impression of Change

There were no usable analyses for the outcome "health status" recorded using the PGIC (see Section 2.4.1). This resulted in no hint of an added benefit of durvalumab + chemotherapy in comparison with the ACT; an added benefit is therefore not proven.

This corresponds to the assessment of the company in that the company presented the analyses for the outcome "PGIC" only as supplementary information and did not use them to derive an added benefit.

Health-related quality of life

EORTC QLQ-C30 (functional scales, global health status scale)

Operationalization

Health-related quality of life was recorded using the global health status and the functional scales of the EORTC QLQ-C30. The mean change in comparison with the start of treatment until progression or month 12 (whichever occurred earlier) using MMRM analyses was considered.

Results

No statistically significant difference between the treatment groups was shown for the functional scales and the global health status scale. This resulted in no hint of an added benefit of durvalumab + chemotherapy in comparison with chemotherapy for each of these scales; an added benefit is therefore not proven.

This deviates from the assessment of the company, which derived an added benefit for the functional scale "emotional functioning" on the basis of responder analyses using a response criterion of 10 points.

Side effects

The significantly shorter observation period in the comparator arm means that, on the basis of the event time analyses, a comparison of the 2 treatment arms for the AE outcomes is only possible over a period of the first approximately 8 months, because all subsequent times of the patients in the comparator arm who were still at risk were censored. Events in the intervention arm after this time point were thus not included in the estimation of the hazard ratio (HR). This is of particular importance for the immune-related AEs, as these mostly occur later than chemotherapy-associated side effects. Therefore, the present benefit assessment examines on an outcome-specific basis whether the event time analyses can be used for the assessment.

SAEs

The event time analyses of the meta-analysis showed no statistically significant difference between the treatment arms for the outcome "SAEs".

There was an effect modification by the characteristic "brain metastases at baseline" for this outcome. For patients with brain metastases at baseline, there was a hint of lesser harm from durvalumab + chemotherapy in comparison with chemotherapy. For patients without brain metastases at baseline, in contrast, no added benefit was shown (see Section 2.4.4).

This deviates from the assessment of the company, which, on the basis of the meta-analysis, derived no hint of greater or lesser harm of durvalumab + chemotherapy in comparison with chemotherapy for the outcome "SAEs".

Severe AEs (CTCAE grade ≥ 3) and discontinuation due to AEs

The event time analysis showed no statistically significant difference between the treatment arms for the outcomes "severe AEs" (CTCAE grade ≥ 3) and "discontinuation due to AEs". This resulted in no hint of greater or lesser harm from durvalumab + chemotherapy in comparison with chemotherapy for each of these outcomes; greater or lesser harm is therefore not proven.

This concurs with the company's assessment.

Specific AEs

Immune-related SAEs and severe AEs

Operationalization

For statements on immune-related AEs, the AEs of special interest (AESI) prespecified in the CASPIAN study were used in the present benefit assessment. Both severe AEs (CTCAE grade 3 or 4) and SAEs were considered. These are considered a sufficient approximation for the recording of immune-related AEs. Immune-related AEs (all CTCAE grades) are presented only

as supplementary information because they include a relevant proportion of non-patient-relevant events such as laboratory values (e.g. hypothyroidism and hyperthyroidism, see Appendix D of the full dossier assessment).

The company also presented the AESI in M4, but not explicitly as an operationalization for the immune-related AEs.

In the CASPIAN study, the basic set of AESIs served as the baseline set for the identification of immune-related AEs. The study protocol in the CASPIAN study described categories for the recording of the AESI. According to the study protocol, these categories are side effects for which (with the exception of infusion-related reactions) an immune-related reaction is the expected cause:

- diarrhoea/colitis/gastrointestinal perforation
- pneumonitis
- hepatitis
- endocrinopathies (e.g. hypophysitis, adrenal insufficiency)
- hyperthyroidism and hypothyroidism, type 1 diabetes mellitus
- rash/dermatitis
- nephritis/creatinine increase
- pancreatitis
- myocarditis
- myositis/polymyositis
- rare or less frequent immune-related AEs including neuromuscular toxicity (e.g. Guillain Barre syndrome, myasthenia gravis)
- other inflammatory events that are rare but have a potentially immune-related aetiology, e.g. pericarditis, sarcoidosis, uveitis and other events involving the eyes, skin, blood; rheumatological diseases, vasculitis, non-infectious meningitis and encephalitis (immune-related AEs can affect all organ systems)
- infusion-related reaction and hypersensitivity/anaphylactic reactions (with other pharmacological aetiology)

Results

There was statistically significant heterogeneity ($p = 0.0497$) between the global cohort and the cohort in China for the outcome “immune-related SAEs”. The event time analysis showed no statistically significant difference between the treatment arms in the global cohort. This resulted in no hint of greater or lesser harm from durvalumab + chemotherapy in comparison with chemotherapy for this outcome in the global cohort; greater or lesser harm is therefore not

proven. No effect estimations, no Kaplan-Meier curves, and no p-values were available for immune-related SAEs for the cohort in China, so an assessment of the results was not possible. The use of another statistical test (e.g. non-stratified log-rank test) would allow testing for statistical significance between the treatment arms in the cohort in China. Since there was no statistically significant result in the global cohort, this remains without consequence, however.

This corresponds to the assessment of the company in that the company also did not derive greater or lesser harm. However, it made this assessment on the basis of the meta-analysis despite statistically significant heterogeneity.

The event time analysis showed no statistically significant difference between the treatment arms for the outcome "immune-related severe AEs" (CTCAE grade ≥ 3). There was an effect modification by the characteristic "sex", however. There was no hint of greater or lesser harm from durvalumab + chemotherapy in comparison with chemotherapy for men; greater or lesser harm is therefore not proven. For women, there was no effect estimation and no p-value available for immune-related severe AEs (CTCAE grade ≥ 3), so an assessment of the results was not possible (see Section 2.4.4 and 2.5.2).

This deviates from the assessment of the company in that the company did not derive greater or lesser harm for the outcome "immune-related severe AEs" (CTCAE-grade ≥ 3) on the basis of the total population of the meta-analysis.

PRO-CTCAE

For the outcome "PRO-CTCAE", no usable analyses were available for the global cohort. The outcome was not recorded in the cohort in China (see Section 2.4.1). This resulted in no hint of an added benefit of durvalumab + chemotherapy in comparison with the ACT; an added benefit is therefore not proven.

This deviates from the assessment of the company, which did not present the outcome in Module 4 A and did not use it for the derivation of an added benefit.

Hypertension (PT, AEs [CTCAE grade ≥ 3]), blood and lymphatic system disorders (SOC, AEs [CTCAE grade ≥ 3])

The event time analyses showed a statistically significant difference between the treatment arms to the disadvantage of durvalumab + chemotherapy in comparison with chemotherapy for the outcome "hypertension" (PT, AEs [CTCAE grade ≥ 3]). This resulted in a hint of greater harm of durvalumab + chemotherapy in comparison with chemotherapy.

The event time analyses showed a statistically significant difference between the treatment arms in favour of durvalumab + chemotherapy in comparison with chemotherapy for the outcome "blood and lymphatic system disorders" (SOC, AEs [CTCAE grade ≥ 3]). In addition, there was an effect modification by the characteristic "brain metastases at baseline" for this outcome. For patients with brain metastases at baseline, there was a hint of lesser harm from

durvalumab + chemotherapy in comparison with chemotherapy. For patients without brain metastases at baseline, in contrast, no added benefit was shown (see Section 2.4.4).

This deviates from the assessment of the company, which did not derive greater or lesser harm on the basis of individual specific AEs, but, in summary, did not derive greater or lesser harm of durvalumab + chemotherapy in comparison with chemotherapy for the specific AEs considered by the company.

2.4.4 Subgroups and other effect modifiers

The following subgroup characteristics were relevant for the present assessment:

- sex (female versus male)
- age (< 65 years versus ≥ 65 years)
- brain metastases at baseline (yes versus no)

The company did not provide any subgroup analyses for the MMRM analyses of the symptom outcomes (symptom scales of the EORTC QLQ-C30, EORTC QLQ-LC13, EQ-5D VAS) and health-related quality of life (functional scales and global health status scale of the EORTC QLQ-C30); these subgroup analyses are necessary for the benefit assessment, however.

In the dossier, the company generally presented subgroup analyses on the basis of the meta-analysis. It presented interaction tests separately for the cohorts only if there was statistically significant heterogeneity between the cohorts in the total population of the meta-analysis. If the data in the meta-analysis were homogeneous, the subgroup analyses were only calculated for the meta-analysis.

Subgroup analyses for the individual cohorts are not available for the subgroups relevant in the benefit assessment. Table 17 therefore only presents the results of the subgroups on the basis of the meta-analysis. Since the added benefit is derived on the basis of the meta-analysis, the lack of these data remains without consequence.

Interaction tests were performed when at least 10 patients per subgroup were included in the analysis. Moreover, for binary data, there must be 10 events in at least one subgroup.

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

Table 17: Subgroups (SAEs, severe immune-related AEs [CTCAE grade ≥ 3]) – RCT, direct comparison: durvalumab + chemotherapy[a] vs. chemotherapy[a] (multipage table)

Study Outcome Characteristic Subgroup	Durvalumab + chemotherapy[a] N	Durvalumab + chemotherapy[a] Median time to event in months [95% CI] Patients with event n (%)	Chemotherapy[a] N	Chemotherapy[a] Median time to event in months [95% CI] Patients with event n (%)	Durvalumab + chemotherapy[a] vs. chemotherapy[a] HR [95% CI][b]	 p-value[c]
CASPIAN – Total						
Side effects						
SAEs						
Brain metastases at baseline						
Yes	37	NA [12.4; NC] 9 (24.3)	37	3.0 [1.5; NC] 19 (51.4)	0.35 [0.14; 0.77]	0.009
No	288	NA [21.6; NC] 101 (35.1)	290	NA 100 (34.5)	0.87 [0.65; 1.15]	0.320
Total					Interaction[d]:	0.030
Immune-related severe AEs[e]						
Sex						
Male	240	NA 8 (3.3)	232	NA 6 (2.6)	1.15 [0.39; 3.52]	0.797
Female	85	NA 6 (7.1)	95	NA 0 (0)	NC	ND[f]:
Total					Interaction[d]:	0.018
Blood and lymphatic system disorders (SOC, severe AEs[e])						
Brain metastases at baseline						
Yes	37	NA 10 (27.0)	37	0.7 [0.5; 2.1] 28 (75.7)	0.24 [0.11; 0.49];	< 0.001
No	288	NA 114 (39.6)	290	NA [3.2; NC] 131 (45.2)	0.84 [0.65; 1.07];	0.161
Total					Interaction[d]:	< 0.001

a. Cisplatin in combination with etoposide or carboplatin in combination with etoposide.
b. HR [95% CI] from Cox regression model, result for meta-analysis stratified by cohort (Global vs. China).
c. p-value based on likelihood ratio test.
d. Test for heterogeneity was conducted with the interaction term treatment x outcome.
e. Operationalized as CTCAE grade ≥ 3.
f. p-value based on likelihood ratio test not calculable.

AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; HR: hazard ratio; N: number of analysed patients; n: number of patients with (at least one) event; NA: not achieved; NC: not calculable; ND: no data; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus

Side effects

SAEs

The meta-analysis showed an effect modification by the characteristic "brain metastases at baseline" for the outcome "SAEs".

In the subgroup of patients with brain metastases at baseline, there was a statistically significant difference in favour of durvalumab + chemotherapy in comparison with chemotherapy for SAEs. This resulted in a hint of lesser harm of durvalumab + chemotherapy in comparison with chemotherapy for these patients.

No statistically significant difference between the treatment arms was shown in the subgroup of patients without brain metastases at baseline, however. There was no hint of greater or lesser harm from durvalumab + chemotherapy in comparison with chemotherapy for these patients; greater or lesser harm is therefore not proven.

This deviates from the assessment of the company, which did not consider this effect modification to be relevant due to the effects in the same direction and consequently derived no hint of lesser harm in patients with brain metastases.

Specific AEs

Immune-related severe AEs (CTCAE grade ≥ 3)

The meta-analysis showed an effect modification by the characteristic "sex" for the outcome "immune-related severe AEs" (CTCAE grade ≥ 3).

There was no statistically significant difference between the treatment arms in the subgroup of men. This resulted in no hint of greater or lesser harm from durvalumab + chemotherapy in comparison with chemotherapy for the subgroup of men; greater or lesser harm for men is therefore not proven.

The company provided no effect estimation, no p-value and no Kaplan-Meier curves in the subgroup of women. Thus, this effect modification cannot be assessed for women. It therefore remains unclear whether there is a hint of greater harm in immune-related severe AEs for women. The calculation of a p-value by means of further statistical tests is necessary (e.g. non-stratified log-rank test) in order to be able to make statements about potentially greater harm in the subgroup of women. Without Kaplan-Meier curves, moreover, no statement can be made about the chronological course of events. For the implications of the missing data for the overall assessment, see Section 2.5.2.

Since the effect estimation and the p-value were not calculable, the company derived no hint of greater harm of durvalumab + chemotherapy in comparison with chemotherapy in women.

Blood and lymphatic system disorders (SOC, severe AEs)

The meta-analysis showed an effect modification by the characteristic "brain metastases at baseline" for the outcome "blood and lymphatic system disorders" (SOC, severe AEs).

In the subgroup of patients with brain metastases at baseline, there was a statistically significant difference in favour of durvalumab + chemotherapy in comparison with chemotherapy for blood and lymphatic system disorders (SOC, severe AEs). This resulted in a hint of lesser harm of durvalumab + chemotherapy in comparison with chemotherapy for these patients.

No statistically significant difference between the treatment arms was shown in the subgroup of patients without brain metastases at baseline, however. There was no hint of greater or lesser harm from durvalumab + chemotherapy in comparison with chemotherapy for these patients; greater or lesser harm is therefore not proven.

This deviates from the assessment of the company, which did not consider this effect modification to be relevant due to the effects in the same direction and consequently derived no hint of lesser harm in patients with brain metastases at baseline.

2.5 Probability and extent of added benefit

Probability and extent of the added benefit at outcome level are presented 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.

2.5.1 Assessment of the added benefit at outcome level

The extent of the respective added benefit at outcome level was estimated from the results presented in Section 2.4 (see Table 18).

Table 18: Extent of added benefit at outcome level: durvalumab + chemotherapy[a] vs. chemotherapy[a] (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Durvalumab + chemotherapy[a] vs. chemotherapy[a]** **Median time to event (months) or mean change or proportion of events (%)** **Effect estimation [95% CI];** **p-value** **Probability[b]**	**Derivation of extent[c]**
Mortality		
Overall survival	Median: 13.4 vs. 10.6 HR: 0.74 [0.63; 0.88] p < 0.001 probability: "hint"	Outcome category: mortality $0.85 \leq CI_u < 0.95$ added benefit, extent: "considerable"
Morbidity		
Symptoms		
EORTC QLQ-C30 (symptom scales) – mean change in the course of the study up to month 12		
Fatigue	−6.78 vs. −5.56 MD: −1.22 [−4.08; 1.64] p = 0.402	Lesser benefit/added benefit not proven
Nausea and vomiting	0.62 vs. 2.40 MD: −1.78 [−3.48; −0.08] p = 0.040 Hedges' g[d]: −0.17 [−0.34; −0.01]	Lesser benefit/added benefit not proven
Pain	−10.06 vs. −10.81 MD: 0.75 [−2.10; 3.60] p = 0.606	Lesser benefit/added benefit not proven
Dyspnoea	−12.39 vs. 11.81 MD: −0.58 [−3.98; 2.82]; p = 0.737	Lesser benefit/added benefit not proven
Insomnia	−10.96 vs. −9.79 MD: −1.17 [−4.39; 2.05] p = 0.476	Lesser benefit/added benefit not proven
Appetite loss	−9.90 vs. −5.74 MD: −4.16 [−7.06; −1.27] p = 0.005 Hedges' g[d]: −0.24 [−0.40; −0.07]	Lesser benefit/added benefit not proven
Constipation	−2.23 vs. −4.06 MD: 1.83 [−1.19; 4.84] p = 0.235	Lesser benefit/added benefit not proven
Diarrhoea	−2.86 vs. −1.49 MD: −1.37 [−2.69; −0.05] p = 0.043 Hedges' g[d]: −0.17 [−0.33; −0.01]	Lesser benefit/added benefit not proven

Table 18: Extent of added benefit at outcome level: durvalumab + chemotherapy[a] vs. chemotherapy[a] (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Durvalumab + chemotherapy[a] vs. chemotherapy[a]** **Median time to event (months) or mean change or proportion of events (%)** **Effect estimation [95% CI];** **p-value** **Probability[b]**	**Derivation of extent[c]**
EORTC QLQ-LC13 (symptom scales) – mean change in the course of the study up to month 12		
Alopecia	17.03 vs. 22.90 MD: −5.88 [−9.48; −2.28] p = 0.001 Hedges' g[d]: −0.27 [−0.43; −0.10]	Lesser benefit/added benefit not proven
Haemoptysis	−4.99 vs. −4.64 MD: −0.35 [−1.47; 0.78] p = 0.544	Lesser benefit/added benefit not proven
Dysphagia	−4.25 vs. −3.53 MD: −0.73 [−2.70; 1.25] p = 0.469	Lesser benefit/added benefit not proven
Dyspnoea	−7.63 vs. −6.98 MD: −0.65 [−3.13; 1.82] p = 0.604	Lesser benefit/added benefit not proven
Cough	−18.08 vs. −17.18 MD: −0.90 [−4.24; 2.44] p = 0.596	Lesser benefit/added benefit not proven
Sore mouth	−0.25 vs. 0.04 MD: −0.29 [−2.08; 1.49] p = 0.749	Lesser benefit/added benefit not proven
Peripheral neuropathy	2.41 vs. 5.11 MD: −2.71 [−6.09; 0.68] p = 0.117	Lesser benefit/added benefit not proven
Pain (arm/shoulder)	−3.61 vs. −4.43 MD: 0.82 [−2.09; 3.73] p = 0.580	Lesser benefit/added benefit not proven
Pain (chest)	−8.70 vs. −8.66 MD: −0.04 [−2.91; 2.83] p = 0.980	Lesser benefit/added benefit not proven
Pain (other)	−5.57 vs. −5.18 MD: −0.39 [−3.59; 2.81] p = 0.811	Lesser benefit/added benefit not proven
Health status		
EQ-5D VAS (mean change in the course of the study up to month 12)	7.02 vs. 6.48 MD: 0.54 [−1.68; 2.76] p = 0.631	Lesser benefit/added benefit not proven
PGIC	No usable data[e]	Lesser benefit/added benefit not proven

Table 18: Extent of added benefit at outcome level: durvalumab + chemotherapy[a] vs. chemotherapy[a] (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Durvalumab + chemotherapy[a] vs. chemotherapy[a]** **Median time to event (months) or mean change or proportion of events (%)** **Effect estimation [95% CI];** **p-value** **Probability[b]**	**Derivation of extent[c]**
Health-related quality of life		
EORTC QLQ-C30 (functional scales, global health status scale) – mean change in the course of the study up to month 12		
Global health status	10.42 vs. 9.17 MD: 1.24 [−1.25; 3.73] p = 0.327	Lesser benefit/added benefit not proven
Physical functioning	5.70 vs. 5.40 MD: 0.30 [−2.21; 2.81] p = 0.815	Lesser benefit/added benefit not proven
Role functioning	6.88 vs. 4.52 MD: 2.36 [−0.84; 5.56] p = 0.148	Lesser benefit/added benefit not proven
Emotional functioning	8.23 vs. 7.98 MD: 0.24 [−2.32; 2.81] p = 0.852	Lesser benefit/added benefit not proven
Cognitive functioning	0.75 vs. −1.02 MD: 1.77 [−0.44; 3.99] p = 0.117	Lesser benefit/added benefit not proven
Social functioning	4.29 vs. 3.21 MD: 1.08 [−1.92; 4.08] p = 0.478	Lesser benefit/added benefit not proven
Side effects		
SAEs Brain metastases at baseline Yes	Median: NA vs. 3.0 HR: 0.35 [0.14; 0.77] p = 0.009 probability: “hint”	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ lesser harm, extent: “considerable”
No	Median: NA vs. NA HR: 0.87 [0.65; 1.15] p = 0.320	Greater/lesser harm not proven
Severe AEs	Median: 0.5 vs. 0.5 HR: 0.98 [0.81; 1.18] p = 0.801	Greater/lesser harm not proven
Discontinuation due to AEs	Median: NA vs. NA HR: 0.98 [0.60; 1.60] p = 0.938	Greater/lesser harm not proven

Table 18: Extent of added benefit at outcome level: durvalumab + chemotherapy[a] vs. chemotherapy[a] (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Durvalumab + chemotherapy[a] vs. chemotherapy[a]** **Median time to event (months) or mean change or proportion of events (%)** **Effect estimation [95% CI];** **p-value** **Probability[b]**	**Derivation of extent[c]**
Immune-related SAEs	Heterogeneous results[f] There was no statistically significant effect in the global cohort; no p-value is available for the cohort in China.	Greater/lesser harm not proven[g]
Immune-related severe AEs Sex Male	Median: NA vs. NA HR: 1.15 [0.39; 3.52] p = 0.797	Greater/lesser harm not proven
Female	No usable data	Greater/lesser harm not proven[h]
PRO-CTCAE	No usable data available[e]	Greater/lesser harm not proven
Hypertension (severe AEs)	Median: NA vs. NA HR: 5.46 [1.47; 35.28] HR[i]: 0.18 [0.03; 0.68] p = 0.009 probability: "hint"	Outcome category: serious/severe side effects $CI_u < 0.75$, risk < 5% greater harm, extent: "considerable"
Blood and lymphatic system disorders (severe AEs) Brain metastases at baseline		
Yes	Median: NA vs. 0.7 HR: 0.24 [0.11; 0.49] p < 0.001 probability: "hint"	Outcome category: serious/severe side effects $CI_u < 0.75$, risk ≥ 5% lesser harm, extent: "major"
No	Median: NA vs. NA HR: 0.84 [0.65; 1.07] p = 0.161	Greater/lesser harm not proven

Table 18: Extent of added benefit at outcome level: durvalumab + chemotherapy[a] vs. chemotherapy[a] (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Durvalumab + chemotherapy[a] vs. chemotherapy[a]** **Median time to event (months) or mean change or proportion of events (%)** **Effect estimation [95% CI];** **p-value** **Probability[b]**	**Derivation of extent[c]**
a. Cisplatin in combination with etoposide or carboplatin in combination with etoposide. b. Probability provided if statistically significant differences are present. c. Depending on the outcome category, estimations of effect size are made with different limits based on the upper limit of the confidence interval (CI_u). d. If the CI of Hedges' g is fully outside the irrelevance range [−0.2; 0.2], this is interpreted to be a relevant effect. In other cases, the presence of a relevant effect cannot be inferred. e. See Section 2.4.1 for reasons. f. No common effect estimation can be provided due to heterogeneous data. g. For the cohort in China, no usable effect estimations and p-values are available for immune-related SAEs. Nevertheless, "greater lesser harm not proven" can be derived in the present data situation (see Section 2.4.3). h. For women, there is an effect modification for immune-related severe AEs (CTCAE grade ≥ 3), but no effect estimation or p-value is available. Therefore, no extent can be derived in the present data situation (see Sections 2.4.3 and 2.4.4). i. Institute's calculation; reversed direction of effect to enable use of limits to derive the extent of the added benefit. AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: European Quality of Life-5 Dimensions; HR: hazard ratio; MD: mean difference; NA: not achieved; NC: not calculable; PGIC: Patient Global Impression of Change; PRO: patient-reported outcome; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-LC-13: Quality of Life Questionnaire-Lung Cancer 13; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus	

2.5.2 Overall conclusion on added benefit

Table 19 summarizes the results considered in the overall conclusion on the extent of added benefit.

Table 19: Positive and negative effects from the assessment of durvalumab + chemotherapy[a] in comparison with chemotherapy[a]

Positive effects	**Negative effects**
Mortality ▪ Overall survival: hint of an added benefit – extent "considerable"	–
Serious/severe side effects ▪ Patients with brain metastases at baseline ▫ SAEs: hint of lesser harm – extent: "considerable" ▫ Blood and lymphatic system disorders (severe AEs): hint of lesser harm – extent: "major"	Serious/severe side effects ▪ Hypertension (severe AEs): hint of greater harm – extent: "considerable"
For the characteristic "sex", there is an effect modification for immune-related severe AEs, but no effect estimation or p-value is available for women. It is therefore unclear whether there is a hint of greater harm from durvalumab + chemotherapy for women for this outcome.	
a. Cisplatin in combination with etoposide or carboplatin in combination with etoposide. AE: adverse event; SAE: serious adverse event	

The overall picture shows both positive and negative effects of durvalumab + chemotherapy in comparison with chemotherapy, in each case with the probability "hint".

On the positive side, there was a hint of considerable added benefit for the outcome "overall survival".

For patients with brain metastases at baseline, there was additionally a hint of lesser harm with the extent "considerable" for the outcome "SAEs" in the category of serious/severe side effects, and a hint of lesser harm with the extent "major" for the outcome "blood and lymphatic system disorders" (category of serious/severe side effects).

On the side of negative effects, there was a hint of greater harm with the extent "considerable" for the outcome "hypertension" in the category of serious/severe side effects, which did not call into question the positive effect in overall survival, however.

For women, there was also a clear numerical disadvantage in the outcome "immune-related severe AEs" (category of serious/severe side effects). However, no usable effect estimation and no p-value allowing an assessment of statistical significance was available for women. Thus, it cannot be ruled out with certainty that there is greater harm from durvalumab affecting the overall conclusion on the added benefit for women. As a result, the overall extent of the added benefit for women was considered non-quantifiable.

In summary, there is a hint of considerable added benefit of durvalumab + chemotherapy in comparison with the ACT for men with extensive-stage small cell lung cancer. For women with extensive-stage small cell lung cancer, there is a hint of a non-quantifiable, at most considerable added benefit in comparison with the ACT.

The result of the assessment of the added benefit of durvalumab in combination with chemotherapy in comparison with the ACT is summarized in Table 20.

Table 20: Durvalumab + chemotherapy[a] – probability and extent of added benefit

Therapeutic indication	**ACT[b]**	**Probability and extent of added benefit**
Extensive-stage small cell lung cancer (ES-SCLC)[c]	Cisplatin in combination with etoposide or carboplatin in combination with etoposide	▪ Men: ▫ hint of considerable added benefit ▪ Women: ▫ Hint of added benefit; extent "non-quantifiable", at most "considerable"

a. Cisplatin in combination with etoposide or carboplatin in combination with etoposide.
b. Presentation of the respective ACT specified by the G-BA.
c. The CASPIAN study only included patients with an ECOG PS of 0 or 1 and with asymptomatic or previously treated brain metastases. It remains unclear whether the observed effects can be transferred to patients with ECOG PS ≥ 2 or with symptomatic brain metastases.

ACT: appropriate comparator therapy; ECOG PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee

The assessment described above deviates from that of the company, which derived an indication of considerable added benefit for the total study population. The company also derived the added benefit on the basis of the meta-analysis, but did not take into account the limitations of the CASPIAN study and the effect modification by the characteristic "sex" for the outcome "immune-related severe AEs".

The G-BA decides on the added benefit.

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.

1. Institute for Quality and Efficiency in Health Care. General methods; Version 6.0 [online]. 2020 [Accessed: 27.05.2021]. URL: https://www.iqwig.de/methoden/general-methods_version-6-0.pdf.

2. Skipka G, Wieseler B, Kaiser T et al. Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. Biom J 2016; 58(1): 43-58. https://dx.doi.org/10.1002/bimj.201300274.

3. AstraZeneca. A Phase III, Randomized, Multicenter, Open-Label, Comparative Study to Determine the Efficacy of Durvalumab or Durvalumab and Tremelimumab in Combination With Platinum-Based Chemotherapy for the First-Line Treatment in Patients with Extensive Disease Small-Cell Lung Cancer (SCLC) (CASPIAN); study D419QC00001; Interim Clinical Study Report [unpublished]. 2019.

4. AstraZeneca. A Phase III, Randomized, Multicenter, Open-Label, Comparative Study to Determine the Efficacy of Durvalumab or Durvalumab and Tremelimumab in Combination With Platinum-Based Chemotherapy for the First-Line Treatment in Patients with Extensive Disease Small-Cell Lung Cancer (SCLC) (CASPIAN): China Cohort; study D419QC00001; Clinical Study Report [unpublished]. 2020.

5. AstraZeneca. A Phase III, Randomized, Multicenter, Open-Label, Comparative Study to Determine the Efficacy of Durvalumab or Durvalumab and Tremelimumab in Combination With Platinum-Based Chemotherapy for the First-Line Treatment in Patients with Extensive Disease Small-Cell Lung Cancer (SCLC) (CASPIAN); study D419QC00001; Clinical Study Report [unpublished]. 2020.

6. AstraZeneca. A Phase III, Randomized, Multicenter, Open-Label, Comparative Study to Determine the Efficacy of Durvalumab or Durvalumab and Tremelimumab in Combination With Platinum-Based Chemotherapy for the First-Line Treatment in Patients with Extensive Disease Small-Cell Lung Cancer (SCLC) (CASPIAN) [online]. [Accessed: 08.10.2020]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2016-001203-23.

7. AstraZeneca. Durvalumab ± tremelimumab in combination with platinum based chemotherapy in untreated extensive-stage small cell lung cancer (CASPIAN) (CASPIAN) [online]. 2020 [Accessed: 08.10.2020]. URL: https://ClinicalTrials.gov/show/NCT03043872.

8. AstraZeneca. A Phase 3, Randomized, Multicenter,Open-Label, Comparative Study to Determine the Efficacy of Durvalumab or Durvalumab and Tremelimumab in Combination With Platinum-Based Chemotherapy for the First-Line Treatment in Patients With Extensive Disease (Stage IV) Small-Cell Lung Cancer (SCLC) [online]. 2018 [Accessed: 08.10.2020]. URL: https://www.clinicaltrials.jp/user/showCteDetailE.jsp?japicId=JapicCTI-173635.

9. European Medicines Agency. Imfinzi; Assessment report [online]. 2020 [Accessed: 20.11.2020]. URL: https://www.ema.europa.eu/documents/variation-report/imfinzi-h-c-4771-ii-0014-g-epar-assessment-report-variation_en.pdf.

10. Goldman JW, Garassino MC, Chen Y et al. Patient-reported outcomes with first-line durvalumab plus platinum-etoposide versus platinum-etoposide in extensive-stage small-cell lung cancer (CASPIAN): a randomized, controlled, open-label, phase III study. Lung Cancer 2020; 149: 46-52. https://dx.doi.org/10.1016/j.lungcan.2020.09.003.

11. Paz-Ares L, Dvorkin M, Chen Y et al. Durvalumab plus platinum-etoposide versus platinum-etoposide in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): a randomised, controlled, open-label, phase 3 trial. Lancet 2019; 394(10212): 1929-1939. https://dx.doi.org/10.1016/S0140-6736(19)32222-6.

12. Goldman JW, Dvorkin M, Chen Y et al. Durvalumab, with or without tremelimumab, plus platinum–etoposide versus platinum–etoposide alone in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): updated results from a randomised, controlled, open-label, phase 3 trial. Lancet Oncol 2020. https://dx.doi.org/https://doi.org/10.1016/S1470-2045(20)30539-8.

13. Leitlinienprogramm Onkologie. S3-Leitlinie - Prävention, Diagnostik, Therapie und Nachsorge des Lungenkarzinoms, Langversion 1.0 [online]. 2018 [Accessed: 20.11.2019]. URL: https://www.leitlinienprogramm-onkologie.de/fileadmin/user_upload/Downloads/Leitlinien/Lungenkarzinom/LL_Lungenkarzinom_Langversion_1.0.pdf.

14. AstraZeneca. Fachinformation Imfinzi 50 mg/ml Konzentrat zur Herstellung einer Infusionslösung. Stand der Information: August 2020.

15. Fresenius Kabi Deutschland. Fachinformation Carboplatin Kabi 10 mg/ml Konzentrat zur Herstellung einer Infusionslösung; Stand der Information: Februar 2020.

16. Hikma Farmacêutica. Fachinformation Cisplatin-Lösung Ribosepharm. Stand der Information: Dezember 2018.

17. Hexal. Fachinformation Etoposid HEXAL®. Stand der Information: Oktober 2019.

18. Gemeinsamer Bundesausschuss. Tragende Gründe zum Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII – Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V; Atezolizumab (neues Anwendungsgebiet: fortgeschrittenes, kleinzelliges Lungenkarzinom, Erstlinie, Kombination mit Carboplatin und Etoposid) [online]. 2020 [Accessed: 03.12.2020]. URL: https://www.g-ba.de/downloads/40-268-6475/2020-04-02_AM-RL-XII_Atezolizumab_nAWG_D-491_TrG.pdf.

19. Sallam M, Wong H, Escriu C. Treatment beyond four cycles of first line Platinum and Etoposide chemotherapy in real-life patients with stage IV Small Cell Lung Cancer: a retrospective study of the Merseyside and Cheshire Cancer network. BMC Pulm Med 2019; 19(1): 195. https://dx.doi.org/10.1186/s12890-019-0948-x.

20. Gemeinsamer Bundesausschuss. Mündliche Anhörung gemäß 5. Kapitel § 19 Abs. 2 Verfahrensordnung des Gemeinsamen Bundesausschusses; hier: Wirkstoff Atezolizumab (D-491) [online]. [Accessed: 19.11.2020]. URL: https://www.g-ba.de/downloads/91-1031-503/2020-02-24_Wortprotokoll-Atezolizumab_D-491pdf.pdf.

21. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Atezolizumab (kleinzelliges Lungenkarzinom): Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung [online]. 2020 [Accessed: 15.01.2020]. URL: https://www.iqwig.de/download/A19-86_Atezolizumab_Nutzenbewertung-35a-SGB-V_V1-0.pdf.

22. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Atezolizumab (kleinzelliges Lungenkarzinom): Addendum zum Auftrag A19-86 [online]. 2020 [Accessed: 06.04.2020]. URL: https://www.iqwig.de/download/A20-18_Atezolizumab_Addendum-zum-Auftrag-A19-86_V1-0.pdf.

23. Blum T, Barlag H, Arbeitsgemeinschaft Deutscher Tumorzentren e. V. Versorgungssituation beim Lungenkarzinom in Deutschland [online]. 2018 [Accessed: 20.11.2019]. URL: https://www.adt-netzwerk.de/forschung_mit_krebsregisterdaten/qualitaetskonferenzen/allgemein/bisherige_auswertungen/7._boqk_2018/thumb.php?pdf&b=L3BkZi9RdWFsaXTDpHRza29uZmVyZW56LzIwMTgvTHVuZ2VfUUtfRnJlaXRhZ18yMzAyMTgucGRm.

24. Kraywinkel K, Barnes B. Epidemiologie des kleinzelligen Lungenkarzinoms in Deutschland. Der Onkologe 2017; 23: 334–339.

25. Robert Koch-Institut, Gesellschaft der epidemiologischen Krebsregister in Deutschland. Krebs in Deutschland für 2015/2016 - 12. Ausgabe [online]. 2019 [Accessed: 31.01.2020]. URL: https://www.krebsdaten.de/Krebs/DE/Content/Publikationen/Krebs_in_Deutschland/kid_2019/krebs_in_deutschland_2019.pdf?__blob=publicationFile.

26. Berghmans T, Scherpereel A, Meert AP et al. A Phase III Randomized Study Comparing a Chemotherapy with Cisplatin and Etoposide to a Etoposide Regimen without Cisplatin for Patients with Extensive Small-Cell Lung Cancer. Front Oncol 2017; 7: 217. https://dx.doi.org/10.3389/fonc.2017.00217.

27. Früh M, Cathomas R, Siano M et al. Carboplatin and paclitaxel plus ASA404 as first-line chemotherapy for extensive-stage small-cell lung cancer: a multicenter single arm phase II trial (SAKK 15/08). Clin Lung Cancer 2013; 14(1): 34-39. https://dx.doi.org/10.1016/j.cllc.2012.04.001.

28. Wolf M, Eberhardt W, Früh M et al. DGHO-Leitlinie - Lungenkarzinom, kleinzellig (SCLC) [online]. 2019 [Accessed: 20.07.2020]. URL: https://www.onkopedia.com/de/onkopedia/guidelines/lungenkarzinom-kleinzellig-sclc/@@guideline/html/index.html.

29. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Dokumentation und Würdigung der Anhörung zum Entwurf der Allgemeinen Methoden 6.0 [online]. 2020 [Accessed: 13.11.2020]. URL: https://www.iqwig.de/download/Allgemeine-Methoden_DWA-Entwurf-fuer-Version-6-0_V1-0.pdf.

30. Basch E, Reeve BB, Mitchell SA et al. Development of the National Cancer Institute's patient-reported outcomes version of the common terminology criteria for adverse events (PRO-CTCAE). J Natl Cancer Inst 2014; 106(9). https://dx.doi.org/10.1093/jnci/dju244.

31. Dueck AC, Mendoza TR, Mitchell SA et al. Validity and Reliability of the US National Cancer Institute's Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE). JAMA Oncol 2015; 1(8): 1051-1059. https://dx.doi.org/10.1001/jamaoncol.2015.2639.

32. Hay JL, Atkinson TM, Reeve BB et al. Cognitive interviewing of the US National Cancer Institute's Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE). Qual Life Res 2014; 23(1): 257-269. https://dx.doi.org/10.1007/s11136-013-0470-1.

33. National Cancer Institute. NCI-PRO-CTCAE items-German [online]. 2020 [Accessed: 08.12.2020]. URL: https://healthcaredelivery.cancer.gov/pro-ctcae/pro-ctcae_german.pdf.

34. Tolstrup LK, Bastholt L, Zwisler AD et al. Selection of patient reported outcomes questions reflecting symptoms for patients with metastatic melanoma receiving immunotherapy. J Patient Rep Outcomes 2019; 3(1): 19. https://dx.doi.org/10.1186/s41687-019-0111-8.

35. Taarnhøj GA, Lindberg H, Johansen C et al. Patient-reported outcomes item selection for bladder cancer patients in chemo- or immunotherapy. J Patient Rep Outcomes 2019; 3(1): 56. https://dx.doi.org/10.1186/s41687-019-0141-2.

36. Dueck AC, Scher HI, Bennett AV et al. Assessment of Adverse Events From the Patient Perspective in a Phase 3 Metastatic Castration-Resistant Prostate Cancer Clinical Trial. JAMA Oncol 2020; 6(2): e193332. https://dx.doi.org/10.1001/jamaoncol.2019.3332.

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