Medicinrådet

Bilag til Medicinrådets vurdering af Durvalumab til limited-stage småcellet lungekræft (LS-SCLC)

Vers. 1.0

Bilagsoversigt

1. Ansøgers notat til Rådet vedr. durvalumab
2. Forhandlingsnotat fra Amgros vedr. durvalumab
3. Ansøgers endelige ansøgning vedr. durvalumab

Medicinrådet
Dampfærgevej 21-23, 3. sal
2100 København Ø

17.12.2025

Note on draft assessment report regarding durvalumab indicated as monotherapy for the treatment of limited-stage small-cell lung cancer (LS-SCLC)

AstraZeneca would like to thank you for the assessment of durvalumab for limited-stage small-cell lung cancer and appreciate the opportunity to comment on the draft assessment report.

Overall, AstraZeneca find the DMC draft assessment report to be balanced and thorough. Further, we notice that DMC highlights that LS-SCLC is an aggressive form of lung cancer characterized by rapid progression and high probability of early metastatic disease. A disease that with the current treatment available, has a poor prognosis with a median survival of 15 months and a 5-year survival rate of 15%.

The data that the application is based on is in the assessment draft report considered to be robust and with few significant uncertainties. However, DMC mention one primary uncertainty which we would like just briefly to comment on.

It is stated that the majority of the patients in the study had only received radiotherapy once a day prior to the start of the study, whereas patients in Denmark usually receive radiotherapy twice a day. According to DMC this may make the observed effect of durvalumab appear relatively greater than what might be expected under Danish treatment conditions. In our opinion it is fair to anticipate that the patients that have received radiotherapy once or twice daily will be evenly distributed between the intervention arm and the placebo arm, and therefore this should not affect the relative efficacy.

Further, Cheng et al., 2024[1)] reported forest plots for OS (Figures 1) and PFS (Figure 2) for subgroup analysis of baseline characteristics including previous radiotherapy schedule which was either once-daily or twice-daily, showing highly similar results. The key takeaway from the forest plots is to visualize the overall trend, assessing whether effects across subgroups are aligned or inconsistent. In both subgroups, the effect favors durvalumab with similar HR estimates versus placebo arm, indicating no meaningful difference in efficacy between once-daily and twice-daily radiotherapy. In addition, since durvalumab will only be used for progression-free patients, this would not constitute a low treatment starting point.

We look forward to receiving the final DMC decision with the hope that durvalumab as monotherapy will be made available for patients with limited-stage small-cell lung cancer. This will allow these patients, where the only option after completion of chemoradiotherapy currently is ‘Watch-and-wait’, to have access to a systemic treatment that has shown positive results on both OS and PFS.

Kind regards,

Mette Lange
Market Access Manager
AstraZeneca A/S

Kun Kim
HTA-Manager
AstraZeneca A/S

1) Cheng, Y., et al., Durvalumab after Chemoradiotherapy in Limited-Stage Small-Cell Lung Cancer. N Engl J Med, 2024. 391(14): p. 1313-1327

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19.12.2025

LSC/DBS

Forhandlingsnotat

Dato for behandling i Medicinrådet	21.01.2026
Leverandør	AstraZeneca
Lægemiddel	Imfinzi (durvalumab)
Ansøgt indikation	Monoterapi behandling af voksne med småcellet lungekræft med begrænset sygdomsstadie (LS-SCLC), hvis sygdom ikke er progredieret efter platinbaseret kemoradioterapi.
Nyt lægemiddel / indikationsudvidelse	Indikationsudvidelse (direkte indplacering)

Prisinformation

Amgros har følgende priser på Imfinzi (durvalumab):

Tabel 1: Udbudsresultat

Lægemiddel	Styrke (pakningsstørrelse)	AIP (DKK)	Nuværende SAIP, (DKK)	Rabat ift. AIP
Imfinzi	50 mg/ml (2,4 ml)	4.091,83	[redacted]	[redacted]
Imfinzi	50 mg/ml (10 ml)	16.943,88	[redacted]	[redacted]

Aftaleforhold

Imfinzi indgår i udbuddet for immunterapier.

[redacted]

[redacted] Der er mulighed for at aktivere en prisregulering i aftaleperioden.

Konkurrencesituationen

Imfinzi er den første immunterapi godkendt i EU til denne indikation, småcellet lungekræft med begrænset sygdomsstadie (LS-SCLC). I dansk klinisk praksis tilbydes der aktuelt ikke systemisk behandling efter afsluttet kemoradioterapi, jf. Medicinrådets vurdering af durvalumab som monoterapi til behandling af LS-SCLC.

Tabel 2 viser lægemiddeludgiften til Imfinzi for et års behandling.

Tabel 2: Lægemiddeludgifter pr. patient

Lægemiddel	Styrke (pakningsstørrelse)	Dosering	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. år (SAIP, DKK)
Imfinzi	50 mg/ml (10 ml)	1.500 mg hver 4. uge, i.v.	[redacted]	[redacted]

Status fra andre lande

Tabel 3: Status fra andre lande

Land	Status	Link
Norge	Anbefalet	Link til anbefaling
England	Anbefalet	Link til anbefaling
Sverige	Anbefalet	Link til anbefaling

Opsummering

[redacted]

Application for the assessment of Imfinzi® (durvalumab) as a treatment for patients with limited-stage small-cell lung cancer (LS-SCLC) whose disease has not progressed following platinum-based chemoradiation therapy

Color scheme for text highlighting	
Color of highlighted text	Definition of highlighted text
	Confidential information
[Other]	[Definition of color-code]

Contact information

Contact information	
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Table of contents

Tables and Figures

Abbreviations

Abbreviation	Definition
AE	Adverse Events
AJCC	American Joint Committee on Cancer.
ALK	Anaplastic Lymphoma Kinase
ASCO	American Society of Clinical Oncology
ATMP	Advanced Therapy Medicinal Products
BICR	Blinded Independent Central Review
BID	Twice Daily (latin: bis in die)
BTC	Biliary Tract Cancer
CRT	Chemoradiotheraphy
cCRT	Concurrent chemoradiotherapy
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DCO	Data Cut Off

DLCG	Danish Lung Cancer Group
DLCR	Danish Lung Cancer Register
DMC	Danish Medicines Council
DOR	Duration Of Response
DOT	Duration Of Treatment
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal Growth Factor Receptor
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
ESMO	European Society for Medical Oncology
FAS	Full Analysis Set (all randomised patients)
FPAS	Full PD-L1 analysis set
GHS	Global Health Status Score
HCC	Hepatocellular Carcinoma
HRQOL	Health related Quality of life
MMRM	Mixed-effect Model Repeat Measurement
MRI	Magnetic Resonance Imaging
NCCN	National Comprehensive Cancer Network
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
OS	Overall survival
PD-L1	Programmed Death-ligand 1
PCI	Prophylactic Cranial Irradiation
PET	Positron Emission Tomography
PFS	Progression free survival
PFS2	Time from randomisation to second progression

PGIS	Patient's Global Impression of Severity
PRO	Patient-Reported Outcomes
PRO-CTCAE	Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events
QoL	Quality of Life
QLQ-C30	Quality of life questionnaire Core 30
QLQ-LC13	Quality of life questionnaire Lung Cancer module 13 items
RECIST	Response Evaluation Criteria in Solid Tumours
SAE	Serious Adverse Events
SCLC	Small Cell Lung Cancer
TNM	Tumour, Node, Metastasis staging
TTDM	Time To Death or Distant Metastasis

1. Regulatory information on the medicine

Overview of the medicine	
Proprietary name	Imfinzi®
Generic name	Durvalumab
Therapeutic indication as defined by EMA	Imfinzi® (durvalumab) as monotherapy treatment of adults with limited-stage small-cell lung cancer (LS-SCLC) whose disease has not progressed following platinum-based chemoradiation therapy [1].
Marketing authorization holder in Denmark	AstraZeneca
ATC code	L01FF03
Combination therapy and/or co-medication	Prior to initiation of durvalumab, four cycles of platinum-based chemoradiation therapy (CRT) should be given (three cycles permitted)[1]
(Expected) Date of EC approval	The European Commission (EC) decision was granted on March 12 2025 (ID II/0069), recommending a change to the terms of the marketing authorisation for durvalumab for a new indication to include treatment as monotherapy of adults with LS-SCLC whose disease has not progressed following platinum-based chemoradiation therapy [1].
Has the medicine received a conditional marketing authorization?	No
Accelerated assessment in the European Medicines Agency (EMA)	No
Orphan drug designation (include date)	No
Other therapeutic indications approved by EMA	Non-Small Cell Lung Cancer (NSCLC): • Durvalumab in combination with platinum-based chemotherapy as neoadjuvant treatment, followed by durvalumab as monotherapy as adjuvant treatment, is indicated for the treatment of adults with resectable NSCLC at high risk of recurrence and no Epidermal Growth Factor Receptor (EGFR) mutations or Anaplastic Lymphoma Kinase (ALK) rearrangements. • Durvalumab as monotherapy is indicated for the treatment of locally advanced, unresectable NSCLC in adults whose tumours express PD-L1 on ≥1% of tumour cells and whose

Overview of the medicine	
	disease has not progressed following platinum-based chemoradiation therapy. • Durvalumab in combination with tremelimumab and platinum-based chemotherapy is indicated for the first-line treatment of adults with metastatic NSCLC with no sensitising EGFR mutations or ALK-positive mutations. Small Cell Lung Cancer (SCLC): • Durvalumab in combination with etoposide and either carboplatin or cisplatin is indicated for the first-line treatment of adults with extensive-stage small cell lung cancer (ES-SCLC). Biliary Tract Cancer (BTC): • Durvalumab in combination with gemcitabine and cisplatin is indicated for the first-line treatment of adults with unresectable or metastatic BTC. Hepatocellular Carcinoma (HCC): • Durvalumab as monotherapy is indicated for the first-line treatment of adults with advanced or unresectable HCC. • Durvalumab in combination with tremelimumab is indicated for the first-line treatment of adults with advanced or unresectable HCC. Endometrial Cancer (EC): • Durvalumab in combination with carboplatin and paclitaxel is indicated for the first-line treatment of adults with primary advanced or recurrent endometrial cancer who are candidates for systemic therapy, followed by maintenance treatment with: o Durvalumab as monotherapy in endometrial cancer that is mismatch repair deficient (dMMR) o Durvalumab in combination with olaparib in endometrial cancer that is mismatch repair proficient (pMMR).
Other indications that have been evaluated by the DMC (yes/no)	Yes, the Danish Medicines Council (DMC) has previously evaluated durvalumab in the following indications: NSCLC: On May 30, 2025 DMC recommended durvalumab for stage III NSCLC in adults with PD-L1 ≥ 1% and whose disease has not progressed following platinum based chemoradiation therapy. SCLC: On 25 September 2024, the DMC recommended durvalumab in combination with etoposide and either carboplatin or cisplatin for the first-line treatment of adults with ES-SCLC. BTC: On 04 March 2025, the DMC recommended durvalumab in combination with gemcitabine and cisplatin for the first-line treatment of adults with unresectable or metastatic BTC in performance status 0 or 1.

Overview of the medicine	
	HCC: On 05 December 2024, the DMC recommended durvalumab in combination with tremelimumab for the first-line treatment of adults with advanced or unresectable HCC. EC: On May 2, 2025, DMC recommended durvalumab in combination with carboplatin and paclitaxel for the first-line treatment of adults with primary advanced or recurrent endometrial cancer. Currently ongoing assessment at DMC: NSCLC: Durvalumab in combination with platinum-based chemotherapy as neoadjuvant treatment, followed by durvalumab as monotherapy as adjuvant treatment, indicated for the treatment of adults with resectable NSCLC at high risk of recurrence and no EGFR mutations or ALK rearrangements.
Joint Nordic assessment (JNHB)	Are the current treatment practices similar across the Nordic countries (DK, FI, IS, NO, SE)? Yes Is the product suitable for a joint Nordic assessment? No If no, why not? No, as this assessment includes an indication extension for durvalumab and follows the DMC 14-week assessment process without a health economic assessment.
Dispensing group	BEGR
Packaging – types, sizes/number of units and concentrations	50 mg/ml, one vial of 10 ml concentrate for solution for infusion (500 mg) 50 mg/ml, one vial of 2.4 ml concentrate for solution for infusion (120 mg)

2. Summary table

Summary	
Indication relevant for the assessment	Durvalumab as monotherapy treatment for adults with limited-stage small-cell lung cancer (LS-SCLC) whose disease has not progressed following platinum-based chemoradiation therapy [1].
Dosage regiment and administration	Durvalumab is given after completion of platinum-based CRT. The dosing is 1,500 mg Q4W, for up to 24 months or until disease progression or unacceptable toxicity [1].
Choice of comparator	'Watch-and-wait' represents the only option currently available following platinum-based CRT in LS-SCLC. Durvalumab can be compared to 'watch-and-wait" using the placebo arm from the ADRIATIC trial.

Summary	
Prognosis with current treatment (comparator)	After first-line treatment, no other therapies are recommended [2, 3]. As a result, a "watch and wait" approach is commonly applied in Danish clinical practice. Based on a study from 2020, the prognosis is poor for LS-SCLC in Denmark, with a median overall survival (OS) of 15 months [4]. Patients with LS-SCLC experience relapse in 90% of cases [5], with most patients progressing or dying within 2 years of treatment [6, 7]. One of the primary reasons for the poor survival is the limited treatment options available once the disease progresses, at which point curative therapy is no longer viable. Moreover, the symptoms of SCLC and the side effects of treatment greatly impact patients' health-related quality of life [8].
Type of evidence for the clinical evaluation	The head-to-head study, ADRIATIC, a Phase III, randomised, double-blind, placebo-controlled, multicenter, global study that assessed durvalumab as consolidation treatment for patients with LS-SCLC who had not progressed after platinum-based CRT [9, 10].
Most important efficacy endpoints (Difference/gain compared to comparator)	The most important efficacy endpoints are progression-free survival (PFS) and OS, the dual primary endpoint in ADRIATIC. At the time of the PFS IA/OS IA1 (15 January 2024), median PFS was 16.6 months in the durvalumab arm compared with 9.2 months in the placebo arm (HR: 0.76; 95% CI: 0.61–0.95; p = 0.0161) and median OS was 55.9 months in the durvalumab arm and 33.4 months in the placebo arm, representing an estimated improvement in median OS of 22.5 months (HR: 0.73; 95% CI: 0.57–0.93; p = 0.0104) [9, 10].
Most important serious adverse events for the intervention and comparator	The most important serious adverse events (SAE) included radiation pneumonitis, which affected 5% of patients treated with durvalumab and 2.6% of those receiving placebo, and pneumonia, which affected 4.6% of patients treated with durvalumab and 3.8% of those receiving placebo [11].
Impact on health-related quality of life	Health-related quality of life (HRQoL) secondary endpoints in the ADRIATIC [11] was assessed using [11]: • 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 module). The domains and key symptoms prespecified in the statistical analysis plan, as endpoints of interest was global health status (GHS)/QoL, physical functioning, role functioning fatigue, and appetite loss (QLQ-C30) and dynspnea, cough, and chest pain (QLQ-LC13). The results showed that there were [redacted] in patients' QoL, the difference in mean change from baseline in GHS/QoL was [redacted] For

Summary	
	results on the other HRQoL endpoints see sections 10.1.3 and 10.1.6. The EuroQol five dimensions five level (EQ-5D-5L), Patient's Global Impression of Severity (PGIS) and Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) [11] questionnaires were collected as exploratory HRQoL endpoints and are not presented here. Health economic model: N/A
Type of economic analysis that is submitted	N/A
Data sources used to model the clinical effects	N/A
Data sources used to model the health-related quality of life	N/A
Life years gained	N/A
QALYs gained	N/A
Incremental costs	N/A
ICER (DKK/QALY)	N/A
Uncertainty associated with the ICER estimate	N/A
Number of eligible patients in Denmark	Incidence: 63 Prevalence: Eligible patient based on incident cases
Budget impact (in year 5)	N/A

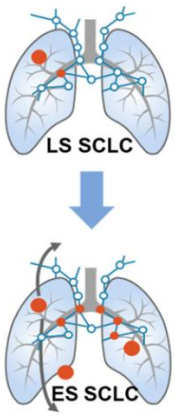
3. The patient population, intervention, choice of comparator(s) and relevant outcomes

3.1 The medical condition

Lung cancer is the leading cause of cancer-related deaths globally [12]. Small-cell lung cancer (SCLC), which accounts for around 15% of all lung cancers, is associated with a more aggressive disease course and a worse prognosis than the more prevalent non-small cell lung cancer (NSCLC) [13-15]. SCLC is divided into two stages: limited-stage (LS) SCLC, which encompasses stages I–III, and extensive-stage (ES) SCLC, corresponding to stage IV [16].

LS-SCLC refers to cases where the tumour is confined to the lung of origin, along with nearby lymph nodes, including those in the mediastinum and ipsilateral supraclavicular lymph nodes. In contrast, ES-SCLC is defined by the tumour's spread beyond one lung, including to the pleura or pericardium, or metastasising to distant parts of the body via the bloodstream. In simpler terms, LS-SCLC is confined to one side of the chest, while ES-SCLC involves both sides and may have spread to other organs (Figure 1) [16].

Figure 1 Representation of tumour size, volume and location in LS-SCLC and ES-SCLC



Source: [15]

The American Joint Committee on Cancer (AJCC) tumour, node, metastasis (TNM) staging system, which classifies SCLC based on tumour size (T), lymph node involvement (N), and metastases (M), is currently the preferred method of staging. Patients are classified into stages I through IV: stages I-III have no metastases (M0), while stage IV is defined by the presence of metastasis (M1) [17]. This staging system is now the standard due to its

superior prognostic value [15]. In this system, LS-SCLC includes tumours that can be treated with radiotherapy (stages I-III), while ES-SCLC refers to advanced cancer (stage IV) [16]. Despite the use of the AJCC system, the definitions of LS- and ES-SCLC from the Veterans Administration Lung study Group (VALG) are still commonly used [16]. Additionally, treatment guidelines from the National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology (ESMO) are used to guide therapy decisions based on staging.

Due to the rapid growth and propensity for metastasis in SCLC, most patients present with symptoms at diagnosis. Approximately two-thirds of patients are diagnosed with ES-SCLC, while only one-third are diagnosed with LS-SCLC [15, 18-20]. The most common symptoms in both LS- and ES-SCLC include coughing, wheezing, dyspnoea, chest pain, fatigue, weight loss, and appetite loss. In cases of ES-SCLC, bone pain and neurological symptoms are indicative of distant metastases [15, 16]. Around 10% of SCLC patients present with brain metastases at diagnosis, and an additional 40–50% develop brain metastases as the disease progresses [15].

The diagnosis of SCLC typically begins with a review of the patient's medical history, including smoking history, followed by imaging tests such as chest X-ray and/or computed tomography (CT) scan to detect tumours. This is often followed by tests to identify cancerous cells in sputum, pleural fluid or tissue biopsies. Additional imaging tests like magnetic resonance imaging (MRI), positron emission tomography (PET) scans, and more biopsies are performed to assess metastasis and accurately stage the disease [21, 22].

Treatment for LS-SCLC has seen few advancements over the past three decades [23]. Standard treatment typically involves platinum-based concurrent or subsequent chemoradiotherapy (CRT), which is intended to be curative. While this approach achieves high response rates, the majority of patients will experience disease progression or die within two years of treatment [6, 7, 22, 24-26].

Based on a 2020 study assessing data from 2006 to 2015, the prognosis for LS-SCLC in Denmark is poor, with a median overall survival (OS) of 15 months and a 5-year survival rate of 15% [4]. The limited treatment advances made in SCLC prior to the introduction of immunotherapy for ES-SCLC are reflected in the outcomes for patients, not improving over nearly three decades, with median OS for SCLC patients reported to be seven months between 1983 and 2012 [23].

In the RENO study, which included Swedish patients (data on file), mean OS was 13.8 months with a 5-year survival probability of 22.21% [18.47-26.71] among the patients who received CRT for LS-SCLC during 2014 – 2023. (mean age: 69, stage III: 83.7%, PS 0-1: 81.6%)

Although LS-SCLC treatment is given with curative intent, initial responses occur in approximately 90% of cases [5], relapse remains common, with most patients progressing or dying within 2 years of treatment [6, 7]. One of the primary reasons for this poor survival is the limited treatment options once the disease progresses, at which point curative therapy is no longer viable. Moreover, the symptoms of SCLC and the side

effects of treatment greatly impact patients' health-related quality of life (HRQoL) [8]. Therefore, preventing disease progression and avoiding the transition to more advanced stages of SCLC is an important and meaningful goal for patients with LS-SCLC.

3.2 Patient population

The patient population for this application consists of adults with LS-SCLC whose disease has not progressed following platinum-based CRT. This aligns with the population in the ADRIATIC clinical trial [9]. Based on the available yearly reports from the Danish Lung Cancer Register, the incidence of lung cancer diagnoses overall in Denmark has been stable over the last five years, with approximately 5,000 incident cases a year, with approximately 600 of those cases being SCLC, representing 11-12% of all lung cancers [27]. It has been reported that one-third (≈34%) of SCLC are classified as LS-SCLC [28, 29], corresponding to about 208 patients a year (see Table 1 for the incidence of LS-SCLC in the past five years, based on the lung cancer register yearly reports).

The prevalence of lung cancer in Denmark has increased. Based on data from NORDCAN (the latest available data is presented for 2023), the prevalence was 14,544 in 2020, rising to 16,909 in 2023. Assuming an approximate 12% of all lung cancer cases are SCLC, and of those 34% are LS-SCLC, the prevalence of LS-SCLC can be estimated to have increased from around 590 to 690 over the same period of time (see Table 1).

The estimated number of eligible patients in Denmark is presented in Table 2, based on the incidence data from the lung cancer register and assumptions. Among the LS-SCLC patients, 41% (≈85 patients) receive treatment first line treatment with CRT. This estimate aligns with the RENO study (data on file) where 45% received CRT. It was assumed that 83% (≈70 patients) do not experience disease progression following CRT and 90% (≈63 patients) of these are considered eligible for durvalumab treatment (see Table 2).

Table 1 Incidence and prevalence in the past 5 years

Year	2020	2021	2022	2023	2024*
Incidence in Denmark	200	208	208	208	208
Prevalence in Denmark**	593	629	656	690	N/A
Global prevalence	N/A	N/A	N/A	N/A	N/A

Note: The estimated for incidence in 2020-2023 are based on the number of patients diagnosed with SCLC from the Danish Lung Cancer Register yearly reports and with 34% assumed to have LS-SCLC [28, 29] *The incidence listed for 2024, is assumed same as for 2023, as no data are yet available for 2024. **The prevalence was estimated based on overall lung cancer prevalence from NORDCAN 2020-2022, applying an assumption of 12% SCLC and 34% being LS-SCLC.

Sources: Dansk Lunge Cancer Register, national årsrapport 2023 [27].

Table 2 Estimated number of patients eligible for treatment

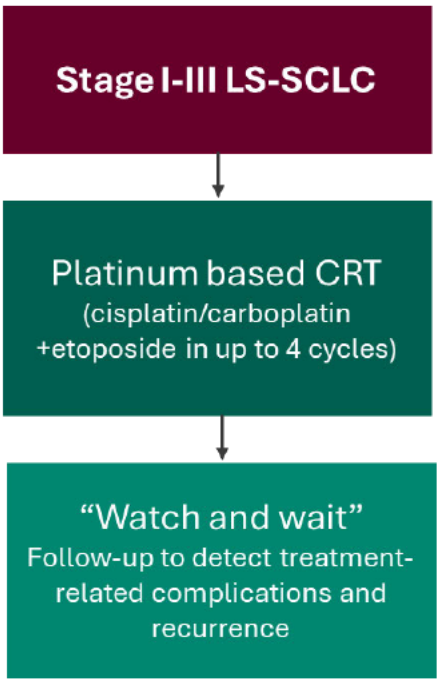
Year	Year 1	Year 2	Year 3	Year 4	Year 5
Number of patients in Denmark who are eligible for treatment in the coming years	63	63	63	63	63

3.3 Current treatment options

In Denmark, the most recent treatment guideline for curative intended treatment of SCLC is from the Danish Lung Cancer Group (DLCG 2024) [2] (see overview for LS-SCLC in Figure 2). For patients with LS-SCLC in stage I-III the recommended treatment is four cycles of platinum-based chemotherapy (cisplatin/carboplatin combined with etoposide) given with radiotherapy [2]. For selected patients, prophylactic cranial irradiation (PCI) may be relevant, with the aim of reducing the risk of brain metastases.

There is currently no systemic consolidation therapy available after platinum-based CRT. A "watch and wait" approach, including follow-up, should be initiated to detect treatment-related complications and recurrence of lung cancer.

Figure 2 Current treatment algorithm and treatment options in Danish clinical practice



Abbreviation: CRT, Chemoradiation therapy; DLCG, Danish Lung Cancer Group; LS-SCLC, Limited stage small cell lung cancer

Source: Adapted based on DLCG treatment guidelines 2024

3.4 The intervention

Imfinzi® (durvalumab) is a high-affinity, human, recombinant IgG1κ monoclonal antibody that specifically blocks the binding of PD-L1 to its receptors, PD-1 and CD80 (B7.1) [30]. PD-L1 is frequently overexpressed on both tumour cells and antigen-presenting cells within the tumour microenvironment, where it inhibits immune responses by suppressing T-cell activation. By blocking this interaction, durvalumab enhances the immune system's ability to target and attack tumour cells, restoring T-cell cytotoxicity, proliferation, and cytokine release [1, 30].

When combined with platinum-based chemotherapy, durvalumab is thought to improve anti-tumour responses by inducing immunogenic effects and upregulation of PD-L1 expression, which may make the tumour more susceptible to immune checkpoint inhibition. The death of tumour cells due to chemotherapy can increase antigen presentation, while higher PD-L1 expression may boost the effectiveness of anti-PD-(L)1 therapies, particularly in tumours with low immunogenicity [31, 32]. This combination of immunotherapy and chemotherapy has shown greater anti-tumour activity, improved response rates, and may help mitigate the risk of treatment resistance [33, 34]. Clinical trial data from metastatic Stage IV NSCLC have demonstrated the efficacy of this combination, suggesting potential benefits in earlier stages of treatment as well [35-38].

An overview of the intervention is provided in Table 3.

Table 3 Overview of the intervention, durvalumab (Imfinzi®)

Overview of intervention	
Indication relevant for the assessment	As monotherapy for the treatment of adults with LS-SCLC whose disease has not progressed following platinum-based CRT.
ATMP	N/A
Method of administration	IV
Dosing	Durvalumab is administered at 1500 mg through IV infusion every 4 weeks [Q4W], up to 24 months or until disease progression or unacceptable toxicity.
Dosing in the health economic model (including relative dose intensity)	N/A
Should the medicine be administered with other medicines?	Prior to initiation of durvalumab, four cycles of platinum-based CRT should be given (three cycles permitted).
Treatment duration / criteria for end of treatment	Until disease progression, unacceptable toxicity, or a maximum of 24 months.
Necessary monitoring, both during administration and during the treatment period	Patients are monitored for adverse reactions during the administration of the drugs and during the treatment period.
Need for diagnostics or other tests (e.g. companion diagnostics). How are these included in the model?	N/A
Package size(s)	50 mg/ml, 10 ml vial 50 mg/ml, 2.4 ml vial.

3.4.1 Description of ATMP

N/A

3.4.2 The intervention in relation to Danish clinical practice

Therapeutic options for the treatment of LS-SCLC are limited both globally and in Denmark (see section 3.3 for an overview). Following platinum-based CRT, there is no available treatment option [2, 3]. Durvalumab monotherapy would be considered for adult Danish patients with LS-SCLC whose disease has not progressed following platinum-based CRT, where there is currently no other available treatment option.

3.4.3 Subsequent treatments

The ADRIATIC trial reports post-discontinuation treatments by line; however, specific agents received as subsequent therapy are not presented per line. Given that most subsequent treatments were received in the first (and second subsequent lines , with a small proportion receiving third or later lines , the specific drug names listed can be interpreted as largely reflecting first- and second-line subsequent therapies [11].

In the first subsequent therapy, among the durvalumab patients, platinum doublet chemotherapy was most common , followed by chemotherapy single agent chemotherapy + immunotherapy other chemotherapy combination and immunotherapy single agent Among the placebo patients, platinum doublet chemotherapy was most common followed by chemotherapy single agent , chemotherapy + immunotherapy , other chemotherapy combination , and immunotherapy single agent In the second subsequent therapy, among the durvalumab patients, chemotherapy single agent was most common , followed by platinum doublet chemotherapy other chemotherapy combination chemotherapy + targeted therapy and chemotherapy + immunotherapy . Among the placebo patients, chemotherapy single agent was most common , followed by platinum doublet chemotherapy other chemotherapy combination chemotherapy + immunotherapy , and targeted therapy single agent

In the durvalumab arm, the majority of subsequent regimens comprised carboplatin plus etoposide in patients and cisplatin plus etoposide in patients Frequently used chemotherapy single-agent included topotecan irinotecan lurbinectedin and paclitaxel 7 patients received the chemo-immunotherapy combination of atezolizumab plus carboplatin plus etoposide. In the placebo arm, the most frequent regimens were carboplatin plus etoposide and cisplatin plus etoposide . Common chemotherapy single-agent included topotecan irinotecan lurbinectedin and paclitaxel 12 received atezolizumab plus carboplatin plus etoposide.

3.5 Choice of comparator(s)

After the platinum-based CRT, as no additional therapies are available, a “watch and wait” approach is applied. This approach reflects the absence of alternative treatment options and includes follow-up to detect treatment-related complications and recurrence. In the head-to-head clinical trial ADRIATIC, durvalumab was evaluated against a placebo, as no other treatment options for patients with LS-SCLC are available. The choice of comparator for this application is therefore watch and wait. As the relevant comparator is ‘watch and wait’, the table below is N/A.

Table 4 Overview of Comparator N/A

Overview of comparator	Watch and wait
Generic name	N/A
ATC code	N/A
Mechanism of action	N/A
Method of administration	N/A
Dosing	N/A
Dosing in the health economic model (including relative dose intensity)	N/A
Should the medicine be administered with other medicines?	N/A
Treatment duration/ criteria for end of treatment	N/A
Need for diagnostics or other tests (i.e. companion diagnostics)	N/A
Package size(s)	N/A

3.6 Cost-effectiveness of the comparator(s)

N/A

3.7 Relevant efficacy outcomes

3.7.1 Definition of efficacy outcomes included in the application

The efficacy outcomes used in this application were sourced from the ADRIATIC clinical trial [9]. The two primary efficacy outcomes were progression free survival (PFS) and OS, while key secondary outcomes included landmark PFS at 18 and 24 months, landmark OS at 24 and 36 months, objective response rate (ORR), time to death or distant metastasis (TTDM), time from randomisation to second progression (PFS2), disease-related symptoms and HRQoL, and the relationship between PD-L1 expression and clinical outcomes. This application focuses on the two primary endpoints and key secondary outcomes as supportive evidence. All outcomes are presented as per the latest data cut off (DCO), January 15, 2024, which constitutes the first interim analysis (IA1).

Table 5 Efficacy outcome measures relevant for the application

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
PFS	Median follow-up not reported	PFS was defined as the time from the date of randomisation until the date of objective disease progression or death (by any cause in the absence of progression) regardless of whether the patient withdrew from therapy or received another anticancer therapy before progression.	Assessed using BICR according to RECIST 1.1.
OS	Median follow-up not reported	OS was defined as the time from the date of randomisation until death due to any cause.	Any patient not known to have died at the time of analysis was censored based on the last recorded date on which the patient was known to be alive.
ORR	Median follow-up not reported	ORR was defined as the number (%) of patients with at least one visit response of CR/PR. Patients who did not have measurable disease at baseline (i.e. CR after cCRT) were excluded from the analysis.	Assessed using BICR according to RECIST 1.1
PFS2	Median follow-up not reported	PFS2 was defined as the time from the date of randomisation to the earliest of the progression event subsequent to first subsequent therapy or death.	Assessed using BICR according to RECIST 1.1. The date of second progression was recorded by the investigator in the eCRF at each assessment and defined according to local standard clinical practice and may involve any of the following: objective radiological imaging, symptomatic progression or death.

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
TTDM	Median follow-up not reported	TTDM was defined as the time from the date of randomisation until the first date of distant metastasis or death in the absence of distant metastasis.	Assessed using BICR according to RECIST 1.1.

* Time point for data collection used in analysis (follow up time for time-to-event measures)

Source: ADRIATIC [9]

Validity of outcomes

As per European Medicines Agency (EMA) guidelines on best clinical practice [39], all the above endpoints align with the endpoints valid for anticancer trials [39]. While PFS is commonly used in advanced settings, OS remains the gold standard when the main objective is to prolong survival [39]. ORR is a relevant endpoint to evaluate the clinical benefit in drug approval processes and provides supportive efficacy evidence, particularly when associated with symptom relief or delay in progression [39]. In addition, TTDM is recognised as a relevant patient-related outcome [39].

4. Health economic analysis

N/A

4.1 Model structure

N/A

4.2 Model features

N/A

Table 6 Features of the economic model N/A

Model features	Description	Justification
Patient population	N/A	N/A
Perspective	N/A	N/A
Time horizon	N/A	N/A
Cycle length	N/A	N/A
Half-cycle correction	N/A	N/A
Discount rate	N/A	N/A
Intervention	N/A	N/A
Comparator(s)	N/A	N/A
Outcomes	N/A	N/A

5. Overview of literature

5.1 Literature used for the clinical assessment

The clinical efficacy and safety of durvalumab compared to a 'watch and wait' approach were based on the head-to-head clinical trial ADRIATIC, using the latest data cut-off of January 15, 2024 [9]. ADRIATIC is a phase 3, randomised, double-blinded, placebo-controlled, multicenter, international study for patients with LS-SCLC who have not progressed following platinum-based CRT. Table 7 below provides an overview of the relevant literature used for the clinical assessment.

Table 7 Relevant literature included in the assessment of efficacy and safety [sample text in table for full paper, data on file and conference abstract]

Reference	Trial name*	NCT identifier	Dates of study	Used in comparison of*
Cheng, Y., et al. Durvalumab after Chemoradiotherapy in Limited-Stage Small-Cell Lung Cancer. New England Journal of Medicine, 2024 Oct 1; 391(14):1313-1327. [9]	ADRIATIC	NCT03703297	Start: 28/09/2018 Completion: ongoing Data cut-off: 15/01/2024	Durvalumab vs watch and wait
AstraZeneca, A Phase III, Randomized, Double-blind, Placebo-controlled, Multi-center, International Study of Durvalumab or Durvalumab and Tremelimumab as Consolidation Treatment for Patients with Limited Stage Small-Cell Lung Cancer Who Have Not Progressed Following Concurrent Chemoradiation Therapy (ADRIATIC)_Clinical study report. 2024. [11]	ADRIATIC	NCT03703297	Start: 28/09/2018 Completion: ongoing Data cut-off: 15/01/2024	Durvalumab vs watch and wait

* If there are several publications connected to a trial, include all publications used.

5.2 Literature used for the assessment of health-related quality of life

The literature used for the assessment of HRQoL is retrieved from the head-to-head clinical study, ADRIATIC presented in section 5.1. For further details regarding the HRQoL, please see section 10.1.

Table 8 Relevant literature included for (documentation of) health-related quality of life (See section 10)

Reference (Full citation incl. reference number)	Health state/Disutility	Reference to where in the application the data is described/applied
Cheng, Y., et al. Durvalumab after Chemoradiotherapy in Limited-Stage Small-Cell Lung Cancer. New England Journal of Medicine, 2024 Oct 1; 391(14):1313-1327. [9]	N/A	See section 10.1
AstraZeneca, A Phase III, Randomized, Double-blind, Placebo-controlled, Multi-center, International Study of Durvalumab or Durvalumab and Tremelimumab as Consolidation Treatment for Patients with Limited Stage Small-Cell Lung Cancer Who Have Not Progressed Following Concurrent Chemoradiation Therapy (ADRIATIC)_Clinical study report. 2024. [11]	N/A	See section 10.1

5.3 Literature used for inputs for the health economic model

N/A

Table 9 Relevant literature used for input to the health economic model N/A

Reference (Full citation incl. reference number)	Input/estimate	Method of identification	Reference to where in the application the data is described/applied
N/A	N/A	N/A	N/A

6. Efficacy

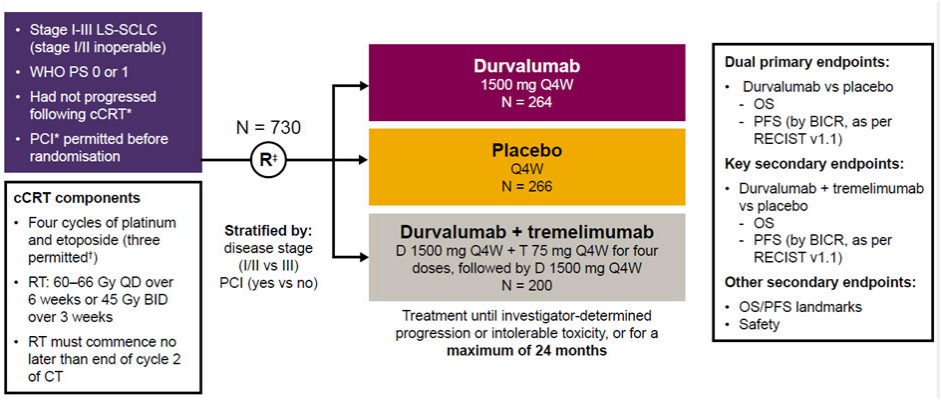
6.1 Efficacy of durvalumab compared to placebo for patient with limited-stage small-cell lung cancer whose disease has not progressed following platinum-based chemoradiation therapy

6.1.1 Relevant studies

The ADRIATIC trial is the only study that provides clinical evidence for durvalumab as monotherapy for the treatment of adults with LS-SCLC whose disease has not progressed following platinum-based CRT. ADRIATIC is an ongoing, multicentre, double-blind, randomised, placebo-controlled, phase 3 trial to assess the efficacy and safety of durvalumab monotherapy and durvalumab plus tremelimumab compared with placebo as consolidation treatment in patients with LS-SCLC whose disease had not progressed following definitive CRT with platinum-based therapy (Figure 3). The ADRIATIC trial included patients who were 18 years or older with confirmed LS-SCLC, an Eastern Cooperative Oncology Group (ECOG) PS of 0 or 1 and who had not progressed after receiving CRT with platinum-based therapy plus etoposide.

This application addresses the durvalumab monotherapy as per the regulatory indication, based on the results of the first interim analysis PFS IA/OS IA1, data cut off (DCO), 15 January 2024. Analysis of the efficacy of the third arm in ADRIATIC, durvalumab + tremelimumab, is ongoing, and the results are expected to be presented at upcoming medical conferences. The results of the PFS IA/OS IA1 are presented in this application for the full analysis set (FAS)/all randomised patients. The safety analysis set included all patients who received at least one dose of study treatment. At the time of the PFS IA/OS IA1, all patients had had the opportunity to receive the maximum 24 months of study treatment.

Figure 3 ADRIATIC study design



Footnote: *cCRT and PCI treatment, if received per local standard of care, must have been completed within 1–42 days prior to randomisation; †If disease control was achieved and no additional benefit was expected with an additional cycle of chemotherapy, in the opinion of the investigator; ‡The first 600 patients were randomised in a 1:1:1 ratio to the three treatment arms; subsequent patients were randomised 1:1 to either durvalumab or placebo.

Source: Spiegel et al., poster from the ASCO Annual Meeting 2024 [10].

Table 10 Overview of study design for studies included in the comparison

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention 1	Intervention 2	Comparator	Outcomes and follow-up time
ADRIATIC, NCT03703297	Phase III, Randomized, Double-blind, Placebo-controlled, Multi-center, International Study	6 years	Patients With Limited Stage Small Cell Lung Cancer Who Have Not Progressed Following Concurrent Chemoradiation Therapy	Durvalumab monotherapy: Durvalumab (1500 mg intravenous [IV]) Q4W in combination with placebo saline solution (IV) Q4W for up to 4 doses/cycles each, followed by durvalumab 1500 mg Q4W.	Durvalumab in combination with tremelimumab: Durvalumab (1500 mg IV) Q4W in combination with tremelimumab (75 mg IV) Q4W for up to 4 doses/cycles each, followed by durvalumab 1500 mg Q4W.	Placebo: Placebo saline solution (IV) Q4W in combination with a second placebo saline solution (IV) Q4W for up to 4 doses/cycles each, followed by a single placebo saline solution Q4W.	Primary endpoints: PFS and OS Key Secondary endpoints: ORR, PFS at 18 months, PFS at 24 months, TTDM, OS at 24 months, OS at and 36 months, PFS2, HRQOL using the EORTC QLQ-C30 v3 and HRQoL using EORTC QLQ-LC13, PD-L1 expression in tumour and/or immune cells relative to response/efficacy outcomes (PFS, OS & ORR) Time Frame: Approximately 6 years

6.1.2 Comparability of studies

As the clinical efficacy and safety for durvalumab as monotherapy for the treatment of adults with LS-SCLC whose disease has not progressed following platinum-based CRT, is based directly on the head-to-head trial, the following section includes only the patient the baseline characteristics from ADRIATIC trial.

6.1.2.1 Comparability of patients across studies

The baseline demographic and disease characteristics in ADRIATIC were generally balanced between the durvalumab and placebo arms (Table 11). The median age was 62.0 years, 69.1% of patients were male, most patients were current or former smokers (90.8%) and most patients had stage III disease (87.4%). In line with eligibility criteria, all patients had a WHO/ECOG PS of 0 (48.7%) or 1 (51.3%) [9].

With respect to prior CRT, the majority of patients received once-daily radiotherapy (72.1%), and the best response to CRT was complete response (CR) in 12.3% of patients and partial response (PR) in 73.8% of patients. Prior PCI was received by approximately half of patients (53.8%) [9].

Overall, the prior therapy received by patients was appropriate curative-intent standard of care (SoC) treatment for patients with LS-SCLC and was reflective of regional variations in SoC and patient preferences [11].

Table 11 Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety

		ADRIATIC		
		Durvalumab (n = 264)	Placebo (n = 266)	Total (N = 530)
Age (years)	Median (range)	62.0 (28–84)	62.0 (28–79)	62.0 (28–84)
Age group (years), n (%)	≥65	104 (39.4)	104 (39.1)	208 (39.2)
Sex, n (%)	Male	178 (67.4)	188 (70.7)	366 (69.1)
	Female	86 (32.6)	78 (29.3)	164 (30.9)
Race, n (%)	White	130 (49.2)	137 (51.5)	267 (50.4)
	Black or African American	1 (0.4)	3 (1.1)	4 (0.8)
	Asian	131 (49.6)	121 (45.5)	252 (47.5)
	Other	2 (0.8)	5 (1.9)	7 (1.3)
Geographic region, n (%)	Asia	129 (48.9)	120 (45.1)	249 (47.0)
	Europe	94 (35.6)	112 (42.1)	206 (38.9)
	North America	39 (14.8)	31 (11.7)	70 (13.2)
	South America	2 (0.8)	3 (1.1)	5 (0.9)
Smoking history, n (%)	Non-smoker	23 (8.7)	26 (9.8)	49 (9.2)
	Smoker	241 (91.3)	240 (90.2)	481 (90.8)
	Former smoker	178 (67.4)	185 (69.5)	363 (68.5)
	Current smoker	63 (23.9)	55 (20.7)	118 (22.3)
WHO/ECOG PS, n (%)	0	132 (50.0)	126 (47.4)	258 (48.7)
	1	132 (50.0)	140 (52.6)	272 (51.3)
TNM stage at diagnosis (stratification), n (%)	I or II	33 (12.5)	34 (12.8)	67 (12.6)
	I	8 (3.0)	11 (4.1)	19 (3.6)
	II	25 (9.5)	23 (8.6)	48 (9.1)

		ADRIATIC		
		Durvalumab (n = 264)	Placebo (n = 266)	Total (N = 530)
	III	231 (87.5)	232 (87.2)	463 (87.4)
PD-L1 status, n (%)	TC and IC <1%	78 (29.5)	73 (27.4)	151 (28.5)
	TC or IC ≥1%	84 (31.8)	98 (36.8)	182 (34.3)
	Missing	102 (38.6)	95 (35.7)	197 (37.2)
Prior chemotherapy regimen, n (%)	Cisplatin + etoposide	173 (65.5)	178 (66.9)	351 (66.2)
	Carboplatin + etoposide	91 (34.5)	88 (33.1)	179 (33.8)
Prior chemotherapy, number of cycles, n (%)	3	29 (11.0)	31 (11.7)	60 (11.3)
	4	234 (88.6)	234 (88.0)	468 (88.3)
	Other	1 (0.4)	1 (0.4)	2 (0.38)
Prior radiotherapy schedule, n (%)	Once daily	195 (73.9)	187 (70.3)	382 (72.1)
	Twice daily	69 (26.1)	79 (29.7)	148 (27.9)
Best response to cCRT, n (%)	CR	31 (11.7)	34 (12.8)	65 (12.3)
	PR	191 (72.3)	200 (75.2)	391 (73.8)
	Stable disease	42 (15.9)	32 (12.0)	74 (14.0)
Time from end of prior chemotherapy to randomisation (days), n (%)	<14	32 (12.1)	32 (12.0)	64 (12.1)
	≥14 – <28	79 (29.9)	80 (30.1)	159 (30.0)
	≥28	153 (58.0)	154 (57.9)	307 (57.9)
Received PCI prior to randomisation, n (%)	Yes	142 (53.8)	143 (53.8)	285 (53.8)
	No	122 (46.2)	123 (46.2)	245 (46.2)

Source: Cheng et al. 2024 [9]

6.1.3 Comparability of the study population(s) with Danish patients eligible for treatment

The population I ADRIATIC is assumed to be representative of the patient in Denmark expected to be treated with durvalumab consisting of adults with LS-SCLC whose disease has not progressed following platinum-based CRT. Based on a study from the Danish lung cancer register, the mean age of patients with SCLC overall in Denmark is 68.5 years and the proportion of SCLC between genders is balanced. The median age in the ADRIATIC trial was younger, 62.0 years with a slightly higher proportion of men than in the overall Danish SCLC patients.

Table 12 Characteristics in the relevant Danish population and in the health economic model

	Value in Danish population (Green et al. 2020 [4])	Value used in health economic model (reference if relevant)
Mean age	68.5 years	N/A
Gender % Males	50.8%	N/A

Source: Green et al. 2020 [4]

6.1.4 Efficacy – results per ADRIATIC

At the time of PFS IA/OS IA1 (DCO 15 January 2024), [redacted] patients [redacted] in the durvalumab arm and [redacted] patients [redacted] in the placebo arm remained in the study and in survival follow-up [11]. All patients had had the opportunity to receive the maximum 24 months of study treatment, and no patients were receiving study treatment at the DCO. Of the patients who received study treatment, 88 patients (33.5%) in the durvalumab arm and 70 patients (26.4%) in the placebo arm completed the maximum 24 months of treatment, respectively [9].

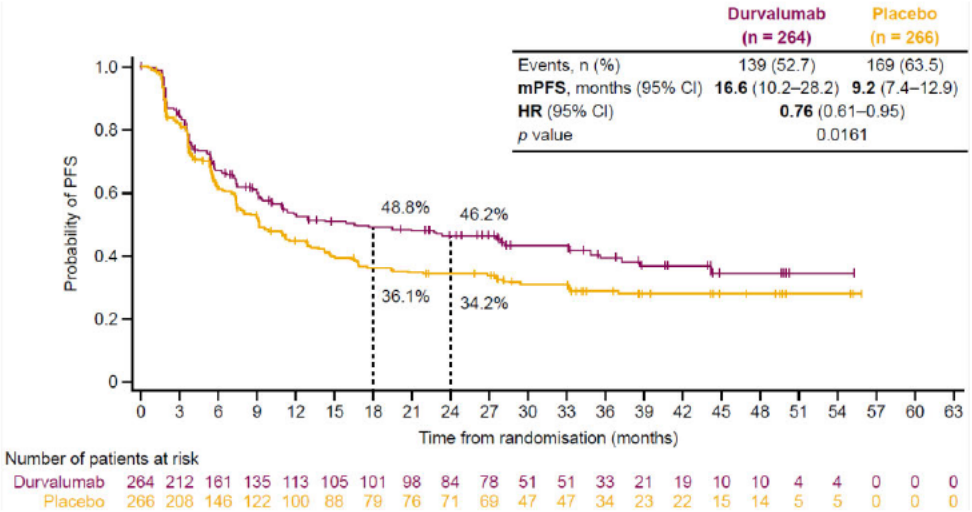
6.1.4.1 Progression-free survival (PFS)

At the time of the PFS IA/OS IA1 (DCO 15 January 2024), the median duration of follow-up for PFS in censored patients was [redacted] [11]. Overall PFS maturity was 58.1%, with 139 and 169 PFS events reported in the durvalumab and placebo arms, respectively [9].

Compared with placebo, patients who received durvalumab had a 24% reduction in the risk of progression or death (HR: 0.76; 95% CI: 0.61–0.95; $p = 0.0161$) [9, 10]. The Kaplan–Meier (KM)-estimated median PFS was 16.6 months in the durvalumab arm compared with 9.2 months in the placebo arm. The KM plot (Figure 4) showed a separation of the durvalumab and placebo arms after 6 months that was sustained thereafter. This was reflected in the landmark estimates of PFS that favoured durvalumab over placebo at 18 months (48.8% vs 36.1%) and 24 months (46.2% vs 34.2%) [9]. The initial delay in the separation of curves may reflect the continued impact of the prior cCRT received by all patients in the study, with the majority of patients having achieved [redacted] with prior cCRT at study entry [11].

Consistent with the FAS, PFS benefits with durvalumab were observed irrespective of PD-L1 expression, with a HR of 0.79 (95% CI: 0.532, 1.158) seen in PD-L1 ≥1% subgroup.

Figure 4 Kaplan–Meier curve for PFS in the durvalumab arm compared with placebo



Footnote: The significance level for testing PFS at this interim analysis was 0.00184 (2-sided) at the 0.5% level, and 0.02805 (2-sided) at the overall 5% level. Statistical significance for PFS was achieved through the recycling multiple-testing procedure framework and testing at the 5% (2-sided) alpha level (adjusted for an interim and final analysis).

Source: Spigel et al., poster from the ASCO Annual Meeting 2024 [10]

The proportional-hazards assumption was assessed using using complementary log–log plots versus log time from randomization to PFS and OS and by fitting a time-dependent covariate. Formal testing supported the assumption for PFS; p=0.79, indicating the plausibility of proportional hazards in the stratified Cox analyses [9].

Figure 5 Progression-free survival, based on BICR assessment according to RECIST 1.1, complementary log-log plot

*Durva: Durvalumab, PFS: Progression-free survvial

Source: CSR [11]

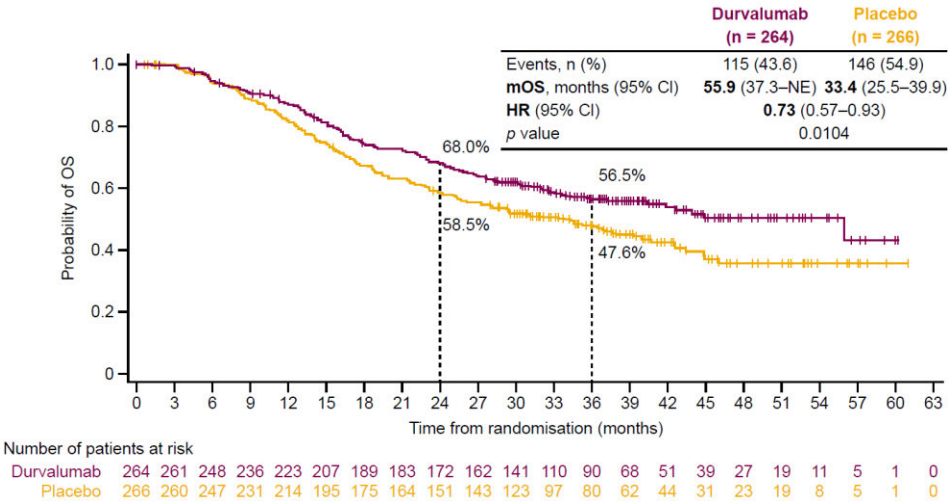
6.1.4.2 Overall survival (OS)

At the time of the PFS IA/OS IA1 (15 January 2024), the median duration of follow-up for OS in censored patients was 37.2 months (range 0.1–60.9). Overall OS maturity was 49.2%, with 115 and 146 deaths reported in the durvalumab and placebo arms, respectively [9].

Compared with placebo, patients treated with durvalumab had a 27% reduction in the risk of death (HR: 0.73; 95% CI: 0.57–0.93; *p* = 0.01042) [9, 10]. The KM-estimated median OS was 55.9 months in the durvalumab arm and 33.4 months in the placebo arm, representing an estimated improvement in median OS of 22.5 months. The KM plot (Figure 6) showed a separation of the durvalumab and placebo arms after 8 months that was sustained thereafter. This was reflected in the landmark estimates of OS that favoured patients who received durvalumab over placebo at 24 months (68.0% vs 58.5%) and 36 months (56.5% vs 47.6%) [9].

Similar to PFS, efficacy in terms of OS was consistent irrespective of PD-L1 expression, with a HR of 0.60 (95% CI: 0.379, 0.923) observed in the PD-L1 ≥1% subgroup.

Figure 6 Kaplan–Meier curve for OS in the durvalumab arm compared with placebo



Footnotes: OS was analysed using a stratified log-rank test adjusted for receipt of PCI (yes vs no). The significance level for testing OS at this interim analysis was 0.01679 (2-sided) at the overall 4.5% level, allowing for strong alpha control across interim and final analysis time points.

Source: Spigel et al., poster from the ASCO Annual Meeting 2024 [10]

Formal testing supported the assumption for OS; p=0.91, indicating the plausibility of proportional hazards in the stratified Cox analyses [9].

Figure 7 Overall survival, complementary log-log plot

[redacted]

*Durva: Durvalumab, OS: Overall survvial

Source: CSR [11]

6.1.4.3 Key secondary outcomes

Table 13 provides an overview of the key secondary endpoints, ORR, TTDM and PFS2. In patients with measurable disease at baseline, a similar ORR (based on unconfirmed responses/no requirement for confirmation, assessed using BICR assessments per RECIST 1.1) was observed for patients treated with durvalumab (30.3%) compared to placebo (32.0%) (difference in proportion: −1.2%; 95% CI: −11.0, 8.5) [9].

Durvalumab treatment resulted in an improvement in PFS2 (determined by the investigator) relative to placebo [redacted] The KM-estimated median PFS2 was [redacted] Treatment with durvalumab compared to placebo resulted in an improvement in PFS2, with a [redacted]

TTDM, using BICR and Investigator assessments, each according to RECIST 1.1, are provided in Table 13. TTDM by BICR was a secondary endpoint in the study and TTDM by Investigator was a planned sensitivity analysis of the TTDM endpoint as assessed by BICR. As shown in Table 13, TTDM results using Investigator and BICR assessments were consistent with each other. For the comparison of durvalumab vs placebo, TTDM using BICR assessments resulted in a [redacted]

Table 13 Key secondary endpoints

Secondary endpoint	Durvalumab (N = 264)	Placebo (N = 266)
ORR[a] per BICR		
Evaluable patients[b], n	175	169
Patients with response n, % (95% CI)	53, 30.3% (23.6–37.7)	54, 32.0% (25.0–39.6)
Difference in % (95% CI)	-1.2 (-11.0, 8.5)	
PFS2		
Median, months (95% CI)	[redacted]	[redacted]
HR (95% CI)	[redacted]	
TTDM[c]		
TTDM as per BICR assessment (95% CI)	[redacted]	[redacted]
HR (95% CI)	[redacted]	
TTDM as per investigator assessment (95% CI)	[redacted]	[redacted]
HR (95% CI)	[redacted]	

Footnotes: [a]Tumour response was assessed by BICR, data shown include unconfirmed responses [b]The analysis was performed with data from patients with measurable disease at baseline. [c]Late in the study, it was observed that for new lesions retrospectively identified by BICR, the date and location description of the new lesion were not always accurately captured or were missing in some cases, which potentially affected the BICR assessment of TTDM. Therefore, both TTDM by BICR and TTDM as per investigator assessment are included in this table.

Source: Cheng et al., 2024 [9] ADRIATIC CSR (31 May 2024) [11]

6.1.5 Efficacy – results based on FPAS

N/A

7. Comparative analyses of efficacy

As clinical evidence is based on a head-to-head study, the following section describing comparative analysis is not applicable. Table 14, has been completed as per the DMC template instructions, with results from ADRIATIC.

7.1.1 Differences in definitions of outcomes between studies

N/A

7.1.2 Method of synthesis

N/A

7.1.3 Results from the comparative analysis

The results from the comparative analysis of durvalumab compared to placebo for patients with LS-SCLC whose disease has not progressed following platinum CRT are presented for the two primary endpoints, in Table 14.

For key secondary outcomes see Appendix B.

Table 14 Results from the comparative analysis of durvalumab compared to placebo for patients with limited-stage small-cell lung cancer whose disease has not progressed following platinum-based chemoradiation therapy

Outcome measure	Durvalumab (N=264)	Placebo (N=266)	Result
mPFS, median follow-up 27.6 months	16.6 months (CI: 10.2-28.2)	9.2 months (CI: 7.4-12.9)	HR: 0.76 (95% CI: 0.61–0.95)
mOS, median follow-up 37.2 months	55.9 months (CI: 37.3-NE)	33.4 months (CI: 25.5-39.9)	HR: 0.73 (95% CI: 0.57–0.93)

Source: Cheng et al., 2024 [9]

7.1.4 Efficacy – results per [outcome measure]

N/A

8. Modelling of efficacy in the health economic analysis

N/A

8.1 Presentation of efficacy data from the clinical documentation used in the model

N/A

8.1.1 Extrapolation of efficacy data

N/A

8.1.1.1 Extrapolation of [effect measure 1]

N/A

Table 15 Summary of assumptions associated with extrapolation of [effect measure] N/A

Method/approach	Description/assumption
Data input	N/A
Model	N/A
Assumption of proportional hazards between intervention and comparator	N/A
Function with best AIC fit	N/A
Function with best BIC fit	N/A
Function with best visual fit	N/A
Function with best fit according to evaluation of smoothed hazard assumptions	N/A
Validation of selected extrapolated curves (external evidence)	N/A
Function with the best fit according to external evidence	N/A
Selected parametric function in base case analysis	N/A
Adjustment of background mortality with data from Statistics Denmark	N/A
Adjustment for treatment switching/cross-over	N/A
Assumptions of waning effect	N/A
Assumptions of cure point	N/A

8.1.1.2 Extrapolation of [effect measure 2]

N/A

8.1.2 Calculation of transition probabilities

N/A

Table 16 Transitions in the health economic model N/A

Health state (from)	Health state (to)	Description of method	Reference
Disease-free survival	N/A	N/A	N/A
	N/A	N/A	N/A
Recurrence	N/A	N/A	N/A
Health state/Transition	N/A	N/A	N/A

8.2 Presentation of efficacy data from [additional documentation]

N/A

8.3 Modelling effects of subsequent treatments

N/A

8.4 Other assumptions regarding efficacy in the model

N/A

8.5 Overview of modelled average treatment length and time in model health state

N/A

Table 17 Estimates in the model N/A

	Modelled average [effect measure] (reference in Excel)	Modelled median [effect measure] (reference in Excel)	Observed median from relevant study
N/A	N/A	N/A	N/A
N/A	N/A	N/A	N/A

Table 18 Overview of modelled average treatment length and time in model health state, undiscounted and not adjusted for half cycle correction (adjust the table according to the model) N/A

Treatment	Treatment length [months]	Health state 1 [months]	Health state 2 [months]
N/A	N/A	N/A	N/A
N/A	N/A	N/A	N/A

9. Safety

Safety was analysed in the safety population, which included all patients who received at least one dose of study treatment [9]. At the time of the PFS IA/OS IA1, all patients had had the opportunity to receive the maximum 24 months of study treatment. Duration of exposure to durvalumab and placebo was similar between treatment arms, and the majority of patients received less than the maximum 24 months (approximately 104 weeks and corresponding to a maximum of 26 treatment cycles) of study treatment. The median total duration of treatment (DOT) was 40.0 weeks for the durvalumab arm and 35.9 weeks for the placebo arm.

9.1 Safety data from the clinical documentation

Durvalumab demonstrated a tolerable and manageable safety profile in patients with LS-SCLC who had received prior platinum-based CRT (see Table 19 and Table 20) [11]. Most patients in the durvalumab and placebo arms experienced an AE (94.3% vs 88.3%). Most AEs were non-serious and Grade 1 or 2 [10].

Numerically more serious AEs (SAEs) were reported in patients receiving durvalumab than in patients receiving placebo (29.8% vs 24.2%, respectively). The majority of SAEs in both treatment groups were assessed by the investigator as not related to the study treatment [9].

Any AE of any Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 or 4 was 26.3% vs 25.7%, respectively. AEs assessed by the investigator as being possibly related to the study treatment were reported at a higher frequency in the durvalumab arm than in the placebo arm (67.2% vs 48.7%, respectively) [11]. The incidence of AEs leading to treatment discontinuation was slightly higher in patients receiving durvalumab than in patients receiving placebo (16.4% vs 10.6%, respectively) [11].

AEs leading to treatment discontinuation and assessed by the investigator as being possibly related to treatment were reported in 11.5% of patients in the durvalumab arm and 5.7% of patients in the placebo arm [9].

Table 19 Overview of safety events, DCO 15 January 2024 (up to 24 months)

	Durvalumab (N = 262)	Placebo (N = 265)	Difference, % (95 % CI)
Number of adverse events, n	N/A	N/A	N/A
Number and proportion of patients[a] with ≥1 adverse events, n (%)	247 (94.3)	234 (88.3)	6 (1.2, 10.8)
Number of serious adverse events*, n	N/A	N/A	N/A
Number and proportion of patients[a] with ≥ 1 serious adverse events*, n (%)	78 (29.8)	64 (24.2)	5.6 (-1.9, 13.2)
Number of CTCAE grade ≥ 3 events, n	N/A	N/A	N/A
Number and proportion of patients with ≥ 1 CTCAE grade ≥ 3 events[§], n (%)	[redacted]	[redacted]	[redacted]
Number of adverse reactions, n	N/A	N/A	N/A
Number and proportion of patients with ≥ 1 adverse reactions, n (%)	176 (67.2)	129 (48.7)	18.5 (10.2, 26.8)
Number and proportion of patients[a] who had a dose reduction, n (%)	91 (34.7)	76 (28.7)	6.1 (-1.9, 14.0)
Number and proportion of patients[a] who discontinue treatment regardless of reason, n (%)	43 (16.4)	28 (10.6)	5.8 (0.0, 11.7)
Number and proportion of	30 (11.5)	15 (5.7)	5.8 (1.0, 10.5)

	Durvalumab (N = 262)	Placebo (N = 265)	Difference, % (95 % CI)
patients[a] who discontinue treatment due to adverse events, n (%)			

* A serious adverse event is an event or reaction that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect (see the ICH's complete definition).

§ CTCAE v. 5.0 must be used if available.

[a]Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories.

Source: ADRIATIC CSR [11]

Table 20 Serious adverse events with a frequency of ≥ 5% recorded in the study (up to 24 months)

Adverse events	Durvalumab (N = 262)		Placebo (N = 265)	
Preferred term	**Number of patients[a] with adverse events**	**Number of adverse events**	**Number of patients[a] with adverse events**	**Number of adverse events**
Radiation pneumonitis	13 (5.0)	n.a.	7 (2.6)	n.a.
Pneumonia	12 (4.6)	n.a.	10 (3.8)	n.a.

c* A serious adverse event is an event or reaction that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect (see the ICH's complete definition).

[a]Patients with multiple SAEs are counted once for each Preferred term.

Source: ADRIATIC CSR [11]

*n.a., not available

Table 21 Adverse events used in the health economic model N/A

Adverse events	Intervention	Comparator		
	Frequency used in economic model for intervention	**Frequency used in economic model for comparator**	**Source**	**Justification**
Adverse event, n (%)	N/A	N/A	N/A	N/A
N/A	N/A	N/A	N/A	N/A

9.2 Safety data from external literature applied in the health economic model

N/A

Table 22 Adverse events that appear in more than X % of patients N/A

Adverse events	Intervention (N=x)			Comparator (N=x)			Difference, % (95 % CI)	
	Number of patients with adverse events	Number of adverse events	Frequency used in economic model for intervention	Number of patients with adverse events	Number of adverse events	Frequency used in economic model for comparator	Number of patients with adverse events	Number of adverse events
Adverse event, n	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

10. Documentation of health-related quality of life (HRQoL)

Secondary endpoints based on patient-reported outcomes included an assessment of European Organisation for Research and Treatment of Cancer (EORTC) 30-item core quality of life questionnaire (QLQ-C30) including global health status/quality of life (GHS/QoL), physical functioning, role functioning, fatigue and appetite loss or the EORTC quality of life questionnaire, lung cancer module (QLQ-LC13) including dyspnoea, cough and chest pain.

In addition, exploratory endpoints included health state utility using EuroQol five dimensions five level questionnaire (EQ-5D-5L), an assessment on Patient's Global Impression of Severity (PGIS) and an assessment of treatment-related side effects using Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE).

The instruments used for the assessment of HRQoL in this application are based on the secondary endpoints in ADRIATIC trial listed in Table 23.

Table 23 Overview of included HRQoL instruments

Measuring instrument	Source	Utilization
EORTC QLQ-C30 (assesses the pre-specified symptoms and domains of interest included the following symptoms: dyspnoea, cough and chest pain)	ADRIATIC, CSR	To assess disease-related symptoms and HRQoL in patients treated with durvalumab monotherapy compared to placebo using the EORTC QLQ-C30 v3 Assesses change in symptoms, functioning, and global health status/QoL
EORTC QLQ-LC13 (assesses the pre-specified symptoms and domains of interest included the following symptoms: fatigue and appetite loss)	ADRIATIC, CSR	To assess disease-related symptoms and HRQoL in patients treated with durvalumab monotherapy compared to placebo using the EORTC QLQ-LC13 Assesses change in symptoms

Source: ADRIATIC CSR [11]

10.1 Presentation of the health-related quality of life EORTC QLQ-C30

10.1.1 Study design and measuring instrument

The EORTC QLQ-C30 is a well-established patient-reported outcome measures in cancer research. The EORTC QLQ-C30 is designed to assess the functional health, symptom burden and HRQoL of patients with cancer. The current version (QLQ-C30 v3.0) contains 30 items. The QLQ-C30 includes 15 scales: five functional scales assessing physical functioning, role functioning, emotional functioning, cognitive functioning and social functioning; nine multi- and single-item scales assessing fatigue, nausea and vomiting, pain, dyspnoea, insomnia, appetite loss, constipation, diarrhoea, financial difficulties and a GHS/QoL scale. The EORTC core model supplements with disease- or treatment-specific modules, e.g. for lung cancer, which was the module used in ADRIATIC, QLQ-LC13.

In ADRIATIC, the EORTC QLQ-C30 were planned to show the overall influence of the benefits and toxicity of the treatment from a patient's perspective and aid in understanding the benefit-risk evaluation [11]. The subscales/items and symptoms prespecified in the statistical analysis plan as endpoints of interest was GHS/QoL, physical functioning, role functioning, fatigue and appetite loss [11].

10.1.2 Data collection

The data for EORTC QLQ-C30 were collected every 4 weeks (±3 days) relative to randomisation until study termination or PFS2 or death [11]. The change from baseline in key symptoms was examined using a mixed-effects model repeated-measures (MMRM) analysis. GHS/QoL function improvement rate and symptom improvement rate were analysed using a logistic regression model. Time to GHS/QoL/function and time to

symptom deterioration were analysed using a stratified log-rank test [11]. Table 24 and Table 25 present pattern of missing data and completion for durvalumab and placebo for EORTC QLQ-C30 [11].

Table 24 Pattern of missing data and completion for durvalumab - EORTC QLQ-C30

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
	Number of patients at randomization	Number of patients for whom data is missing (% of patients at randomization)	Number of patients "at risk" at time point X	Number of patients who completed (% of patients expected to complete)
Baseline	[redacted]	[redacted]	[redacted]	[redacted]
Week 4	[redacted]	[redacted]	[redacted]	[redacted]
Week 16	[redacted]	[redacted]	[redacted]	[redacted]
Week 36	[redacted]	[redacted]	[redacted]	[redacted]
Week 84	[redacted]	[redacted]	[redacted]	[redacted]
Week 104	[redacted]	[redacted]	[redacted]	[redacted]
Week 152	[redacted]	[redacted]	[redacted]	[redacted]
Week 200	[redacted]	[redacted]	[redacted]	[redacted]
Week 268	[redacted]	[redacted]	[redacted]	[redacted]

Source: ADRIATIC CSR [11]

Table 25 Pattern of missing data and completion for placebo - EORTC QLQ-C30

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
	Number of patients at randomization	Number of patients for whom data is missing (% of patients at randomization)	Number of patients "at risk" at time point X	Number of patients who completed (% of patients expected to complete)
Baseline	[redacted]	[redacted]	[redacted]	[redacted]
Week 4	[redacted]	[redacted]	[redacted]	[redacted]
Week 16	[redacted]	[redacted]	[redacted]	[redacted]
Week 36	[redacted]	[redacted]	[redacted]	[redacted]
Week 84	[redacted]	[redacted]	[redacted]	[redacted]
Week 104	[redacted]	[redacted]	[redacted]	[redacted]
Week 152	[redacted]	[redacted]	[redacted]	[redacted]
Week 200	[redacted]	[redacted]	[redacted]	[redacted]
Week 268	[redacted]	[redacted]	[redacted]	[redacted]

Source: ADRIATIC CSR [11]

10.1.3 HRQoL results

Overall, there were no clinically important differences in changes from baseline between the durvalumab and placebo groups. [redacted]. Patients in the durvalumab group reported [redacted]

The adjusted mean change from baseline in the EORTC QLQ-C30 primary subscales from MMRM over time are summarised in Table 26 and for the respective EORTC QLQ-C30 primary subscale in Table 27 - Table 31 and Figure 8 - Figure 12.

Table 26 Adjusted Mean Change (95% CI) from Baseline (Average Over 24 Months) in Key EORTC QLQ-C30 Endpoints, MMRM (FAS)

	Durvalumab (N = 264)		Placebo (N = 266)		Intervention vs. comparator
Subscale	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GHS/QoL[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Physical functioning[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Role functioning[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Appetite loss[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Note: [a]Negative change from baseline indicates deterioration in GHS/QoL and functioning scales. [b]Positive change from baseline indicates deterioration in symptom scales.

Source: ADRIATIC CSR [11]

Table 27 HRQoL summary statistics QLQ-C30 GHS/QoL

	Durvalumab (N = 264)		Placebo (N = 266)		Intervention vs. comparator
	N	Mean (SE)	N	Mean (SE)	Difference (95% CI) p-value
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 36	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 48	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 64	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 80	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 96	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 104	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: ADRIATIC CSR [11]

Figure 8 Adjusted Mean Change from Baseline in EORTC QLQ-C30, global health status / QoL MMRM (FAS)

Note: EORTC QLQ-C30 scales were scored from 0 to 100, with a higher score representing a higher level of symptoms for symptom scores, and a higher level of functioning for functioning scores and GHS/QoL. Error bars represent the 95% CI for each respective adjusted mean. N at baseline = Number of patients with baseline and at least one post-baseline value included in the analysis.

Source: ADRIATIC CSR [11]

Table 28 HRQoL QLQ-C30 physical functioning, summary statistics

	Durvalumab N = 264		Placebo N = 266		Intervention vs. comparator
	N	Mean (SE)	N	Mean (SE)	Difference (95% CI) p-value
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 36	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 48	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 64	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 80	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 96	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 104	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: ADRIATIC CSR [11]

Figure 9 Adjusted Mean Change from Baseline in EORTC QLQ-C30, physical functioning, MMRM (FAS)

Note: EORTC QLQ-C30 scales were scored from 0 to 100, with a higher score representing a higher level of symptoms for symptom scores, and a higher level of functioning for functioning scores and GHS/QoL. Error bars represent the 95% CI for each respective adjusted mean. N at baseline = Number of patients with baseline and at least one post-baseline value included in the analysis.

Source: ADRIATIC CSR [11]

Table 29 HRQoL QLQ-C30 role functioning, summary statistics

	Durvalumab N = 264		Placebo N = 266		Intervention vs. comparator
	N	Mean (SE)	N	Mean (SE)	Difference (95% CI) p-value
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 36	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 48	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 64	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 80	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 96	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 104	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: ADRIATIC CSR [11]

Figure 10 Adjusted Mean Change from Baseline in EORTC QLQ-C30, role functioning, MMRM (FAS)

Note: EORTC QLQ-C30 scales were scored from 0 to 100, with a higher score representing a higher level of symptoms for symptom scores, and a higher level of functioning for functioning scores and GHS/QoL. Error bars represent the 95% CI for each respective adjusted mean. N at baseline = Number of patients with baseline and at least one post-baseline value included in the analysis.

Source: ADRIATIC CSR [11]

Table 30 HRQoL QLQ-C30 fatigue symptom, summary statistics

	Durvalumab N = 264		Placebo N = 266		Intervention vs. comparator
	N	Mean (SE)	N	Mean (SE)	Difference (95% CI) p-value
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 36	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 48	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 64	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 80	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]86
Week 96	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 104	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: ADRIATIC CSR [11]

Figure 11 Adjusted Mean Change from Baseline in EORTC QLQ-C30, fatigue symptom, MMRM (FAS)


[redacted]

Note: EORTC QLQ-C30 scales were scored from 0 to 100, with a higher score representing a higher level of symptoms for symptom scores, and a higher level of functioning for functioning scores and GHS/QoL. Error bars represent the 95% CI for each respective adjusted mean. N at baseline = Number of patients with baseline and at least one post-baseline value included in the analysis.

Source: ADRIATIC CSR [11]

Table 31 HRQoL QLQ-C30 appetite loss symptom, summary statistics

	Durvalumab N = 264		Placebo N = 266		Intervention vs. comparator
	N	Mean (SE)	N=266	Mean (SE)	Difference (95% CI) p-value
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 36	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 48	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 64	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 80	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 96	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 104	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: ADRIATIC CSR [11]

Figure 12 Adjusted Mean Change from Baseline in EORTC QLQ-C30, apetite loss symptom, MMRM (FAS)


[redacted]

Note: EORTC QLQ-C30 scales were scored from 0 to 100, with a higher score representing a higher level of symptoms for symptom scores, and a higher level of functioning for functioning scores and GHS/QoL. Error bars represent the 95% CI for each respective adjusted mean. N at baseline = Number of patients with baseline and at least one post-baseline value included in the analysis.

Source: ADRIATIC CSR [11].

10.1.4 Study design and measuring instrument

The EORTC QLQ-LC13 covers 13 typical symptoms of lung cancer patients and was the first module developed in conjunction with the EORTC QLQ questionnaire. These questionnaires are well-established instruments that have been previously included in cancer clinical studies. The QLQ-LC13 supplement the EORTC QLQ-C30 by a 13-item lung cancer-specific questionnaire module. In ADRIATIC the EORTC QLQ-LC13 were planned to show the overall influence of the benefits and toxicity of the treatment from a patient's perspective and aid in understanding the benefit - risk evaluation [11].

The results prespecified in the statistical analysis plan as endpoints of interest was EORTC QLQ-LC13 dynspnea, QLQ-LC13 cough, and QLQ-LC13 chest pain.

10.1.5 Data collection

The data for EORTC QLQ-LC13, was collected every 4 weeks (±3 days) relative to randomization until study termination or PFS2 or death [11]. The change from baseline in key symptoms was examined using the MMRM analysis. Symptom improvement rate was analysed using a logistic regression model. Time to symptom deterioration were analysed using KM estimates, a stratified log-rank tests and Cox proportional hazards models.

Table 32 and Table 33 present pattern of missing data and completion for durvalumab and placebo for EORTC QLQ-LC13 [11].

Table 32 Pattern of missing data and completion for durvalumab - EORTC QLQ- LC13

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
	Number of patients at randomization	Number of patients for whom data is missing (% of patients at randomization)	Number of patients "at risk" at time point X	Number of patients who completed (% of patients expected to complete)
Baseline	[redacted]	[redacted]	[redacted]	[redacted]
Week 4	[redacted]	[redacted]	[redacted]	[redacted]
Week 16	[redacted]	[redacted]	[redacted]	[redacted]
Week 36	[redacted]	[redacted]	[redacted]	[redacted]
Week 84	[redacted]	[redacted]	[redacted]	[redacted]
Week 104	[redacted]	[redacted]	[redacted]	[redacted]
Week 152	[redacted]	[redacted]	[redacted]	[redacted]
Week 200	[redacted]	[redacted]	[redacted]	[redacted]
Week 268	[redacted]	[redacted]	[redacted]	[redacted]

Source: ADRIATIC CSR [11]

Table 33 Pattern of missing data and completion for placebo - EORTC QLQ- LC13

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
	Number of patients at randomization	Number of patients for whom data is missing (% of patients at randomization)	Number of patients "at risk" at time point X	Number of patients who completed (% of patients expected to complete)
Baseline	[redacted]	[redacted]	[redacted]	[redacted]
Week 4	[redacted]	[redacted]	[redacted]	[redacted]
Week 16	[redacted]	[redacted]	[redacted]	[redacted]
Week 36	[redacted]	[redacted]	[redacted]	[redacted]
Week 84	[redacted]	[redacted]	[redacted]	[redacted]
Week 104	[redacted]	[redacted]	[redacted]	[redacted]
Week 152	[redacted]	[redacted]	[redacted]	[redacted]
Week 200	[redacted]	[redacted]	[redacted]	[redacted]
Week 268	[redacted]	[redacted]	[redacted]	[redacted]

Source: ADRIATIC CSR [11]

10.1.6 HRQoL results

Overall, there were no clinically important differences in changes from baseline between the durvalumab and placebo groups. The adjusted mean change from baseline in the QLQ-LC13 primary subscales from MMRM over time is summarised in Table 34 and for the respective QLQ-LC13 primary subscale in Table 35-Table 37 and Figure 13 - Figure 15.

Table 34 Adjusted Mean Change (95% CI) from Baseline (Average Over 24 Months) in Key EORCT QLQ-LC13 Endpoints, MMRM (FAS)

	Durvalumab (N = 264)		Placebo (N = 266)		Intervention vs. comparator
Subscale	N	Mean (SE)	N	Mean (SE)	Difference (95% CI) p-value
Dyspnea[a]	[redacted]				
Cough[a]	[redacted]				
Chest pain[a]	[redacted]				

Note: [a]Positive change from baseline indicates deterioration in symptom scales.

Source: ADRIATIC CSR [11]

Table 35 HRQoL QLQ-LC13 dyspnoea symptom, summary statistics

	Durvalumab N = 264		Placebo N = 266		Intervention vs. comparator
	N	Mean (SE)	N=266	Mean (SE)	Difference (95% CI) p-value
Baseline	[redacted]				
Week 4	[redacted]				
Week 16	[redacted]				
Week 36	[redacted]				
Week 48	[redacted]				
Week 64	[redacted]				
Week 80	[redacted]				
Week 96	[redacted]				
Week 104	[redacted]				

Source: ADRIATIC CSR [11]

Figure 13 Adjusted Mean Change from Baseline in EORTC QLQ-LC13, dyspnea symptom, MMRM (FAS)

Note: EORTC QLQ-LC13 scales were scored from 0 to 100, with a higher score representing a higher level of symptoms for symptom scores. Error bars represent the 95% CI for each respective adjusted mean. N at baseline = Number of patients with baseline and at least one post-baseline value included in the analysis. For symptom scale items in EORTC QLQ-LC13, for Week 0 to 8 the number of patients are presented vertically in 3 rows. The first row contains Week 0, 3 and 6, second row contains Week 1, 4 and 7, and the third row contains Week 2, 5 and 8.

Source: ADRIATIC CSR [11]

Table 36 HRQoL QLQ-LC13 cough symptom, summary statistics

	Durvalumab N = 264		Placebo N = 266		Intervention vs. comparator
	N	Mean (SE)	N=266	Mean (SE)	Difference (95% CI) p-value
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 36	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 48	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 64	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 80	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 96	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 104	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: ADRIATIC CSR [11]

Figure 14 Adjusted Mean Change from Baseline in EORTC QLQ-LC13, cough symptom, MMRM (FAS)

Note: EORTC QLQ-LC13 scales were scored from 0 to 100, with a higher score representing a higher level of symptoms for symptom scores. Error bars represent the 95% CI for each respective adjusted mean. N at baseline = Number of patients with baseline and at least one post-baseline value included in the analysis. For symptom scale items in EORTC QLQ-LC13, for Week 0 to 8 the number of patients are presented vertically in 3 rows. The first row contains Week 0, 3 and 6, second row contains Week 1, 4 and 7, and the third row contains Week 2, 5 and 8.

Source: ADRIATIC CSR [11]

Table 37 HRQoL QLQ-LC13 chest pain symptom, summary statistics

	Durvalumab N = 264		Placebo N = 266		Intervention vs. comparator
	N	Mean (SE)	N=266	Mean (SE)	Difference (95% CI) p-value
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 36	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 48	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 64	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 80	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 96	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 104	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: ADRIATIC CSR [11]

Figure 15 Adjusted Mean Change from Baseline in EORTC QLQ-LC13, chest pain symptom, MMRM (FAS)

Note: EORTC QLQ-LC13 scales were scored from 0 to 100, with a higher score representing a higher level of symptoms for symptom scores. Error bars represent the 95% CI for each respective adjusted mean. N at baseline = Number of patients with baseline and at least one post-baseline value included in the analysis. For symptom scale items in EORTC QLQ-LC13, for Week 0 to 8 the number of patients are presented vertically in 3 rows. The first row contains Week 0, 3 and 6, second row contains Week 1, 4 and 7, and the third row contains Week 2, 5 and 8.

Source: ADRIATIC CSR [11]

10.2 Health state utility values (HSUVs) used in the health economic model

N/A

10.2.1 HSUV calculation

N/A

10.2.1.1 Mapping

N/A

10.2.2 Disutility calculation

N/A

10.2.3 HSUV results

N/A

Table 38 Overview of health state utility values [and disutilities] N/A

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
HSUVs				
HSUV A	N/A	N/A	N/A	N/A
HSUV B	N/A	N/A	N/A	N/A

10.3 Health state utility values measured in other trials than the clinical trials forming the basis for relative efficacy

N/A

10.3.1 Study design

N/A

10.3.2 Data collection

N/A

10.3.3 HRQoL Results

N/A

10.3.4 HSUV and disutility results

N/A

Table 39 Overview of health state utility values [and disutilities] N/A

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
HSUVs				
HSUV A	N/A	N/A	N/A	N/A
HSUV B	N/A	N/A	N/A	N/A
N/A	N/A	N/A	N/A	N/A

Table 40 Overview of literature-based health state utility values N/A

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
HSUV A				
Study 1	N/A	N/A	N/A	N/A
HSUV B				
...	N/A	N/A	N/A	N/A
N/A				
...	N/A	N/A	N/A	N/A

11. Resource use and associated costs

N/A

11.1 Medicines - intervention and comparator

N/A

Table 41 Medicines used in the model

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
N/A	N/A	N/A	N/A	N/A
N/A	N/A	N/A	N/A	N/A

11.2 Medicines– co-administration

N/A

11.3 Administration costs

N/A

Table 42 Administration costs used in the model N/A

Administration type	Frequency	Unit cost [DKK]	DRG code	Reference
N/A	N/A	N/A	N/A	N/A

11.4 Disease management costs

N/A

Table 43 Disease management costs used in the model N/A

Activity	Frequency	Unit cost [DKK]	DRG code	Reference
N/A	N/A	N/A	N/A	N/A

11.5 Costs associated with management of adverse events

N/A

Table 44 Cost associated with management of adverse events N/A

	DRG code	Unit cost/DRG tariff
N/A	N/A	N/A
N/A	N/A	N/A

11.6 Subsequent treatment costs

N/A

Table 45 Medicines of subsequent treatments N/A

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
N/A	N/A	N/A	N/A	N/A
N/A	N/A	N/A	N/A	N/A

11.7 Patient costs

N/A

Table 46 Patient costs used in the model N/A

Activity	Time spent [minutes, hours, days]
Activity	N/A

11.8 Other costs (e.g. costs for home care nurses, out-patient rehabilitation and palliative care cost)

N/A

12. Results

N/A

12.1 Base case overview

N/A

Table 47 Base case overview N/A

Feature	Description
Comparator	N/A
Type of model	N/A
Time horizon	N/A
Treatment line	N/A
Measurement and valuation of health effects	N/A
Costs included	N/A
Dosage of medicine	N/A
Average time on treatment	N/A
Parametric function for PFS	N/A
Parametric function for OS	N/A
Inclusion of waste	N/A
Average time in model health state Health state 1	N/A

Feature	Description
Health state 2	
Health state 3	
Death	

12.1.1 Base case results

N/A

Table 48 Base case results, discounted estimates N/A

	[Intervention]	[Comparator]	Difference
Medicine costs	N/A	N/A	N/A
Medicine costs – co-administration	N/A	N/A	N/A
Administration	N/A	N/A	N/A
Disease management costs	N/A	N/A	N/A
Costs associated with management of adverse events	N/A	N/A	N/A
Subsequent treatment costs	N/A	N/A	N/A
Patient costs	N/A	N/A	N/A
Palliative care costs	N/A	N/A	N/A
Total costs	**N/A**	**N/A**	**N/A**
Life years gained (health state A)	N/A	N/A	N/A
Life years gained (health state B)	N/A	N/A	N/A
Total life years	**N/A**	**N/A**	**N/A**
QALYs (state A)	N/A	N/A	N/A
QALYs (state B)	N/A	N/A	N/A

	[Intervention]	[Comparator]	Difference
QALYs (adverse reactions)	N/A	N/A	N/A
Total QALYs	**N/A**	**N/A**	**N/A**
Incremental costs per life year gained		**N/A**	
Incremental cost per QALY gained (ICER)		**N/A**	

12.2 Sensitivity analyses

N/A

12.2.1 Deterministic sensitivity analyses

N/A

Table 49 One-way sensitivity analyses results N/A

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
Base case	N/A	N/A	N/A	N/A	N/A
N/A	N/A	N/A	N/A	N/A	N/A

12.2.2 Probabilistic sensitivity analyses

N/A

13. Budget impact analysis

N/A

Number of patients (including assumptions of market share)

Table 50 Number of new patients expected to be treated over the next five-year period if the medicine is introduced (adjusted for market share)

	Year 1	Year 2	Year 3	Year 4	Year 5
			Recommendation		
N/A	N/A	N/A	N/A	N/A	N/A
N/A	N/A	N/A	N/A	N/A	N/A
			Non-recommendation		
N/A	N/A	N/A	N/A	N/A	N/A
N/A	N/A	N/A	N/A	N/A	N/A

Budget impact

Table 51 Expected budget impact of recommending the medicine for the indication

	Year 1	Year 2	Year 3	Year 4	Year 5
The medicine under consideration is recommended	N/A	N/A	N/A	N/A	N/A
The medicine under consideration is NOT recommended	N/A	N/A	N/A	N/A	N/A
Budget impact of the recommendation	N/A	N/A	N/A	N/A	N/A

14. List of experts

N/A

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Appendix A. Main characteristics of studies included

Table 52 Main characteristics of studies included

Trial name: ADRIATIC	NCT03703297
Objective	The primary objective was to evaluate the efficacy and safety of Durvalumab for the treatment of LS-SCLC in patients who do not have disease progression after standard concurrent platinum-based chemoradiotherapy.
Publications – title, author, journal, year	Durvalumab after Chemoradiotherapy in Limited-Stage Small-Cell Lung Cancer. Cheng, Y., et al. New England Journal of Medicine, 2024 [9]
Study type and design	ADRIATIC is an ongoing, phase 3, randomised, double-blinded, placebo-controlled, multi-centre, international clinical trial study. Randomisation was conducted with stratification based on disease stage (I or II vs. III) and whether prophylactic cranial irradiation was administered (yes vs.no).
Sample size (n)	N = 530 (Durvalumab: 264, Placebo: 266)

Main inclusion criteria	• Age ≥18
	• Histologically or cytologically documented LS-SCLC (stage I to III) according to the AJCC Cancer Staging Manual, 8th Edition or the IASLC Staging Manual in Thoracic Oncology 2016
	  ○ Patients with stage I or II disease had to have medically inoperable disease
	• WHO/ECOG PS of 0–1
	• Received four cycles of first-line cCRT consisting of platinum-based therapy plus etoposide
	• No progression after the receipt of definitive cCRT
	  ○ Patients must have received four cycles of platinum-based cCRTa, which had to be completed within 1 to 42 days prior to randomisation and the first dose of study treatment
	  ○ The chemotherapy regimen had to contain platinum and IV etoposide, administered as per local standard-of-care regimens
	  ○ Patients must have received a total dose of radiation of 60 to 66 Gy over 6 weeks for standard once-daily radiation schedules or 45 Gy over 3 weeks for hyperfractionated twice-daily radiation schedules

Trial name: ADRIATIC	NCT03703297
	○ Radiotherapy must have commenced no later than the end of cycle 2 of chemotherapy ○ Patients must have achieved a complete response, partial response or stable disease and had not progressed following platinum-based cCRT ○ PCI could be delivered at the discretion of the investigator and local standard of care, conducted at the end of cCRT and completed 1–42 days before randomisation and the first dose of study treatment
Main exclusion criteria	• Mixed SCLC and NSCLC histology • ES-SCLC • Any history of Grade ≥2 pneumonitis • Known allergy/hypersensitivity to any of the study drugs • Patients who received sequential CRT for LS-SCLC (no overlap of radiotherapy with chemotherapy) and PCI treatment • Patients whose condition had progressed while receiving cCRT • Any unresolved toxicity NCI CTCAE Grade ≥2 from previous CRT with the exception of alopecia, vitiligo and the laboratory values defined in the inclusion criteria
Intervention	Durvalumab (n = 264) is given after completion of concurrent chemo-radiotherapy (cCRT). The dosing is 1500 mg Q4W, for up to 24 months or until disease progression or unacceptable toxicity.
Comparator(s)	As there are currently no active comparators in Denmark relevant for durvalumab in this setting, a 'watch-and-wait' approach represents the only option currently available following cCRT in LS-SCLC. Durvalumab can be compared with placebo using the ADRIATIC trial.
Follow-up time	At the time of the PFS IA/OS IA1, all patients had the opportunity to receive the maximum 24 months of study treatment. Median duration of follow-up for PFS in censored patients was 27.6 months (range 0.0–55.8). Median duration of follow-up for OS in censored patients was 37.2 months (range 0.1–60.9).
Is the study used in the health economic model?	N/A
Primary, secondary and exploratory endpoints	Primary endpoints: • PFS, assessed using BICR according to RECIST 1.1.

Trial name: ADRIATIC	NCT03703297
	• OS, which was defined as the time from the date of randomisation until death due to any cause. Secondary endpoints: • Landmark PFS at 18 and 24 months, assessed using BICR according to RECIST 1.1. • Landmark OS at 24 and 36 months. • ORR, was assessed using BICR according to RECIST 1.1 for unconfirmed (no requirement for confirmation) and confirmed (required confirmation of response no sooner than 4 weeks after the initial CR/PR was conducted) responses. • TTDM and PFS2 were both assessed using BICR according to RECIST 1.1. • Disease-related symptoms and HRQoL, assessed using EORTC QLQ-C30, version 3 and EORTC QLQ-LC13. • Relationship between PD-L1 expression and clinical outcomes. • Safety, assessing the safety and tolerability profile of durvalumab vs placebo.
Method of analysis	All efficacy analysis was performed on the full analysis set (FAS/all randomised patients). For analysing PFS, OS, TTDM, and PFS2, the stratified log-rank test (using the TEST statement in PROC LIFETEST) adjusting for tumour, node, metastasis (TNM) stage (I/II vs III) and receipt of PCI (yes vs no) for generating the p value and using the Efron approach for handling ties was used. The treatment effect was estimated by the HR together with its corresponding CI (95% and [1-adjusted α] × 100%) from a stratified Cox proportional hazards model (with ties = Efron and the stratification variables included in the strata statement) and the CI calculated using a profile likelihood approach. For PFS18 and PFS24, KM estimates and CIs of PFS at 18 and 24 months were used. For OS24 and OS36, KM estimates and CIs of survival at 24 and 36 months. For analysis of ORR, the Cochran–Mantel–Haenszel test, stratified using the same stratification factors as for the PFS endpoint was used. This analysis was performed in a subset of patients with measurable disease at baseline.
Subgroup analyses	N/A
Other relevant information	N/A

Source: [9, 10]

Appendix B. Efficacy results per study

Results per ADRIATIC

Table 53 Results per ADRIATIC, FAS population

Results of ADRIATIC (NCT03703297)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
Median PFS	Durvalumab	264	16.6 (10.2-28.2) months	7.4 months	N/A	N/A	HR: 0.76	0.61–0.95	0.0161	Performed using a stratified log-rank test adjusting for TNM stage (I/II vs III) and receipt of PCI (yes vs no) for generation of the p-value and using the Efron approach for handling ties (Efron 1977). The effect of D vs placebo treatment was estimated by the HR together with its corresponding CI (95% and [1-adjusted alpha] × 100%) from a stratified Cox proportional hazards model (Cox 1972) (with ties = Efron and the stratification variables included in the strata statement) and the CI calculated using a profile	[27]
	Placebo	266	9.2 (7.4-12.9) months								

Results of ADRIATIC (NCT03703297)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
										likelihood approach. To ensure there were at least 5 events within each strata, if there were too few events observed in the TNM Stage I/II stratification level, then TNM stage may have been excluded from the stratified models, leaving receipt of PCI as the sole stratification factor. The covariates in the statistical modelling were based on the values entered into IVRS at randomization, even if it was subsequently discovered that these values were incorrect.	
Median OS	Durvalumab	264	55.9 (37.3-NE) months	22.5 months	N/A	N/A	HR: 0.73	0.57–0.93	0.01042	Analyzed using stratified log-rank tests using the same methodology as described for the PFS endpoint. The treatment effect was estimated by the HR together with its corresponding CI (95%	[27]
	Placebo	266	33.4 (25.5-39.9) months								

Results of ADRIATIC (NCT03703297)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
										and [1-adjusted alpha] × 100%) from a stratified Cox proportional hazards model.	
ORR	Durvalumab	175	30.3% (23.6–37.7)	-1.7%	N/A	N/A	-1.2%	-11.0-8.5	N/A	The ORR was based on the programmatically derived RECIST 1.1 using BICR assessments for unconfirmed (no requirement for confirmation) and confirmed (required confirmation of response no sooner than 4 weeks after the initial CR/PR was conducted) responses. Confirmed ORR was included for completeness. The analysis was performed using a Cochran-Mantel-Haenszel test, stratified using the same stratification factors as for the PFS endpoint. This analysis was performed in a subset of patients with measurable disease at baseline	[27]
	Placebo	169	32.0% (25.0–39.6)								

Results of ADRIATIC (NCT03703297)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
Median PFS2	Durvalumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Performed using the same methodology as for the primary analysis of PFS	[11]
	Placebo	[redacted]	[redacted]								
TTDM per BICR	Durvalumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	The TTDM was analysed using identical methods as outlined for the analysis of PFS (i.e., a stratified log-rank test), but no subgroup analyses were performed. A sensitivity analysis of TTDM was performed using site Investigator assessments according to RECIST 1.1.	[11]
	Placebo	[redacted]	[redacted]								
TTDM per investigator	Durvalumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	A sensitivity analysis of TTDM was performed using site Investigator assessments according to RECIST 1.1 The TTDM was analysed using identical methods as outlined for the analysis of PFS (i.e., a stratified log-rank test), but no subgroup analyses were	[11]
	Placebo	[redacted]	[redacted]								

Results of ADRIATIC (NCT03703297)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
										performed. A sensitivity analysis of TTDM was performed using site Investigator assessments according to RECIST 1.1.	

Appendix C. Comparative analysis of efficacy

N/A, see above for comparison of the main outcomes from ADRIATIC.

Table 54 Comparative analysis of studies comparing [intervention] to [comparator] for patients with [indication] N/A

Outcome		Absolute difference in effect			Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
	Studies included in the analysis	Difference	CI	P value	Difference	CI	P value		
Example: median overall survival	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Example: 1-year survival	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Example: HRQoL	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Appendix D. Extrapolation

N/A

D.1 Extrapolation of [effect measure 1]

N/A

D.1.1 Data input

N/A

D.1.2 Model

N/A

D.1.3 Proportional hazards

N/A

D.1.4 Evaluation of statistical fit (AIC and BIC)

N/A

D.1.5 Evaluation of visual fit

N/A

D.1.6 Evaluation of hazard functions

N/A

D.1.7 Validation and discussion of extrapolated curves

N/A

D.1.8 Adjustment of background mortality

N/A

D.1.9 Adjustment for treatment switching/cross-over

N/A

D.1.10 Waning effect

N/A

D.1.11 Cure-point

N/A

D.2 Extrapolation of [effect measure 2]

N/A

Appendix E. Serious adverse events

All serious adverse events observed in ADRIATIC are presented below.

Table 55 SAEs by system organ class and preferred term (Safety analysis set)

Adverse events	Durvalumab (N = 262)		Placebo (N = 265)	
Preferred term	**Number of patients[a] with adverse events**	**Number of adverse events**	**Number of patients[a] with adverse events**	**Number of adverse events**
Subjects with any SAE	78 (29.8)	n.a.	64 (24.2)	n.a.
Infections and infestations	20 (7.6)	n.a.	19 (7.2)	n.a.
Appendicitis	1 (0.4)	n.a.	0	n.a.
Bacterial sepsis	1 (0.4)	n.a.	0	n.a.
Bronchitis	1 (0.4)	n.a.	1 (0.4)	n.a.
Cellulitis	0	n.a.	1 (0.4)	n.a.
COVID-19	0	n.a.	1 (0.4)	n.a.
Device related infection	0	n.a.	1 (0.4)	n.a.
Empyema	0	n.a.	1 (0.4)	n.a.
Hepatitis E	0	n.a.	1 (0.4)	n.a.
Infection	0	n.a.	1 (0.4)	n.a.
Lower respiratory tract infection	1 (0.4)	n.a.	0	n.a.
Ophthalmic herpes zoster	1 (0.4)	n.a.	0	n.a.
Pneumocystis jirovecii pneumonia	0	n.a.	1 (0.4)	n.a.
Pneumonia	12 (4.6)	n.a.	10 (3.8)	n.a.

Adverse events	Durvalumab (N = 262)		Placebo (N = 265)	
Preferred term	Number of patients[a] with adverse events	Number of adverse events	Number of patients[a] with adverse events	Number of adverse events
Pneumonia bacterial	3 (1.1)	n.a.	0	n.a.
Pneumonia legionella	0	n.a.	1 (0.4)	n.a.
Respiratory tract infection	0	n.a.	1 (0.4)	n.a.
Sepsis	1 (0.4)	n.a.	1 (0.4)	n.a.
Staphylococcal sepsis	1 (0.4)	n.a.	0	n.a.
Upper respiratory tract infection	0	n.a.	1 (0.4)	n.a.
Urinary tract infection	1 (0.4)	n.a.	0	n.a.
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (0.8)	n.a.	5 (1.9)	n.a.
Acute promyelocytic leukaemia	0	n.a.	1 (0.4)	n.a.
Adenocarcinoma gastric	1 (0.4)	n.a.	0	n.a.
Breast cancer	0	n.a.	1 (0.4)	n.a.
Chronic myeloid leukaemia	0	n.a.	1 (0.4)	n.a.
Non-small cell lung cancer	0	n.a.	1 (0.4)	n.a.
Prostate cancer	1 (0.4)	n.a.	0	n.a.
Squamous cell carcinoma of lung	0	n.a.	1 (0.4)	n.a.
Squamous cell carcinoma of the hypopharynx	0	n.a.	1 (0.4)	n.a.

Adverse events	Durvalumab (N = 262)		Placebo (N = 265)	
Preferred term	**Number of patients[a] with adverse events**	**Number of adverse events**	**Number of patients[a] with adverse events**	**Number of adverse events**
Blood and lymphatic system disorders	2 (0.8)	n.a.	1 (0.4)	n.a.
Anaemia	2 (0.8)	n.a.	0	n.a.
Febrile neutropenia	0	n.a.	1 (0.4)	n.a.
Endocrine disorders	2 (0.8)	n.a.	0	n.a.
Adrenal insufficiency	1 (0.4)	n.a.	0	n.a.
Hypopituitarism	1 (0.4)	n.a.	0	n.a.
Metabolism and nutrition disorders	3 (1.1)	n.a.	2 (0.8)	n.a.
Diabetic ketoacidosis	1 (0.4)	n.a.	0	n.a.
Electrolyte imbalance	0	n.a.	1 (0.4)	n.a.
Hyperglycaemia	1 (0.4)	n.a.	0	n.a.
Hyponatraemia	0	n.a.	1 (0.4)	n.a.
Type 2 diabetes mellitus	1 (0.4)	n.a.	0	n.a.
Psychiatric disorders	2 (0.8)	n.a.	1 (0.4)	n.a.
Alcoholic psychosis	1 (0.4)	n.a.	0	n.a.
Delirium	1 (0.4)	n.a.	0	n.a.
Depression	0	n.a.	1 (0.4)	n.a.
Nervous system disorders	6 (2.3)	n.a.	4 (1.5)	n.a.
Cerebral infarction	0	n.a.	1 (0.4)	n.a.
Cerebral ischaemia	0	n.a.	1 (0.4)	n.a.

Adverse events	Durvalumab (N = 262)		Placebo (N = 265)	
Preferred term	Number of patients[a] with adverse events	Number of adverse events	Number of patients[a] with adverse events	Number of adverse events
Cerebrovascular accident	2 (0.8)	n.a.	0	n.a.
Encephalitis autoimmune	1 (0.4)	n.a.	0	n.a.
Encephalopathy	1 (0.4)	n.a.	0	n.a.
Facial nerve disorder	1 (0.4)	n.a.	0	n.a.
Ischaemic stroke	0	n.a.	1 (0.4)	n.a.
Metabolic encephalopathy	0	n.a.	1 (0.4)	n.a.
Partial seizures	1 (0.4)	n.a.	0	n.a.
Eye disorders	1 (0.4)	n.a.	2 (0.8)	n.a.
Cataract	1 (0.4)	n.a.	1 (0.4)	n.a.
Retinal artery occlusion	0	n.a.	1 (0.4)	n.a.
Cardiac disorders	7 (2.7)	n.a.	1 (0.4)	n.a.
Acute left ventricular failure	1 (0.4)	n.a.	0	n.a.
Acute myocardial infarction	1 (0.4)	n.a.	0	n.a.
Angina unstable	1 (0.4)	n.a.	0	n.a.
Atrial fibrillation	1 (0.4)	n.a.	0	n.a.
Cardiac failure	1 (0.4)	n.a.	0	n.a.
Cardiac failure acute	0	n.a.	1 (0.4)	n.a.
Myocarditis	1 (0.4)	n.a.	0	n.a.

Adverse events	Durvalumab (N = 262)		Placebo (N = 265)	
Preferred term	**Number of patients[a] with adverse events**	**Number of adverse events**	**Number of patients[a] with adverse events**	**Number of adverse events**
Sinus node dysfunction	1 (0.4)	n.a.	0	n.a.
Vascular disorders	0	n.a.	5 (1.9)	n.a.
Arterial occlusive disease	0	n.a.	1 (0.4)	n.a.
Hypotension	0	n.a.	1 (0.4)	n.a.
Iliac artery stenosis	0	n.a.	1 (0.4)	n.a.
Peripheral arterial occlusive disease	0	n.a.	1 (0.4)	n.a.
Venous thrombosis limb	0	n.a.	1 (0.4)	n.a.
Respiratory, thoracic and mediastinal disorders	24 (9.2)	n.a.	15 (5.7)	n.a.
Acute respiratory failure	1 (0.4)	n.a.	1 (0.4)	n.a.
Chronic obstructive pulmonary disease	1 (0.4)	n.a.	4 (1.5)	n.a.
Haemoptysis	1 (0.4)	n.a.	1 (0.4)	n.a.
Immune-mediated lung disease	4 (1.5)	n.a.	0	n.a.
Interstitial lung disease	6 (2.3)	n.a.	0	n.a.
Pleural effusion	1 (0.4)	n.a.	0	n.a.
Pneumonitis	8 (3.1)	n.a.	6 (2.3)	n.a.
Pneumothorax	1 (0.4)	n.a.	1 (0.4)	n.a.
Pulmonary artery thrombosis	0	n.a.	1 (0.4)	n.a.
Pulmonary embolism	2 (0.8)	n.a.	1 (0.4)	n.a.

Adverse events	Durvalumab (N = 262)		Placebo (N = 265)	
Preferred term	**Number of patients[a] with adverse events**	**Number of adverse events**	**Number of patients[a] with adverse events**	**Number of adverse events**
Gastrointestinal disorders	9 (3.4)	n.a.	6 (2.3)	n.a.
Constipation	1 (0.4)	n.a.	0	n.a.
Diarrhoea	2 (0.8)	n.a.	1 (0.4)	n.a.
Dysphagia	1 (0.4)	n.a.	0	n.a.
Gastritis	1 (0.4)	n.a.	0	n.a.
Ileus	1 (0.4)	n.a.	1 (0.4)	n.a.
Inguinal hernia	0	n.a.	1 (0.4)	n.a.
Oesophageal achalasia	1 (0.4)	n.a.	0	n.a.
Oesophagitis ulcerative	1 (0.4)	n.a.	0	n.a.
Peptic ulcer	1 (0.4)	n.a.	0	n.a.
Rectal haemorrhage	0	n.a.	1 (0.4)	n.a.
Small intestinal obstruction	0	n.a.	1 (0.4)	n.a.
Vomiting	0	n.a.	1 (0.4)	n.a.
Hepatobiliary disorders	4 (1.5)	n.a.	2 (0.8)	n.a.
Bile duct stone	1 (0.4)	n.a.	0	n.a.
Cholecystitis	0	n.a.	1 (0.4)	n.a.
Hepatic cirrhosis	1 (0.4)	n.a.	0	n.a.
Hepatitis	1 (0.4)	n.a.	1 (0.4)	n.a.
Liver injury	1 (0.4)	n.a.	0	n.a.

Adverse events	Durvalumab (N = 262)		Placebo (N = 265)	
Preferred term	**Number of patients[a] with adverse events**	**Number of adverse events**	**Number of patients[a] with adverse events**	**Number of adverse events**
Musculoskeletal and connective tissue disorders	2 (0.8)	n.a.	2 (0.8)	n.a.
Back pain	1 (0.4)	n.a.	0	n.a.
Exostosis	0	n.a.	1 (0.4)	n.a.
Greater trochanteric pain syndrome	1 (0.4)	n.a.	0	n.a.
		n.a.		n.a.
Musculoskeletal disorder	1 (0.4)	n.a.	0	n.a.
Osteoarthritis	0	n.a.	1 (0.4)	n.a.
Renal and urinary disorders	1 (0.4)	n.a.	1 (0.4)	n.a.
Acute kidney injury	0	n.a.	1 (0.4)	n.a.
Urinary retention	1 (0.4)	n.a.	0	n.a.
General disorders and administration site conditions	3 (1.1)	n.a.	5 (1.9)	n.a.
Asthenia	0	n.a.	3 (1.1)	n.a.
Device related thrombosis	1 (0.4)	n.a.	0	n.a.
Fatigue	1 (0.4)	n.a.	1 (0.4)	n.a.
Hernia	1 (0.4)	n.a.	0	n.a.
Pyrexia	0	n.a.	1 (0.4)	n.a.
Investigations	2 (0.8)	n.a.	0	n.a.
Lymphocyte count decreased	1 (0.4)	n.a.	0	n.a.

Adverse events	Durvalumab (N = 262)		Placebo (N = 265)	
Preferred term	Number of patients[a] with adverse events	Number of adverse events	Number of patients[a] with adverse events	Number of adverse events
Weight decreased	1 (0.4)	n.a.	0	n.a.
Injury, poisoning and procedural complications	17 (6.5)	n.a.	13 (4.9)	n.a.
Femur fracture	0	n.a.	1 (0.4)	n.a.
Foot fracture	1 (0.4)	n.a.	0	n.a.
Limb injury	1 (0.4)	n.a.	0	n.a.
Limb traumatic amputation	1 (0.4)	n.a.	0	n.a.
Pelvic fracture	0	n.a.	1 (0.4)	n.a.
Rib fracture	0	n.a.	1 (0.4)	n.a.
Spinal compression fracture	1 (0.4)	n.a.	1 (0.4)	n.a.
Sternal fracture	0	n.a.	1 (0.4)	n.a.
Product issues	0	n.a.	1 (0.4)	n.a.
Device dislocation	0	n.a.	1 (0.4)	n.a.

[a]Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories.

Source: ADRIATIC CSR [11]

*n.a., not available

Appendix F. Health-related quality of life

N/A

Appendix G. Probabilistic sensitivity analyses

N/A

Table 56. Overview of parameters in the PSA N/A

Input parameter	Point estimate	Lower bound	Upper bound	Probability distribution
Probabilities				
Efficacy Outcome A	N/A	N/A	N/A	N/A
	N/A	N/A	N/A	N/A
HSUV				
State A	N/A	N/A	N/A	N/A
Costs				
Hospitalization	N/A	N/A	N/A	N/A

Appendix H. Literature searches for the clinical assessment

N/A

H.1 Efficacy and safety of the intervention and comparator(s)

N/A

Table 57 Bibliographic databases included in the literature search N/A

Database	Platform/source	Relevant period for the search	Date of search completion
Embase	N/A	N/A	N/A
Medline	N/A	N/A	N/A
CENTRAL	N/A	N/A	N/A

Table 58 Other sources included in the literature search N/A

Source name	Location/source	Search strategy	Date of search
e.g. NICE	N/A	N/A	N/A
e.g. EMA website	N/A	N/A	N/A

Table 59 Conference material included in the literature search N/A

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
Conference name	N/A	N/A	N/A	N/A

H.1.1 Search strategies

N/A

Table 60 Search strategy table for [name of database] N/A

No.	Query	Results
#1	N/A	N/A
#2	N/A	N/A

No.	Query	Results
#3	N/A	N/A
#4	N/A	N/A
#5	N/A	N/A
#6	N/A	N/A
#7	N/A	N/A
#8	N/A	N/A
#9	N/A	N/A
#10	N/A	N/A

H.1.2 Systematic selection of studies

N/A

Table 61 Inclusion and exclusion criteria used for assessment of studies N/A

Clinical effectiveness	Inclusion criteria	Exclusion criteria	Changes, local adaption
Population	N/A	N/A	N/A
Intervention	N/A	N/A	N/A
Comparators	N/A	N/A	N/A
Outcomes	N/A	N/A	N/A
Study design/publication type	N/A	N/A	N/A
Language restrictions	N/A	N/A	N/A

Table 62 Overview of study design for studies included in the analyses N/A

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
Study 1	N/A	N/A	N/A	N/A	N/A	N/A
Study 2	N/A	N/A	N/A	N/A	N/A	N/A

H.1.3 Excluded fulltext references

N/A

H.1.4 Quality assessment

N/A

H.1.5 Unpublished data

N/A

Appendix I. Literature searches for health-related quality of life

N/A

I.1 Health-related quality-of-life search

N/A

Table 63 Bibliographic databases included in the literature search N/A

Database	Platform	Relevant period for the search	Date of search completion
Embase	N/A	N/A	N/A
Medline	N/A	N/A	N/A

Database	Platform	Relevant period for the search	Date of search completion
Specific health economics databases[1]	N/A	N/A	N/A

Table 64 Other sources included in the literature search N/A

Source name	Location/source	Search strategy	Date of search
e.g. NICE	N/A	N/A	N/A
CEA Registry	N/A	N/A	N/A

Table 65 Conference material included in the literature search N/A

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
Conference name	N/A	N/A	N/A	

I.1.1 Search strategies

N/A

Table 66 Search strategy for [name of database]

No.	Query	Results
#1	N/A	N/A
#2	N/A	N/A
#3	N/A	N/A
#4	N/A	N/A
#5	N/A	N/A
#6	N/A	N/A
#7	N/A	N/A
#8	N/A	N/A

[1] Papaioannou D, Brazier J, Paisley S. Systematic searching and selection of health state utility values from the literature. Value Health. 2013;16(4):686-95.

No.	Query	Results
#9	N/A	N/A
#10	N/A	N/A

I.1.2 Quality assessment and generalizability of estimates

N/A

I.1.3 Unpublished data

N/A

Appendix J. Literature searches for input to the health economic model

N/A

J.1 External literature for input to the health economic model

N/A

J.1.1 Example: Systematic search for [...]

N/A

Table 67 Sources included in the search N/A

Database	Platform/source	Relevant period for the search	Date of search completion
Embase	N/A	N/A	N/A
Medline	N/A	N/A	N/A
CENTRAL	N/A	N/A	N/A

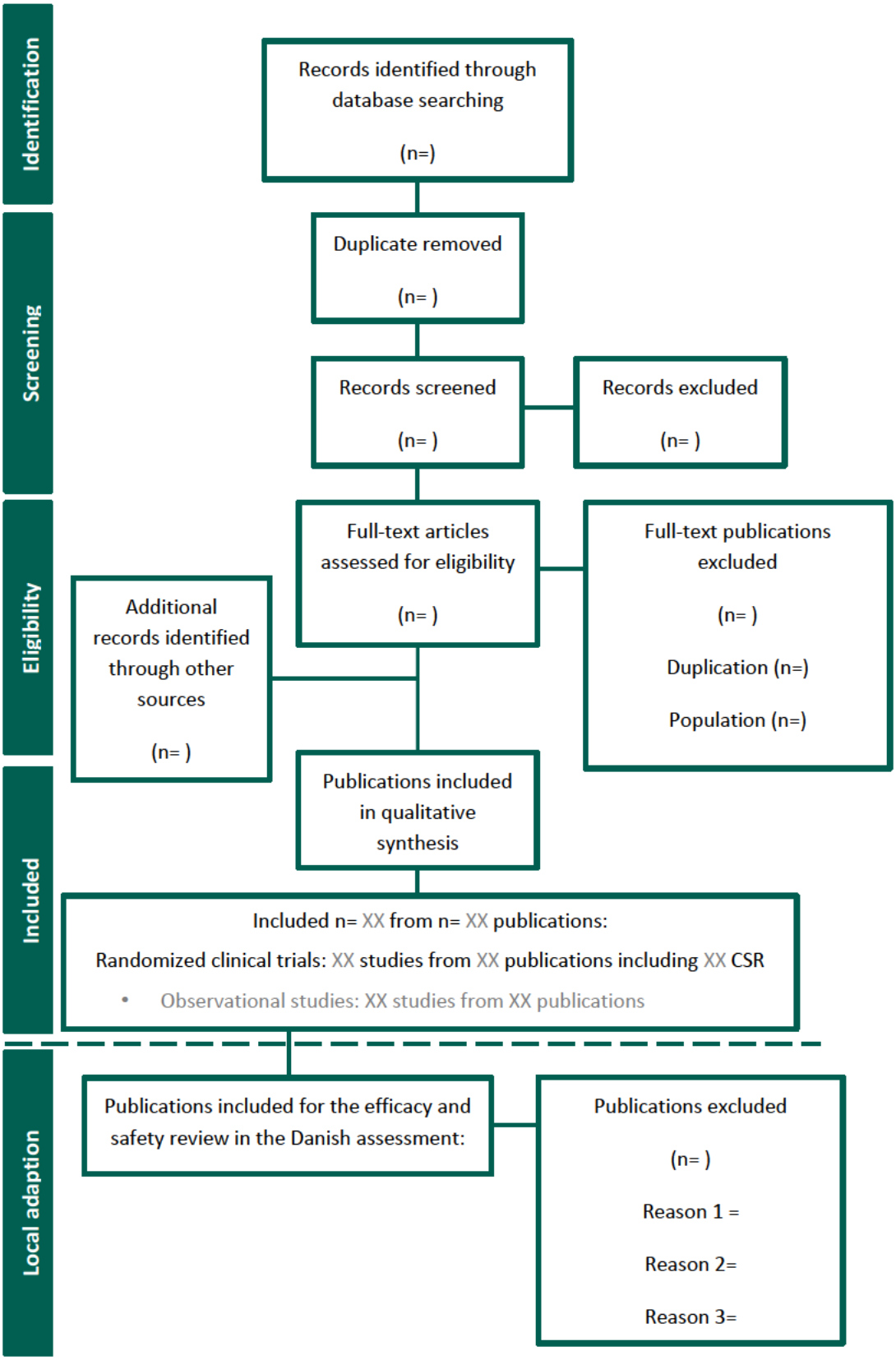
J.1.2 Example: Targeted literature search for [estimates]

N/A

Table 68 Sources included in the targeted literature search N/A

Source name/ database	Location/source	Search strategy	Date of search
e.g. NICE	N/A	N/A	N/A

N/A Example of PRISMA diagram. The diagram is editable and may be used for recording the records flow for the literature searches and for the adaptation of existing SLRs.



Appendix K. Answer on DMC questions as of 06112025

K.1 Question regarding subsequent treatment

Question: Please indicate whether patients who receive subsequent treatment are included. If this is the case, you should clearly state the specific treatment patients received in each treatment arm at the line-of-care level/treatment line level

Answer: Patients who received subsequent anticancer therapy after discontinuation of study treatment are included in the analysis set, and the study reports their post-discontinuation treatments by arm and treatment line.

- Overall subsequent therapy: Post-discontinuation disease-related anticancer treatment was given to [redacted] patients in the durvalumab arm and [redacted] in the placebo arm.
- Subsequent cytotoxic chemotherapy: [redacted] in the durvalumab arm and [redacted] in the placebo arm received cytotoxic chemotherapy, most commonly platinum doublet chemotherapy [redacted] and [redacted], respectively).
- Subsequent immunotherapy: [redacted] the durvalumab arm and [redacted] in the placebo arm received immunotherapy components as part of their first subsequent therapy.

These figures reflect line-of-care/treatment-line reporting as captured in the CSR [11]; arm-specific details by treatment class and line are provided in tables below.

Tabel 69 Post-discontinuation disease-related anti-cancer therapy (FAS)

Source: AstraZeneca CSR [11]

K.2 Question regarding dose and administration of the platinum-based chemoradiotherapy by type of chemo

Question: Please indicate the dose and administration of the platinum-based chemoradiotherapy by type of chemo.

Answer: Concurrent chemoradiotherapy comprised platinum–etoposide. Patients received 4 cycles of platinum (cisplatin or carboplatin) plus intravenous etoposide per protocol. Arm-level distributions of cisplatin–etoposide versus carboplatin–etoposide and radiotherapy fractionation/dose are detailed in CSR see table below.

Tabel 70 Prior cCRT and PCI (FAS)

Characteristic	Number (%) of patients		
	D (N = 264)	Placebo (N = 266)	Total (N = 530)
Number of chemotherapy cycles			
2	0	1 (0.4)	1 (0.2)
3	29 (11.0)	31 (11.7)	60 (11.3)
4	234 (88.6)	234 (88.0)	468 (88.3)
6	1 (0.4)	0	1 (0.2)
Chemotherapy regimen [a]			
Cisplatin + etoposide	173 (65.5)	178 (66.9)	351 (66.2)
Carboplatin + etoposide	91 (34.5)	88 (33.1)	179 (33.8)
Radiotherapy regimen (total dose, Gy) [b]			
Once daily	195 (73.9)	187 (70.3)	382 (72.1)
< 57	8 (3.0)	2 (0.8)	10 (1.9)
≥ 60 to ≤ 66	175 (66.3)	178 (66.9)	353 (66.6)
≥ 57 to ≤ 70 (excluding ≥ 60 to ≤ 66)	12 (4.5)	7 (2.6)	19 (3.6)
> 70	0	0	0
Twice daily	69 (26.1)	79 (29.7)	148 (27.9)
< 42.75	0	0	0
45	67 (25.4)	76 (28.6)	143 (27.0)
≥ 42.75 to ≤ 47.25 (excluding 45)	1 (0.4)	0	1 (0.2)
> 47.25	1 (0.4)	3 (1.1)	4 (0.8)

Source: AstraZeneca CSR [11]

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