Durvalumab
(small cell lung cancer, non-advanced)

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

EXTRACT

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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.

Patient and family involvement

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

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Part I: Benefit assessment

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

I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
AJCC	American Joint Committee on Cancer
BSC	best supportive care
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DGHO	Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie (German Society for Haematology and Medical Oncology)
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30
EORTC QLQ-LC13	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Lung Cancer 13
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IASLC	International Association for the Study of Lung Cancer
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
LS-SCLC	limited-stage small cell lung cancer
MRI	magnetic resonance imaging
PCI	prophylactic cranial irradiation
PFS	progression-free survival
PGIS	Patient's Global Impression of Severity
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SmPC	Summary of Product Characteristics

I 1 Executive summary of the benefit assessment

Background

In accordance with § 35a Social Code Book 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 29 July 2025.

Research question

The aim of this report is to assess the added benefit of durvalumab compared with best supportive care (BSC) as appropriate comparator therapy (ACT) in adults with limited-stage small cell lung cancer (LS-SCLC) whose disease has not progressed following platinum-based chemoradiation therapy.

The research question shown in Table 2 was defined in accordance with the ACT specified by the G-BA.

Table 2: Research question of the benefit assessment of durvalumab

Therapeutic indication	**ACT**[a]
Adults with LS-SCLC whose disease has not progressed following platinum-based chemoradiation therapy	BSC[b, c]
a. Presented is the ACT specified by the G-BA. b. BSC refers to the therapy that provides the patient with the best possible, individually optimized supportive treatment to alleviate symptoms and improve quality of life. c. It is assumed that BSC in the context of a study is offered both in the control group and in the intervention group. ACT: appropriate comparator therapy; BSC: best supportive care; G-BA: Federal Joint Committee; LS-SCLC: limited-stage small cell lung cancer	

The company followed the G-BA's specification of the 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 to derive the added benefit. This concurred with the company's inclusion criteria.

Study pool and study design

The ADRIATIC study is used for the benefit assessment. The ADRIATIC study is an ongoing double-blind, 3-arm RCT. The comparison of the durvalumab arm (hereinafter referred to as the intervention arm) with the placebo arm (hereinafter referred to as the comparator arm) is relevant for this assessment. The study included adults with LS-SCLC (stage I to III SCLC [any T, any N, M0] according to the American Joint Committee on Cancer (AJCC) Staging Manual or the International Association for the Study of Lung Cancer (IASLC)), who had previously

received simultaneous chemoradiation therapy. The primary tumour in patients with stage I or II LS-SCLC had to be deemed to be unresectable by the investigator. The chemoradiation therapy administered within the pretreatment was largely in line with the guidelines. The study included patients who, following the completion of simultaneous chemoradiation therapy, achieved a complete response, a partial response or stable disease and did not develop disease progression.

The arms of the ADRIATIC study which were relevant for this assessment included 530 patients. 264 patients were randomly assigned to the intervention arm and 266 patients to the comparator arm.

Treatment with durvalumab was in compliance with the Summary of product characteristics (SmPC). In the comparator arm, a placebo was administered corresponding to the intervention.

Primary outcomes of the ADRIATIC study were progression-free survival (PFS) and overall survival. Secondary outcomes were outcomes from the categories morbidity, health-related quality of life, and side effects.

Implementation of the ACT

The G-BA specified BSC as ACT.

According to the study protocol, BSC was permitted for all patients in both arms of the ADRIATIC study where necessary. In addition, a placebo was administered in the comparator arm to ensure blinding. BSC included, among other things, the treatment of metabolic disorders, symptom control and pain therapy. The use of these treatments was documented as part of the study and occurred to a relevant extent in both arms. In summary, the ACT was adequately implemented in the ADRIATIC study.

Subsequent therapies

In Module 4A, the company does not provide any information on the subsequent therapies used in the ADRIATIC study. The study report only contains aggregated information on subsequent systemic antineoplastic therapies, without specifying the drugs used.

In the ADRIATIC study, subsequent antineoplastic therapies were permitted without restrictions in both study arms. Due to the lack of specific guideline recommendations for second-line systemic therapy for patients with disease progression following initial LS-SCLC or insufficient evidence, it is not generally assumed that effective subsequent systemic antineoplastic therapies were unavailable to patients to a relevant extent, despite the lack of information on the drugs used.

Risk of bias

The risk of bias across outcomes for the ADRIATIC study is rated as low.

The risk of bias of the results on the outcomes overall survival and discontinuation due to adverse events (AEs) was rated as low. For all other outcomes, the risk of bias of the results was rated as high. Although the risk of bias for the outcome discontinuation due to AEs was low, the certainty of results for this outcome was limited.

Results

Mortality

Overall survival

For the outcome overall survival, a statistically significant difference was found in favour of durvalumab in comparison with placebo. There is an indication of added benefit of durvalumab in comparison with the ACT.

Morbidity

Failure of the curative treatment approach

No suitable data were available for the outcome of failure of the curative treatment approach. This results in no hint of an added benefit of durvalumab over the ACT; greater or lesser harm is therefore not proven for the outcome failure of the curative treatment approach.

Symptoms (recorded using European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30 [EORTC QLQ-C30], European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Lung Cancer 13 [EORTC QLQ-LC13] and Patient's Global Impression of Severity [PGIS])

There was no statistically significant difference between the treatment arms for each of the outcomes fatigue, nausea and vomiting, pain, dyspnoea, loss of appetite, constipation and diarrhoea (recorded using the EORTC QLQ-C30), the outcomes cough, haemoptysis, dyspnoea, chest pain, pain in other parts of the body, sore mouth, dysphagia, peripheral neuropathy and alopecia (recorded using the EORTC QLQ-LC13), and symptoms recorded using the PGIS. There is no hint of an added benefit of durvalumab over the ACT for any of these outcomes; an added benefit is therefore not proven for these outcomes.

Insomnia

For the outcome insomnia (recorded using the EORTC QLQ-C30), no statistically significant difference between treatment arms was found when considering the total population. There was an effect modification by the characteristic sex for this outcome. For men, there is a hint of lesser benefit of durvalumab in comparison with the ACT. For women, there is no hint of an added benefit or lesser benefit of durvalumab in comparison with the ACT; an added benefit is therefore not proven for women.

Pain in the arm or shoulder

For the outcome pain in the arm or shoulder, a statistically significant difference was found in favour of durvalumab over placebo. This results in a hint of added benefit of durvalumab in comparison with the ACT.

Health status (recorded with the EQ-5D VAS)

No statistically significant difference between the treatment arms was shown for the outcome health status (recorded using the EQ-5D VAS). There is no hint of an added benefit of durvalumab over the ACT; an added benefit is therefore not proven for this outcome.

Health-related quality of life

No statistically significant difference between the treatment arms was found for any of the outcomes global health status, physical functioning, role functioning, cognitive functioning, emotional functioning and social functioning (recorded using the EORTC QLQ-C30). There is no hint of an added benefit of durvalumab over the ACT for any of these outcomes; an added benefit is therefore not proven for these outcomes.

Side effects

Serious AEs (SAEs), severe AEs, discontinuation due to AEs, and pneumonitis

No statistically significant difference between treatment arms was found for any of the outcomes SAEs, severe AEs, discontinuation due to AEs and pneumonitis. For each of them, there is no hint of greater or lesser harm from durvalumab in comparison with the ACT; greater or lesser harm is therefore not proven for these outcomes.

A (PRO-CTCAE)

No suitable data are available for PRO-CTCAE. This results in no hint of an added benefit of durvalumab over the ACT; greater or lesser harm is therefore not proven for PRO-CTCAE.

Immune-mediated SAEs and immune-mediated severe AEs

For each of the outcomes immune-mediated SAEs and immune-mediated severe AEs, a statistically significant difference was found to the disadvantage of durvalumab in comparison with placebo. This results in a hint of greater harm from durvalumab in comparison with the ACT for both outcomes.

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

On the basis of the results presented, the probability and extent of added benefit of the drug durvalumab in comparison with the ACT is assessed as follows:

Overall, both positive and negative effects of durvalumab were shown in comparison with the ACT. On the positive effects side, there is an indication of considerable added benefit in the outcome overall survival and a hint of minor added benefit for pain in the arm or shoulder. On the other hand, there are hints of greater harm with considerable extent for serious and severe immune-mediated AEs in particular for serious and severe side effects, as well as a hint of a lesser benefit in men in terms of insomnia.

In summary, for adults with LS-SCLC whose disease has not progressed following platinum-based chemoradiation therapy, there is an indication of a minor added benefit of durvalumab over the ACT (BSC).

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

Table 3: Durvalumab – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adults with LS-SCLC whose disease has not progressed following platinum-based chemoradiation therapy	BSC[b, c]	Indication of minor added benefit[d]

a. Presented is the ACT specified by the G-BA.
b. BSC refers to the therapy that provides the patient with the best possible, individually optimized supportive treatment to alleviate symptoms and improve quality of life.
c. It is assumed that BSC in the context of a study is offered both in the control group and in the intervention group.
d. The ADRIATIC study included only patients with an ECOG PS of 0 or 1. It remains unclear whether the observed effects are transferable to patients with an ECOG PS ≥ 2.

ACT: appropriate comparator therapy; BSC: best supportive care; ECOG PS: Eastern Cooperative Oncology Group – Performance Status; G-BA: Federal Joint Committee; LS-SCLC: limited-stage small cell lung cancer

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

[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].

I 2 Research question

The aim of this report is to assess the added benefit of durvalumab compared with BSC as ACT in adults with LS-SCLC whose disease has not progressed following platinum-based chemoradiation therapy.

The research question shown in Table 4 was defined in accordance with the ACT specified by the G-BA.

Table 4: Research question of the benefit assessment of durvalumab

Therapeutic indication	**ACT**[a]
Adults with LS-SCLC whose disease has not progressed following platinum-based chemoradiation therapy	BSC[b, c]
a. Presented is the ACT specified by the G-BA. b. BSC refers to the therapy that provides the patient with the best possible, individually optimized supportive treatment to alleviate symptoms and improve quality of life. c. It is assumed that BSC in the context of a study is offered both in the control group and in the intervention group. ACT: appropriate comparator therapy; BSC: best supportive care; G-BA: Federal Joint Committee; LS-SCLC: limited-stage small cell lung cancer	

The company followed the G-BA's specification of the 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 to derive the added benefit. This concurred with the company's inclusion criteria.

I 3 Information retrieval and study pool

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

Sources used by the company in the dossier:

- Study list on durvalumab (status: 27 May 2025)
- Bibliographical literature search on durvalumab (last search on 27 May 2025)
- Search in trial registries/trial results databases for studies on durvalumab (last search on 27 May 2025)
- Search on the G-BA website for durvalumab (last search on 27 May 2025)

To check the completeness of the study pool:

- Search in trial registries for studies on durvalumab (last search on 13 August 2025); for search strategies, see Appendix I A of the full dossier assessment

The search did not identify any additional relevant studies.

I 3.1 Studies included

The study presented in the following Table 5 was included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: durvalumab vs. BSC

Study	Study category			Available sources		
	Study for the marketing authorization of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	CSR (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication and other sources[c] (yes/no [citation])
ADRIATIC	Yes	Yes	No	Yes [3]	Yes [4-6]	Yes [7,8]

a. Study sponsored by the company.
b. Citation of the trial registry entries and, if available, of the reports on study design and/or results listed in the trial registries.
c. Other sources: documents from the search on the G-BA website and other publicly available sources.

BSC: best supportive care; RCT: randomized controlled trial

I 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 vs. placebo

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
ADRIATIC	RCT, double-blind, parallel	Adult patients with LS-SCLC ▪ whose disease has not progressed following platinum-based chemoradiation therapy ▪ ECOG PS ≤ 1	Durvalumab (N = 264) durvalumab + tremelimumab (N = 200)[b] placebo (N = 266)	Screening: up to 42 days[c] treatment: until disease progression, unacceptable toxicity, reaching the maximum duration of therapy (24 months) observation[d]: outcome-specific, at most until death or end of studye	164 centres in Argentina, Belgium, Canada, China, Czech Republic, Germany, India, Italy, Japan, Netherlands, Poland, Russia, South Korea, Spain, Taiwan, Turkey, United Kingdom, United States, Vietnam 09/2018–ongoing data cut-offs: ▪ 06 December 2023[f] ▪ 15 January 2024[g]	Primary: PFS, overall survival secondary: morbidity, health-related quality of life, AEs

a. Primary outcomes include information without taking into account the relevance for this benefit assessment. Secondary outcomes only include information on relevant available outcomes for this benefit assessment.
b. The study arm is not relevant for the assessment and is not shown in the next tables.
c. Following simultaneous chemoradiation therapy and prophylactic cranial irradiation (where applicable).
d. Outcome-specific information is provided in Table 8.
e. Patients who withdrew their consent to participate in the study continued to be monitored for overall survival, provided they did not explicitly object to this. Hospital records, death registers or information provided by the treating physicians should be consulted in order to record the survival status of patients who were classified as 'lost to follow-up' or who withdrew their consent to participate in the study.
f. For the analysis of the outcomes on pharmacokinetic and anti-drug antibodies.
g. Prespecified interim analysis on PFS and OS (planned after approximately 308 PFS events or approximately 242 deaths).

AE: adverse event; ECOG PS: Eastern Cooperative Oncology Group – Performance Status; LS-SCLC: limited-stage small cell lung cancer; N: number of randomized patients; OS: overall survival; PFS: progression-free survival; RCT: randomized controlled trial; RECIST: Response Evaluation Criteria in Solid Tumours

Table 7: Characteristics of the intervention – RCT, direct comparison: durvalumab vs. placebo (multipage table)

Study	Intervention	Comparison
ADRIATIC	Durvalumab 1500 mg IV every 4 weeks[a]	Placebo IV, every 4 weeks[a]
	▪ Dose reduction was not allowed[b].	
	Disallowed prior and concomitant treatment ▪ allogeneic organ transplantation ▪ sequential chemoradiation therapy, without any overlap between radiotherapy and chemotherapy ▪ chemotherapy comprising more than four cycles, or other chemotherapies not based on platinum or etoposide ▪ any other simultaneously administered chemotherapy, immunotherapy, or biological or hormonal therapy for oncological treatment other than the investigational therapy ▪ live vaccines within 30 days before the first and up to 30 days after the last dose of the study medication ▪ major surgery according to the investigator's definition within 42 days before the first dose of study medication ▪ monoclonal antibodies directed against CTLA-4, PD-1, PD-L1 or PD-L2 or other immune-mediated therapies ▪ previous (within 2 weeks prior to the first dose of durvalumab) or simultaneous administration of immunosuppressants (e.g. systemic corticosteroids ≥ 10 mg/day prednisone or equivalent, methotrexate, azathioprine, tumour necrosis factor-α (TNF-α) inhibitors) ▪ EGFR tyrosine kinase inhibitors ▪ sunitinib ▪ herbal and natural remedies with potential immunomodulatory effect **allowed concomitant treatment** ▪ BSC, including: ▫ antibiotics ▫ nutritional support ▫ treatment of metabolic disorders ▫ symptom control and pain management, including palliative radiotherapy for non-target lesions ▫ acetaminophen, diphenhydramine, or other medications deemed necessary by the investigator for appropriate prophylactic or supportive treatment ▪ hormonal therapy for the treatment of non-oncological diseases ▪ intranasal, inhaled, topical steroids, or local steroid injections (e.g. intra-articular injection) (e.g. intra-articular injection) ▪ systemic corticosteroids in physiological doses of ≤10 mg/day of prednisone or its equivalent ▪ steroids as premedication for hypersensitivity reactions ▪ inactivated viruses, e.g. Influenza vaccination ▪ steroids, infliximab and mycophenolate as rescue medication for immune-mediated AEs	

a. Due to the third study arm, in which durvalumab was combined with tremelimumab over four cycles, an additional intravenous placebo was administered for the first four cycles in both study arms to ensure blinding; treatment was continued until unacceptable toxicity, clinical disease progression/disease progression as defined by RECIST 1.1, or for up to a total of 24 months (whichever occurred first).
b. Patients with a body weight ≤ 30 kg were to receive a weight-based dosing of 20 mg/kg of durvalumab or placebo every 4 weeks until the body weight increased to > 30 kg.

Table 7: Characteristics of the intervention – RCT, direct comparison: durvalumab vs. placebo (multipage table)

Study	Intervention	Comparison
AE: adverse event; BSC: best supportive care; CTLA-4: cytotoxic T-lymphocyte-associated antigen 4; EGFR: epidermal growth factor receptor; IV: intravenous; PD-1: programmed cell death 1; PD-L1/2: programmed cell death ligand 1/2; RCT: randomized controlled trial; RECIST: Response Evaluation Criteria in Solid Tumours		

Study characteristics

The ADRIATIC study is an ongoing double-blind, 3-arm RCT. The comparison of the durvalumab arm (hereinafter referred to as the intervention arm) with the placebo arm (hereinafter referred to as the comparator arm) is relevant for this assessment. The third study arm, durvalumab in combination with tremelimumab, is not considered further in this benefit assessment.

The study included adults with LS-SCLC (stage I to III SCLC [any T, any N, M0] according to the AJCC Staging Manual or the IASLC), who had previously received simultaneous chemoradiation therapy. The primary tumour in patients with stage I or II LS-SCLC had to be deemed to be unresectable by the investigator. The chemotherapy had to comprise 4 cycles of platinum-based doublet chemotherapy in combination with etoposide in accordance with local treatment standards, and had to be completed between 42 and 1 day(s) prior to the first dose of study medication (screening period). Patients who had undergone three cycles of chemotherapy were also eligible for inclusion if their disease was under control and, at the investigator's discretion, no added benefit was expected from a further cycle. Radiotherapy had to have started by the end of the second cycle of chemotherapy at the latest. Patients who had undergone sequential chemoradiation therapy were excluded. According to the S3 guideline on the prevention, diagnosis, treatment and follow-up of lung cancer [9], radiotherapy in patients with SCLC in tumour stages T3-4 N0-1 and T1-4 N2-3 M0 should be administered simultaneously to chemotherapy with cisplatin and etoposide. Carboplatin-based protocols should only be used in cases where there are contraindications to cisplatin. The chemoradiation therapy used in the pretreatment of included patients was largely in accordance with the guidelines (see Table 9).

The study included patients who achieved a complete response following the completion of simultaneous chemoradiation therapy, a partial response or stable disease and did not develop disease progression. The examination was performed using computed tomography (CT) or magnetic resonance imaging (MRI) following the completion of the simultaneous chemoradiation therapy and between 42 and 1 day(s) prior to the first dose of the study medication.

The general condition of the patients had to concur with an Eastern Cooperative Oncology Group – Performance Status (ECOG PS) or a WHO PS of 0 or 1. Patients had to have a life expectancy of at least 12 weeks and a body weight of more than 30 kg.

The arms of the ADRIATIC study which were relevant for this assessment included 530 patients. 264 patients were randomly assigned to the intervention arm and 266 patients to the comparator arm. Randomization was stratified by the TNM classification (tumour size, lymph node involvement and metastases; I/II vs. III) and by administration of prophylactic cranial irradiation (PCI) (yes vs. no).

Treatment with durvalumab was in compliance with the SmPC [10]. A dose of 1500 mg durvalumab was administered intravenously at four-week intervals. Treatment was continued until unacceptable toxicity, clinical disease progression/disease progression as defined by RECIST Version 1.1, or for up to a total of 24 months (whichever occurred first). In the comparator arm, a placebo was administered corresponding to the intervention.

Primary outcomes of the ADRIATIC study were PFS and overall survival. Secondary outcomes were outcomes from the categories morbidity, health-related quality of life, and side effects.

Implementation of the ACT

The G-BA specified BSC as ACT.

The S3 guideline [9] does not specify any specific measures for BSC in LS-SCLC. The section on palliative treatment for metastatic lung cancer focuses primarily on the relief of dyspnoea and pain. It is assumed that appropriate BSC should include measures for symptom control and pain therapy even in the non-advanced stage of the disease. These are intended to improve quality of life. As SCLC has a neuroendocrine origin [11] and paraneoplastic syndromes occur in approximately 10% of patients with lung cancer [9], including endocrine disorders, the treatment of metabolic disorders should also be considered to be part of BSC.

According to the study protocol, BSC was permitted for all patients in both arms of the ADRIATIC study where necessary. In addition, a placebo was administered in the comparator arm to ensure blinding. As described in Table 7, the BSC included, among other things, treatment of metabolic disorders, symptom control and pain therapy. The use of these treatments was documented as part of the study and occurred to a relevant extent in both arms.

In summary, the ACT was adequately implemented in the ADRIATIC study.

Data cut-offs

The company has presented results on the data cut-off of 15 January 2024. This data cut-off was performed for the PFS interim analysis, which was planned once a total of approximately 308 PFS events had occurred in the two study arms considered here (durvalumab vs. placebo). The first prespecified interim analysis of overall survival was to take place at the same time, provided that approximately 242 deaths had occurred in the two arms by that point. By the data cut-off date of 15 January 2024, 308 patients in the intervention or the comparator arm had experienced disease progression, and 261 had died. The submitted data cut-off of 15 January 2024 is relevant for this benefit assessment. A final analysis is still pending.

Planned duration of follow-up

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

Table 8: Planned duration of follow-up observation – RCT, direct comparison: durvalumab versus placebo

Study **outcome category** **outcome**	**Planned follow-up observation**
ADRIATIC	
Mortality	
Overall survival	Until death or study end
Morbidity	
Symptoms (EORTC QLQ-C30 and EORTC QLQ-LC13, PGIS)	Until the second disease progression, end of the study or death (whichever came first)
Health status (EQ-5D VAS)	Until the second disease progression, end of the study or death (whichever came first)
Health-related quality of life (EORTC QLQ-C30)	Until the second disease progression, end of the study or death (whichever came first)
Side effects	
All outcomes of the side effects category (except PRO-CTCAE)	Until 90 days after the last dose of the study medication
PRO-CTCAE	Until the second disease progression, end of the study or death (whichever came first)

AE: adverse event; EORTC: European Organisation for Research and Treatment of Cancer; PGIS: Patient Global Impression of Severity; PRO-CTCAE: Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events; 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; VAS: visual analogue scale

The observation periods for the outcomes of the categories morbidity, health-related quality of life and side effects were systematically shortened. Side effects (except for the PRO-CTCAE) were only recorded up to 90 days after the last dose of the study medication. The outcomes

of the categories morbidity and health-related quality of life as well as the PRO-CTCAE were observed beyond the first disease progression, but only up to the second disease progression. However, drawing a reliable conclusion on the total study period or the time to patient death would require recording these outcomes for the total period, as was done for survival.

Table 9 shows the patient characteristics of the included study.

Table 9: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: durvalumab versus placebo (multipage table)

Study characteristic category	**Durvalumab N = 264**	**Placebo N = 266**
ADRIATIC		
Age [years], mean (SD)	62 (9)	61 (9)
Sex [F/M], %	33/67	29/71
Body weight [kg], mean (SD)	71.7 (15.1)	72.6 (15.1)
BMI, mean (SD)	25.4 (4.2)	25.7 (4.6)
Family origin, n (%)		
White	130 (49)	137 (52)
Black or African American	1 (< 1)	3 (1)
Asian	131 (50)	121 (45)
Other	2 (< 1)	5 (2)
Geographical region, n (%)		
Asia	129 (49[a])	120 (45[a])
Europe	94 (36[a])	112 (42[a])
North/South America	41 (16[a])	34 (13[a])
Smoking status, n (%)		
Never smoker	23 (9)	26 (10)
Active	63 (24)	55 (21)
Former	178 (67)	185 (70)
ECOG PS, n (%)		
0	132 (50)	126 (47)
1	132 (50)	140 (53)
PD-L1 status, n (%)[b]		
TC and IC < 1%	78 (30)	73 (27)
TC and IC ≥ 1%	84 (32)	98 (37)
Missing	102 (39)	95 (36)

Table 9: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: durvalumab versus placebo (multipage table)

Study characteristic category	**Durvalumab N = 264**	**Placebo N = 266**
Number of chemotherapy cycles, n (%)		
2	0 (0)	1 (< 1)
3	29 (11)	31 (12)
4	234 (89)	234 (88)
6	1 (< 1)	0 (0)
Chemotherapy, n (%)		
Cisplatin and etoposide	173 (66)	178 (67)
Carboplatin and etoposide	91 (34)	88 (33)
Radiotherapy, n (%)		
Once daily	195 (74)	187 (70)
Twice daily	69 (26)	79 (30)
Response to simultaneous chemoradiation therapy, n (%)		
Complete response	31 (12)	34 (13)
Partial response	191 (72)	200 (75)
Stable disease	42 (16)	32 (12)
TNM classification based on IVRS, n (%)		
I/II	36 (14)	37 (14)
III	228 (86)	229 (86)
AJCC staging at the time of diagnosis, n (%)		
I	8 (3)	11 (4)
II	25 (9)	23 (9)
III	231 (88)	232 (87)
Receipt of PCI based on IVRS, n (%)		
Yes	142 (54)	144 (54)
No	122 (46)	122 (46)
Treatment discontinuation, n (%)[c]	175 (66[a])	195 (73[a])
Study discontinuation, n (%)[d]	124 (47[a])	155 (58[a])

a. Institute's calculation.
b. The PD-L1 expression of the tumour tissue was determined by immunohistochemistry using the SP263 assay.
c. Common reasons for treatment discontinuation in the intervention vs. the comparator arm were (percentages based on randomized patients): deterioration of the condition (46% vs. 58%) and AEs (16% vs. 11%). In addition, one patient in each group never started the treatment.
d. The reason for study discontinuation in the intervention vs. the comparator arm was patient decision in 3% vs. 4% (percentages refer to randomized patients). The data also comprise patients who died during the course of the study (44% vs. 54%; percentages refer to the randomized patients).

Table 9: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: durvalumab versus placebo (multipage table)

Study characteristic category	Durvalumab N = 264	Placebo N = 266
AE: adverse event; AJCC: American Joint Committee on Cancer; BMI: body mass index; ECOG PS: Eastern Cooperative Oncology Group – Performance Status; f: female; IC: immune cell; IVRS: interactive voice/web response system; m: male; n: number of patients in the category; N: number of randomized patients; PCI: prophylactic cranial irradiation; PD-L1: programmed cell death ligand 1; RCT: randomized controlled trial; SD: standard deviation; TC: tumour cell; TNM: tumour size, lymph node involvement and metastases		

Patient characteristics

The patient characteristics in the ADRIATIC study are largely comparable between the treatment arms. The mean age of patients in the intervention arm was 62 years, while the mean age of patients in the comparator arm was 61 years; the majority were male (67% vs. 71%). Almost all of them were white or Asian. Around half had an ECOG PS of 0 or 1. 11% versus 12% of patients received only three cycles of chemotherapy. This was permitted under the study protocol if, at the investigator's discretion, no further benefit was to be gained from an additional cycle. Following simultaneous chemoradiation therapy, 12% vs. 13% achieved complete response; the majority achieved partial response (72% vs. 75%). The author does not specify which imaging technique (MRI or CT) was used to record the response.

Limitations of the ADRIATIC study

Detection of brain metastases upon study inclusion

To rule out cerebral metastasis, both MRI (preferred) and high-quality CT scans, preferably with contrast agent, were accepted following the completion of simultaneous chemoradiation therapy in the ADRIATIC study. The S3 guideline [9] recommends the detection of brain metastases using MRI; a contrast-enhanced CT scan should only be used as an alternative in cases where MRI is contraindicated. The sole examination by means of CT is not suitable to rule out cerebral metastases with certainty. It is therefore possible that patients with brain metastases were included in the study who were not covered by the therapeutic indication. The company did not present data on the use of CT and MRI scans of the cranium that had been recorded in the case report form.

PCI

According to the current S3 guideline [9], PCI should be offered to all patients. The ADRIATIC study was open to patients who underwent PCI at the discretion of the investigator and in accordance with local treatment standards. The PCI had to be performed following completion of the simultaneous chemoradiation therapy and between 42 and 1 day(s) prior to the first dose of the study medication. In total, 54% of patients in both study arms underwent PCI. It is

unclear what proportion of patients in the ADRIATIC study were offered PCI but did not undergo the procedure due to cognitive side effects or other reasons.

Overall, it is assumed that the described limitations of the ADRIATIC study have no relevant influence on the study results. They therefore remain without consequences for the dossier assessment.

Information on the course of the study

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

Table 10: Information on the course of the study – RCT, direct comparison: durvalumab versus placebo (multipage table)

Study **duration of the study phase** **outcome category/outcome**	**Durvalumab** **N = 264**	**Placebo** **N = 266**
ADRIATIC		
Treatment duration [months][a, b]		
Median [min; max]	9.2 [0.9; 24.8]	8.3 [0.9; 24.8]
Mean (SD)	12.5 (9.2)	11.3 (8.8)
Observation period [months]		
Overall survival[c]		
Median [Q1; Q3]	30.8 [16.3; 39.5]	28.6 [14.1; 37.7]
Mean (SD)	ND	ND
Symptoms, health-related quality of life (EORTC QLQ-C30)[d]		
Median [min; max]	12.9 [0.0; 58.0]	10.1 [0.0; 58.8]
Mean (SD)	ND	ND
Symptoms (EORTC QLQ-LC13)[d]		
Median [min; max]	12.9 [0.0; 57.0]	10.1 [0.0; 58.8]
Mean (SD)	ND	ND
Symptoms (PGIS)[d]		
Median [min; max]	12.8 [0.0; 57.0]	9.2 [0.0; 58.8]
Mean (SD)	ND	ND
Health status (EQ-5D VAS)[d]		
Median [min; max]	12.8 [0.0; 57.0]	9.2 [0.0; 58.8]
Mean (SD)	ND	ND
Side effects[b, e]		
Median [min; max]	10.3 [1.3; 26.9]	9.2 [1.1; 26.9]
Mean (SD)	ND	ND

Table 10: Information on the course of the study – RCT, direct comparison: durvalumab versus placebo (multipage table)

Study duration of the study phase outcome category/outcome	Durvalumab N = 264	Placebo N = 266
a. According to the company, the duration of treatment is defined as the number of days from the first dose of the study medication to the last dose of the study medication (+ 27 days; end of the treatment cycle), until death or until the data cut-off, whichever occurs first. b. Patients who received at least one dose of the study medication; patients were assigned to the treatment they actually received (safety analysis set; N = 262 vs. N = 265). c. According to the company, the individual observation period is defined as the time from randomization to the date of the event, if it occurred, or to the date of the last available recording. Information on the calculation method of the median is not available. d. No information is available regarding the determination of the individual observation duration or on the methodology used to calculate the median. e. According to the company, the individual observation duration is defined as the time from the first administration of the study medication until the data cut-off, until 90 days after discontinuation of study treatment, until the start of follow-up therapy, or until death, whichever occurs first. Information on the calculation of the median is not available. EORTC: European Organisation for Research and Treatment of Cancer; max: maximum; min: minimum; N: number of analysed patients; PGIS: Patient Global Impression of Severity; PRO-CTCAE: Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events; 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		

Both the median treatment duration and the median observation periods are longer in the intervention arm than in the comparator arm for all outcomes. However, for the outcome overall survival, which is observed throughout the entire course of the study, the relative difference in median observation times is clearly smaller than for the outcomes that were observed over a shorter period. This applies to all outcomes of the categories morbidity, health-related quality of life, and side effects.

Subsequent therapies

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

Table 11: Information on subsequent systemic antineoplastic therapies[a] – RCT, direct comparison: durvalumab versus placebo

Study therapy	Patients with subsequent therapy, n (%)	
	durvalumab N = 264	placebo N = 266
ADRIATIC		
Total	95 (36.0)	127 (47.7)
Cytotoxic chemotherapy, monotherapy	22 (23.2[b])	31 (24.4[b])
Cytotoxic chemotherapy, platinum-based doublet therapy	48 (50.5[b])	51 (40.2[b])
Chemotherapy + immunotherapy	9 (9.5[b])	26 (20.5[b])
Chemotherapy + targeted therapy	1 (1.1[b])	1 (0.8[b])
Chemotherapy + immunotherapy + targeted therapy	0 (0[b])	2 (1.6[b])
Another chemotherapy combination	5 (5.3[b])	9 (7.1[b])
Immunotherapy, monotherapy	5 (5.3[b])	5 (3.9[b])
Immunotherapy + immunotherapy	2 (2.1[b])	0 (0[b])
Immunotherapy + targeted therapy	1 (1.1[b])	0 (0[b])
Targeted therapy, monotherapy	1 (1.1[b])	2 (1.6[b])
Antibody-drug conjugate, monotherapy	1 (1.1[b])	0 (0)

a. First subsequent therapy following discontinuation of treatment; taken directly from study documents without adjustment.
b. Institute's calculation; percentages refer to the number of patients receiving subsequent antineoplastic therapy.

n: number of patients with subsequent therapy; N: number of analysed patients; RCT: randomized controlled trial

Subsequent therapies

In Module 4A, the company does not provide any information on the subsequent therapies used in the ADRIATIC study. The study report only contains the aggregated information presented on subsequent systemic antineoplastic therapies, without specifying the drugs used.

In the ADRIATIC study, subsequent antineoplastic therapies were permitted without restrictions in both study arms.

The S3 guideline [9] distinguishes between local and systemic progression or recurrence in its recommendations for second-line therapy. It recommends local therapy (resection or radiotherapy) for the treatment of local recurrence/progression in patients with an initially limited tumour stage. However, it is unclear what proportion of local recurrences/progressions were observed in the ADRIATIC study, and what treatment – local or systemic therapy – was administered in such cases. In total, 66.9% versus 73.8% of patients

with radiological progression received subsequent systemic antineoplastic therapy. This proportion seems plausible in this therapeutic indication.

As shown in Table 11, the majority of patients in the intervention and the comparator arm (73.7% vs. 64.6%) of the ADRIATIC study received chemotherapy (monotherapy or doublet therapy) as subsequent therapy (in each case relating to patients with subsequent systemic antineoplastic therapy). Approximately 9.5% versus 20.5% received chemoimmunotherapy; however, it is unclear from the available data whether the chemotherapy consisted of a platinum-based doublet therapy or a monotherapy. A difference between the study arms in the use of chemoimmunotherapy as subsequent therapy appears plausible given the first-line treatment administered in the respective study arms, as patients in the comparator arm had not yet received immunotherapy. A small number of patients also received immunotherapy or targeted therapy as subsequent therapy, either as monotherapy, doublet therapy or in combination (9.5% vs. 5.5%).

The S3-guideline does not provide any specific recommendations for second-line systemic therapy in patients with LS-SCLC who received chemoradiation therapy (± maintenance therapy with durvalumab). Regardless of the stage (LS or ES) and the first-line treatment received, chemotherapy with topotecan is the primary recommendation for second-line systemic therapy of SCLC. However, the percentage of topotecan in the second-line chemotherapies used in the ADRIATIC study is unclear. In accordance with the recommendations of the German Society for Haematology and Medical Oncology (DGHO) [11], patients with progressive LS-SCLC should be treated with chemoimmunotherapy following simultaneous chemoradiation therapy (± maintenance therapy with durvalumab), analogous to the first-line treatment of ES-SCLC. It is assumed that this recommendation is based on studies on durvalumab (CASPIAN) and atezolizumab (IMpower133). However, the transferability of the results from these studies to patients in this therapeutic indication is unclear. The CASPIAN study did not include patients with initial LS-SCLC who had previously been treated with chemoradiation therapy. No data are available for the IMpower133 study regarding the number of patients with initial LS-SCLC who were treated with chemoradiation therapy ± durvalumab.

Due to the lack of specific guideline recommendations for second-line systemic therapy for patients with disease progression following initial LS-SCLC or insufficient evidence, it is not generally assumed that effective subsequent systemic antineoplastic therapies were unavailable to patients to a relevant extent, despite the lack of information on the drugs used.

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 versus placebo

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			
ADRIATIC	Yes	Yes	Yes	Yes	Yes	Yes	Low
RCT: randomized controlled trial							

The risk of bias across outcomes for the ADRIATIC study is rated as low.

Transferability of the study results to the German health care context

The company points out that the patient characteristics of the study population in the ADRIATIC study—in terms of proportion of men, age, smoking status, tumour stage, and symptoms—largely reflect the situation in the German population, citing, among other sources, registry data from the Robert Koch Institute (RKI) [12-14]. It explains that the median age of 62 years in the ADRIATIC study was only slightly below the median age of 67 years upon diagnosis [12]. Furthermore, the majority of patients were male, consisted of current and former smokers, and had stage III disease.

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

I 4 Results on added benefit

I 4.1 Outcomes included

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

- Mortality
  - overall survival
- Morbidity
  - failure of the curative treatment approach
  - symptoms
    - symptoms recorded using the EORTC QLQ-C30 and EORTC QLQ-LC13
    - recorded using the PGIS
  - health status, recorded using the EQ-5D VAS
- Health-related quality of life
  - recorded with the EORTC QLQ-C30
- Side effects
  - SAEs
  - severe AEs (CTCAE grade 3 or 4)
  - discontinuation due to AEs
  - PRO-CTCAE
  - immune-mediated AEs, SAEs and severe AEs
  - pneumonitis (AEs)

The selection of patient-relevant outcomes deviated 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 included study.

Table 13: Matrix of outcomes – RCT, direct comparison: durvalumab versus placebo

Study	Outcomes												
	Overall survival	Failure of the curative treatment approach	Symptoms (EORTC QLQ-C30, EORTC QLQ-LC13, PGIS)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30)	SAEs	Severe AEs[a]	Discontinuation due to AEs	PRO-CTCAE	Immune-mediated SAEs[b]	Immune-mediated severe AEs[b]	Pneumonitis (AEs)[c]	Other specific AEs
ADRIATIC	Yes	No[d]	Yes	Yes	Yes	Yes	Yes	Yes	No[d]	Yes	Yes	Yes	No[e]

a. In Module 4A, the company operationalizes severe AEs as CTCAE grade ≥ 3. Based on the information in the study documents, it is clear that these are operationalized as CTCAE grade 3 or 4.
b. The predefined operationalization of AESI is used in each case, excluding infusion-related reactions and hypersensitivity reactions/anaphylactic reactions.
c. Operationalized using the GT pneumonitis or radiation pneumonitis.
d. No suitable data available; for reasons, see the following text section.
e. No further specific AEs were identified based on the AEs occurring in the relevant study.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; GP: grouped term; PGIS: Patient Global Impression of Severity; PRO-CTCAE: patient-reported outcome – CTCAE; 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; VAS: visual analogue scale

Failure of the curative treatment approach

In this therapeutic indication, simultaneous chemoradiation therapy, with or without maintenance therapy with durvalumab, represents a curative treatment approach. If the disease recurs or progresses during or after this treatment, it means that the curative treatment approach has failed. Failure of the curative treatment approach was therefore considered to be patient-relevant in this assessment.

In the ADRIATIC study, failure of the curative treatment approach was not directly recorded as an outcome. In Module 4A, the company presents data on PFS and discusses its relevance for the assessment of the outcome failure of the curative treatment approach. In the ADRIATIC study, PFS was operationalized as the time from randomization to disease progression or death from any cause, whichever occurred first. In the current situation, the PFS results are not suitable for reflecting the outcome of failure of the curative treatment approach. This is explained below.

In order to meaningfully assess the failure of the curative approach, it is generally necessary to carry out a sufficiently long follow-up period after the end of treatment, extending beyond

the high-risk period. This applies in particular to the current situation of chemoradiation therapy and, in relation to the experimental intervention, means a sufficiently long follow-up period after the end of the maximum 24-month maintenance therapy with durvalumab. This is intended to ensure that, once treatment is discontinued, relapses are actually prevented rather than merely delayed. No information is available on the duration of the high-risk period in this therapeutic indication. The DGHO [11] recommends close follow-up at 3- to 6-month intervals during the first 2 years, followed by annual follow-up for a further 3 years.

Information on the follow-up durations for patients in the ADRIATIC study who had not experienced a PFS event by the data cut-off date is not available, but can be estimated based on the following data: the median follow-up durations for the outcome overall survival were 30.8 months versus 28.6 months. The maximum possible follow-up duration for the first randomized person was approximately 63 months. The minimum possible follow-up duration for the last randomized person was approximately 29 months. Overall, based on the available data, it is assumed that the follow-up period after the end of the maximum 24-month treatment with durvalumab is not sufficiently long for a relevant proportion of patients who have not experienced a PFS event to reliably rule out the occurrence of recurrences/progression following the discontinuation of treatment. This assessment is also supported by the fact that, four years after randomization, the proportion of patients still under observation is very low—9% versus 18%—when compared to those who had not experienced an event.

Patient-reported outcomes on symptoms, health status and health-related quality of life

In Module 4A, the company provides post-hoc responder analyses for the time to first deterioration for the patient-reported outcomes on symptoms (recorded using the EORTC QLQ-C30, EORTC QLQ-LC13 and the PGIS), for health status (recorded using the EQ-5D VAS), and for health-related quality of life (recorded using the EORTC QLQ-C30). This is comprehensible before the background of different follow-up periods between the study arms (see also the following section). These analyses were used in this benefit assessment.

EORTC-QLQ-C30 and EORTC-QLQ-LC13

Analyses for the time to confirmed deterioration or death were prespecified for the patient-reported outcomes recorded using the EORTC-QLQ-C30 and EORTC-QLQ-LC13. In principle, the confirmed deterioration is relevant in terms of content, as it reflects a more sustainable change than a one-off deterioration. However, the company does not present this analysis in Module 4A of the dossier. At first glance, this is understandable, as the observation periods differ between the study arms. However, given the comparable response rates—particularly in the first year—and the fact that the follow-up periods are generally sufficient to achieve a confirmation of deterioration, the prespecified analyses of confirmed deterioration may be usable provided that the uncertainties described below are resolved.

In the ADRIATIC study, the operationalization of confirmed deterioration or death included the following events:

- A deterioration by ≥ 10 points, confirmed at the next recording at least 14 days later
- a one-off deterioration by ≥ 10 points in the absence of follow-up recordings
- Death without prior deterioration

Deteriorations by ≥ 10 points or deaths occurring after two missed visits were not counted as events. With this operationalization, it is possible for patients who experienced an event to be included in the analysis, even though their deterioration could not be confirmed due to a lack of follow-up recordings. Information on how many patients were affected by this is not available in the clinical study report. It is therefore unclear whether the results of these analyses can be interpreted as a confirmed deterioration. In order to assess this, information is needed on how many patients were included in the analysis whose deterioration was not confirmed due to the lack of a subsequent recording. Furthermore, although data are available on how many patients who died without prior deterioration were included in the analysis, sensitivity analyses not considering these events—as well as the unconfirmed deteriorations described above—would be desirable.

PGIS

The PGIS consists of a single question by means of which the patients were to assess their cancer symptoms at the day of recording. There are 6 possible responses (“no symptoms”, “very mild”, “mild”, “moderate”, “severe”, “very severe”). The recording of symptoms by means of a PGIS is regarded as patient relevant. In Module 4A, the company presents post hoc responder analyses for the time to first deterioration, defining a deterioration as an increase by ≥ 1 point from baseline. An increase by ≥ 1 point from baseline is considered a deterioration that is sufficiently certain to reflect a noticeable change for the patients. The time-to-event analyses on the first deterioration presented by the company were used for the present benefit assessment.

Side effects

Severe AEs

In Module 4A, the company operationalized severe AEs a CTCAE grade ≥ 3. Based on the information in the study documents, it becomes clear that these were operationalized as CTCAE grade 3 or 4.

PRO-CTCAE

According to the study protocol, the ADRIACTIC study also recorded AEs using the PRO-CTCAE instrument. The PRO-CTCAE was only recorded in countries where a translation of the questionnaire into the national language was available. Overall, the PRO-CTCAE system is a

valuable addition to the usual recording and analysis of AEs. The system comprises a total of 81 symptomatic AEs of the CTCAE system (Version 4), which are compiled into a questionnaire adapted to the respective study situation. The selection process is to be planned a priori and carried out transparently. The selection of the individual symptomatic AEs must be transparent, e.g. the recording of all important potential AEs of the drugs in the intervention and the comparator arm. For a comprehensive description of the PRO-CTCAE system, see the corresponding explanations in benefit assessment A20-87 [15].

The company presents no information on the PRO-CTCAE in Module 4 A. The study protocol does not explain why 9 PRO-CTCAE items were selected from the available items. The company does not provide more detailed information on its approach, e.g. on the search or the type of documents reviewed. Approaches to selecting the items are described by Tolstrup [16] or Taarnhøj [17] (see also [15]). Overall, it is not clear what criteria were used to select the items, nor whether the side effects of durvalumab are adequately reflected.

Overall, the outcome of PRO-CTCAE was disregarded in the benefit assessment due to the nontransparent selection process and the inexplicable selection of items for depicting the symptomatic AEs of durvalumab.

Immune-related AEs

Immune-mediated AEs are a relevant aspect of the side effect profile of PD-L1 inhibitors such as durvalumab. In the ADRIATIC study, AESIs assumed to be potentially caused by an inflammatory or immune-mediated reaction and which may require close observation and/or an intervention with steroids, immunosuppressants and/or endocrine therapy were recorded. In addition, AEs of possible interest (AEPIs) were recorded which may potentially have been caused by an inflammatory or immune-mediated reaction, but the likelihood of cause is considered to be low. In Module 4A, the company provides analyses of AESIs that do not take into account infusion-related reactions and hypersensitivity/anaphylactic reactions, or AEs of particular interest (AEPIs). This operationalization can be used to map immune-mediated AEs, as the underlying categories (GTs) and the PTs included therein are considered a sufficient approximation.

The ADRIATIC study also directly recorded immune-mediated AEs. According to the study protocol, these were defined as AEs identified within the framework of the AESIs and AEPIs (except for infusion-related reactions and hypersensitivity/anaphylactic reactions) and which required an intervention with steroids, immunosuppressants and/or endocrine therapy. The operationalization of immune-mediated AEs without taking into account infusion-related reactions and hypersensitivity/anaphylactic reactions is appropriate; however, linking immune-mediated AEs to a treatment is not appropriate. These data on immune-mediated AEs are therefore not suitable for the present benefit assessment.

Pneumonitis

For the specific AE pneumonitis, the SMQ interstitial lung disease [narrow] is considered a sufficient approximation to represent this specific AE. The PT list for the GT pneumonitis or radiation pneumonitis (consisting of the PTs immune-mediated lung disease, interstitial lung disease, pneumonitis, radiation fibrosis of the lung, and radiation-induced pneumonitis) analysed post hoc in the ADRIATIC study can be used as a suitable operationalization for this benefit assessment by comparing the AEs that occurred with this SMQ.

By taking into account the AESIs and the GT pneumonitis included therein as an operationalization for immune-mediated AEs, and the GT pneumonitis or radiation pneumonitis, events recorded in the GT pneumonitis were recorded in both operationalizations. This was taken into account in the overall assessment.

The relative risk (RR) determined in each case by the Institute's calculation is used for the outcomes in the side effects category, based on the corresponding 2x2 table.

I 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 versus placebo

Study	Study level	Outcomes											
		Overall survival	Failure of the curative treatment approach	Symptoms (EORTC QLQ-C30, EORTC QLQ-LC13, PGIS)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30)	SAEs	Severe AEs[a]	Discontinuation due to AEs	PRO-CTCAE	Immune-mediated severe AEs[b]	Immune-mediated SAEs[b]	Pneumonitis (AEs)[c]
ADRIATIC	L	L	–[d]	H[e]	H[e]	H[e]	H[f]	H[f]	L[g]	–[d]	H[f]	H[f]	H[f]

a. In Module 4A, the company operationalizes severe AEs as CTCAE grade ≥ 3. Based on the information in the study documents, it is clear that these are operationalized as CTCAE grade 3 or 4.
b. The predefined operationalization of AESI is used in each case, excluding infusion-related reactions and hypersensitivity reactions/anaphylactic reactions.
c. Operationalized using the GT pneumonitis or radiation pneumonitis.
d. No suitable data available; for the reasoning, see Section I 4.1 of this dossier assessment.
e. A high proportion of patients not considered in the analysis, incomplete observations for potentially informative reasons, or decreasing questionnaire response rates.
f. Incomplete observations for potentially informative reasons.
g. Despite the low risk of bias, the certainty of results for the outcome discontinuation due to AEs was assumed to be restricted (see Sections I 4.1 and I 4.2).

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; GP: grouped term; h: high; l: low; PGIS: Patient Global Impression of Severity; PRO-CTCAE: Patient-Reported Outcomes version of the CTCAE; 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; VAS: visual analogue scale

The risk of bias of the results on the outcomes overall survival and discontinuation due to AEs was rated as low. For all other outcomes, the risk of bias of the results was rated as high.

With regard to the results on patient-reported outcomes in the categories morbidity and health-related quality of life (recorded using the EORTC QLQ-C30, EORTC QLQ-LC13, EQ-5D VAS and PGIS), one reason for the high risk of bias is that a large proportion of patients were not included in the analysis. According to the company, all randomized patients were included in the analyses. At the same time, however, the company stated that patients with no baseline value or no value in the further course of the study were censored on Day 1. Thus, no times of these patients were actually included in the analysis. About 20 % of the patients had no baseline value. It is unclear how many more patients were enrolled in the course of the study without a further value being recorded. However, it is assumed that this proportion is < 10%. In addition to the problem described, the response rate continued to decrease as the study

progressed. Another factor here is that follow-up was discontinued, among other things, following the second progression of the disease. Up to the data cut-off of 15 January 2024, this was the case for 31% of patients in the intervention arm versus 41% in the comparator arm. Due to a possible correlation between the reason for the end of follow-up and these outcomes, there are incomplete observations for potentially informative reasons.

For the outcomes in the side effects category, with the exception of discontinuation due to AEs, the reason for the high risk of bias is that observations are incomplete for potentially informative reasons. According to company, the analyses included all AEs that occurred up to 90 days after administration of the last study medication. The observation period is therefore determined by the reasons for treatment discontinuation (primarily due to a deterioration in the patient's condition: 46% vs. 58%). Due to a possible correlation between the reason for treatment discontinuation and these outcomes, there are incomplete observations for potentially informative reasons.

Although the risk of bias for the outcome discontinuation due to AEs was low, the certainty of results for this outcome was limited. Premature treatment discontinuation for reasons other than AEs is a competing event for the outcome discontinuation due to AEs to be recorded. This means that, although AEs that would have led to discontinuation of therapy may occur after discontinuation for other reasons, the criterion discontinuation is no longer applicable to them. It was impossible to estimate how many AEs this affected.

I 4.3 Results

Table 15 and Table 16 summarize the results of the comparison of durvalumab with placebo in adults with LS-SCLC whose disease has not progressed following platinum-based chemoradiation therapy. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier.

The Kaplan-Meier curves for the time-to-event analyses are presented in I Appendix B of the full dossier assessment, the results on common AEs, SAEs, severe AEs, and discontinuations due to AEs at SOCs and PTs can be found in I Appendix D of the full dossier assessment, and the results on common immune-related AEs, SAEs and severe AEs are presented in I Appendix E.

Table 15:Results (mortality, morbidity, health-related quality of life) – RCT, direct comparison: durvalumab versus placebo (multipage table)

Study outcome category outcome	Durvalumab N	Durvalumab median time to event in months [95% CI] patients with event n (%)	Placebo N	Placebo median time to event in months [95% CI] patients with event n (%)	Durvalumab vs. placebo HR [95% CI]; p-value[a]
ADRIATIC					
Mortality					
Overall survival	264	55.9 [37.3; NC] 115 (43.6)	266	33.4 [25.5; 39.9] 146 (54.9)	0.72 [0.56; 0.92]; 0.008
Morbidity					
Failure of the curative treatment approach	No suitable data[b]				
Symptoms (EORTC QLQ-C30 – time to first deterioration by ≥ 10 points[c])					
Fatigue	ND[d]	1.9 [1.8; 3.6] 159 (60.2[e])	ND[d]	2.7 [1.9; 3.6] 153 (57.5[e])	1.08 [0.86; 1.35]; 0.530
Nausea and vomiting	ND[d]	14.7 [8.3; 23.9] 109 (41.3[e])	ND[d]	16.6 [11.0; 28.6] 96 (36.1[e])	1.09 [0.83; 1.45]; 0.524
Pain	ND[d]	3.7 [2.9; 4.7] 155 (58.7[e])	ND[d]	2.8 [1.8; 5.5] 154 (57.9[e])	0.87 [0.70; 1.09]; 0.261
Dyspnoea	ND[d]	4.5 [2.8; 5.6] 142 (53.8[e])	ND[d]	7.3 [3.7; 9.1] 125 (47.0[e])	1.16 [0.91; 1.47]; 0.242
Insomnia	ND[d]	5.6 [4.5; 7.3] 134 (50.8[e])	ND[d]	8.3 [6.4; 12.9] 114 (42.9[e])	1.24 [0.97; 1.60]; 0.089
Appetite loss	ND[d]	5.6 [3.7; 9.2] 131 (49.6[e])	ND[d]	7.4 [4.6; 11.9] 115 (43.2[e])	1.11 [0.86; 1.43]; 0.411
Constipation	ND[d]	11.9 [5.6; 17.6] 113 (42.8[e])	ND[d]	9.3 [6.5; 16.5] 105 (39.5[e])	0.97 [0.75; 1.28]; 0.858
Diarrhoea	ND[d]	26.6 [14.7; 44.2] 87 (33.0[e])	ND[d]	22.0 [13.8; 32.2] 82 (30.8[e])	0.95 [0.70; 1.29]; 0.738
Symptoms (EORTC QLQ-LC13 – time to first deterioration by ≥ 10 points[c])					
Cough	ND[d]	2.7 [1.6; 5.5] 147 (55.7[e])	ND[d]	4.6 [2.7; 9.1] 128 (48.1[e])	1.14 [0.90; 1.45]; 0.296
Haemoptysis	ND[d]	NA 60 (22.7[e])	ND[d]	NA 47 (17.7[e])	1.13 [0.77; 1.67]; 0.527
Dyspnoea	ND[d]	1.1 [1.0; 1.4] 184 (69.7[e])	ND[d]	1.4 [0.9; 1.8] 167 (62.8[e])	1.16 [0.94; 1.43]; 0.177
Chest pain	ND[d]	5.6 [2.8; 11.0] 129 (48.9[e])	ND[d]	5.5 [1.7; 11.0] 123 (46.2[e])	0.90 [0.70; 1.15]; 0.420
Pain in the arm or shoulder	ND[d]	8.3 [5.6; 14.7] 125 (47.3[e])	ND[d]	4.5 [1.8; 6.4] 143 (53.8[e])	0.70 [0.55; 0.89]; 0.004

Table 15:Results (mortality, morbidity, health-related quality of life) – RCT, direct comparison: durvalumab versus placebo (multipage table)

Study outcome category outcome	Durvalumab N	Durvalumab median time to event in months [95% CI] patients with event n (%)	Placebo N	Placebo median time to event in months [95% CI] patients with event n (%)	Durvalumab vs. placebo HR [95% CI]; p-value[a]
Pain in other parts of the body	ND[d]	4.6 [3.6; 7.3] 135 (51.1[e])	ND[d]	2.8 [1.6; 6.4] 136 (51.1[e])	0.91 [0.72; 1.16]; 0.454
Sore mouth	ND[d]	15.6 [8.3; 29.4] 106 (40.2[e])	ND[d]	18.5 [8.2; 30.3] 100 (37.6[e])	0.97 [0.74; 1.28]; 0.841
Dysphagia	ND[d]	27.5 [15.7; NC] 92 (34.8[e])	ND[d]	31.3 [18.4; NC] 84 (31.6[e])	0.99 [0.73; 1.33]; 0.930
Peripheral neuropathy	ND[d]	6.5 [5.5; 10.1] 127 (48.1[e])	ND[d]	6.5 [4.5; 10.1] 129 (48.5[e])	0.89 [0.69; 1.14]; 0.356
Alopecia	ND[d]	18.3 [12.8; 33.2] 100 (37.9[e])	ND[d]	22.2 [12.8; NC] 87 (32.7)	1.08 [0.81; 1.44]; 0.632
Symptoms (PGIS - time to first deterioration by ≥ 1 point[f])	ND[d]	3.7 [1.9; 7.3] 132 (50.0[e])	ND[d]	5.5 [3.6; 5.5] 127 (47.7[e])	1.09 [0.85; 1.39]; 0.569
Health status (EQ-5D-5L VAS – time to first deterioration by ≥ 15 points[g])	ND[d]	11.0 [9.1; 16.5] 111 (42.0[e])	ND[d]	18.3 [7.4; 31.2] 90 (33.8[e])	1.17 [0.88; 1.55]; 0.295
Health-related quality of life					
EORTC QLQ-C30 - time to first deterioration by ≥ 10 points[h]					
Global health status	ND[d]	3.6 [2.7; 4.5] 143 (54.2[e])	ND[d]	4.5 [2.7; 8.2] 130 (48.9[e])	1.08 [0.85; 1.38]; 0.498
Physical functioning	ND[d]	5.5 [3.6; 7.4] 134 (50.8[e])	ND[d]	8.3 [5.5; 11.0] 123 (46.2[e])	1.17 [0.91; 1.49]; 0.228
Role functioning	ND[d]	4.7 [2.8; 7.4] 138 (52.3[e])	ND[d]	3.8 [2.7; 6.4] 139 (52.3[e])	0.83 [0.66; 1.06]; 0.142
Cognitive functioning	ND[d]	4.7 [3.6; 6.4] 140 (53.0[e])	ND[d]	5.5 [3.7; 8.2] 136 (51.1[e])	0.98 [0.77; 1.24]; 0.880
Emotional functioning	ND[d]	8.2 [5.5; 11.9] 125 (47.3[e])	ND[d]	7.3 [3.6; 10.2] 124 (46.6[e])	0.91 [0.70; 1.16]; 0.451
Social functioning	ND[d]	4.6 [3.6; 7.3] 140 (53.0[e])	ND[d]	5.6 [3.7; 8.3] 132 (49.6[e])	1.03 [0.81; 1.31]; 0.792

Table 15:Results (mortality, morbidity, health-related quality of life) – RCT, direct comparison: durvalumab versus placebo (multipage table)

Study outcome category outcome	Durvalumab N	Durvalumab median time to event in months [95% CI] patients with event n (%)	Placebo N	Placebo median time to event in months [95% CI] patients with event n (%)	Durvalumab vs. placebo HR [95% CI]; p-value[a]
a. HR and CI: Cox proportional hazards model, p-value: log-rank test; each stratified by TNM classification (I/II vs. III) and receipt of PCI (yes vs. no), based on data from the IVRS; for patient-reported outcomes, censoring was performed as follows: if neither deterioration nor death occurred, at the time of the last recording or on Day 1 if no recordings or baseline data were available during the course of the study; if deterioration or death occurred after 2 missed visits, at the time of the last recording prior to the 2 missed visits; if death occurred without prior deterioration within two visits following the last recording, at the time of death. The company does not describe the approach used for a baseline value that did not allow for a deterioration of 10 or 15 points. It is assumed that no censoring took place on Day 1, but that the same rules were applied as in other cases without deterioration. b. See Section I 4.1 for reasons. c. An increase by ≥ 10 points from baseline is considered a clinically relevant deterioration (scale range: 0 to 100). d. According to the company, all randomized patients were included in the analysis. At the same time the company stated that patients with no baseline value or no value in the course of the study were censored on Day 1. Thus, no times of these patients were actually included in the analysis. The exact number of these patients cannot be calculated. e. Percentage refers to the number of patients randomized into this arm. f. A score increase by ≥ 1 points from baseline is considered a clinically relevant deterioration (6-point scale). g. A decrease by ≥ 15 points from baseline is considered a clinically relevant deterioration (scale range: 0 to 100). h. A decrease by ≥ 10 points from baseline is considered a clinically relevant deterioration (scale range: 0 to 100). CI: confidence interval; EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: Quality of Life Questionnaire 5 Dimensions; HR: hazard ratio; IVRS: Interactive Voice Response System; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; NC: not calculable; ND: no data; PCI: prophylactic cranial irradiation; PGIS: Patient Global Impression of Severity; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-LC-13: Quality of Life Questionnaire – Lung Cancer 13; RCT: randomized controlled trial; TNM: tumour size, lymph node involvement and metastases; VAS: visual analogue scale				

Table 16: Results (side effects) – RCT, direct comparison: durvalumab versus placebo

Study outcome category outcome	Durvalumab		Placebo		Durvalumab vs. placebo
	N	patients with event n (%)	N	patients with event n (%)	RR [95% CI]; p-value[a]
ADRIATIC					
Side effects					
AEs (supplementary information)	262	247 (94.3)	265	234 (88.3)	–
SAEs	262	78 (29.8)	265	64 (24.2)	1.23 [0.93; 1.64]; 0.152
Severe AEs[b, c]	262	69 (26.3)	265	68 (25.7)	1.03 [0.77; 1.37]; 0.898
Discontinuation due to AEs	262	43 (16.4)	265	28 (10.6)	1.55 [1.00; 2.42]; 0.051
PRO-CTCAE	No suitable data[d]				
Immune-related AEs (supplementary information)	262	134 (51.1)	265	73 (27.5)	–
Immune-mediated SAEs	262	25 (9.5)	265	8 (3.0)	3.16 [1.45; 6.88]; 0.002
Immune-mediated severe AEs[b,e]	262	16 (6.1)	265	4 (1.5)	4.05 [1.37; 11.94]; 0.006
Pneumonitis (AEs)[f]	262	100 (38.2)	265	80 (30.2)	1.26 [1.00; 1.61]; 0.055

a. Institute's calculation of RR, CI (asymptotic) and p-value (unconditional exact test, CSZ method according to [18]).
b. In Module 4A, the company operationalizes severe AEs as CTCAE grade ≥ 3. Based on the information in the study documents, it is clear that these are operationalized as CTCAE grade 3 or 4.
c. 5 (1.9%) vs. 4 (1.5%) patients experienced a grade 5 event.
d. See Section I 4.1 for reasons.
e. 1 (0.4%) vs. 0 patients had a grade 5 event.
f. Operationalized using the GT pneumonitis or radiation pneumonitis.

AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; GT: grouped term; n: number of patients with (at least one) event; N: number of analysed patients; PRO-CTCAE: Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event

On the basis of the available information, at most hints, e.g. of an added benefit, can be determined for all outcomes, except for the outcome overall survival. For the outcome overall survival, at most an indication, e.g. of an added benefit, can be determined (see Section I 4.2).

Mortality

For the outcome overall survival, a statistically significant difference was found in favour of durvalumab in comparison with placebo. There is an indication of added benefit of durvalumab in comparison with the ACT.

Morbidity

Failure of the curative treatment approach

No suitable data were available for the outcome of failure of the curative treatment approach. This results in no hint of an added benefit of durvalumab over the ACT; greater or lesser harm is therefore not proven for the outcome failure of the curative treatment approach.

Symptoms (recorded using the EORTC QLQ-C30, EORTC QLQ-LC13 and PGIS)

There was no statistically significant difference between the treatment arms for each of the outcomes fatigue, nausea and vomiting, pain, dyspnoea, loss of appetite, constipation and diarrhoea (recorded using the EORTC QLQ-C30), the outcomes cough, haemoptysis, dyspnoea, chest pain, pain in other parts of the body, sore mouth, dysphagia, peripheral neuropathy and alopecia (recorded using the EORTC LC13), and symptoms recorded using the PGIS. There is no hint of an added benefit of durvalumab over the ACT for any of these outcomes; an added benefit is therefore not proven for these outcomes.

Insomnia

For the outcome insomnia (recorded using the EORTC QLQ-C30), no statistically significant difference between treatment arms was found when considering the total population. There is an effect modification by the characteristic sex for this outcome (see Section I 4.4). For men, there is a hint of lesser benefit from durvalumab in comparison with the ACT. For women, there is no hint of an added benefit or lesser benefit of durvalumab in comparison with the ACT; an added benefit is therefore not proven for women.

Pain in the arm or shoulder

For the outcome pain in the arm or shoulder, a statistically significant difference was found in favour of durvalumab over placebo. This results in a hint of added benefit of durvalumab in comparison with the ACT.

Health status (recorded with the EQ-5D VAS)

No statistically significant difference between the treatment arms was shown for the outcome health status (recorded using the EQ-5D VAS). There is no hint of an added benefit of durvalumab over the ACT; an added benefit is therefore not proven for this outcome.

Health-related quality of life

No statistically significant difference between the treatment arms was found for any of the outcomes global health status, physical functioning, role functioning, cognitive functioning, emotional functioning and social functioning (recorded using the EORTC QLQ-C30). There is no hint of an added benefit of durvalumab over the ACT for any of these outcomes; an added benefit is therefore not proven for these outcomes.

Side effects

SAEs, severe AEs, discontinuation due to AEs, and pneumonitis

No statistically significant difference between treatment arms was found for any of the outcomes SAEs, severe AEs, discontinuation due to AEs and pneumonitis. For each of them, there is no hint of greater or lesser harm from durvalumab in comparison with the ACT; greater or lesser harm is therefore not proven for these outcomes.

PRO-CTCAE

No suitable data are available for PRO-CTCAE. This results in no hint of an added benefit of durvalumab over the ACT; greater or lesser harm is therefore not proven for PRO-CTCAE.

Immune-mediated SAEs and immune-mediated severe AEs

For each of the outcomes immune-mediated SAEs and immune-mediated severe AEs, a statistically significant difference was found to the disadvantage of durvalumab in comparison with placebo. This results in a hint of greater harm from durvalumab in comparison with the ACT for both outcomes.

I 4.4 Subgroups and other effect modifiers

The following subgroup characteristics were taken into account for this benefit assessment:

- Age (< 65 years versus ≥ 65 years)
- Sex (male versus female)
- TNM stage based on IVRS (I/II vs. III)

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

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

The results are presented in Table 17. The Kaplan-Meier curves on the subgroup results are presented in I Appendix C of the full dossier assessment.

For outcomes assessed over the time to event, the company conducted an interaction test using the appropriate interaction term in the unstratified Cox model.

For the outcomes in the side effects category, except for pneumonitis, interaction testing was carried out using the Institute's calculations (via the Q-test) based on the RRs in the respective subgroups.

For the operationalization used, there are no data on the distribution of patients with event to the subgroups for the outcome pneumonitis. An own test for interactions is not possible for this outcome.

Table 17: Subgroups (morbidity) – RCT, direct comparison: durvalumab versus placebo

Study outcome characteristic subgroup	Durvalumab N	Durvalumab median time to event in months [95 % CI] patients with event n (%)	Placebo N	Placebo median time to event in months [95 % CI] patients with event n (%)	Durvalumab vs. placebo HR [95% CI][a]	Durvalumab vs. placebo p-value[a]
ADRIATIC						
Morbidity						
Symptoms (EORTC QLQ-C30 – time to first deterioration ≥ 10 points[b])						
Insomnia						
Sex						
Male	ND[c]	5.5 [3.6; 6.5] 101 (56.7)	ND[c]	11.9 [7.3; 35.8] 78 (41.5)	1.52 [1.13; 2.06]	0.005
Female	ND[c]	6.4 [3.7; 12.9] 33 (38.4)	ND[c]	6.4 [3.6; 8.2] 36 (46.2)	0.72 [0.45; 1.16]	0.175
Total					Interaction:	0.009[d]

a. HR, CI and p-value: Cox proportional hazards model; unstratified; for patient-reported outcomes, censoring was performed as follows: if neither deterioration nor death occurred, at the time of the last recording or on Day 1 if no recordings or baseline data were available during the course of the study; if deterioration or death occurred after 2 missed visits, at the time of the last recording prior to the 2 missed visits; if death occurred without prior deterioration within two visits following the last recording, at the time of death. The company does not describe the approach used for a baseline value that did not allow for a deterioration of 10 or 15 points. It is assumed that no censoring took place on Day 1, but that the same rules were applied as in other cases without deterioration.

b. An increase by ≥ 10 points from baseline is considered a clinically relevant deterioration (scale range: 0 to 100).

c. According to the company, all randomized female patients (86 vs. 78) and male patients (178 vs. 188) were included in the analysis. At the same time the company stated that patients with no baseline value or no value in the course of the study were censored on Day 1. Thus, no times of these patients were actually included in the analysis. The exact number of these patients cannot be calculated.

d. Interaction test: Cox proportional hazards model with corresponding interaction term; likelihood ratio test.

CI: confidence interval; EORTC: European Organisation for Research and Treatment of Cancer; HR: hazard ratio; n: number of patients with (at least one) event; N: number of analysed patients; ND: no data; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial

Morbidity (symptoms)

Insomnia (recorded with the EORTC QLQ-C30)

For the outcome insomnia (recorded with the EORTC QLQ-C30), there was a statistically significant effect modification by the characteristic sex. A statistically significant difference to the disadvantage of durvalumab compared with placebo was shown for men. For men, there is a hint of lesser benefit of durvalumab in comparison with the ACT. For women, however, there was no statistically significant difference between the treatment arms. For this subgroup, there is no hint of an added benefit of durvalumab in comparison with the ACT; an added benefit for women is therefore not proven for this outcome.

I 5 Probability and extent of added benefit

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

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

I 5.1 Assessment of added benefit at outcome level

The extent of the respective added benefit at outcome level was assessed based on the results presented in Chapter I 4 (see Table 18).

Determination of the outcome category for symptom outcomes

For the symptoms outcomes below, it cannot be inferred from the dossier whether they are serious/severe or non-serious/non-severe. Reasoning is provided for the classification of these outcomes.

Insomnia (recorded using the EORTC QLQ-C30) and pain in the arm or shoulder (recorded using the EORTC QLQ-LC13)

There is insufficient information available to classify the severity categories for the outcomes insomnia (recorded using the EORTC QLQ-C30) and pain in the arm or shoulder (recorded using the EORTC QLQ-LC13). The outcomes insomnia and pain in the arm or shoulder are therefore assigned to the outcome category non-serious/non-severe symptoms/late complications.

Table 18: Extent of added benefit at outcome level: durvalumab vs. BSC (multipage table)

Outcome category **outcome** **effect modifier** **subgroup**	**Durvalumab vs. placebo** **time to event (months) or proportion of events (%)** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Outcomes with observation over the entire study duration		
Mortality		
Overall survival	55.9 vs. 33.4 months HR: 0.72 [0.56; 0.92]; p = 0.008 probability: indication	Outcome category: mortality $CI_u < 0.95$ added benefit, extent: considerable
Outcomes with shortened observation period		
Morbidity		
Failure of the curative treatment approach	No suitable data	Greater/lesser harm not proven
Symptoms (EORTC QLQ-C30 - time to first deterioration)		
Fatigue	1.9 vs. 2.7 months HR: 1.08 [0.86; 1.35]; p = 0.530	Lesser benefit/added benefit not proven
Nausea and vomiting	14.7 vs. 16.6 months HR: 1.09 [0.83; 1.45]; p = 0.524	Lesser benefit/added benefit not proven
Pain	3.7 vs. 2.8 months HR: 0.87 [0.70; 1.09]; p = 0.261	Lesser benefit/added benefit not proven
Dyspnoea	4.5 vs. 7.3 months HR: 1.16 [0.91; 1.47]; p = 0.242	Lesser benefit/added benefit not proven
Insomnia Sex Male	5.5 vs. 11.9 months HR: 1.52 [1.13; 2.06]; HR: 0.66 [0.49; 0.88][c]; p = 0.005 probability: hint	Outcome category: non-serious/non-severe symptoms/late complications $0.80 \leq CI_u < 0.90$ lesser benefit, extent: “minor”
Female	6.4 vs. 6.4 months HR: 0.72 [0.45; 1.16]; p = 0.175	Lesser benefit/added benefit not proven
Appetite loss	5.6 vs. 7.4 months HR: 1.11 [0.86; 1.43]; p = 0.411	Lesser benefit/added benefit not proven

Table 18: Extent of added benefit at outcome level: durvalumab vs. BSC (multipage table)

Outcome category **outcome** **effect modifier** **subgroup**	**Durvalumab vs. placebo** **time to event (months) or proportion of events (%)** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Constipation	11.9 vs. 9.3 months HR: 0.97 [0.75; 1.28]; p = 0.858	Lesser benefit/added benefit not proven
Diarrhoea	26.6 vs. 22.0 months HR: 0.95 [0.70; 1.29]; p = 0.738	Lesser benefit/added benefit not proven
Symptoms (EORTC QLQ-LC13 – time to first deterioration)		
Cough	2.7 vs. 4.6 months HR: 1.14 [0.90; 1.45]; p = 0.296	Lesser benefit/added benefit not proven
Haemoptysis	NA vs. NA HR: 1.13 [0.77; 1.67]; p = 0.527	Lesser benefit/added benefit not proven
Dyspnoea	1.1 vs. 1.4 months HR: 1.16 [0.94; 1.43]; p = 0.177	Lesser benefit/added benefit not proven
Chest pain	5.6 vs. 5.5 months HR: 0.90 [0.70; 1.15] p = 0.420	Lesser benefit/added benefit not proven
Pain in the arm or shoulder	8.3 vs. 4.5 months HR: 0.70 [0.55; 0.89]; p = 0.004 probability: hint	Outcome category: non-serious/non-severe symptoms/late complications $0.80 \leq CI_u < 0.90$ Added benefit, extent: “minor”
Pain in other parts of the body	4.6 vs. 2.8 months HR: 0.91 [0.72; 1.16]; p = 0.454	Lesser benefit/added benefit not proven
Sore mouth	15.6 vs. 18.5 months HR: 0.97 [0.74; 1.28]; p = 0.841	Lesser benefit/added benefit not proven
Dysphagia	27.5 vs. 31.3 months HR: 0.99 [0.73; 1.33]; p = 0.930	Lesser benefit/added benefit not proven
Peripheral neuropathy	6.5 vs. 6.5 months HR: 0.89 [0.69; 1.14]; p = 0.356	Lesser benefit/added benefit not proven

Table 18: Extent of added benefit at outcome level: durvalumab vs. BSC (multipage table)

Outcome category **outcome** **effect modifier** **subgroup**	**Durvalumab vs. placebo** **time to event (months) or proportion of events (%)** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Alopecia	18.3 vs. 22.2 months HR: 1.08 [0.81; 1.44]; p = 0.632	Lesser benefit/added benefit not proven
Symptoms (PGIS – time to first deterioration)	3.7 vs. 5.5 months HR: 1.09 [0.85; 1.39]; p = 0.569	Lesser benefit/added benefit not proven
Health status (EQ-5D-5L VAS - time to first deterioration)	11.0 vs. 18.3 months HR: 1.17 [0.88; 1.55]; p = 0.295	Lesser benefit/added benefit not proven
Health-related quality of life		
EORTC-QLQ C30 – time to first deterioration		
Global health status	3.6 vs. 4.5 months HR: 1.08 [0.85; 1.38]; p = 0.498	Lesser benefit/added benefit not proven
Physical functioning	5.5 vs. 8.3 months HR: 1.17 [0.91; 1.49]; p = 0.228	Lesser benefit/added benefit not proven
Role functioning	4.7 vs. 3.8 months HR: 0.83 [0.66; 1.06]; p = 0.142	Lesser benefit/added benefit not proven
Cognitive functioning	4.7 vs. 5.5 months HR: 0.98 [0.77; 1.24]; p = 0.880	Lesser benefit/added benefit not proven
Emotional functioning	8.2 vs. 7.3 months HR: 0.91 [0.70; 1.16]; p = 0.451	Lesser benefit/added benefit not proven
Social functioning	4.6 vs. 5.6 months HR: 1.03 [0.81; 1.31]; p = 0.792	Lesser benefit/added benefit not proven
Side effects		
SAEs	29.8% vs. 24.2% RR: 1.23 [0.93; 1.64]; p = 0.152	Greater/lesser harm not proven
Severe AEs	26.3% vs. 25.7% RR: 1.03 [0.77; 1.37]; p = 0.898	Greater/lesser harm not proven

Table 18: Extent of added benefit at outcome level: durvalumab vs. BSC (multipage table)

Outcome category **outcome** **effect modifier** **subgroup**	**Durvalumab vs. placebo** **time to event (months) or proportion of events (%)** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Discontinuation due to AEs	16.4% vs. 10.6% RR: 1.55 [1.00; 2.42]; p = 0.051	Greater/lesser harm not proven
PRO-CTCAE	No suitable data	Greater/lesser harm not proven
Immune-mediated SAEs	9.5% vs. 3.0% RR: 3.16 [1.45; 6.88]; RR: 0.32 [0.15; 0.69][c]; p = 0.002 probability: hint	Outcome category: serious/severe side effects CI_u < 0.75 and risk ≥ 5% greater harm, extent: “major”
Immune-mediated severe AEs	6.1% vs. 1.5% RR: 4.05 [1.37; 11.94]; RR: 0.25 [0.08; 0.73][c]; p = 0.006 probability: hint	Outcome category: serious/severe side effects CI_u < 0.75 and risk ≥ 5% greater harm, extent: “major”
Pneumonitis (AEs)	38.2% vs. 30.2% RR: 1.26 [1.00; 1.61]; p = 0.055	greater/lesser harm not proven

a. Probability provided if there is a statistically significant and relevant effect.
b. Depending on the outcome category, the effect size is estimated using different limits based on the upper limit of the confidence interval (CI_u).
c. Institute’s calculation; inverse direction of effect to enable use of limits to derive the extent of the added benefit.

AE: adverse event; BSC: best supportive care; CI: confidence interval; CI_u: upper limit of the confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; HR: hazard ratio; NA: not achieved; PGIS: Patient Global Impression of Severity; PRO-CTCAE: Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-LC-13: Quality of Life Questionnaire – Lung Cancer 13; RR: relative risk; SAE: serious adverse event; VAS: visual analogue scale

I 5.2 Overall conclusion on added benefit

Table 19 summarizes the results taken into account for the overall conclusion on the extent of the added benefit.

Table 19: Positive and negative effects from the assessment of durvalumab in comparison with BSC

Positive effects	**Negative effects**
Outcomes with observation over the entire study duration	
Mortality ▪ overall survival indication of added benefit – extent: “considerable”	
Outcomes with shortened observation period	
	Non-serious/non-severe symptoms/late complications ▪ insomnia ▫ sex (male) hint of lesser benefit – extent: “minor”
Non-serious/non-severe symptoms/late complications ▪ pain in the arm or shoulder hint of an added benefit – extent: “minor”	
	Outcome category: serious/severe side effects ▪ immune-mediated SAEs Hint of greater harm – extent: “major” ▪ immune-mediated severe AEs hint of greater harm – extent: “major”
AE: adverse event; BSC: best supportive care; SAE: serious adverse event	

Overall, both positive and negative effects of durvalumab were shown in comparison with the ACT. On the positive effects side, there is an indication of considerable added benefit in the outcome overall survival and a hint of minor added benefit for pain in the arm or shoulder. On the other hand, there are hints of greater harm with considerable extent for serious and severe immune-mediated AEs in particular for serious and severe side effects, as well as a hint of a lesser benefit in men in terms of insomnia.

In summary, for adults with LS-SCLC whose disease has not progressed following platinum-based chemoradiation therapy, there is an indication of a minor added benefit of durvalumab over the ACT (BSC).

Table 20 summarizes the result of the assessment of added benefit of durvalumab in comparison with the ACT.

Table 20: Durvalumab – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adults with LS-SCLC whose disease has not progressed following platinum-based chemoradiation therapy	BSC[b, c]	Indication of minor added benefit[d]

a. Presented is the ACT specified by the G-BA.
b. BSC refers to the therapy that provides the patient with the best possible, individually optimized supportive treatment to alleviate symptoms and improve quality of life.
c. It is assumed that BSC in the context of a study is offered both in the control group and in the intervention group.
d. The ADRIATIC study included only patients with an ECOG PS of 0 or 1. It remains unclear whether the observed effects are transferable to patients with an ECOG PS ≥ 2.

ACT: appropriate comparator therapy; BSC: best supportive care; ECOG PS: Eastern Cooperative Oncology Group – Performance Status; G-BA: Federal Joint Committee; LS-SCLC: limited-stage small cell lung cancer

The assessment described above deviates from that by the company, which derived an indication of considerable added benefit of durvalumab over the ACT for adults with LS-SCLC whose disease has not progressed following platinum-based chemoradiation therapy.

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

I 6 References for English extract

Please see full dossier assessment for full reference list.

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

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