Medicinrådet

Bilag til Medicinrådets anbefaling vedrørende durvalumab i kombination med etoposid og enten carboplatin eller cisplatin til behandling af småcellet lungekræft i udvidet sygdomsstadie (ES-SCLC)

Vers. 1.0

Bilagsoversigt

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

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

30.08.2024

Draft assessment report regarding durvalumab in combination with etoposide and either carboplatin or cisplatin indicated for the first-line treatment of adults with extensive-stage small cell lung cancer (ES-SCLC)

AstraZeneca would like to thank you for the assessment of durvalumab in combination with etoposide and either carboplatin or cisplatin indicated for first-line treatment of adults with ES-SCLC and appreciate the opportunity to comment on the draft report.

Overall, AstraZeneca find the DMC report to be balanced and thorough. However, we just have two comments we would like to highlight.

First of all, we would like to remind that the CASPIAN trial remains the only phase III randomized clinical trial with robust, pre-specified, and comparator-controlled 3-year overall survival (OS) analysis for ES-SCLC. The updated OS analysis of the trial was conducted at 86% data maturity, showing statistically significantly improved OS. Durvalumab in combination with etoposide and either carboplatin or cisplatin reduced the risk of death by 29% compared to etoposide and either carboplatin or cisplatin alone (HR 0.71 [95% CI 0.60-0.86; nominal p=0.0003]).

Secondly, we have a comment regarding treatment duration and the effect on the ICER. For the efficacy data from the CASPIAN trial included in the assessment, a median of 7 doses of durvalumab was administered (range: 1-52), indicating that the longest treatment duration equates to approximately four years (52 doses). Nevertheless, in the draft assessment report from DMC it is mentioned that the duration of treatment for immunotherapies in Denmark often is limited to a maximum of two years. Assuming the treatment duration of immunotherapies commonly practiced in Denmark this will reduce the overall cost and hence likely improve the ICER.

In conclusion, considering the significant improvements in overall survival observed in CASPIAN trial, we hope that durvalumab will be made available as 1st line treatment for patients with ES-SCLC, a particularly aggressive cancer form that as of today mainly is treated palliatively.

Kind regards,

Mette Lange
Market Access Manager
AstraZeneca A/S

Amgros I/S
Dampfærgevej 22
2100 København Ø
Danmark

T +45 88713000
F +45 88713008

Medicin@amgros.dk
www.amgros.dk

27.08.2024
DBS/CAF

Forhandlingsnotat

Dato for behandling i Medicinrådet	25.09.2024
Leverandør	AstraZeneca
Lægemiddel	Imfinzi (durvalumab)
Ansøgt indikation	Durvalumab er i kombination med etoposid og enten carboplatin eller cisplatin indiceret til førstelinjebehandling af voksne med småcellet lungecancer i udvidet sygdomsstadie (ES-SCLC).
Nyt lægemiddel / indikationsudvidelse	Indikationsudvidelse

Prisinformation

Amgros har følgende pris på Imfinzi (durvalumab):

Tabel 1: Forhandlingsresultat

Lægemiddel	Styrke	Pakningsstørrelse	AIP (DKK)	Forhandlet SAIP (DKK)	Rabatprocent ift. AIP
Imfinzi	50 mg/ml	10 ml	17.672,28	[redacted]	[redacted]
Imfinzi	50 mg/ml	2,4 ml	4.278,62	[redacted]	[redacted]

Aftaleforhold

Amgros har en aftale på Imfinzi i perioden fra den 01.01.2024 til den 31.12.2025 med mulighed for prisregulering i hele aftaleperioden. Imfinzi er en del af samme udbud som Opdivo (nivolumab), Tecentriq (atezolizumab), Keytruda (pembrolizumab), Libtayo (cemiplimab) og Bavencio (avelumab).

Konkurrencesituationen

[redacted]

Tabel 2: Sammenligning af 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 IV hver 3. uge i 4 cykler. Herefter 1.500 mg IV hver 4. uge.	[redacted]	[redacted]
Tecentriq	1.200 mg	1 stk.	1.200 mg IV hver 3. uge	[redacted]	[redacted]

Status fra andre lande

Tabel 3: Status fra andre lande

Land	Status	Link
Norge	Ikke anbefalet	Link til anbefaling
England	Ansøgning trukket tilbage	Link til information

Konklusion

[redacted]

Application for the assessment of Imfinzi® (durvalumab) in combination with etoposide and platinum-based chemotherapy for the first-line treatment of patients with extensive stage small-cell lung cancer

- Submitted by AstraZeneca 19.04.2024
- Updated version re-submitted 08.05.2024
- Updated version re-submitted 31.05.2024
- Updated version incl. EQ-5D-VAS re-submitted 28.06.2024

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

Contact information

Contact information	
Name	**Mette Lange / AstraZeneca**
Title	Market Access Manager, Denmark
Phone number	+45 28925125
E-mail	mette.lange@astrazeneca.com
Name (External representation)	**Not applicable**
Title	
Phone number	Not applicable
E-mail	

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Abbreviations

Abbreviation	Definition	Abbreviation	Definition
2L	Second-line	**3L**	Third-line
ADA	Anti-Drug Antibody	**AE**	Adverse event
AESI	Adverse events of special interest	**AIC**	Akaike information criterion
AJCC	American Joint Committee on Cancer	**ALK**	Anaplastic lymphoma kinase
ATC	Anatomical Therapeutic Chemical	**AUC**	Area under the curve
BEGR	Medicines only to be dispensed to hospitals	**BIC**	Bayesian information criterion
BSA	Body surface area	**BTC**	Biliary tract cancer
CAV	Combination of cyclophosphamide, doxorubicin and vincristine	**CEAC**	Cost-effectiveness acceptability curve
CI	Confidence interval	**CNS**	Central nervous system
CR	Complete response	**CSR**	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events	**D**	Durvalumab

DCE	Discrete choice experiment	**DCO**	Data cut-off
DK	Denmark	**DKK**	Danish krona
DMC	Danish Medicines Council	**DMCG**	Danish Multidisciplinary Cancer Group
DNA	Deoxyribonucleic acid	**DoR**	Duration of response
DRG	Diagnosis-related group	**EC**	European Commission
ECG/EKG	Electrocardiogram	**ECOG**	Eastern Cooperative Oncology Group
EGFR	Estimated glomerular filtration rate	**EP**	Combination of etoposide plus platinum-based chemotherapy
EMA	European Medicines Agency	**EORTC QLQ**	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire
EQ-5D	5-dimension EuroQol questionnaire	**ES**	Extensive stage
ESMO	European Society for Medical Oncology	**ES-SCLC**	Extensive-stage small cell lung cancer
GFR	Glomerular filtration rate	**GHS**	Global health status
HCC	Hepatocellular carcinoma	**HIV**	Human immunodeficiency virus
HR	Hazard ratio	**HRQoL**	Health-related quality of life
HSUV	Health state utility value	**HTA**	Health technology assessment
ICER	Incremental cost-effectiveness ratio	**IFN**	Interferon

IgG1κ	Immunoglobulin G1 kappa	**ITT**	Intention-to-treat
IV	Intravenous	**KM**	Kaplan-Meier curve
KOL	Key opinion leader	**LS**	Limited stage
LTFU	Long-term follow-up	**M**	Metastases
MCS	Mental Component Summary	**MMRM**	Mixed model repeated measures
mOS	Median overall survival	**mPFS**	Median progression-free survival
N	Lymph nodes	**NA**	Not applicable
NCT	National Clinical Trial number	**NICE**	National Institute for Health and Care Excellence
NTL	Non-target lesion	**NSCLC**	Non-small cell lung cancer
ORR	Objective relapse rate	**OS**	Overall survival
OWSA	One-way sensitivity analysis	**PartSA**	Partitioned survival model
PCI	Prophylactic cranial irradiation	**PCS**	Physical Component Summary
PD	Progressed disease	**PD-L1**	Programmed cell death ligand-1
PFS	Progression-free survival	**PH**	Proportional hazard
PNS	Paraneoplastic syndrome	**PPS**	Post-progression survival
PR	Partial response	**PRO**	Patient reported outcome
PS	Performance status	**PSA**	Probabilistic sensitivity analysis
Q3W	Once every 3 weeks	**Q4W**	Once every 4 weeks
QALY	Quality-adjusted life year	**QoL**	Quality of life

R	Randomisation	**RDI**	Relative dose intensity
RECIST 1.1	Response Evaluation Criteria in Solid Tumors, version 1.1	**REML**	Restricted maximum likelihood method
RNA	Ribonucleic acid	**SAE**	Serious adverse event
SCLC	Small cell lung cancer	**SD**	Standard deviation
SE	Standard error	**SEER**	Surveillance, Epidemiology, and End Results Program
SF-36	36-item Short-Form Health Survey	**SmPC**	Summary of product characteristics
SoC	Standard of care	**T**	Tumour size
TLs	Target lesion	**TTD**	Time to treatment discontinuation
TTP	Time to progression	**USA**	United States of America
WBC	White blood count	**WHO**	World health organization

1. Regulatory information on the medicine

Overview of the medicine	
Proprietary name	Imfinzi®
Generic name	Durvalumab
Therapeutic indication as defined by EMA	Imfinzi® 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).
Marketing authorization holder in Denmark	AstraZeneca AB SE-151 85 Södertälje Sverige
ATC code	L01FF03

Overview of the medicine	
Combination therapy and/or co-medication	Etoposide and either carboplatin or cisplatin
(Expected) Date of EC approval	1st of September 2020
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	See Appendix K Other indications
Other indications that have been evaluated by the DMC (yes/no)	See Appendix K Other indications
Dispensing group	BEGR
Packaging – types, sizes/number of units and concentrations	Vial 50 mg/ml 10 ml conc. Infusion Vial 50 mg/ml 2.4 ml conc. infusion

2. Summary table

Summary	
Therapeutic indication relevant for the assessment	Imfinzi® 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).
Dosage regiment and administration	1,500 mg[a] in combination with chemotherapy every 3 weeks (21 days) for 4 cycles, followed by 1,500 mg every 4 weeks as monotherapy. Imfinzi® is administered as an intravenous (IV) infusion over 1 hour.
Choice of comparator	Etoposide and either carboplatin or cisplatin

Summary	
Prognosis with current treatment (comparator)	The current treatment for patients with ES-SCLC is palliative. The 5-year survival rates for patients with ES-SCLC at diagnosis have been reported as 2%. Additionally, several studies have reported a substantially lower QoL for these patients compared to the general population.
Type of evidence for the clinical evaluation	Head-to-Head study: The CASPIAN clinical trial.
Most important efficacy endpoints (Difference/gain compared to comparator)	Overall survival (OS): Median OS was 12.9 months (95% CI: 11.3-14.7) for patients treated with Imfinzi® in combination with etoposide and either carboplatin or cisplatin compared with 10.5 months (95% CI: 9.3-11.2) for patients treated with etoposide and either carboplatin or cisplatin alone. (HR, 0.75 [98.22% CI: 0.63, 0.91], *p* = 0.0032. In an updated OS analysis, Imfinzi® in combination with etoposide and either carboplatin or cisplatin reduced the risk of death by 29% compared with etoposide and either carboplatin or cisplatin alone (HR: 0.71 95% CI (0.60-0.86), p=0.0003. Progression-free survival (PFS) rate at 12 months: PFS rate at 12 months was 17.9% (95% CI: 13.5-22.8) for patients treated with Imfinzi® in combination with etoposide and either carboplatin or cisplatin compared with 5.3% (95% CI: 2.9-8.8) for patients treated with etoposide and either carboplatin or cisplatin alone.
Most important serious adverse events for the intervention and comparator	In total, 86 (32.5%) and 97 (36.5%) patients experienced serious adverse events (SAEs) in the intervention and comparator arm, respectively. Most SAEs were hematological, or related to hematological toxicities, i.e., pneumonia, and occurred more frequently in the comparator group. The only SAEs occurring more frequently in the Imfinzi® plus etoposide and either carboplatin or cisplatin group were chronic obstructive pulmonary disease (1.1% vs 0.4%) and pancytopenia (1.5% vs 1.1%).
Impact on health-related quality of life	Clinical documentation: EQ-5D-5L utility data were collected in the CASPIAN clinical study in line with the clinical study protocol. The Danish EQ-5D-5L value set published by Jensen, C.E., et al. was used to obtain utility scores. Health state utility values (HSUVs): Pre-progressions state: 0.834; Post-progression state: 0.802
Type of economic analysis that is submitted	Cost-utility analysis – partitioned survival model
Data sources used to model the clinical effects	CASPIAN clinical study

Summary	
Data sources used to model the health-related quality of life	CASPIAN clinical study
Life years gained	0.99 years
QALYs gained	0.78 QALY
Incremental costs	DKK 931,340
ICER (DKK/QALY)	DKK 1,188,412 /QALY
Uncertainty associated with the ICER estimate	The parameters with the greatest impact on the ICER were discount rates (both for outcomes and costs) and the utility value used in the progression-free health state.
Number of eligible patients in Denmark	Incidence: 160 Prevalence: Not relevant – see section 3.2
Budget impact (in year 5)	Approximately DKK 71 million

[a]ES-SCLC patients with a body weight of 30 kg or less must receive weight-based dosing of Imfinzi® at 20 mg/kg. In combination with chemotherapy dose every 3 weeks (21days), followed by 20 mg/kg every 4 weeks as monotherapy until weight increases to greater than 30 kg.

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

3.1 The medical condition

Small-cell lung cancer (SCLC) is a high-grade neuroendocrine tumor. Pathological diagnosis is made according to the World Health Organization (WHO) classification using morphology (uniform round to spindle-shaped small cells, sparse cytoplasm, high mitotic index and necrotic areas) [1-3]. SCLC cells may be positive for epithelial and/or neuroendocrine markers, with markers of neuroendocrine differentiation found in approximately 75% of cases [1, 4].

SCLC is a particularly aggressive cancer. Two-thirds of patients present with distant metastatic disease at diagnosis [5, 6]. Brain metastasis is present in 10–18% [6] of cases.

SCLC is staged according to the TNM staging system. For treatment decisions SCLC is classified as limited stage (LS) or extensive-stage (ES) disease [7]. LS-SCLC is defined as tumor confined to the hemithorax of origin, the mediastinum and supraclavicular lymph nodes, which can be encompassed within a tolerable radiation therapy port. Patients with SCLC who are not considered to have LS-SCLC have ES-SCLC [8].

ES-SCLC corresponds to AJCC stage IV disease, the criterion for which is the presence of tumors of any size present in both lungs or in the lungs and another organ, or stage T3–4 disease [5].

Frequent symptoms of SCLC include coughing, dyspnoea, fatigue, weight loss and pain [5, 9], which are common to other conditions e.g., asthma, chest infection or chronic obstructive pulmonary disease, and may not be recognized as SCLC. For these reasons patients have ES-SCLC at diagnosis [10-16].

The life expectancy of patients with SCLC is poor, and this is particularly the case for patients with ES-SCLC at diagnosis. A Danish study in SCLC including 6,353 patients diagnosed with SCLC between 2006-2015 in the Danish cancer Registry, showed that majority, 68.2% had ES-SCLC. The study showed that the survival is poor for the Danish patients with ES-SCLC, with many patients dying before completing treatment, death within 60 days from diagnosis was shown in 31.1% and median survival was 6.2 months. The 5-year survival was only 2% for ES-SCLC [17].

Interviews with patients with ES-SCLC revealed that symptoms of SCLC (such as a burning sensation, fatigue, cough, discomfort, shortness of breath) and treatment-related side-effects (such as constipation, diarrhea, fatigue, hair loss, vomiting) had an impact on many aspects of their life, including daily activities, emotional functioning, physical functioning and social functioning/relationships, as well as having cognitive, financial and school/work-related effects. The most frequently reported impact of ES-SCLC was reduced physical exertion (n = 11, 64.7%) [18].

Various studies have compared HRQoL for patients with lung cancer, including patients with SCLC, with that of the general population. A US study including 841 patients with SCLC reported HRQoL using the 36-item Short-Form Health Survey (SF-36). The mean Physical Component Summary (PCS) score was 39.0 and the mean Mental Component Summary (MCS) score was 51.1, whereas the assumed mean PCS or MCS score was 50 for the general population [19]. Another study has reported a mean EORTC QLQ-C30 global health status (GHS) score of 38.3 for patients with ES-SCLC [20], which was substantially lower than the normative value used as reference (67.1) [21]. Additionally, patients included in the CASPIAN and IMpower133 (double-blind, placebo-controlled, phase 3 trial to evaluate atezolizumab plus carboplatin and etoposide in patients with extensive-stage small-cell lung cancer who had not previously received treatment) trials had baseline GHS scores of 54–56 [22], and 52–54 [23], respectively. Two further studies have reported mean 5-dimension EuroQol questionnaire (EQ-5D) scores of 0.52 [24] and 0.74 [25], compared with a UK population norm of 0.78 for 65–74 year olds [26].

Finally, there is evidence that patients with ES disease have lower HRQoL than those with LS disease. A systematic review that identified 27 studies reporting on HRQoL in patients with SCLC found that the impact on HRQoL across SCLC stages appeared greatest in

patients with ES-SCLC who were treatment naïve, and lower in those who responded to treatment (either LS or ES). Effects were greatest on physical functioning and activities of daily living [27].

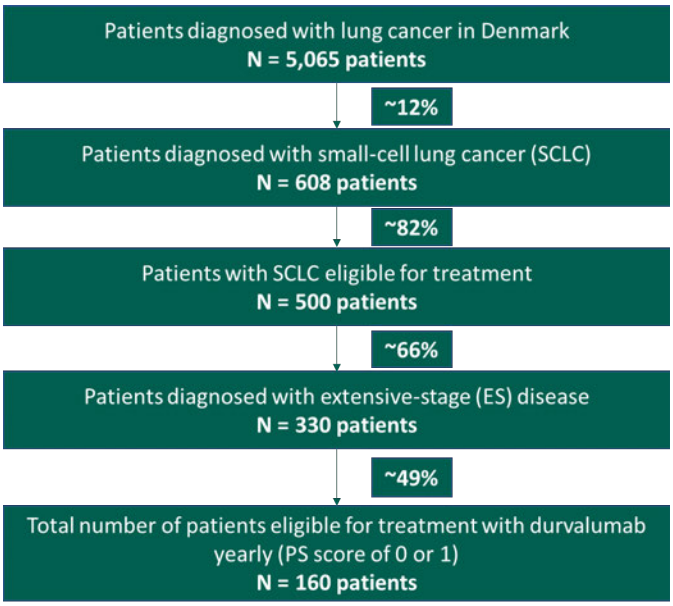
3.2 Patient population

The relevant population for the assessment is adult patients with ES-SCLC (PS 0-1) who have not been treated.

According to the Danish Lung Cancer Registry, in 2022, there were 5,065 patients diagnosed with lung cancer in Denmark [28]. Of these, 608 (12.0%) patients were diagnosed with SCLC [29]. However, according to the Danish expert, not all these patients would be treated i.e., due to being too ill [30]. The clinical expert estimated that approximately 500 patients with SCLC are treated yearly in Denmark [30].

As described in section 3.1, due to the rapid growth and early metastases of SCLC tumors, it is estimated that approximately two in three patients at diagnosis have extensive-stage (ES) disease [13, 14, 16, 31]. Furthermore, in the application of Tecentriq® (atezolizumab) to the DMC, it was estimated that 49% of ES-SCLC patients have a performance status of 0 or 1 [29]. This results in approximately 160 patients being eligible for treatment with Imfinzi® yearly in Denmark (Figure 1).

Figure 1. Relevant population for the assessment in Denmark



The estimated incidence for the Danish population is described in Table 1. A constant incidence in the last five years was assumed. Table 2 includes the expected number of patients eligible for treatment yearly with Imfinzi® in Denmark. The number of incident patients each year were assumed to be the patients eligible for treatment with Imfinzi® yearly.

Table 1. Incidence and prevalence in the past 5 years

Year	2019	2020	2021	2022	2023
Incidence in Denmark (ES)	330	330	330	330	330
Prevalence in Denmark	Not relevant	Not relevant	Not relevant	Not relevant	Not relevant
Global prevalence*	Not relevant	Not relevant	Not relevant	Not relevant	Not relevant

* For small patient groups, also describe the worldwide prevalence.

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	160	160	160	160	160

3.3 Current treatment options

According to the Danish Multidisciplinary Cancer Group (DMCG) guidelines, the treatment for patients with ES-SCLC is palliative [32].

The guidelines state that, if patients can tolerate it, the standard treatment is the combination of carboplatin and etoposide (4-6 cycles). Alternatively, etoposide monotherapy can be given. Carboplatin is recommended as a standard treatment instead of cisplatin due to its shorter treatment time and lower non-hematological toxicity [32]. This was confirmed by the clinical expert [30]. Nonetheless, the expert indicated that both carboplatin and cisplatin can be used in Danish clinical practice although the standard is to use carboplatin [30].

In 2012, a systematic review was conducted to elucidate the effect of cisplatin-based chemotherapy compared with carboplatin-based chemotherapy for first-line treatment of ES-SCLC [33]. Four studies were identified with a total of 663 patients. No difference in survival was found with a median survival of 9.6 months vs. 9.4 months for cisplatin and carboplatin, respectively, with HR=1.10 (95% CI; 0.94-1.29, p=0.25). Hematological toxicity was more frequent with carboplatin treatment, while non-hematological toxicity (including renal toxicity and neurotoxicity) was more frequent with cisplatin treatment [33].

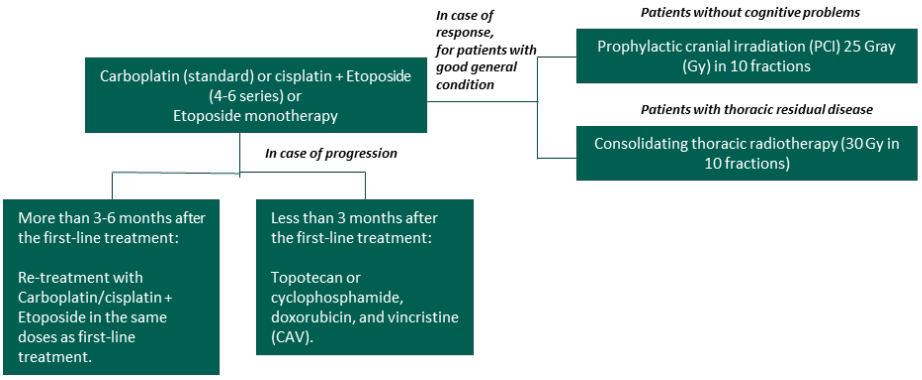
Younger patients in good general condition, with response to palliative chemotherapy, and without cognitive problems can be given prophylactic cranial irradiation (PCI) 25 Gray (Gy) in 10 fractions [32].

In case of a radiological response to chemotherapy, patients in good general condition (PS 0-2) with thoracic residual disease can be given consolidating thoracic radiotherapy (30 Gy in 10 fractions) [32].

Patients who relapse more than 3-6 months after the first-line treatment can be retreated with the combination of carboplatin/cisplatin and etoposide in the same doses as in first-line treatment. In case of progression less than 3 months after the first-line treatment, patients can be treated with topotecan or cyclophosphamide, doxorubicin, and vincristine (CAV) [32].

Figure 2 illustrates the current treatment algorithm, which was validated by the Danish expert [30].

Figure 2. Treatment algorithm for ES-SCLC in Denmark



3.4 The intervention

Imfinzi® (durvalumab) is a fully human, immunoglobulin G1 kappa (IgG1κ) monoclonal antibody that selectively blocks the interaction of PD-L1 with PD-1 and CD80 [34].

Expression of programmed cell death ligand-1 (PD-L1) protein is an adaptive immune response that helps tumours evade detection and elimination by the immune system. PD-L1 can be induced by inflammatory signals (e.g., IFN-gamma) and can be expressed on both tumour cells and tumour-associated immune cells in tumour micro-environment. PD-L1 blocks T-cell function and activation through interaction with PD-1 and CD80. By binding to its receptors, PD-L1 reduces cytotoxic T-cell activity, proliferation and cytokine production [34].

Therefore, selective blockade of PD-L1/PD-1 and PD-L1/CD80 interactions enhances anti-tumour immune responses and increases T-cell activation [34].

Imfinzi® has been approved by the EMA for the treatment of several diseases including hepatocellular carcinoma, biliary tract cancer and non-small cell lung cancer (NSCLC). However, the relevant and approved indication for this assessment is [35]:

"Imfinzi® 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)".

The pharmaceutical features of Imfinzi® are described below. These were informed by the summary of product characteristics (SmPC) [34].

Overview of intervention	
Therapeutic indication relevant for the assessment	Imfinzi® 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).
Method of administration	Imfinzi® is administered as an intravenous (IV) infusion over 1 hour.
Dosing	1,500 mg[a] in combination with chemotherapy every 3 weeks (21 days) for 4 cycles, followed by 1,500 mg every 4 weeks as monotherapy.
Dosing in the health economic model (including relative dose intensity)	1,500 mg intravenous (IV) infusions every 3 weeks for 12 weeks (4 cycles) and every 4 weeks thereafter until progressed disease (PD) or other discontinuation criteria. Relative dose intensity: 95.4%.
Should the medicine be administered with other medicines?	Imfinzi® is given in combination with etoposide and either carboplatin or cisplatin.
Treatment duration / criteria for end of treatment	Treatment until disease progression or unacceptable toxicity.
Necessary monitoring, both during administration and during the treatment period	Treatment must be initiated and supervised by a physician experienced in the treatment of cancer. Alanine aminotransferase, aspartate aminotransferase, total bilirubin, and alkaline phosphatase levels should be monitored prior to initiation of treatment and prior to each subsequent infusion. Additional monitoring is to be considered based on clinical evaluation. **Patients should be monitored for signs and symptoms of:** - pneumonitis or radiation pneumonitis. - colitis/diarrhea and intestinal perforation **Patients should be monitored for:** - abnormal thyroid function tests prior to and periodically during treatment and as indicated based on clinical evaluation. - clinical signs and symptoms of adrenal insufficiency

Overview of intervention	
	- clinical signs and symptoms of type 1 diabetes mellitus. - clinical signs and symptoms of hypophysitis or hypopituitarism. - abnormal renal function tests prior to and periodically during treatment. - signs and symptoms of rash or dermatitis. - signs and symptoms of immune-mediated myocarditis. - signs and symptoms of immune-mediated pancreatitis. - signs and symptoms of other immune-related adverse reactions. - signs and symptoms of infusion-related reactions. In case of overdose, patients should be closely monitored for signs or symptoms of adverse reactions.
Need for diagnostics or other tests (e.g. companion diagnostics). How are these included in the model?	Not applicable.
Package size(s)	Each ml of concentrate for solution for infusion contains 50 mg of Imfinzi®. One vial of 2.4 ml of concentrate contains 120 mg of Imfinzi®. One vial of 10 ml of concentrate contains 500 mg of Imfinzi®.

[a]ES-SCLC patients with a body weight of 30 kg or less must receive weight-based dosing of Imfinzi® at 20 mg/kg. In combination with chemotherapy dose every 3 weeks (21days), followed by 20 mg/kg every 4 weeks as monotherapy until weight increases to greater than 30 kg.

3.4.1 The intervention in relation to Danish clinical practice

As described in section 3.3, the current standard of care (SoC) for the first-line treatment of adult patients with ES-SCLC is the combination of carboplatin/cisplatin and etoposide or etoposide monotherapy if the combination treatment is not tolerated [32]. Imfinzi® is added to etoposide and platinum-based chemotherapy (cisplatin or carboplatin), the current SoC.

In the CASPIAN pivotal trial, the addition of Imfinzi® to etoposide and platinum-based chemotherapy (cisplatin or carboplatin) resulted in a statistically significant and sustained improvement in OS and a clinically meaningful prolongation of PFS compared to etoposide and platinum-based chemotherapy (cisplatin or carboplatin) alone. Additionally, the OS and PFS were consistently improved in the pre-specified subgroups considered i.e., including the patients receiving carboplatin as the platinum-based chemotherapy. Furthermore, Imfinzi® was well tolerated and the safety profile of Imfinzi® in combination with etoposide and platinum-based chemotherapy was similar to that of etoposide and platinum-based chemotherapy alone [36-38].

Therefore, Imfinzi® in combination with carboplatin/cisplatin and etoposide will be an additional treatment option to carboplatin/cisplatin and etoposide as the SoC in the treatment algorithm for the first-line treatment of adult patients with ES-SCLC.

3.5 Choice of comparator(s)

In accordance with sections 3.3 and 3.4, the most relevant comparator for this analysis is expected to be the combination of carboplatin/cisplatin and etoposide based on Danish treatment guidelines, clinical expert interview and the treatments administered in the CASPIAN trial [30, 32, 38].

Details on the pharmaceutical features of carboplatin, cisplatin and etoposide are shown below.

Overview of comparator	Carboplatin [39]	Cisplatin [40]	Etoposide [41]
Generic name	Carboplatin	Cisplatin	Etoposide
ATC code	L01XA02	L01XA01	L01CB01

Overview of comparator	Carboplatin [39]	Cisplatin [40]	Etoposide [41]
Mechanism of action	Carboplatin, like cisplatin, creates DNA crosslinks between different and within the individual DNA strands in cells that are exposed to the substance. The DNA reactivity is correlated with the cytotoxicity.	Cisplatin is a platinum-containing antineoplastic agent. Cisplatin has biochemical properties similar to those of bifunctional alkylating agents. The substance inhibits DNA synthesis by forming intrastrand and interstrand cross-links in DNA. Protein and RNA synthesis is also inhibited, to a lesser extent. Although cisplatin's main mechanism of action appears to be inhibition of DNA synthesis, other mechanisms of action, including enhancement of tumor immunogenicity, may also contribute to its antineoplastic activity. Cisplatin also has immunosuppressive, radiosensitizing and antimicrobial properties. Cisplatin does not appear to be cell cycle or cell phase specific.	The main action of etoposide appears to be in the late S and early G2 part of the cell cycle in mammalian cells. Two dose-dependent reactions are seen: At high concentrations (10 micrograms/ml or more), cells are lysed, which starts mitosis. At low concentrations (0.3 to 10 micrograms/ml), cells are prevented from entering prophase. Composition of microtubules is not affected. The dominant macromolecular action of etoposide appears to be double-strand break by an interaction with DNA topoisomerase II or by the formation of free radicals. Etoposide has been shown to cause metaphase arrest in chicken fibroblasts.
Method of administration	IV infusion over 15 to 60 minutes.	IV infusion over a period of 6 to 8 hours.	IV infusion over a period of 30-60 minutes

Dosing	The recommended dose of carboplatin for previously untreated adult patients with normal renal function (creatinine clearance > 60 ml/min) is 400 mg/m². Alternatively, the dose can be calculated according to Calvert's formula below: Dose (mg) = target AUC (mg/ml x min) x [GFR ml/min + 25]. Treatment should not be repeated until 4 weeks after the previous course of carboplatin and/or before the neutrophil count is at least 2000 cells/mm³ and the platelet count is at least 100,000 cells/mm³. The initial dose should be reduced by 20-25% in patients with risk factors such as previous bone marrow suppressive treatment and/or poor treatment outcome (ECOG-Zubrod 2-4 or Karnofsky below 80). The optimal use of carboplatin in combination with other myelosuppressive agents necessitates dose adjustments according to regimen and schedule. In patients over 65 years of age, adjustment of the dose of carboplatin according to the patient's general condition is necessary during the first and subsequent courses of treatment.	If cisplatin is used in combination therapy, a typical dose is 20 mg/m² or more once every 3 to 4 weeks. In patients with renal impairment or bone marrow depression, the dose should be reduced appropriately.	The usual dose for adult patients is 50 to 100 mg/m2 /day on days 1 to 5 or 100 to 120 mg/m2 /day on days 1, 3 and 5 every 3 to 4 weeks. Dosage should be modified to take into account the myelosuppressive effects of other drugs in the combination therapy, or the effect of previous radiation therapy or chemotherapy, which may have compromised bone marrow reserves. The dose following the initial dose should be adjusted if the neutrophil count is below 500 cells/mm3 for more than 5 days. Furthermore, the dose must be adjusted in case of fever, infections or a platelet count below 25,000 cells/mm3, which is not caused by the disease. Follow-up doses should be adjusted if grade 3 or 4 toxicities occur or if renal creatinine clearance is less than 50 ml/min. At a reduced creatinine clearance of 15-50 ml/min, a dose reduction of 25% is recommended. It is not necessary to adjust the dose

Overview of comparator	Carboplatin [39]	Cisplatin [40]	Etoposide [41]
			in elderly patients (age > 65 years).
Dosing in the health economic model (including relative dose intensity)	AUC 5 (434 mg, 1 administration per cycle with a cycle length of 3 weeks). Relative dose intensity: D+EP: 100% EP: 93.3%.	75 mg/m^2, 1 administration per cycle with a cycle length of 3 weeks. Relative dose intensity: D+EP: 100% EP: 93.3%.	100 mg/m^2 (3 administrations per cycle with a cycle length of 3 weeks). Relative dose intensity: D+EP: 100% EP: 90.3%.
Should the medicine be administered with other medicines?	Carboplatin is given in combination with etoposide.	Cisplatin is given in combination with etoposide.	Etoposide is given in combination with either carboplatin or cisplatin.
Treatment duration/ criteria for end of treatment	4-6 cycles (12-18 weeks) / Treatment can be discontinued due to disease progression or unacceptable toxicity.	4-6 cycles (12-18 weeks) / Treatment can be discontinued due to disease progression or unacceptable toxicity.	4-6 cycles (12-18 weeks) / Treatment can be discontinued due to disease progression or unacceptable toxicity.
Need for diagnostics or other tests (i.e. companion diagnostics)	Not applicable.	Not applicable.	Not applicable.
Package size(s)	15 or 45 ml at a strength of 10 mg/ml.	50 or 100 ml at a strength of 1 mg/ml.	20 mg/ml 5 or 25 ml

3.6 Cost-effectiveness of the comparator(s)

The comparators in use for the current cost-utility analysis are in line with the SoC for the first-line treatment of adult patients with ES-SCLC in Denmark. Additionally, they have been accepted as comparators in a previous assessment by the Danish Medicines Council in the same indication [29]. Therefore, no supplementary analysis is provided.

3.7 Relevant efficacy outcomes

3.7.1 Definition of efficacy outcomes included in the application.

The health economic analysis of Imfinzi® within this assessment compares Imfinzi® in combination with etoposide and carboplatin/cisplatin with etoposide and carboplatin/cisplatin alone. This comparison is based on the pivotal clinical trial CASPIAN and all relative efficacy outcomes are based on data from the CASPIAN trial [36-38]. There are currently three data cut-offs (DCO) available from CASPIAN. In this dossier, the efficacy and utility estimations are based on either the final data cut-off (DCO 27 January 2020) [38], or the long-term follow-up (DCO 22 March 2021) [36, 37]. The relative efficacy outcomes from CASPIAN used to compare Imfinzi® in combination with etoposide and carboplatin/cisplatin with etoposide and carboplatin/cisplatin alone are shown in Table 3.

Table 3. Efficacy outcome measures relevant for the application

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
Overall survival (OS) CASPIAN	27/01/2020 (2 years follow-up). 22/03/2021 (3 years follow-up).	OS was defined as the time from date of randomization 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. Median OS was calculated using the Kaplan-Meier technique.	
Progression free survival (PFS) CASPIAN	27/01/2020 (2 years follow-up).	PFS was defined as time from date of randomization until date of objective disease progression or death (by any cause in the absence of progression), regardless of whether the patient withdrew from randomized therapy or received another anticancer therapy prior to progression. Progression (i.e., PD) was defined as at least a 20% increase in the sum of diameters of target lesions (TLs), taking as reference the smallest previous sum of diameters (nadir) and an absolute increase of ≥5 millimeters (mm) for the sum from nadir. For evaluation of non-target lesions (NTLs), PD was defined as unequivocal progression of existing NTLs. Median PFS was calculated using the Kaplan-Meier technique.	Per Response Evaluation Criteria in Solid Tumors, version 1.1 [RECIST 1.1] using Investigator assessments. Tumour scans were performed at baseline, Week 6, Week 12 and then every 8 weeks relative to the date of randomization.

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
Objective response rate (ORR) CASPIAN	27/01/2020 (2 years follow-up).	ORR was defined as the percentage of patients with at least 1 visit response of Complete Response (CR) or Partial Response (PR). CR was defined as disappearance of all TLs since baseline (any pathological lymph nodes selected as TLs must have a reduction in short axis diameter to <10 mm) or disappearance of all NTLs since baseline (all lymph nodes must be non-pathological in size [<10 mm short axis]). PR was defined as at least a 30% decrease in the sum of diameters of TLs (taking as reference the baseline sum of diameters).	Per RECIST 1.1 using Investigator assessments. Tumour scans were performed at baseline, Week 6, Week 12 and then every 8 weeks relative to the date of randomization until RECIST 1.1-defined progression.
Duration of response (DoR) CASPIAN	27/01/2020 (2 years follow-up).	Duration of response is the time from the first confirmed CR/PR until the date of first documented progression, or death in the absence of progression. Patients who have not progressed or died are censored at their PFS censoring date.	Per RECIST 1.1 using Investigator assessments.
HRQoL CASPIAN	27/01/2020 (2 years follow-up).	Time to Deterioration of HRQoL and Patient Reported Outcome (PRO) Symptoms, assessed using EORTC QLQ. The EORTC QLQ-Core 30 version 3 (QLQ-C30 v3) was included for assessing HRQoL. It assesses HRQoL/health status through 9 multi-item scales: 5 functional scales (physical, role, cognitive, emotional, and social), 3 symptom scales (fatigue, pain, and nausea and vomiting), and a global health and QoL scale. 6 single-item symptom measures are also included: dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties. Scores from 0 to 100 were derived for each of the 15 domains, with higher scores representing greater functioning, greater HRQoL, or greater level of symptoms. Time to deterioration (calculated using the Kaplan-Meier technique) was defined as time from randomization until the date of first	EORTC QLQ-C30 EORTC QLQ-LC13 EQ-5D

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
		clinically meaningful deterioration (a decrease in score from baseline of ≥10) that is confirmed at a subsequent visit or death (by any cause) in the absence of a clinically meaningful deterioration. Time to Deterioration of PRO Symptoms, Assessed Using EORTC QLQ-Lung Cancer Module 13 (QLQ-LC13). The EORTC QLQ-LC13 is a disease-specific 13-item self-administered questionnaire for lung cancer, to be used in conjunction with the EORTC QLQ-C30. It comprises both multi-item and single-item measures of lung cancer-associated symptoms (i.e., coughing, hemoptysis, dyspnea, and pain) and side effects from conventional chemotherapy and radiotherapy (i.e., hair loss, neuropathy, sore mouth, and dysphagia). Scores from 0 to 100 were derived for each symptom item, with higher scores representing greater level of symptoms. Time to deterioration (calculated using the Kaplan-Meier technique) was defined as time from randomization until the date of first clinically meaningful deterioration (an increase in score from baseline of ≥10) that is confirmed at a subsequent visit or death (by any cause) in the absence of a clinically meaningful deterioration. Change From Baseline in Primary Symptoms, Assessed Using EORTC QLQ-C30 and EORTC QLQ-LC13 (Assessed up to 12 months). A mixed model repeated measures (MMRM) analysis of EORTC QLQ-C30 and EORTC QLQ-LC13 was performed for 5 primary PRO symptoms (cough, dyspnea, chest pain, fatigue, and appetite loss), and considered all data from baseline to PD or 12 months, excluding visits with excessive missing data (defined as >75% missing data).	

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
		An outcome variable consisting of a score from 0 to 100 was derived for each of the symptom scales/symptom items, with higher scores representing greater symptom severity. An improvement in symptoms was indicated by a negative change from baseline. A positive change from baseline indicated a deterioration of symptoms. A minimum clinically meaningful change was defined as an absolute change from baseline of ≥10.	
		5-level EuroQol questionnaire (EQ-5D-5L). The EQ-5D-5L rates HRQoL from a score of less than 0 (worse than death), to 0 (equivalent to death) and to 1 (best imaginable health). Mixed models with repeated measures were used and modelled utility as a function of treatment, progression or response status, time to death, and any other available variables known to impact utility (i.e. treatment status, timing of assessment, occurrence of adverse events).	

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

Validity of outcomes

The goal of treatment of ES-SCLC is life extension and symptom relief [42]. The most persuasive outcome to demonstrate efficacy in anticancer trials is OS and possible primary efficacy endpoints include PFS, and patient-reported outcomes [43]. Data on ORR, DoR, time to progression (TTP)/PFS and confirmed ORR are considered suitable markers of anti-tumor activity. Additionally, in DMC´s evaluation of Tecentriq® for the same indication, the committee pre-specified OS, PFS, ORR and QoL (assessed via the EORTC QLQ-C30) as critical or important efficacy measures [42]. All of these outcome measures were defined as endpoints in the CASPIAN trial [36-38]. Further, the cost-effectiveness model was directly based on the key outcomes of the CASPIAN trial, which directly represent treatment goals for ES-SCLC in Denmark: OS, PFS and QoL.

4. Health economic analysis

A cost-utility analysis was performed for this submission.

4.1 Model structure

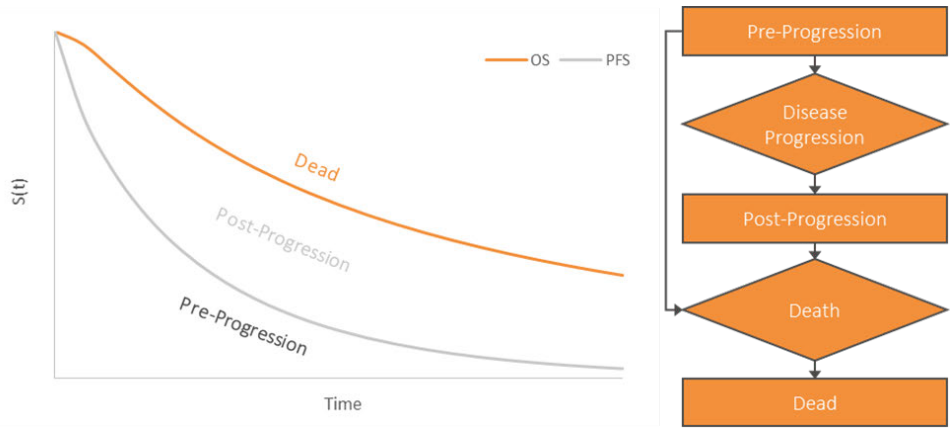
The model structure is a three-state area under the curve (AUC) model, also known as a partitioned survival model (PartSA). The three health states considered in the model are distinct and mutually exclusive:

- Progression-free survival (PFS)
- Post-progression survival (PPS)
- Death

All patients start in the PFS state. Then, they can move to the PPS state and then to the death state or directly from the PFS state to the death state. Patients do not return to the PFS state once they have progressed. OS and PFS curves are used in the model to derive the percentage of patients in each health state.

As shown in Figure 3, the model estimates the proportion of a cohort in each state based upon survival curves, with separate survival functions for OS and PFS.

Figure 3. Model structure



As some treatments are recommended for use until disease progression and some patients discontinue treatment prior to progression, the model accounts for on versus off treatment. Some patients may also continue treatment post-progression. In order to accurately capture treatment-related costs, treatment discontinuation was modelled using a time to treatment discontinuation (TTD) curve derived from the CASPIAN pivotal trial [38].

The modelling approach is flexible and adequately quantifies the primary objectives of treating individuals with ES SCLC. Moreover, it directly uses trial-based time-to-event endpoints from the CASPIAN study [36-38].

4.2 Model features

Table 4 shows the features of the economic model.

Table 4. Features of the economic model

Model features	Description	Justification
Patient population	ITT of the CASPIAN trial. Adult patients (aged ≥18 years) with histologically or cytologically documented extensive disease (American Joint Committee on Cancer Stage (7th edition) IV SCLC [T any, N any, M1 a/b]), or T3-4 due to multiple lung nodules that are too extensive or have tumor/nodal volume that is too large to be encompassed in a tolerable radiation plan, and WHO/ECOG performance status of 0 or 1.	Same population as described in Section 3.2
Perspective	Limited societal perspective.	According to DMC guidelines
Time horizon	Lifetime (30 years).	To capture all health benefits and costs in line with DMC guidelines [44]. Based on mean age at diagnosis in the Danish population (70 years). Validated by Danish clinical expert [30].
Cycle length	7 days.	Consistent with length of treatment cycle (day 1 every 7 days)
Half-cycle correction	Yes.	NA
Discount rate	3.5%	The DMC applies a discount rate of 3.5 % for all years
Intervention	Imfinzi® in combination with etoposide and platinum-based chemotherapy.	NA
Comparator(s)	Etoposide with platinum-based chemotherapy.	According to national treatment guideline. Validated by Danish clinical expert [30].

Model features	Description	Justification
Outcomes for efficacy	OS, PFS and TTD.	These are standard efficacy inputs used to model in the oncology setting.

5. Overview of literature

5.1 Literature used for the clinical assessment.

This application for Imfinzi® concerns the first line treatment of adult patients with ES-SCLC and was based on the head-to-head study CASPIAN, with a comparator (carboplatin or cisplatin in combination with etoposide) considered relevant to Danish clinical practice. A systematic literature review was therefore not the basis for assessing clinical efficacy and safety.

An overview of the relevant literature included in the assessment of efficacy and safety (the CASPIAN trial) is presented in Table 5.

Table 5 Relevant literature included in the assessment of efficacy and safety

Reference (Full citation incl. reference number)*	Trial name*	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison of*
Paz-Ares, L. et al. Durvalumab plus platinum-etoposide versus platinum-etoposide in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): a randomised, controlled, open-label, phase 3 trial. Lancet, doi:10.1016/S0140-6736(19)32222-6 (2019) [45]. Paz-Ares, L. et al. PD-L1 expression, patterns of progression and patient-reported outcomes (PROs) with durvalumab plus platinum-etoposide in ES-SCLC: Results from CASPIAN (LBA89). Ann Oncol 30 (Suppl 5), doi:10.1093/annonc/mdz394.089 (2019) [22]. Paz-Ares, L. G. et al. Durvalumab ± tremelimumab + platinum-etoposide in first-line extensive-stage SCLC (ES-SCLC): Updated results from the phase III CASPIAN study. Journal of Clinical Oncology 38, 9002-9002, doi:10.1200/JCO.2020.38.15_suppl.9002 (2020) [38]. AstraZeneca. Data on file: A Phase III, Randomized, Multicenter, Open-Label, Comparative Study to Determine the Efficacy of Durvalumab or Durvalumab and Tremelimumab in Combination With Platinum-Based Chemotherapy for the First-Line Treatment in Patients with Extensive Disease Small-Cell Lung Cancer (SCLC) (CASPIAN). CSR 06 July 2021 [36]. Paz-Ares L, Chen Y, Reinmuth N, et al. Durvalumab, with or without tremelimumab, plus platinum-etoposide in first-line treatment of extensive-stage small-cell lung cancer: 3-year overall survival update from CASPIAN. ESMO Open. 2022 Apr;7(2):100408. doi: 10.1016/j.esmoop.2022.100408. Epub 2022 Mar 10. PMID: 35279527; PMCID: PMC9161394 [37].	CASPIAN	NCT03043872	Start: 27/03/2017. Completion: 29/03/2024. Data cut-off: Interim analysis: 11/03/2019 Final analysis: 27/01/2020 Global cohort long-term follow-up analysis: 22/03/2021 Future data cut-offs: There are no expected future data cut-offs.	Imfinzi® in combination with carboplatin /cisplatin and etoposide vs. carboplatin /cisplatin and etoposide alone for the first-line treatment of adult patients with ES-SCLC.

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

Health-related quality of life (HRQoL) data was obtained from the head-to-head study CASPIAN, with a comparator (carboplatin/cisplatin in combination with etoposide) relevant to Danish clinical practice. Utility decrements associated with AEs were not explicitly collected in the CASPIAN study. Therefore, these values were sourced from published literature, identified through a targeted search of electronic sources (PubMed and previous HTA) [46-50], see Table 60. Table 6 Table 6 shows the relevant literature included for the documentation of HRQoL.

Table 6. Relevant literature included for (documentation of) health-related quality of life

Reference (Full citation incl. reference number)	Health state/Disutility	Reference to where in the application the data is described/applied
Paz-Ares, L. G. et al. Durvalumab ± tremelimumab + platinum-etoposide in first-line extensive-stage SCLC (ES-SCLC): Updated results from the phase III CASPIAN study. Journal of Clinical Oncology 38, 9002-9002, doi:10.1200/JCO.2020.38.15_suppl.9002 (2020) [38].	Progression-free: 0.834 (95% CI: 0.819-0.849) Progressed disease: 0.802 (95% CI: 0.781-0.824) Dead: 0	Section 10.2.3
Nafees B, Stafford M, Gavriel S, Bhalla S, Watkins J. Health state utilities for non-small cell lung cancer. Health Qual Life Outcomes. 2008;6:84. [48]. Huang W-C, Lee C-H, Wu M-F, Huang C-C, Hsu C-H, Chen H-C, et al. Clinical features, bacteriology of endotracheal aspirates and treatment outcomes of patients with chronic obstructive pulmonary disease and community-acquired pneumonia in an intensive care unit in Taiwan with an emphasis on eosinophilia versus non-eosinophilia: a retrospective case–control study. BMJ open. 2018;8(9). [47].	Anemia: -0.073 Diarrhea (Grade 2): -0.047 Diarrhea (Grade 3/4): -0.047 Febrile Neutropenia: -0.090 Leukopenia: -0.090 (Equal to neutropenia) Lipase Increased: -0.019 (Assumption) Nausea/Vomiting: -0.048	Section 10.2.3

Reference (Full citation incl. reference number)	Health state/Disutility	Reference to where in the application the data is described/applied
Schremser K, Rogowski WH, Adler-Reichel S, Tufman AL, Huber RM, Stollenwerk B. Cost-effectiveness of an individualized first-line treatment strategy offering erlotinib based on EGFR mutation testing in advanced lung adenocarcinoma patients in Germany. Pharmacoeconomics. 2015;33(11):1215-28. [49]. Birkmeyer J, Goodnough L, AuBuchon J, Noordsij P, Littenberg B. The cost-effectiveness of preoperative autologous blood donation for total hip and knee replacement. Transfusion. 1993;33(7):544-51. [46]. Sejean K, Calmus S, Durand-Zaleski I, Bonnichon P, Thomopoulos P, Cormier C, et al. Surgery versus medical follow-up in patients with asymptomatic primary hyperparathyroidism: a decision analysis. European journal of endocrinology. 2005;153(6):915-27. [50].	Neutropenia: -0.090 Neutrophil Count Decrease: -0.090 (Equal to neutropenia) Platelet Count Decrease: -0.090 (Equal to thrombocytopenia) Pneumonia/Pneumonitis: -0.090 Thrombocytopenia: -0.053 WBC Count Decrease: -0.090 Hepatitis: -0.038 Hyperthyroidism: -0.095 Hypothyroidism: -0.106 Infusion-Related Reaction: -0.15 Pneumonitis: -0.090 Rash: -0.032	

5.3 Literature used for inputs for the health economic model

The clinical inputs were based on the head-to-head trial CASPIAN and were extrapolated over time. Resource use and cost were based on publicly available sources relevant for Denmark. Consequently, a systematic literature search was not conducted. Table 7 shows the relevant literature used for input to the health economic model.

Table 7. Relevant literature used for input to the health economic model

Reference (Full citation incl. reference number)	Input/estimate	Method of identification	Reference to where in the application the data is described/applied
AstraZeneca. Data on file: A Phase III, Randomized, Multicenter, Open-Label, Comparative Study to Determine the Efficacy of Durvalumab or Durvalumab and Tremelimumab in Combination With Platinum-Based Chemotherapy for the First-Line Treatment in Patients with Extensive Disease Small-Cell Lung Cancer (SCLC) (CASPIAN). CSR 06 July 2021 [36]. Paz-Ares L, Chen Y, Reinmuth N, et al. Durvalumab, with or without tremelimumab, plus platinum-etoposide in first-line treatment of extensive-stage small-cell lung cancer: 3-year overall survival update from CASPIAN. ESMO Open. 2022 Apr;7(2):100408. doi: 10.1016/j.esmoop.2022.100408. Epub 2022 Mar 10. PMID: 35279527; PMCID: PMC9161394 [37].	OS	Based on head-to-head trial CASPIAN.	Section 8.
Paz-Ares, L. G. et al. Durvalumab ± tremelimumab + platinum-etoposide in first-line extensive-stage SCLC (ES-SCLC): Updated results from the phase III CASPIAN study. Journal of Clinical Oncology 38, 9002-9002, doi:10.1200/JCO.2020.38.15_suppl.9002 (2020) [38].	PFS	Based on head-to-head trial CASPIAN.	Section 8.

Reference (Full citation incl. reference number)	Input/estimate	Method of identification	Reference to where in the application the data is described/applied
Publicly available sources/literature	Resource use and cost	Drug costs were sourced from medicinpriser.dk, administration, monitoring cost and patient cost from the DMC report of valuation of unit costs and AE cost from relevant Danish DRGs. Resource use was estimated by a clinical expert and not based on literature.	Section 11.

6. Efficacy

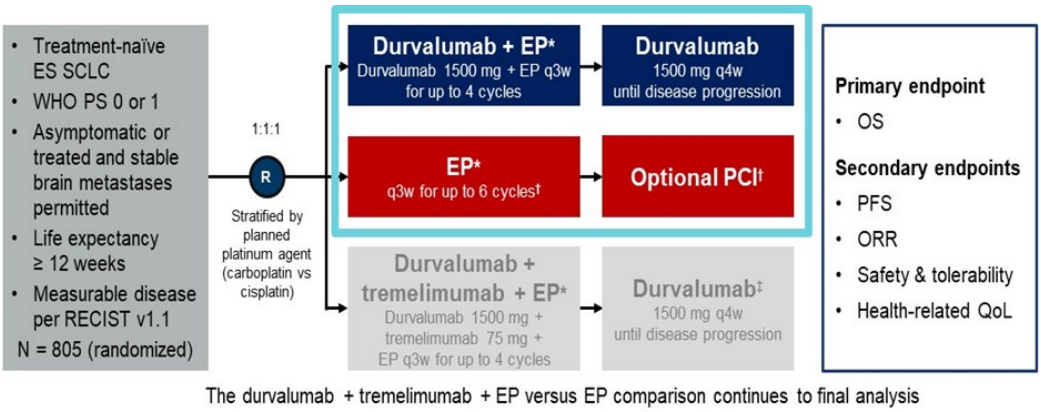
6.1 Efficacy of durvalumab in combination with etoposide and platinum-based chemotherapy compared to etoposide in combination with platinum-based chemotherapy for the first-line treatment of patients with extensive stage small-cell lung cancer

6.1.1 Relevant studies

The key clinical trial for efficacy and safety of durvalumab in combination with etoposide and platinum-based chemotherapy for the first-line treatment of patients with extensive stage small-cell lung cancer is the pivotal study CASPIAN [22, 36, 38, 45] [37]. CASPIAN (NCT03043872) is a phase 3, randomized, open-label, multicenter study examining the efficacy and safety of durvalumab with or without tremelimumab plus etoposide with either carboplatin or cisplatin (EP) versus EP alone as first-line treatment in adult patients with ES-SCLC.

The trial design is summarized in Figure 4 and Table 9. The patient disposition is presented in Figure 5. The data-cuts from CASPIAN are shown in Table 8.

Figure 4. CASPIAN study design



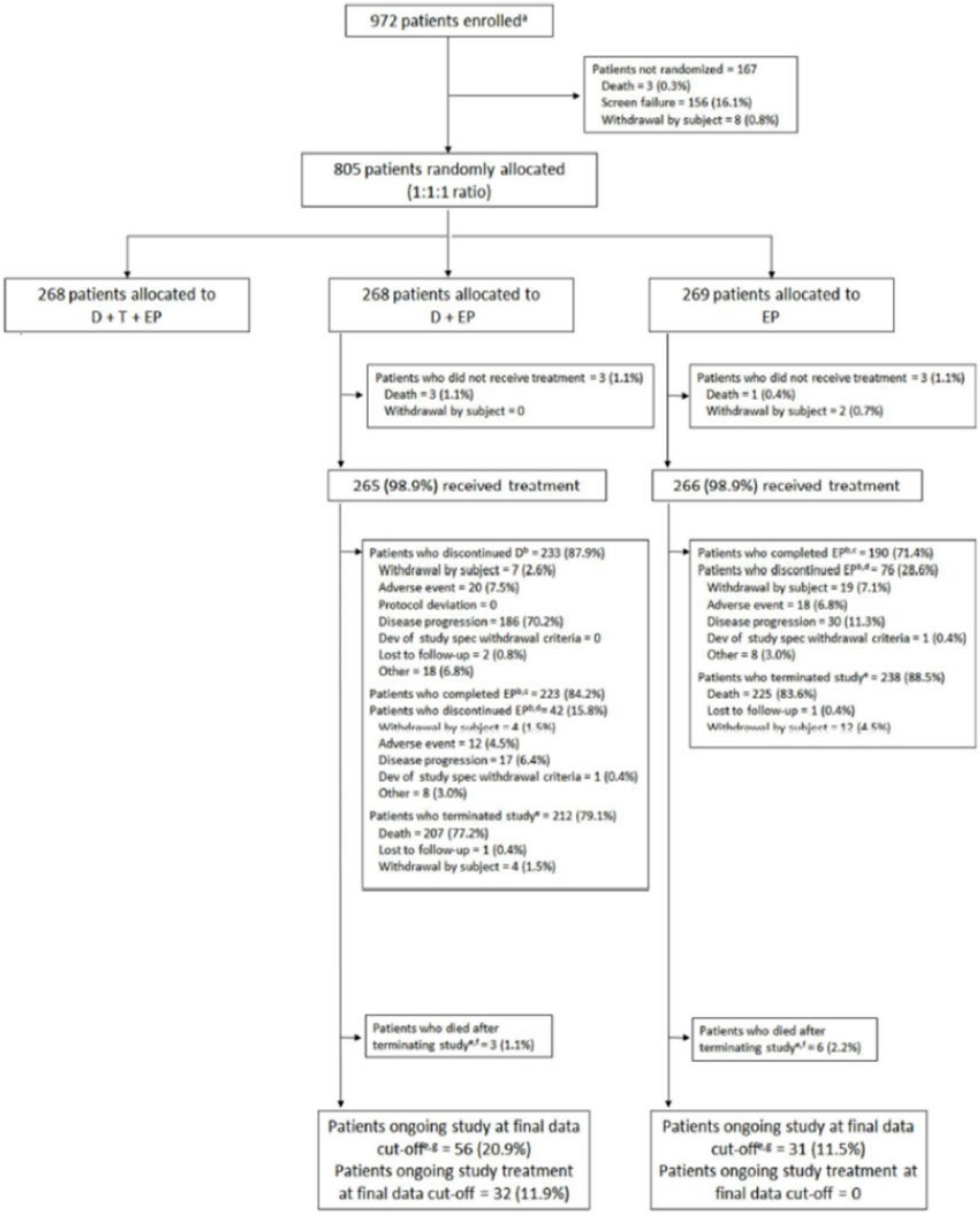
*EP consists of etoposide 80–100 mg/m2 with either carboplatin AUC 5–6 or cisplatin 75–80 mg/m2.

†Patients could receive an additional 2 cycles of EP (up to 6 cycles total) and PCI at the investigator's discretion (in CASPIAN, PCI was allowed only in the EP arm).

‡Patients received an additional dose of tremelimumab post-EP.

Source: Paz-Ares et al., 2019 [45]

Figure 5. Patient disposition in CASPIAN



Patient disposition is based on the global cohort. [a]Patients giving informed consent. Any re-screened patients are counted once. [b]Percentages are calculated from number of patients who received treatment. [c]Patients who completed EP have "Maximum cycle of chemotherapy reached" reported for any EP molecule on the eCRF. [d]A patient is considered as having discontinued EP combination when all molecules are discontinued. If different reasons for discontinuation are collected, the last discontinuation reason by date is selected. [e]Percentages are calculated from number of patients who were randomized. [f]Obtained from public records or survival follow-up. [g]Patients ongoing study consist of those randomized patients still receiving treatment, those randomized patients who have completed treatment and are in safety follow-up or those randomized patients who are still in survival follow-up regardless of whether they were administered treatment or not [51]. Source: Paz-Ares et al., 2019 [45] (1-year interim analysis).

Table 8. Summary of data cuts in CASPIAN

- This was a planned exploratory analysis. It is reported in the publication by Paz-Ares April 2022

	Date	Analysis	Median follow-up, months	Events, n (%)
OS	11 Mar 2019	Interim	14.2	D+EP: 155(57.8) EP:181(67.3) Total: 336(62.6) events
	27 Jan 2020	Final	25.1	D + EP: 210(78.4) EP: 231(85.9) Total: 441(82.1)) events
	22 Mar 2021*	Global cohort long-term follow-up	D + EP: 39.33 EP: 37.98	D + EP: 221((82.5) EP: 248(92.2) Total: 469(87.3) events
PFS	11 Mar 2019	Interim	14.2	D + EP: 226 (84.3) EP: 233 (86.6)
	27 Jan 2020	Final	25.1	D + EP: 234 (87.3) EP: 236 (87.7)

Table 9. Overview of study design for studies included in the comparison

Trial name, NCT-number [22, 36, 38, 45] [37]	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up period
CASPIAN, NCT03043872	Randomized, open-label, parallel-group, active-controlled, multicenter, global study	Study start: 2017-03-27 Study Completion (Estimated): 2023-12-29	Adult patients (aged ≥ 18 years) with untreated, histologically or cytologically documented stage IV SCLC (as defined by American Joint Committee on Cancer staging system, [7th edition], : T any, N any, M1 a/b), or T3–4 due to multiple lung nodules that are too extensive or have tumor/nodal volume that is too large to be encompassed	<u>Arm 1</u> • During chemotherapy: durvalumab 1500 mg + etoposide 80 to 100 mg/m^2 + carboplatin AUC 5–6 or cisplatin 75 to 80 mg/m^2; Q3W for 4 cycles • After chemotherapy: durvalumab 1500 mg until disease progression <u>Arm 3</u> • During chemotherapy: durvalumab	<u>Arm 2</u> • During chemotherapy: etoposide 80 to 100 mg/m^2 + carboplatin AUC 5–6 or cisplatin 75 to 80 mg/m^2; Q3W for 4 cycles (can be given for an additional 2 cycles Q3W on weeks 12 and 15 (i.e. total of 6 cycles post-randomization at investigator's discretion) • After chemotherapy: Prophylactic	<u>Primary endpoint</u> • Overall survival[a] <u>Secondary endpoints</u> • Progression-free survival per RECIST 1.1 using investigator assessments[b] • Objective response rate[c] • Duration of response • Proportion of patients alive and progression free at 6 and 12 months[e] • Proportion of patients alive at 18 months[f] <u>Exploratory endpoints</u> • Time from randomization to second progression[g] <u>Other outcome measures</u> HRQoL, as assesed using the: • EORTC QLQ-C30 v3 (core) • EORTC QLQ-LC13 (lung cancer module)

Trial name, NCT-number [22, 36, 38, 45] [37]	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up period
			in a tolerable radiation plan, and WHO/ECOG performance status of 0 or 1	1500 mg + tremelimumab 75 mg + etoposide 80 to 100 mg/m^2 + carboplatin AUC 5–6 or cisplatin 75 to 80 mg/m^2; Q3W for 4 cycles • After chemotherapy: durvalumab 1500 mg (tremelimumab 75 mg at week 16) until disease progression	cranial irradiation, if clinically indicated	• Patient-reported outcomes version of the CTCAE • Patient's Global Impression of Change • 5-dimension, 5-level EuroQol questionnaire Hospital attendance and length of hospital/intensive care unit stay <u>There are three available data cut-offs:</u> Interim analysis: 11/03/2019 – 1 year follow-up. Final analysis: 27/01/2020 – 2 years follow-up. Global cohort long-term follow-up analysis: 22/03/2021 – 3 years follow-up.

[a]The time from the date of randomization until death due to any cause; [b]The time from the date of randomization until the date of objective disease progression or death (by any cause in the absence of progression); [c]The number (%) of patients with at least one visit assessment of complete response or partial response; [d]The best response a patient has had following randomization but prior to starting any subsequent anti-cancer therapy; [e]The Kaplan–Meier estimate of PFS at 6 and 12 months; [f]The Kaplan–Meier estimate of OS at 18 months; [g]The time from the date of randomization to the earliest of the progression events subsequent to that used for the PFS endpoint or death.

Source: Paz-Ares et al., 2019 [45].

6.1.2 Comparability of studies

Not relevant as CASPIAN is a head-to-head study and the only study considered in this application.

6.1.2.1 Comparability of patients across studies

From the 27th of March 2017, 268 patients were randomized in the durvalumab plus EP group and 269 in the EP alone group. Patients with ES-SCLC were recruited from 209 sites in 23 countries across Europe, Asia, North America, and South America. Key patient demographics and baseline characteristics are presented in Table 10.

Most (> 80%) patients were white, approximately two-thirds were male and the median age was 62–63 years. Most (> 90%) were current or ex-smokers. Approximately 10% had brain or CNS metastases at baseline and approximately 40% had liver metastases at baseline. The two treatment groups were generally well-balanced and the characteristics were consistent and representative of patients with ES-SCLC receiving first-line therapy.

Table 10. Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety

Characteristic (ITT population)	CASPIAN	
	Durvalumab + EP n = 268	EP n = 269
Median age, years (range)	62 (28–82)	63 (35–82)
Mean age, years (SD)	62.4 (8.12)	62.4 (8.34)
Male sex: n (%)	190 (70.9)	184 (68.4)
Race, %		
White	85.4	82.2
Asian	13.4	15.6
Other	1.1	2.2
WHO/ECOG PS, n (%)		
0	99 (36.9)	90 (33.5)
1	169 (63.1)	179 (66.5)
Smoking status, n (%)		
Non-smoker	22 (8.2)	15 (5.6)
Ex-smoker	126 (47)	127 (47.6)
Current smoker	120 (44.8)	127 (46.8)
AJCC stage IV, n (%)	240 (89.6)	245 (91.1)

Characteristic (ITT population)	CASPIAN	
	Durvalumab + EP n = 268	EP n = 269
Brain metastases at baseline, n (%)	28 (10.4)	27 (10.0)
Liver metastases at baseline, n (%)	108 (40.3)	104 (38.7)

Source: Paz-Ares et al., 2019 [45] (1-year interim analysis).

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

As described in section 6.1.1, CASPIAN is a phase 3, randomized, open-label, multicenter study in untreated adult patients with ES-SCLC and PS 0 or 1. According to Danish clinical expertise, the ITT population in CASPIAN is representative of the population considered eligible for treatment with durvalumab in combination with carboplatin/cisplatin and etoposide in Denmark. Nonetheless, the expert indicated that patient age at treatment initiation is higher in Danish clinical practice than in the CASPIAN trial i.e., around 70 years old [30].

Model baseline inputs related to patient characteristics are age at treatment initiation, body weight, body surface area and proportion of males/females All inputs were derived from the ITT population of the CASPIAN trial [45] and verified to be relevant for the Danish population by the Danish clinical expert [30].

Table 11. Characteristics in the relevant Danish population and the health economic model

	Value in Danish population [30, 45].	Value used in health economic model [30, 45].
Age (years) at treatment initiation	70	70
Body weight (Kg)	73.1	73.1
Body surface area (m2)	1.83	1.83
Proportion of males/females	69.6%/30.4%	69.6%/30.4%

6.1.4 Efficacy – results in CASPIAN

At the time of final data cut-off (27 January 2020), 56 (20.9%) patients in the durvalumab plus EP group and 31 (11.5%) patients in the EP group remained in the study. No patients in the EP group were receiving ongoing study treatment. In both arms, disease progression was the most common reason for treatment discontinuation, while death was the main reason for termination from the study. The proportion of patients that

discontinued the study in each arm and the reason for discontinuation are shown in Figure 5.

A summary of the key efficacy findings in CASPIAN is presented below.

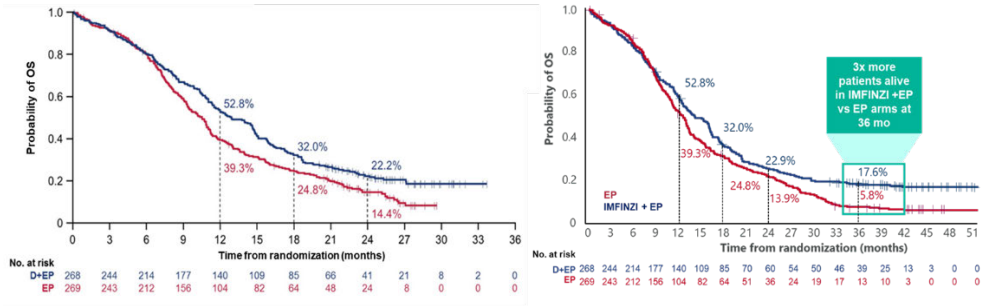
6.1.4.1 Primary outcome – Overall Survival (OS)

At the 2-year final CASPIAN analysis (DCO 27 January 2020 - median follow up of 25.20 months for durvalumab plus EP and 23.24 months for EP alone in censored patients), the median OS for durvalumab plus EP was 12.9 months versus 10.5 months for EP (HR, 0.75 (95% CI: 0.62, 0.91), p = 0.0032 (Figure 6) [38]. Furthermore, the OS benefit of durvalumab plus EP versus EP alone was evident in the subgroups of patients with or without brain metastasis at baseline; Durvalumab plus EP (versus EP alone) prolonged OS (hazard ratio, 95% confidence interval) in patients with (0.79, 0.44–1.41) or without (0.76, 0.62–0.92) brain metastases [52].

The results were consistent at the 3-years long-term follow-up (LTFU, DCO 22 March 2021 - median follow-up of 39.33 months for durvalumab plus EP and 37.98 months for EP). At this data cut, durvalumab plus EP significantly improved OS, reducing the risk of death by 29% compared with EP alone (HR, 0.71 [95% CI: 0.60, 0.86], p = 0.0003; Figure 6) [36, 37].

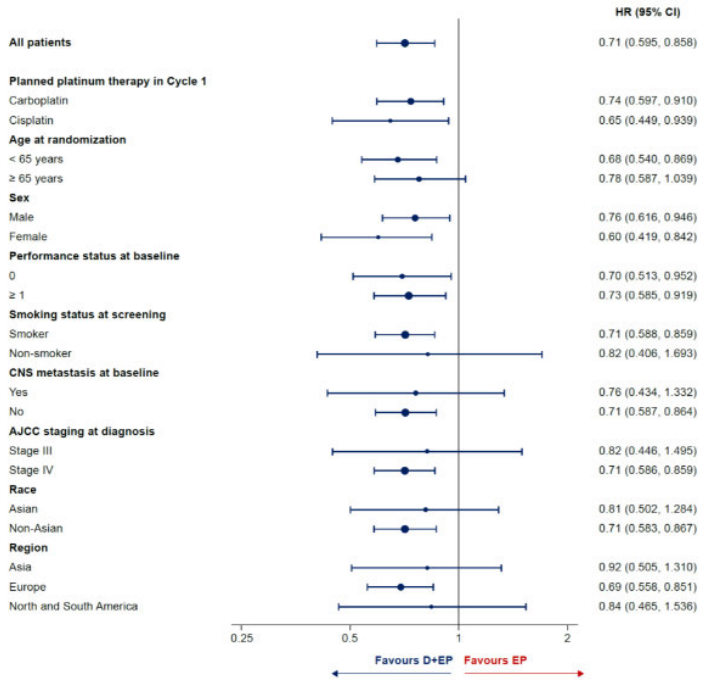
Durvalumab plus EP demonstrated a statistically significant and sustained improvement in OS versus EP alone at 12 (52.8% vs 39.3% patients alive, respectively), 24 (22.2% vs 14.4% patients alive, respectively) and 36 months (17.6% vs 5.8% patients alive, respectively) (Figure 6) [36-38]. Furthermore, the OS benefit of durvalumab plus EP versus EP alone was evident in all pre-specified subgroups considered (Figure 7) [36, 37].

Figure 6. Overall survival in CASPIAN; 2-year final analysis (DCO 27 January 2020, left) and 3-year LTFU analysis (DCO 22 March 2021, right)



Source: Paz-Ares et al., 2020 [38], CASPIAN 3-year LTFU CSR 2021 [36], Paz-Ares et al., 2022 [37].

Figure 7. Subgroup analysis of overall survival for CASPIAN; 3-year follow-up analysis (DCO 22 March 2021)



Source: CASPIAN 3-year LTFU CSR 2021 [36]; Paz-Ares et al., 2022 [37].

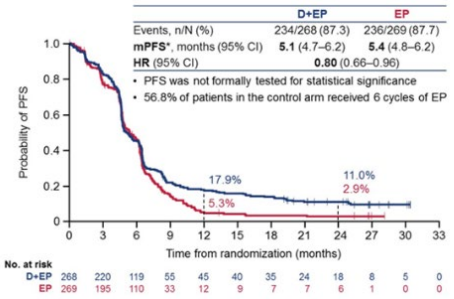
6.1.4.2 Secondary outcome – Progression-free survival (PFS) (final analysis, DCO 27 January 2020)

PFS could not be tested for statistical significance within the multiple-testing procedure of the trial. Nonetheless, durvalumab plus EP provided a clinically meaningful prolongation of PFS compared with EP alone. The KM plots for the two treatment groups are similar over the first 6 months, possibly reflecting the fact that over half (56.8%) of patients in the EP alone arm received 6 cycles of EP while patients in the durvalumab plus EP arm could only receive up to 4 cycles [45]. However, beyond 6 months, the survival curves separate showing an advantage for the durvalumab plus EP group, resulting in a 20% reduction in the risk of disease progression or death (HR, 0.80 [95% CI: 0.67, 0.96], p = 0.0157; Figure 8).

In the interim data cut at 12 months (11 March 2019), 17.9% of patients in the durvalumab plus EP arm remained progression-free, compared with 5.3% in the EP alone arm. At the final analysis (24 months, DCO 27 January 2020) this was 11.0% versus 2.9%, respectively [38]. The 36-month follow-up did not include additional PFS analyses. Nonetheless, 10.1% of patients were still on treatment with durvalumab at the time of data cut-off.

According to the subgroup analyses, PFS was consistently improved in the durvalumab plus EP arm compared with the EP alone arm e.g., PFS was prolonged with durvalumab plus EP, versus EP, in patients with (HR = 0.73, 95% CI: 0.42-1.29) or without (HR = 0.80, 95% CI: 0.66-0.97) brain metastases at baseline [52].

Figure 8. Progression-free survival in CASPIAN; final analysis (DCO 27 January 2020)



Landmark PFS, %	D+EP (n=268)	EP (n=269)
6 months	45.4	45.8
12 months	17.9	5.3
18 months	13.9	3.4
24 months	11.0	2.9

*Investigator assessed per RECIST v1.1.Source: Paz-Ares et al., 2020 [38] (2-year final analysis).

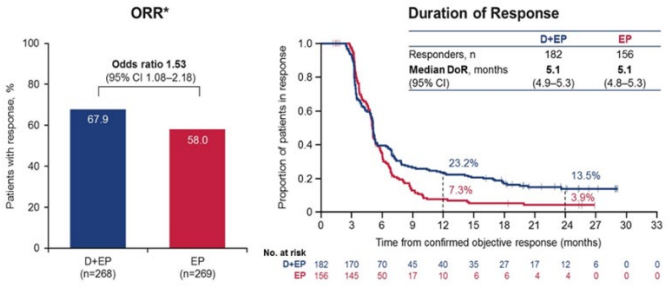
6.1.4.3 Secondary outcomes – Objective response rate (ORR) and duration of response (DoR) (final analysis, DCO 27 January 2020)

At the 2-year data cut, durvalumab plus EP was associated with an increase in confirmed and unconfirmed ORR of approximately 10% compared to EP alone (confirmed ORR, 68% vs 58%; OR, 1.53 [95% CI: 1.08, 2.19], p = 0.0173; Figure 9) [38, 51].

The median DoR was 5.1 months in both treatment arms. However, a difference in the proportion of patients in response in the two treatment arms can be observed after the first 6 months from the confirmed objective response. At 12 months, 23.2% of the durvalumab plus EP group remained in confirmed response, compared with 7.3% in the EP alone group. At 24 months, the proportions were 13.5% and 3.9%, respectively (Figure 9).

For the LTFU 3-year data cut, ORR and DoR were not updated.

Figure 9. a) Confirmed objective response rate and b) duration of response in CASPIAN; final analysis (DCO 27 January 2020)



*Investigator assessed per RECIST v1.1.

Source: Paz-Ares et al., 2020 [38] (2-year final analysis).

6.1.5 Efficacy – results per [study 2]

NA

7. Comparative analyses of efficacy

As a head-to-head study (CASPIAN) directly comparing the intervention and comparator is included as evidence of efficacy (see section 6), the following section describing comparative analysis is not of relevance. However, following the guidelines, Table 12 has been completed with the results from CASPIAN.

7.1.1 Differences in definitions of outcomes between studies

Not applicable.

7.1.2 Method of synthesis

Not applicable.

7.1.3 Results from the comparative analysis

The efficacy results from the CASPIAN pivotal study are summarized in Table 12. For further information on the efficacy results, see section 6.1.4.

Table 12. Results from the comparative analysis of durvalumab plus EP vs. EP alone for the first-line treatment of patients with extensive stage small-cell lung cancer

Outcome measure	Durvalumab plus EP (N=268)	EP alone (N=269)	Result
OS, DCO 27 January 2020	Median: 12.9 months	Median: 10.5 months	2.4 months HR, 0.75 (95% CI: 0.62, 0.91), p = 0.0032
OS, DCO 22 March 2021	Median: 12.9 months (95% CI: 11.3-14.7) / 10.5 months (95% CI: 9.3-11.2) for Durvalumab plus EP / EP alone Durvalumab plus EP reduced the risk of death by 29% compared with EP alone.		2.4 months HR, 0.71 (95% CI: 0.60, 0.86), p = 0.0003
PFS, DCO 27 January 2020	Median: 5.1 months (95% CI: 4.7, 6.2)	Median: 5.4 months (95% CI: 4.8, 6.2)	-0.3 months HR, 0.80 (95% CI: 0.66, 0.96)
PFS, DCO 11 March 2019	PFS rate at 12 months: 17.9% (95% CI: 13.5, 22.8)	PFS rate at 12 months: 5.3% (95% CI: 2.9, 8.8)	12.6%
ORR, DCO 27 January 2020	Confirmed ORR, 68%	Confirmed ORR, 58%	10%

Outcome measure	Durvalumab plus EP (N=268)	EP alone (N=269)	Result
			OR, 1.53 (95% CI: 1.08, 2.19), p = 0.0173
DoR, DCO 27 January 2020	Responders, n = 182 Median: 5.1 months (95% CI: 4.9, 5.3)	Responders, n = 156 Median: 5.1 months (95% CI: 4.8, 5.3)	0 months

Sources: Paz-Ares et al., 2020 [38] (2-year final analysis); CASPIAN 3-year LTFU CSR 2021 [36]; Paz-Ares et al., 2022 [37].

7.1.4 Efficacy – results in CASPIAN

See section 6.1.4.

8. Modelling of efficacy in the health economic analysis

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

The efficacy inputs used in the health economic model for Imfinzi® were sourced from the CASPIAN trial and were PFS and OS. The intention-to-treat (ITT) population from the CASPIAN trial was used to conduct the survival analyses for OS and PFS. The PFS analysis was based on the 2-year data from the CASPIAN trial (DCO 27 January 2020), whereas the OS data were based on the 3-year data from the CASPIAN trial (DCO 22 March 2021).

8.1.1 Extrapolation of efficacy data

8.1.1.1 Extrapolation of progression-free survival

Table 13 presents the summary of assumptions associated with extrapolation of PFS.

Table 13. Summary of assumptions associated with extrapolation of PFS

Method/approach	Description/assumption
Data input	ITT population of the CASPIAN trial (DCO 27 January 2020) [38]
Model	There were 16 models fitted to the individual subject data in CASPIAN: Standard parametric models: Exponential, Weibull, Gompertz, Lognormal, Loglogistic, Generalised gamma, Gamma.

Method/approach	Description/assumption
	Flexible parametric models: Spline Hazard (1 knot), Spline Hazard (2 knots), Spline Hazard (3 knots), Spline Odds (1 knot), Spline Odds (2 knots), Spline Odds (3 knots), Spline Normal (1 knot), Spline Normal (2 knots) and Spline Normal (3 knots).
Assumption of proportional hazards between intervention and comparator	No.
Function with best AIC fit	D+EP: Spline Odds 2 knots EP: Spline Hazard 3 knots
Function with best BIC fit	D+EP: Spline Odds 2 knots EP: Spline Hazard 3 knots
Function with best visual fit	Only evaluated for the chosen distribution: D+EP: Spline Hazard 3 knots EP: Spline Hazard 3 knots
Function with best fit according to evaluation of smoothed hazard assumptions	Not evaluated. The assessment of the statistical fit of the PFS was deemed acceptable to determine the distribution for PFS given the relative maturity of the PFS data in the CASPIAN trial (>87% of events observed) and reasonably similar extrapolations across distributions. The overall best fitting distribution was Spline Hazard 3 knots.
Validation of selected extrapolated curves (external evidence)	Not evaluated. The assessment of the statistical fit of the PFS was deemed acceptable to determine the distribution for PFS given the relative maturity of the PFS data in the CASPIAN trial (>87% of events observed) and reasonably similar extrapolations across distributions. The overall best fitting distribution was Spline Hazard 3 knots.
Function with the best fit according to external evidence	Not evaluated. The assessment of the statistical fit of the PFS was deemed acceptable to determine the distribution for PFS given the relative maturity of the PFS data in the CASPIAN trial (>87% of events observed) and reasonably similar extrapolations across distributions. The overall best fitting distribution was Spline Hazard 3 knots.
Selected parametric function in base case analysis	D+EP: Spline Hazard 3 knots EP: Spline Hazard 3 knots
Adjustment of background mortality with data from Statistics Denmark	Yes.

Method/approach	Description/assumption
Adjustment for treatment switching/cross-over	No.
Assumptions of waning effect	No.
Assumptions of cure point	No.

D+EP, durvalumab + etoposide + platinum-based chemotherapy; EP, etoposide + platinum-based chemotherapy

Figure 10 shows the curve for the spline hazard (3 knots) model fitted with the PFS data, over the entire time horizon of the model.

95% CI: 95% Confidence Interval; SoC: Standard of Care

See Appendix D for more details on the extrapolation of progression-free survival.

8.1.1.2 Extrapolation of overall survival

Table 14 presents the summary of assumptions associated with extrapolation of OS.

Table 14. Summary of assumptions associated with extrapolation of OS

Method/approach	Description/assumption
Data input	ITT population of the CASPIAN trial (DCO 22 March 2021) [36-38].
Model	There were 16 models fitted to the individual subject data in CASPIAN:

Method/approach	Description/assumption
	Standard parametric models: Exponential, Weibull, Gompertz, Lognormal, Loglogistic, Generalised gamma, Gamma. Flexible parametric models: Spline Hazard (1 knot), Spline Hazard (2 knots), Spline Hazard (3 knots), Spline Odds (1 knot), Spline Odds (2 knots), Spline Odds (3 knots), Spline Normal (1 knot), Spline Normal (2 knots) and Spline Normal (3 knots).
Assumption of proportional hazards between intervention and comparator	No.
Function with best AIC fit	D+EP: Spline Hazard 3 knots EP: Spline Hazard 2 knots
Function with best BIC fit	D+EP: Spline Hazard 3 knots EP: Spline Odds 1 knot
Function with best visual fit	Standard survival distributions do not appear to be a good fit, whereas spline models showed good fit to the data. However, it was difficult to select the most appropriate model based on visual factors.
Function with best fit according to evaluation of smoothed hazard assumptions	Not evaluated.
Validation of selected extrapolated curves (external evidence)	Compared with real world data (Flatiron [from the assessment of atezolizumab [53]] and SEER [54]). Validated by a Danish clinical expert [30].
Function with the best fit according to external evidence	D+EP: Spline Odds 2 knots EP: Spline Odds 2 knots
Selected parametric function in base case analysis	D+EP: Spline Odds 2 knots EP: Spline Odds 2 knots
Adjustment of background mortality with data from Statistics Denmark	Yes.
Adjustment for treatment switching/cross-over	No.
Assumptions of waning effect	No.
Assumptions of cure point	No.

D+EP, durvalumab + etoposide + platinum-based chemotherapy; EP, etoposide + platinum-based chemotherapy

Figure 11 shows the curve for the spline odds (2 knots) model fitted with the OS data, over the entire time horizon of the model.

See Appendix D for more details on the extrapolation of overall survival.

8.1.1.3 Extrapolation of time to treatment discontinuation

In the base case analysis, treatment duration was set to be equal to progression-free survival, in both the intervention and comparator arms. This was validated by a Danish clinical expert, who mentioned it is not common to treat the ES-SCLC patient population beyond disease progression [30]. Please refer to Section 8.1.1.1 on the extrapolation of PFS for more details on the extrapolation of TTD.

8.1.2 Calculation of transition probabilities

Not applicable as the model is a partitioned survival model.

Table 15. Transitions in the health economic model

Health state (from)	Health state (to)	Description of method	Reference
Not applicable.			

8.2 Presentation of efficacy data from [additional documentation]

Not applicable.

8.3 Modelling effects of subsequent treatments

Patients who are alive and experience disease progression following treatment with the combination of Imfinzi®, etoposide and carboplatin/cisplatin or the combination of etoposide and carboplatin/cisplatin move to the progressed health state and may receive subsequent treatment (both second-line and third-line treatment were included in the health economic analysis).

The list of subsequent therapies, respective proportion of patients and time on treatment included in the analysis were sourced from CASPIAN trial data. Regimens available in the model are those reported as being used in at least 2% of patients at the corresponding line of treatment in CASPIAN. This information was used to calculate the costs associated with subsequent treatment.

Regarding efficacy, no additional adjustment on survival was required as any survival benefit attributable to subsequent treatment is implicitly captured in the OS data. Further details on the proportion of patients, treatment duration and costs for subsequent treatment are presented in Section 11.6.

8.4 Other assumptions regarding efficacy in the model

Not applicable. All efficacy inputs used in the model were sourced from the CASPIAN trial.

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

Table 16 - Table 18 present the estimates used in the model concerning PFS, OS and TTD, respectively.

[redacted]

	Modelled average PFS (reference in Excel)	Modelled median PFS (reference in Excel)	Observed median from relevant study
Durvalumab + EP	[redacted]	[redacted]	[redacted]
EP	[redacted]	[redacted]	[redacted]

[redacted]

	Modelled average OS (reference in Excel)	Modelled median OS (reference in Excel)	Observed median from relevant study
Durvalumab + EP	[redacted]	[redacted]	[redacted]
EP	[redacted]	[redacted]	[redacted]

[redacted]

	Modelled average TTD (reference in Excel)	Modelled median TTD (reference in Excel)	Observed median from relevant study
Durvalumab + EP	[redacted]	[redacted]	[redacted]
EP	[redacted]	[redacted]	[redacted]

Table 19 summarizes the modelled average treatment length and time in PFS and OS.

[redacted]

Treatment	Treatment length [months]	PFS [months]	OS [months]
Durvalumab + EP	[redacted]	[redacted]	[redacted]
EP	[redacted]	[redacted]	[redacted]

9. Safety

9.1 Safety data from the clinical documentation

Patients in the durvalumab plus EP group received a median (range) of 7 (1–52) doses of durvalumab and 24.2% of patients received 12 or more doses. 32 (12.1%) patients received at least 28 cycles of durvalumab (representing approximately 2 years of dosing) and 24 (9.1%) of patients received durvalumab for 3 or more years [36, 37]. The median

duration of exposure to durvalumab plus EP was 28 weeks and was thus long enough to evaluate the safety profile of the combination regimen [55].

The median (range) number of EP cycles received was 4 (1–6) in the durvalumab plus EP group and 86.8% of patients received 4 cycles or more. In the EP alone group, the median number of EP cycles received was 6 and 56.8% of patients received 6 cycles. Therefore, exposure to EP was greater in the EP alone group, as expected from the study design.

Approximately 50% of patients in both groups required dose delays, largely due to AEs.

The overall safety profile was comparable between the durvalumab plus EP and the EP alone groups and was consistent with the known safety profile of individual treatment components. At the 36-month LTFU, there were no new safety signals identified or significant changes in the safety profile for durvalumab plus EP versus EP alone, demonstrating consistency in patient tolerability.

The overview of safety events is shown in Table 20.

Table 20. Overview of safety events. Data from the 27 Jan 2020 DCO unless otherwise referenced - Safety analysis set

	Durvalumab + EP (N=265) [38].	EP alone (N=266) [38].	Difference, % (95 % CI)
Number of adverse events, n	Not available (n.a.)	n.a.	n.a.
Number and proportion of patients with ≥1 adverse events, n (%)	260 (98.1%)	258 (97.0%)	1.1% (-1.75 - 4.10) RR=1.006 (0.89 -1.14)
Number of serious adverse events, n [36, 37]	n.a.	n.a.	n.a.
Number and proportion of patients with ≥ 1 serious adverse events, n (%) [36, 37]	86 (32.5%)	97 (36.5%)	4.4% (-3.62-12.34) RR=0.98(0.71 - 1.17)
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 (%)	165 (62.3%)	167 (62.8%)	0.5%(-7.64 - 8.63) RR=0.99(0.84 to 1.18)

	Durvalumab + EP (N=265) [38].	EP alone (N=266) [38].	Difference, % (95 % CI)
Number of adverse reactions, n	n.a.	n.a.	n.a.
Number and proportion of patients with ≥ 1 adverse reactions*, n (%)	237 (89.4%)	239 (89.8%)	0.4% (-4.84 - 5.65) RR=0.99(0.88 to 1.14)
Number and proportion of patients who had a dose reduction, n (%)**	Etoposide: 236 (89.1%) Carboplatin: 186 (89.4%) Cisplatin: 60 (92.3%) Mean relative dose intensity of durvalumab: 95.30%	Etoposide: 226 (85.0%) Carboplatin: 186 (89.4%) Cisplatin: 55 (82.1%)	Etoposide: 4.1% RR = 1.026 (**0.89 - 1.17**) Carboplatin: 0% RR = 1.002(0.86 - 1.17) Cisplatin: 10.2% 95 % CI n.a.
Number and proportion of patients who discontinued treatment regardless of reason, n (%) [45]	Patients who discontinued durvalumab: 233 (87.9%) Patients who discontinued EP***: 42 (15.8%)	Patients who discontinued EP***: 76 (28.6%)	59.3%/-12.8% 95 % CI n.a.
Number and proportion of patients who discontinue treatment due to adverse events**, n (%)**	27 (10.2%)	25 (9.4%)	0.8% (-4.84 - 5.65) RR=1.08(**0.64 - 1.81**)

*Causally related to any of the study treatments, as assessed by the investigator. Missing responses are counted as related. ** Dose reduction is based on Exposure eCRF item "Action taken" = "Dose reduced" and only considered as a reduction if the previous dose is greater than the current dose. For Etoposide, only the first administration within a cycle is considered. *** A patient is considered as having discontinued EP combination when all molecules are discontinued. ****AEs on the AE CRF form with Action taken = "Drug permanently discontinued" for at least one treatment.

In both groups, haematological AEs were the most frequently reported grade 3/4 AEs and the only grade 3/4 AEs reported in more than 5% of patients (Table 21). The incidence of grade 3/4 neutropenia, anaemia and thrombocytopenia were higher in the control group. The only grade 3/4 AEs reported to occur at a higher incidence (difference of ≥ 1.5%) in the durvalumab plus EP group were increased lipase levels, increased amylase levels and hypertension, while pneumonia occurred more frequently in the control group.

Table 21. Incidence of grade 3/4 AEs reported in at least 2% of patients in either treatment group in CASPIAN

AEs, n (%)	Durvalumab + EP N = 265	EP N = 266
Any grade 3/4 AEs	165 (62.3)	167 (62.8)
Neutropenia	64 (24.2)	88 (33.1)
Anaemia	24 (9.1)	48 (18)
Thrombocytopenia	15 (5.7)	25 (9.4)
Febrile neutropenia	14 (5.3)	17 (6.4)
Neutrophil count decreased	17 (6.4)	17 (6.4)
Leukopenia	17 (6.4)	14 (5.3)
Hyponatraemia	10 (3.8)	7 (2.6)
Pneumonia	5 (1.9)	9 (3.4)
White blood cell count decreased	4 (1.5)	6 (2.3)
Lipase increased	9 (3.4)	4 (1.5)
Platelet count decreased	4 (1.5)	6 (2.3)
Hypertension	8 (3)	1 (0.4)
Amylase increased	6 (2.3)	1 (0.4)

Paz-Ares *et al.*, 2019

The most common serious adverse events (frequency ≥ 2 patients in any treatment group in CASPIAN) are presented in Table 22. There were no serious adverse events occurring in ≥ 5% of patients recorded in CASPIAN.

Table 22. Most common SAEs (frequency ≥ 2 patients in any treatment group in CASPIAN (DCO 11 March 2019)

Adverse events	Durvalumab + EP (N=265)		EP alone (N=266)	
	Number of patients with adverse events	Number of adverse events	Number of patients with adverse events	Number of adverse events
Adverse event, Number (%) of patients				
Febrile neutropenia	12 (4.5)	n.a.*	12 (4.5)	n.a.
Pneumonia	6 (2.3)	n.a.	11 (4.1)	n.a.
Anaemia	5 (1.9)	n.a.	12 (4.5)	n.a.

Adverse events	Durvalumab + EP (N=265)		EP alone (N=266)	
Pancytopenia	4 (1.5)	n.a.	3 (1.1)	n.a.
Hyponatraemia	2 (0.8)	n.a.	4 (1.5)	n.a.
Neutropenia	2 (0.8)	n.a.	7 (2.6)	n.a.
Diarrhoea	2 (0.8)	n.a.	4 (1.5)	n.a.
Pneumonitis	3 (1.1)	n.a.	3 (1.1)	n.a.
Chronic obstructive pulmonary disease	3 (1.1)	n.a.	1 (0.4)	n.a.
Septic shock	3 (1.1)	n.a.	0	n.a.
Sepsis	3 (1.1)	n.a.	1 (0.4)	n.a.
Thrombocytopenia	1 (0.4)	n.a.	9 (3.4)	n.a.
Vomiting	0	n.a.	3 (1.1)	n.a.
Dyspnoea	0	n.a.	3 (1.1)	n.a.
Cerebrovascular accident	0	n.a.	3 (1.1)	n.a.
Hypokalaemia	0	n.a.	3 (1.1)	n.a.

[36, 37, 45]*We do not have exact numbers for events.

Given previous trends in the modelling of adverse events in oncology, the analysis considered only grade 3 or higher treatment-emergent adverse events occurring in greater than 2% of any included trial arm.

The decision to include these adverse events is based on their meaningful impact on treatment costs and patient quality of life. The proportion of patients experiencing the selected list of adverse events was sourced from the CASPIAN trial.

Table 23 presents the adverse events included in the base case of the health economic analysis. The costs associated with these AEs are presented in Table 37.

Table 23. Adverse events used in the health economic model

Adverse events	Durvalumab + EP	EP		
	Frequency used in economic model for intervention	**Frequency used in economic model for comparator**	**Source**	**Justification**
Adverse event, n (%)				

Adverse events	Durvalumab + EP	EP		
Anaemia	7.9%	14.3%	Paz-Ares et al., 2019 [45], 3-year global LTFU CASPIAN CSR [36]	See text above.
Diarrhoea (Grade 3/4)	0.8%	0.8%		
Febrile Neutropenia	4.9%	6.4%		
Leukopenia	5.7%	5.3%		
Lipase Increased	3.0%	0.4%		
Nausea/Vomiting	0.0%	2.6%		
Neutropenia	23.0%	32.3%		
Neutrophil Count Decrease	6.0%	6.4%		
Platelet Count Decrease	1.5%	2.3%		
Pneumonia/Pneumonitis	0.8%	0.4%		
Thrombocytopenia	5.3%	9.0%		
WBC Count Decrease	1.5%	2.3%		

EP, etoposide + platinum-based chemotherapy

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

Not applicable.

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

According to the Danish DMC guidelines, HRQoL must be based on the generic measuring instrument EQ-5D-5L [44]. The CASPIAN trial assessed QoL using this instrument. Therefore, the focus of this section is on the EQ-5D-5L data derived from the CASPIAN trial (Table 24).

Table 24. Overview of included HRQoL instruments

Measuring instrument	Source	Utilization
EQ-5D-5L	CASPIAN clinical study	The EQ-5D-5L data collected in the CASPIAN clinical study was used to derive the HSUVs (health state utility values).

10.1 Presentation of the health-related quality of life

10.1.1 Study design and measuring instrument

QoL was assessed within CASPIAN using the EQ-5D-5L. The EQ-5D is a standardised measure of self-reported health, developed by the EuroQol Group. There are 5 dimensions or domains: mobility, self-care, usual activities, pain and discomfort, and anxiety and depression. In the 5-level ('5L') version of the questionnaire, there are 5 possible levels of response that a subject can give for each dimension: no, mild, moderate, severe, and severe / unable to.

An EQ-5D profile consists of a 5 digit value, with each digit representing a subject's response for each domain. The EQ-5D profiles can be converted to a health state utilities using country-specific value sets that are reflective of the country of interest. The maximum health state utility value is 1, which represents 'full health'. A value of 0 corresponds to a quality of life equivalent to being dead, and negative values are possible which represent a quality of life worse than death.

EQ-5D-5L data were collected for the ITT population in the CASPIAN clinical study in line with the clinical study protocol. The analysis included all completed EQ-5D-5L measures (excluding EQ-5D-5L with any missing domain responses).

In total, 4,264 EQ-5D-5L observations were available from 520 patients. Of these, 3,593 observations were recorded pre-progression, and 671 were recorded after progression.

Preference weights based on a representative cross section of the Danish adult population [56] were used to obtain the HSUVs.

Both the used instrument and the preference weights are in accordance with the DMC guidelines [44].

10.1.2 Data collection

In the CASPIAN clinical trial, EQ-5D-5L questionnaires were completed at baseline, and at the beginning of each cycle of therapy (i.e. 3-weekly during the chemotherapy phase of the trial and 4-weekly thereafter) until disease progression. Thereafter, measures were completed at day 28, 2 months post-disease progression and then every 8 weeks (Q8W; ± 2 weeks) until second progression/death (whichever comes first).

[redacted]

	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted] 1				
[redacted]				
[redacted]				

	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				

	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				

	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
[redacted]				

10.1.3 HRQoL results EQ-5D5L

The descriptive summary statistics of EQ-5D-5L utility scores at relevant data collection time points are presented in Table 26. Figure 12 shows the mean change from baseline in EQ-5D-5L scores through different data collection time points for both Durvalumab + EP and EP alone.

[redacted]

		Baseline	Cycle 5 Day 1	Cycle 10 Day 1	Cycle 15 Day 1	Cycle 20 Day 1	Cycle 25 Day 1	Cycle 30 Day 1	Follow-up 28 days	Follow-up 2 months	Follow-up 4 months	Follow-up 6 months	Follow-up 8 months	Follow-up 10 months	Follow-up 12 months
Number of patients	Durva + EP	245	180	60	36	27	18	10	136	70	61	32	16	13	8
	EP	245	145	24	9	2	2	3	89	51	34	21	10	4	1

Durva, Durvalumab; EP, Etoposide + platinum-based chemotherapy. *The UK valuation set was used for this graph as the corresponding values using the Danish value set were not available.

Table 26. HRQoL EQ-5D-5L summary statistics

	Durvalumab + EP		EP alone		Durvalumab + EP vs. EP alone
	N (observations)	Mean (SD)	N (observations)	Mean (SD)	Difference (95% CI) p-value
Baseline	232	0.78 (0.25)	220	0.77 (0.27)	0.01(- 0.038 – 0.0581)) P=0.6829
All visits	2,553	0.87 (0.17)	1,648	0.84 (0.19)	0.03(0.019 – 0.041) P < 0.0001 .
Pre-progression	2,144	0.87 (0.17)	1,386	0.85 (0.19)	0.02(0.008 – 0.320) P=0.0011
Post-progression	409	0.85 (0.21)	262	0.81 (0.23)	0.04(0.0061 – 0.0739) P=0.0207)

EP, Etoposide + platinum-based chemotherapy; n.a., not available; SD, standard deviation

10.1.4 Study design and measuring instrument EQ-5D-VAS

EQ-5D-VAS was also recorded. It was measured as the mean change in comparison with the start of treatment until progression or month 12 (whichever occurred earlier).

10.1.5 Data collection EQ-5D-VAS

Below in Table 27 the data collection scheme and cycles are captured.

Table 27 HRQoL EQ-5D-VAS summary statistics

	HRQoL population N	Missing N (%)	Completion N (%)	Mean change from baseline
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				

	HRQoL population N	Missing N (%)	Completion N (%)	Mean change from baseline
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Follow-up 12 [redacted]	[redacted]	[redacted]	[redacted]	[redacted]

10.1.6 HRQoL results EQ-5D-VAS

Mean change from baseline data from Table 27 is shown in Figure 13.

[redacted]

Durva, Durvalumab; EP, Etoposide + platinum-based chemotherapy.

[redacted]

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

10.2.1 HSUV calculation

The statistical relationship between EQ-5D-5L health state utility and treatment, and health status was assessed using regression analysis. To account for the repeated measurements in the study, a mixed model for repeated measures (MMRM) method was used to model EQ-5D-5L health state utilities [57]. The MMRM analysis was performed on a dataset excluding any observations recorded after the time of censoring for progression. Due to censoring, the EQ-5D-5L observations obtained during this period have an unknown/missing health status and therefore, must be omitted from the analysis.

The MMRM analysis was performed using the restricted maximum likelihood method (REML) with the following covariates included as fixed effects:

- (Randomised) Treatment
- Progression status (pre-progression, post-progression)

- Treatment + Progression status
- Treatment + Progression status + Treatment * Progression status (Both terms and their interaction included)

The correlation of repeated utility measurements within subjects over time was captured via the specification of covariance structures for the MMRM. The results presented are from the models using the first covariance structure in the sequence that successfully converged for all models (i.e., for each of the 4 covariate options). If for a particular set of covariates none of the models converged, then no results were presented for that model, and the remaining model results were based on the most flexible covariance structure for which the models converged.

The hierarchy of covariance structures tested, in order of most to least flexible, is shown below:

1. Unstructured – each visit is allowed to have a different variance, and each combination of visits is allowed to have a different covariance.
2. Toeplitz with heterogeneity – each visit is allowed to have a different variance, covariances between measurements depend on how many visits apart they are.
3. **Autoregressive, order 1** (AR(1)) with heterogeneity – each visit is allowed to have a different variance, and covariances decrease based on how many visits apart they are. Covariances decrease towards zero as the number of visits between observations increases.
4. Toeplitz – as above for number 2, but each visit shares the same variance.
5. Autoregression, order 1 (AR(1)) – as above for number 3, but each visit shares the same variance.

For each model, the marginal ('least square') means are presented including 95% confidence intervals (based on robust standard error estimates). The marginal ('least square') mean provides a model-based estimate of the mean utility score by status (treatment and/or Progression status) that is averaged over observations and with adjustment for repeated measures. The estimated marginal mean and its associated standard error or confidence interval were used as utility inputs in the present cost-utility model.

The results presented in this section were generated from MMRMs with the following covariance structure: Autoregressive - order 1 (Table 28). The best fitting model in terms of AIC was the model including a term for Progression status.

Table 28. Goodness of fit statistics of the MMRM (covariance structure: Autoregressive - order 1)

Description	converges	AIC	BIC
Treatment	TRUE	-4279.3	-4270.8
Progression status	TRUE	-4285.5	-4277.0

Treatment + Progression status	TRUE	-4282.1	-4273.6
Treatment * Progression status	TRUE	-4276.2	-4267.7

Table 29 summarizes the marginal means produced from each model. The HSUV used in the health economic model were the ones generated by the model including a term for Progression status (highlighted in bold).

[redacted]

Parameter	Treatment	Progression status	Treatment + Progression status	Treatment * Progression status
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				

Results for the point estimates from each model are presented in the Appendix F.

The obtained HSUV were age-adjusted in the model, in accordance with the recommendations from the DMC [44].

10.2.1.1 Mapping

Not applicable.

10.2.2 Disutility calculation

Utility decrements associated with AEs were not explicitly collected in the CASPIAN trial. Instead, disutility values were found from the literature (most relevant source for utility was considered) and the duration of each event was either from the CASPIAN trial or literature (Table 30). Disutility values are applied as a one off-decrement in the model. Please see Table 60 in Appendix.

10.2.3 HSUV results

Both HSUV and utility decrements used in the base case of the health economic analysis are shown in Table 30. As previously mentioned, the HSUVs selected for the base case were the ones generated by the model, including a term for Progression status, with an Autoregressive - order 1 covariance structure (highlighted in bold in Table 29). Regarding the AE duration, if no sources were identified, an assumption was made due to the marginal effect of the duration on the ICER. A scenario analysis in which AE duration is set to one month (30 days) is shown in Table 47.

Table 30. Overview of health state utility values (base case) and disutilities

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
HSUVs				
Progression-free state	0.834 [0.819, 0.849]	EQ-5D-5L	DK	NA
Progressed state	0.802 [0.781, 0.824]	EQ-5D-5L	DK	NA
Disutilities				
Anaemia	-0.073 [48]		NA	Used fatigue value. Duration: 14 days. Source: Assumption
Diarrhoea (Grade 3/4)	-0.047 [48]		NA	Duration: 32.4 days. Source: CASPIAN [36, 38]
Febrile Neutropenia	-0.090 [48]		NA	Duration: 7 days. Source: de Naurois 2010 [58]
Leukopenia	-0.090 [48]		NA	Utility decrement is same as neutropenia. Duration: 10 days (same as neutropenia). Source: Assumption

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
Lipase Increased	-0.019		NA	Assumption Duration: 11 days. Source: [59]
Nausea/Vomiting	-0.048 [48]		NA	Duration: 5 days. Source: Assumption
Neutropenia	-0.090 [48]		NA	Duration: 10 days. Source: Assumption
Neutrophil Count Decrease	-0.090 [48]		NA	Utility decrement is same as neutropenia. Duration: 10 days. Source: Assumption
Platelet Count Decrease	-0.090 [49]		NA	Utility decrement is same as thrombocytopenia Duration: 10 days (same as neutropenia). Source: Assumption
Pneumonia/Pneumonitis	-0.090 [47]		NA	Duration: 64.9 days. Source: CASPIAN [36, 38]
Thrombocytopenia	-0.053 [49]		NA	Duration: 10 days (same as neutropenia). Source: Assumption
WBC Count Decrease	-0.090 [48]		NA	Duration: 10 days (same as neutropenia). Source: Assumption
Hepatitis	-0.038 [46]		NA	Duration: 63 days. Source: CASPIAN [36, 38]
Hyperthyroidism	-0.095 [50]		NA	Duration: 66.2 days. Source: CASPIAN [36, 38]
Hypothyroidism	-0.106 [50]		NA	Duration: 66.6 days. Source: CASPIAN [36, 38]
Infusion-Related Reaction	-0.150		NA	Utility decrement based on an assumption. Duration: 2.1 days. Source: CASPIAN [36, 38]
Pneumonitis	-0.090 [47]		NA	Duration: 64.9 days. Source: CASPIAN [36, 38]

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
Rash	-0.032 [48]		NA	Duration: 43.4 days. Source: CASPIAN [36, 38]

CI, confidence interval; DK, Denmark; HSUV, health state utility value; NA, Not applicable

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

Not applicable.

10.3.1 Study design

Not applicable.

10.3.2 Data collection

Not applicable.

10.3.3 HRQoL Results

Not applicable.

10.3.4 HSUV and disutility results

Not applicable.

Table 31. Overview of health state utility values [and disutilities]

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
NA				
NA	NA	NA		
NA	NA	NA		
NA				
NA	NA	NA		
NA				

Table 32. Overview of literature-based health state utility values

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
NA				
NA	NA	NA	NA	NA
NA	NA	NA	NA	NA
NA	NA	NA	NA	NA
NA				
NA	NA	NA	NA	NA
NA				
NA	NA	NA	NA	NA

11. Resource use and associated costs

Cost parameters included in the base case of the health economic analysis were medicine acquisition and administration costs (both first-line and subsequent treatment), costs associated with disease management and the management of adverse events, and non-medical costs. All costs are reported in DKK at the 2024 cost level. Resource use was validated as relevant to the Danish setting by a Danish clinical expert [30].

11.1 Medicine costs - intervention and comparator

The modelled dose, RDI, treatment administration frequency and assumption on vial sharing are presented in Table 33. The acquisition costs for the intervention and comparator are summarized in Table 34.

In the base case analysis, it was assumed no vial sharing (wastage). Total vial sharing (no wastage) was tested in scenario analyses.

Also in the base case analysis, treatment duration was set to be equal to progression-free survival, in both the intervention and comparator arms. This was validated by a Danish clinical expert, who mentioned it is not common to treat this patient population beyond disease progression [30].

Durvalumab regimen (dose, length of treatment course, etc.) was obtained from CASPIAN trial data. The posology for all other included treatments was sourced from key pivotal trials, or corresponding Summary of Product Characteristics (SmPC) or label.

Table 33. Medicine costs used in the model

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
Intervention: Durvalumab + EP				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

EP, etoposide + platinum-based chemotherapy; Q3W, once every three weeks; Q4W, once every four weeks.

Table 34. Medicine costs used in the model (cost information)

Medicine	Strength	Package size	Pharmacy purchase price [DKK]
Intervention: Durvalumab + EP*			
Durvalumab (Imfinzi®)	50 mg/ml	2.4 ml	4,278.62
	50 mg/ml	10 ml	17,677.28
Comparator: EP			
Etoposide "Fresenius Kabi"	20 mg/ml	5 ml	71.37
Etoposide "Fresenius Kabi"	20 mg/ml	25 ml	278.72
Carboplatin "Accord"	10 mg/ml	15 ml	295.00
Carboplatin "Accord"	10 mg/ml	45 ml	226.00
Cisplatin "Accord"	1 mg/ml	50 ml	100.00
Cisplatin "Accord"	1 mg/ml	100 ml	200.00

*The costs presented for the comparator (EP) are also applicable in the intervention arm. EP, etoposide + platinum-based chemotherapy. Source: Medicinpriser.dk 2024-04-11 [60]).

11.2 Administration costs

An administration cost is associated with IV treatments. Table 35 summarizes the standard chemotherapy cost used in the base case analysis. If treatments were administered orally, it was assumed there was no administration cost.

Table 35. Administration costs used in the model

Administration type	Frequency	Unit cost [DKK]	DRG code	Reference
Standard chemotherapy	Dependent on the administration frequency of the different medicines	1,625	09MA98 "MDC09 1-dagsgruppe, pat. mindst 7 år"	Sundhedsdatastyrelsen [61]

11.3 Medicine costs – co-administration

Not applicable.

11.4 Disease management costs

The costs associated with the health care resource use and respective utilization frequencies are presented in Table 36. Both resource items and respective frequencies were validated by a Danish clinical expert as relevant for the Danish setting [30].

Table 36. Disease management costs used in the model

Activity	Proportion of patients (%)	Frequency	Unit cost [DKK]	DRG code	Reference
Health care visits					
Oncology visit (oncologist and nurse)	100%	Progression-free: 1.45 (monthly), once every 3 weeks.	1,625	09MA98 "MDC09 1-dagsgruppe, pat. mindst 7 år"	Sundhedsdatastyrelsen. DRG-takster 2024 [61]
	50%	Progressed: 1 (monthly)			
Scans and monitoring					

Activity	Proportion of patients (%)	Frequency	Unit cost [DKK]	DRG code	Reference
CT-scan	100%	0.5 scan (monthly), once every 2nd month	2,021	30PR07 "CT-scanning, ukompliceret, el. Osteodensitometri ".	Sundhedsdatastyrelsen. DRG-takster 2024 [61]
ECG	100%	0.15 exams (monthly) - estimated to 0.1 - 0.2 monthly by the clinician	196	"Elektrokardiogram (EKG) - 12 afledninger".	Takstkort 29A - Laboratorieundersøgelser [62]
Prophylactic cranial irradiation (Only in the comparator arm, as in CASPIAN, PCI was allowed only in the EP arm)	30%	10 fractions	44,255	Assumed same as other radiotherapy. 27MP05 Strålebehandling, konventionel, mindst 5 fraktioner.	Sundhedsdatastyrelsen. DRG-takster 2024 [61]
Thoracic & other radiotherapy (progression)	20%	10 fractions	44,255	27MP05 Strålebehandling, konventionel, mindst 5 fraktioner.	Sundhedsdatastyrelsen. DRG-takster 2024 [61]
Blood test to estimate GFR	50%	1 test (monthly)	75	"7112 P-kreatinin"	Takstkort 29A - Laboratorieundersøgelser [62]

11.5 Costs associated with management of adverse events

The costs associated with AEs are summarized in Table 37. The respective frequencies for the AEs included in the base case are described in Table 23.

AEs are applied as a one-off event in the first model cycle. As mentioned in Section 9.1, in the base case analysis, only grade 3 or higher treatment-emergent adverse events occurring in greater than 2% of any included trial arm were included.

Table 37. Cost associated with management of adverse events

	Unit cost [DKK]	DRG code/source
Anaemia	3,959	16MP06 Mangelanæmier, full cost divided by the number of days (21). Source: Sundhedsdatastyrelsen. DRG-takster 2024 [61]
Febrile neutropenia	10,430	48PR02 Immunmodulerende behandling, 1-dags (DKK 10,545) + 16PR02 Transfusion af blod (DKK 3,969). Source: Sundhedsdatastyrelsen. DRG-takster 2024 [61]
Leukopenia	37,129	16MA03 Granulo- og trombocytopeni. Source: Sundhedsdatastyrelsen. DRG-takster 2024 [61]
Lipase increased	1,989	17MA98 MDC17 1-dagsgruppe, pat. mindst 7 år. Source: Sundhedsdatastyrelsen. DRG-takster 2024 [61]
Nausea/vomiting	3,419	06MA17 Observation for sygdom i fordøjelsesorganerne, u. endoskopi. Source: Sundhedsdatastyrelsen. DRG-takster 2024 [61]
Neutropenia	37,129	16MA03 Granulo- og trombocytopeni. Source: Sundhedsdatastyrelsen. DRG-takster 2024 [61]
Neutrophil count decrease	1,989	17MA98 MDC17 1-dagsgruppe, pat. mindst 7 år. Source: Sundhedsdatastyrelsen. DRG-takster 2024 [61]
Platelet count decrease	1.989	17MA98 MDC17 1-dagsgruppe, pat. mindst 7 år. Source: Sundhedsdatastyrelsen. DRG-takster 2024 [61]
Thrombocytopenia	37,129	16MA03 Granulo- og trombocytopeni. Source:

	Unit cost [DKK]	DRG code/source
		Sundhedsdatastyrelsen. DRG-takster 2024 [61]
WBC count decrease	1,989	17MA98 MDC17 1-dagsgruppe, pat. mindst 7 år. Source: Sundhedsdatastyrelsen. DRG-takster 2024 [61]

11.6 Subsequent treatment costs

The model estimates the cost of subsequent lines of treatment after progression, as one-off costs. Subsequent treatments were accounted for in terms of costs, with efficacy assumed to remain equal to extrapolated estimates (see Section 8.3). Costs were calculated in terms of proportion of patients receiving subsequent therapies, the distribution of treatments used at each line and time on treatment. The proportion of patients receiving subsequent treatment are sourced from the CASPIAN trial and are presented in Table 38.

[redacted]

	Durvalumab + EP	Etoposide + Platinum
Patients receiving 2nd line therapy post-1st line discontinuation	[redacted]	[redacted]
Patients receiving 3rd line therapy post-2nd line discontinuation	[redacted]	[redacted]

Source: CASPIAN

The list of subsequent therapies included in the analysis were sourced from CASPIAN trial data. Regimens available in the model are those reported as being used in at least 2% of patients at the corresponding line of treatment in CASPIAN and are described in Table 39.

[redacted]

Regimen	D+EP				EP			
	2nd Line		3rd+ Line		2nd Line		3rd+ Line	
Single Agent Chemotherapy	N	%	N	%	N	%	N	%
[redacted]	[redacted]							
[redacted]	[redacted]							

Durations of subsequent therapies are based on reported means from the CASPIAN trial (calculated using an exponential assumption based on the median time on treatment).

For the time spent on each subsequent therapy, data from CASPIAN was used. Based on the trial data, parametric models were built to estimate the mean duration of subsequent treatment for the following components:

- EP or D+EP as first line treatment
- 2nd line or 3rd line
- Immunotherapy, Chemotherapy or Single Agent Chemotherapy

The best model in terms of BIC and AIC was the Weibull model, which results are presented in Table 40.

Table 40. Weibull estimates for subsequent treatment duration

Parameter	Estimate
EP	0.000
D+EP	-0.082
2nd Line	0.000
3rd+ Line	0.283
Immunotherapies	0.000
Chemotherapy Regimens	0.245
Single Agent Chemotherapy	0.356
Shape	-1.170
Scale	-0.235

Based on this Weibull model, the mean survival time for each component was calculated (Table 41).

[redacted]

Group	Mean duration (months)
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Finally, the acquisition costs for subsequent treatment are summarized in Table 42. In the base case analysis, the RDI was assumed 100% for all subsequent treatments. Furthermore, it was assumed that there was no vial sharing (wastage), similar to the assumption done for the intervention and comparator.

Table 42. Medicine costs of subsequent treatments

Medicine	Strength	Package size	Pharmacy purchase price [DKK]	Relative dose intensity	Average duration of treatment
Epirubicin "Teva"	2 mg/ml	25 ml	110.60	100%	[redacted]
Epirubicin "Accord"	2 mg/ml	50 ml	980.00		
Epirubicin "Teva"	2 mg/ml	100 ml	442.76		
Docetaxel "Accord"	20 mg/ml	1 ml	71.90		
Docetaxel "Accord"	20 mg/ml	4 ml	151.02		
Docetaxel "Accord"	20 mg/ml	8 ml	309.00		
Etoposide	See Table 34				
Gemcitabin "SUN"	10 mg/ml	120 ml	310.00		
Gemcitabin "SUN"	10 mg/ml	140 ml	330.00		
Gemcitabin "SUN"	10 mg/ml	160 ml	350.00		

Medicine	Strength	Package size	Pharmacy purchase price [DKK]	Relative dose intensity	Average duration of treatment
Gemcitabin "SUN"	10 mg/ml	180 ml	370.00		
Gemcitabin "SUN"	10 mg/ml	200 ml	385.00		
Gemcitabin "SUN"	10 mg/ml	220 ml	420.00		
Irinotecan "Fresenius Kabi"	20 mg/ml	5 ml	125.00		
Irinotecan "Fresenius Kabi"	20 mg/ml	25 ml	350.00		
Paclitaxel "Fresenius Kabi"	6 mg/ml	16.7 ml	110.50		
Paclitaxel "Fresenius Kabi"	6 mg/ml	50 ml	201.50		
Topotecan "Accord"	1 mg/ml	1 ml	222.00		
Topotecan "Accord"	1 mg/ml	4 ml	290.00		
Navelbine (vinorelbine, oral)	30 mg	1	618.75		
Docetaxel + Cisplatin	See above and Table 34				[redacted]
Etoposide + Carboplatin	See Table 34				[redacted]
Etoposide + Cisplatin	See Table 34				[redacted]
Gemcitabine + Carboplatin	See above and Table 34				[redacted]

Medicine	Strength	Package size	Pharmacy purchase price [DKK]	Relative dose intensity	Average duration of treatment
Gemcitabine + Cisplatin	See above and Table 34				
Irinotecan + Carboplatin	See above and Table 34				
Irinotecan + Cisplatin	See above and Table 34				
Paclitaxel + Carboplatin	See above and Table 34				
Topotecan + Carboplatin	See above and Table 34				
Cyclophosphamid "2care4"	200 mg	1	72.18		
Cyclophosphamid "2care4"	500 mg	1	180.00		
Doxorubicin "Accord"	2 mg/ml	25 ml	120.00		
Doxorubicin "Accord"	2 mg/ml	100 ml	350.00		
Oncovin (vincristine)	1 mg/ml	1 ml	390.00		
Oncovin (vincristine)	1 mg/ml	2 ml	645.00		
Cyclophosphamide + Epirubicin + Vincristine	See above				
Holoxan (Ifosfamide) [used in the combination Etoposide + Ifosfamide + Cisplatin]	1 g	1	390.00		

Medicine	Strength	Package size	Pharmacy purchase price [DKK]	Relative dose intensity	Average duration of treatment
Etoposide + Paclitaxel + Carboplatin	See above				
Nivolumab (Opdivo)	40 mg/4 ml	1	3,431.27		[redacted]
Nivolumab (Opdivo)	100 mg/10 ml	1	8,523.80		
Nivolumab (Opdivo)	120 mg/12 ml	1	10,228.57		
Nivolumab (Opdivo)	240 mg/24 ml	1	20,457.13		
Ipilimumab (Yervoy) [used in the combination Nivolumab + Ipilimumab]	5 mg/ml	10 ml	23,850.38		
Ipilimumab (Yervoy) [used in the combination Nivolumab + Ipilimumab]	5 mg/ml	40 ml	95,188.99		
Pembrolizumab (Keytruda)	25 mg/ml	4 ml	21,537.58		

Source: Medicinpriser.dk 11-04-2024 [60].

11.7 Patient costs

The analysis adopted a limited societal perspective. This includes non-medical costs due to time spent due to treatment. The costs were based on an hourly wage (DKK 209) taken from Værdisætning af Enhedsomkostninger, by the DMC [63]. Transportation costs were applied for each healthcare visit. Transportation costs (DKK 164 for a round trip) were also sourced from Værdisætning af Enhedsomkostninger, by the DMC [63] (Table 43). Both costs inflated to the 2024 cost level using the net price index excluding energy (Danmarks Statistik Nettopriskindeks, accessed 04-18-2024).

The non-medical costs were applied according to the use of time for the disease management. It was assumed that each visit took in average 4 hours. The time

calculations were based on the frequencies for health care utilization for each health state (Table 36). In the progression-free health state, 100% of the patients were assumed to incur in non-medical costs, compared to only 50% of carers. In the case of progression, it was assumed that 50% of patients and 50% of carers incurred in non-medical costs (the remaining patients were assumed to be too weak to visit the hospital).

Table 43. Patient costs used in the model

Activity	Unit cost [DKK]	Time spent [minutes, hours, days]
Patients (hourly rate)	209 [63]	Assumption: 4 hours Progression free: 100% of patients Progressed: 50% of patients
Carers (hourly rate)	209 [63]	Assumption: 4 hours Progression free: 50% of carers Progressed: 50% of carers
Transportation costs (round trip)	164 [63]	Progression free: 100% of patients Progressed: 50% of patients Carers were not included as it was assumed they share transport with patients.

12. Results

12.1 Base case overview

The base case settings for the cost-effectiveness analysis of Imfinzi® are presented in Table 44.

Table 44. Base case overview

Feature	Description
Comparator	Combination of etoposide and platinum-based chemotherapy (i.e., carboplatin or cisplatin)
Perspective	Limited societal
Type of model	Partitioned survival model
Time horizon	30 years (lifetime)
Treatment line	First-line treatment. Second- and third-line subsequent treatment lines is included.

Feature	Description
Measurement and valuation of health effects	Health-related quality of life measured with EQ-5D-5L in study CASPIAN. Danish population weights were used to estimate health-state utility values.
Costs included	Medicine costs (both intervention, comparator and subsequent treatment) Administration costs Disease management Costs of adverse events Patient costs (designated as non-medical costs)
Dosage of medicine	Based on weight
Average time on treatment	Set to equal to PFS
Parametric function for PFS	D+EP: Spline Hazard 3 knots EP: Spline Hazard 3 knots
Parametric function for OS	D+EP: Spline Odds 2 knots EP: Spline Odds 2 knots
Inclusion of waste	No
Average time in model health state	
OS	[redacted]
PFS	[redacted]
Death	[redacted]

OS, Overall survival; PFS, Progression-free survival

12.1.1 Base case results

The base case results are summarized in Table 45. The results of the base case show that the cost of an additional QALY gained from using Imfinzi® + EP, compared to EP, is predicted to be DKK 1,188,412. Treatment with Imfinzi® +EP is predicted to lead to 0.78 additional QALYs and 0.99 additional life years compared with EP. Treatment with Imfinzi® + EP is predicted to lead to additional costs of DKK 931,340 compared to treatment with EP.

Table 45. Base case results, discounted estimates

	Imfinzi® + EP	EP	Difference
Medicine costs	DKK 922,021	DKK 4,753	DKK 917,268

	Imfinzi® + EP	EP	Difference
Medicine costs – co-administration		-	-
Administration	54,536	76,342	-21,806
Disease management costs	85,415	64,006	21,409
Costs associated with management of adverse events	14,158	19,202	-5,044
Subsequent treatment costs	18,916	19,058	-142
Patient costs	41,975	22,321	19,654
Total costs	**1,137,021**	**205,681**	**931,340**
Life years gained (Progression free)	1.30	0.65	0.65
Life years gained (Progressed)	0.92	0.58	0.34
Total life years	2.21	1.22	0.99
QALYs (Progression free)	1.056	0.539	0.52
QALYs (Progressed)	0.728	0.462	0.27
QALYs (adverse reactions)	-0.001	-0.002	0.0005
Total QALYs	**1.78**	**1.00**	**0.78**
Incremental costs per life year gained		**945,154 DKK**	
Incremental cost per QALY gained (ICER)		**1,188,412 DKK**	

EP, Etoposide plus platinum-based chemotherapy; ICER, Incremental cost-effectiveness ratio; QALY, Quality-adjusted life years

12.2 Sensitivity analyses

12.2.1 Deterministic sensitivity analyses

12.2.1.1 One-way sensitivity analysis

The impact of individual parameters on the ICER was tested in one-way deterministic sensitivity analyses. Key model settings, cost inputs and utility inputs were systematically and independently varied over a plausible range. Where possible, confidence intervals (CI) or published ranges were used as alternative values. The ICER was recorded at the upper and lower values to produce a tornado diagram.

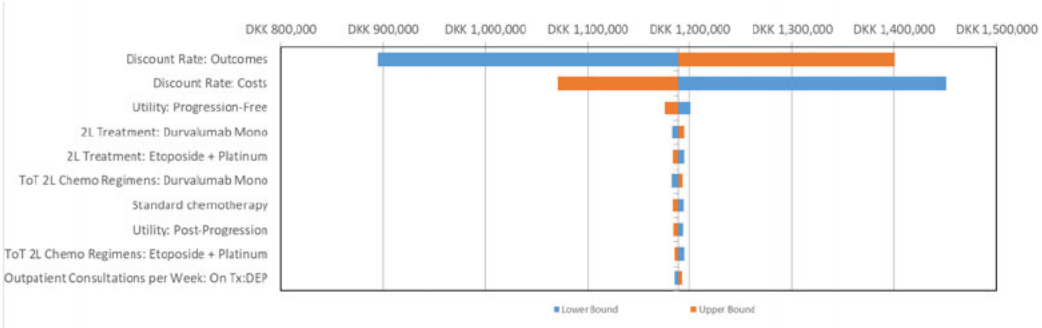
The results of the deterministic sensitivity analyses are presented in Table 46 and Figure 14. The tornado diagram and table present the ten parameters that have the greatest impact on the ICER for Imfinzi® + EP compared to EP. The parameters that had the greatest impact on the ICER were the discount rates (both for outcomes and costs) and the utility value used in the progression-free health state.

Table 46. One-way sensitivity analyses results

	Change – Lower bound/Upper bound	Reason / Rational / Source	Incremental cost (DKK) - Lower bound/Upper bound	Incremental benefit (QALYs) Lower bound/Upper bound	ICER (DKK/QALY) Lower bound/Upper bound
Base case	-	-	931,340	0.78	1,188,412
Discount Rate: Outcomes	0%/6%	Key model parameter	931,340/931,340	1.04/0.67	849,982/1,400,720
Discount Rate: Costs	0%/6%	Key model parameter	1,136,574/839,348	0.78/0.78	1,450,296/1,071,028
Utility: Progression-Free	0.821/0.847	Key model parameter	931,340/931,340	0.78/0.79	1,201,193/1,175,901
2L Treatment: Durvalumab Mono	0.4/0.6	Key model parameter	927,045/935,570	0.78/0.78	1,182,932/1,193,811
2L Treatment: Etoposide + Platinum	0.4/0.6	Key model parameter	935,554/927,077	0.78/0.78	1,193,790/1,182,973

	Change – Lower bound/Upper bound	Reason / Rational / Source	Incremental cost (DKK) - Lower bound/Upper bound	Incremental benefit (QALYs) Lower bound/Upper bound	ICER (DKK/QALY) Lower bound/Upper bound
ToT 2L Chemo Regimens: Durvalumab Mono	1.4/4.3	Key model parameter	926,560/934,393	0.78/0.78	1,182,313/1,192,308
Standard chemotherapy	DKK 1322.2/1958.6	Key model parameter	935,120/927,176	0.78/0.78	1,193,236/1,183,099
Utility: Post-Progression	0.793/0.811	Key model parameter	931,340/931,340	0.78/0.79	1,193,018/1,183,842
ToT 2L Chemo Regimens: EP	1.2/3.9	Key model parameter	926,560/934,393	0.78/0.78	1,182,313/1,192,308
Outpatient Consultations per Week: On Tx:DEP	16.2/18.6	Key model parameter	932,844/929,836	0.78/0.78	1,190,331/1,186,494

Figure 14. Tornado diagram



12.2.1.2 Scenario analyses

Table 47 shows the results for different scenario analyses. The scenario analyses indicated that the base case results were stable to changes in key parameters. The results were most sensitive to the choice of OS distribution and shorter time horizons.

Table 47. Scenario analyses

Parameter	Base case	Scenario	Incremental costs [DKK]	Incremental QALYs	ICER [DKK/QALY]
Base case	-	-	931,340	0.78	1,188,412
Starting age	70	62.4	931,332	0.80	1,166,241
Time horizon	30 years	5 years	612,998	0.36	1,717,060
		10 years	747,903	0.57	1,320,750
		15 years	824,923	0.66	1,244,641
		20 years	874,274	0.72	1,213,117
PFS projection	Spline Hazard (3 knots)	Spline Odds (2 knots)	994,943	0.79	1,260,869
		Spline Odds (3 knots)	983,354	0.79	1,249,683
OS projection	Spline Odds (2 knots)	Spline Hazard (3 knots)	957,285	1.19	807,400
		Spline Hazard (1 knot)	680,183	0.41	1,663,537
TTD	Equal to Progression-Free Survival	CASPIAN TTD Data	931,340	0.78	1,188,412
Discount rates	Costs: 3.5%, QALYs: 3.5%	Costs: 4.5%; QALYs: 4.5%	890,591	0.73	1,217,570
		Costs: 4.5%; QALYs: 0%	1,136,574	0.73	1,553,866
Perspective	Limited societal	Payer	911,686	0.78	1,163,333

Age-adjustment	Yes	No	931,340	0.81	1,147,782
Vial Sharing Assumptions	No Vial Sharing	Total Vial Sharing	910,553	0.78	1,161,888
AE duration	Based on different sources and assumptions (see Table 30)	30 days	931,340	0.78	1,186,869

12.2.2 Probabilistic sensitivity analyses

The results of the PSA are presented graphically in Figure 15 and Figure 16. The incremental-cost effectiveness scatterplot presents the variation in incremental costs and incremental QALYs over 1,000 replications of Imfinzi® + EP vs. EP. The curves indicate that Imfinzi® + EP has a 50% probability of being cost-effective at a willingness-to-pay of approximately DKK 1,195,000.

Figure 15. Cost-effectiveness plane

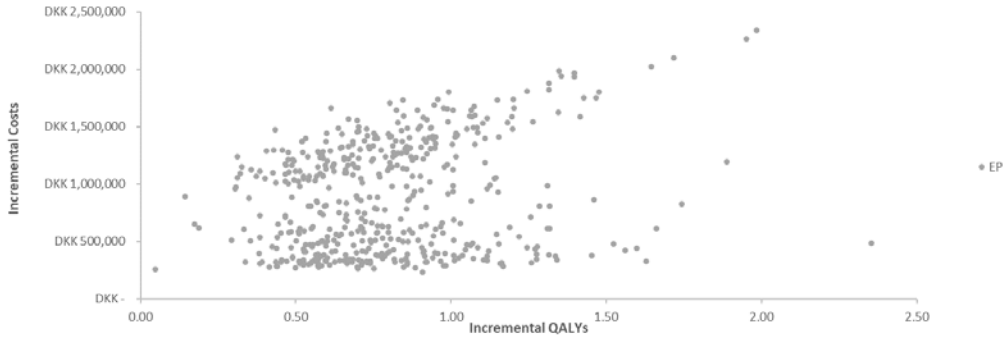
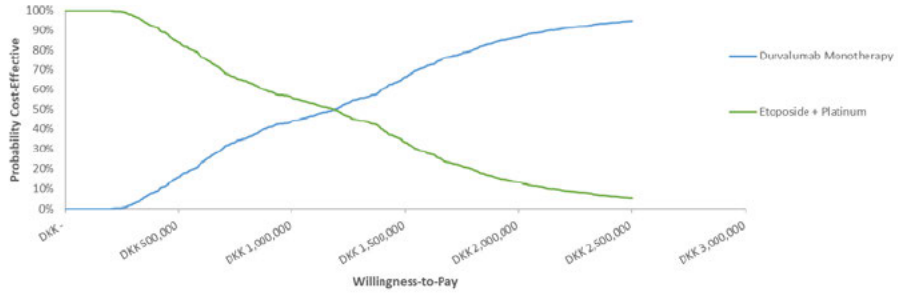


Figure 16. Cost-effectiveness acceptability curve



13. Budget impact analysis

A budget impact analysis was conducted and incorporated in the CEM, as per DMC guidelines [44]. A five-year projection was used in the analysis and costs were estimated for two scenarios. In one scenario Imfinzi® is introduced as a first-line treatment for ES-SCLC patients, and in scenario two it is not introduced. Costs were estimated based on the expected number of eligible patients (described in Section 3.2).

The budget impact calculations were based on Pharmacy Purchasing Price of all treatments. The following undiscounted costs (described in Section 11) were included in the analysis:

- Medicine costs
- Administration costs
- Subsequent treatment
- Disease management costs
- Management of AE costs.

Number of patients (including assumptions of market share)

Based on the incidence of ES-SCLC patients presented in Section 3.2, it was assumed that approximately 160 patients would be eligible for treatment with Imfinzi®. A constant incidence rate was assumed over the five-year period. Table 48 presents the estimated patient numbers for both scenarios one and two.

The market share was assumed 30% in the first year, 50% in the second year, with increases of 10% in the following years, reaching 80% in year 5. The Danish expert confirmed that the numbers presented in Table 48 are realistic [30].

Table 48. 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		
Imfinzi® + EP	48	80	96	112	128

	Year 1	Year 2	Year 3	Year 4	Year 5
EP	112	80	64	48	32
			Non-recommendation		
Imfinzi® + EP	0	0	0	0	0
EP	160	160	160	160	160

Budget impact

The expected budget impact of introducing Imfinzi® in combination with etoposide and either carboplatin or cisplatin for the first-line treatment of adults with extensive-stage small cell lung cancer (ES-SCLC) is presented in Table 49. At year five, Imfinzi® is expected to have a budget impact of approximately DKK 76 million.

Table 49. Expected budget impact of recommending the medicine for the indication [DKK]

	Year 1	Year 2	Year 3	Year 4	Year 5
The medicine under consideration is recommended	41,595,715.2	59,986,593.5	72,861,808.3	85,558,553.2	98,413,134.9
The medicine under consideration is NOT recommended	23,240,089.4	25,363,984.6	26,425,562.2	27,154,422.3	27,731,022.1
Budget impact of the recommendation	18,355,625.7	34,622,608.9	46,436,246.1	58,404,130.9	70,682,112.9

14. List of experts

[redacted]

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Appendix A. Main characteristics of studies included

Table 50 describes the main characteristics of the clinical trial used to inform the cost effectiveness analysis, CASPIAN.

Table 50. Main characteristic of studies included

Trial name: CASPIAN	**NCT number: NCT03043872**
Objective	Examining the efficacy and safety of durvalumab with or without tremelimumab plus EP (carboplatin or cisplatin + etoposide) versus EP alone as first-line treatment in adult patients with ES-SCLC.
Publications – title, author, journal, year	• Paz-Ares, L. et al. Durvalumab plus platinum-etoposide versus platinum-etoposide in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): a randomised, controlled, open-label, phase 3 trial. Lancet, doi:10.1016/S0140-6736(19)32222-6 (2019). • Paz-Ares, L. et al. PD-L1 expression, patterns of progression and patient-reported outcomes (PROs) with durvalumab plus platinum-etoposide in ES-SCLC: Results from CASPIAN (LBA89). Ann Oncol 30 (Suppl 5), doi:10.1093/annonc/mdz394.089 (2019). • Paz-Ares, L. G. et al. Durvalumab ± tremelimumab + platinum-etoposide in first-line extensive-stage SCLC (ES-SCLC): Updated results from the phase III CASPIAN study. Journal of Clinical Oncology 38, 9002-9002, doi:10.1200/JCO.2020.38.15_suppl.9002 (2020). • Paz-Ares L, Chen Y, Reinmuth N, et al. Durvalumab, with or without tremelimumab, plus platinum-etoposide in first-line treatment of extensive-stage small-cell lung cancer: 3-year overall survival update from CASPIAN. ESMO Open. 2022 Apr;7(2):100408. doi: 10.1016/j.esmoop.2022.100408. Epub 2022 Mar 10. PMID: 35279527; PMCID: PMC9161394.
Study type and design	Phase 3, randomized, open-label, parallel-group, active-controlled, multicentre, global study. All patients were randomized in a 1:1:1 ratio in a stratified manner according to the planned platinum-based therapy for Cycle 1 (cisplatin or carboplatin) to receive treatment with durvalumab + tremelimumab + EP (Arm 1), durvalumab + EP (Arm 2), or standard of care- EP (Arm 3).
Sample size (n)	Arm 1 (n =268): durvalumab + tremelimumab + EP Arm 2 (n =268): durvalumab + EP

Trial name: CASPIAN		NCT number: NCT03043872
	Arm 3 (n =269): EP	
Main inclusion criteria	1. Histologically or cytologically documented extensive disease. Brain metastases; must be asymptomatic or treated and stable off steroids and anti-convulsants for at least 1 month prior to study treatment. 2. Suitable to receive a platinum-based chemotherapy regimen as 1st line treatment. 3. Life expectancy ≥12 weeks at Day 1. 4. ECOG 0 or 1 at enrolment. 5. No prior exposure to immune-mediated therapy excluding therapeutic anticancer vaccines.	
Main exclusion criteria	1. Any history of radiotherapy to the chest prior to systemic therapy or planned consolidation chest radiation therapy (except palliative care outside of the chest). 2. Paraneoplastic syndrome of autoimmune nature, requiring systemic treatment or clinical symptomatology suggesting worsening of PNS. 3. Active infection including tuberculosis, HIV, hepatitis B anc C. 4. Active or prior documented autoimmune or inflammatory disorders. 5. Uncontrolled intercurrent illness, including but not limited to interstitial lung disease.	
Intervention	Arm 1 (n =268): durvalumab + tremelimumab + EP (carboplatin or cisplatin + etoposide): • Durvalumab 1,500 mg intravenous (IV) infusions every 3 weeks for 12 weeks (4 cycles) and every 4 weeks thereafter until progressed disease (PD) or other discontinuation criteria. • Tremelimumab (T) 75 mg IV infusions every 3 weeks for 12 weeks (4 cycles). An additional dose of tremelimumab will be administered in the week 16. • Carboplatin area under the curve (AUC) 5-6 up to 4 cycles every 3 weeks. • Cisplatin 75 to 80 mg/m^2 up to 4 cycles every 3 weeks. • Etoposide 80 to 100 mg/m^2 up to 4 cycles every 3 weeks. Arm 2 (n =268): durvalumab + EP (carboplatin or cisplatin + etoposide): • Durvalumab 1,500 mg intravenous (IV) infusions every 3 weeks for 12 weeks (4 cycles) and every 4 weeks thereafter	

Trial name: CASPIAN	NCT number: NCT03043872
	until progressed disease (PD) or other discontinuation criteria. • Carboplatin area under the curve (AUC) 5-6 up to 4 cycles every 3 weeks. • Cisplatin 75 to 80 mg/m^2 up to 4 cycles every 3 weeks. • Etoposide 80 to 100 mg/m^2 up to 4 cycles every 3 weeks.
Comparator(s)	Arm 3 (n =269): EP (carboplatin or cisplatin + etoposide): • Carboplatin area under the curve (AUC) 5-6 up to 6 cycles every 3 weeks. • Cisplatin 75 to 80 mg/m^2 up to 6 cycles every 3 weeks. • Etoposide 80 to 100 mg/m^2 up to 6 cycles every 3 weeks.
Follow-up time	• At the interim analysis, DCO 11 March 2019: 1 year follow-up. • At the final analysis, DCO 27 January 2020: 2-year follow-up (median follow up of 25.20 months for durvalumab plus EP and 23.24 months for EP alone in censored patients). • At the long-term follow-up, DCO 22 March 2021: 3 years follow-up (median follow-up of 39.33 months for durvalumab plus EP and 37.98 months for EP).
Is the study used in the health economic model?	Yes.
Primary, secondary and exploratory endpoints	**Endpoints included in this application:** • The primary endpoint was OS. Secondary endpoints included PFS, ORR, DoR (Per RECIST 1.1 using Investigator assessments), HRQoL (assessed using EORTC QLQ-C30, EORTC QLQ-LC13 and EQ-5D-5L) and safety. **Other endpoints:** • OS in the Global Cohort; Assessed at Global Cohort Final Analysis (DCO 27 January 2020 - maximum of approximately 33 months); D + T + EP Compared with D + EP. • Percentage of Patients Alive and Progression Free at 6 Months (APF6) in the Global Cohort; Assessed at 6 months post-randomization. • Percentage of Patients Alive at 18 Months (OS18) in the Global Cohort; Assessed at the global cohort final analysis (DCO 27 January 2020).

Trial name: CASPIAN	NCT number: NCT03043872
	• Pharmacokinetics (PK) of Durvalumab; Peak and Trough Serum Concentrations in the Global Cohort; Assessed at the global cohort final analysis (DCO 27 January 2020). • PK of Tremelimumab; Peak and Trough Serum Concentrations in the Global Cohort; Assessed at the global cohort final analysis (DCO 27 January 2020). • Number of Patients with Anti-Drug Antibody (ADA) Response to Durvalumab in the Global Cohort; Assessed at the global cohort final analysis (DCO 27 January 2020). • Number of Patients with ADA Response to Tremelimumab in the Global Cohort; Assessed at the global cohort final analysis (DCO 27 January 2020). • Change From Baseline in Primary PRO Symptoms as Assessed by EORTC QLQ in the Global Cohort; D + T + EP Compared With EP; Assessed up to 12 months.
Method of analysis	All efficacy analyses were performed for the intention-to-treat (ITT) population, defined as including all randomized patients. All safety analyses were performed for the safety population, consisting of all patients who received at least one dose of study treatment. Appropriate censoring rules were applied for determining PFS and OS by using the Kaplan–Meier method for survival estimates. The stratified log-rank test was used to assess between-group differences and the stratified Cox proportional hazards model were fitted to compute hazard ratios and corresponding 95% CIs. The stratification factors used at randomization were applied to all stratified analyses.
Subgroup analyses	Pre-specified subgroup analyses were also performed to investigate the treatment effect across prespecified stratification factors and subgroups based on demographics, geographical region, carboplatin or cisplatin use, and disease characteristics.
Other relevant information	*N/A.*

Appendix B. Efficacy results per study

Results per study

Table 51. Results per study

Results of CASPIAN (NCT03043872)											
				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 OS	Durvalumab + EP (carboplatin or cisplatin + etoposide)	268	12.9 months (11.3-14.7)	2.4 months	n.a.	n.a.	HR: 0.71	0.595 – 0.858	0.0003	The median OS is based on the Kaplan-Meier estimator. CIs for median OS were derived based on the Brookmeyer-Crowley method and using the log-log transformation. HR and CI were calculated using stratified Cox proportional hazards model, adjusting for planned platinum therapy at Cycle 1 (Carboplatin or Cisplatin), and ties handled by Efron approach. For the p-value, the analysis was performed using the stratified log-rank test, adjusting for planned platinum therapy in Cycle 1 (Carboplatin or Cisplatin), and using the rank tests of association approach. CI for absolute value calculated by AstraZeneca. DCO 27 January 2020	[36, 37]
	EP (carboplatin or cisplatin + etoposide)	269	10.5 months (9.3-11.2)								

Results of CASPIAN (NCT03043872)											
				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		
OS rate at 36 months	Durvalumab + EP	268	17.6% (13.3-22.4)	11.8%	6.43-17.27	P<0.0001	OR=0.29	0.15-0.54	P=0.0001	The OS rate is based on the Kaplan-Meier estimator. CI for absolute value calculated by AstraZeneca. DCO 27 January 2020	[38].
	EP	269	5.8% (3.4-9.1)								
Median PFS	Durvalumab + EP	268	5.1 months (4.7-6.2) 233 (87.3%)	-0.3 months(0.4%)	n.a.	n.a.	HR: 0.80	0.67–0.96	0.0157	The median PFS is based on the Kaplan-Meier estimator. CIs for median PFS were derived based on the Brookmeyer-Crowley method and using the log-log transformation. HR and CI were calculated using stratified Cox proportional hazards model, adjusting for planned platinum therapy at Cycle 1 (Carboplatin or Cisplatin), and ties handled by Efron approach. PFS was not formally tested for statistical significance. DCO 27 January 2020	[38].
	EP	269	5.4 months (4.8-6.2) 236 (87.7)								
PFS rate at 12 months	Durvalumab + EP	268	17.9% (13.5-22.8)	12.6%	7.28-18.1	P < 0.0001.	OR=0.25	0.14 – 0.47	P < 0.0001	Calculated using the Kaplan-Meier technique. CI for absolute value calculated by AstraZeneca. DCO 27 January 2020	[38].
	EP	269	5.3% (2.9-8.8)								

Results of CASPIAN (NCT03043872)											
				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		
Confirmed ORR	Durvalumab + EP	268	68%	10%	1.83 – 18.0	P = 0.0165	OR: 1.53	1.08-2.19	0.0173	ORR (per RECIST 1.1 using Investigator assessments) was defined as the percentage of patients with at least 1 visit response of Complete Response (CR) or Partial Response (PR) and a confirmatory scan no sooner than 4 weeks after the initial CR/PR. CR was defined as disappearance of all target lesions (TLs) since baseline (any pathological lymph nodes selected as TLs must have a reduction in short axis diameter to <10 mm) or disappearance of all non-target lesions (NTLs) since baseline (all lymph nodes must be non-pathological in size [<10 mm short axis]). PR was defined as at least a 30% decrease in the sum of diameters of TLs (taking as reference the baseline sum of diameters). Tumour scans were performed at baseline, Week 6, Week 12 and then every 8 weeks relative to the date of randomization until RECIST 1.1-defined progression. The comparison (vs EP) was performed using a logistic regression model,	[38].
	EP	269	58%								

Results of CASPIAN (NCT03043872)											
				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		
										adjusting for planned platinum therapy in Cycle 1 (Carboplatin or Cisplatin), with 95% CI calculated by profile likelihood. P-value, derived from logistic regression model, is based on twice the change in log-likelihood resulting from the addition of a treatment factor to the model. DCO 27 January 2020 CI for absolute value calculated by AstraZeneca	
Median DoR	Durvalumab + EP	182 responders	5.1 months (4.9-5.3)	0 months	n.a.	n.a.	n.a.	n.a.	n.a.	The median DoR is based on the Kaplan-Meier estimator. CI for median duration of response is derived based on Brookmeyer-Crowley method and using the log-log transformation.	[38].
	EP	156 responders	5.1 months (4.8-5.3)								
Median time to deteriorati	Durvalumab + EP	261	TTD for cognitive functioning: 8.4 months	2.4 months	n.a.	n.a.	HR: 0.60	0.466-0.759	< 0.0001	Time to Deterioration of Health-Related Quality of Life (HRQoL) and Patient Reported Outcome (PRO) Symptoms,	[38].

Results of CASPIAN (NCT03043872)											
				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		
on (TTD) of HRQoL and Patient Reported Outcome (PRO) Symptoms			TTD for physical functioning: 8.4 months	1.9 months			HR: 0.74	0.573-0.946	0.0162	Assessed Using European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ) in the Global Cohort. The EORTC QLQ-Core 30 version 3 (QLQ-C30 v3) was included for assessing HRQoL. It assesses HRQoL/health status through 9 multi-item scales: 5 functional scales (physical, role, cognitive, emotional, and social), 3 symptom scales (fatigue, pain, and nausea and vomiting), and a global health and QoL scale. 6 single-item symptom measures are also included: dyspnoea, insomnia, appetite loss, constipation, diarrhoea, and financial difficulties. Scores from 0 to 100 were derived for each of the 15 domains, with higher scores representing greater functioning, greater HRQoL, or greater level of symptoms. Time to deterioration (calculated using the Kaplan-Meier technique) was defined as time from randomization until the date of first clinically meaningful deterioration (a	
			TTD for role functioning: 7.4 months	1.5 months			HR: 0.69	0.544-0.887	0.0034		
			TTD for emotional functioning: 11.8 months	4.5 months			HR: 0.61	0.464-0.789	0.0002		
			TTD for social functioning: 7.4 months	1.1 months			HR: 0.68	0.531-0.863	0.0016		
	EP	260	TTD for cognitive functioning: 6.0 months				Statistically significant differences in TTD between treatment groups were also seen for insomnia,				
			TTD for physical functioning: 6.5 months								

Results of CASPIAN (NCT03043872)											
				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		
			TTD for role functioning: 5.9 months TTD for emotional functioning: 7.3 months TTD for social functioning: 6.3 months				appetite loss, constipation, diarrhoea, haemoptysis, chest pain and arm/shoulder pain.			decrease in score from baseline of ≥10) that is confirmed at a subsequent visit or death (by any cause) in the absence of a clinically meaningful deterioration. Time to Deterioration of PRO Symptoms, Assessed Using EORTC QLQ-Lung Cancer Module 13 (QLQ-LC13) in the Global Cohort. The EORTC QLQ-LC13 is a disease-specific 13-item self-administered questionnaire for lung cancer, to be used in conjunction with the EORTC QLQ-C30. It comprises both multi-item and single-item measures of lung cancer-associated symptoms (i.e., coughing, haemoptysis, dyspnoea, and pain) and side effects from conventional chemotherapy and radiotherapy (i.e., hair loss, neuropathy, sore mouth, and dysphagia). Scores from 0 to 100 were derived for each symptom item, with higher scores representing greater level of symptoms. Time to deterioration (calculated using the Kaplan-Meier technique) was defined as time from randomization until the date of first	

Results of CASPIAN (NCT03043872)											
				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		
										clinically meaningful deterioration (an increase in score from baseline of ≥10) that is confirmed at a subsequent visit or death (by any cause) in the absence of a clinically meaningful deterioration. The median TTD was calculated using the Kaplan-Meier technique. The hazard ratio and confidence intervals were calculated using a stratified Cox proportional hazards model, adjusting for planned platinum therapy in Cycle 1 (Carboplatin or Cisplatin), and ties handled by Efron approach. P-value: The analysis was performed using the stratified log-rank test, adjusting for planned platinum therapy in Cycle 1 (Carboplatin or Cisplatin), and using the rank tests of association approach.	
Change From Baseline in Primary Symptoms (Assessed	Durvalumab + EP	261	Clinically relevant improvements in the pre-defined key symptoms were observed	In some cases, the improvements occurred earlier in the durvalumab	n.a.	n.a.	n.a.	n.a.	n.a.	Assessed Using EORTC QLQ-C30 and EORTC QLQ-LC13 in the Global Cohort. A mixed model repeated measures (MMRM) analysis of EORTC QLQ-C30 and EORTC QLQ-LC13 was performed for 5 primary PRO symptoms (cough,	[38].
	EP	260									

Results of CASPIAN (NCT03043872)											
				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		
up to 12 months)			in both groups between baseline and 12 months follow-up	plus EP group. However, reductions in symptoms (fatigue, cough, dyspnoea, appetite loss and chest pain) did not differ significantly between treatment groups.						dyspnoea, chest pain, fatigue, and appetite loss), and considered all data from baseline to progressed disease (PD) or 12 months, excluding visits with excessive missing data (defined as >75% missing data). An outcome variable consisting of a score from 0 to 100 was derived for each of the symptom scales/symptom items, with higher scores representing greater symptom severity. An improvement in symptoms was indicated by a negative change from baseline. A positive change from baseline indicated a deterioration of symptoms. A minimum clinically meaningful change was defined as an absolute change from baseline of ≥10.	
Any AE	Durvalumab + EP	265	260 (98.1%)	1.1 %	-1.80-4.16	P = 0.4180	OR= 1.61	0.52-4.99	P = 0.4076	Calculated by AstraZeneca DCO 22 March 2021	[38]
	EP	266	258 (97.0%)								

Results of CASPIAN (NCT03043872)											
				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		
Serious AEs	Durvalumab + EP	265	86 (32.5%)	4.0%	-4.16%-12.09%	P = 0.3383	OR=0.84	0.58-1.20		Calculated by AstraZeneca DCO 22 March 2021	[38]
	+ EP	266	97 (36.5%)								

Appendix C. Comparative analysis of efficacy

No additional meta-analyses nor indirect comparisons have been performed for the submitted application. Therefore, this appendix is not applicable.

Table 52. Comparative analysis of studies comparing [intervention] to [comparator] for patients with [indication] (NA)

Outcome	Absolute difference in effect	Relative difference in effect	Method used for quantitative synthesis	Result used in the health economic analysis?
NA	NA	NA	NA	NA

Appendix D. Extrapolation

Survival analyses were used to estimate parametric survival models for PFS, OS and TTD. The proportional hazard (PH) assumption was evaluated for the health economic model for both OS and PFS (not relevant for TTD, as the Kaplan-Meier curve was complete for the chemotherapy arm and treatment during PFS was assumed). Visual inspection of loglog plots (log cumulative hazard versus log time) were used to assess the PH assumption. The curves showed non-parallel or crossing lines indicating a violation of the PH assumption.

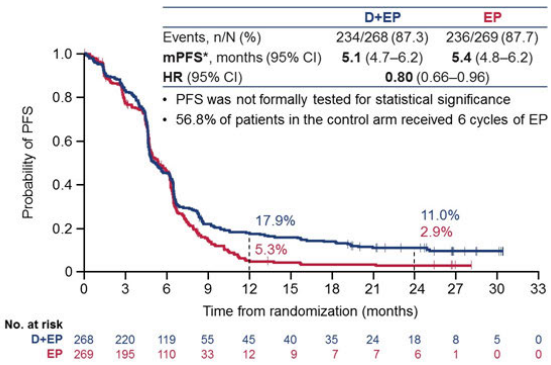
D.1 Extrapolation of progression-free survival

The choice of distribution for the extrapolation of PFS does not impact the results of the analysis as data was mature. All fitted models predicted reasonably similar extrapolations for the PFS curve.

D.1.1 Data input

The Kaplan-Meier curves assessed by investigator for the durvalumab plus EP and EP treatment arms are presented in Figure 17. At the final analysis (24 months, 27 January 2020), 11.0% of patients in the Imfinzi® plus EP group remained free of progression, compared with 2.9% in the control group. The 36-month follow-up did not include additional PFS analyses, although 10.1% of patients were still on treatment with durvalumab at the time of data cut-off. The median PFS in the population receiving durvalumab plus EP was 5.1 months (95% CI: 4.7-6.2), compared to 5.4 months (95% CI: 4.8-6.2) in the EP group.

Figure 17. Kaplan-Meier curve for progression-free survival in CASPIAN (DCO 27 January 2020)



Landmark PFS, %	D+EP (n=268)	EP (n=269)
6 months	45.4	45.8
12 months	17.9	5.3
18 months	13.9	3.4
24 months	11.0	2.9

*Investigator assessed per RECIST v1.1.

CI, confidence interval; D, durvalumab; DCO, data cut off; EP, etoposide plus platinum-based chemotherapy; HR, hazard ratio; (m)PFS, (median) progression-free survival

Source: [38].

Althought the PFS data from the CASPIAN trial were mature (>87% of events observed), it still was required extrapolation to estimate the unrestricted mean differnece in PFS between the two arms needed for health economic analysis. Considering that the treatment effect of Imfinzi® is unlikely to be constant over the entire time horizon of the analysis, the base case analysis did not assume a hazard ratio and only independent model fits were considered.

D.1.2 Model

There were 16 models fitted to the individual subject data in CASPIAN:

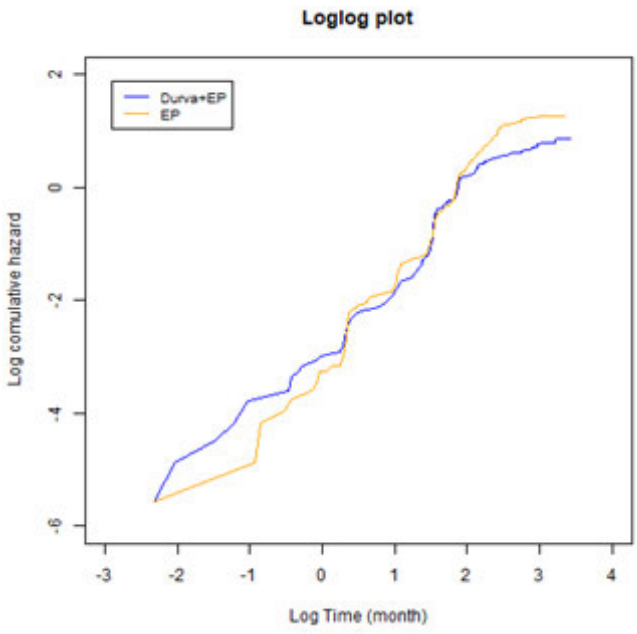
- Standard parametric models: Exponential, Weibull, Gompertz, Lognormal, Loglogistic, Generalised gamma, Gamma.
- Flexible parametric models: Spline Hazard (1 knot), Spline Hazard (2 knots), Spline Hazard (3 knots), Spline Odds (1 knot), Spline Odds (2 knots), Spline Odds (3 knots), Spline Normal (1 knot), Spline Normal (2 knots) and Spline Normal (3 knots).

The presented KM curve (Figure 17) show evidence of time-varying hazards during the trial period. As suggested by Palmer et al. 2023, when there is evidence of time-varying hazards, spline models should routinely be tested [64]. Furthermore, spline odds and spline normal models frequently give more accurate predictions of 10- year survival than standard parametric models [64]. For this reason, flexible parametric models (e.g. spline models) were also fitted in addition to the standard parametric models.

D.1.3 Proportional hazards

Visual inspection of loglog plot (log cumulative hazard versus log time) was used to assess the PH assumption (Figure 18). The curve showed non-parallel or crossing lines indicating a violation of the PH assumption. As a result, individual models were fitted to each treatment arm.

Figure 18. Cumulative logarithmic risk curves of the PFS for Durvalumab + Etoposide + Platinum agent and Etoposide + Platinum agent (CASPIAN trial)



EP = Etoposide + Platinum agent

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

The distributions fitted to PFS (previously described) with the corresponding goodness-of-fit statistics (Akaike information criterion [65] and Bayesian information criterion [BIC]) are presented in Table 53. The goodness-of-fit statistics are presented using ΔAIC_{min}, calculated as $\Delta AIC_{min} = AIC_{chosen\ distribution} - AIC_{distribution\ with\ lowest\ AIC}$. The same calculation was applied to BIC. A ΔAIC_{min} <10 for any arm of the trial means the distribution is supported by the underlying data.

Spline Normal with 1 or 2 knots did not converge and were omitted from the table. Spline models showed the best fits (highlighted in bold).

Table 53. Goodness of fit statistics for progression free survival.

	Imfinzi®+E+P		E+P		Both arms (stratified fit)	
Distribution	ΔAIC_{min}	ΔBIC_{min}	ΔAIC_{min}	ΔBIC_{min}	ΔAIC_{min}, total	ΔBIC_{min}, total
Exponential	105.86	95.09	120.42	106.04	226.28	201.13
Weibull	105.08	97.9	72.59	61.81	177.67	159.71
Gompertz	100.45	93.26	115.06	104.28	215.51	197.54
Lognormal	76.96	69.77	71.74	60.96	148.7	130.73
Loglogistic	47.19	40	41.24	30.46	88.43	70.46
Generalised Gamma	76.24	72.64	56.61	49.43	132.85	122.07
Gamma	98.39	91.2	57.77	46.99	156.16	138.19
Spline Odds 1 knot	49.01	45.42	26.88	19.7	75.89	65.12
Spline Odds 2 knots	**0**	**0**	**27.23**	**23.64**	**27.23**	**23.64**
Spline Odds 3 knots	**1.65**	**5.24**	**2.29**	**2.29**	**3.94**	**7.53**
Spline Hazard 1 knot	63.72	60.12	60.03	52.85	123.75	112.97
Spline Hazard 2 knots	0.7	0.69	14.69	11.1	15.39	11.79
Spline Hazard 3 knots	**0.35**	**3.93**	**0**	**0**	**0.35**	**3.93**
Spline Normal (3 Knots)	6.67	10.26	1.52	1.63	8.19	11.89

D.1.5 Evaluation of visual fit

Goodness-of-fit statistics alone were used to guide the choice of survival distribution for PFS. This was motivated by the relative maturity of the data informing PFS (>87% of events observed) and because all distributions predicted reasonably similar extrapolations for the PFS curve. The overall best fitting distribution was the spline hazard 3 knots (Figure 19).

[redacted]

95% CI: 95% Confidence Interval; SoC: Standard of Care

D.1.6 Evaluation of hazard functions

The development of the risk of progression predicted by the selected survival model is shown in Figure 20.

Years

D.1.7 Validation and discussion of extrapolated curves

The assessment of goodness-of-fit statistics of the PFS curves was deemed acceptable to determine the distribution for PFS, given the maturity of the patient-level data from the CASPIAN trial and reasonably similar extrapolations across the distributions. Based on goodness-of-fit statistics, the spline hazard 3 knots distribution was the one with the best fit to the PFS data.

Furthermore, the spline hazard 3 knots distribution appeared clinically plausible with converging hazards over time, and hence it was selected for the extrapolation of PFS in the base case of the health economic analysis (Figure 21). The spline odds (2 knots) and spline odds (3 knots) distributions were explored in scenario analyses.

[redacted]

D.1.8 Adjustment of background mortality

The general mortality for the Danish population was used – the risk of progression or death was not allowed to be lower than the risk of death for the general population.

D.1.9 Adjustment for treatment switching/cross-over

Not applicable.

D.1.10 Waning effect

Not applicable. The treatment effect diminish with time since the hazards of the selected survival models converge with time.

D.1.11 Cure-point

Not applicable.

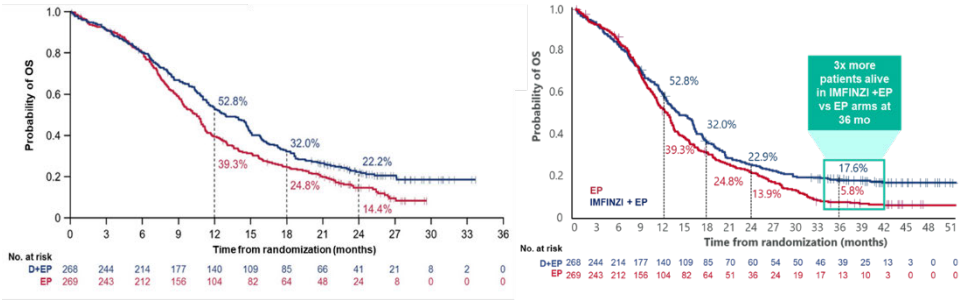
D.2 Extrapolation of overall survival

D.2.1 Data input

The Kaplan-Meier curves for the durvalumab plus EP and EP treatment arms are presented in Figure 22.

At 3-year long-term follow-up (LTFU, DCO 22 March 2021), with a median follow-up 39.33 months for durvalumab plus EP and 37.98 months for EP), the addition of durvalumab to EP significantly improved OS, reducing the risk of death by 29% compared with EP alone (HR, 0.71 [95% CI: 0.60, 0.86], $p = 0.0003$). Based on the KM estimates, 17.6% and 5.8% of patients were alive at the end of 3 years in the durvalumab plus EP and EP treatments arms, respectively. The median OS in the population receiving durvalumab plus EP was 12.9 months, compared to 10.5 months in the EP group (HR, 0.75 (95% CI: 0.62, 0.91), $p = 0.0032$).

Figure 22. Overall survival in CASPIAN; 2-year final analysis (DCO 27 January 2020, left) and 3-year LTFU analysis (DCO 22 March 2021, right)



CI, confidence interval; DCO, data cut off; EP, etoposide + platinum-based chemotherapy; HR, hazard ratio; LTFU, long-term follow up; mo, months; (m)OS, (median) overall survival

Source: [36, 37].

D.2.2 Model

There were 16 models fitted to the individual subject data in CASPIAN:

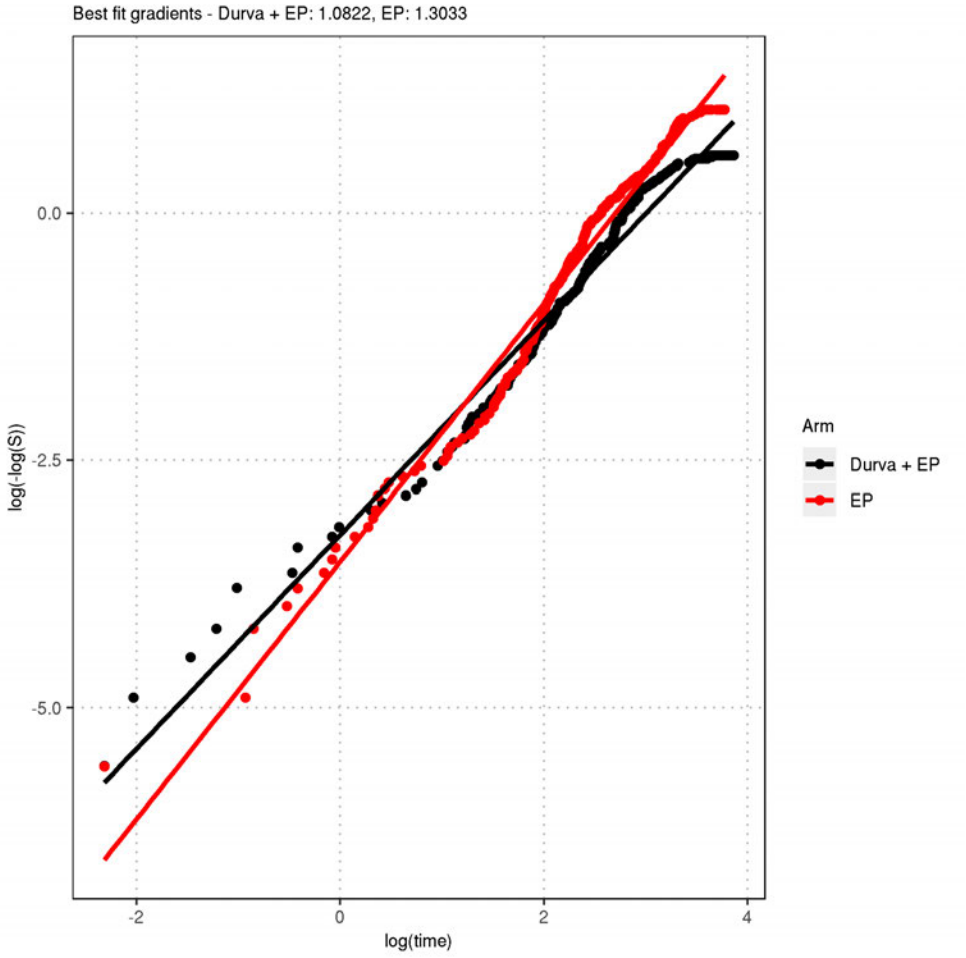
- Standard parametric models: Exponential, Weibull, Gompertz, Lognormal, Loglogistic, Generalised gamma, Gamma.
- Flexible parametric models: Spline Hazard (1 knot), Spline Hazard (2 knots), Spline Hazard (3 knots), Spline Odds (1 knot), Spline Odds (2 knots), Spline Odds (3 knots), Spline Normal (1 knot), Spline Normal (2 knots) and Spline Normal (3 knots).

The presented KM curve (Figure 22) show evidence of time-varying hazards. For this reason, flexible parametric models (e.g. spline models) were also fitted [64].

D.2.3 Proportional hazards

Visual inspection of loglog plot (log cumulative hazard versus log time) was used to assess the PH assumption (Figure 23). The curve showed non-parallel or crossing lines indicating a violation of the PH assumption. As a result, individual models were fitted to each treatment arm.

Figure 23. Log-cumulative hazard plot of Durvalumab + Etoposide + Platinum agent and Etoposide + Platinum agent (CASPIAN trial)



D.2.4 Evaluation of statistical fit (AIC and BIC)

The distributions fitted to OS (previously described) with the corresponding goodness-of-fit statistics (AIC and BIC) are presented in Table 54. The goodness-of-fit statistics are presented using ΔAIC_{min}, calculated as $\Delta AIC_{min} = AIC_{chosen\ distribution} - AIC_{distribution\ with\ lowest\ AIC}$. The same calculation was applied to BIC. A ΔAIC_{min} <10 for any arm of the trial means the distribution is supported by fit statistics.

Under the assumption that the distribution of event times should not be different between the two arms (in line with recommendations from NICE), the total ΔAIC_{min} over both arms is used to guide the selection of the most suitable distribution. Furthermore, the more mature EP arm should guide the selection of distribution.

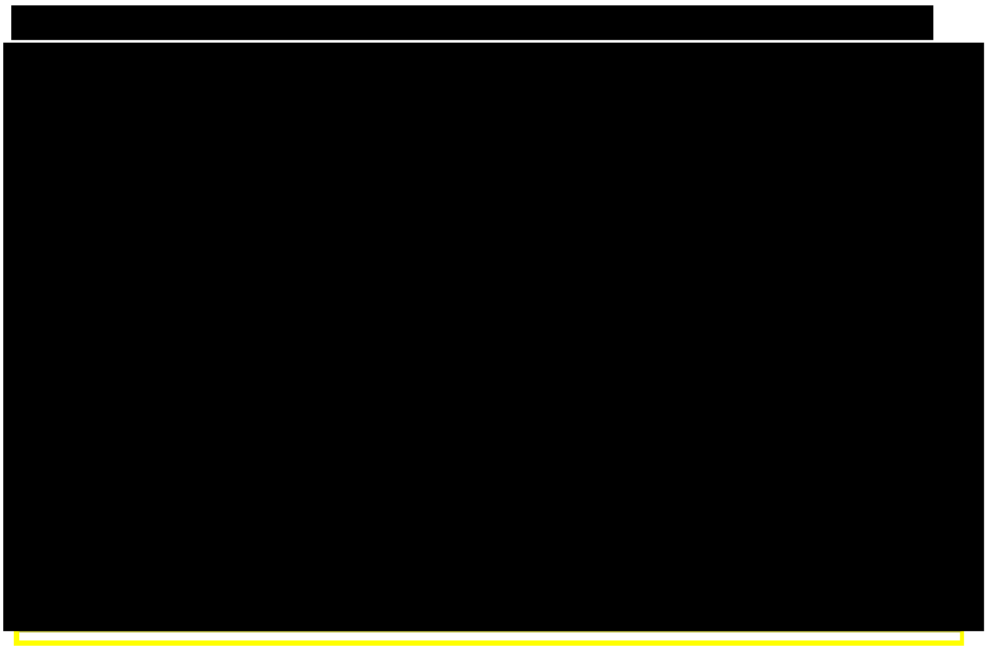
As shown in Table 54, and similarly to PFS, spline models had the best fits to the OS data (highlighted in bold).

Table 54. Goodness of fit statistics for overall survival

	Imfinzi®+E+P		E+P		Both arms (stratified fit)	
Distribution	ΔAIC_{min}	ΔBIC_{min}	ΔAIC_{min}	ΔBIC_{min}	ΔAIC_{min}, total	ΔBIC_{min}, total
Exponential	41.63	27.27	41.14	32.81	82.77	60.08
Weibull	42.57	31.8	20.26	15.53	62.83	47.33
Gompertz	40.91	30.14	37.91	33.18	78.82	63.32
Lognormal	50.31	39.54	41.69	36.96	92	76.5
Loglogistic	24.53	13.76	11.07	6.34	35.6	20.1
Generalised Gamma	37.84	30.66	16.94	15.8	54.78	46.46
Gamma	40.98	30.21	15.82	11.09	56.8	41.3
Spline Hazard (1 knot)	39.94	32.76	18.96	17.82	58.9	50.58
Spline Hazard (2 knots)	5.92	2.33	0	2.46	**5.92**	**4.79**
Spline Hazard (3 Knots)	**0**	**0**	**1.73**	**7.78**	**1.73**	**7.78**
Spline Odds (1 Knot)	21.53	14.35	1.14	0	22.67	14.35
Spline Odds (2 Knots)	**11.65**	**8.07**	**0.47**	**2.92**	**12.12**	**10.99**
Spline Odds (3 Knots)	**2.23**	**2.23**	**2.73**	**8.79**	**4.96**	**11.02**
Spline Normal (2 Knots)	16.61	13.02	4.83	7.29	21.44	20.31

D.2.5 Evaluation of visual fit

The figures below (Figure 24 - Figure 31) compare the different survival distributions with the Kaplan-Meier data. From the visual inspection, the standard survival distributions did not appear good fits. This was most evident for the Imfinzi® arm. In turn, the spline models showed good fit to the data. However, it was difficult to select the most appropriate spline model based solely on statistical and visual factors.



[redacted]

D.2.6 Evaluation of hazard functions

Considering the development of hazard with time (Figure 32 - Figure 45) for the different survival distributions - it is expected increasing hazards of death in the short term followed by decreasing hazards over the long term (in line with clinical expectations) of higher risk at diagnosis and converging hazards with time.

Hence, the fitted exponential, Weibull, and Gompertz distributions were considered clinically implausible, as these distributions did not predict the expected development of the hazard over time. All remaining distributions projected hazard shapes that were clinically plausible, however it was difficult to select the most appropriate model based on the evaluation of the hazard function.

Given the low clinical plausibility of the survival models with worse statistical fit, the spline models were considered the models with the best fit.

Figure 32. Hazard of Death (OS) over time with exponential extrapolation

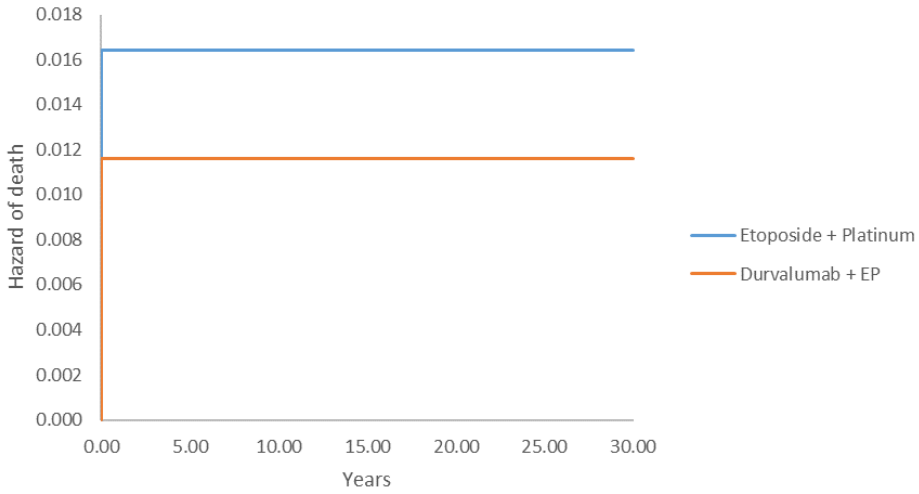


Figure 33: Hazard of Death (OS) over time with Weibull extrapolation

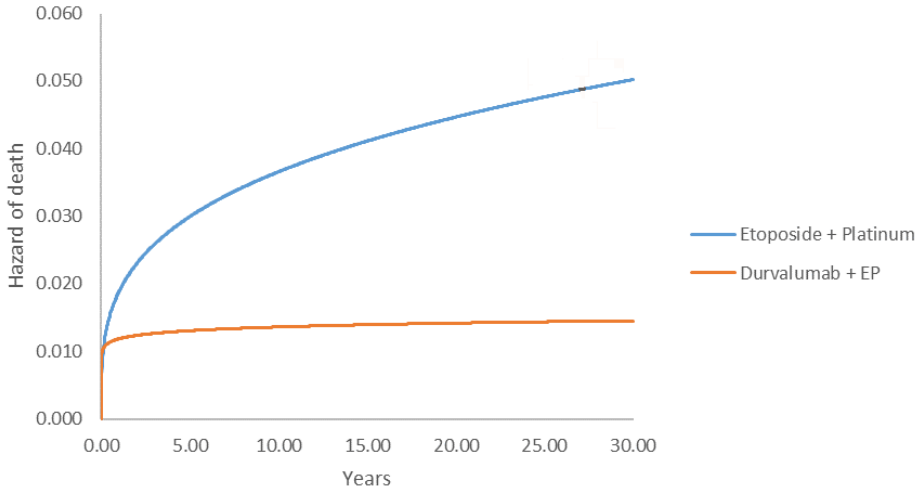


Figure 34. Hazard of Death (OS) over time with Gompertz extrapolation

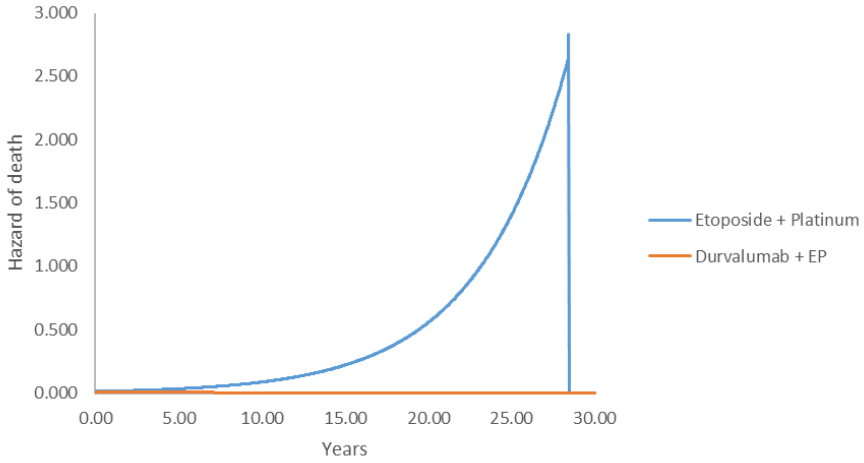


Figure 35. Hazard of Death (OS) over time with lognormal extrapolation

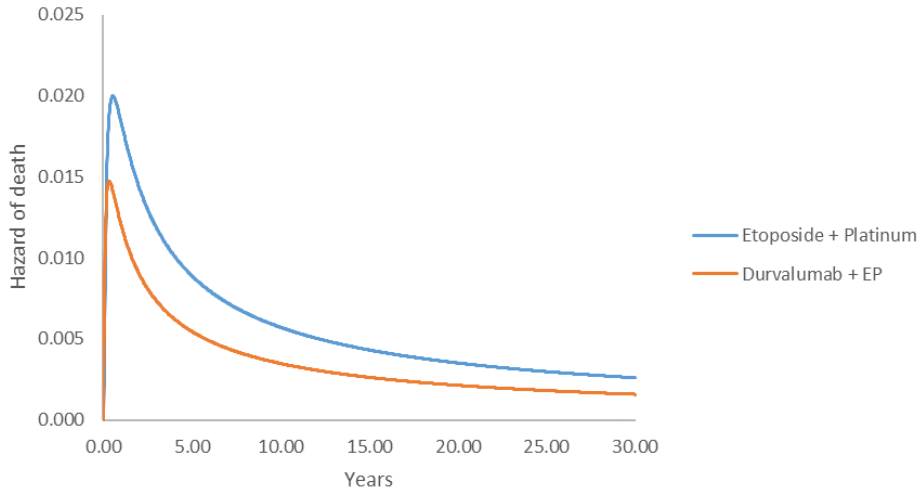


Figure 36. Hazard of Death (OS) over time with log-logistic extrapolation

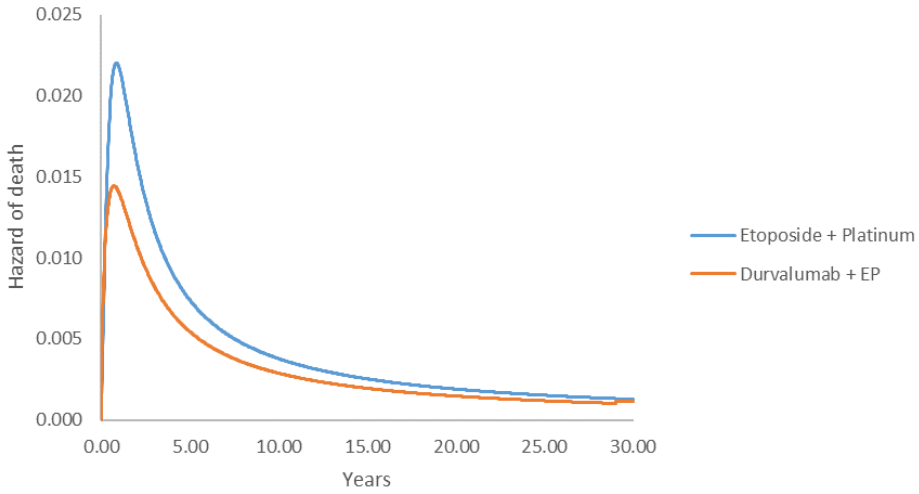


Figure 37. Hazard of Death (OS) over time with generalized gamma extrapolation

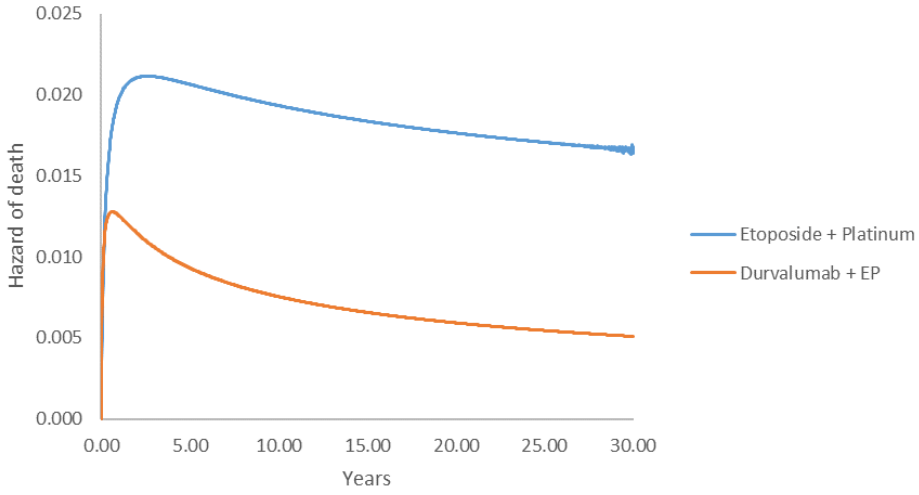


Figure 38. Hazard of Death (OS) over time with gamma extrapolation

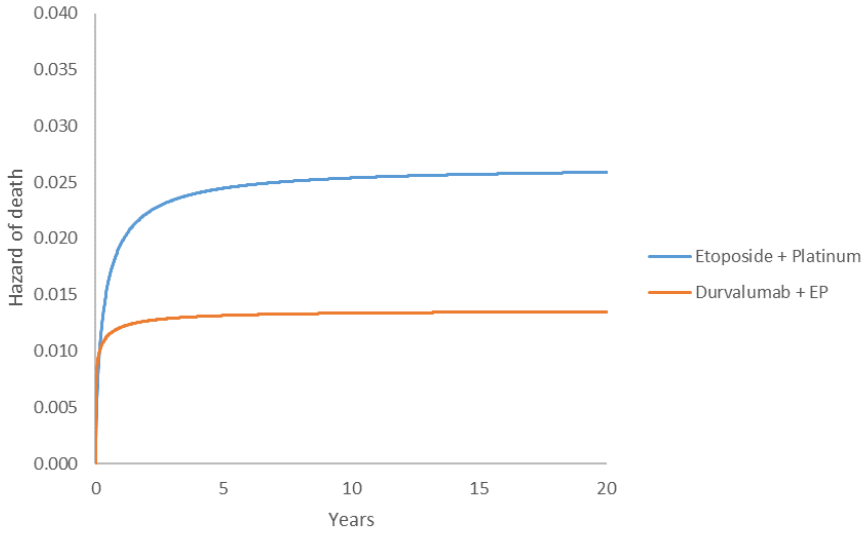


Figure 39. Hazard of Death (OS) over time with Spline hazard 1 knot extrapolation

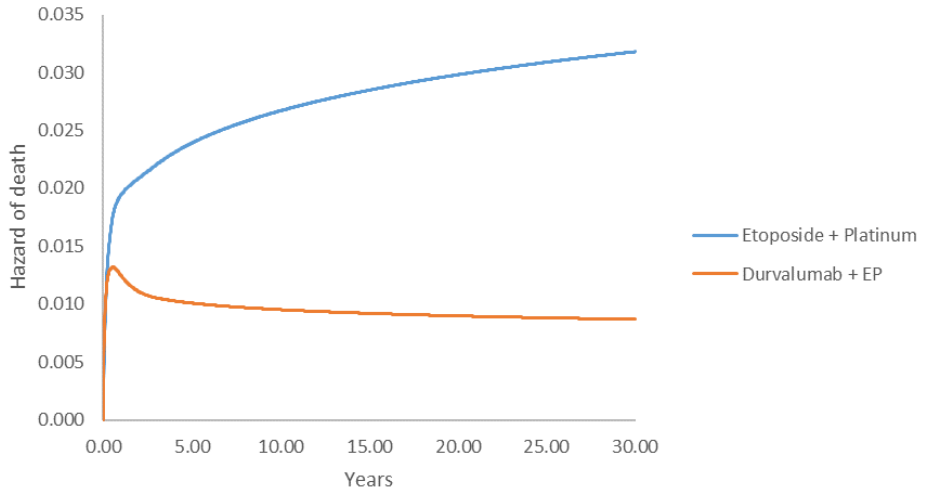


Figure 40. Hazard of Death (OS) over time with Spline hazard 2 knots extrapolation

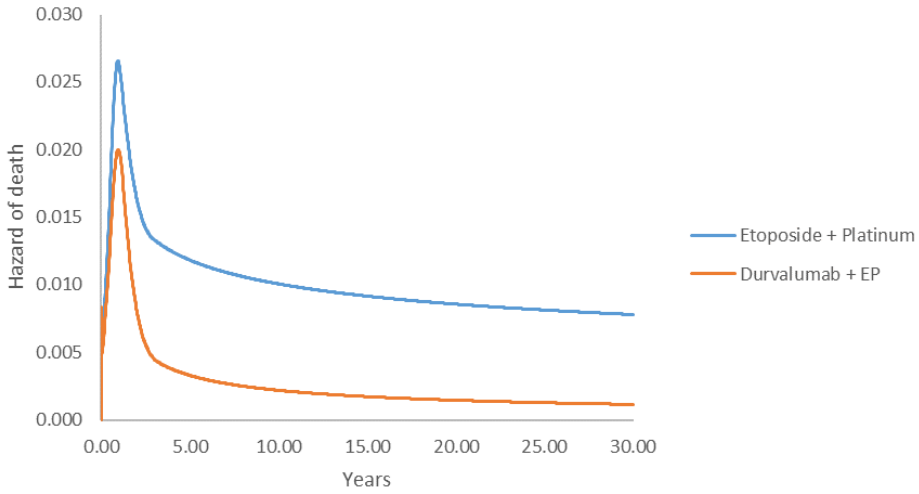


Figure 41. Hazard of Death (OS) over time with Spline hazard 3 knots extrapolation

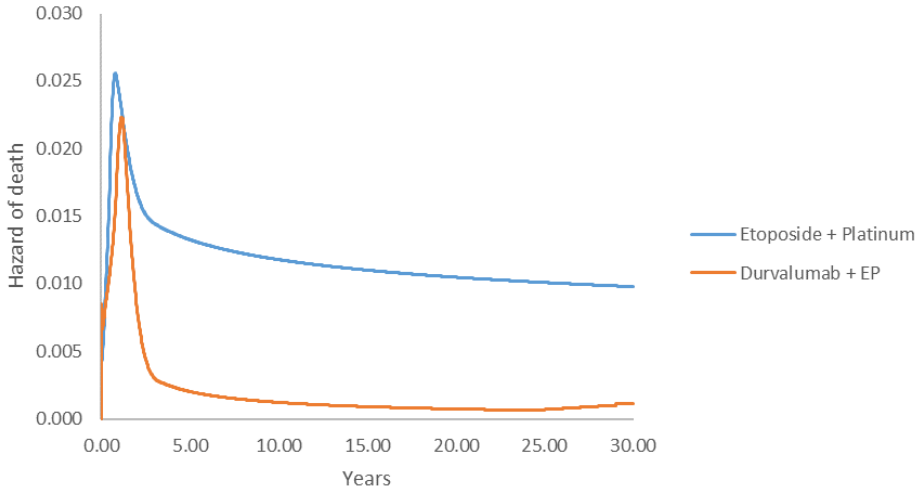


Figure 42. Hazard of Death (OS) over time with Spline odds 1 knot extrapolation

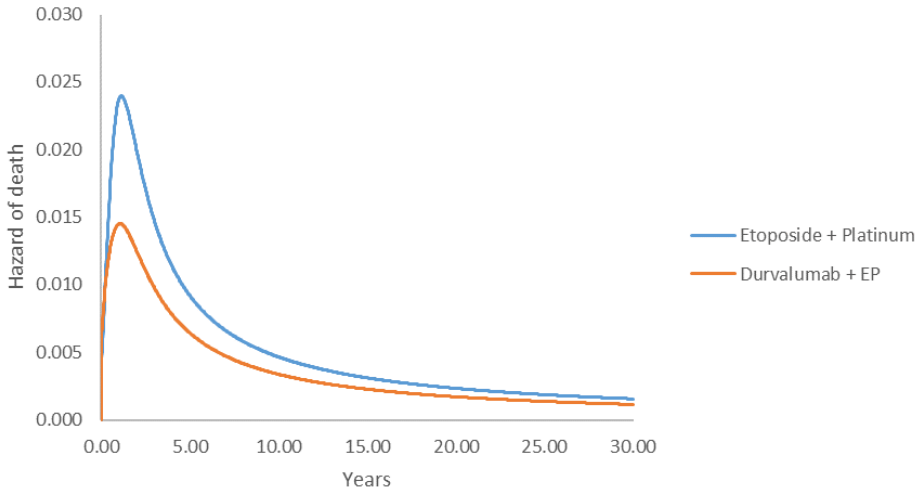


Figure 43. Hazard of Death (OS) over time with Spline odds 2 knots extrapolation

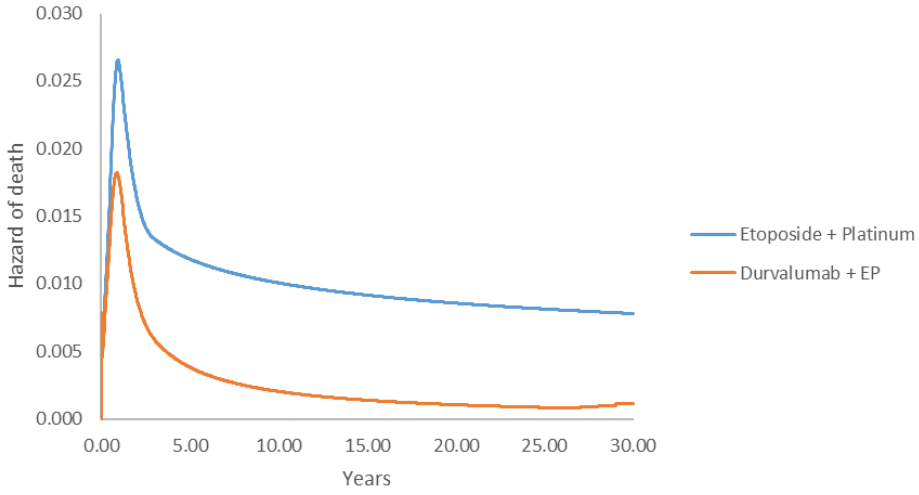


Figure 44. Hazard of Death (OS) over time with Spline odds 3 knots extrapolation

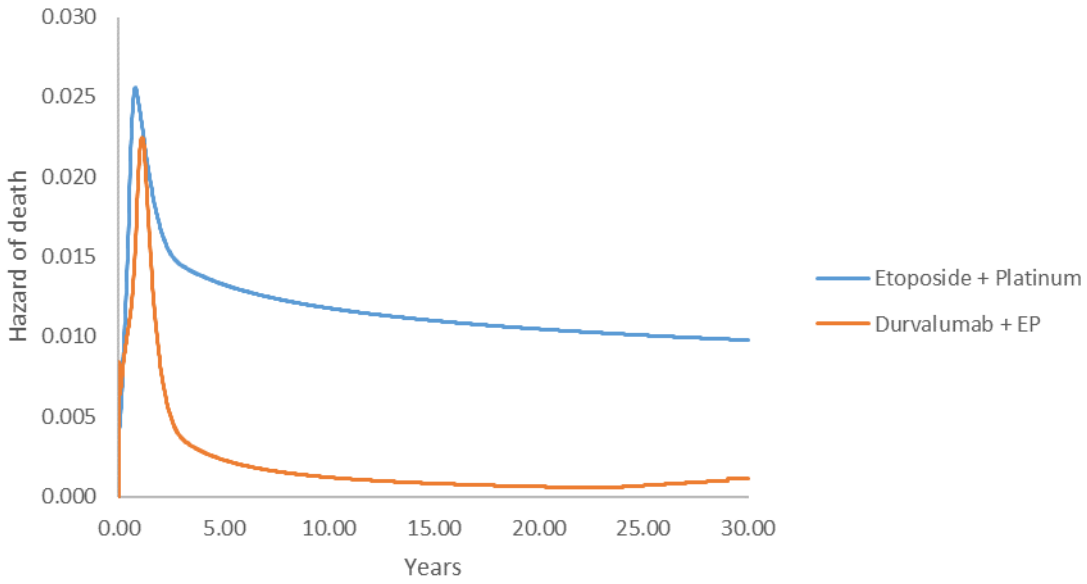
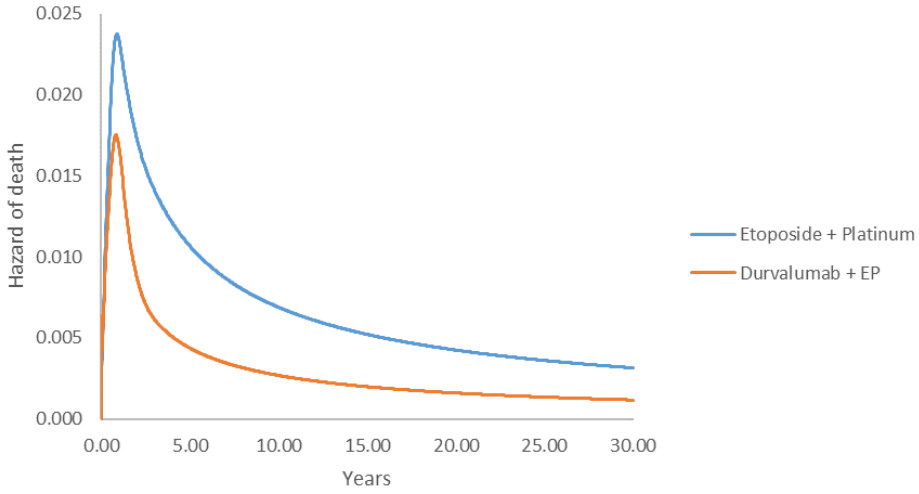


Figure 45. Hazard of Death (OS) over time with Spline normal 2 knots extrapolation



D.2.7 Validation and discussion of extrapolated curves

Landmark survival rates for the different survival models for EP are given in Table 55 and compared to the Kaplan-Meier estimates as well as real world data (Flatiron [from the assessment of atezolizumab [53]] and SEER [54]). Standard survival models appear to overestimate the survival at earlier landmarks compared to what is observed in CASPIAN and the real-world data. This is also true for spline models with only one knot – i.e., these may not be flexible enough to capture the changes in the hazard.

It should be noted that the Flatiron data is restricted to PS 0-1 but data from SEER is not. SEER also represents relative survival and not overall survival. Further, it is reported that there were very few patients left at 5-years in the Flatiron data, making this estimate uncertain.

Spline models with 2-3 knots estimate similar survival rates but only the odds model predicts residual survival at 10 years, as reported in SEER.

Table 55. Extrapolated overall survival rates for EP arm in the model compared to observations and external data

		Standard parametric survival models							Spline models							Real world evidence		
Landmark	Observed*	Exponential	Weibull	Gompertz	Lognormal	Loglogistic	Gen. gamma	Gamma	Hazard 1 knot	Hazard 2 knot	Hazard 3 knot	Odds 1 knot	Odds 2 knot	Odds 3 knot	Normal 2 knot	Flatiron	SEER, male	SEER, female
6 months	81%	65%	73%	69%	69%	75%	73%	74%	73%	77%	77%	76%	77%	77%	76%		-	-
1 year	39%	43%	47%	45%	42%	43%	45%	46%	45%	42%	41%	44%	42%	42%	42%	36%	22.5%	27.7
2 years	14%	18%	16%	17%	18%	16%	15%	15%	16%	14%	15%	14%	14%	14%	15%	13%	7%	9.9%
3 years	6%	8%	4%	6%	9%	8%	5%	5%	5%	7%	7%	6%	7%	7%	7%	7%	4%	5.8%
5 years	-	1%	0%	0%	3%	3%	1%	0%	0%	2%	2%	2%	2%	2%	2%	5%	2.5%	3.8%
10 years	-	0%	0%	0%	1%	1%	0%	0%	0%	0%	0%	0%	1%	1%	0%		1.4%	2%
15 years	-	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%			
20 years	-	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%			
25 years	-	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%			
30 years	-	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%			

Table 56. Extrapolated overall survival rates for Imfinzi arm in the model compared to observations and external data

		Standard parametric survival models							Spline models							Real world evidence		
Landmark	Observed*	Exponential	Weibull	Gompertz	Lognormal	Loglogistic	Gen. gamma	Gamma	Hazard 1 knot	Hazard 2 knot	Hazard 3 knot	Odds 1 knot	Odds 2 knot	Odds 3 knot	Normal 2 knot	Flatiron	SEER, male	SEER, female
6 months	80%	74%	76%	72%	73%	77%	75%	76%	75%	81%	80%	77%	80%	80%	78%	-	-	-
1 year	40%	55%	56%	52%	52%	53%	54%	56%	54%	51%	54%	54%	51%	54%	51%	36%	22.5%	27.7
2 years	18%	30%	30%	30%	30%	28%	29%	29%	29%	25%	23%	26%	26%	24%	27%	13%	7%	9.9%
3 years	17%	16%	16%	18%	20%	17%	16%	15%	17%	18%	18%	15%	18%	18%	18%	7%	4%	5.8%
5 years	-	5%	4%	8%	10%	9%	6%	4%	6%	12%	14%	7%	11%	13%	11%	5%	2.5%	3.8%
10 years	-	0%	0%	2%	3%	3%	1%	0%	0%	6%	9%	2%	5%	9%	5%	-	1.4%	2%
15 years	-	0%	0%	1%	2%	2%	0%	0%	0%	4%	7%	1%	4%	7%	2%			
20 years	-	0%	0%	1%	1%	1%	0%	0%	0%	3%	6%	1%	3%	5%	2%			
25 years	-	0%	0%	0%	0%	1%	0%	0%	0%	2%	4%	0%	2%	4%	1%			
30 years	-	0%	0%	0%	0%	0%	0%	0%	0%	1%	2%	0%	1%	2%	0%			

The corresponding landmark survival rates for the Imfinzi® arm are presented in Table 56. Considering statistical fit, visual comparison and clinical plausibility the spline odds 2 or 3 knots are candidates for the base case. A discussion with a Danish clinical expert with experience in treating ES-SCLC patients in Denmark, allowed to select the spline odds 2 knots distribution as the best fit for both arms (OS data) [30]. This was because, according to the Danish clinical expert, this distribution was the one that predicted the the most plausible survival rates at the landmarks of 1 year, 5 years, 10 years, 20 years and 30 years.

Hence, the spline odds 2 knots distribution was selected for the extrapolation of OS data in the base case analysis, as it gives the best combination of both statistical fit, clinical plausibility, and has been validated by a Danish clinical expert. The spline hazard 3 knots and spline hazard 1 knot distributions were tested in scenario analyses.

D.2.8 Adjustment of background mortality

The general mortality for the Danish population was used.

D.2.9 Adjustment for treatment switching/cross-over

Not applicable.

D.2.10 Waning effect

Not applicable.

D.2.11 Cure-point

Not applicable.

D.3 Extrapolation of time to treatment discontinuation

D.3.1 Data input

A Danish clinical expert considered ES-SCLC patients would commonly only be treated until progression [30]. Hence, in the base case analysis, TTD was set to equal to PFS. See Appendix D.1 on the extrapolation for PFS.

D.3.2 Model

See Appendix D.1 on the extrapolation for PFS.

D.3.3 Proportional hazards

See Appendix D.1 on the extrapolation for PFS.

D.3.4 Evaluation of statistical fit (AIC and BIC)

See Appendix D.1 on the extrapolation for PFS.

D.3.5 Evaluation of visual fit

See Appendix D.1 on the extrapolation for PFS.

D.3.6 Evaluation of hazard functions

See Appendix D.1 on the extrapolation for PFS.

D.3.7 Validation and discussion of extrapolated curves

See Appendix D.1 on the extrapolation for PFS.

D.3.8 Adjustment of background mortality

See Appendix D.1 on the extrapolation for PFS.

D.3.9 Adjustment for treatment switching/cross-over

See Appendix D.1 on the extrapolation for PFS.

D.3.10 Waning effect

See Appendix D.1 on the extrapolation for PFS.

D.3.11 Cure-point

See Appendix D.1 on the extrapolation for PFS.

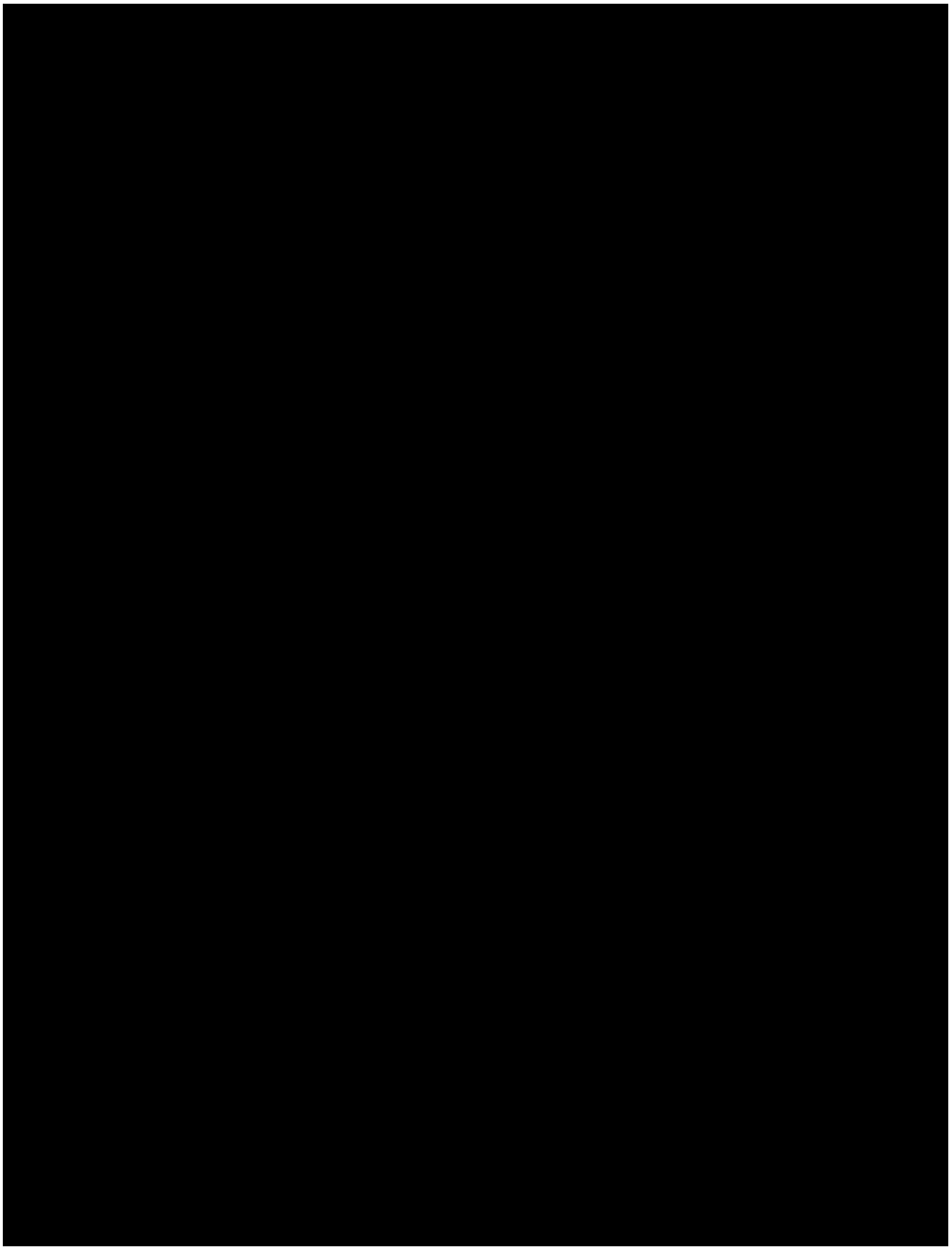
Appendix E. Serious adverse events

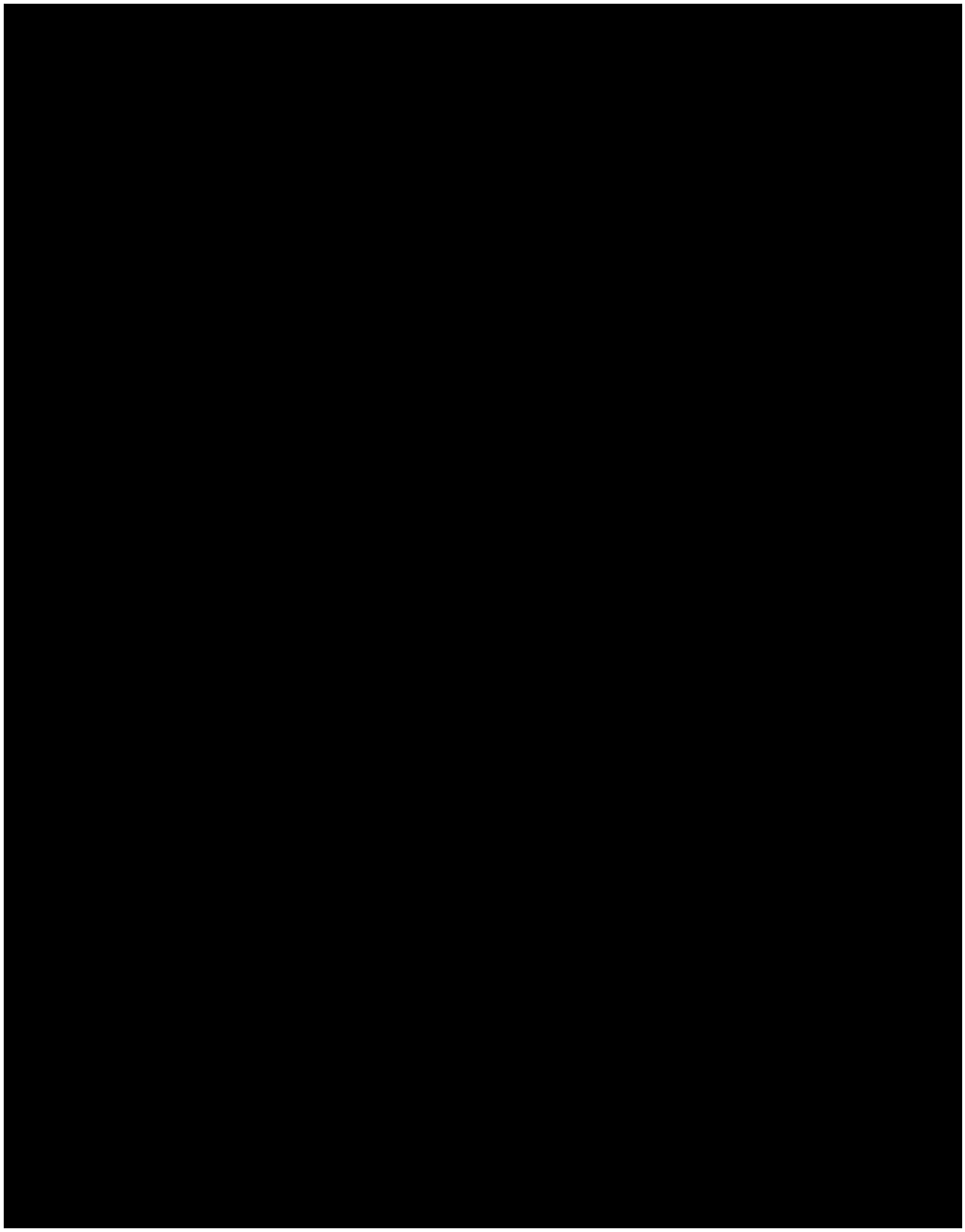
All the serious adverse events observed in CASPIAN are described in Table 57.

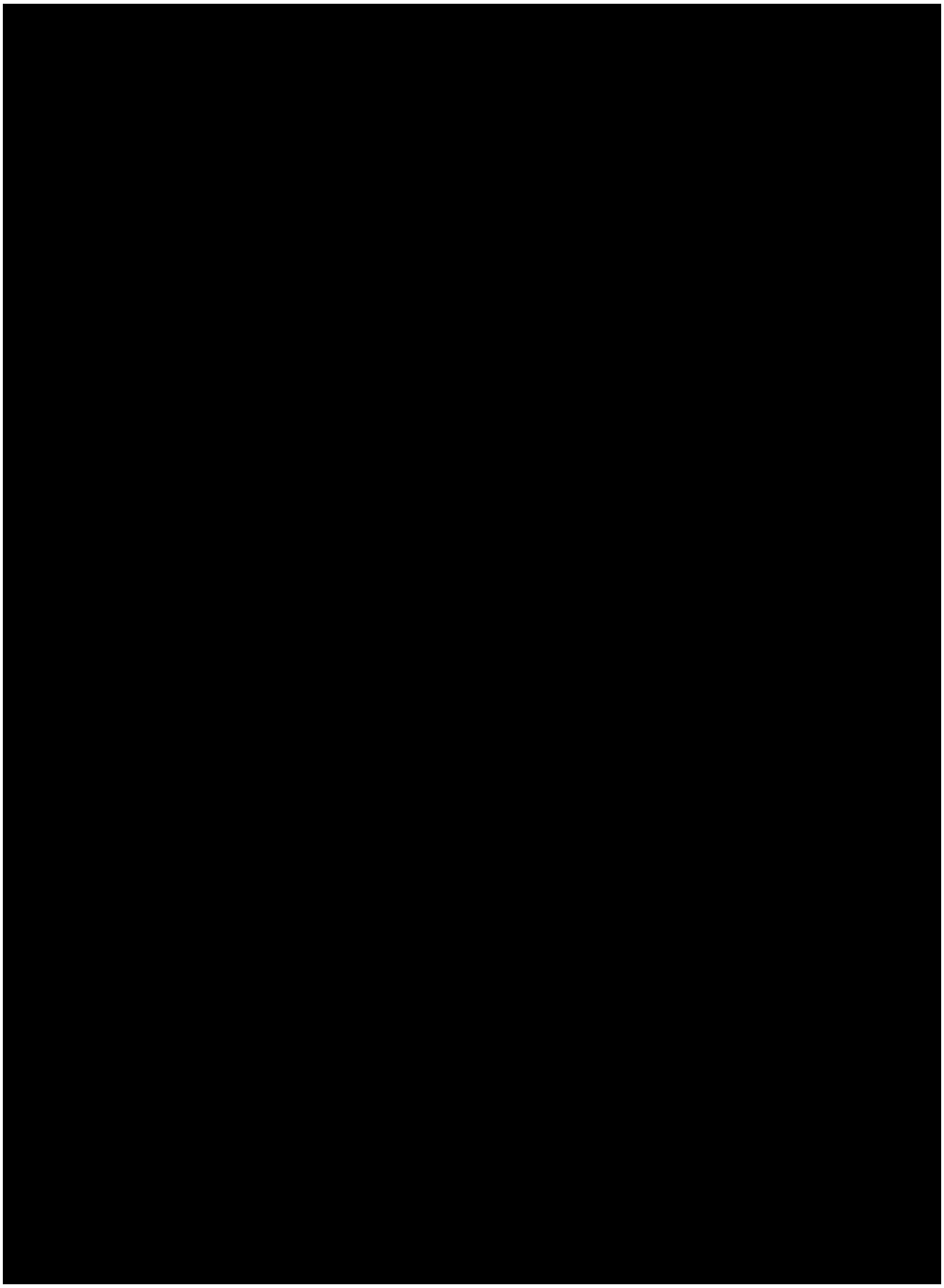
[redacted]

[redacted]

[redacted]







Appendix F. Health-related quality of life

No specific domains from the assessment instrument used for the submitted application need to be highlighted, as they are in line with the guidelines and described in section 0. Therefore, this appendix is used to provide the pattern of missing data and completion for durvalumab + EP and EP alone ([redacted] as well as the results for the remaining models.

[redacted]

	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				

	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				

	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				

	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
[redacted]				

	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
[redacted]				

Parameter	Treatment	Progression status	Treatment + Progression status	Treatment * Progression status
[redacted]				

Durva, durvalumab; EP, etoposide + platinum-based chemotherapy; SE, standard error

The disutilities used for AEs in the model were based on literature identified by a targeted search of electronic sources, e.g., prior HTA. The studies used in the model are detailed below in Table 60.

Table 60. Studies used for the disutility of adverse events.

Reference	Study design	Population	QoL instrument/Elicitation method	Transferability/relevance
Nafees 2008 [48]	Societal-based valuation study	Patients with non-small cell lung cancer	Standard gamble	Typical adverse events associated with cancer treatment are described as health states and valued by the general population/public. They are widely used in health economic evaluations of lung cancer therapies [62]. This study was used for the majority of adverse events.
Sejean 2005 [50]	Cost-effectiveness analysis	Patients with asymptomatic primary hyperparathyroidism	Time trade-off	The disutility associated with hyperparathyroidism is used as a proxy for hyper- and hypothyroidism.
Schremser 2015 [49]	Cost-effectiveness analysis	Patients with advanced (predominantly stage IV) adenocarcinoma of the lung	Not reported	Disutility for thrombocytopenia is sourced from Shremser 2015 – a cost-effectiveness analysis in stage IV lung cancer.
Huang 2018 [47]	Retrospective case-control study	Patients with chronic obstructive pulmonary disease and community-acquired pneumonia	Not reported	Co-morbid pneumonia.
Birkmeyer 2013 [46]	Cost-effectiveness analysis	Patients undergoing total hip and knee replacement	Not reported	Used for the adverse event hepatitis.

Appendix G. Probabilistic sensitivity analyses

Table 61 summarizes information on the parameters included in the PSA.

Table 61. Overview of parameters in the PSA

Input parameter	Point estimate	Lower bound	Upper bound	Probability distribution
Age	70.0	69.30	70.70	Normal
Proportion Male	69.6%	0.66	0.73	Beta
Durvalumab OS: Gamma0	-4.029	-4.60	-3.46	Multivariate Normal
Durvalumab OS: Gamma1	0.564	0.14	0.98	
Durvalumab OS: Gamma2	-0.512	-0.78	-0.24	
Durvalumab OS: Gamma3	0.705	0.30	1.11	
Chemotherapy OS: Gamma0	-4.216	-4.80	-3.63	Multivariate Normal
Chemotherapy OS: Gamma1	0.635	0.08	1.19	
Chemotherapy OS: Gamma2	-0.370	-0.76	0.02	
Chemotherapy OS: Gamma3	0.405	-0.14	0.94	
Durvalumab PFS: Gamma0	-3.946	-4.60	-3.29	Multivariate Normal
Durvalumab PFS: Gamma1	0.624	0.10	1.14	
Durvalumab PFS: Gamma2	-2.723	-5.38	-0.06	
Durvalumab PFS: Gamma3	2.809	-1.38	7.00	

Durvalumab PFS: Gamma4	0.109	-1.51	1.73	
Chemotherapy PFS: Gamma0	-2.918	-3.55	-2.29	Multivariate Normal
Chemotherapy PFS: Gamma1	1.927	0.79	3.06	
Chemotherapy PFS: Gamma2	1.772	0.82	2.72	
Chemotherapy PFS: Gamma3	-6.605	-9.01	-4.20	
Chemotherapy PFS: Gamma4	5.431	3.80	7.06	
Durvalumab TTD: Gamma0	-3.424	-3.89	-2.96	Multivariate Normal
Durvalumab TTD: Gamma1	0.457	0.23	0.68	
Durvalumab TTD: Gamma2	-0.995	-1.20	-0.79	
Durvalumab TTD: Gamma3	1.226	0.97	1.48	
Chemotherapy TTD: Gamma0	-3.145	-3.78	-2.51	Multivariate Normal
Chemotherapy TTD: Gamma1	0.498	0.22	0.78	
Chemotherapy TTD: Gamma2	10.126	7.85	12.40	
Chemotherapy TTD: Gamma3	-18.983	-23.11	-14.86	
Subsequent Treatments: D+EP	-0.082	-0.33	0.17	Multivariate Normal
Subsequent Treatments: 3rd+ Line	0.283	0.00	0.57	
Subsequent Treatments:	0.245	-0.37	0.86	

Chemotherapy Regimens				
Subsequent Treatments: Single Agent Chemo	0.356	-0.25	0.96	
Subsequent Treatments: Scale	-1.170	-1.79	-0.55	
Subsequent Treatments: Shape	-0.235	-0.34	-0.13	
Durvalumab Mono AE: Anaemia	7.9%	0.05	0.11	Beta
Durvalumab Mono AE: Diarrhoea (Grade 2)	1.9%	0.01	0.04	Beta
Durvalumab Mono AE: Diarrhoea (Grade 3+)	0.8%	0.00	0.02	Beta
Durvalumab Mono AE: Febrile Neutropenia	4.9%	0.03	0.08	Beta
Durvalumab Mono AE: Leukopenia	5.7%	0.03	0.09	Beta
Durvalumab Mono AE: Lipase Increased	3.0%	0.01	0.05	Beta
Durvalumab Mono AE: Nausea/Vomiting	0.0%	0.00	0.00	Beta
Durvalumab Mono AE: Neutropenia	23.0%	0.18	0.28	Beta
Durvalumab Mono AE: Neutrophil Count Decrease	6.0%	0.03	0.09	Beta
Durvalumab Mono AE: Platelet Count Decrease	1.5%	0.00	0.03	Beta
Durvalumab Mono AE: Pneumonia	0.8%	0.00	0.02	Beta

Durvalumab Mono AE: Thrombocytopenia	5.3%	0.03	0.08	Beta
Durvalumab Mono AE: WBC Count Decrease	1.5%	0.00	0.03	Beta
Durvalumab Mono AE: Placeholder1	0.0%	0.00	0.00	Beta
Durvalumab Mono AE: Placeholder2	0.0%	0.00	0.00	Beta
Durvalumab Mono AE: Placeholder3	0.0%	0.00	0.00	Beta
Durvalumab Mono AE: Placeholder4	0.0%	0.00	0.00	Beta
Durvalumab Mono AE: Placeholder5	0.0%	0.00	0.00	Beta
Durvalumab Mono AE: Placeholder6	0.0%	0.00	0.00	Beta
Durvalumab Mono AE: Placeholder7	0.0%	0.00	0.00	Beta
Durvalumab Mono AE: Hepatitis	0.0%	0.00	0.00	Beta
Durvalumab Mono AE: Hyperthyroidism	0.0%	0.00	0.00	Beta
Durvalumab Mono AE: Hypothyroidism	0.0%	0.00	0.00	Beta
Durvalumab Mono AE: Infusion Reaction	0.0%	0.00	0.00	Beta
Durvalumab Mono AE: Pneumonitis	0.0%	0.00	0.00	Beta
Durvalumab Mono AE: Rash	0.0%	0.00	0.00	Beta

Etoposide + Platinum AE: Anaemia	14.3%	0.10	0.19	Beta
Etoposide + Platinum AE: Diarrhoea (Grade 2)	1.9%	0.01	0.04	Beta
Etoposide + Platinum AE: Diarrhoea (Grade 3+)	0.8%	0.00	0.02	Beta
Etoposide + Platinum AE: Febrile Neutropenia	6.4%	0.04	0.10	Beta
Etoposide + Platinum AE: Leukopenia	5.3%	0.03	0.08	Beta
Etoposide + Platinum AE: Lipase Increased	0.4%	0.00	0.01	Beta
Etoposide + Platinum AE: Nausea/Vomiting	2.6%	0.01	0.05	Beta
Etoposide + Platinum AE: Neutropenia	32.3%	0.27	0.38	Beta
Etoposide + Platinum AE: Neutrophil Count Decrease	6.4%	0.04	0.10	Beta
Etoposide + Platinum AE: Platelet Count Decrease	2.3%	0.01	0.04	Beta
Etoposide + Platinum AE: Pneumonia	0.4%	0.00	0.01	Beta
Etoposide + Platinum AE: Thrombocytopenia	9.0%	0.06	0.13	Beta

Etoposide + Platinum AE: WBC Count Decrease	2.3%	0.01	0.04	Beta
Etoposide + Platinum AE: Placeholder1		0.00	0.00	Beta
Etoposide + Platinum AE: Placeholder2		0.00	0.00	Beta
Etoposide + Platinum AE: Placeholder3		0.00	0.00	Beta
Etoposide + Platinum AE: Placeholder4		0.00	0.00	Beta
Etoposide + Platinum AE: Placeholder5		0.00	0.00	Beta
Etoposide + Platinum AE: Placeholder6		0.00	0.00	Beta
Etoposide + Platinum AE: Placeholder7		0.00	0.00	Beta
Etoposide + Platinum AE: Hepatitis	0.0%	0.00	0.00	Beta
Etoposide + Platinum AE: Hyperthyroidism	0.0%	0.00	0.00	Beta
Etoposide + Platinum AE: Hypothyroidism	0.0%	0.00	0.00	Beta
Etoposide + Platinum AE: Infusion Reaction	0.0%	0.00	0.00	Beta
Etoposide + Platinum AE: Pneumonitis	0.0%	0.00	0.00	Beta

Etoposide + Platinum AE: Rash	0.0%	0.00	0.00	Beta
Utility: Progression-Free	0.834	0.82	0.85	
Utility: Post-Progression	0.802	0.79	0.81	
Disutility: Anaemia	-0.073	-0.04	-0.11	Beta
Disutility: Diarrhoea (Grade 2)	-0.047	-0.02	-0.08	Beta
Disutility: Diarrhoea (Grade 3+)	-0.047	-0.02	-0.08	Beta
Disutility: Febrile Neutropenia	-0.090	-0.06	-0.12	Beta
Disutility: Leukopenia	-0.090	-0.06	-0.12	Beta
Disutility: Lipase Increased	-0.019	-0.02	-0.02	Beta
Disutility: Nausea/Vomiting	-0.048	-0.02	-0.08	Beta
Disutility: Neutropenia	-0.090	-0.06	-0.12	Beta
Disutility: Neutrophil Count Decrease	-0.090	-0.06	-0.12	Beta
Disutility: Platelet Count Decrease	-0.090	-0.06	-0.12	Beta
Disutility: Pneumonia	-0.090	-0.06	-0.12	Beta
Disutility: Thrombocytopenia	-0.053	-0.04	-0.06	Beta
Disutility: WBC Count Decrease	-0.090	-0.06	-0.12	Beta
Disutility: Hepatitis	-0.038	-0.03	-0.05	Beta

Disutility: Hyperthyroidism	-0.095	-0.08	-0.11	Beta
Disutility: Hypothyroidism	-0.106	-0.09	-0.13	Beta
Disutility: Infusion Reaction	-0.150	-0.12	-0.18	Beta
Disutility: Pneumonitis	-0.090	-0.06	-0.12	Beta
Disutility: Rash	-0.032	-0.01	-0.06	Beta
Cost: Carboplatin Vial (150mg)	DKK 295	240.0	355.6	Gamma
Cost: Carboplatin Vial (450mg)	DKK 226	183.88	272.40	Gamma
Cost: Cisplatin Vial (50mg)	DKK 100	81.36	120.53	Gamma
Cost: Cisplatin Vial (100mg)	DKK 200	162.73	241.06	Gamma
Cost: Cyclophosphamide Vial (500mg)	DKK 180	146.46	216.95	Gamma
Cost: Cyclophosphamide Vial (200mg)	DKK 72	58.73	87.00	Gamma
Cost: Docetaxel Vial (20mg)	DKK 72	58.5	86.7	Gamma
Cost: Docetaxel Vial (80mg)	DKK 151	122.9	182.0	Gamma
Cost: Docetaxel Vial (160mg)	DKK 309	251.41	372.43	Gamma
Cost: Doxorubicin Vial (50mg)	DKK 120	97.64	144.63	Gamma
Cost: Doxorubicin Vial (200mg)	DKK 350	284.77	421.85	Gamma
Cost: Epirubicin Vial (50mg)	DKK 111	89.99	133.31	Gamma

Cost: Epirubicin Vial (100mg)	DKK	980	797.37	1181.18	Gamma
Cost: Epirubicin Vial (200mg)	DKK	443	360.25	533.65	Gamma
Cost: Etoposide Vial (100mg)	DKK	71	58.07	86.02	Gamma
Cost: Etoposide Vial (500mg)	DKK	279	226.78	335.94	Gamma
Cost: Gemcitabine Vial (1200mg)	DKK	310	252.23	373.64	Gamma
Cost: Gemcitabine Vial (1400mg)	DKK	330	268.50	397.75	Gamma
Cost: Gemcitabine Vial (1600mg)	DKK	350	284.77	421.85	Gamma
Cost: Gemcitabine Vial (1800mg)	DKK	370	301.05	445.96	Gamma
Cost: Gemcitabine Vial (2000mg)	DKK	385	313.25	464.04	Gamma
Cost: Gemcitabine Vial (2200mg)	DKK	420	341.73	506.22	Gamma
Cost: Irinotecan Vial (100mg)	DKK	125	101.70	150.66	Gamma
Cost: Irinotecan Vial (500mg)	DKK	350	284.77	421.85	Gamma
Cost: Paclitaxel Vial (100mg)	DKK	111	89.91	133.18	Gamma
Cost: Paclitaxel Vial (300mg)	DKK	202	163.95	242.87	Gamma
Cost: Vincristine Vial (1mg)	DKK	390	317.32	470.06	Gamma
Cost: Vincristine Vial (2mg)	DKK	645	524.80	777.41	Gamma
Cost: Vinorelbine Vial (30mg)	DKK	619	542.17	700.32	Gamma

Standard chemotherapy	DKK	1,634	1329.49	1969.44	Gamma
Cost: PD-L1 Test	DKK	-	0.00	0.00	Gamma
Cost: TMB Test	DKK	-	0.00	0.00	Gamma
Cost: Outpatient Visit	DKK	1,634	1470.60	1797.40	Gamma
Cost: CT Scan	DKK	2,023	1820.70	2225.30	Gamma
Cost: GFR-test	DKK	73	66.07	80.75	Gamma
Cost: Electrocardiograph	DKK	191	171.77	209.94	Gamma
Cost: PCI	DKK	40,193	36173.70	44212.30	Gamma
Cost: Radiotherapy	DKK	40,193	36173.70	44212.30	Gamma
Cost: End-of-life	DKK	74,945	67450.50	82439.50	Gamma
Cost: Anaemia	DKK	4,210	3918.91	4485.80	Gamma
Cost: Diarrhoea (Grade 2)	DKK	3,425	3188.19	3649.37	Gamma
Cost: Diarrhoea (Grade 3/4)	DKK	26,929	25067.08	28693.14	Gamma
Cost: Febrile Neutropenia	DKK	14,514	13510.48	15464.83	Gamma
Cost: Leukopenia	DKK	38,209	35567.17	40712.11	Gamma
Cost: Lipase Increased	DKK	2,005	1866.37	2136.35	Gamma
Cost: Nausea/Vomiting	DKK	3,425	3188.19	3649.37	Gamma
Cost: Neutropenia	DKK	38,209	35567.17	40712.11	Gamma
Cost: Neutrophil Count Decrease	DKK	2,005	1866.37	2136.35	Gamma
Cost: Platelet Count Decrease	DKK	2,005	1866.37	2136.35	Gamma
Cost: Pneumonia	DKK	33,134	30843.06	35304.64	Gamma

Cost: Thrombocytopenia	DKK 38,209	35567.17	40712.11	Gamma
Cost: WBC Count Decrease	DKK 2,005	1866.37	2136.35	Gamma
Cost: Placeholder 7				Gamma
Cost: Hepatitis	38,628.00	35957.20	41158.56	Gamma
Cost: Hyperthyroidism	25,342.00	23589.81	27002.18	Gamma
Cost: Hypothyroidism	25,342.00	23589.81	27002.18	Gamma
Cost: Infusion-Related Reaction	4,342.00	4041.79	4626.45	Gamma
Cost: Rash	1,634.00	1521.02	1741.04	Gamma
Non-medical costs PFS - D+EP	452.85	421.54	482.52	Gamma
Non-medical costs PFS -EP	452.85	421.54	482.52	Gamma
Non-medical costs PPS	202.84	188.82	216.13	Gamma
Outpatient Consultations per Week: On Tx	17.40	16.23	18.57	Normal
CT Scans per Week: On Tx	0.50	0.47	0.53	Normal
GRF-tests per Week: On Tx	1.00	0.93	1.07	Normal
ECGs per Week: On Tx	0.15	0.14	0.16	Normal
Radiotherapy Fractions per Week: PFS	0.00	#NUM!	#NUM!	Normal
Outpatient Consultations per Week: Off Tx	12.00	11.19	12.81	Normal

CT Scans per Week: Off Tx	0.50	0.47	0.53	Normal
GFR-tests per Week: Off Tx	1.00	0.93	1.07	Normal
ECGs per Week: Off Tx	0.15	0.14	0.16	Normal
Radiotherapy Fractions: PPS	10.00	9.33	10.67	Normal
Patients Receiving PCI: Chemotherapy (1st Line)	30.0%	0.24	0.36	Beta
Received Radiotherapy: Durvalumab (PPS)	20.0%	0.16	0.24	Beta
Received Radiotherapy: Chemotherapy (PPS)	20.0%	0.16	0.24	Beta
2L Treatment: Durvalumab Mono		0.42	0.63	Beta
2L Treatment: Durvalumab Combo		0.00	0.00	Beta
2L Treatment: Etoposide + Platinum		0.38	0.56	Beta
3L Treatment: Durvalumab Mono		0.28	0.41	Beta
3L Treatment: Etoposide + Platinum		0.32	0.47	Beta
ToT 2L Immunotherapies: Durvalumab Mono	4.00	1.99	5.35	Gamma
ToT 2L Chemo Regimens: Durvalumab Mono	3.13	1.36	4.26	Gamma

ToT 2L Single Agent: Durvalumab Mono	2.80	1.13	3.83	Gamma
ToT 2L Immunotherapies: Etoposide + Platinum	3.68	1.76	4.96	Gamma
ToT 2L Chemo Regimens: Etoposide + Platinum	2.88	1.19	3.94	Gamma
ToT 2L Single Agent: Etoposide + Platinum	2.58	0.98	3.54	Gamma
ToT 3L+ Immunotherapies: Durvalumab Mono	3.01	1.28	4.11	Gamma
ToT 3L+ Chemo Regimens: Durvalumab Mono	2.36	0.84	3.25	Gamma
ToT 3L+ Single Agent: Durvalumab Mono	2.11	0.68	2.92	Gamma
ToT 3L+ Immunotherapies: Etoposide + Platinum	2.77	1.12	3.80	Gamma
ToT 3L+ Chemo Regimens: Etoposide + Platinum	2.17	0.72	3.00	Gamma
ToT 3L+ Single Agent: Etoposide + Platinum	1.94	0.58	2.69	Gamma

Appendix H. Literature searches for the clinical assessment

The clinical assessment was informed by the head-to-head study (CASPIAN) used in this application. Therefore, this appendix is not applicable.

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

Not applicable.

Table 62. Bibliographic databases included in the literature search (NA)

Database	Platform/source	Relevant period for the search	Date of search completion
NA	NA	NA	NA

Table 63. Other sources included in the literature search (NA)

Source name	Location/source	Search strategy	Date of search
NA	NA	NA	NA

Table 64. Conference material included in the literature search (NA)

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
NA	NA	NA	NA	**NA**

H.1.1 Search strategies

Not applicable.

Table 65. of search strategy table for [name of database] (NA)

No.	Query	Results
NA	NA	NA

H.1.2 Systematic selection of studies

Not applicable.

Table 66. Inclusion and exclusion criteria used for assessment of studies (NA)

Clinical effectiveness	Inclusion criteria	Exclusion criteria
NA	NA	NA

Table 67. Overview of study design for studies included in the analyses (NA)

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
NA	NA	NA	NA	NA	NA	NA

H.1.3 Quality assessment

Not applicable.

H.1.4 Unpublished data

Not applicable.

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

The health-related quality of life data was informed by the head-to-head study (CASPIAN) used in this application. Therefore, this appendix is not applicable.

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

Not applicable.

Table 68. Bibliographic databases included in the literature search (NA)

Database	Platform	Relevant period for the search	Date of search completion
NA	NA	NA	NA

Table 69. Other sources included in the literature search (NA)

Source name	Location/source	Search strategy	Date of search
NA	NA	NA	NA

Table 70. Conference material included in the literature search (NA)

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
NA	NA	NA	NA	NA

I.1.1 Search strategies

Not applicable.

Table 71. Search strategy for [name of database] (NA)

No.	Query	Results
NA	NA	NA

I.1.2 Quality assessment and generalizability of estimates

Not applicable.

I.1.3 Unpublished data

Not applicable.

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

Inputs for the health economic model were sourced via targeted search in publicly available sources. Therefore, this appendix is not applicable.

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

Not applicable.

J.1.1 Ex. Systematic search for […]

Not applicable.

Table 72. Sources included in the search (NA)

Database	Platform/source	Relevant period for the search	Date of search completion
NA	NA	NA	NA

J.1.2 Ex. Targeted literature search for [estimates]

Not applicable.

Table 73. Sources included in the targeted literature search (NA)

Source name/ database	Location/source	Search strategy	Date of search
NA	NA	NA	NA

Appendix K. Other indications

Table 74. Other approved indications for Imfinzi®

Disease	Indication	The Danish Medicine Council
Non-small cell Lung Cancer (NSCLC)	IMFINZI® as monotherapy is indicated for the treatment of locally advanced, unresectable non-small cell lung cancer (NSCLC) in adults whose tumours express PD-L1 on ≥ 1% of tumour cells and whose disease has not progressed following platinum-based chemoradiation therapy	Assessed by the DMC (Decision 2019)
	IMFINZI® 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.	
Biliary Tract Cancer (BTC)	IMFINZI® in combination with gemcitabine and cisplatin is indicated for the first-line treatment of adults with unresectable or metastatic biliary tract cancer (BTC).	Under assessment
Hepatocelluar Carcinoma (HCC)	IMFINZI® in combination with tremelimumab is indicated for the first line treatment of adults with advanced or unresectable hepatocellular carcinoma (HCC).	Under assessment

Medicinrådet

Danish Medicines Council

Secretariat

Dampfærgevej 21-23, 3rd floor

DK-2100 Copenhagen Ø

+ 45 70 10 36 00

medicinraadet@medicinraadet.dk

www.medicinraadet.dk